CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	209575
Submission Date:	June 21, 2019
Relevant IND(s):	106499
Submission Type; Code:	Resubmission (Response to CR); 505(b)(2)
Brand Name:	Numbrino
Generic Name:	Cocaine Hydrochloride Topical Solution 4% and 10%
Formulation; Strength(s):	Aqueous solution of 4% cocaine hydrochloride (40 mg/mL) and 10% cocaine hydrochloride ([redacted] (b) (4)
Clinical Pharmacology Reviewer:	Deep Kwatra, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia, Analgesia and Addiction Products
Sponsor:	Cody Laboratories Inc.
Proposed Indication:	NUMBRINO is a liquid formulation of cocaine hydrochloride indicated for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities
Proposed Dosage Regimen:	One (1) mL of NUMBRINO should be applied to each pledget. One (1) or two (2) pledgets that are ½" x 3" containing anesthetic solution should be applied topically per nostril, with a maximum of 2 pledgets used per nostril; maximum of 4 pledgets per procedure. Pledgets should be retained in the nasal cavity for 20 minutes, with removal occurring immediately prior to the patient's procedure or surgery.

TABLE OF CONTENTS

LIST OF FIGURES 3

LIST OF TABLES 3

1 EXECUTIVE SUMMARY 4

1.1 RECOMMENDATION ***4***
1.2 PHASE 4 COMMITMENTS ***4***
1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS ***4***
IR Sent to the Sponsor 11
QT-IRT Review 13
Reviewer Comments: 14
Bio-analytical Facility: 14
Bio-analytical Method: 14

2 DETAILED LABELING RECOMMENDATIONS **17**

12.2 PHARMACODYNAMICS ***17***
2.1 INDIVIDUAL STUDY SYNOPSES: ***18***
2.1.1 Study Designs *18*
2.1.2 Study Synopses *18*
Study LNT-P6-741 18
2.2 SPONSOR'S PROPOSED LABEL: ***19***

LIST OF FIGURES

Figure 1: Plasma Linear Profile of the Mean for Cocaine (160mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%) 7
Figure 2: Plasma Semi-Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%) 7
Figure 3: Plasma Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl 4%, Test-1; 400 mg Cocaine HCl 10%, Test-2) 9
Figure 4: Predicted ΔΔQTcI Interval at Geometric Mean Peak Cocaine Plasma Concentrations (PK/QTc Population) 10
Figure 5: Cocaine Plasma Linear Profile of the Mean Following Intranasal Administration of Cocaine Hydrochloride Topical Solution, 10% (LNT-P6-733 and LNT-P6-741) 12
Figure 6: QTcI Interval: Placebo-corrected change-from-baseline QTcI (ΔΔQTcI) (QT/QTc analysis population) 13
Figure 7: Representative Calibration Curve for Cocaine in Human Plasma 16

LIST OF TABLES

Table 1: Predicted ΔΔQTcI at Geometric Mean Peak Cocaine and Moxifloxacin Concentration (PK/QTc population) 6
Table 2: Summary of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%) 8
Table 3: Summary of the Statistical Analysis of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%) 8
Table 4: Summary of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl 4%, and 400 mg Cocaine HCl 10%) 10

1 Executive Summary

1.1 Recommendation

In response to the clinical deficiency identified in the first review cycle "You have not provided adequate information to characterize the effects of your product on the QTc interval", the Sponsor completed a thorough-QT (t-QT) study to assess the effects of intranasal single therapeutic doses of cocaine HCl topical solutions, 4% and 10%, on cardiac repolarization (the QT interval and other ECG parameters).

Based on the review by the clinical pharmacology team in conjunction with the QT internal review team (QT-IRT), it was determined that the 4% cocaine solution does not present concerns of QTc prolongation. (b) (4) [redacted]

All other aspects of clinical pharmacology for the product were adequately addressed in the first review cycle and will not be discussed in this review. Overall, all Clinical Pharmacology aspects of the application have now been addressed and the NDA may be approved from a Clinical Pharmacology Perspective. The labeling negotiations are ongoing with the sponsor at the time of this review.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Cody Laboratories Inc (a wholly owned subsidiary of Lannett Co Inc.) submitted the original 505 (b)(2) application seeking U.S. marketing approval of Cocaine HCl Topical Solution, 4% and 10% for the for the introduction of topical anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities on September 21st, 2017. The original clinical development program for Cocaine Hydrochloride Topical Solution included two Phase 3 studies Study COCA4vs10-001 and COCA4vs10-002) evaluating the safety and efficacy of Cocaine HCl Topical Solution, 4% and 10% for diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. The clinical development program also includes a Phase 1, single dose, perspective, double-blind, single center, randomized, crossover study of Cocaine HCl Topical Solution 4% and 10% to evaluate the pharmacokinetics (LNT-P6-733). In addition to the clinical and *in vitro* studies used to support the clinical pharmacology information in the submission, the sponsor has evaluated scientific literature for cocaine and provided a summary of the published data for the clinical pharmacology and PK of cocaine as a part of the original NDA.

To address the QT prolongation potential for the original NDA application, the sponsor did not perform a dedicated TQT study but instead conducted a subpopulation analysis using cardiac monitoring in their phase III study. This submission was reviewed by the QT-Internal Review Team (IRT) and the QT-IRT deemed that the data submitted did not adequately address the QT prolongation potential and therefore a dedicated tQT study was required to fulfill the QT requirements. The IRT deferred it to the Division to decide whether the study should be conducted pre- or post-approval. Based on the discussion with the clinical team it was determined that the product has effects on heart rate and potential for QT prolongation and since there has been no significant information provided to alleviate these concerns, it amounts to a safety issue and hence a tQT study would be required pre-approval. This was communicated to the sponsor and the sponsor has in turn submitted a TQT protocol to the division for review. The comments on this study protocol were sent to the sponsor on June 13th, 2018. Since the completed study reports for this study were not submitted within time to allow for a substantial review, a Complete Response Letter (CRL) was issued to the sponsor on July 20, 2018. It contained one clinical and two non-clinical deficiencies. The clinical deficiency stated that "You have not provided adequate information to characterize the effects of your product on the QTc interval." And the remedy to resolve this deficiency was to "Submit the results of a thorough QT study."

In response to the CRL the sponsor completed a tQT study (LNT-P6-741 (Sponsor Project No. COCA-QT-01)) and submitted it in the resubmission. This was a triple-blinded (except for moxifloxacin), randomized, 4-arm crossover design, thorough QT Study in order to assess the effects of intranasal single therapeutic doses of cocaine HCl topical solutions, 4% and 10%, on cardiac repolarization (the QT interval and other ECG parameters). Thirty-two (32) healthy male and female subjects were randomized to receive a treatment sequence that included all 4 of the following treatment regimens:

- Placebo topical solution (negative control; Treatment A)
- Moxifloxacin 400 mg as a positive pharmacologic control (to demonstrate assay sensitivity; Treatment B)
- 4 mL of cocaine HCl topical solution, 4% (160 mg dose), therapeutic dose (Treatment C)
- 4 mL of cocaine HCl topical solution, 10% (400 mg dose), higher therapeutic dose (Treatment D)

As described above moxifloxacin was used as a positive control. the standard dose of moxifloxacin (400 mg) used for a variety of infections, produced an increase in mean QTcI of 12.81 ms (90% UCI 14.64 ms) in the concentration-QTc analysis. The cocaine hydrochloride topical solution, 4% strength produced no clinically significant change in QTc. The QTc increase produced by the higher (10%) strength of intranasal cocaine was smaller than that produced by the clinical dose of moxifloxacin and barely crossed the "threshold of regulatory concern". No SAEs and no deaths were reported during the study and there was no unresolved AE. The predicted ΔΔQTcI at the geometric mean peak

concentrations of cocaine for each cocaine dose and for moxifloxacin are shown in Table 1.

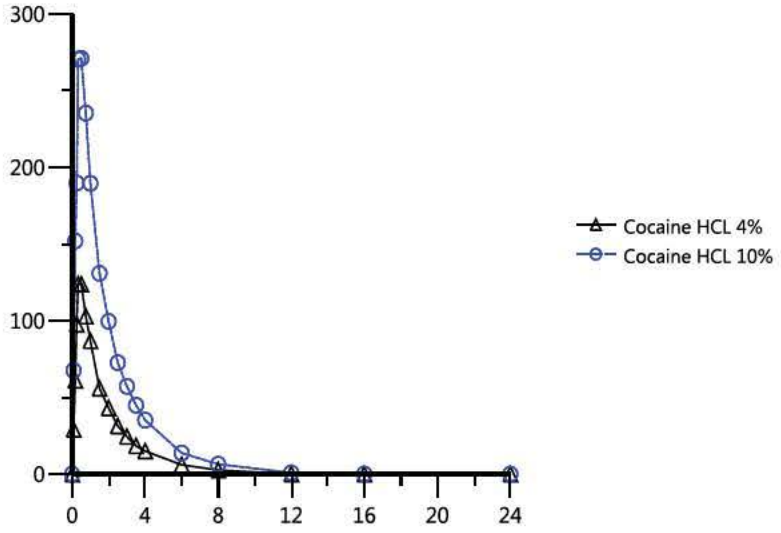
Table 1: Predicted ΔΔQTcI at Geometric Mean Peak Cocaine and Moxifloxacin Concentration (PK/QTc population)

Analyte	Treatment	Geometric Mean (ng/mL) (90% CI)	ΔΔQTcI Estimate (ms) (90% CI)
Cocaine (parent)	Cocaine HCl 4%	127.1 (114.11; 141.62)	3.87 (2.76, 4.99)
	Cocaine HCl 10%	273.5 (250.09; 299.16)	8.14 (5.77, 10.50)
	10 ms Threshold	261	7.77 (5.52, 10.03)
Moxifloxacin	400 mg	2002.4 (1853.55; 2163.22)	12.81 (10.98, 14.64)

A review of plasma concentration profiles for the cocaine metabolites by the sponsor demonstrated that metabolite T_{max} values were much longer compared to cocaine and did not match the time course of QTc changes. Concentration/QTc analysis for the metabolites demonstrated no correlation between the metabolite plasma concentrations and ΔQTcI. In the full model including cocaine and all metabolites, only cocaine was found to have any effect on QTc.

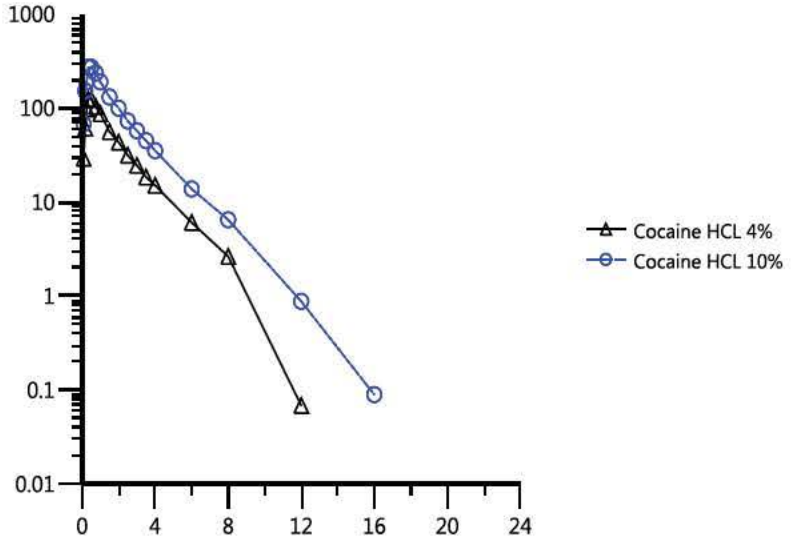
In the tQT study, the maximum cocaine plasma concentration (Cmax) observed after the 160 mg dose of Cocaine HCl Topical Solution, 4% was 134.35 ng/mL and 284.95 ng/mL after the 400 mg dose of Cocaine HCl Topical Solution, 10%; a 2.1-fold value greater than that observed after the 160 mg dose of cocaine HCl, which is approximately equivalent to the ratio of the doses administered (2.5-fold). The mean plasma concentration-time profiles are displayed by treatment in Figure 1 (linear scale) and Figure 2 (logarithmic scale). Plasma pharmacokinetic parameter values are summarized by treatment and presented in Table 1. A summary of the statistical analysis of Cmax and AUC for cocaine by treatment is given in Table 2. The intra-subject variability reflects the residual variability observed in the pharmacokinetic parameters after accounting for possible differences between sequence, period, and formulation effects as well as accounting for between-subjects variations. The intra-subject coefficients of variation were 28.0%, 25.6% and 24.8% for Cmax, AUC0-T, and AUC0-∞, respectively (Table 2).

Figure 1: Plasma Linear Profile of the Mean for Cocaine (160mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%)



Source: CSR Study LNT-P6-741, Figure 1.

Figure 2: Plasma Semi-Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%)



Source: CSR Study LNT-P6-741, Figure 2.

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

	Treatment							
	Cocaine HCl Topical Solution, 4%				Cocaine HCl Topical Solution, 10%			
Parameter	**n**	**Mean**	**SD**	**CV%**	**n**	**Mean**	**SD**	**CV%**
C_{max} (ng/mL)	30	134.35	43.85	32.6	30	284.95	84.60	29.7
T_{max} (hours)[a]	30	0.50	(0.25 – 1.00)		30	0.50	(0.25 – 0.77)	
AUC_{0-T} (ng·h/mL)	30	235.72	66.03	28.0	30	540.73	146.84	27.2
$AUC_{0-\infty}$ (ng·h/mL)	30	243.67	66.51	27.3	30	551.75	146.80	26.6
$AUC_{0-T/0-\infty}$ (%)	30	96.48	1.67	1.7	30	97.88	0.99	1.0
λ_z (hours^{-1})	30	0.4370	0.0655	15.0	30	0.4201	0.0837	19.9
T_{half} (hours)	30	1.62	0.25	15.7	30	1.72	0.40	23.0

[a] Median (range)

Source: CSR Study LNT-P6-741, Table 5.

Table 3: Summary of the Statistical Analysis of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl Topical Solution, 4% and 400 mg Cocaine HCl Topical Solution, 10%)

Parameter	Intra-Subject CV (%)	Geometric LSmeans[a]		Ratio (C/D) (%)	90% Confidence Limits (%)	
		Cocaine HCl Topical Solution, 4% (Treatment C) (n=30)	Cocaine HCl Topical Solution, 10% (Treatment D) (n=30)		Lower	Upper
C_{max} (ng/mL)	28.0	125.43	272.02	46.11	40.81	52.10
AUC_{0-T} (ng·h/mL)	25.6	223.48	520.42	42.94	38.39	48.04
$AUC_{0-\infty}$ (ng·h/mL)	24.8	231.73	531.63	43.59	39.10	48.59

Abbreviations: CV%= coefficient of variation; LSmeans=least squares mean

[a] Statistical analyses were performed post-hoc using natural-log transformed parameter values.

Source: CSR Study LNT-P6-741, Table 6.

The exposure of cocaine observed in the tQT study were significantly lower than those observed in the original Phase 1 study (LNT-P6-733) submitted in the first cycle for the NDA. The mean plasma concentration-time profiles are displayed by treatment in (Figure

3). A summary of the statistical analysis of Cmax and AUC for cocaine by treatment is given in Table 3 for this study. The mean plasma concentration-time profiles are displayed by treatment in Figure 3 (linear scale) for this study. Though there were only marginal increase in exposures observed for the 4% cocaine treatment, the exposure difference between the tQT study and the original Phase 1 PK study (study LNT-P6-733) was much starker for the 10% treatment. Based on the cross-study comparison the Cmax was approximately 59% higher and the AUC approximately 80% higher in the previous study as compared to the tQT study for the 10% treatment. Based on the sponsors prediction for QT interval submitted (Figure 4) the 10 ms threshold for QT prolongation would be crossed at a Cmax of 261 ng/mL. The concentrations observed in the study LNT-P6-733 were much higher than that.

