CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209-575
Drug Name:	Topical cocaine 4% and 10%
Indication(s):	Induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults
Applicant:	Cody Laboratories, Inc.
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Statistical Reviewer:	Feng Li, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Medical Officer: Renee Petit-Scott, M.D. Deputy Director: Rigoberto Roca, M.D.
Project Manager:	Shelly Kapoor
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1. EXECUTIVE SUMMARY

Cody Laboratories, Inc. submitted a New Drug Application (NDA) for cocaine hydrochloride (HCl) topical solution 4% and 10%. This application seeks an indication for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults. Two confirmatory phase 3 efficacy studies, study COCA4vs10-001 (study 1) and study COCA4vs10-002 (study 2), were conducted to demonstrate the efficacy of cocaine HCl topical solution 4% and 10% in comparison to placebo.

Both studies were multicenter, randomized, double-blind, placebo-controlled, parallel trials that evaluated the efficacy and safety of two strengths of cocaine HCl topical solution, 4% and 10%, in subjects undergoing diagnostic procedures or surgeries through the accessible mucous membranes of the nasal cavities. Efficacy was to be established if the analgesic success rate of a cocaine arm was statistically greater than that of the placebo arm. For a subject in either cocaine arm, the analgesic success was defined as reporting a pain score of 0 for the Von Frey filament test and not requesting additional analgesic medication for subsequent surgery or diagnostic procedures. For a placebo subject, the analgesic success was defined as reporting a pain score of 0 for the Von Frey filament test. Note that only cocaine subjects who reported a pain score of 0 had the scheduled diagnostic or surgical procedure performed.

The analgesic success rate was analyzed using a Fisher's Exact test. Primary analysis results of the two studies are presented in the table below.

Study	Statistics	Placebo	Cocaine 4%	Cocaine 10%
1	N	40	39	(b) (4)
	Von Frey filament test pain=0	15	21	
	Requested additional analgesics	NA	0	
	Success	15 (37.5%)	21 (54%)	
	p-value*		0.1782	
2	N	127	258	
	Von Frey filament test pain=0	25	186	
	Requested additional analgesics #	NA	2	
	Success	25 (20%)	183 (71%)	
	p-value*		<0.0001	

*: Fisher's exact test. NA: not applicable. #: One subject missing analgesic medication status imputed as failure.

In study 1, (b) (4) Study 2 was conducted to further demonstrate the efficacy of cocaine 4%. In this study, the analgesic success rate of (b) (4) 4% groups was higher than that of placebo with statistical significance.

Based on my review, overall, there was evidence from the two studies to support the analgesic efficacy of cocaine 4% (b) (4) over placebo based on the primary endpoint. However, the following limitations of the study should be noted.

- The surgery or diagnostic procedures conducted in the studies were clinically not considered very painful. It is unclear whether cocaine 4% or 10% would be efficacious for more painful procedures.
- (b) (4) However, almost all subjects treated with either strength successfully went through the studied procedures without additional analgesics.

The review team should consider (b) (4) If the division decides to approve this product, I recommend the indication be limited to the surgery or diagnostic procedures comparable to those performed in the two studies.

2. INTRODUCTION

2.1 Overview

Cocaine as a topical solution has been used as a local anesthetic in surgical procedures involving the nose, throat, larynx and lower respiratory passages. Cocaine HCl 4% topical solution was approved on December 14, 2017 with an indication for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults. Cocaine HCl 10% topical solution is currently available as a marketed unapproved product. In September, 2017, the applicant submitted this NDA for cocaine HCl topical solution 4% and 10% for the same indication. The clinical program was initiated by Lannet under IND 106,499. The IND was transferred to the applicant in September 2016.

The clinical development program for cocaine was discussed between the division and the applicant on several occasions. On December 16, 2011, the division issued a Special Protocol Assessment (SPA) agreement letter on study 1. The applicant later amended the study protocol. On September 24, 2013, the division issued a SPA modification agreement letter on study 1. At the meeting held on January 6, 2015, the interim analyses result of study 1 were discussed and the failure of 4% cocaine solution on the primary endpoint was noted. The division advised the applicant to conduct another clinical study to demonstrate the efficacy of 4% cocaine. On May 14, 2015, a teleconference was held between the division and the applicant to discuss the design and analyses of the second efficacy study. The division issued a SPA agreement letter for study 2 on July 9, 2015 and a subsequent SPA modification agreement letter for the same study on March 21, 2016 after protocol amendments.

