CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209575Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	January 10, 2020
From	Rigoberto Roca, MD
Subject	Division Director Summary Review
NDA No.	209575
Applicant Name	Cody Laboratories, Inc.
Date of Original Submission	September 21, 2017 Complete Response letter issued July 20, 2018
Date of Complete Response Submission	June 21, 2019
PDUFA Goal Date	December 21, 2019
Proprietary Name / Established (USAN) Name	Numbrino / Cocaine Hydrochloride
Dosage Forms / Strength	Topical Solution, 4% and 10%
Proposed Indications	Induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults
Action	Approval (of 4% only)

Material Reviewed/Consulted: OND Action Package, including	
Clinical Review	Renee Petit-Scott, MD
Pharmacology Toxicology Review	BeLinda A. Hayes, PhD; Newton Woo, PhD; Dan Mellon, PhD
Clinical Pharmacology Review	Deep Kwatra, PhD; Yun Xu, PhD
OPQ	Venkateswara R. Pavuluri, PhD, RPh; Julia Pinto, PhD
Project Management Staff	Shelly Kapoor, PharmD; Parinda Jani
DMEPA	James Schlick, MBA, RPh; Cameron Johnson, PharmD; Otto Townsend, PharmD
DCRP QT-IRT	Girish Bende, PhD; Yu Yi Hsu, PhD; Mohammad Rahman, PhD; Michael Li, PhD; Lars Johannesen, PhD; Christine Garnett, PharmD

DCRP = Division of Cardiovascular and Renal Products
DMEPA = Division of Medication Error Prevention and Analysis
OND = Office of New Drugs
OPDP = Office of Prescription Drug Product
OPQ = Office of Pharmaceutical Quality
QT-IRT = QT Interdisciplinary Review Team

1. Introduction

This summary memorandum will serve as the Cross-Discipline Team Leader (CDTL) review of this new drug application (NDA), as well as the Division's summary review for the decision on the regulatory action.

The Applicant, Cody Laboratories, Inc. (a wholly-owned subsidiary of Lannett Holdings, Inc.), submitted a new drug application (NDA) on September 21, 2017 for a 4% solution and 10% solution of cocaine hydrochloride, for topical administration, for use as an anesthetic in diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. The Applicant relied on the published literature to support certain aspects of the application, in addition to data from its own drug development program; therefore, the submission was a 505 (b)(2) submission.

The review team determined that the data provided in the application was sufficient for filing purposes to permit a substantive review. However, at the end of the review cycle, the review team recommended against approval of the application due to lack of adequate information to support approval for the following: support for the safety of several genetic toxicology studies and an adequate leachables evaluation to justify the safety of the proposed container closure system, characterization of the potential of the drug product for QT prolongation, and sources of support for the proposed language for the package insert. The Division issued a Complete Response letter on July 20, 2018.

The Applicant submitted a response to the Complete Response letter on June 21, 2019, which included purity information and certificate of analyses for the test articles evaluated in the genotoxicity evaluation, leachables data on their container closure system, the results of a thorough QT study, and a modified package insert.

2. Background

As noted in Dr. Petit-Scott's review of July 19, 2018, cocaine hydrochloride solution has been used for decades as an anesthetic and vasoconstrictive agent for surgeries involving the nasal mucosa, septum and superficial sinuses.

The regulatory history and interactions with the Applicant are well-summarized in Dr. Petit-Scott's review. These included a Pre-IND meeting in December 2009; a special protocol assessment (SPA) in December 2011; initiation of an IND in February 2013; and pre-NDA meeting in April 2017.

The clinical development program was conducted under IND 106499, and included one clinical pharmacology studies and two Phase 3 studies. These studies are summarized in the table below, reproduced from my Division Summary memo of July 20, 2018.

Study Identifier and Study Period (Start and End)	Study Design	Study Objective	Number of Subjects
Phase 1			
LNT-P6-733 09/26/2016 – 11/02/2016	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	18 male and 18 female healthy adults Average age 29.4 years 36 enrolled 31 completed
Phase 3			
COCA4vs10001 05/06/2014 – 11/26/2014	Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled	Compare efficacy to placebo and characterize risk profile following topical pledget application of investigational test products to the nasal cavity	159 enrolled 156 completed 68 males 91 females
COCA4vs10002 09/17/2015 – 07/21/2016	Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled	Compare efficacy to placebo and characterize risk profile following topical pledget application of investigational test products to the nasal cavity	646 enrolled 637 completed 253 males 39 3 females

The Complete Response letter of July 20, 2018, had the following specific wording regarding the deficiencies identified during the first review cycle:

CLINICAL

1. You have not provided adequate information to characterize the effects of your product on the QTc interval.

To resolve this deficiency:
Submit the results of a thorough QT study.

NONCLINICAL

2. You have not provided adequate leachables evaluation to justify the safety of the proposed container closure system. Specifically, your leachables evaluation did not evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies as we advised at the Pre-NDA meeting and in accordance with best practices per USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. Further, you have not provided an adequate extractables-leachables correlation to ensure that leachable compound levels can be extrapolated from data collected from simulation studies under accelerated conditions.

To resolve this deficiency:
Conduct a new leachables study under standard storage conditions that evaluates at least three batches of the to-be-marketed topical cocaine solution products for leachables and include assessments at multiple timepoints over the course of your stability studies (beginning, middle, and end of proposed shelf-life) in order to identify trends in leachable levels over time. Evaluate all container closure systems you intend to market. Clearly delineate how you leveraged the existing extraction studies to inform your leachables assessment. Submit a toxicological assessment justifying the safety of the maximum level achieved over the course of stability for any leachable that exceeds 5 mcg/day, taking

into consideration the maximum daily dose of the drug product. Submit a discussion of the extractables leachables correlation of the findings.

3. Several of your final study reports did not report the purity of the test articles.

To resolve this deficiency:
Revise the final study reports for Study 16-01138-G2, 16-01139-G2, and 16-01140- G2 to include purity information of the test articles evaluated.

REGULATORY

4. Your annotated draft labeling (b) (4) as the sources of the proposed language.

To resolve this deficiency:
Non-US labeling or non-US regulatory authority assessments may not be relied upon as these are neither FDA's findings related to a listed drug, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature. If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug you must identify the listed drugs in accordance with the Agency's regulations at 21 CFR 14.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which you intend to rely. In addition, you must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. (b) (4) submit revised labeling and identify the appropriate source(s) of information upon which you propose to rely.

As noted above, the Applicant's submission of June 21, 2019, included purity information and certificate of analyses for the test articles evaluated in the genotoxicity evaluation, leachables data on their container closure system, the results of a thorough QT study, and a modified package insert.

(b) (4)

3. Chemistry, Manufacturing, and Controls (CMC)

The review team members from the Office of Pharmaceutical Quality (OPQ) evaluated the data submitted by the Applicant to support the drug product quality. There were several information requests sent to the Applicant throughout the first review cycle, with responses that were deemed to be acceptable by the review team. The summary of quality assessments was reproduced in my summary memorandum of July 20, 2018, and I concurred with the OPQ review team's final assessment that there were no product quality issues or concerns that would have precluded approval of the NDA.

During this review cycle, the OPQ review team reviewed data submitted in support of the response to the nonclinical deficiency. As noted in Dr. Pavuluri and Dr. Pinto's review:

Review Summary for this cycle: **The quality information provided in the resubmission of NDA and subsequent responses to request for information is adequate for approval of the NDA from CMC perspective.**

In response to a Non-clinical deficiency related to extractables and leachables studies, as written in the complete response letter Dt 20-JUL-2018, at the end of 1st review cycle, applicant provided leachables test data on additional batches of the 4% presentation. No organic non-volatile, semi-volatile or volatile leachables were reported leaching from the CCS, in any of the batches tested thus far. Elemental impurities present were well below 30% of the Permitted Daily Exposure (PDE) limits. The Applicant also provided commitment for submitting additional leachables data from the new leachables study initiated on three freshly manufactured batches, estimated to be available in October / November 2019 for the mid-point and in June 2020 for the end-point, as soon as it becomes available.

Applicant also provided the final study report from a Thermal cycling study, fulfilling commitment made during previous review cycle.

List Submissions reviewed in this cycle (table):

Document(s) reviewed (GSR Seq. #)	Date Received
Resubmission following a CRL (#0025	21-JUN-2019
Response to Information Request (#0028)	21-AUG-2019
Response to Information Request (#0029)	21-AUG-2019

Highlight Key Outstanding Issues from Last Cycle: None for CMC. Non-clinical deficiency below resulted in submission of additional quality information.

Once again, I concur with the OPQ review team's final assessment that there are no product quality issues or concerns that would preclude approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The Applicant's nonclinical program consisted of one general toxicology studies, and ten genetic toxicology studies. The descriptions of these studies are summarized in the table below, reproduced from Dr. Hayes' review:

Report №	Study Title	Module/CTD Description
Study Report	**General Toxicology**	
№ 16-01711-G1	A 14-day repeat dose intranasal instillation toxicity study in Sprague-Dawley rats with a 14-day recovery period.	4.2.3.2.1
	Genetic Toxicology	
№ 11-4138-G1	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	
№ 16-01138-G3 Amended	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	

№ 16-01139-G3 Amended	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	4.2.3.3.1
№ 16-01140-G3	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	
№ 11-4138-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01138-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01139-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01140-G2	Chromosomal Aberration Assay – OECD 473	
№ 11-4138-G3	Rodent bone marrow micronucleus assay- OECD 474 cocaine.	
№ 54873.0001	Evaluation of micronuclei in B6C3F1in mice and DNA damage In Sprague Dawley rats administered ecgonine hydrochloride.	

The Applicant also submitted published literature to address all other aspects of the NDA. A summary of the nonclinical findings by the pharmacology/toxicology review team, as noted in Dr. Hayes' review, was reproduced in my summary memorandum of July 20, 2018.

The final recommendation of the pharmacology/toxicology team during the first review cycle was that the application could not be approved due to inadequate data to support the safety of the container closure system and inadequate study reports for several genetic toxicology studies (lacked purity information). The identified deficiencies were conveyed to the Applicant in the Complete Response letter, as noted above.

The team also recommended the following postmarketing requirements:

1) The standard battery of reproductive and developmental toxicology studies outlined in ICH S5(R2), including pharmacokinetic data for the following:

   a) a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

   b) an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

   c) an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

   d) a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional and behavioral assessments, and reproductive capacity of the offspring.

2) A juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing.

I concurred with the review team that the identified deficiencies precluded approval of the NDA, and that the Applicant would need to complete post-marketing requirements as noted above.