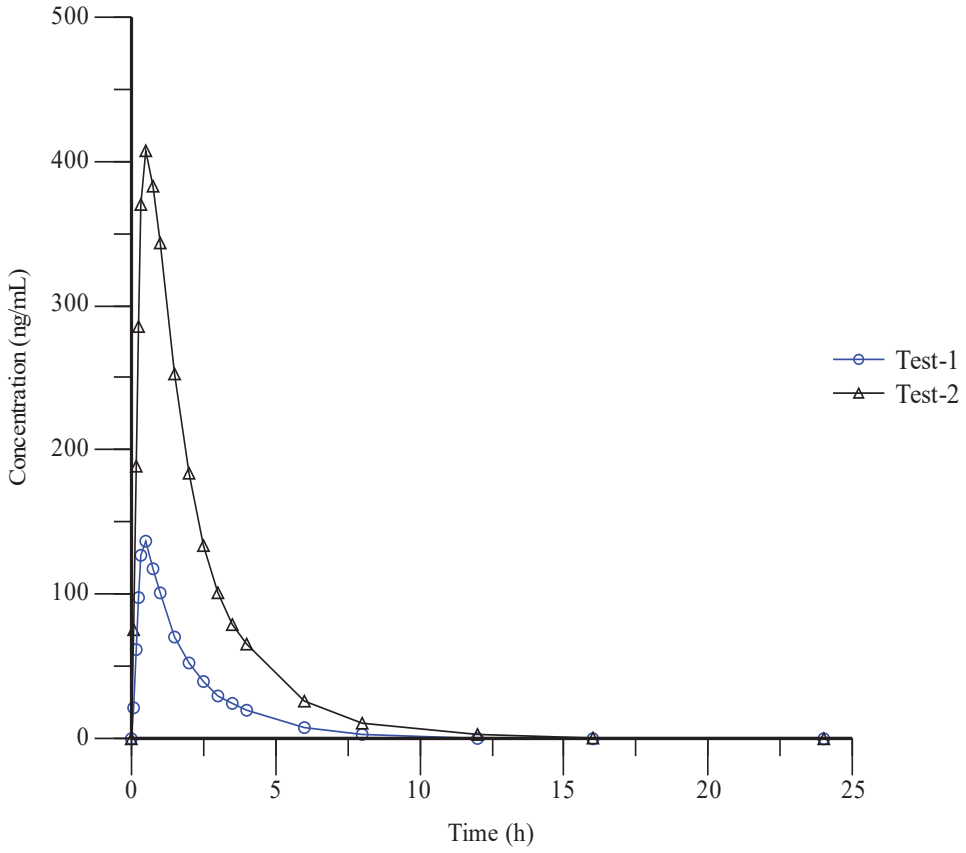


Figure 3: Plasma Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl 4%, Test-1; 400 mg Cocaine HCl 10%, Test-2) in study LNT-P6-733

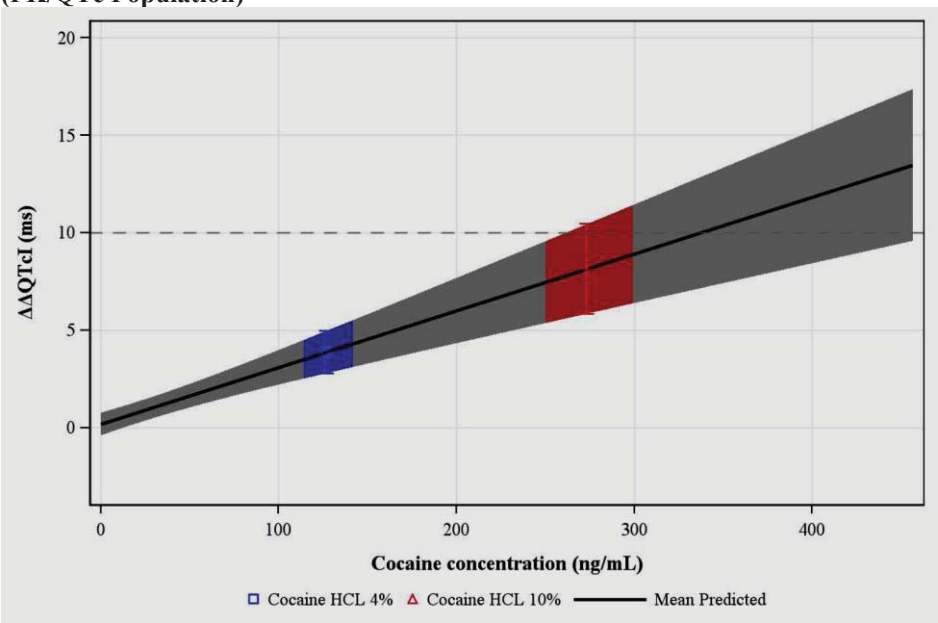
Table 4: Summary of Plasma Cocaine Pharmacokinetic Parameters (160 mg Cocaine HCl 4%, and 400 mg Cocaine HCl 10%) in study LNT-P6-733

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,**

Figure 4: Predicted ΔΔQTcI Interval at Geometric Mean Peak Cocaine Plasma Concentrations (PK/QTc Population)



IR Sent to the Sponsor

Since the exposure previously observed in study LNT-P6-733 was much higher than that observed in the dedicated QT study, an IR was sent to the sponsor to explain the differences and how the predictions would apply to the *concentrations previously observed. The following IR was sent to the sponsor of August 1st 2019. " We are reviewing NDA 209575 and have the following request for information: In your Clinical Study Report (CSR) for LNT-P6-741, Table 16, the observed mean Cmax after administration of 10% topical cocaine was* [redacted] (b) (4)

The sponsor responded by stating that the [redacted] (b) (4)

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For further details of the QT-IRT review and recommendations refer to the QT-IRT review in DARRTS documented on 08/19/2019.

Reviewer Comments:

(b) (4)

The exposure for 4% cocaine seen in all the studies submitted by the sponsor and the literature is well within the limits of the exposures for the dedicated QT study. Although a concentration dependent QT increase was observed with 4% and 10% solutions, the change in QT observed and predicted are well within the regulatory threshold of concern for the 4% solution and so a clinically meaningful QT prolongation is not expected with the 4% solution.

Bio-analytical Facility:

The methods were developed and validated by (b) (4) Sample extraction was performed by (b) (4) Sample analysis was conducted in accordance with FDA Guidance for Industry, Bioanalytical Method Validation (May 2001) and EMA Guideline on Bioanalytical Method Validation (2009).

Bio-analytical Method:

(b) (4)

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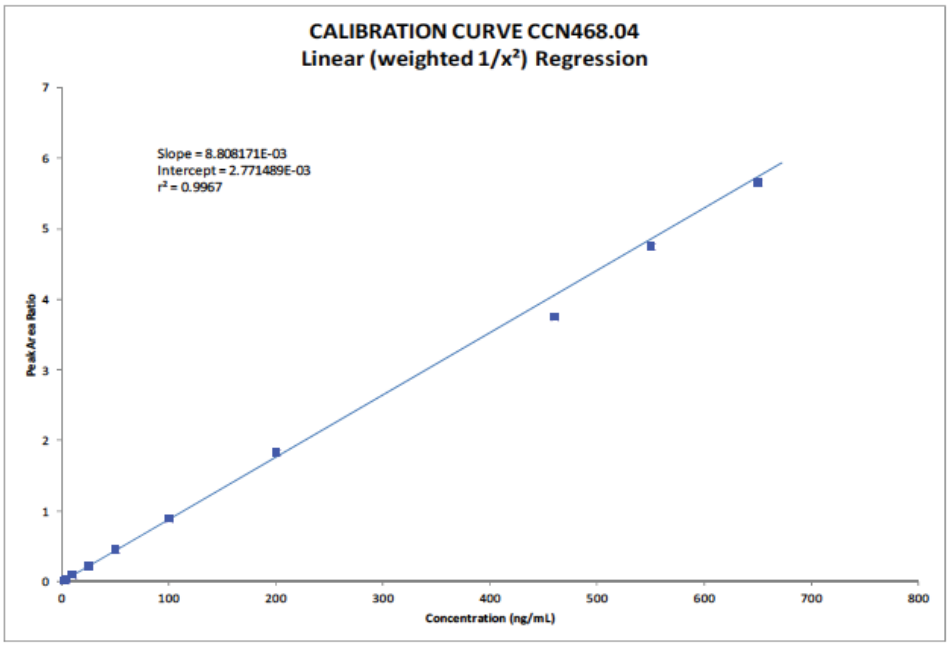
Figure 7: Representative Calibration Curve for Cocaine in Human Plasma



Source: Validation Report CCN-V6-468

2 Detailed Labeling Recommendations

The following labeling comments are proposed by this reviewer. Deletion is shown by ~~Strike-through text~~ and addition is shown by underline text. The labeling recommendations in this review only deal with the QT prolongation effects. The other labeling recommendations previously proposed, can be found in the original Clinical Pharmacology Review for the first cycle in DARRTS documented on 06/20/2018.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of cocaine hydrochloride topical solution (4% and 10%) on the QTc interval was evaluated in a randomized, positive- and placebo-controlled four-period crossover thorough QTc study in 32 healthy subjects. (b) (4)

Numbrino is associated with concentration-dependent QTc prolongation. Based on the concentration-QTc relationship, the mean placebo corrected change from the baseline QTcF (90% two-sided upper confidence interval) are 4.7 ms (6.2 ms) and 15.4 ms (20.1 ms) at peak concentrations of 143 ng/mL (corresponds to 4% single dose, 160 mg) and 434 ng/mL (corresponds to 10% single dose, 400 mg)*, respectively. The estimates of the QTcF interval are confounded by increased heart rates. The QTc prolongation observed with Numbrino (4% single dose) was found to be below the regulatory threshold for concern.

Numbrino is associated with increases in heart rate. The mean placebo corrected change from baseline heart rate (90% two-sided upper confidence interval) are 12 (14) bpm and 20 (22) bpm for the 4% and 10%, respectively

* (b) (4) the information regarding the 10% product should be included in the label as this product was used as a marketed unapproved product. Hence, there is still a possibility of it being compounded in compounding pharmacies and therefore this information should be available to help guide the practitioner.

2.1 Individual Study Synopses:

Note: Study synopses in this section were extracted from the NDA submission

2.1.1 Study Designs

Randomized, Positive- and Placebo-Controlled Trial to Evaluate the Effects of Cocaine HCl Topical Solutions on Cardiac Repolarization following Intranasal Administration in Healthy Subjects

2.1.2 Study Synopses

Study LNT-P6-741

Appears this way on the original

2.2 Sponsor's Proposed Label:

Appears this way on the original

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

/s/

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CLINICAL PHARMACOLOGY REVIEW

NDA:	209575
Submission Date:	September 21st 2017
Relevant IND(s):	106499
Submission Type; Code:	Original NDA; 505(b)(2)
Brand Name:	Numbrino
Generic Name:	Cocaine Hydrochloride Topical Solution 4% and 10%
Formulation; Strength(s):	Aqueous solution of 4% cocaine hydrochloride (40 mg/mL) and 10% cocaine hydrochloride (b) (4))
Clinical Pharmacology Reviewer:	Deep Kwatra, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
Division Director:	Chandrahas Shajwalla. Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia Analgesia and Addiction Products
Sponsor:	Cody Laboratories Inc.
Proposed Indication:	NUMBRINO is a liquid formulation of cocaine hydrochloride indicated for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities
Proposed Dosage Regimen:	One (1) mL of NUMBRINO should be applied to each pledget. One (1) or two (2) pledgets that are ½" x 3" containing anesthetic solution should be applied topically per nostril, with a maximum of 2 pledgets used per nostril; maximum of 4 pledgets per procedure. Pledgets should be retained in the nasal cavity for 20 minutes, with removal occurring immediately prior to the patient's procedure or surgery.

TABLE OF CONTENTS

LIST OF FIGURES 4

LIST OF TABLES 4

1 EXECUTIVE SUMMARY 5

1.1 RECOMMENDATION *5*
1.2 PHASE 4 COMMITMENTS *5*
1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS *5*
1.3.1 Clinical Pharmacology Studies: *8*
Phase 1 Study LNT-P6-733: 8
1.3.2 Clinical Studies: *8*
Phase 3 Study (with commercial scale formulation): 8
1.3.3 Pharmacokinetic Single-Dose Study Study LNT-P6-733 of Cocaine HCl Topical Solution, 4% and 10%: *9*
1.3.4 Summary of DDI Information: *10*

2 QUESTION BASED REVIEW **12**

2.1 GENERAL ATTRIBUTES OF THE DRUG ***12***
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? *12*
2.1.2 What is the regulatory history of Cocaine Hydrochloride? *12*
2.1.3 What is the composition of the to-be-marketed formulation of Cocaine Hydrochloride Topical Solution, 4% and 10%? *13*
2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)? *13*
2.1.5 What are the proposed dosage and route of administration? *13*
2.1.6 What is the core studies submitted in this NDA? *14*
2.2 GENERAL CLINICAL PHARMACOLOGY ***14***
2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured? *15*
2.2.2 What are the general PK characteristics of the drug? *15*
Absorption: Study LNT-P6-733 15
Absorption: Literature Summary 18
Distribution: 21
Metabolism: 21
Excretion: 23
Dose-proportionality of Topical cocaine: 24
2.3 INTRINSIC FACTORS ***24***
Gender 25
Age 26
Race 26
Renal Impairment 26
Hepatic Impairment 27
Effect of a Butyrylcholinesterase Deficiency 27
2.3.1 What is the pediatric plan? *28*
2.4 EXTRINSIC FACTORS ***29***
2.4.1 Pharmacokinetic Drug Interactions: *29*
2.4.2 Potential Pharmacodynamic Drug-Drug Interactions: *31*
Sympathomimetics: 32
CNS Stimulants: 32
Beta Blockers: 32
Anti-Depressants 33
Clozapine 33
Monoamine-Oxidase Inhibitors 34

Ethanol 34
Alpha-modifying Agents 34
Halothane Anesthesia 35
2.5 ANALYTICAL SECTION 35
2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method? 35
Bio-analytical Facility: 35
Bio-analytical Method: 35
Bio-analytical Validation: 36

3 DETAILED LABELING RECOMMENDATIONS 47

7.2 CHOLINESTERASE INHIBITORS 47
7.7 DISULFIRAM 47
8.6 HEPATIC IMPAIRMENT 48
8.7 RENAL IMPAIRMENT 48
8.8 PSEUDOCHOLINESTERASE DEFICIENCY 48
12.3 PHARMACOKINETICS 49

4 APPENDICES 52

4.1 REFERENCES 52
4.2 INDIVIDUAL STUDY SYNOPSES: 57
4.2.1 Study Designs 57
4.2.2 Study Synopses 57
Study LNT-P6-733 57
4.3 SPONSOR'S PROPOSED LABEL: 58

LIST OF FIGURES

Figure 1: Concentration-Time profile in healthy adult subjects after a single intranasal dose of topical cocaine (4%); Source studies CTS 2015016, CTS 2015013 and CTS 2015014 17
Figure 2: Mean Serum Cocaine Concentrations After Pledget Application of Cocaine HCl 4% and Cocaine HCl 10%. Source: Liao, 1999 20
Figure 3: Systemic Metabolic Pathways of Cocaine. Source: Kolbrich, 2006 22

LIST OF TABLES

Table 1: Physical-Chemical Properties of Cocaine Hydrochloride 12
Table 2: Composition of Cocaine Hydrochloride Topical Solution, 4% and 10 % 13
Table 3: PK parameter values in healthy adult subjects after a single intranasal dose of topical cocaine (4%); Source studies CTS 2015016, CTS 2015013 and CTS 2015014 15
Table 4: Cocaine, Benzoylecgonine, and Ecgonine Methyl Ester Pharmacokinetic Parameters. Source: Kolbrich, 2006 23
Table 5: Assay Performance for Cocaine 37
Table 6: Assay Performance for (b) (4) 39
Table 7: Assay Performance for (b) (4) 41
Table 8: Assay Performance for (b) (4) 43
Table 9: Assay Performance for (b) (4) 45

1 Executive Summary

1.1 Recommendation

The sponsor has not fully completed the QT evaluation requirements for the NDA 209575 as the data submitted is insufficient (Based on the review by the QT-IRT group). The sponsor submitted a new protocol during the NDA review period for a new Thorough QT (tQT) study which has been reviewed and the comments have been conveyed to the sponsor. The final study report for that study has not been submitted yet. Hence, from the Clinical Pharmacology perspective, NDA 209963 is NOT ACCEPTABLE until the sponsor fulfills the QT evaluation requirements.

Based on internal team discussion, if the sponsor submits the study report for the tQT study prior to end of the PADUFA clock (July 21, 2018), the clock can be extended for this application to give the team time to review the new tQT report. However, if the report cannot be submitted before the PADUFA date, then from a clinical pharmacology prospective, this submission is not acceptable. However, barring lack of the tQT evaluation, other aspects of the clinical pharmacology have been adequately addressed.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Cody Laboratories Inc (a wholly owned subsidiary of Lannett Co Inc.) submitted a 505 (b)(2) application seeking U.S. marketing approval of Cocaine HCl Topical Solution, 4% and 10% for the for the introduction of topical anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. The clinical development program for Cocaine Hydrochloride Topical Solution included two Phase 3 studies Study COCA4vs10-001 and COCA4vs10-002) evaluating the safety and efficacy of Cocaine HCl Topical Solution, 4% and 10% for diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. The clinical development program also includes a single Phase I PK, prospective, double-blind, single center, randomized, crossover study of Cocaine HCl Topical Solution 4% and 10% (LNT-P6-733). In addition to the clinical and *in vitro* studies used to support the clinical pharmacology information in the submission, the sponsor has evaluated scientific literature for cocaine and provided a summary of the published data for the clinical and nonclinical pharmacology, PK, single- and repeated-dose toxicity, reproductive and developmental toxicology, and carcinogenicity potential of cocaine as a part of this NDA.

Prior to submission of the NDA the sponsor was informed of the need to provide full articles if literature was used to support any pertinent clinical pharmacology information. Additionally, an IR was sent to the sponsor stating "For all human PK studies, you cited and summarized from literature, we are unable to locate the bioanalytical validation/performance data and raw PK data in your NDA submission. We recommend you to contact the authors to obtain this information. Due diligence is required to acquire

such information about the studies, otherwise you must provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product." Sponsor claimed that only two literature references discuss PK through intranasal route and were therefore considered primary supportive articles, while the remaining involved other routes of cocaine administration and were considered secondary supportive articles. The sponsor contacted the authors for these relevant articles for raw data and bioanalytical information. The sponsor stated that the raw data was no longer available and the bioanalytical information was adequately described and that both studies were before the first FDA Bioanalytical Method Validation Guidance document publication in the year 2001.

It appears that most of the information is consistent across different publication regardless which analytical methods used. Also, most of the clinical pharmacology claims the sponsor has submitted and will be populated within the label is being derived from the Phase-I studies conducted by the sponsor. The efficacy and safety information is also being derived from the pivotal Phase-III study. Hence the review team has decided that the safety and efficacy of the proposed dosing regimen has been established.

An additional IR was sent to the sponsor stating "It appears that you have not conducted dedicated studies or subpopulation analysis to study the pharmacokinetics of your product in special populations such as hepatically impaired or renal impaired patients. Your literature summary also does not provide sufficient details to guide dosing in these special populations. Summarize the available literature and provide full articles to guide dosing in these patients. Additionally, cite and summarize any articles that discuss any pharmacokinetic differences or lack there off, related to age, sex, or race for cocaine HCl." The sponsor responded with stating that Additional Literature searches were done in hepatic and renal impaired patient populations and no literature was identified to guide dosing in these populations. Sponsor also claimed that due to limited elimination of unchanged drug in Urine (1-5%) patients with significant renal impairment would not be expected to be clinically impacted by the product's elimination from the body. But since metabolism is the main mechanism of elimination for cocaine products, a decreased liver function has a potential to result in increased exposure of cocaine in hepatic impaired subjects. Additionally, there is a lack of dedicated study or literature evidence provided by the sponsor to prove otherwise, a conservative approach to labeling is warranted. Hence, the product will be labeled to not to be used in subjects with hepatic impairment and to use alternative anesthetics if there is no data available. The sponsor would be advised to conduct dedicated hepatic impairment study as even though the lack of this study is not an approvability issues, a conservative recommendation in labeling would be an only path forward. For patients with renal impairment, since renal is not the main elimination pathway for parent drug or active metabolites and the product is not for chronic use, a dedicated renal impairment study may not be required according to the renal impairment guidance. It could be handled by labeling language alone.