2.2 Data Sources

All data were supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR): \\Cdsesub1\evsprod\NDA209575\0001\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets and associated define files were of acceptable quality, and were sufficient for validating study results. However, the applicant did not include subgroup analyses results by sex, age, and race in the initial NDA submission. Moreover, neither the datasets nor the clinical study report (CSR) for the two studies reviewed contained information on when the Von Frey Filament test was administered or the time of treatment unblinding.

The applicant subsequently submitted those subgroup results in response to the division's information request. Regarding the timing of the of Von Frey filament test and treatment unblinding, the applicant stated that this information was not part of the case report form agreed under the SPA and thus not collected for either study. The applicant further stated that "each protocol had specific instructions for the order of applying the test product, performing the von Frey testing, and unblinding the treatment for active versus placebo only, prior to the diagnostic procedure or surgery. Each Investigator was thoroughly trained on the protocol, which contained the sequence of events, during the Site Initiation Visit and monitored throughout the study, and all Investigators agreed to strict compliance with all protocol procedures and requirements."

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1

This was a randomized, double-blind, placebo-controlled, parallel group, single-dose, multicenter study that evaluated the safety and efficacy of cocaine HCl topical solution (4% and 10%) for local anesthesia during diagnostic procedures or surgeries on or through the mucous membranes of the nasal cavities in subjects at least 18 years old. The study enrolled subjects at 10 sites in the United States. The study was conducted in two phases. The first phase of the study was designed to evaluate both the safety and efficacy of cocaine 4% and 10% in comparison to placebo. The second phase of the study was designed to evaluate safety of the two cocaine strengths and did not contain a placebo arm.

Subjects enrolled in phase one were randomized equally to receive either cocaine 4%, cocaine 10% or placebo topical solution. The study medication was dosed as a single application of up to 4 mL of solution placed on, and saturated into, cotton pledgets and inserted into the nose for 20

minutes. Per the applicant, cocaine 4% therapy delivers up to 160 mg of cocaine, while the cocaine 10% therapy delivers up to 400 mg of cocaine depending on the amount of solution used to soak the pledgets. The dose of study medication was determined by the volume of solution dispersed onto the pledget(s). The investigator determined the total dose based on the procedure to be undertaken and the subject's variables, i.e., anesthesia requirement, number and size of the nares requiring anesthesia, and their clinical status.

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

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

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

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

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

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

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

Study 2

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

- A stiffer V on Frey filament was used, 5.88 (60 gram) versus 5.18 (15 gram).
- The Von Frey filament test was performed immediately before anesthesia and right after anesthesia so the subjects could discriminate and experience the sensation of the test without anesthesia.
- Standardized language was used by the investigators to ask the subjects to describe their pain.
- The exact dose administered was determined by the number of pledgets used (1 pledget delivered 1 mL of drug product). In Study 1, the exact dose administered was determined by measuring the amount of solution left in the bottle subtracted from the original bottle.
- Subjects were randomized in a ratio of 2:2:1 to either cocaine 10%, cocaine 4% or placebo. Study 1 utilized equal randomization.

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

3.2.2 Statistical Methodologies

For both studies, the primary efficacy endpoint was analyzed using a two-tailed Fisher's exact test. Efficacy analyses were carried out using the intent-to-treat (ITT) population, defined as all randomized subjects who received study drug. For study 1, the primary efficacy population included the subjects enrolled for the first phase of the study. To control the overall type I error at two-sided level of 0.05, each cocaine strength was compared to placebo at level of 0.0356 based on a multiplicity adjustment method proposed by Zhang et al. (1997). For study 2, the pre-specified primary analysis was to compare cocaine 4% with placebo at level 0.05. As a post-hoc analysis, each cocaine strength was also compared to placebo at level of 0.0356. For both studies, subjects with missing primary efficacy endpoints were marked as analgesic failures.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 1

A total of 156 subjects were randomized and received study drug, 40 to placebo, 57 to cocaine 4%, and 59 to cocaine 10% (Table 1). All subjects completed the study. A total of 120 subjects were randomized in the first phase of the study (efficacy phase). Both cocaine groups randomized 18 subjects for the second phase (safety only phase) of the study.