During this review cycle, the pharmacology/toxicology team reviewed new leachables data and information on the genetic toxicology studies. The following summary of the nonclinical findings are reproduced from Dr. Hayes' review:

In the NDA resubmission, the Applicant submitted new leachables data from nine different lots of Cocaine Hydrochloride topical solution (4%) (b) (4) in the proposed container closure system intended for marketing. It is noted that in the resubmission, the Applicant states they will only market (b) (4) originally proposed container closure systems, which is the (b) (4) container closure configuration and therefore new leachables data was only submitted for this container closure configuration. Three timepoints (beginning of stability, mid, and end of stability) were evaluated for the 4% Cocaine Hydrochloride topical solution. (b) (4)

As per the CMC review team the extractable/leachable data were considered acceptable for the (b) (4) container closure system. All leachables detected in the leachables assessment were lower than the 5 mcg/mL qualification threshold. Thus, there are no nonclinical safety concerns with the container closure. To address the second nonclinical deficiency, the Applicant submitted purity information and certificate of analyses for the test articles evaluated in the genotoxicity evaluation and has adequately addressed this deficiency. Taken together, the Applicant has addressed all nonclinical deficiencies. However, there are several outstanding issues with regard to the potential effects of cocaine on reproductive and developmental endpoints and its potential effects on the CNS and reproductive organs in the adolescent pediatric population and therefore postmarketing requirements will be recommended to address these outstanding issues.

I concur with the pharmacology/toxicology team that there are no pharmacology/toxicology issues that would preclude approval of this NDA.

5. Clinical Pharmacology/Biopharmaceutics

As noted in Dr. Kwatra's of June 20, 2018, the Applicant submitted data from one clinical pharmacology study and information from the published literature to support the clinical pharmacology section of the NDA. The information from the study and the published literature that was utilized to describe the general pharmacokinetic characteristics of the drug are well described in Dr. Kwatra's review first cycle review, portions of which were reproduced in my Division summary memorandum of July 20, 2018, and will not be repeated here.

As noted in those documents, the Applicant opted to conduct a subgroup analysis of patients in their Phase 3 studies. The data from the electrocardiogram monitoring was reviewed by the QT Interdisciplinary Review Team in the Division of Cardiovascular and Renal Products. Their conclusion was that the data were not adequate to satisfy the thorough QT requirements, citing the following two reasons (reproduced from Dr. Garnett's and Dr. Johannesen's review of February 21, 2018:

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 Tmax 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 waive the requirement for a positive control.

Subsequently, the only aspect of the clinical pharmacology information addressed in the original submission, and which precluded approval of the NDA during the first cycle, was the characterization of the potential of the drug product for QT prolongation.

As noted above, the Applicant submitted the results of a thorough QT study with this submission. The study is well-described in Dr. Kwatra's clinical pharmacology review and the consultation review by the Interdisciplinary Review Team for QT Studies in the Division of Cardiovascular and Renal Products. The summary in the review by the interdisciplinary team stated the following:

> Concentration-dependent QTc prolongation effect of Numbrino® (cocaine hydrochloride solution) was detected in this QT assessment. Large increases in heart rate were also detected, which confounds the estimate of the QTc interval.
>
> The effect of cocaine hydrochloride was evaluated in a randomized, cross-over, positive- and placebo-controlled thorough QT study (Study # COCA-QT-01). The highest dose evaluated was 400 mg (single-dose), which covers the maximum therapeutic dose (section 3.1). The data were analyzed using exposure-response analysis as the primary analysis, which showed that cocaine hydrochloride is associated with significant QTc prolonging effect at the maximum therapeutic dose (cocaine hydrochloride 10% solution; 400 mg single dose), see Table 1 for overall results. Because the peak concentrations of cocaine observed in the present study (mean: 285 ng/mL; range: 162-457 ng/mL) were lower compared to those observed in other study (434 ng/mL; range: 175-1273 ng/mL), the QT effects of cocaine were predicted from the exposure-response model at Cmax values obtained from Study LNT-P6-733.

Table 1: The Point Estimates and the 90% CIs – Drug Effect (FDA Analysis)

ECG parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (ms)	90% CI (ms)
QTc	Cocaine hydrochloride 4% solution* (160 mg single dose)	127.1	4.1	(2.6, 5.5)
QTc	Cocaine hydrochloride 10% solution* (400 mg single dose)	273.5	9.5	(6.4, 12.5)
QTc	Cocaine hydrochloride 4% solution (160 mg single dose)	142.7	4.7#	(3.0, 6.2)#
QTc	Cocaine hydrochloride 10% solution (400 mg single dose)	433.5	15.4#	(10.6, 20.1)#

**The liquid formulation of cocaine hydrochloride solution (4 mL) was applied to the mucous membranes of nasal cavities using pledgets (1 mL/pledget; 4 pledgets) for 20 min. #The predicted effects at similar dose level based on the Cmax from previous clinical study (Study LNT-P6-733).*

Cocaine caused large increases in heart rate (Table 2). As a result, the estimate of drug-induced QTc prolongation is confounded by the heart rate increases. The sponsor's use of an individual corrected QTc is not appropriate because the baseline data, upon which the correction is based, do not cover at least the heart rate range observed in study drug.

Table 2 The Point Estimates and the 90% CIs for HR (FDA Analysis)

ECG parameter	Treatment	Time (h)	ΔΔHR	90% CI
HR	Cocaine hydrochloride 4% solution (160 mg single dose)	0.5	11.6	(9.8, 13.5)
HR	Cocaine hydrochloride 10% solution (400 mg single dose)	0.5	20.2	(18.3, 22.0)

(b) (4)

6. Clinical Microbiology

The product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The original submission included the result of two clinical trials to support the efficacy of their product. The design, conduct, and results of the trials are well described in Dr. Petit-Scott's and Dr. Li's individual reviews from the first review cycle.

The overall assessment of the review team during the first review cycle was that the Applicant had submitted adequate data to support the efficacy of the product. Consequently, this was not identified as a deficiency in the Complete Response letter, and the Applicant did not submit any new data to support the efficacy of the product.

However, Dr. Petit-Scott recommended (b) (4)

- (b) (4)

(b) (4)

[redacted]

8. Safety

The safety database in the drug development program consisted of 347 subjects and patients exposed to 4% cocaine topical solution, and 341 subjects and patients exposed to 10% cocaine topical solution. The types of safety assessments that were included in the Phase 1 pharmacokinetic studies and the Phase 3 clinical trials are well-described in Dr. Petit-Scott's original review.

As noted in Dr. Petit-Scott's review, there were no deaths reported in the drug development program. The most commonly reported adverse events were hypertension and tachycardia, which were not unexpected.

The new safety information submitted during this cycle consisted of the safety data from the thorough QT study, the results of a FAERS search. Dr. Petit-Scott assessment of the new safety data was as follows:

- Thorough QT Study (COCA-QT-01)
  - No SAEs
  - No deaths
  - Single discontinuation due to an adverse event (elevated ALT)
  - 77 TEAEs in 22 subjects
    - 78% related to study drug
  - All mild with exception of one moderate headache
    - Subject treated with 10% cocaine
  - Drug-related TEAEs were reported in a higher proportion of subjects following administration of cocaine HCl 4% (40%) or cocaine HCl 10% (53%) compared with placebo (20%)
  - No clinically relevant changes in lab values post-treatment
  - Vital signs
    - No clinically significant changes in mean values
- FAERS search (January 1, 2018 to April 30, 2019)
  - three cases identified related to the administration of cocaine
    - one recreational use case report (fatal OD)

- two therapeutic use case reports – no dose or procedure information provided
  - atrial fibrillation
  - hypersensitivity reaction

Dr. Petit-Scott's conclusion was that there were no adverse events reported in the QT study that would impact the safety profile of the drug product.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on October 21, 2015 and it was agreed upon on October 14, 2016. (b) (4)

The proposed pediatric studies evaluating 4% cocaine HCl are as follows:

(b) (4)

As noted in Dr. Petit-Scott's original review, the Applicant planned to submit a partial waiver for the 0 to <8-year-old cohort. In the interim between the first review cycle and the current submission, the Applicant has requested a waiver for all pediatric patients under the age of 12 years. This request was presented to the Pediatric Review Committee (PeRC) on October 29, 2019. The PeRC concurred with the request, but during the meeting, PeRC members questioned the need for juvenile animal toxicology studies given that cocaine has a long history of clinical use and the single dose administration proposed.

As noted in Dr. Hayes' review, single administration of cocaine has been demonstrated to produce effects on reproductive organs. Furthermore, other literature have demonstrated that single administration of other CNS active drugs may have profound effects on brain and the current published literature suggested CNS alterations with no clear NOAEL identified. Therefore, the Division feels that the Applicant should be required to conduct the juvenile studies to characterize the potential for long-term effects of cocaine on the developing brain

during the critical periods of brain development and the potential for effects on reproductive organs during development.

11. Other Relevant Regulatory Issues

There were no relevant regulatory issues associated with this submission.

12. Labeling

Consultations were obtained from the following: the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), the Division of Pediatric and Maternal Health (DPMH), and Division of Cardiovascular and Renal Products (DCRP). Their recommendations were considered and incorporated into the label.

13. Decision/Action Risk Benefit Assessment

Regulatory Action

Approval of the 4% solution.

Risk:Benefit Assessment

(b) (4)

(b) (4)

(b) (4)

[redacted]

[redacted]

Post-Marketing Requirements

I concur with the pharmacology/toxicology recommendation that the Applicant should be required to conduct the following studies:

1) The standard battery of reproductive and developmental toxicology studies outlined in ICH S5(R2), including pharmacokinetic data for the following:

   a) a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

   b) an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

   c) an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

   d) a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional and behavioral assessments, and reproductive capacity of the offspring.

2) A juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing.

3) A multicenter trial to evaluate the pharmacokinetic and safety profiles of a single topical administration of NUMBRINO for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in pediatric subjects 12 years of age to less than 17 years of age.

Post-marketing Risk Management Activities

None.

Other Post-marketing Study Commitments

None.