For the literature related to age, sex or race, they stated that additional literature searches were done in these patient populations and no literature was identified regarding PK in different ages and race. Various PK literature was identified and summarized for cocaine, and/or its metabolites, which have been evaluated in adult patients or animals for gender differences between males and females (and over the menstrual cycle). No gender differences were identified in literature.

To address the QT prolongation evaluation of the NDA application, the sponsor did not perform a dedicated TQT study but instead decided to do subpopulation analysis using cardiac monitoring in their phase III study. This submission was reviewed by the office's QT-Internal Review Team (IRT) and the QT-IRT deemed that the data submitted was insufficient and that a dedicated tQT study was required to fulfill the QT requirements. The IRT deferred it to the Division to decide whether the study should be conducted pre- or post-approval. Based on the discussion with the clinical team it was determined that the product has effects on heart rate and potential for QT prolongation and since there has been no significant information provided to alleviate these concerns, it amounts to a safety issue and hence a TQT study would be required pre-approval. This was communicated to the sponsor and the sponsor has in turn submitted a TQT protocol to the division for review. The comments on this study protocol were sent to the sponsor on June 13th 2018. If the completed study reports for this study are not submitted within time to allow for a substantial review, then this amounts to an approvability issue and based on the discussions with the clinical team the recommendation would be not to approve the product. For details on the QT-IRTs review on the adequacy of the initially submitted data, refer to the QT-IRT review by Dr. Lars Johannesen, submitted to DARRTS on February 21st 2018. For further details on clinical team's thoughts on the QT data, refer to the clinical review by Dr. Renee Pettit Scott (medical officer). A summary of the two major deficiencies identified in the QT-IRT review are mentioned below.

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.

For decades, cocaine has been used as an anesthetic and vasoconstricting agent by physicians. However, despite this prolonged usage of cocaine hydrochloride as a local anesthetic for a variety of surgical and diagnostic procedures, there was no cocaine product approved by the agency for such indications at the time of submission of this NDA.

Cocaine Hydrochloride (HCl) is an effective local anesthetic which binds to and blocks the voltage-gated sodium channels in the neuronal cell membrane. Although the compound has had a long and varied history of use, it is now primarily used in otolaryngology, as its unique properties (being both a local vasoconstrictor and a topical anesthetic, coupled with rapid onset and short duration of action) make it a suitable agent for otolaryngological procedures

For this NDA, A Pre-NDA meeting was healed on April 18th, 2017. A written response only Pre-IND meeting, and A Type-C guidance meeting were held on 08/07/2013, 01/29/2015 respectively under IND 118527. The clinical development program includes four phase 1 clinical pharmacology studies with TBM formulation (reviewed) and one pivotal phase 3 safety and efficacy study using the TBM formulation.

1.3.1 Clinical Pharmacology Studies:

One clinical pharmacology Study LNT-P6-733 was conducted for this application. The study was conducted with commercial scale formulation and the literature provided by the sponsor all together fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

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.

1.3.2 Clinical Studies:

Sponsor conducted two pivotal Phase 3 clinical studies. The Phase 3 study, Study 2013011 was conducted with commercial scale formulation and serves for assessing the clinical safety and efficacy for this product.

Phase 3 Study (with commercial scale formulation):

- **Study COCA4vs10-001** Phase III, Randomized, Double-blind, Placebo controlled, Multicenter study to compare efficacy to placebo and characterize risk profile of either single topical application of Cocaine HCl 4% at a maximum of 160 mg or Cocaine HCl 10% at a maximum of 400 mg in subjects with need for

diagnostic procedure or surgery on or through the nasal membranes that merits use of anesthesia. The total number of subjects in this study were 159 with 116 getting the drug (59 at 10%, 57 at 4%) and 40 getting placebo.

- **Study COCA4vs10-002** Phase III, Randomized, Double-blind, Placebo controlled, Multicenter study to compare efficacy to placebo and characterize risk profile of either single topical application of Cocaine HCl 4% at a maximum of 160 mg or Cocaine HCl 10% at a maximum of 400 mg in subjects with need for diagnostic procedure or surgery on or through the nasal membranes that merits use of anesthesia. The total number of subjects in this study were 646 with 518 getting the drug (259 at 10%, 259 at 4%) and 128 getting placebo.

Next is summary of the key findings in the Clinical Pharmacology Study.

1.3.3 Pharmacokinetic Single-Dose Study LNT-P6-733 of Cocaine HCl Topical Solution, 4% and 10%:

Study LNT-P6-733 was a single center, randomized, single dose, double blind (investigator- and subject-blinded to Test-1 versus Test-2), laboratory-blinded, 2-period, 6-sequence, crossover design in healthy male and female subjects. The following investigational products and doses were administered: Test-1 (single 160 mg dose, using Cocaine HCl topical solution 4%); Test-2 (single 400 mg dose, using Cocaine HCl topical solution 10%); and placebo (topical solution). Thirty-six subjects entered the study and 31 subjects completed the study. Study subjects were randomized to 1 of 6 treatment sequences. The randomization was stratified by gender to ensure inclusion of both males and females into each of the placebo and non-placebo sequences.
The study treatments (placebo, 160 mg cocaine HCl, and 400 mg cocaine HCl) were administered topically, in the nasal cavity, i.e., four pledgets were treated with 4 mL of the assigned solution (160 mg cocaine HCl 4%, 400 mg cocaine HCl 10%, or placebo). 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. Subjects could leave the clinical site 24 hours following pledget removal. The drug administrations (last pledget placement in each study period) were separated by 7 calendar days.

- Cocaine exhibits plasma peak and total systemic exposure which is comparable to that reported in the medical literature, being approximately dose-proportional, with <35% absorption of cocaine from the pledgets. 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)
- In this study cocaine was rapidly absorbed during the drug exposure period. The mean Cmax for 4% solution was (142.7 ± 11.1 ng/mL) observed shortly after the

time of pledget removal (Tmax of 0.5 hours). The mean Cmax for 10% solution was (433.5 ± 39.1 ng/mL) similarly observed shortly after the time of pledget removal (Tmax of 0.6 hours)

- Plasma concentrations then fell rapidly after pledget removal, with a mean $t_{½}$ of 1.5 hours for the 4% solution and 2 hours for the 10% and cleared from the plasma compartment within 6 hours.
- The mean AUC0-∞ for 4% solution was (239.1 ± 13.5 ng·h/mL). The mean AUC0-∞ for 10% solution was (903.1 ± 92.5 ng·h/mL)
- Overall, the mean peak cocaine concentration in plasma was approximately 3 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3-3.5 times greater for the higher strength. The median time to peak concentration was similar between the two strengths (0.5 hours), as was the half-life (approximately 1.5 to 2 hours). The intra-subject coefficients of variation were 28.4%, 26.6% and 26.4% for C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$, respectively which indicates that the drug products are not highly variable.

1.3.4 Summary of DDI Information:

No *in vitro or in vivo* PK DDI studies were conducted with the topical cocaine solution. *In vivo* cocaine DDI studies were identified in the literature with disulfiram (potential treatment for cocaine dependence). When administered by nasal insufflation, disulfiram increased the plasma concentrations of cocaine by several folds (C_{max} by 2-3-fold AUC by 3-5-fold) and decreased cocaine clearance by 3-4-fold. Considering the several-fold increase for both Cmax and AUC with intranasal route of cocaine with co-administration of disulfiram, Cocaine Hydrochloride Topical Solution should be avoided in patients taking disulfiram and consider using other local anesthetic agents.
Additional possible Pharmacodynamic interactions have been reported in literature with cocaine and sympathomimetics (epinephrine), CNS Stimulants, beta-blockers, Anti-depressants including tricyclic anti-depressants and selective serotonin reuptake inhibitors (SSRIs), Clozapine, MAO inhibitors (isocarboxazid, phenelzine, selegiline and tranylcypromine), ethanol and alpha modifying agents (reserpine).

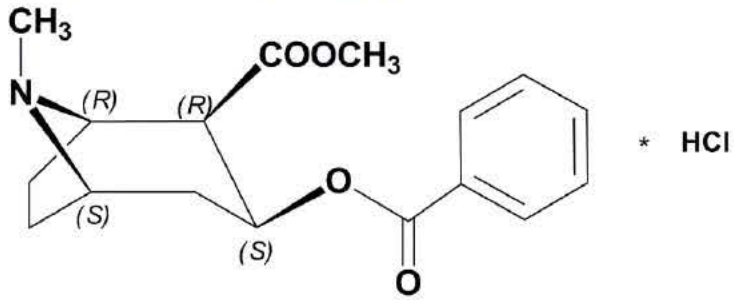
Overall, adequate information has not been provided characterizing the clinical pharmacology aspects of Cocaine Hydrochloride Topical Solution, mainly for QT prolongation evaluation. Unless the Sponsor can submit the result of the proposed tQT study in time, the current available information provided regarding the QT prolongation effects of the drug are not sufficient to make proper risk assessment with the product. The Sponsor will be recommended to conduct a hepatic impairment study, although it is not considered as an approvability issue since it can be handled by labeling recommendation. The edited labeling can be sent to the sponsor with the revised warning language in patient with hepatic impairment and other situations to inform the sponsor.

Appears this way on the original

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Table 1: Physical-Chemical Properties of Cocaine Hydrochloride	
Proprietary Name of Drug Product:	Numbrino™
Non-proprietary Name of Drug Product:	Cocaine Hydrochloride Topical Solution
Non-proprietary Name of Drug Substance:	Cocaine Hydrochloride, USP
Strengths:	4% (40 mg/mL) and 10% ([redacted] (b) (4)
Chemical Name	Ecgonine methyl ester benzoate hydrochloride (1R,2R,3S,5S)-methyl 3-(benzyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride
Structure	
Molecular Formula	$C_{17}H_{21}NO_4 \cdot HCl$
Molecular Weight	339.81

Formulation:
The proposed cocaine hydrochloride topical solution, 40 mg/mL (4%) [redacted] (b) (4) Clear, blue-green solution, no precipitate or sediment evident., packaged in a in [redacted] (b) (4) glass bottles with [redacted] (b) (4) caps. The fill volume is 4 mL.

2.1.2 What is the regulatory history of Cocaine Hydrochloride?

The US Food and Drug Administration (FDA) approved GOPRELTO (cocaine hydrochloride nasal solution, 4%) on December 14th 2017 from Genus Life Sciences for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults. This applicant did not list GOPRELTO as the listed drug for their 505(b)(2) application so they may not rely on the previous findings for GOPRELTO.

2.1.3 What is the composition of the to-be-marketed formulation of Cocaine Hydrochloride Topical Solution, 4% and 10%?

The proposed cocaine hydrochloride topical solution, 40 mg/mL (4%) (b) (4) Clear, blue-green solution, no precipitate or sediment evident., packaged in a in amber USP light resistant glass bottles with (b) (4) caps. The fill volumes are 4 and 10 mL for the 4% (b) (4) Table 2 provides the quantitative composition of the proposed topical solution and the function of each component.

Table 2: Composition of Cocaine Hydrochloride Topical Solution, 4% and 10 %

Component	Quality Standard	Function	40 mg/mL (4%)		(b) (4) (10%)	
			(mg/mL)	(%w/v)	(mg/mL)	(mg/mL)
Cocaine Hydrochloride, USP	USP	Active Ingredient	40	4.0	(b) (4)	(b) (4)
Sodium Benzoate, NF	NF	(b) (4)				
D & C Yellow #10	N/A					
FD & C Green #3	N/A					
Citric Acid Anhydrous, USP	USP					
Purified Water, USP	USP					

NF - National Formulary, USP = United States Pharmacopeia

2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Cocaine HCl is a local anesthetic, which binds to and blocks the voltage-gated sodium channels in the neuronal cell membrane. Cocaine produces potent sympathomimetic effects by increasing norepinephrine concentrations in postsynaptic receptors by inhibiting presynaptic reuptake. Cocaine HCl blocks the initiation or conduction of nerve impulses following local application. When applied topically to mucous membranes, the drug produces a reversible loss of sensation and vasoconstriction. The proposed Cocaine hydrochloride topical solutions (4% and 10%) are indicated for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities.

2.1.5 What are the proposed dosage and route of administration?

The following are the dosage and administration recommendations for Numbrino.

- The recommended dose of NUMBRINO varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia.
- NUMBRINO should be administered by means of cotton or rayon applicator pledgets applied to the nasal mucosa.

- One (1) mL of NUMBRINO should be applied to each pledget. One (1) or two (2) pledgets that are ½" x 3" containing anesthetic solution should be applied topically per nostril, with a maximum of 2 pledgets used per nostril; maximum of 4 pledgets per procedure.
- Pledgets should be retained in the nasal cavity for 20 minutes, with removal occurring immediately prior to the patient's procedure or surgery.
- Pledgets should be removed immediately upon any sign or symptoms of untoward adverse events.

2.1.6 What is the core studies submitted in this NDA?

The core clinical development program includes one phase 1 clinical pharmacology study and two Phase 3 safety and efficacy studies using the final to-be marketed formulation.

- **Study COCA4vs10-001** Phase III, Randomized, Double-blind, Placebo controlled, Multicenter study to compare efficacy to placebo and characterize risk profile of either single topical application of Cocaine HCl 4% at a maximum of 160 mg or Cocaine HCl 10% at a maximum of 400 mg in subjects with need for diagnostic procedure or surgery on or through the nasal membranes that merits use of anesthesia. The total number of subjects in this study were 159 with 116 getting the drug (59 at 10%, 57 at 4%) and 40 getting placebo.
- **Study COCA4vs10-002** Phase III, Randomized, Double-blind, Placebo controlled, Multicenter study to compare efficacy to placebo and characterize risk profile of either single topical application of Cocaine HCl 4% at a maximum of 160 mg or Cocaine HCl 10% at a maximum of 400 mg in subjects with need for diagnostic procedure or surgery on or through the nasal membranes that merits use of anesthesia. The total number of subjects in this study were 646 with 518 getting the drug (259 at 10%, 259 at 4%) and 128 getting placebo.
- **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

2.2 General Clinical Pharmacology

The clinical efficacy studies, COCA4vs10-001 and COCA4vs10-002 for in subjects with need for diagnostic procedure or surgery on or through the nasal membranes that merits use of anesthesia and the clinical pharmacology study LNT-P6-733 form the basis to support the dosing for this NDA along with some information being derived from the literature.

For final assessment of the safety and efficacy findings, see Clinical review by Dr. Renee Petit-Scott (Clinical Reviewer).

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. In Phase 3 study the primary endpoint was anesthetic success immediately after application and sustained throughout the diagnostic procedure or surgery. A subject was considered a treatment success if they met the following for each nostril that received the study drug application:

- Prior to the procedure or surgery, a zero out of ten-pain score on the 11-point pain scale (0 = no pain, 10 = unbearable pain) based on the von Frey filament challenge after one application of the assigned treatment solution (placebo, Cocaine HCl Topical Solution 4% or 10%).
- During the procedure or surgery, no further anesthetic or analgesic treatment was required (only Cocaine HCl Topical Solution 4% and 10% subjects who receive a procedure or surgery).

Otherwise, the subject was considered a treatment failure

2.2.2 What are the general PK characteristics of the drug?

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 3.

Table 3: 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) [redacted], 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).

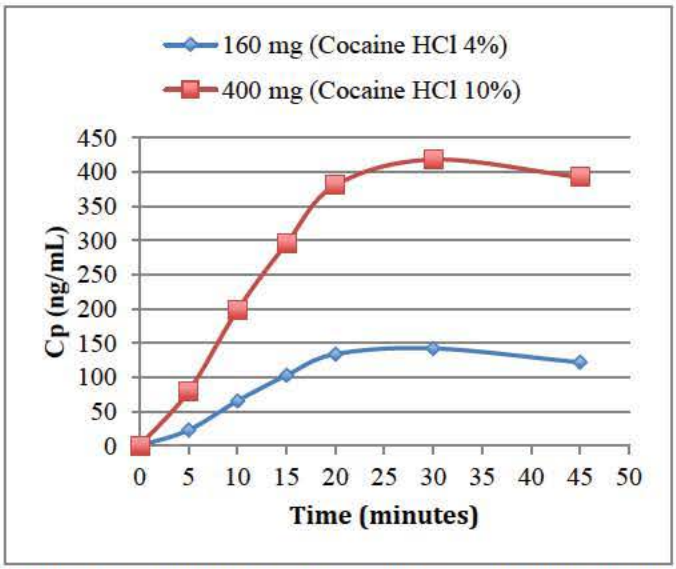


Figure 1: Systemic Plasma Cocaine Concentrations (Time 0 to 45 Minutes) After Cocaine HCl Topical Solution, 4% & 10%, Applied to the Nasal Mucosa by Pledgets (For 20 minutes)

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.