Table 1: Patient Disposition – Study 1

	Placebo	Cocaine 4%		Cocaine 10%	
Population	**Efficacy**	**Efficacy**	**Total**	**Efficacy**	**Total**
Randomized and treated	**N=40**	**N=39**	**N=57**	(b) (4)	
Completed, n (%)	40 (100%)	39 (100%)	57 (100%)		
Discontinued, n(%)	0	0			

Source: Reviewer and Clinical Study Report, Table 14.1.1

The demographic and baseline characteristics were comparable across treatment groups except that there were more white people in the placebo group versus the cocaine groups (Table 2). About 56% of the 120 subjects in the efficacy population were female and 83% were white, with a mean age of 37.8 years (18 to 70 years).

Table 2: Summary of Demographics and Baseline Characteristics – Study 1

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

Source: Reviewer and Clinical Study Report, Table 14.1.2.; SD: standard deviation

Study 2

A total of 646 subjects were randomized, 128 to placebo, 259 to cocaine 4%, and 259 to cocaine 10% (Table 3). There were seven subjects who were randomized but did not receive treatment, one subject in the placebo group, one subject in the cocaine 4% group, and five subjects in the cocaine 10% group. Only two subjects in the cocaine 4% group discontinued after receiving treatment. The primary efficacy population excluded the seven subjects who did not receive the study treatment.

Table 3: Patient Disposition – Study 2

	Placebo	Cocaine 4%	Cocaine 10%
Randomized	**N=128**	**N=259**	**N=259**
Treated (ITT)	**N=127**	**N=258**	**N=254**
Completed, n (%)	127 (99%)	256 (99%)	254 (98%)
Discontinued, n(%)	1 (1%)	3 (1%)	5 (2%)
before receiving treatment	1 (1%)	1 (0.8%)	5 (2%)
Reason for withdrawal			
Adverse event		1 (0.4%)	
Subject decision		1 (0.4%)	2 (0.8%)
Physician decision	1 (1%)		2 (0.8%)
Other reason		1 (0.4%)	1 (0.4)

Source: Reviewer and Clinical Study Report, Table 14.1.1

The demographic and baseline characteristics were generally similar across treatment groups (Table 4). About 61% of the randomized subjects were female and 81% were white, with a mean age was 37.6 years (range 18 to 76 years).

Table 4: Summary of Demographics and Baseline Characteristics – Study 2

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

Source: Reviewer and Clinical Study Report, Table 14.1.2.; SD: standard deviation

3.2.4 Results and Conclusions

I reproduced the applicant's primary efficacy results for both studies and my results were consistent with the applicant's results.

Study 1

The observed proportion of subjects achieving analgesic success in both cocaine groups was greater than that of the placebo group (Table 5). The proportion of subjects achieving analgesic success was 37.5% in the placebo group, 54% in the cocaine 4% group, and (b) (4) n all cases the primary endpoint was evaluated, i.e. there were no missing data.

The reason for analgesic failure in all treatment groups was failure to achieve a pain score of 0 during the Von Frey filament test. All cocaine subjects who reported a pain score of 0 for the Von Frey filament test proceeded with the scheduled procedure. Additionally, three subjects in the cocaine 4% group and two subjects in the cocaine 10% group reported a pain score greater than 0 but proceeded with the procedure. No subject who underwent a surgery or diagnostic procedure required additional analgesic medication (Table 5).

Table 5: Primary Analysis on Analgesic Success – Study 1

Event	Placebo (N=40)		Cocaine 4% (N=39)		Cocaine 10% (N=41)	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	15 (37.5%)	25 (62.5%)	21 (54%)	18 (46%)	(b) (4)	
Procedure performed	NA	NA	21	3		
Additional Analgesic needed	NA	NA	0	0		
Adequate hemostasis	NA	NA	21	3		
Analgesic success	15 (37.5%)		21 (54%)			
Difference from placebo			16%			
95% CI #			(-6.6%, 37.8%)			
P-value*			0.1782			

Source: Reviewer. *: Fisher's exact test. NA: not applicable; #: 95% exact confidence interval.

The most common diagnostic or surgical procedure was nasal endoscopy (Appendix Table 11). Approximately 60% (34/57) of performed procedures were nasal endoscopy. The second and third most common procedures were nasal laryngoscopy (21%) and nasal pharyngoscopy (16%).

Given that the Von Frey filament test and treatment unblinding could have occurred within the same minute, it is possible that some subjects may have been accidentally unblinded before the

filament test. Since the time of the Von Frey filament test and time of unblinding were not recorded in the study, it could not be confirmed whether unblinding occurred after the test for each subject. If some subjects were accidentally unblinded before the Von Frey filament test, the comparison between placebo and cocaine groups could be biased in favor of cocaine.