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/

RIGOBERTO A ROCA
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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	July 20, 2018
From	Rigoberto Roca, MD
Subject	Deputy Division Director Summary Review
NDA No.	209575
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Date of Submission	September 21, 2017
PDUFA Goal Date	July 20, 2018
Proprietary Name / Established (USAN) Name	Numbrino / Cocaine Hydrochloride
Dosage Forms / Strength	Topical Solution, 4% and 10%
Proposed Indications	Induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults
Action	Complete Response

Material Reviewed/Consulted: OND Action Package, including	
Clinical Review	Renee Petit-Scott, MD
Pharmacology Toxicology Review	BeLinda A. Hayes, PhD; Newton Woo, PhD; Dan Mellon, PhD
Clinical Pharmacology Review	Deep Kwatra, PhD; Yun Xu, PhD
Biostatistics	Feng Li, PhD; David Petullo, MS
OPQ	Sam Bain, PhD, Venkat Pavuluri, PhD; Tarun Mehta, PhD; Renee Marcsisin, PhD; Frank Wackes, PhD; Steven Kinsley, PhD; Ciby Abraham, PhD; Caryn McNAb, PhD
Project Management Staff	Shelly Kapoor, PharmD; Parinda Jani
DPMH	Jane Liedtka,, MD; Miriam Dinatale, DO; Lynne P. Yao, MD
OPDP	Koung Lee, RPh, MSHS; Sam Skariah, PharmD
DMEPA	James Schlick, MBA, RPh; Otto Townsend, PharmD
DCRP QT-IRT	Christine Garnett, PharmD
GCPAB/DCCE/OSI	Damon Green, MD, MS; Phillip Kronstein, MD; Kassa Ayalew, MD
CSS	Dominic Chiapperino, PhD; Silvia Calderon, PhD; Katherine Bonson, PhD

CSS = Controlled Substance Staff
DCCE = Division of Clinical Compliance Evaluation
DCRP = Division of Cardiovascular and Renal Products
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
GCPAB = Good Clinical Practice Assessment Branch
OND = Office of New Drugs
OPDP = Office of Prescription Drug Product
OPQ = Office of Pharmaceutical Quality
QT-IRT = QT Interdisciplinary Review Team
OSI = Office of Scientific Investigations

1. Introduction

This summary memorandum will serve as the Cross-Discipline Team Leader (CDTL) review of this new drug application (NDA), as well as the Division's summary review for the decision on the regulatory action.

The Applicant, Cody Laboratories, Inc. (a wholly-owned subsidiary of Lannett Holdings, Inc.), has submitted a new drug application (NDA) for a 4% solution and 10% solution of cocaine hydrochloride, for topical administration, for use as an anesthetic in diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. The Applicant is relying on the published literature to support certain aspects of the application, in addition to data from its own drug development program; therefore, this submission is a 505 (b)(2) submission.

This memo will also capture the final outcome of any items that were still under discussion at the time that Dr. Petit-Scott's review was finalized.

2. Background

As noted in Dr. Petit-Scott's review, cocaine hydrochloride solution has been used for decades as an anesthetic and vasoconstrictive agent for surgeries involving the nasal mucosa, septum and superficial sinuses.

The regulatory history and interactions with the Applicant are well-summarized in Dr. Petit-Scott's review. These included a Pre-IND meeting in December 2009; a special protocol assessment (SPA) in December 2011; initiation of an IND in February 2013; and pre-NDA meeting in April 2017.

The clinical development program was conducted under IND 106499, and included one clinical pharmacology studies and two Phase 3 studies. These studies are summarized in the table below.

Study Identifier and Study Period (Start and End)	Study Design	Study Objective	Number of Subjects
		Phase 1	
LNT-P6-733 09/26/2016 – 11/02/2016	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	18 male and 18 female healthy adults Average age 29.4 years 36 enrolled 31 completed
		Phase 3	
COCA4vs10001 05/06/2014 – 11/26/2014	Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled	Compare efficacy to placebo and characterize risk profile following topical pledget application of investigational test products to the nasal cavity	159 enrolled 156 completed 68 males 91 females
COCA4vs10002	Phase 3, Multi-Center, Randomized, Double-	Compare efficacy to placebo and characterize risk profile following	646 enrolled 637 completed

Study Identifier and Study Period (Start and End)	Study Design	Study Objective	Number of Subjects
09/17/2015 – 07/21/2016	blind, Placebo-controlled	topical pledget application of investigational test products to the nasal cavity	253 males 39 3 females

3. Chemistry, Manufacturing, and Controls (CMC)

The review team members from the Office of Pharmaceutical Quality (OPQ) evaluated the data submitted by the Applicant to support the drug product quality. There were several information requests sent to the Applicant throughout the review cycle, with responses that were deemed to be acceptable by the review team. The summary of quality assessments stated the following in the product overview (reproduced from the OPQ review):

> The applicant provided a letter of authorization to access DMF# 029120 Cocaine HCl by Cody laboratories, Inc. The DMF was reviewed by Dr. Sukhamaya Bain and found adequate for this submission on 6/13/2018. Cocaine HCl is a white crystal or powder that readily dissolves in water (1 gram in 0.4 mL). The melting point is approximately 195°C. The drug substance is stored at room temperature in (b) (4). The retest period is (b) (4) months.
>
> Cocaine HCl Topical Solution 40 mg/ml and (b) (4) are clear blue-green solutions, (b) (4) 4% (40 mg/mL) in 4 mL single-use (b) (4) vials (b) (4) (b) (4) container closure configurations are shown below.

Start of Applicant Material.

Packaging Configuration 1	
Bottle Size & Description:	(b) (4) (USP Type III) bottle
Bottle Code No.:	(b) (4)
Cap Size & Description:	(b) (4) cap, (b) (4)
Cap Code No.:	(b) (4)
Product Strength / Fill Size	4% - 4 mL and 10 mL; (b) (4)
(b) (4)	

Bottle Code No.:	(b) (4)
Cap Size & Description:	(b) (4)
Cap Code No.:	(b) (4)
Product Strength / Fill Size	4% - 4 mL and 10 mL; (b) (4)

End of Applicant Material.

The applicant performed limited extractables/leachables on the three different container closure systems. Additional information will be needed on the extractables/leachables study. See the Pharmacology/Toxicology review for additional details.

The proposed expiration dates are acceptable for each of the respective dosage strength and presentations as described below, when the drug product is stored at controlled room temperature (20 -25°C as per USP) in their proposed container closure system (b) (4). 14 month expiry for Cocaine Hydrochloride Topical Solution, 4% (b) (4)

The review team's final recommendation was for approval of the NDA. I concur with the review team that there are no product quality issues or concerns that would preclude approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The Applicant's nonclinical program consisted of one general toxicology studies, and ten genetic toxicology studies. The descriptions of these studies are summarized in the table below, reproduced from Dr. Hayes' review:

Report №	Study Title	Module/CTD Description
Study Report	**General Toxicology**	
№ 16-01711-G1	A 14-day repeat dose intranasal instillation toxicity study in Sprague-Dawley rats with a 14-day recovery period.	4.2.3.2.1
	Genetic Toxicology	
№ 11-4138-G1	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	4.2.3.3.1
№ 16-01138-G3 Amended	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	
№ 16-01139-G3 Amended	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	
№ 16-01140-G3	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (OECD 471)	
№ 11-4138-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01138-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01139-G2	Chromosomal Aberration Assay – OECD 473	
№ 16-01140-G2	Chromosomal Aberration Assay – OECD 473	
№ 11-4138-G3	Rodent bone marrow micronucleus assay- OECD 474 cocaine.	
№ 54873.0001	Evaluation of micronuclei in B6C3F1in mice and DNA damage In Sprague Dawley rats administered ecgonine hydrochloride.	

The Applicant also submitted published literature to address all other aspects of the NDA. A summary of the nonclinical findings by the pharmacology/toxicology review team, as noted in Dr. Hayes' review, is reproduced below:

Given the long clinical history of use of cocaine hydrochloride via the intranasal route of administration, the Agency agreed that nonclinical general or reproductive and developmental toxicology studies with cocaine would not be required to support filing the NDA. However, the Applicant was required to submit a detailed literature review to address all requirements for the NDA and submit a comprehensive evaluation of the genotoxic potential of cocaine. The adequacy of the literature to address the standard requirements could only be determined upon review of the literature submitted and the adequacy of the scientific bridge to the referenced studies.

The proposed drug substance and drug product specifications are acceptable. The Applicant provided adequate qualification data for the systemic toxicity and local safety of the drug product formulation and any specifications that exceeded the ICH Q3A/B qualification thresholds. In addition, the Applicant submitted genetic toxicology assays to qualify several impurities/degradants, including (b) (4) Therefore, these impurities have been adequately qualified for safety at the proposed specifications.

The Applicant provided extractable and leachable studies to characterize and justify the safety of potential leachables arising from the container closure systems to be employed in the proposed drug products. However, the leachable studies were deficient because they were not performed using at least three batches of the drug product with testing at multiple timepoints over the course of stability studies. The Applicant should be required to submit adequate leachable data over the course of stability to support the safety of the container closure systems.

A standard battery of genotoxicity assays, including the Ames, in vitro chromosome aberration, in vivo bone marrow micronucleus assays were submitted to characterize the genotoxic potential of cocaine. Cocaine tested negative in these studies.

The Applicant submitted a literature search to address the reproductive and developmental toxicity study requirements for cocaine. The literature search was limited and included references to numerous abstracts, which were not reviewed because these data may be preliminary, not reproducible, not peer reviewed, and lack adequate detail to permit substantive review. Based on a preliminary search of the literature, the submitted published studies identified by the Applicant are not complete given the vast literature on cocaine. However, the studies could be used to inform labeling until definitive studies with pharmacokinetic data are completed.

As true for all acute use drug product, the interpretation of reproductive and developmental studies is challenging. To adequately characterize the effect of a drug on rapidly developing systems, dosing must be done over critical periods of development. This requires more prolonged exposure in order to minimize the use of animals and characterize risk. Although some of the adverse effects reported in such studies may not occur with single doses, we cannot dismiss the risks reported given that adverse findings have been reported after a single dose and have to assume they could have been the result of exposures during critical periods unless definitively demonstrated otherwise.

Adequate data appear to exist in the published literature to address male fertility consistent with the endpoints outlined in ICH S5A including fertility, sperm motility and morphology, male reproductive tissue histopathology, and sexual behavior. Although many of the published studies do not clearly define a NOAEL, at least one study suggests that doses of up to 3.9 times the human referenced dose of 37.5 mg via the use

of the 4% product are not likely to result in adverse effects on adult male fertility. Younger males appear to be more susceptible to adverse testicular effects and higher doses can clearly result in adverse histopathology finding in the rat testes.

Adequate published studies to fully characterize the impact of cocaine on female fertility and early embryonic development were not identified by the Applicant. The published studies do suggest that cocaine can alter female reproductive hormones and cyclicity suggesting a potential impact on female fertility and early embryonic effects. These findings should be included in labeling. A definitive study should be completed.