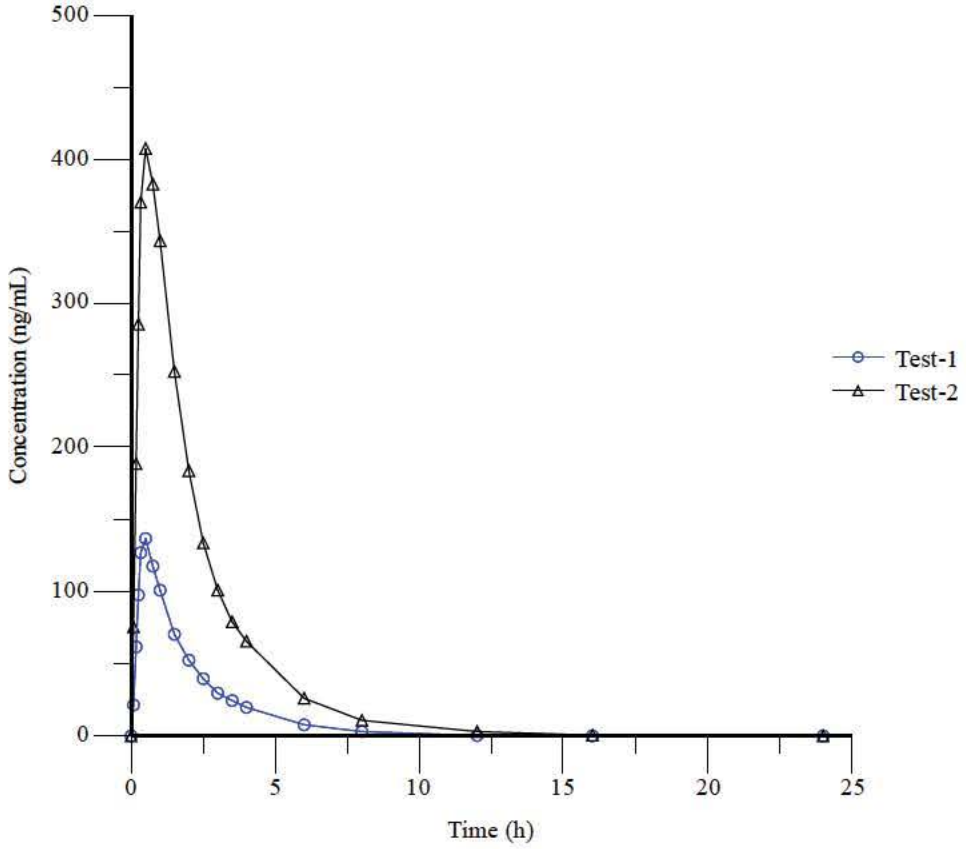


Figure 2: Plasma Logarithmic Profile of the Mean for Cocaine (160 mg Cocaine HCl 4%, Test-1; 400 mg Cocaine HCl 10%, Test-2)

Table 4: 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.

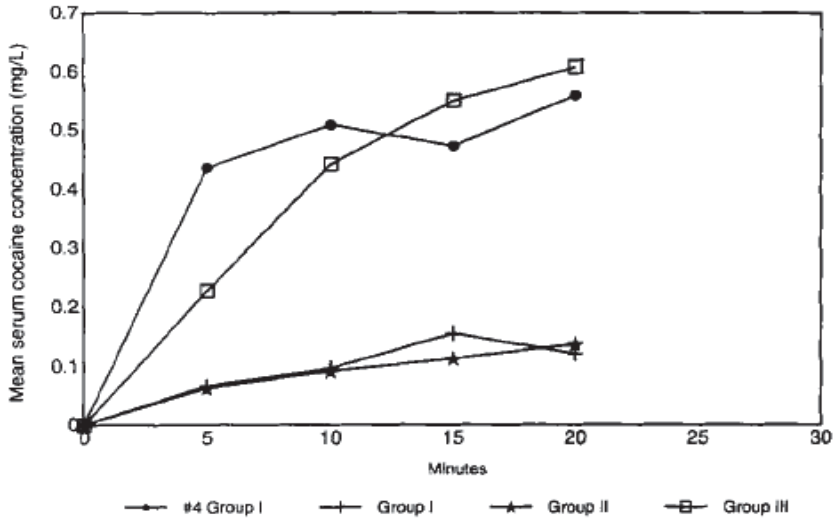


Fig. 1. Graphic comparison of mean serum cocaine concentration (milligrams per kilogram) in Groups I, II, III, and patient 4. Group I measured at 5, 10, 15, and 20 min after application of cocaine pledget.

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].

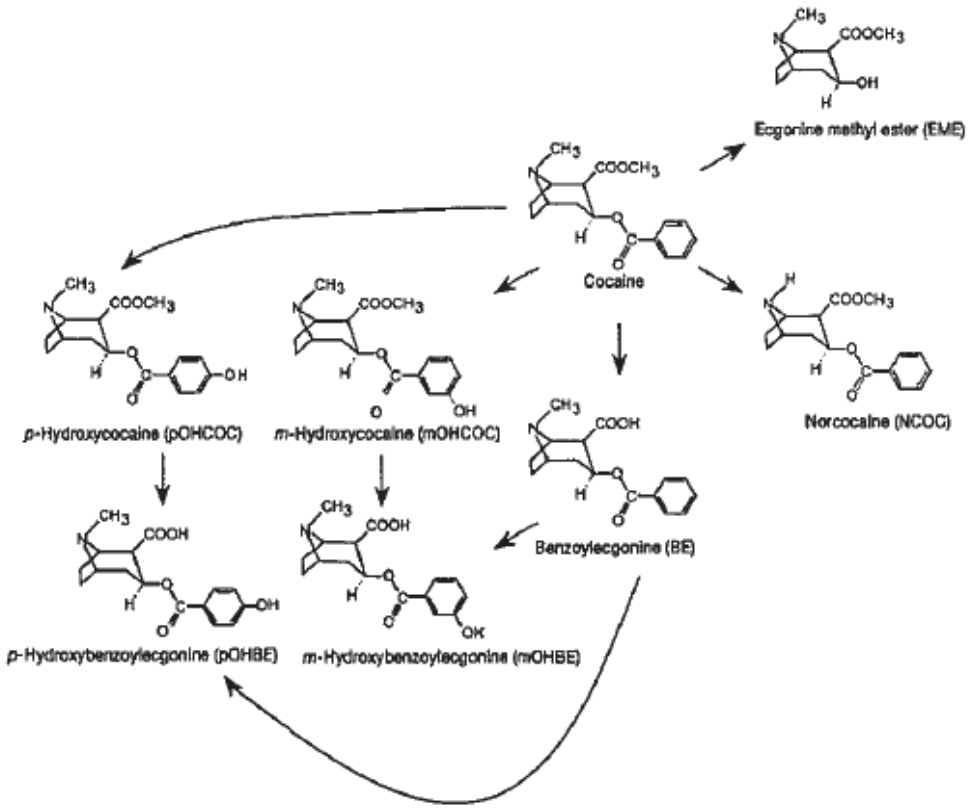


Figure 4: Systemic Metabolic Pathways of Cocaine. Source: Kolbrich, 2006

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 5: 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
C_{max} (ng/mL)	16	300.4 ± 24.6	13	639.1 ± 56.8	15	321.3 ± 18.4	13	614.7 ± 46.0	15	47.4 ± 3.0	14	124.4 ± 18.2
T_{max} (h)	16	0.53 ± 0.05	14	0.63 ± 0.08	15	3.34 ± 0.42	13	4.57 ± 0.70	15	3.07 ± 0.46	14	2.43 ± 0.29
$AUC_{0-\infty}$ (h · ng/mL)	14	863.1 ± 63.2	11	2040.5 ± 124.6	13	5309.4 ± 226.0	11	9736.6 ± 627.3	10	703.1 ± 66.1	9	1535.9 ± 134.1

* Number of participants included in mean calculations.

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 3 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3 to 3.5 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.

2.3 Intrinsic factors

The effect of intrinsic factors (ie, age, gender, body weight and BMI) on the PK of cocaine following topical nasal administration of topical we not studied by the sponsor. Additionally, The Sponsor did not conduct dedicated studies (or subpopulation analyses) regarding the PK profile of a single-dose of its product in special populations, i.e., hepatic or renal impaired patients.

Literature searches were conducted from December 21, 2017 to January 11, 2018. Searches were conducted in multiple databases, including PubMed, CINAHL, EMBASE, and IPA. The following search criteria were used, in humans and animals, as combinations of 'and/or' (but not limited to), for the pharmacokinetics of cocaine HCl (including metabolites) evaluated for gender, age and/or race (human only).

- Age (adult) Assessment – young adult or old adult or geriatric or elderly, and
- Race Assessment – race, white, Caucasian, or black, African-American, or ethnic or ethnicity, and
- Gender Assessment – gender or male or female, and
- Cocaine or cocaine HCl or cocaine metabolites (benzoylecgonine (BE), ecgonine methyl ester (EME), ecgonine (E), or norcocaine (NORC)), and
- Anesthesia, topical or anesthesia, nasal or anesthesia, IV or anesthesia, inhalation or anesthesia) and pharmacokinetics, toxicology or toxicokinetics.

No PK data was discovered for cocaine, or its metabolites, assessed in adult patients or animals over various ages. Pediatrics age categories are under evaluation as part of the

PSP. No PK data was discovered for cocaine, or its metabolites, assessed in humans for various races or ethnicities. Various PK data sets exist for cocaine, and/or its metabolites, which have been evaluated in adult patients or animals for gender differences between males and females (and over the menstrual cycle).

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. The 10% concentration of cocaine HCl is not recommended for use in children due to the increased risk and severity of systemic toxicities [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.

Effect of a Butyrylcholinesterase Deficiency

Cocaine 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.

2.3.1 What is the pediatric plan?

Lannett's planned pediatric studies will be conducted sequentially beginning with the adolescent pediatric cohort (ages 12 to 17 years), (b) (4) [redacted]

Study #1 is an open-label, PK and safety study in 12 to 17 year old adolescent subjects requiring a topical anesthetic to the nasal mucosa prior to an otolaryngology procedure. This study will assess the to-be-marketed 4% cocaine HCl topical solution product and will utilize a flexible dosing regimen using pledgets for the product's application, with the dose selected on the basis of the procedure to be performed and the subjects' body weight (maximum of 3 mg/kg or 160 mgs, whichever is lowest), with dose administration controlled by the number of pledgets inserted into the nasal cavity. (b) (4) [redacted]

2.4 Extrinsic Factors

2.4.1 Pharmacokinetic Drug Interactions:

No in *vitro or in vivo* PK DDI studies were conducted with the topical cocaine solutions and Neither the API (i.e., synthetic cocaine HCl) in the Cocaine HCl Topical Solution, 4% and 10% formulation, nor the pledget administration technique are expected to present any novel or unique drug-drug interactions.
No clinically significant CYP3A4 interactions are expected, or noted in the medical literature, because <10% of cocaine is eliminated via this metabolic route [23, 25].
he 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.

The effects of lovastatin (lipid lowering), thioridazine (antipsychotic) [49], amitriptyline (antidepressant) [50], and procainamide (antiarrhythmic) [50, 51] on the degradation of cocaine in vitro in human serum or human liver homogenates has been examined. These drugs were examined because published studies suggested they could inhibit esterases. In serum, cocaine degradation was negligibly decreased by lovastatin (cocaine concentration decreased by 86% with versus 89% without lovastatin) and inhibited in a concentration-dependent manner by thioridazine (cocaine concentration decreased by 87% without versus 71% and 55% with 5.4 μM and 10.80 μM thioridazine, respectively).
Amitriptyline (1.8 μM) modestly inhibited the degradation of cocaine in human serum (extent of degradation inhibited by 4.2%) whereas procainamide inhibited the degradation of cocaine in both human serum (inhibited by 42.7%) and a human liver homogenate (inhibited by 42.2% to 61.1%).
The authors suggested that thioridazine, amitriptyline, and procainamide may therefore potentially increase the half-life of cocaine in vivo. However, *in vivo* interaction studies were not performed, so it is unknown how clinically relevant the *in vitro* findings may be.
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 [52], which far exceed the observed mean Cmax in humans (142.7 ng/mL and 433.5 ng/mL) after an intranasal dose of 4% topical cocaine solution. Both factors may serve to temper the impact of pseudocholinesterase inhibition on cocaine disposition in vivo.

In vivo cocaine DDI studies were identified in the literature with disulfiram (potential treatment for cocaine dependence). In these studies, cocaine was administered either IV or by nasal insufflation. When administered by nasal insufflation, disulfiram increased the plasma concentrations of cocaine by several fold (C_{max} by 2-3 fold AUC by 3-5 fold) and decreased cocaine clearance by 3-4 fold. [53]. When administered by IV disulfiram

did not impact the C_{max} of cocaine but, increased AUC by around 2 fold [54]. Considering the several fold increase for both Cmax and AUC with intranasal route of cocaine with co-administration of disulfiram, Cocaine Hydrochloride Topical Solution should be avoided in patients taking disulfiram and consider using other local anesthetic agents.

Summary of all publications related to interaction between cocaine and Disulphiram are described below as submitted by the sponsor in response to an IR

Suh et al 2006 reviewed seven clinical trials of subjects who were treated with disulfiram for concomitant alcohol/cocaine dependence (a total of 486 patients). These studies suggest that disulfiram had a direct influence on reducing cocaine use, possibly because disulfiram inhibits dopamine beta hydroxylase, which converts dopamine to noradrenaline and increases the concentration of dopamine. Disulfiram also impedes cocaine metabolism leading to a higher than expected plasma cocaine level. The net effect is very high dopamine levels, which may result in an unpleasant high. The authors concluded that disulfiram could be a viable treatment for cocaine dependence, although toxicity is also possible[55].

Malcolm et al. 2008 found that disulfiram demonstrated efficacy in six randomized clinical trials with 556 subjects (5 of these studies were also included in the Suh et al. 2006 analysis above) for the treatment of cocaine dependence, but that it is rarely used in clinical practice due to safety concerns. In these studies, after eliminating subjects with serious health conditions (cardiovascular, hepatic, and psychiatric disorders), side effects of disulfiram over placebo included headache, fatigue, sleepiness, and anxiety. It appears that disulfiram and its metabolites inhibit microsomal carboxylesterase and plasma cholinesterase (the major cocaine metabolic pathways), and that this is responsible for the increases in cocaine plasma levels. The authors concluded that, when patients are screened for medical and psychiatric stability, disulfiram in a dose of ≤ 250 mg/day has an acceptable side-effect profile for treating cocaine dependence with or without alcohol dependence [56].

McCance-Katz et al. 1998 conducted a randomized, double-blind, placebo-controlled within subject's design to determine whether pretreatment with disulfiram (placebo, 250 mg, or 500 mg/day) altered the response to subsequent intranasal cocaine (placebo, 1 mg/kg, or 2 mg/kg). The subjects (n=7) were actively abusing both alcohol and cocaine. Disulfiram increased plasma cocaine concentrations 3-6 times (with significant increases in both AUC and C_{max}) and significantly increased cocaine-associated cardiovascular responses but did not significantly alter behavioral responses to cocaine. The authors speculated that disulfiram may affect the disposition of cocaine through increased intranasal absorption or reduced metabolic clearance; decreased catecholamines at synaptic nerve endings; reduced vasoconstriction; or inhibition of cocaine metabolism by disulfiram's major metabolite (diethyldithocarbamate)[53].

Hameedi et al. 1995 evaluated the effect of disulfiram pretreatment on the behavioral, physiological, and pharmacological effects of an acute dose of cocaine, using a double-blind, placebo-controlled, within-subject design. The subjects were 6 men and 2 women who were free-base cocaine smokers; 7 of the subjects also abused alcohol. Subjects received disulfiram (250 mg) or placebo; 1 hour later, they received either 2 mg/kg intranasal cocaine or oral placebo. Cocaine and disulfiram together increased nervousness and paranoia in 3 subjects, but the combination did not increase heart rate or blood pressure more than cocaine alone. Disulfiram increased plasma cocaine levels but the increased levels were not associated with paranoia. The authors speculated that disulfiram increased cocaine absorption, but that the mechanism of this effect needs further study[57].

Roache et al. 2011 investigated the potential for cardiac risks among subjects taking alcohol, cocaine, and disulfiram. In a double-blind, placebo-controlled study, 22 cocaine-dependent subjects were randomized to placebo, 250 mg/day or 500 mg/day disulfiram for 7 days. The 500 mg/day dose of disulfiram was eliminated after several subjects had severe hypotensive episodes. On days 4-7 of the study, subjects were given 30 mg intravenous cocaine and 0.4 g/kg ethanol. Disulfiram did not enhance the cardiovascular effects of cocaine and may have reduced the subjective high from cocaine. Hypotension and tachycardia were seen with ethanol alone in disulfiram-treated subjects, but this was not exacerbated by cocaine. The authors concluded that the moderate use of cocaine and ethanol in individuals treated with moderate doses of disulfiram (≤ 250 mg/day) may not be a problematic as previously thought[58].

Baker et al. 2007 conducted a randomized, double-blind, placebo-controlled, within-subject study to examine the interaction of disulfiram with intravenous cocaine. Nine subjects (all actively abusing cocaine; most were abusing/dependent on alcohol) received disulfiram (placebo, 62.5 mg/day, or 250 mg/day); 2 hours later, subjects received cocaine intravenously (placebo, 0.25 mg/kg, or 0.5 mg/kg) over 1 minute. After the administration of disulfiram and 0.25 mg/kg cocaine, plasma cocaine AUC was significantly increased, and cocaine clearance was significantly decreased. Disulfiram also significantly decreased cocaine clearance for the 0.5 mg/kg cocaine dose. Cardiovascular responses to disulfiram plus cocaine were not significantly different from those to cocaine alone. Subjective effects (any high, cocaine high, and rush) were significantly decreased with disulfiram and 0.25 mg/kg cocaine (but not the 0.5 mg/kg dose). The authors concluded that disulfiram decreased cocaine clearance and diminished the cocaine "high" without causing toxicity, indicating it could be a promising treatment for some cocaine dependent individuals [54].

2.4.2 Potential Pharmacodynamic Drug-Drug Interactions:

Sympathomimetics:

Use of other sympathomimetics (epinephrine) may enhance the cardiovascular effects of either or both medications and the risk of adverse effects by increasing the levels of circulating catecholamines [1, 59, 60]. Patients receiving ADHD/stimulants, or anorexiants (amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate, phentermine) should be closely observed and the lowest dose of cocaine applied. Other sympathomimetics, including epinephrine have been described in reports due to their vasoconstrictor effects. Additional cardiovascular adverse events are noted with concomitant use of cocaine and vasoconstrictor agents [61].

CNS Stimulants:

Concurrent use of other CNS stimulation-producing medications with cocaine may result in excessive CNS stimulation, leading to nervousness, irritability, insomnia, or possibly convulsions or cardiac arrhythmias [1].

Beta Blockers:

While beta-blockers are commonly used drugs to address cardiac dysfunction, use in a patient population exposed to cocaine has additional concerns. Cocaine use results in stimulation of alpha-adrenergic receptors, which can lead to tachycardia and significant hypertension [62]. The American Heart Association issued guidance in 2008 that "beta blockers should not be administered acutely in patients with cocaine-associated chest pain and/or MI [myocardial infarction] because of concern about provoking or exacerbating coronary spasm". (Gallelli et al. 2017) and other reports have documented fatal interactions between beta blockers and cocaine[63]. Lange et al. 1990 studied the effects of beta blocker administration on cocaine induced coronary vasoconstriction in 30 patients in a randomized double-blind, placebo-controlled trial. Half of the patients received intranasal saline (n=15) and half received 10% cocaine hydrochloride solution (n=15, 2 mg/kg) [64]. Then patients received saline or propranolol. In patients who received cocaine initially and propranolol in the second portion, significant differences were seen with a decrease in coronary sinus blood flow and an increase in coronary vascular resistance ($p < .05$). The betablocker propranolol was concluded to potentiate the effects of cocaine on coronary vasoconstriction. The authors recommended against using beta blockers with cocaine. Ramoska et al. 1985 presented a case report describing a 53-year-old man who was a chronic intermittent cocaine abuser [65]. After snorting cocaine, he presented to the Emergency Department with drug-mediated hypertension and tachycardia. He was treated with IV propranolol, which caused a decrease in heart rate but a paroxysmal increase in blood pressure. It was necessary to give nitroprusside to control the elevated blood pressure. Cocaine acts through decreasing uptake of secreted catecholamines. In this case, there was unopposed alpha stimulation as a result of beta-2 receptor blockade due to propranolol; the authors suggest using propranolol in cocaine users with caution. Overall, Cocaine Hydrochloride Topical Solution should be avoided in patients taking beta-blockers and consider using other local anesthetic agents.

Anti-Depressants

Anti-depressants including tricyclic anti-depressants and selective serotonin reuptake inhibitors (SSRIs), have been reported to have a potential interaction with cocaine [1, 66]. These anti-depressants are strong inhibitors of neurotransmitter reuptake, specifically serotonin. Serotonin syndrome can result from any combination of drugs that has the net effect of increasing serotonin. There have been case reports of cocaine users who also took SSRIs and developed serotonin syndrome [63]. Tricyclic antidepressants (amitriptyline, imipramine), increase the activity of the Sympathetic Nervous System, which is also increased by administration of cocaine HCl [1].

Kotwal and Cutrona 2015 presented a case report describing a 24-year-old woman who developed serotonin syndrome. The patient had biopolar disorder and PTSD; she intentionally took 4 gm lamotrigine and 80 mg aripiprazole while abusing cocaine. She experienced nausea, dizziness, jitteriness, vertigo, diaphoresis, and tachycardia. Lamotrigine has a weak inhibitory effect at the 5-HT3 receptor, aripiprazole is a partial agonist at the 5-HT1A receptor and an antagonist at the serotonin reuptake transporter, and cocaine increases the release and inhibits the reuptake of serotonin at the synaptic cleft [67].

Malik and Kuman 2012 described a 20-year-old man with depression and anxiety who crushed and snorted multiple tablets of percocet, escitolapram, quetiapine, and clonazepam. He had been a recreational cocaine user for the past year. He developed altered mental status and agitation, as well as tachycardia, elevated body temperature, and neuromuscular hyperreactivity alterations requiring intubation and mechanical ventilation. This was later considered to be serotonin syndrome. The combination of cocaine (which blocks serotonin uptake) and escitolapram (an SSRI) resulted in excessive serotonin levels [68].

Clozapine

A review by Galleli et al. 2017 noted that clozapine could induce cardiovascular toxicity in cocaine users in a dose-dependent manner, probably related to the noradrenergic system [63]. However, the data on this topic are limited, involving very few subjects, so firm conclusions cannot be drawn. Farren et al. 2000 conducted an experimental study in which 8 male cocaine addicts underwent four oral challenges with ascending doses of clozapine (placebo, 12.5, 25, 50 mg) followed two hours later by a 2 mg/kg dose of intranasal cocaine [69]. Clozapine pretreatment increased the peak serum cocaine levels in a dose-dependent manner. It also significantly diminished the subjective positive effects of cocaine. Clozapine caused a near-syncopal episode in one subject. This study was not designed to establish the mechanism underlying the clozapine-cocaine interaction. However, the authors speculated that a metabolic interaction is unlikely. Rather, they suggested that the interaction may be mediated by effects on neurotransmitters (either through raising or potentiating norepinephrine or binding to dopamine receptors).

Hameedi et al. 1996 performed an experimental study in which a male cocaine abuser was given intranasal cocaine (155 mg) two hours after pretreatment with clozapine (12.5 mg orally)[70]. The man experienced near syncope, with hypotension and bradycardia. A possible mechanism is that cocaine is an indirect agonist of both α1 and α2 adrenergic receptors. Clozapine has strong α1 antagonistic properties. Stimulation of α2 receptors in the presence of α1 antagonism by clozapine may lead to a further decrease in blood pressure. If a patient on clozapine uses cocaine, there may be an initial increase in pulse and BP followed by sudden drop in both with symptoms of near syncope. Concomitant use of clozapine and cocaine should be avoided.

Monoamine-Oxidase Inhibitors

Cocaine has been reported to potentiate the effects and toxicity of MAO inhibitors, including isocarboxazid, phenelzine, selegiline, tranylcypromine [71]. Other studies indicated that some MAO inhibitors may not have an interaction. Haberny et al. 1995 studied selegiline and cocaine in 5 cocaine users in a double blind, non-randomized crossover design. Co-administration of oral selegiline and intravenous cocaine in this study did not result in a significant alteration of the profile of effects of cocaine on most physiological and subjective measures[72].

Ethanol

Two reviews of simultaneous cocaine and alcohol use have shown there is an interaction between both substances. Cami et al. 1998 reported that administration of cocaine in subjects who have consumed social doses of ethanol can enhance or antagonize some of the characteristic effects of each drug such as increase euphoria, increase cardiovascular effects of cocaine, and antagonize some of the deleterious effects of alcohol[73]. Plasma levels of cocaine were higher during co-administration with alcohol. The simultaneous administration led to increased toxicity and behavioral changes. Gorelick et al. 1992 also supported this claim [74]. Both papers indicated that simultaneous administration of alcohol and cocaine results in the biosynthesis of a newly active metabolite, cocaethylene, which is biologically active and like cocaine in terms of pharmacology and toxicologic profile. Cocaethylene is metabolized by the same pathway as cocaine, but it is eliminated more slowly than cocaine. The presence of Cocaethylene may contribute to the rise in toxic effects seen during co-administration of alcohol and cocaine.

Alpha-modifying Agents

Postganglionic blocking agents (reserpine) potentiate cocaine-induced sympathetic stimulation; concurrent use may increase the risk of hypertension and cardiac arrhythmias [71].

Halothane Anesthesia

Maintenance of anesthesia with halothane, a volatile anaesthetic agent, may augment any interaction between cocaine and catecholamines by sensitizing the myocardium [1, 75]. However, deeper levels of general anesthesia inhibit adrenal release of catecholamines and may conversely decrease the potential arrhythmogenic effects [1, 76].

2.5 Analytical Section

2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Bio-analytical Facility:

Method Development and Validation: (b) (4)

Sample extraction and Analysis: (b) (4)

Bio-analytical Method:

Plasma

A validated RP-HPLC method using MS/MS detection was employed in determining sample concentrations of cocaine, and its metabolites, benzoylecgonine, ecgonine methyl ester, ecgonine and norcocaine in human plasma. Sample analysis was conducted in accordance with FDA Guidance for Industry, Bioanalytical Method Validation (May 2001) and EMA Guideline on Bioanalytical Method Validation (2009).

Sample pre-treatment required protein precipitation extraction of cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine and norcocaine from 0.200 mL of human plasma. Norcocaine-D3 (for cocaine and norcocaine), benzoylecgonine-D8, ecgonine methyl ester-D3, and ecgonine-D3 reagents were used as the internal standards. Analyte free human plasma, using NaFKO as an anticoagulant, was used to prepare the 10 non-zero calibrants and 6 levels of quality control (QC) samples (stored at -80ºC nominal) containing cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine, and norcocaine.

Calibrant concentrations of cocaine and benzoylecgonine ranged from 2.00 ng/mL to 650.00 ng/mL, with QC samples concentrations of 6.00, 15.00, 38.00, 75.20, 325.00, and 500.00 ng/mL. Calibrant concentrations of ecgonine methyl ester ranged from 1.00

ng/mL to 100.00 ng/mL. Calibrant concentrations of ecgonine ranged from 0.500 ng/mL to 100.00 ng/mL. Calibrant concentrations of norcocaine ranged from 0.150 ng/mL to 100.00 ng/mL. Concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using a weighted (1/x2) linear (y=mx+b) least squares regression analysis for cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine, and norcocaine.

Additional QC levels containing cocaine and benzoylecgonine (15.00 ng/mL and 38.00 ng/mL), ecgonine methyl ester (6.00 ng/mL and 12.00 ng/mL), ecgonine (3.00 ng/mL and 6.00 ng/mL), and norcocaine (1.50 ng/mL and 3.00 ng/mL), were incorporated into the analysis to reflect most expected study sample concentrations. An AB Sciex API 5000 quadrupole mass spectrometer using a Turbo V ion source with electrospray (ES) probe and operating in positive ion mode was used for the detection of cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine, and norcocaine.

The assay for cocaine was linear over the range of 2.00 to 650.00 ng/mL with a lower limit of quantitation of 2.00 ng/mL. Intra-assay accuracy ranged from 96.1% to 99.8% and precision ranged from 3.8% to 4.8%. Inter-assay accuracy ranged from 97.2% to 103.6%, and precision ranged from 3.8% to 13.8%. No specific interference was observed. Extracted samples of cocaine were stable at room temperature for 23.9 hours. Long-term stability of the samples in human plasma covered 85 days at -80ºC nominal. The duration of actual sample storage was 59 days.

Urine

A validated RP-HPLC method using MS/MS detection was employed in determining sample concentrations of cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine, and norcocaine in human urine. The methods, procedures, equipment, internal standards, and processes utilized to determine plasma concentrations were used to determine urine concentrations of cocaine and its metabolites. The one exception being the different theoretical concentrations, which were 5.00 ng/mL to 2500.00 ng/mL for cocaine, 30.00 ng/mL to 15000.00 ng/mL for benzoylecgonine and ecgonine methyl ester, 10.00 ng/mL to 5000.00 ng/mL for ecgonine, and 2.00 ng/mL to 1000.00 ng/mL for norcocaine.
The assay for cocaine was linear over the range of 5.00 to 2500.00 ng/mL with a lower limit of quantitation of 5.00 ng/mL. Intra-assay accuracy ranged from 95.4% to 111.4% and precision ranged from 1.8% to 3.0%. Inter-assay accuracy ranged from 99.2% to 109.0%, and precision ranged from 1.8% to 3.0%. No specific interference was observed. Extracted samples of cocaine were stable at room temperature for 24.0 hours. Long-term stability of the samples in human urine covered 85 days at -80ºC nominal. The duration of actual sample storage was 43 days.

Bio-analytical Validation:

The assay performance for the analytical methods for human plasma for cocaine and its metabolites are presented below (Table 5-9).

Table 6: Assay Performance for Cocaine

Analytical Validation Report	CCN-V6-468	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Cocaine	
Internal standard (IS)	Norcocaine-D3	
Calibration concentrations	2.00 ng/mL to 650.00 ng/mL.	
QC concentrations	2.00 ng/mL, 6.00 ng/mL, 75.20 ng/mL, 325.00 ng/mL and 500.00 ng/mL.	
Specificity	No significant interference observed in the 8 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No significant interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	2.00 ng/mL Between-run accuracy 103.6% Between-run precision 13.8% Within-run accuracy 96.1% Within-run precision 4.0%	
Between-run accuracy	97.2% to 103.6%	
Between-run precision	3.8% to 13.8%	
Within-run accuracy	96.1% to 99.8%	
Within-run precision	3.8% to 4.8%	
Largest batch size	(b) (4)	
Matrix Effect (Calculation of the Matrix Factor (MF)) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.0250 Mean IS MF: 1.0101 Mean IS-Normalized: 1.0148 % C.V.: 1.7	High QC Mean Analyte MF: 1.0031 Mean IS MF: 1.0100 Mean IS-Normalized: 0.9932 % C.V.: 1.3
Dilution integrity	1950.00 ng/mL diluted 5-fold. Accuracy(% nominal): 88.2% Precision: 4.5%	
Recovery of analyte (P.E.Y.)	67.5% to 71.8%	
Recovery of IS (P.E.Y.)	70.3%	
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 25.1 hours for Cocaine in Cold ACN at 400.00 µg/mL at 4°C nominal. % deviation: -2.2%. Confirmed up to 25.1 hours for Cocaine in Cold ACN at 0.20 µg/mL at 4°C nominal. % deviation: 0.7%. Confirmed up to 25.1 hours for Norcocaine-D3 in Cold ACN at 8.00 µg/mL at 4°C nominal. % deviation: 3.7%. Confirmed up to 44.8 hours for Norcocaine-D3 in Cold ACN at 26.00 ng/mL at 4°C nominal. % deviation: -0.6%.	

Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 93 days for Cocaine in Cold ACN at 400.00 µg/mL at -20°C nominal. % deviation: 0.0%. Confirmed up to 93 days for Cocaine in Cold ACN at 0.20 µg/mL at -20°C nominal. % deviation: 1.3%. Confirmed up to 93 days for Norcocaine-D3 in Cold ACN at 8.00 µg/mL at -20°C nominal. % deviation: -3.1%. Confirmed up to 152 days for Norcocaine-D3 in Cold ACN at 26.00 ng/mL at -20°C nominal. % deviation: -5.6%.
Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 23.9 hours at 4°C nominal. Accuracy (% nominal): 96.4% for Low Stability QC and 109.8% for High Stability QC.
Stability in whole blood	Confirmed up to 2.2 hours in an Ice/Water Bath. % deviation: 6.7% for Low QCs and 3.2% for High QCs.
Freeze and thaw stability (Observed change %)	3 cycles. Accuracy (% nominal): 89.7% for Low Stability QC and 103.2% for High Stability QC.
Autosampler storage stability (referred to as processed reconstituted stability) (Observed change %)	Confirmed up to 93.1 hours at 4°C nominal. Accuracy (% nominal): 91.5% for Low Stability QC and 101.3% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 85 days at -80°C nominal. Accuracy (% nominal): 107.1% for Low Stability QC and 98.5% for High Stability QC.
Partial validation	N/AP
Cross validation(s)	N/AP

Table 7: Assay Performance for Benzoylecgonine

Analytical Validation Report	CCN-V6-468	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Benzoylecgonine	
Internal standard (IS)	Benzoylecgonine-D8	
Calibration concentrations	2.00 ng/mL to 650.00 ng/mL.	
QC concentrations	2.00 ng/mL, 6.00 ng/mL, 75.20 ng/mL, 325.00 ng/mL and 500.00 ng/mL.	
Specificity	No significant interference observed in the 8 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	2.00 ng/mL Between-run accuracy 106.1% Between-run precision 3.4% Within-run accuracy 108.1% Within-run precision 2.9%	
Between-run accuracy	100.1% to 106.1%	
Between-run precision	2.5% to 4.3%	
Within-run accuracy	99.3% to 108.1%	
Within-run precision	0.9% to 4.5%	
Largest batch size	(b) (4)	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.0143 Mean IS MF: 0.9984 Mean IS-Normalized: 1.0160 % C.V.: 1.4	High QC Mean Analyte MF: 0.9909 Mean IS MF: 0.9749 Mean IS-Normalized: 1.0186 % C.V.: 2.1
Dilution integrity	1950.00 ng/mL diluted 5-fold. Accuracy (% nominal): 92.2% Precision 3.3%	
Recovery of analyte (P.E.Y.)	76.5% - 79.6%	
Recovery of IS (P.E.Y.)	82.5%	
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 25.1 hours for Benzoylecgonine in Cold MeOH at 400.00 µg/mL at 4°C nominal. % deviation: -1.6%. Confirmed up to 20.6 hours for Benzoylecgonine in Cold ACN at 65.00 µg/mL at 4°C nominal. % deviation: -0.3%. Confirmed up to 25.1 hours for Benzoylecgonine in Cold ACN at 0.20 µg/mL at 4°C nominal. % deviation: 1.8%. Confirmed up to 25.1 hours for Benzoylecgonine-D8 in Cold MeOH at 8.00 µg/mL at 4°C nominal. % deviation: -0.4%.	