The Applicant submitted many published studies that dosed pregnant animals during organogenesis which contain some of the standard embryofetal development (EFD) study endpoints outlined in ICH S5. Many of these identify clear adverse effects at relatively high doses and via routes that are likely to result in higher C_{max} values than the proposed drug product but fail to define a no adverse effect level (NOAEL). The Applicant maintains that "cocaine is a human and animal teratogen" and proposes to include labeling to that effect. These adverse effects should be included in labeling should the product be approved; however, dedicated embryo-fetal studies in the rat and rabbit are recommended as post-marketing requirements not only to provide valid GLP studies but also to obtain adequate toxicokinetic data to provide a comparison to the human exposures via this route of administration and further inform labeling.

Similar to EFD studies, the published literature submitted also contain some endpoints similar to modern pre- and postnatal development studies (PPD) described by ICH S5. These studies suggest the potential for adverse effects, particularly on the central nervous system and testes in the offspring of pups born to pregnant mothers treated with cocaine. None of the studies dosed the pregnant animals during gestation and through weaning as per standard protocols. Nonetheless, offspring birth weights and brain weights are reduced at higher doses of cocaine. Offspring survival is also impacted in some studies. Limited postnatal functional studies were submitted; however, the data does suggest the potential for adverse effects on the CNS. The significance of the findings are not clear given the lack of adequate PK data to compare to the human exposures via this drug product. A definitive GLP study with PK data is recommended to be completed as a PMR to fully characterize the effects of cocaine on PPD, including defining a NOAEL, to fully inform labeling and risk.

The Applicant submitted inadequate data to characterize the effects of cocaine on juvenile animals. Although their submitted references cited do suggest that cocaine can have an impact on the developing brain, many of the cited documents were primarily abstracts and are not considered adequate for the reasons cited above. Preliminary searches and review of selected publications by the review team noted that there are a considerable number of publications that address the developmental effects of cocaine that were not submitted or reviewed by the Applicant. For example, a PubMed search for "cocaine and 'brain development' and animal" alone conducted on June 12, 2018 resulted in 70 publications retrieved. Nonetheless, as most of these studies will not be via the intranasal route and will not likely identify a NOAEL or include all appropriate endpoints, they are not likely to be adequate to justify the safety of the product. An appropriate juvenile animal study would include a comprehensive evaluation that includes histopathology plus functional behavioral assessments to support pediatric studies is recommended. As agreed in the pediatric study plan (PSP) dedicated juvenile animal studies will be completed. The studies should be designed to test the effects of cocaine on brain development and should be completed prior to clinical studies in pediatric patients. Therefore, dedicated juvenile animal studies are recommended to be completed as post-marketing requirements should the product be approved. The design of the study will be dictated by the age range this product is believed to be useful for. PeRC concluded that the pediatric development plan should address safety in children

aged 8 to >17 and were willing to consider a waiver for studies under the age of 8 if adequately justified by the Applicant.

The final recommendation of the pharmacology/toxicology team was that the application not be approved due to inadequate data to support the safety of the container closure system and inadequate study reports for several genetic toxicology studies (lacked purity information). They recommended that the following deficiencies be conveyed to the Applicant:

1. You have not provided adequate leachables evaluation to justify the safety of the proposed container closure system. Specifically, your leachables evaluation did not evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies as we advised at the Pre-NDA meeting and in accordance with best practices per USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. Further, you have not provided an adequate extractables-leachables correlation to ensure that leachable compound levels can be extrapolated from data collected from simulation studies under accelerated conditions.

To resolve this deficiency:

Conduct a new leachables study under standard storage conditions that evaluates at least three batches of the to-be-marketed topical cocaine solution products for leachables and include assessments at multiple timepoints over the course of your stability studies (beginning, middle, and end of proposed shelf-life) in order to identify trends in leachable levels over time. Evaluate all container closure systems you intend to market. Clearly delineate how you leveraged the existing extraction studies to inform your leachables assessment. Submit a toxicological assessment justifying the safety of the maximum level achieved over the course of stability for any leachable that exceeds 5 mcg/day, taking into consideration the maximum daily dose of the drug product. Submit a discussion of the extractables leachables correlation of the findings.

2. Several of your final study reports did not report the purity of the test articles.

To resolve this deficiency:

Revise the final study reports for Study 16-01138-G2, 16-01139-G2, and 16-01140-G2 to include purity information of the test articles evaluated.

The team also recommended the following postmarketing requirements:

1) The standard battery of reproductive and developmental toxicology studies outlined in ICH S5(R2), including pharmacokinetic data for the following:

   a) a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

   b) an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

   c) an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

d) a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional and behavioral assessments, and reproductive capacity of the offspring.

2) A juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing.

I concur with the review team that the identified deficiencies preclude approval of the NDA, and that the Applicant would need to complete post-marketing requirements as noted above.

5. Clinical Pharmacology/Biopharmaceutics

As noted in Dr. Kwatra's review, the Applicant submitted data from one clinical pharmacology study and information from the published literature to support the clinical pharmacology section of the NDA. The study is described below (reproduced from Dr. Kwatra's review):

Phase 1 Study LNT-P6-733:

- Phase 1, single dose crossover bioavailability study of Cocaine HCL 4% and 10% solutions following topical application in the nasal cavity in healthy male and female volunteers.

Based on the information from the study and the published literature, the review team described the general pharmacokinetic characteristics of the drug as follows (reproduced from Dr. Kwatra's review):

Absorption: Study LNT-P6-733

One PK study was performed which sought to demonstrate the minimal amount of cocaine absorbed when Cocaine HCl Topical Solution, 4% and 10%, was applied by pledget administration in adults. The maximum doses that could be applied to the nasal mucosa were administered, i.e., a 160-mg dose from the Cocaine HCl Topical Solution, 4% and a 400-mg dose from the Cocaine HCl Topical Solution, 10%. Tabular summaries of the mean plasma absorption (%) and PK parameters (AUC0-∞, Cmax, Tmax, and Thalf) for cocaine are provided in Table 1.

Table 1: Percentage absorption and other PK characteristics of a single intranasal dose of topical cocaine (4% & 10%)

Study/ Protocol # (Canada)	Product ID / Lot # / Dose / Pledgets*	# Subjects Entered/ Completed (M/F)	Treatment Dose, Form, Route	Mean Parameters (SD)				
				%F[a]	$AUC_{0-\infty}$ (ng·h/mL)[b]	C_{max} (ng/mL)[b]	T_{max} (h)[c]	T_{half} (h)[d]
LNT-P6-733	**Cocaine HCl Topical Solution, 4%** (2016139654) **160 mg** (Test-1)	36/31 (18M/18F)	160 mg per 4 mL Intranasal	23.44 (8.88)	286.68 (45.6)	142.68 (44.9)	0.50 (0.17-1.00)	1.54 (13.5)
	Cocaine HCl Topical Solution, 10% (2016119525) **400 mg** (Test-2)		400 mg per 4 mL Intranasal	33.34 (10.71)	960.09 (43.1)	433.53 (49.3)	0.50 (0.33-1.00)	2.01 (36.8)

*By intranasal application, Pledget Brand: (b) (4), Size: 0.5" x 3''. The study treatments (160 mg cocaine HCl, 400 mg cocaine HCl, and placebo) were administered topically, in the nasal cavity as follows: For each administration, four pledgets were treated with 4 mL of the assigned solution (160 mg cocaine HCl, 400 mg cocaine HCl, or placebo). The 4-mL treatment of Cocaine HCl Topical Solution, 4% corresponded to a 160-mg dose of cocaine HCl. The 4-mL treatment of the Cocaine HCl Topical Solution, 10% corresponded to a 400-mg dose of cocaine HCl. Two pledgets were placed into each nostril (one pledget on the inner left side and one pledget on the inner right side of each nostril). The pledgets were retained in the nasal cavity for 20 minutes prior to being removed. Subjects remained seated for at least 1 hour following placement of the pledgets into the nasal cavity.

[a] %F= % of cocaine absorbed
[b] C.V. (%) [c] Median (range)
[d] T_{half}= $t_{1/2}$

A mean of 23.44% of the total administered cocaine HCl dose was absorbed for the 160 mg Test-1 dose (4% cocaine solution) (n=34) and a mean of 33.34 % of the total administered cocaine HCl dose was absorbed for the 400 mg Test-2 dose (10% cocaine solution) (n=32). For understanding the limited amount of systemic absorption of cocaine, the rate and extent of exposure of cocaine during the pledget insertion and immediately after removal is shown in Figure 1.
The time point at which the maximum cocaine plasma concentrations (Tmax) were observed occurred within 10 minutes after the removal of the pledgets from the nasal cavity for both the Cocaine HCl Topical Solutions, 4% and 10%. The maximum cocaine plasma concentration (Cmax) observed after the 160 mg dose of Cocaine HCl Topical Solution, 4% was 142.7 ng/mL and 433.5 ng/mL after the 400 mg dose of Cocaine HCl Topical Solution, 10%; a 3.0 fold value greater than that observed after the 160 mg dose of cocaine HCl, which is approximately equivalent to the ratio of the doses administered (2.5 fold).

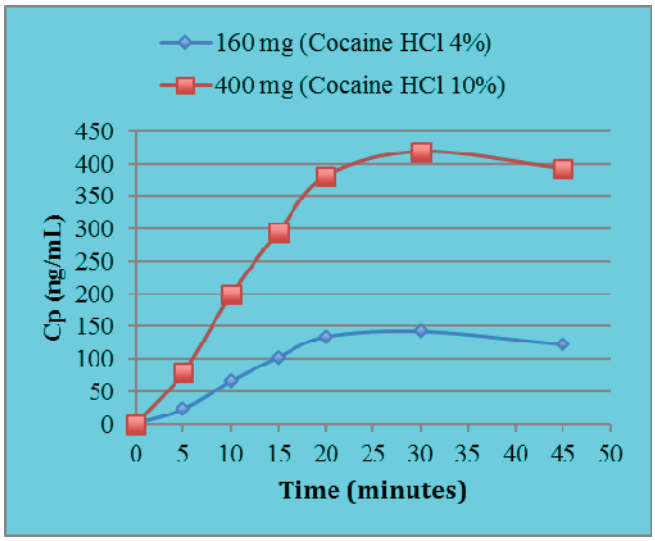

Figure 1: Systemic Plasma Cocaine Concentrations (Time 0 to 45 Minutes) After Cocaine HCl Topical Solution, 4% & 10%, Applied to the Nasal Mucosa by Pledgets (For 20 minutes)

Cocaine HCl Topical Solution, 4% and 10%, demonstrate PK characteristics consistent with a slow and constant delivery of drug product over the retention time of the pledget delivery system for both concentrations, peaking 10 minutes after pledget removal, with a subsequent rapid elimination (mean half-life, 1.5-2.0 h). It is expected that if the nasal procedure commences immediately after pledget removal, adequate therapeutic drug concentrations will be maintained for the duration of the nasal procedures (at least 20-30 minutes). The mean plasma concentration-time profiles are displayed by treatment in (Figure 2). A summary

of the statistical analysis of Cmax and AUC for cocaine by treatment is given in Table 4.