	Confirmed up to 44.8 hours for Benzoylecgonine-D8 in Cold ACN at 270.08 ng/mL at 4°C nominal. % deviation: 0.6%.
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 93 days for Benzoylecgonine in Cold MeOH at 400.00 µg/mL at -20°C nominal. % deviation: -3.3%. Confirmed up to 93 days for Benzoylecgonine in Cold ACN at 65.00 µg/mL at -20°C nominal. % deviation: -8.5%. Confirmed up to 93 days for Benzoylecgonine in Cold ACN at 0.20 µg/mL at -20°C nominal. % deviation: -2.7%. Confirmed up to 93 days for Benzoylecgonine-D8 in Cold MeOH at 8.00 µg/mL at -20°C nominal. % deviation: 0.3%. Confirmed up to 152 days for Benzoylecgonine-D8 in Cold ACN at 270.08 ng/mL at -20°C nominal. % deviation: 6.8%.
Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 23.9 hours at 4°C nominal. Accuracy (% nominal): 105.3% for Low Stability QC and 101.2% for High Stability QC.
Stability in whole blood	Confirmed up to 2.2 hours in an Ice/Water Bath. % deviation: 6.1% for Low Stability QC and 1.4% for High Stability QC.
Freeze and thaw stability (Observed change %)	3 cycles. Accuracy (% nominal): 103.4% for Low Stability QC and 103.1% for High Stability QC.
Autosampler storage stability (referred to as processed reconstituted stability) (Observed change %)	Confirmed up to 93.1 hours at 4°C nominal. Accuracy (% nominal): 101.1% for Low Stability QC and 99.8% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 85 days at -80°C nominal. Accuracy (% nominal): 105.9% for Low Stability QC and 107.4% for High Stability QC.
Partial validation	N/AP
Cross validation(s)	N/AP

Table 8: Assay Performance for Ecgonine Methyl Ester

Analytical Validation Report	CCN-V6-468	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Ecgonine Methyl Ester	
Internal standard (IS)	Ecgonine Methyl Ester-D3	
Calibration concentrations	1.00 ng/mL to 100.00 ng/mL.	
QC concentrations	1.00 ng/mL, 3.00 ng/mL, 24.00 ng/mL, 50.00 ng/mL and 75.00 ng/mL.	
Specificity	No significant interference observed in the 8 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	1.00 ng/mL Between-run accuracy 100.5% Between-run precision 3.1% Within-run accuracy 101.7% Within-run precision 2.4%	
Between-run accuracy	97.3% to 100.5%	
Between-run precision	3.1% to 5.6%	
Within-run accuracy	98.4% to 101.7%	
Within-run precision	1.7% to 4.5%	
Largest batch size	(b) (4)	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 0.9943 Mean IS MF: 1.0061 Mean IS-Normalized: 0.9887 % C.V.: 2.9	High QC Mean Analyte MF: 0.9881 Mean IS MF: 1.0099 Mean IS-Normalized: 0.9786 % C.V.: 1.4
Dilution integrity	300.00 ng/mL diluted 5-fold. Accuracy (% nominal): 90.4% Precision 3.3%	
Recovery of analyte (P.E.Y.)	97.7% - 101.2%	
Recovery of IS (P.E.Y.)	104.8%	
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 25.1 hours for Ecgonine Methyl Ester in Cold ACN at 50.00 µg/mL at 4°C nominal. % deviation: -1.5%. Confirmed up to 25.1 hours for Ecgonine Methyl Ester in Cold ACN at 0.10 µg/mL at 4°C nominal. % deviation: -0.6%. Confirmed up to 25.1 hours for Ecgonine Methyl Ester-D3 in Cold ACN at 8.00 µg/mL at 4°C nominal. % deviation: -1.6%. Confirmed up to 44.8 hours for Ecgonine Methyl Ester-D3 in Cold ACN at 104.96 ng/mL at 4°C nominal. % deviation: -1.6%.	

Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 93 days for Ecgonine Methyl Ester in Cold ACN at 50.00 µg/mL at -20°C nominal. % deviation: -1.0%. Confirmed up to 93 days for Ecgonine Methyl Ester in Cold ACN at 0.10 µg/mL at -20°C nominal. % deviation: 0.3%. Confirmed up to 93 days for Ecgonine Methyl Ester-D3 in Cold ACN at 8.00 µg/mL at -20°C nominal. % deviation: -0.4%. Confirmed up to 152 days for Ecgonine Methyl Ester-D3 in Cold ACN at 104.96 ng/mL at -20°C nominal. % deviation: -3.8%.
Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 23.9 hours at 4°C nominal. Accuracy (% nominal): 101.2% for Low Stability QC and 95.9% for High Stability QC.
Stability in whole blood	Confirmed up to 2.2 hours in an Ice/Water Bath. % deviation: 8.0% for Low Stability QC and 2.0% for High Stability QC.
Freeze and thaw stability (Observed change %)	3 cycles. Accuracy (% nominal): 100.6% for Low Stability QC and 98.0% for High Stability QC.
Autosampler storage stability (referred to as processed reconstituted stability) (Observed change %)	Confirmed up to 93.1 hours at 4°C nominal. Accuracy (% nominal): 98.9% for Low Stability QC and 98.1% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 85 days at -80°C nominal. Accuracy (% nominal): 101.3% for Low Stability QC and 103.8% for High Stability QC.
Partial validation	N/AP
Cross validation(s)	N/AP

Table 9: Assay Performance for Ecgonine

Analytical Validation Report	CCN-V6-468	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Ecgonine	
Internal standard (IS)	Ecgonine-D3	
Calibration concentrations	0.500 ng/mL to 100.000 ng/mL.	
QC concentrations	0.500 ng/mL, 1.500 ng/mL, 12.000 ng/mL, 50.000 ng/mL and 75.000 ng/mL.	
Specificity	No significant interference observed in the 8 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	0.500 ng/mL Between-run accuracy 106.5% Between-run precision 4.4% Within-run accuracy 111.2% Within-run precision 2.6%	
Between-run accuracy	98.0% to 106.5%	
Between-run precision	3.1% to 5.5%	
Within-run accuracy	98.0% to 111.2%	
Within-run precision	1.6% to 4.1%	
Largest batch size	(b) (4)	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 0.7416 Mean IS MF: 0.7385 Mean IS-Normalized: 1.0013 % C.V.: 2.5	High QC Mean Analyte MF: 0.7015 Mean IS MF: 0.6907 Mean IS-Normalized: 1.0157 % C.V.: 1.2
Dilution integrity	300.000 ng/mL diluted 5-fold. Accuracy (% nominal): 86.5% Precision 3.4%	
Recovery of analyte (P.E.Y.)	96.4% - 101.1%	
Recovery of IS (P.E.Y.)	103.7%	
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 25.1 hours for Ecgonine in Cold MeOH at 50.00 µg/mL at 4°C nominal. % deviation: -2.5%. Confirmed up to 20.6 hours for Ecgonine in Cold ACN at 10.00 µg/mL at 4°C nominal. % deviation: -1.3%. Confirmed up to 25.1 hours for Ecgonine in Cold ACN at 0.05 µg/mL at 4°C nominal. % deviation: -2.2%. Confirmed up to 25.1 hours for Ecgonine-D3 in Cold MeOH at 8.00 µg/mL at 4°C nominal. % deviation: 2.2%.	

	Confirmed up to 44.8 hours for Ecgonine-D3 in Cold ACN 135.04 ng/mL at 4°C nominal. % deviation: -0.9%.
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 93 days for Ecgonine in Cold MeOH at 50.00 µg/mL at -20°C nominal. % deviation: 0.6%. Confirmed up to 93 days for Ecgonine in Cold ACN at 10.00 µg/mL at -20°C nominal. % deviation: -7.3%. Confirmed up to 93 days for Ecgonine in Cold ACN at 0.05 µg/mL at -20°C nominal. % deviation: -1.0%. Confirmed up to 93 days for Ecgonine-D3 in Cold MeOH at 8.00 µg/mL at -20°C nominal. % deviation: -0.5%. Confirmed up to 152 days for Ecgonine-D3 in Cold ACN at 135.04 ng/mL at -20°C nominal. % deviation: 3.0%.
Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 23.9 hours at 4°C nominal. Accuracy (% nominal): 108.2% for Low Stability QC and 102.3% for High Stability QC.
Stability in whole blood	Confirmed up to 2.2 hours in an Ice/Water Bath. % deviation: 3.3% for Low Stability QC and 1.2% for High Stability QC.
Freeze and thaw stability (Observed change %)	3 cycles. Accuracy (% nominal): 108.1% for Low Stability QC and 104.0% for High Stability QC.
Autosampler storage stability (referred to as processed reconstituted stability) (Observed change %)	Confirmed up to 93.1 hours at 4°C nominal. Accuracy (% nominal): 103.2% for Low Stability QC and 102.6% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 85 days at -80°C nominal. Accuracy (% nominal): 107.3% for Low Stability QC and 105.0% for High Stability QC.
Partial validation	N/AP
Cross validation(s)	N/AP

Table 10: Assay Performance for Norcocaine

Analytical Validation Report	CCN-V6-468	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Norcocaine	
Internal standard (IS)	Norcocaine-D3	
Calibration concentrations	0.150 ng/mL to 100.000 ng/mL.	
QC concentrations	0.150 ng/mL, 0.450 ng/mL, 8.500 ng/mL, 50.000 ng/mL and 75.000 ng/mL.	
Specificity	No significant interference observed in the 8 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	0.150 ng/mL Between-run accuracy 102.4% Between-run precision 5.0% Within-run accuracy 106.9% Within-run precision 3.3%	
Between-run accuracy	96.4% to 102.4%	
Between-run precision	2.8% to 5.1%	
Within-run accuracy	96.8% to 106.9%	
Within-run precision	3.3% to 4.5%	
Largest batch size	(b) (4)	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 0.9994 Mean IS MF: 1.0101 Mean IS-Normalized: 0.9896 % C.V.: 2.3	High QC Mean Analyte MF: 1.0040 Mean IS MF: 1.0100 Mean IS-Normalized: 0.9941 % C.V.: 1.4
Dilution integrity	300.000 ng/mL diluted 5-fold. Accuracy (% nominal): 89.0% Precision 3.7%	
Recovery of analyte (P.E.Y.)	64.7% - 70.0%	
Recovery of IS (P.E.Y.)	70.3%	
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 25.1 hours for Norcocaine in Cold ACN at 50.00 µg/mL at 4°C nominal. % deviation: -2.5%. Confirmed up to 25.1 hours for Norcocaine in Cold ACN at 15.00 ng/mL at 4°C nominal. % deviation: 0.3%.	
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 93 days for Norcocaine in Cold ACN at 50.00 µg/mL at -20°C nominal. % deviation: 0.3%. Confirmed up to 93 days for Norcocaine in Cold ACN at 15.00 ng/mL at -20°C nominal. % deviation: -0.6%.	

Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 23.9 hours at 4°C nominal. Accuracy (% nominal): 99.5% for Low Stability QC and 95.4% for High Stability QC.
Stability in whole blood	Confirmed up to 2.2 hours in an Ice/Water Bath. % deviation: 5.8% for Low Stability QC and 3.1% for High Stability QC.
Freeze and thaw stability (Observed change %)	3 cycles. Accuracy (% nominal): 99.8% for Low Stability QC and 97.9% for High Stability QC.
Autosampler storage stability (referred to as processed reconstituted stability) (Observed change %)	Confirmed up to 93.1 hours at 4°C nominal. Accuracy (% nominal): 95.6% for Low Stability QC and 96.5% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 85 days at -80°C nominal. Accuracy (% nominal): 99.1% for Low Stability QC and 101.2% for High Stability QC.
Partial validation	N/AP
Cross validation(s)	N/AP

3 Detailed Labeling Recommendations

The following labeling comments are proposed by this reviewer. Deletion is shown by ~~Strike-through text~~ and addition is shown by underline text.

Reviewer Comments:

7.2 Cholinesterase Inhibitors

Cocaine has been described in literature to be primarily metabolized and inactivated by non-enzymatic ester hydrolysis and hepatic carboxylesterase, and also by plasma cholinesterase, hepatic carboxylesterase, and CYP3A4. The pharmacokinetics of NUMBRINO in patients with reduced plasma cholinesterase activity has not been studied.

Plasma cholinesterase activity may be decreased by chronic administration of certain monoamine oxidase inhibitors, oral contraceptives, glucocorticoids (b) (4) [redacted] antimyasthenics (neostigmine), cyclophosphamide, and possibly thiotepa, It may also be diminished by administration of irreversible plasma cholinesterase inhibitors such as echothiophate, organophosphate insecticides, and certain antineoplastic agents. Patients with reduced plasma cholinesterase (pseudocholinesterase) activity may have reduced clearance and increased exposure of plasma cocaine after administration of NUMBRINO.

Since cocaine is metabolized by multiple enzymes, the effect of reduced plasma cholinesterase activity on cocaine exposure may be limited. No dosage adjustment of NUMBRINO is needed in patients with reduced plasma cholinesterase. Monitor patients with reduced plasma cholinesterase activity for adverse reactions such as headache, epistaxis, and clinically-relevant increases in heart rate or blood pressure. (b) (4) [redacted]

7.7 Disulfiram

Published literature reported that disulfiram treatment increased plasma cocaine exposure, including both AUC and Cmax, by several folds after acute intranasal cocaine administration. Another literature reported that co-administration of disulfiram increased AUC of plasma cocaine by several folds after intravenous cocaine administration [see Clinical Pharmacology (12.3)].

Avoid using Cocaine Hydrochloride Topical Solution in patients taking disulfiram. Consider using other local anesthesia.

8.6 Hepatic Impairment

(b) (4) [redacted]

According to literature, cocaine is eliminated predominantly by metabolism in humans. Since the clearance of NUMBRINO, 4% and 10%, (b) (4) [redacted] -has not been evaluated in (b) (4) [redacted] hepatic impaired patient populations when compared to patients with normal hepatic function, and since data is not available in literature to guide dosing in these subjects, it is thus not recommended to dose NUMBRINO in patients with hepatic impairment. (b) (4) [redacted]

[see Clinical Pharmacology (12.3)].

8.7 Renal Impairment

According to literature, cocaine is eliminated predominantly by metabolism in humans, with little excreted unchanged in the urine. (b) (4) [redacted] The pharmacokinetics of NUMBRINO in patients with renal impairment has not been studied. Based on information available on the metabolism and excretion of cocaine, dose initiation in patients with renal impairment should follow a conservative approach. (b) (4) [redacted] Monitor patients with renal impairment for adverse reactions such as headache, epistaxis, and clinically-relevant increases in heart rate or blood pressure. *[see Clinical Pharmacology (12.3)].*

8.8 Pseudocholinesterase Deficiency

Pharmacokinetics of NUMBRINO in patients with reduced plasma cholinesterase activity has not been studied.

Genetic abnormalities of plasma cholinesterase (e.g., patients who are heterozygous or homozygous for atypical plasma cholinesterase gene), disease conditions such as malignant tumors, severe liver or kidney disease, decompensated heart disease, infections, burns, anemia, peptic ulcer, or myxedema or other physiological states such as pregnancy may lead to reduced plasma cholinesterase activity. Patients with reduced plasma cholinesterase (pseudocholinesterase) activity may have reduced clearance and increased exposure of plasma cocaine after administration of NUMBRINO.

Since cocaine is metabolized by multiple enzymes, the effect of reduced plasma cholinesterase activity on cocaine exposure may be limited. No dosage adjustment of NUMBRINO is needed in patients with reduced plasma cholinesterase. Monitor patients with reduced plasma cholinesterase activity for adverse reactions such as headache, epistaxis, and clinically-relevant increases in heart rate or blood pressure.

(b) (4)

12.3 Pharmacokinetics

NUMBRINO is an aqueous solution of cocaine hydrochloride for topical use only.

Absorption

Application of NUMBRINO for 20 minutes by pledget administration to the nasal mucosa in healthy adults significantly minimizes the systemic absorption of the applied dose of cocaine hydrochloride . The mean systemic absorption of cocaine from a single 160 mg dose (4 mL, 4%) was 23.44% of the topically applied dose. (b) (4)

(b) (4)

Table 2. Systemic Absorption of NUMBRINO in Healthy Adult Subjects Minimized by Pledget Administration (single nasal dose of 160 mg and 400 mg Cocaine Hydrochloride Topical Solution over 20 minutes)

NUMBRINO Dose (4 mL)	Age Range (yr)	Application Time (min)	Estimated[1] Systemic Absorption	Mean C_{max} (ng/mL)	Median T_{max} (min) C_{max} (ng/mL)
160 mg (4%)	20-40	20	23.44%	142.68 n=33	30 142.7
(b) (4)					

[1]Estimated absorbed dose was calculated by subtracting the residual amount of drug in the pledgets from the administered dose; T_{max} includes time 0 (the start of pledget insertion to pledget removal (20 minutes) to the time C_{max} was observed, i.e. 10 minutes after removal of the pledgets.

Distribution

Cocaine has been described in literature as approximately 84-92% bound to human plasma proteins. Cocaine is extensively distributed to tissues and crosses the blood brain barrier. Its volume of distribution is approximately 2 L/kg. Cocaine crosses the placenta by simple diffusion, and accumulates in the fetus after repeated use.

Metabolism

Cocaine is metabolized by two major hydrolytic pathways. Cocaine (b) (4) is metabolized by hydrolysis to benzoylecgonine (major, but inactive metabolite) by hepatic carboxylesterase-1. Cocaine (b) (4) is also metabolized by hydrolysis to ecgonine methyl ester (major, but inactive metabolite) by plasma butyrylcholinesterase and hepatic carboxylesterase-2.

Cocaine is minimally metabolized by hydrolysis to ecgonine (minor, inactive metabolite) by carboxylesterase-2.

Cocaine (b) (4) is N-demethylated by the CYP3A4 enzyme system to produce the active metabolite, norcocaine. Total systemic exposure of norcocaine is less than one percent that observed with cocaine.

Excretion

Cocaine is excreted almost exclusively in the urine, as metabolites. Only a minor fraction of cocaine is eliminated unchanged in the urine (<5%).

The apparent elimination half-life (mean ± (%CV)) of cocaine following administration of NUMBRINO (by pledgets) was 1.54 hours ((b) (4)) for the 4% concentration. (b) (4) .

Special Populations

Elderly: The pharmacokinetics of NUMBRINO in patients over the age of 65 has not of been studied.

Hepatic Impairment: The pharmacokinetics of NUMBRINO in patients with hepatic impairment has not been studied.

Renal Impairment: The pharmacokinetics of NUMBRINO in patients with renal impairment has not been studied.

Drug-drug Interactions:

Disulfiram

It has been reported in the published literature that disulfiram treatment increased plasma cocaine exposure, including both AUC and C_{max}, by several folds after acute intranasal cocaine administration. Another published literature reported that co-administration of disulfiram increased AUC of plasma cocaine by several folds after intravenous cocaine administration *[see DRUG INTERACTIONS (7.1)]*.