Figure 2: Plasma Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl 4%, Test-1; 400 mg Cocaine HCl 10%, Test-2)

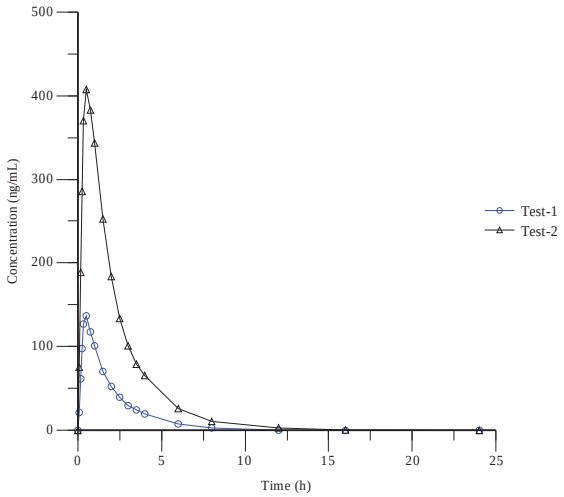

Table 2: Summary of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl 4%, and 400 mg Cocaine HCl 10%)

Parameter (Units)	Cocaine HCl (Test-1) 160 mg (n=33)		Cocaine HCl (Test-2) 400 mg (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: CSR Study LNT-P6-733,

Absorption: Literature Summary
Cocaine is absorbed by all routes of administration (oral, nasal, or local application). The amount of cocaine absorbed depends on the route of administration. Two major factors which influence the rate of absorption from any site of administration are the rate of blood flow to that site and the surface area over which absorption may occur.
Topical intranasal cocaine HCl (1.5 mg/kg) is rapidly absorbed, with peak plasma concentrations (120-474 ng/mL) occurring within 30-60 minutes [1]. The bioavailability of topical intranasal cocaine HCl, measured by the area under the plasma concentration-time curve, is estimated to be four to six times less than reported for an equivalent intravenous dose (0.19-2.0 mg/kg) [2]. Five clinical studies evaluating the absorption of intranasal cocaine, using non-pledget methods of administration (1976-1988), are presented in a review article [1]. Absorption following nasal dosing was faster than following oral dosing [3]. Peak absorption occurred at 30 minutes in one study [4] and between 15 to 60 minutes or 60 to 120 minutes in other studies [5, 6]. Exposure increased linearly with increasing intranasal dose [2, 7] and time of peak concentration lengthened with increasing intranasal dose [2]. Concentrations decreased gradually following Cmax [6], with cocaine persisting in the plasma for 4 to 6 hours and detectable on the nasal mucosa for 3 hours

Cocaine Absorption through pledgets in Literature: Cocaine HCl administration using pledgets decreases absorption of cocaine compared with its direct application to the nasal mucosa [8]. Approximately one third of the dose of cocaine HCl is absorbed systemically after its application to the nasal mucosa using pledgets at concentrations of 4% (160 mg dose/4 mL) retained for 10 or 20 minutes, and 10% (400 mg dose/4 mL) retained for 20 minutes, prior to standard procedures related to rhinologic surgery [7].
Specifically, at surgery for a septoplasty or septorhinoplasty, with patients (N=12) under general anesthesia, nostrils were packed with 6 standard surgical 3.5-inch pledgets, 1 each along the roof, middle turbinate, and floor of the nose (3/nostril). Group I subjects received pledgets soaked with 4 mL of 4% cocaine HCl solution (160 mg) retained for 10 minutes. Group II subjects received pledgets soaked with 4 mL of 4% cocaine HCl solution (160 mg) retained for 20 minutes, and Group III subjects received pledgets soaked with 4 mL of 10% cocaine HCl solution (400 mg) retained for 20 minutes.
Mean systemic absorption rates were 33% in Group I, 32% in Group II, and 38% in Group III (range, 28% to 42%) with a 35% mean for all groups combined. Combining the data among all groups reveals that 17% of cocaine applied to the nasal mucosa was absorbed within 5 minutes, 25% was absorbed within 10 minutes, and 32% was absorbed within 15 minutes.
With one exception, serum cocaine concentrations were linearly related to cocaine dose by using linear regression analysis and the coefficient of variability (r2=0.79). Serum cocaine concentration (y-axis) in milligrams per liter, correlated with cocaine dose (x-axis) in milligrams per kilogram through the equation Y = 0.11X - 0.055. The range of cocaine serum concentrations in Group I, II and III, were 70-220 ng/mL (excluding subject 4), 100-180 ng/L and 520-720 ng/L, respectively.

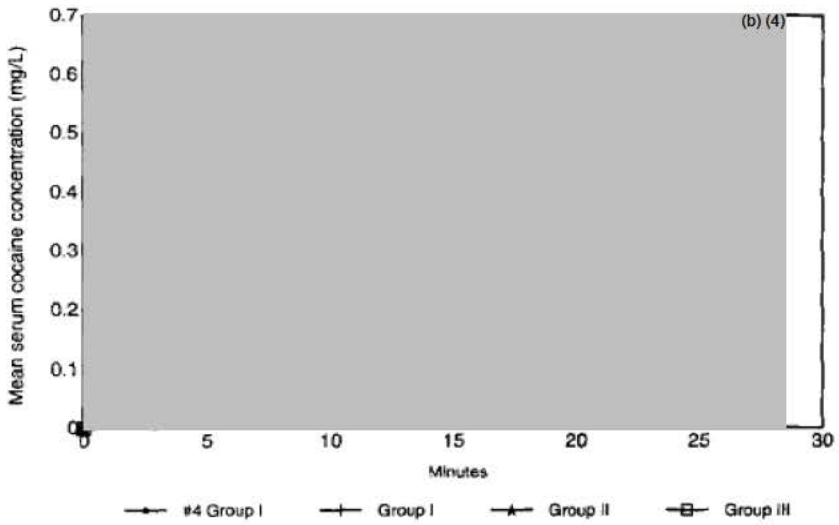

Fig. 1. Graphic comparison of mean serum cocaine concentration (milligrams per kilogram) in Groups I, II, III, and patient 4. Group I measured at 5, 10, 15, and 20 min after application of cocaine pledget.

Figure 3: Mean Serum Cocaine Concentrations After Pledget Application of Cocaine HCl 4% and Cocaine HCl 10%. Source: Liao, 1999

The relationship between the time of pledget mucosal contact and systemic cocaine absorption was investigated in 12 adult patients undergoing nasal surgery (septoplasty, endoscopic sinus surgery, or maxillectomies) [9]. Subjects underwent general anesthesia; a few required a local anesthesia and intravenous sedation alternative. At surgery, both nostrils were packed with two standard 0.5 by 3-inch pledgets soaked with 4 mL of 4% cocaine HCl solution (160 mg). Two pledgets were placed in each nostril and the variable time of mucosal contact recorded (range 10 to 30 minutes; median 15 minutes, and mean 17.2 minutes). Once removed from the nose, all 4 pledgets were stored frozen. Blood was drawn for cocaine analysis 45 minutes after placement of the pledgets, processed, and stored frozen. Pledgets were processed and analyzed for cocaine by GC, while serum cocaine concentrations were determined by radioimmunoassay. Total exposure was approximately 35% of the dose administered (applied to the nasal mucosa) with a maximum observed cocaine plasma concentration achieved within 10 minutes of removal of the pledgets from the nasal cavity.

Comparative analysis of literature with the result of the studies conducted by the sponsor suggests that the exposure values achieved are very similar. In literature, it has been reported that following topical intranasal administration of cocaine using cotton pledgets, approximately 64-65% of the applied cocaine dose was recovered from the pledgets after removal, suggesting that approximately 35-36% of the dose was available for systemic absorption [7, 9]. Absorption following intranasal administration was rapid with cocaine detected in plasma as early as 5 minutes following the start of administration [7] In surgical patients that received 160 mg of a 4% cocaine solution by application of soaked cotton pledgets to the nasal mucosa [7], mean plasma cocaine concentrations at 20 minutes after the start of administration of 4% cocaine (166 ng/mL) were only slightly higher than those in healthy subjects that received cocaine under a similar dosing paradigm in the sponsors study (142.68 ng/mL).

Distribution:
No studies of the distribution, metabolism, and excretion of cocaine following topical intranasal administration of cocaine were identified in the literature. However, the distribution,

metabolism, and elimination of cocaine have been examined in several published clinical studies with different routes of cocaine administration, including IV, insufflation, and smoked.

After intake, cocaine was widely distributed throughout body tissues and crosses the blood brain barrier. Volume of distribution ranged between 1.5 and 2 L/kg [10-14], which exceeds total body water volume (approximately 0.6 L/kg) [15] Cocaine accumulated in the heart, kidneys, adrenals, and liver, with the rate of uptake and clearance varying among organs [16]. Cocaine and its metabolites are excreted in breast milk [17, 18]; they cross the placenta by simple diffusion, and accumulate in the fetus after repeated use [19].

The free fraction of cocaine averaged 0.083 (91.7% bound) in serum at 25 ng/mL [20] Concentration dependence in binding was observed, with free fraction remaining reasonably stable up to 100 ng/mL (free fraction of 0.084 [20] and 0.16 [21]) and increasing at higher concentrations. Increases in free fraction were most pronounced at concentrations above 5 μg/mL [20].

Metabolism:
Cocaine is primarily eliminated by hydrolysis to benzoylecgonine (BE) and ecgonine methyl ester (EME), its two major (inactive) metabolites, with subsequent renal elimination [1, 2, 13, 22-26]. Carboxylesterases are located in the endoplasmic reticulum and catalyze the hydrolysis of lipophilic esters (cocaine) to their more water-soluble alcohol and acyl substituents. hCE1 and hCE2 are low affinity, high capacity enzymes able to hydrolyze a wide variety of structurally dissimilar esters. There is evidence for the involvement of carboxylesterases in the metabolism of endogenous substrates such as lipids and steroids, but their primary function is to protect the body from foreign substances encountered through the diet and other routes [26]. Metabolism of cocaine to its two major and minor metabolites is shown in Figure 3 [25]. BE is one of the major metabolites in plasma after all routes of administration. BE is formed from spontaneous chemical hydrolytic conversion and hepatic carboxylesterase-1 (hCE-1) [26]. Specifically, hCE-1 demethylates 40-45% of cocaine to BE [23]. BE is further oxidized to minor metabolites m- and p-hydroxylbenzoylecgonine (mOHBE and pOHBE) [25]. An additional metabolite, cocaethylene (also known as ethylcocaine), was identified when cocaine and ethanol were co-incubated in a crude human liver homogenate [27]. Cocaethylene appears to be formed from BE by carboxylesterase via transesterification [28]. Cocaethylene was identified in the plasma, urine, and body tissue of people who used cocaine and ethanol simultaneously [29].

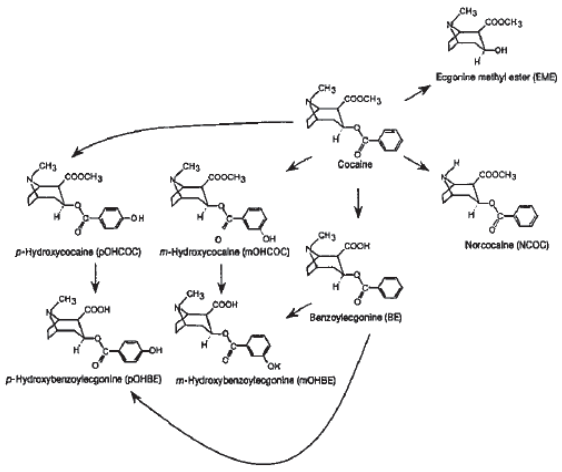

Figure 4: Systemic Metabolic Pathways of Cocaine. Source: Kolbrich, 2006

Enzymatic hydrolysis of cocaine by butyrylcholinesterase (hBChE) in plasma (and other tissues), and by hepatic esterases (carboxylesterase-2 (hCE-2) [25], forms the other major, but pharmacologically inactive metabolite, EME. Serum hBChE hydrolyzes 40-45% of cocaine

into ecgonine methyl ester and benzoic acid [23]. EME is present in plasma concentrations considerably lower than those of BE [25].

Ecgonine (E), another inactive metabolite, is produced by hepatic esterase hydrolysis with subsequent renal elimination [1]. Plasma concentrations of E are less than 5% of those observed with cocaine [1].

Hepatic P450 CYP3A4 N-demethylates approximately 5-10% of cocaine, a minor pathway, to norcocaine (NCOC), an active metabolite [23, 25, 30, 31]. NCOC may be metabolized to N-hydroxynorcocaine, norcocaine nitroxide, and finally, to the hepatotoxic norcocaine nitrosonium ion (in certain animal species) [1].

A second minor pathway of cocaine metabolism is the hydroxylation of cocaine to p- and m-hydroxycocaine (pOHCOC and mOHCOC) [23, 25]. Cocaine and its metabolite plasma concentrations were evaluated (N=18, healthy subjects) after receiving low (75 mg/70 kg) and high (150 mg/70 kg) subcutaneous cocaine hydrochloride doses [23, 25]. Plasma specimens were collected prior to and up to 48 h after dosing and analyzed by gas chromatography-mass spectrometry (2.5 ng/mL limit of quantification). Cocaine was detected within 5 min, with mean ± SE peak concentrations of 300.4 ± 24.6 ng/mL (low) and 639.1 ± 56.8 ng/mL (high) 30-40 min after dosing. BE and EME generally were first detected in plasma 5-15 min post-dose. Two to four hours after dosing, BE and EME reached mean maximum concentrations of 321.3 ± 18.4 (low) and 614.7 ± 46.0 ng/mL (high) and 47.4 ± 3.0 (low) and 124.4 ± 18.2 ng/mL (high), respectively. Times of last detection were BE > EME > cocaine. Minor metabolites were detected much less frequently for up to 32 h, with peak concentrations 18 ng/mL for all analytes except pOHBE (up to 57.7 ng/mL). Peak plasma concentrations, time to achieve peak levels and the area under the concentration curve for cocaine and its major metabolites is presented in Table 2.7.2.1.2-2.

Table 3: Cocaine, Benzoylecgonine, and Ecgonine Methyl Ester Pharmacokinetic Parameters. Source: Kolbrich, 2006

	Cocaine				Benzoylecgonine				Ecgonine Methyl Ester			
	N*	75 mg/70 kg	N	150 mg/70 kg	N	75 mg/70 kg	N	150 mg/70 kg	N	75 mg/70 kg	N	150 mg/70 kg

Excretion:
Cocaine is rapidly excreted from the body in humans, with, half-life values reported in the literature in the range of 1 hour [1, 10, 14]. Systemic clearance of cocaine after IV administration in humans has been reported to be approximately 2 L/min [1](29 mL/min/kg, assuming a 70 kg body weight) [10, 12, 14], which exceeds estimated human plasma flow in the liver (approximately 12 mL/min/kg) and kidney (approximately 10 mL/min/kg), as well as glomerular filtration rate (GFR; 1.8 mL/min/kg) [15]. This suggests that significant routes of cocaine elimination are extrahepatic and extrarenal, which is consistent with the role of plasma esterases and non-enzymatic ester hydrolysis in cocaine elimination.
Urinary excretion was the principal route of elimination. BE and EME accounted for 80% to 90% of the urinary metabolites and had a $t_{½}$ of 3 to 6 h and 3 to 4 h, respectively, based on urinary excretion rates [11, 22, 32]. Cocaine's metabolites can be detected in the urine for 14-60 hours after cocaine administration[1]. Only a small percentage of cocaine was excreted as unchanged drug (1% to 9%) [12, 33] and norcocaine (2% to 6%) [13]. The elimination half-life

for cocaine and its metabolites was generally longer when cocaine was administered following insufflation compared to the smoked and IV routes. Cocaine CLr has been reported to be 31 mL/min (approximately 0.47 mL/min/kg based on mean body weight of 67 kg), or approximately 1.4% of total CL [10]. This is similar to the mean CLr observed after administration of topical cocaine solution (47 mL/min or 0.66 mL/min/kg). These low CLr values are consistent with the minimal recovery of unchanged cocaine in urine.

Dose-proportionality of Topical cocaine:
The mean peak cocaine concentration in plasma was approximately (b) times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about (b) (4) times greater for the higher strength. Cocaine $t_{1/2}$ values were similar after the two treatments. These data suggest that the increase in cocaine exposure was approximately dose proportional from 160 mg to 400 mg. Literature also stats that peak plasma concentrations are proportional to the dose administered[2]. Overall, the plasma PK estimates for cocaine and its metabolites (Cmax and AUC) were proportional to dose. In general, these results are consistent with those from the medical literature.

Intrinsic factors

The Applicant did not conduct any studies to determine whether intrinsic factors, e.g., gender, age, body weight, or degree of organ dysfunction, had any effect on the pharmacokinetics of the product. Literature searches were conducted, which identified the following information, as summarized in Dr. Kwatra's review:

Gender
Plasma cocaine concentrations are not expected to be affected by gender. Although, population PK analyses have not been conducted to support the lack of gender effect on the pharmacokinetics of cocaine, the Phase III trials did not indicate a significant difference existed between the genders.

No significant human gender difference exists in the PK profile for cocaine when misused or abused (i.e., non-anesthetic use), as summarized in a systematic review by various routes of administration (intranasal, intravenous, or smoked) for cocaine [34]. Graziani's systematic review was conducted (Medline searched, 1990 to 2014) to discover articles related to gender differences in alcohol, cocaine and cocaethylene pharmacokinetics and pharmacodynamics. No significant gender differences were found in the pharmacokinetics of cocaine (taken alone) in cocaine-dependent or cocaine-using subjects in 7 studies, ages 20-45 years of age; administered as 0.06 to 2 mg/kg single-intranasal doses (2 studies); 0.2-0.4 mg/kg single-intravenous doses (1 study); and as 0.4 mg/kg, 6 x 50 mg, and 6 x 6 mg or 12mg or 25 mg single and repeated doses smoked (as base) (3 studies). In one additional intra-nasal study, the plasma cocaine concentrations after a 0.9 mg/kg singe-dose of cocaine, were lower in women overall, with peak plasma cocaine concentrations greater in the follicular phase compared to the luteal phase.
An additional review demonstrated no significant human gender differences in the PK profile for cocaine when abused [35, 36]; which included no difference in gender for non-human primates. Six of the seven human articles in this review by Evans (2010) are included in the Graziani's (2014) review. In addition, the Evans' review suggests that peak cocaine plasma levels do not vary between the follicular and luteal phases of the menstrual cycle in women who either smoked or used cocaine intranasally. Similarly, there were no sex differences or menstrual cycle phase differences for the metabolites of cocaine plasma concentrations[34, 35]. These cocaine PK findings in humans and non-human primates are consistent with other studies in humans; i.e., including one additional intravenous (IV) cocaine investigation using 0.2-0.4 mg/kg single-doses of cocaine [37] included in the review by Evans (2010).

No significant animal gender difference exists in the PK profile for cocaine, as studied in the rhesus monkey after IV administration of cocaine [38]. No PK differences were observed in female rabbits compared to humans using cocaine at recreational doses [39]. Gender does influence the PK of cocaine in rodents. However, the rodent model (mice and rats) has been shown

to not be applicable to humans [40-42], i.e., human studies demonstrate gender does not influence the PK profile of cocaine.

Age

Geriatric

Plasma cocaine concentrations are not expected to be affected by age. The clearance of cocaine has not been evaluated in this patient population when compared to younger patients. However, Cocaine HCl Topical Solution, 4% and 10%, should be used with caution in elderly patients (65 years and older), since they are more likely to exhibit vascular side effects associated with the drug product.

Pediatric

The PK of cocaine and its metabolites from Cocaine HCl Topical Solutions, 4% and 10%, have not been studied in pediatric patients. A pediatric study plan for Cocaine HCl Topical Solution, 4%, is included in the NDA. (b) (4) [43].

Race

Plasma cocaine concentrations are not expected to be affected by race. Although, population PK analyses have not been conducted to support the lack of race effect on pharmacokinetics of cocaine, the Phase III trials did not indicate a significant difference existed between races.

Renal Impairment

The pharmacokinetics of Cocaine HCl Topical Solution, 4% and 10%, in patients with renal impairment has not been studied. In the Sponsor's clinical trials, subjects with decreased renal function were ineligible for inclusion, which prevents an evaluation of the influence of renal insufficiency on the drug product.

No PK data was discovered for cocaine, or its metabolites, in patients with renal impairment, which would provide sufficient detail to guide the single-dose application with the Sponsor's drug product. However, according to literature, cocaine is eliminated predominantly by metabolism in humans, with little excreted unchanged in the urine. Only 1 -10% of a dose of cocaine is eliminated unmetabolized in urine [11, 12, 22, 44]. Consistent with this low urinary recovery, cocaine CLr is less than 2% of CL [10]. CLr values are less than 40% of human GFR (125 mL/min) [15]. With low amounts of (unchanged) cocaine eliminated by renal clearance, patients with significant renal impairment would
not be expected to be clinically impacted by the product's elimination from the body. Metabolites of cocaine are excreted in urine but they are inactive metabolites.