4 Appendices

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4.2 Individual Study Synopses:

Note: Study synopses in this section were extracted from the NDA submission

4.2.1 Study Designs

Phase I, Two-period cross-over, Randomized, Double-blind, Placebo-controlled for the Vaso-constriction Measurement

4.2.2 Study Synopses

Study LNT-P6-733

Table of Contents

1. SYNOPSIS 3
- Title of Study: 3
- Protocol No: 3
- Principal Investigator: 3
- Study Center: 3
- Publication (reference): 3
- Phase of Development: 3
- Clinical Activities: 3
- Objectives: 3
- Methodology: 3
- Number of Subjects (Planned): 4
- Number of Subjects (Analyzed for Plasma): 4
- Number of Subjects (Analyzed for Urine): 4
- Diagnosis and Main Criteria of Inclusion: 4
- Test-1 Product, Strength and Mode of Administration, Batch Number: 5
- Test-2 Product, Strength and Mode of Administration, Batch Number: 5
- Placebo Product, Strength and Mode of Administration, Batch Number: 5
- Treatments administered: 5
- Study Treatments Sequence Planned 5
- Treatment Periods 6
- Duration of Treatment: 6
- Blood Sampling Points: 6
- Urine Sampling: 6
- Criteria for Evaluation 6
- Analytical Methods (Plasma): 6
- Safety: 7
- Mathematical Model and Statistical Methods of Pharmacokinetic Parameters 7
- ANOVA model: 8
- Safety: 8
- Vasoconstriction: 8
- Summary of Vasoconstriction Measurements 9
- Summary – Results and Conclusions 10
- Pharmacokinetic Results: 10
- Safety Results: 10
- Summary of Safety Population 11
- Summary of Absorption of Cocaine from Pledgets 13
- Conclusions: 13
- Pharmacokinetic Conclusions (Plasma): 13

Pharmacokinetic Conclusions \(Urine\): 14
Overall Pharmacokinetic Conclusions: 15
Overall Vasoconstriction Conclusion: 15
Overall Absorption and Residual Cocaine from Pledgets Conclusion: 15
Safety Conclusions:.....15
Pharmacokinetic Parameters – Cocaine in Plasma 16
Summary of Statistical Analysis – Cocaine in Plasma 16
Pharmacokinetic Parameters – Cocaine in Urine.....17
Pharmacokinetic Parameters – Benzoylecgonine in Plasma.....18
Summary of Statistical Analysis – Benzoylecgonine in Plasma.....18
Pharmacokinetic Parameters – Benzoylecgonine in Urine 19
Pharmacokinetic Parameters – Ecgonine Methyl Ester in Plasma.....20
Summary of Statistical Analysis – Ecgonine Methyl Ester in Plasma.....20
Pharmacokinetic Parameters – Ecgonine Methyl Ester in Urine 21
Pharmacokinetic Parameters – Ecgonine in Plasma 22
Summary of Statistical Analysis – Ecgonine in Plasma 22
Pharmacokinetic Parameters – Ecgonine in Urine.....23
Pharmacokinetic Parameters – Norcocaine in Plasma 24
Summary of Statistical Analysis – Norcocaine in Plasma 24
Pharmacokinetic Parameters – Norcocaine in Urine.....25

1. SYNOPSIS

Title of Study:

Single Dose Crossover Bioavailability Study of Cocaine HCl 4% and 10% Solutions Following Topical Applications in the Nasal Cavity in Healthy Male and Female Volunteers

Protocol No:

LNT-P6-733

Principal Investigator:

Eric Sicard, MD, Clinical Principal Investigator (through 2016/06/06)

Benoît Deschamps, MD, Clinical Principal Investigator (after 2016/06/06)

Study Center:

Algorithme Pharma, 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1

Publication (reference):

None

Phase of Development:

Phase I

Clinical Activities:

Study Initiation Date: 2016/09/26

Scheduled Study Completion Date: 2016/11/02

Objectives:

The primary objective of this study was to evaluate the pharmacokinetics of cocaine and its metabolites and to assess the effect of the investigational products on the nasal mucosa following topical application in the nasal cavity of each of the investigational products (Test-1 and Test-2).

The secondary objective of this study was to determine nasal mucosa vasoconstriction, the safety, and the tolerability of Test-1 product compared to Test-2 product in healthy volunteers.

Methodology:

Single center, randomized, single dose, double blind (investigator- and subject-blinded to Test-1 versus Test-2), laboratory-blinded, 2-period, 6-sequence, crossover study.

(b) (4)

Number of Subjects (Planned):

Planned for inclusion: 36
Included: 36
Participation discontinued: 5
Completed the study: 31
Considered in the safety analysis: 36

Number of Subjects (Analyzed for Plasma):

Analyzed:

- 34 for all analytes

Considered in the pharmacokinetic and statistical analysis:

- 33 for cocaine, benzoylecgonine, ecgonine methyl ester and ecgonine
- 30 for the analysis of norcocaine. Subjects (b) (6) and (b) (6) were included in the analysis of norcocaine for the parameters C_{max} and T_{max} only.

Number of Subjects (Analyzed for Urine):

Analyzed:

- 34 for all analytes

Considered in the pharmacokinetic and statistical analysis:

- 34 for cocaine
- 29 for benzoylecgonine, ecgonine methyl ester and ecgonine
- 25 for norcocaine

Diagnosis and Main Criteria of Inclusion:

Subjects were male or female, at least 20 years of age but not older than 40 years. The main inclusion criteria were:

- non- or ex-smokers
- body mass index (BMI) $\geq$18.50 kg/m^2 and <30.00 kg/m^2
- no clinically significant abnormality found in the 12-lead ECG performed at study entry
- negative pregnancy test for female subjects
- healthy according to medical history, complete physical examination (including vital signs and nasal cavity examination) and laboratory tests (general biochemistry, hematology and urinalysis)

(b) (4)

Test-1 Product, Strength and Mode of Administration, Batch Number:

Name: Cocaine HCl topical solution 4% w/v (40 mg/ mL)

Dosage form/Route of administration: Pledget/ Intranasal, 1/2" x 3" pledget, Brand: (b) (4)

Regimen: Single dose of 160 mg

Batch no.: 2016139654

Test-2 Product, Strength and Mode of Administration, Batch Number:

Name: Cocaine HCl topical solution 10% w/v ((b) (4))

Dosage form/Route of administration: Pledget/ Intranasal, 1/2" x 3" pledget, Brand: (b) (4)

Regimen: Single dose of 400 mg

Batch no.: 2015518047

Placebo Product, Strength and Mode of Administration, Batch Number:

Name: Cocaine HCl Topical Solution Placebo

Dosage form/Route of administration: Pledget/ Intranasal, 1/2" x 3" pledget, Brand: (b) (4)

Regimen: Not applicable

Batch no.: 2016119525

Treatments administered:

The study treatments (placebo, Test-1 and Test-2) were administered topically, in the nasal cavity. Study subjects were randomized to 1 of 6 treatment sequences, as follows:

Study Treatments Sequence Planned

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

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

Treatment Periods

	Group A: subjects (b) (6)	Group B: subjects (b) (6)	Group C: subject (b) (6)	Group D: subjects (b) (6)	Group E: subjects (b) (6)	Group F: subjects (b) (6)
Period 1 (Day 1):	2016/09/27	2016/09/28	2016/10/07	2016/10/11	2016/10/19	2016/10/25
Period 2 (Day 8):	2016/10/04	2016/10/05	2016/10/14	2016/10/18	2016/10/26	2016/11/01

Duration of Treatment:

A single cocaine or placebo solution was administered via treated pledgets placed into the nasal cavity in each study period.

For each administration, 4 pledgets were treated with 4 mL of the assigned solution (Test-1, Test-2 or placebo).

- *The 4 mL treatment of the Test-1 (4% cocaine HCl solution) corresponded to a 160 mg dose of cocaine.*
- *The 4 mL treatment of the Test-2 (10% cocaine HCl solution) corresponded to a 400 mg dose of cocaine.*

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.

The drug administrations (pledget placement in each study period) were separated by 7 calendar days.

Drug Accountability:

With regard to drug accountability, there was no observation or indication of any diversion and there were no accountability irregularities.

Blood Sampling Points:

In each study period, 19 blood samples were collected. The first blood sample was collected prior to placing the pledgets into the nasal cavity while the others were collected up to 24 hours following pledget placement.

Urine Sampling:

In each study period, pre-dose urine samples were collected beginning 2 hours prior to placing the pledgets into the nasal cavity. Thereafter, urine samples were collected over 24 hours at four intervals; 0-4, 4-8, 8-12 and 12-24 hours following pledget placement.

Criteria for Evaluation

Analytical Methods (Plasma):

Analyte: Cocaine and benzoylecgonine in human plasma

Method: HPLC with MS/MS detection

(b) (4)

Assay range: 2.00 ng/mL to 650.00 ng/mL

Analyte: Ecgonine Methyl Ester in human plasma

Method: HPLC with MS/MS detection

Assay range: 1.00 ng/mL to 100.00 ng/mL

Analyte: Ecgonine in human plasma

Method: HPLC with MS/MS detection

Assay range: 0.500 ng/mL to 100.000 ng/mL

Analyte: Norcocaine in human plasma

Method: HPLC with MS/MS detection

Assay range: 0.150 ng/mL to 100.000 ng/mL

Analytical Methods (Urine):

Analyte: Cocaine in urine

Method: HPLC with MS/MS detection

Assay range: 5.00 ng/mL to 2500.00 ng/mL

Analyte: Benzoyleconine and ecgonine methyl ester in urine

Method: HPLC with MS/MS detection

Assay range: 30.0 ng/mL to 15000.0 ng/mL

Analyte: Ecgonine in urine

Method: HPLC with MS/MS detection

Assay range: 10.0 ng/mL to 5000.0 ng/mL

Analyte: Norcocaine in urine

Method: HPLC with MS/MS detection

Assay range: 2.00 ng/mL to 1000.00 ng/mL

Safety:

Safety evaluations including vital signs, safety laboratory tests, 12-lead safety ECGs, nasal cavity examination, adverse event (AE) collection, and concomitant medication recording were conducted prior to and during each period. A physical examination was performed at the end of the study (including a nasal cavity examination).

Mathematical Model and Statistical Methods of Pharmacokinetic Parameters

The main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate

area under the curve. The terminal phase estimation was based on maximizing the coefficient of determination.

The pharmacokinetic parameters derived from plasma data in this study were to be: C_{max}, AUC_{0-T} and $AUC_{0-\infty}$. Other parameters including T_{max}, $AUC_{0-T/\infty}$, λ_Z and T_{half} were to be calculated and provided for information purposes only.

The pharmacokinetic parameters derived from urine data in this study were to be: Amount excreted (Ae) and Fraction excreted (fe).

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ was based on ln-transformed data; the T_{max} was rank-transformed.

ANOVA model:

- Fixed factors: study group, treatment received, period at which it is given (nested within study group), sequence in which each treatment is received, study group-by-sequence interaction and study group-by-treatment interaction (whenever statistically significant at the two-sided 5% level).
- Random factors: subject effect (nested within the study group-by-sequence interaction).

Safety:

Safety data (laboratory tests, vital signs, nasal cavity examination findings, physical examination findings, ECG findings, and AEs) and vasoconstriction measurements were summarized with descriptive statistics (N, mean, standard deviation, median, minimum, maximum values) and frequency tables.

Vasoconstriction:

Vasoconstriction was measured by the capillary blood flow (Flux measurement). Capillary blood flow in the nasal mucosa was quantified using the moorVMS-LDF Laser Doppler Flow Monitor at specific time points in each study period.

In order to determine that the Flux measurement was optimal, a secondary supportive measurement, DC, was performed. DC indicates the backscattered laser light intensity; it is used to check the function of the laser Doppler probes. The DC measurement was provided for completeness of the vasoconstriction measurements; however, it is not a vasoconstriction parameter. The DC measurement is an indicator of the instrument performance, which was displayed on the moorVMS-LDF Laser Doppler Flow Monitor and recorded on the CRF. If the probe is not positioned for reading, the DC value is usually high. When the probe is in perfect position, the DC value drops and remains constant between ~50 AU and ~100 AU depending on probe, staff, volunteer, etc. DC values over ~150 AU are usually due to bad positioning of the probe or the probe is not being used (e.g., outside of nostril).

The capillary blood flow was measured by the Flux data. A summary of vasoconstriction measurements is presented next:

Summary of Vasoconstriction Measurements

			Test-1 (N=36)	Test-2 (N=36)	Placebo (N=24)
			Mean (SD)	Mean (SD)	Mean (SD)
Vasoconstriction Measurements	**Visit**	**Time Points**			
		Nasal Cavity			
DC Result (AU)	**Period 1 Day 1**	**pre-dose**			
		left	67.12 (27.586)	56.27 (25.202)	54.72 (18.335)
		right	63.35 (29.377)	51.48 (13.468)	56.08 (19.265)
		5 min			
		left	60.36 (15.927)	57.04 (19.187)	53.30 (19.511)
		right	61.09 (12.707)	68.13 (30.125)	49.98 (23.563)
		10 min			
		left	57.56 (19.531)	63.63 (25.850)	71.61 (34.042)
		right	61.26 (24.415)	57.72 (30.562)	58.96 (20.001)
		20 min			
		left	58.58 (21.012)	64.73 (14.471)	56.75 (23.322)
		right	61.41 (24.327)	58.92 (26.110)	61.34 (21.015)
		30 min			
		left	59.98 (24.180)	56.48 (20.492)	62.13 (23.190)
		right	54.75 (22.274)	57.22 (14.652)	55.35 (17.027)
	Period 2 Day 8	**pre-dose**			
		left	46.58 (18.256)	77.43 (39.556)	62.21 (23.552)
		right	55.75 (19.378)	58.73 (15.550)	62.02 (34.194)
		5 min			
		left	58.86 (26.599)	57.74 (17.586)	63.29 (24.208)
		right	59.98 (23.940)	74.26 (19.644)	65.50 (27.826)
		10 min			
		left	58.34 (17.101)	65.76 (21.748)	65.21 (30.146)
		right	63.61 (19.323)	71.42 (25.864)	63.61 (23.960)
		20 min			
		left	58.88 (19.685)	62.95 (27.627)	61.09 (25.805)
		right	51.92 (17.375)	63.99 (21.583)	68.22 (26.648)
		30 min			
		left	59.19 (19.910)	62.34 (30.474)	62.66 (38.211)
		right	52.09 (14.040)	65.57 (28.420)	60.73 (22.545)
Flux Result (PU)	**Period 1 Day 1**	**pre-dose**			
		left	475.91 (192.621)	400.33 (209.959)	474.33 (156.843)
		right	519.59 (168.943)	456.99 (189.176)	487.71 (212.287)
		5 min			
		left	320.63 (168.753)	355.44 (143.278)	476.38 (205.469)
		right	323.66 (141.231)	423.09 (161.121)	562.46 (176.155)
		10 min			
		left	322.82 (153.748)	365.82 (137.815)	532.45 (118.767)
		right	331.11 (101.303)	432.14 (155.779)	542.53 (171.129)
		20 min			
		left	275.76 (170.847)	379.94 (121.510)	400.69 (162.282)
		right	333.78 (181.898)	369.11 (101.573)	523.15 (199.536)
		30 min			
		left	331.43 (119.529)	343.92 (134.832)	397.75 (192.932)
		right	319.04 (107.853)	384.87 (129.103)	492.10 (151.416)
	Period 2 Day 8	**pre-dose**			
		left	545.82 (209.657)	431.18 (133.034)	420.16 (93.462)
		right	554.05 (203.015)	519.12 (172.394)	467.55 (111.420)
		5 min			
		left	356.28 (199.546)	385.21 (109.217)	522.00 (130.052)
		right	412.21 (241.504)	366.30 (131.591)	506.42 (190.490)

		10 min			
		left	453.12 (199.038)	331.86 (185.502)	599.14 (186.456)
		right	385.32 (170.467)	326.87 (174.569)	509.30 (155.114)
Flux Result (PU)	**Period 2 Day 8**	**20 min**			
		left	390.09 (136.857)	291.39 (125.582)	638.84 (215.111)
		right	373.13 (132.373)	338.13 (141.293)	469.55 (148.933)
		30 min			
		left	414.82 (146.673)	302.79 (130.417)	494.08 (130.360)
		right	399.61 (163.230)	302.53 (132.034)	509.85 (153.496)

Capillary blood flow, as measured by Flux and DC supportive measurement, were statistically analyzed using an Analysis of Variance (ANOVA) model. A separate repeated measures ANOVA model accounting for measurements over time was performed for each comparison of interest (Test-1 *versus* Placebo and Test-2 *versus* Placebo).

The null hypothesis that there is no difference between the test products and placebo was tested at the 5% level of significance.

Summary – Results and Conclusions

Pharmacokinetic Results:

A single center, randomized, single dose, double blind (investigator- and subject-blinded to Test-1 versus Test-2), laboratory-blinded, 2-period, 6-sequence, crossover comparative bioavailability study was conducted on 36 healthy male and female subjects. The rate and extent of absorption of cocaine and its metabolites (benzoylecgonine, ecgonine methyl ester, ecgonine and norcocaine) were measured and compared in both plasma and urine following a single dose of the study treatments. The results from measured data are presented in the summary tables on pages 14 to 23

Safety Results:

A total of 36 subjects entered the study, and were randomized to receive 1 of 6 treatment sequences (6 subjects per sequence). Of the 36 subjects randomized to receive Test-1 (Cocaine HCl topical solution 4%) and Test-2 (Cocaine HCl topical solution 10%), 34 subjects (94%) were dosed with Test-1 and 32 subjects (89%) with Test-2. Twenty-two of the 24 (92%) subjects randomized to receive Placebo (Cocaine HCl Topical Solution Placebo) were dosed.

A summary of the safety population is provided below:

Summary of Safety Population

Subjects dosed N=36						
Period 1						
	Sequence 1 (AB)	Sequence 2 (BA)	Sequence 3 (AD)	Sequence 4 (BC)	Sequence 5 (CB)	Sequence 6 (DA)
Dosed	6	6	6	6	6	6
Dismissed/Withdrew	0	1	0	0	1	0
Completed Period 1	6	5	6	6	5	6
Wash-out						
Dismissed/Withdrew	1	0	2	0	0	0
Period 2						
	Sequence 1 (AB)	Sequence 2 (BA)	Sequence 3 (AD)	Sequence 4 (BC)	Sequence 5 (CB)	Sequence 6 (DA)
Dosed	5	5	4	6	5	6
Dismissed/Withdrew	0	0	0	0	0	0
Completed Period 2	5	5	4	6	5	6
Total subjects completed N=31						
A: Cocaine HCl topical solution 4%, 160 mg dose (Test-1) B: Cocaine HCl topical solution 10%, 400 mg dose (Test-2) C: Placebo topical solution (Placebo) followed by Test-1 D: Placebo topical solution (Placebo) followed by Test-2						

No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. No subject was withdrawn by the investigator for safety reasons.