Based on information available on the metabolism and excretion of cocaine, dose initiation in patients with renal impairment should follow a conservative approach. Dosages should be adjusted per the clinical situation.

Hepatic Impairment

The pharmacokinetics of Cocaine HCl Topical Solution, 4% and 10%, in patients with impaired hepatic function has not been studied. No PK data was discovered for cocaine, or its metabolites, in patients with hepatic impairment, which would provide sufficient detail to guide the single-dose application with the Sponsor's drug product.

Cocaine appears to show non-renal and non-oxidative, non-CYP450 esterases metabolic pathway for elimination and NCOC exhibits plasma peak and total systemic exposure that is less than 1% of that achieved with cocaine, and is cleared from the plasma compartment/systemic circulation within 8 hours, which minimizes its potential pharmacologic activity plasma cocaine concentrations may not be expected to be affected in patients with hepatic impairment. However, based on the proprietary information that the agency is aware of regarding increased exposures of cocaine in hepatic impaired patients there is a high possibility of increased exposures and hence increased adverse events with Cocaine HCl Topical Solution, 4% and 10% in these subjects.

> Hence, since the clearance of cocaine has not been evaluated in these patient populations when compared to patients with normal hepatic function and sufficient information is not available to guide dosing in these subjects it is thus not advisable to dose NUMBRINO in patients with hepatic impairment.

Butyrylcholinesterase Deficiency

As noted above, butyrylcholinesterase (also referred to as pseudocholinesterase or plasma cholinesterase) is responsible for formation of ecgonine, a metabolite formed after sequential de-esterification steps. The potential clinical implications of this enzyme's deficiency and the team's recommendation are summarized in the paragraph below, reproduced from Dr. Kwatra's review:

> **C**ocaine is rapidly metabolized in plasma by butyrylcholinesterase and thus, its metabolism may be diminished in individuals with butyrylcholinesterase deficiency; however, whether this might have clinically significant effects is not clear.
> Many genotypes are possible, depending on the combination of alleles (wild type and/or at least 50 variants, four of which are most prevalent) inherited by an individual [45-47]. Based on responses of individuals to succinylcholine, a genetically-determined reduction of 30% or less in butyrylcholinesterase activity is associated with minimal clinical significance. The frequency of the homozygous, wild type genotype, which confers normal enzyme activity in an individual, is as high as 98% in the general population. Of the alternative genotypes, those that may result in moderately to extremely enhanced sensitivity to succinylcholine range in frequency from 0.0007% to 0.03% of the general population. However, cocaine is administered as a topical intranasal dose instead of IV like succinylcholine and has very low systemic exposure. Additionally there are several collateral metabolic pathways involved in the biotransformation of cocaine in vivo, and serum and liver cholinesterases have been shown to have very high capacities, with conservative maximum enzyme velocity (Vmax) estimates of approximately 10 nmol/mL (~3000 ng/mL) and 115 nmol/g (~35,000 ng/g), respectively, per 30 minutes [Stewart et al, 1979], which far exceed the observed mean Cmax in humans (142.7 ng/mL and 433.5 ng/mL) after an intranasal dose of 4% and 10% topical cocaine solutions. With the combination of these multiple factors the likelihood of butyrylcholinesterase deficiency exerting a clinically relevant effect on the disposition cocaine is low. However, cocaine should still be used carefully in patients with reduced cholinesterase activity. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for atypical plasma cholinesterase gene), pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Additionally, plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors, and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiopate, and certain antineoplastic drugs). In either case. No dosage adjustment of Cocaine Hydrochloride Topical Solution is advised in patients. But patients with reduced plasma cholinesterase activity should be monitored for adverse reactions such as headache, epistaxis, and clinically-relevant increases in heart rate or blood pressure.

Extrinsic factors

The Applicant did not conduct any in vitro or in vivo drug-drug interaction studies. Dr. Kwatra noted in his review that neither the active pharmaceutical ingredient (cocaine), or the administration technique (via pledgets) are expected to present any new or unique drug-drug interaction. In addition, no clinically significant CYP3A4 interactions are expected, or noted in the medical literature, because <10% of cocaine is eliminated via this metabolic route. He also noted that the potential for cocaine to interact with the ABC efflux transporters P-gp and BCRP,

in human embryonic kidney cells transfected with either human P-gp or human BCRP was reported in the literature [48]. Cocaine (100 μM) did not inhibit either P-gp or BCRP.

QT Prolongation Evaluation

The Applicant did not conduct a dedicated thorough QT study to evaluate the product's potential for QT prolongation. They opted instead to do a subgroup analysis of patients in their Phase 3 studies. The data from the electrocardiogram monitoring was reviewed by QT-Interdisciplinary Review team in the Division of Cardiovascular and Renal Products. Their conclusion was that the data were not adequate to satisfy the thorough QT requirements, citing the following two reasons (reproduced from Dr. Garnett's review):

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 Tmax 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 waive the requirement for a positive control.

Dr. Garnett also noted in her review that that the peak plasma concentration of cocaine following the maximum recommended dose (400 mg) of the Applicant's product exceeded the supratherapeutic dose included in the TQT study for another cocaine containing product Goprelto (Numbrino: 433 ng/mL; Goprelto: 146 ng/mL).

It is important to note that the Applicant did not reference the Goprelto NDA in support of their application, and that NDA is not being used by the review team to support this NDA. The review team's observation regarding the results obtained in studies conducted by the applicant of the Goprelto NDA are only being cited as background information, in order to put the lack of QT data in this NDA into perspective.

The final recommendation from the clinical pharmacology review team was that, from a clinical pharmacology perspective, the Applicant submitted most of the clinical pharmacology information needed for approval. However, the lack of adequate characterization of the potential for QT prolongation did not support a recommendation for approval.

I concur with the clinical pharmacology team's assessment that lack of adequate information to characterize the Applicant's product potential for QT prolongation will preclude approval of this NDA.

6. Clinical Microbiology

The product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant submitted the result of two trials to support the efficacy of their product. The design, conduct, and results of the studies are well described in Dr. Petit-Scott's and Dr. Li's individual reviews. Only the major observations will be briefly summarized here.

The following table is adapted from Dr. Petit-Scott's review:

Trial Identity	Trial Design	Regimen, Schedule, and Route	Study Objectives	Study Population	No. of patients enrolled	Number and location of centers
COCA4vs10001	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	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. Average age 37.6 years	646 enrolled 637 completed 253 males 393 females	16 study sites, all located in the United States

The following description of the studies is reproduced from Dr. Feng's review (note: "Study 1" is COCA4vs10-001, and "Study 2" is COCA4vs10-002):

Study 1

This was a randomized, double-blind, placebo-controlled, parallel group, single-dose, multicenter study that evaluated the safety and efficacy of cocaine HCl topical solution (4% and 10%) for local anesthesia during diagnostic procedures or surgeries on or through the mucous membranes of the nasal cavities in subjects at least 18 years old. The study enrolled subjects at 10 sites in the United States. The study was conducted in two phases. The first phase of the study was designed to evaluate both the safety and efficacy of cocaine 4% and 10% in comparison to placebo. The

second phase of the study was designed to evaluate safety of the two cocaine strengths and did not contain a placebo arm.

Subjects enrolled in phase one were randomized equally to receive either cocaine 4%, cocaine 10% or placebo topical solution. The study medication was dosed as a single application of up to 4 mL of solution placed on, and saturated into, cotton pledgets and inserted into the nose for 20 minutes. Per the applicant, cocaine 4% therapy delivers up to 160 mg of cocaine, while the cocaine 10% therapy delivers up to 400 mg of cocaine depending on the amount of solution used to soak the pledgets. The dose of study medication was determined by the volume of solution dispersed onto the pledget(s). The investigator determined the total dose based on the procedure to be undertaken and the subject's variables, i.e., anesthesia requirement, number and size of the nares requiring anesthesia, and their clinical status.

The nasal mucous membranes were then tested for local analgesia using a Von Frey filament test with a filament of size 5.18 (15 gram). The level of pain induced by the filament was rated and recorded using an 11-point Visual Numerical Rating Scale (VNRS) where 0 indicated no pain and 10 was unbearable pain.

For subjects in the first phase of the study, the study blind was broken relative to placebo versus cocaine after administration of the Von Frey filament test. Subjects in the cocaine arms did not know if they had received 4% or 10% cocaine. Placebo subjects were required to have their diagnostic procedure or surgery delayed for at least 24 hours after removal of pledgets or until study termination. Cocaine subjects who reported no pain for the Von Frey filament test received their scheduled procedure. Cocaine subjects who reported a pain score greater than 0 followed the same procedure as placebo subjects.

After 120 subjects completed the first phase (efficacy phase) of the study, the second phase (safety only) of the study was initiated. All study procedures were supposed to be the same for both phases of the study including the reporting of all safety and efficacy data with the following exceptions: there was no placebo arm in the safety only phase of the study and therefore no requirement for breaking blind.

The primary efficacy endpoint was defined as the analgesic success immediately after study drug application and sustained analgesia through the diagnostic procedure or surgery. A subject receiving cocaine was defined as an analgesic success if he/she met both of the following criteria:

- had a VNRS score of 0 based on the Von Frey filament test prior to the diagnostic procedure or surgery
- had no need for further analgesic medication during the diagnostic procedure or surgery.

A placebo subject was defined as a treatment success if the subject had a pain score of 0 based on the Von Frey filament challenge.

After phase one of the study was complete, the applicant conducted their efficacy analysis. The analysis failed to demonstrate the superiority of cocaine 4% over placebo although the observed success rate was numerically higher than that of placebo, and the study was hence terminated. At the point of termination, the study had enrolled 36 subjects into the second phase.

Study 2

The design of study 2 was very similar to the first phase of study 1. The primary differences are summarized as follows:

- A stiffer V on Frey filament was used, 5.88 (60 gram) versus 5.18 (15 gram).
- The Von Frey filament test was performed immediately before anesthesia and right after anesthesia so the subjects could discriminate and experience the sensation of the test without anesthesia.

- Standardized language was used by the investigators to ask the subjects to describe their pain.
- The exact dose administered was determined by the number of pledgets used (1 pledget delivered 1 mL of drug product). In Study 1, the exact dose administered was determined by measuring the amount of solution left in the bottle subtracted from the original bottle.
- Subjects were randomized in a ratio of 2:2:1 to either cocaine 10%, cocaine 4% or placebo. Study 1 utilized equal randomization.

The primary endpoint, analgesic success, was identical to study 1.

The trials did not formally assess the vasoconstricting effects of cocaine with a protocol pre-specified quantitative vasoconstriction endpoint because the procedure would not be able to be completed in the absence of local vasoconstriction.

COCA4vs10-001: 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

The trial enrolled 156 subjects. The baseline demographics for the study population are summarized in the table below, reproduced from Dr. Li's review.

	Placebo	**Cocaine 4%**		**Cocaine 10%**	
Characteristics	**N=40**	**Efficacy (N=39)**	**Total (N=57)**	**Efficacy(N=41)**	**Total (N=59)**
Age (days)					
Mean (SD)	35 (14)	39 (13)	39 (13)	39 (13)	41 (12)
Median	30	40	39	41	43
Min, Max	19, 70	18, 62	18, 66	18, 67	18, 68
Sex, n (%)					
Female	23 (58%)	20 (51%)	30 (53%)	24 (59%)	37 (63%)
Male	17 (43%)	19 (49%)	27 (47%)	17 (41%)	22 (37%)
Race, n (%)					
American Indian or Alaska	0	1 (3%)	1 (2%)	0	0
Asian	1 (3%)	1 (3%)	2 (4%)	1 (2%)	1 (2%)
Black or African American	2 (5%)	6 (15%)	9 (16%)	8 (20%)	15 (25%)
White	37 (93%)	31 (79%)	45 (79%)	32 (78%)	43 (73%)
Height (in)					
Mean (SD)	67 (4)	67 (4)	67 (4)	67 (5)	67 (4)
Median	67	67	67	67	66
Min, Max	59, 75	60, 73	60, 73	52, 76	52, 76
Weight at screening (lb)					
Mean (SD)	194 (55)	186 (45)	187 (49)	186 (47)	184 (44)
Median	184	179	178	176	179
Min, Max	112, 310	110, 300	110, 300	119, 310	113, 310

All the subjects completed the study. Dr. Li was able to reproduce the Applicant's results. The summary of his findings are summarized in the table below, reproduced from Dr. Li's review.

Event	**Placebo (N=40)**		**Cocaine 4% (N=39)**		**Cocaine 10% (N=41)**	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	15 (37.5%)	25 (62.5%)	21 (54%)	[redacted] (b) (4)		
Procedure performed	NA	NA	21			

Event	Placebo (N=40)		Cocaine 4% (N=39)		Cocaine 10% (N=41)	
Additional Analgesic needed	NA	NA	0	0	[redacted]	(b) (4)
Adequate hemostasis	NA	NA	21	3		
Analgesic success	15 (37.5%)		21 (54%)			
Difference from placebo			16%			
95% CI #			(-6.6%, 37.8%)			
P-value*			0.1782			

Dr. Petit-Scott noted in her review that the Applicant considered the lack of efficacy of the cocaine HCl 4% solution to be related to a large placebo response, use of a low strength von Frey filament for assessing analgesia, and no specific language for describing pain response. Dr. Petit-Scott also considered inconsistent dosing (discussed in detail in her review) and whether the evaluated procedures differed between the cocaine groups.

COCA4vs10-002: 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

The trial enrolled 646 subjects. The baseline demographics for the study population are summarized in the table below, reproduced from Dr. Li's review.

Characteristics	Placebo N=128	Cocaine 4% N=259	Cocaine 10% N=259
Age (days)			
Mean (SD)	36 (12)	38 (13)	38 (13)
Median	34	37	36
Min, Max	19, 68	18, 76	18, 71
Sex, n (%)			
Female	68 (53%)	169 (65%)	156 (60%)
Male	60 (47%)	90 (35%)	103 (40%)
Race, n (%)			
American Indian or Alaska	0	0	2 (1%)
Asian	10 (8%)	9 (4%)	12 (5%)
Black or African American	12 (9%)	43 (17%)	30 (12%)
Native Hawaiian or other Pacific Islander	1 (1%)	0	3 (1%)
White	105 (82%)	205 (80%)	212 (82%)
Height (in)			
Mean (SD)	67 (4)	66 (4)	67 (4)
Median	67	66	66
Min, Max	59, 77	56, 78	59, 79
Weight at screening (lb)			
Mean (SD)	180 (44)	177 (47)	182 (47)
Median	175	174	175
Min, Max	105, 360	102, 365	100, 380

As noted by Dr. Li in his review, were seven subjects who were randomized did not receive treatment: one subject in the placebo group, one subject in the cocaine 4% group, and five

subjects in the cocaine 10% group. Only two subjects in the cocaine 4% group discontinued after receiving treatment. The primary efficacy population excluded the seven subjects who did not receive the study treatment.

Dr. Li was able to reproduce the Applicant's results. The summary of his findings are noted in the table below, reproduced from Dr. Li's review.

Event	Placebo (N=127)		Cocaine 4% (N=258)		Cocaine 10% (N=254)	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	25 (20%)	102 (80%)	186 (72%)	(b) (4)		
Procedure performed	NA	NA	185			
Additional Analgesic needed	NA	NA	2 (0.8%)			
Adequate hemostasis	NA	NA	185			
Analgesic success	25 (20%)		183 (71%)			
Difference from placebo			51%			
95% CI #			(42%, 60%)			
P-value*			<0.0001			
Difference from 4%						
95% CI#						
P-value*						

As was noted in Dr. Petit-Scott's and Dr. Li's individual reviews, the von Frey filament assessment and collection of the subject-reported pain score on the VNRS, the blind to placebo versus cocaine topical solution was broken; the blind with respect to the dose of cocaine topical solution, 4% versus 8%, remained unbroken. This raised the possibility that the decision to administer additional analgesic medication for the subsequent diagnostic or surgery procedure might have been influenced by knowledge of the treatment assignment.

(b) (4)

A similar sensitivity analysis was conducted for Study COCA4vs10-002, and Dr. Li concluded that to overturn the statistical significance, one would need to assume that more than 44% of the

4% solution treatment group and more than 56% of the 10% solution treatment group had been accidentally unblinded before the Von Frey filament test, which was deemed to be unlikely.

8. Safety

The safety database in the drug development program consisted of 347 subjects and patients exposed to 4% cocaine topical solution, and 341 subjects and patients exposed to 10% cocaine topical solution. The types of safety assessments that were included in the Phase 1 pharmacokinetic studies and the Phase 3 clinical trials are well-described in Dr. Petit-Scott's review.

There were no deaths reported in the drug development program. The most commonly reported adverse events were hypertension and tachycardia. There was one serious adverse event in Study COCA4vs10-001, in a 49-year-old male patient who was observed to have asymptomatic isolated T-wave inversion and isolated ST depression on the electrocardiogram after receiving a dose of the 10% solution. Follow-up evaluation 72 hours later revealed an increase in creatine kinase MB isozyme from 0.5 ng/mL to 3.3 ng/mL, still within normal limits and Troponin-I levels within normal limits. The electrocardiogram on follow-up was interpreted as within normal limits. The lack of additional information, i.e., serial laboratory assessments, makes it difficult to determine exactly the clinical extent of what occurred in this patient who appears to have experienced an episode of myocardial ischemia.

Two patients withdrew from Study COCA4vs10-002 due to an adverse event. The following descriptions are reproduced from Dr. Petit-Scott's review:

- 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.

Dr. Petit-Scott noted in her review that the Applicant also identified significant adverse events of interest. She noted the following for Study COCA4vs10-001:

> 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.

For Study COCA4vs10-002, she noted the following:

> 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. The most commonly reported adverse events were headache, epistaxis, and nausea and most were mild in intensity.

Dr. Petit-Scott analyzed the safety data with respect to demographic subgroups. There did not appear to be any difference in the incidence of treatment-emergent adverse events between males and females. With respect to age, Dr. Petit-Scott noted that a greater proportion of the patients in the >65 year-old group experienced adverse events, compared to the <35 year-old group, and more patients in the >65-year-old group treated with cocaine experienced hypertension compared to those treated with placebo.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on October 21, 2015 and it was agreed upon on October 14, 2016. (b) (4)

The proposed pediatric studies evaluating 4% cocaine HCl are as follows:

(b) (4)

(b) (4)

As noted in Dr. Petit-Scott's review, the Applicant plans to submit a partial waiver for the 0 to <8 year-old cohort.

11. Other Relevant Regulatory Issues

Routine audits were conducted at two sites by the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (OSI). The sites were selected for inspection due to high enrollment. The following table, reproduced from Dr. Green's review, summarizes the information on the sites and the outcomes of the inspections:

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #1130 **Dr. Michael Major** 5896 S. Ridgeline Drive, Suite A Ogden, UT 84405	COCA4vs10-001 Subjects: 44 COCA4vs10-002 Subjects: 167	09-13 Apr 2018	NAI
Site #1190 **Dr. Michael Armstrong** 8700 Stony Point Pkwy, Suite 110 Richmond, VA 23235	COCA4vs10-001 Subjects: 29 COCA4vs10-002 Subjects: 131	29 May to 01 Jun 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable.

Dr. Green's overall assessment of findings and recommendations were noted as follows:

> The clinical sites of Drs. Major and Armstrong were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.
>
> The final compliance classification of the inspections of Drs. Major and Armstrong was No Action Indicated (NAI).

12. Labeling

Consultations were obtained from the following: the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), the Division of Pediatric and Maternal Health (DPMH), and Division of Cardiovascular and Renal Products (DCRP). Their recommendations were considered and incorporated into the label.

Discussions with the Applicant regarding the text of the label will conducted during the next review cycle.

13. Decision/Action Risk Benefit Assessment

Regulatory Action
Complete Response

Risk:Benefit Assessment
I concur with the review team that the lack of data to characterize the effects of the product on the QTc interval poses an unfavorable risk:benefit assessment and precludes approval of this application at this time.

Furthermore, I concur with the pharmacology/toxicology review team that the lack of data to support the safety of the container closure system and inadequate study reports for several genetic toxicology studies (lacked purity information) should be considered deficiencies.

With respect to the approvability of the two solutions, the Applicant has provided adequate data to support the efficacy. (b) (4)

I agree with the three observations made by Dr. Petit-Scott – (b) (4)

(b) (4)

Post-Marketing Requirements

I concur with the pharmacology/toxicology recommendation that, if this application gets approved, the Applicant be required to conduct the following studies:

1) The standard battery of reproductive and developmental toxicology studies outlined in ICH S5(R2), including pharmacokinetic data for the following:

   a) a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

   b) an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

   c) an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

   d) a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional and behavioral assessments, and reproductive capacity of the offspring.

2) A juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing.

Post-marketing Risk Management Activities

None.

Other Post-marketing Study Commitments

None.

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/

RIGOBERTO A ROCA
07/20/2018