A total of 280 treatment-emergent adverse events (TEAEs) were reported by 34 (94%) of the 36 subjects who participated in this study. Of these events, 101 occurred after administration of Test-1, 171 after dosing with Test-2, and the other 8 after administration of Placebo. Most TEAEs were considered related (93%) to drug administration.

The TEAEs experienced most commonly in this study were dysgeusia and hypoesthesia. Dysgeusia was reported by 16 subjects (44%) after administration of Test-1, 18 subjects (50%) after administration of Test-2, and 2 subjects (8%) after administration of Placebo. Hypoesthesia was reported by 11 subjects (31%) after administration of Test-1, and 17 subjects (47%) after administration of Test-2. None of the subjects experienced TEAEs related to symptoms of cocaine withdrawal.

The incidence of TEAEs was similar for subjects dosed with Test-1 and Test-2 (81% and 86%, respectively) and higher than the one reported for subjects dosed with Placebo (17%). Drug-related TEAEs were also reported with a similar incidence for subjects dosed with Test-1 and Test-2 (81% and 83%, respectively).

The TEAEs experienced during the study were deemed mild (266/280, 95%), moderate (13/280, 5%), and severe (1/280; 0%) in intensity. Subject (b) (6) experienced somnolence of severe intensity following dosing with Test-2, which was considered related to drug administration and was resolved by the end of the study.

All TEAEs considered related to drug administration were resolved at the end of the study with the exception of 2: nasal congestion which was not recovered and urine leukocyte esterase positive whose outcome was unknown (subject was lost to follow-up; refer to Listing 16.2.7.1).

Overall, the mean values from baseline to end-of-study of general biochemistry, hematology, urinalysis, vital signs, and ECGs were comparable.

All the abnormal clinical laboratory values were marginally higher or lower than their reference ranges and none were considered clinically significant by the investigator. Furthermore, there were no clinically significant abnormalities in the vital signs, ECGs, general and nasal cavity physical examinations of the subjects in this study.

Vasoconstriction results:

Vasoconstriction measurements (capillary blood flow, as measured by Flux, and DC supportive measurement) were statistically analyzed using an Analysis of Variance (ANOVA) model. A separate repeated measures ANOVA model accounting for measurements over time was performed for each comparison of interest (Test-1 *versus* Placebo and Test-2 *versus* Placebo). The null hypothesis that there is no difference between the test products and placebo was tested at the 5% level of significance.

Flux measurement (PU):

Test-1 and Test-2 flux mean values were lower than Placebo; and both Test-1 and Test-2 mean values were statistically significantly different from Placebo (each comparison $p < 0.0001$) suggesting reduced blood flow and increased vasoconstriction compared to Placebo.

DC Measurement (AU):

The DC measurement is provided for completeness, helping to determine when the Flux reading is optimal, and is not a vasoconstriction parameter. The capillary blood flow is measured by the Flux data.

When DC was assessed, Test-1 mean value was found to be statistically significantly different from Placebo (p 0.0075), whereas Test-2 mean value was not (p 0.4209). However, it should be noted that DC measurement, which is an indication only of optimal probe placement, was shown by the data to be appropriate and optimally placed during the study (probe range readings between 50 AU and 100 AU).

Residual cocaine results:

Residual cocaine was extracted from the administered pledgets and resulting concentration data was used to derive values for the percent of total cocaine dose that was absorbed systemically.

A mean of 23.44% of the total administered cocaine dose was absorbed for the Test-1 (4% cocaine solution) (n 34) and a mean of 33.34 % of the total administered cocaine dose was absorbed for the Test-2 (10% cocaine solution) (n 32).

A table summarizing the percentage of administered dose absorbed for each treatment is provided next:

Summary of Absorption of Cocaine from Pledgets

			Test-1 (N=36)	Test-2 (N=36)
Amount of cocaine absorbed (%)	Value	N	34	32
		Mean (SD)	23.44 (8.876)	33.34 (10.710)
		Median	23.91	34.13
		Min, Max	6.9, 36.9	14.3, 67.5
Amount of cocaine remaining on pledgets (%)	Value	N	34	32
		Mean (SD)	76.49 (8.844)	66.54 (10.681)
		Median	76.10	65.75
		Min, Max	63.1, 93.1	32.6, 85.8

Conclusions:

Pharmacokinetic Conclusions (Plasma):

Cocaine:

For cocaine, the mean peak concentration in plasma was approximately 3 times greater for Test 2 (10% solution), with respect to Test 1 (4% solution). Similarly, the total exposure (AUC) was about 3-3.5 times greater for the higher strength.

Median time to peak concentration was similar between the two strengths (0.5 hours), as was the half-life (approximately 1.5 to 2 hours).

The intra-subject coefficients of variation were all below 30%, which indicates that the drug products are not highly variable.

Residual cocaine HCl remaining on the pledgets was analyzed separately and addressed in the clinical study report.

Benzoylecgonine:

For benzoylecgonine, the mean peak concentration in plasma was approximately 3.5 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3-3.3 times greater for the higher strength.

Median time to peak concentration was similar between the two strengths (2.5 hours and 3 hours for the 4% and 10% solutions, respectively), as was the half-life (approximately 7 hours for both strengths).

Ecgonine Methyl Ester:

For ecgonine methyl ester, the mean peak concentration in plasma was approximately 4 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3.5 times greater for the higher strength.

Median time to peak concentration was similar between the two strengths (2.5 hours), as was the half-life (4.3 hours).

Ecgonine:

For ecgonine, the mean peak concentration in plasma was approximately 3 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3-4 times greater for the higher strength.

Median time to peak concentration was 8 hours and 6 hours for the 4% and 10% solutions, respectively. The half-life was similar between the two strengths (approximately 10-10.5 hours).

Norcocaine:

For norcocaine, the mean peak concentration in plasma was approximately 5 times greater for the 10% solution, with respect to the 4% solution. Similarly, the total exposure (AUC) was about 3.5-5 times greater for the higher strength.

Median time to peak concentration was similar between the two strengths (1.5 hours), as was the half-life (about 2.3-2.7 hours).

Several subjects showed non-evaluable exposure (AUC) for norcocaine. This observation is in line with the fact that norcocaine is confirmed as a minor metabolite of cocaine, with only traces present in plasma.

Pharmacokinetic Conclusions (Urine):

Cocaine:

For cocaine, the mean amount excreted in urine (Ae) was approximately 3 times greater for the 10% solution (Test-2), with respect to the 4% solution (Test-1). The fraction excreted for the higher strength was about 19% greater than that for the lower strength.

As only 0.18% and 0.22% fraction excreted (fe) were observed for Test-1 and Test-2, respectively, it is concluded that only a small portion of cocaine is eliminated unchanged in urine.

Benzoylecgonine:

For benzoylecgonine, the mean amount excreted in urine was approximately 3 times greater for the 10% solution, with respect to the 4% solution.

Ecgonine Methyl Ester:

For ecgonine methyl ester, the mean amount excreted in urine was approximately 3.5 times greater for the 10% solution, with respect to the 4% solution.

Ecgonine:

For ecgonine, the mean amount excreted in urine was approximately 3 times greater for the 10% solution, with respect to the 4% solution.

Norcocaine:

For norcocaine, the mean amount excreted in urine was approximately 7.5-8 times greater for the 10% solution, with respect to the 4% solution.

Overall Pharmacokinetic Conclusions:

The nominal dose of Test-2 (10% Solution) was 2.5 times higher than that of Test-1 (4% Solution). The observed relative plasma exposures of Test-2 versus Test-1 for parent cocaine and its metabolites, as measured by C_{max} and/or AUC, during the study ranged between 3 to 4 times higher, except for norcocaine which was 3.5 to 5. These exposure multiples between the higher and the lower doses are on the order of those expected based on the difference in the nominal doses of the test products.

Overall Vasoconstriction Conclusion:

Capillary blood flow was assessed by Flux measurement. Flux statistical analysis showed that Test-1 and Test-2 are significantly different from Placebo (each comparison $p < .0001$), suggesting a reduced blood flow and increased vasoconstriction compared to Placebo.

Overall Absorption and Residual Cocaine from Pledgets Conclusion:

A mean of 23.44% of the total administered cocaine dose was absorbed for the Test-1 (4% cocaine solution) and a mean of 33.34 % of the total administered cocaine dose was absorbed for the Test-2 (10% cocaine solution). These results are in line with published literature which indicates that the expected percentage of the total cocaine dose absorbed systemically from absorption from the nasal mucosa is around 30-35%.

Safety Conclusions:

Overall, the drugs tested were generally safe and relatively well-tolerated even though a high incidence of adverse events possibly related to the study drugs was observed during the study.

Nasal cavity examination via bilateral anterior rhinoscopy was performed at screening and after each study drug application period, and there were no clinically significant findings, which can be interpreted as very good local tolerability.

Pharmacokinetic Parameters – Cocaine in Plasma

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

[a] Median (range)

Summary of Statistical Analysis – Cocaine in Plasma

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Test-1/Test-2 Ratio (%)	90% Confidence Limits (%)	
		Test-1 (n=33)	Test-2 (n=30)		Lower	Upper
C_{max}	28.4	129.48	389.99	33.20	29.41	37.49
AUC_{0-T}	26.6	257.35	869.29	29.61	26.42	33.17
$AUC_{0-\infty}$	26.4	265.22	879.71	30.15	26.93	33.75

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

Pharmacokinetic Parameters – Cocaine in Urine

Parameter (Units)	Test-1 (n=34)		Test-2 (n=31)	
	Mean	**(C.V. %)**	**Mean**	**(C.V. %)**
Ae (mg)	0.293	(72.0)	0.895	(116.7)
fe (%)	0.18	(72.0)	0.22	(116.7)

Pharmacokinetic Parameters – Benzoylecgonine in Plasma

Parameter (Units)	Test-1 (n=33)		Test-2 (n=30)	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	180.52	(53.9)	601.78	(51.8)
ln (C_{max})	5.0585	(10.6)	6.2520	(9.3)
T_{max} (hours)[a]	2.50	(1.00-4.03)	3.00	(1.50-4.00)
AUC_{0-T} (ng·h/mL)	1995.24	(52.7)	6499.52	(45.6)
ln (AUC_{0-T})	7.4761	(6.7)	8.6598	(6.1)
$AUC_{0-\infty}$ (ng·h/mL)	2235.31	(52.5)	7214.53	(44.5)
ln ($AUC_{0-\infty}$)	7.5895	(6.6)	8.7690	(5.9)
$AUC_{0-T/0-\infty}$ (%)	89.40	(5.2)	89.77	(5.0)
λ_Z (hours^{-1})	0.1027	(22.6)	0.1047	(21.6)
T_{half} (hours)	7.06	(21.3)	6.91	(20.6)

[a] Median (range)

Summary of Statistical Analysis – Benzoylecgonine in Plasma

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Test-1/Test-2 Ratio (%)	90% Confidence Limits (%)	
		Test-1 (n=33)	Test-2 (n=30)		Lower	Upper
C_{max}	30.1	156.68	519.64	30.15	26.51	34.30
AUC_{0-T}	28.2	1758.99	5789.74	30.38	26.92	34.29
$AUC_{0-\infty}$	27.9	1970.19	6456.13	30.52	27.08	34.40

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

Pharmacokinetic Parameters – Benzoylecgonine in Urine

Parameter (Units)	Test-1 (n=29)		Test-2 (n=26)	
	Mean	**(C.V. %)**	**Mean**	**(C.V. %)**
Ae (mg)	8.809	(41.0)	28.507	(46.9)

Pharmacokinetic Parameters – Ecgonine Methyl Ester in Plasma

Parameter (Units)	Test-1 (n=33)		Test-2 (n=30)	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	21.29	(54.8)	83.07	(55.6)
ln (C_{max})	2.9292	(17.3)	4.2766	(13.0)
T_{max} (hours)[a]	2.50	(1.00-3.50)	2.50	(1.50-4.00)
AUC_{0-T} (ng·h/mL)	171.79	(54.5)	605.69	(40.2)
ln (AUC_{0-T})	5.0331	(9.2)	6.3271	(6.5)
$AUC_{0-\infty}$ (ng·h/mL)	182.10	(51.8)	620.87	(39.5)
ln ($AUC_{0-\infty}$)	5.1027	(8.6)	6.3554	(6.3)
$AUC_{0-T/0-\infty}$ (%)	93.32	(3.4)	97.22	(1.6)
λ_Z (hours^{-1})	0.1668	(18.8)	0.1665	(19.7)
T_{half} (hours)	4.30	(18.2)	4.30	(17.4)

[a] Median (range)

Summary of Statistical Analysis – Ecgonine Methyl Ester in Plasma

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Test-1/Test-2 Ratio (%)	90% Confidence Limits (%)	
		Test-1 (n=33)	Test-2 (n=30)		Lower	Upper
C_{max}	45.6	18.68	72.13	25.89	21.45	31.26
AUC_{0-T}	39.4	153.31	558.89	27.43	23.27	32.33
$AUC_{0-\infty}$	37.6	164.37	575.07	28.58	24.42	33.45

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

Pharmacokinetic Parameters – Ecgonine Methyl Ester in Urine

Parameter (Units)	Test-1 (n=29)		Test-2 (n=26)	
	Mean	**(C.V. %)**	**Mean**	**(C.V. %)**
Ae (mg)	3.814	(44.3)	12.806	(44.0)

Pharmacokinetic Parameters – Ecgonine in Plasma

Parameter (Units)	Test-1 (n=33) [b]		Test-2 (n=30) [c]	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	3.782	(45.7)	12.190	(43.8)
ln (C_{max})	1.2396	(34.5)	2.3951	(20.4)
T_{max} (hours)[a]	8.00	(4.00-12.00)	6.00	(4.00-8.07)
AUC_{0-T} (ng·h/mL)	63.328	(47.3)	195.126	(42.0)
ln (AUC_{0-T})	4.0533	(10.8)	5.1791	(8.9)
$AUC_{0-\infty}$ (ng·h/mL)	66.278	(31.3)	264.239	(38.7)
ln ($AUC_{0-\infty}$)	4.1496	(7.9)	5.5025	(7.8)
$AUC_{0-T/0-\infty}$ (%)	75.98	(5.7)	75.37	(6.4)
λ_Z (hours^{-1})	0.0692	(10.9)	0.0669	(13.7)
T_{half} (hours)	10.11	(11.0)	10.52	(12.6)

[a] Median (range)
[b] n=7 for $AUC_{0-\infty}$, $AUC_{0-T/0-\infty}$, λ_Z and T_{half}
[c] n=8 for $AUC_{0-\infty}$, $AUC_{0-T/0-\infty}$, λ_Z and T_{half}

Summary of Statistical Analysis – Ecgonine in Plasma

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Test-1/Test-2 Ratio (%)	90% Confidence Limits (%)	
		Test-1 (n=33) [b]	Test-2 (n=30) [c]		Lower	Upper
C_{max}	30.9	3.452	11.021	31.32	27.46	35.72
AUC_{0-T}	28.5	57.592	178.101	32.34	28.63	36.53
$AUC_{0-\infty}$	34.9	53.347	233.442	22.85	11.60	45.00

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$
[b] n 7 for $AUC_{0-\infty}$
[c] n 8 for $AUC_{0-\infty}$

Pharmacokinetic Parameters – Ecgonine in Urine

Parameter (Units)	Test-1 (n=29)		Test-2 (n=26)	
	Mean	**(C.V. %)**	**Mean**	**(C.V. %)**
Ae (mg)	0.424	(43.4)	1.298	(43.4)

Pharmacokinetic Parameters – Norcocaine in Plasma

Parameter (Units)	Test-1 (n=17) [b]		Test-2 (n=28) [c]	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	0.517	(95.7)	2.648	(103.3)
ln (C_{max})	-0.9856	-(77.7)	0.4134	(287.0)
T_{max} (hours)[a]	1.50	(0.75-2.00)	1.50	(1.00-2.50)
AUC_{0-T} (ng·h/mL)	1.797	(115.7)	9.174	(104.2)
ln (AUC_{0-T})	-0.0160	-(7019.0)	1.5421	(88.1)
$AUC_{0-\infty}$ (ng·h/mL)	2.873	(79.1)	10.766	(92.0)
ln ($AUC_{0-\infty}$)	0.7767	(100.1)	1.9516	(50.3)
$AUC_{0-T/0-\infty}$ (%)	66.27	(26.1)	84.73	(15.6)
λ_Z (hours^{-1})	0.3100	(12.2)	0.3191	(38.4)
T_{half} (hours)	2.26	(11.6)	2.69	(61.7)

[a] Median (range)

[b] n 13 for AUC_{0-T}, n 10 for $AUC_{0-\infty}$, $AUC_{0-T/0-\infty}$, λ_Z and T_{half}

[c] n 27 for AUC_{0-T}, n=25 for $AUC_{0-\infty}$, $AUC_{0-T/0-\infty}$, λ_Z and T_{half}

Summary of Statistical Analysis – Norcocaine in Plasma

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Test-1/Test-2 Ratio (%)	90% Confidence Limits (%)	
		Test-1 (n=17) [b]	Test-2 (n=28) [c]		Lower	Upper
C_{max}	54.9	0.260	1.534	16.92	12.29	23.31
AUC_{0-T}	65.4	0.569	4.541	12.52	8.02	19.56
$AUC_{0-\infty}$	58.6	1.377	6.943	19.83	12.60	31.22

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

[b] n 10 for $AUC_{0-\infty}$

[c] n 25 for $AUC_{0-\infty}$

(b) (4)

Pharmacokinetic Parameters – Norcocaine in Urine

Parameter (Units)	Test-1 (n=21)		Test-2 (n=25)	
	Mean	(C.V. %)	Mean	(C.V. %)
Ae (mg)	0.004	(85.5)	0.031	(137.9)

4.3 Sponsor's Proposed Label:

Appears this way on the original

18 pages of draft labeling have been withheld as (b)(4) immediately following this page

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/s/

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