On the other hand, based on the protocol, treatment unblinding was only with respect to placebo or cocaine. Whether a cocaine treated subject received the 4% or the 10% strength should remain blinded throughout the procedure. In addition, the 36 subjects enrolled for the safety only phase were not unblinded. Therefore, the comparison between cocaine 4% and 10% was not subject to potential bias due to unblinding.

Including all subjects randomized to cocaine in both phases of the study, the analgesic success rate was (b) (4) in the cocaine 10% group and 61% in the cocaine 4% group (Table 6) (b) (4) mall sample size due to early termination could contribute to the lack of statistical significance. Moreover, this study was not powered to compare the two cocaine treatment arms. Note that all subjects randomized to cocaine (4% and 10%) who underwent a diagnostic or surgical procedure completed the procedure without the need for additional analgesic medication (b) (4) was determined by the differential responses to the Von Frey filament test.

Table 6: Dose Response on Analgesic Success (including phase 2 population) - Study 1

Event	Cocaine 4% (N=57)		Cocaine 10% (N=59)	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	35 (61%)	22 (39%)	(b) (4)	
Procedure performed, n	35	3		
Additional Analgesic needed	0	0		
Adequate hemostasis	35	3		
Analgesic success, n(%)	35 (61%)			
Difference (95% CI #)				
p-value*				

Source: Reviewer. *: Two-sided p-value from Fisher's exact test.
#: 95% exact confidence interval.

(b) (4)

(b) (4)

Study 2

The observed proportion of subjects achieving analgesic success in both cocaine groups was greater than that of the placebo group with statistical significance (Table 7). The proportion of subjects achieving analgesic success was 20% in the placebo group, 71% in the cocaine 4% group, and (b) (4) in the cocaine 10% group. (b) (4) Two subjects in the 4% cocaine group were missing the primary endpoint and imputed as analgesic failures. One subject had missing pain score for the Von Frey filament test and the other had missing analgesic medication status for the procedure.

Table 7: Primary Analysis on Analgesic Success - Study 2

Event	Placebo (N=127)		Cocaine 4% (N=258)		Cocaine 10% (N=254)	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	25 (20%)	102 (80%)	186 (72%)	72 (28%)	(b) (4)	
Procedure performed	NA	NA	185	1		
Additional Analgesic needed	NA	NA	2 (0.8%)	0		
Adequate hemostasis	NA	NA	185	1		
Analgesic success	25 (20%)		183 (71%)			
Difference from placebo			51%			
95% CI #			(42%, 60%)			
P-value*			<0.0001			
Difference from 4%						
95% CI#						
P-value*						

Source: Reviewer. *: Fisher's exact test. NA: not applicable; #: 95% exact confidence interval.

The primary reason for analgesic failure in all groups was failure to achieve a pain score of 0 for the Von Frey filament test (Table 7). All cocaine subjects who reported a pain score of 0 for the Von Frey filament test proceeded with the scheduled procedure. Additionally, one subject in each cocaine group reported a pain score greater than 0 but proceeded with the procedure. Except for two subjects in the cocaine 4% group and one subject in the cocaine 10% group, no subjects requested additional analgesics during the procedure.

The most common diagnostic or surgical procedure was nasal endoscopy (Appendix Table 12). Approximately 62% (247/398) of the performed procedures were nasal endoscopy. The next most common procedures were transnasal pharyngoscopy (24%).

As in study 1, treatment unblinding was only supposed to reveal whether a subject received a placebo or cocaine. Whether a cocaine treated subject received the 4% or the 10% strength should remain blinded throughout the procedure. (b) (4)

To explore the potential impact of unblinding, as in Study 1, I conducted a tipping point analysis. My tipping point analysis revealed that, to overturn the statistical significance, one needs to assume that more than 44% of the cocaine 4% group and more than 56% of the cocaine 10% had been accidentally unblinded before the Von Frey filament test. This seems unlikely (Appendix Figure 2).

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Renee Petit-Scott Based on Dr. Petit-Scott's review, the system organ class (SOC) with the largest number of reported treatment emergent adverse events (TEAE) was vascular disorders, and hypertension was the most frequently reported TEAE. The reported incidence of hypertension was numerically higher for subjects in the 10% cocaine treatment group, compared to subjects in the 4% cocaine treatment group and subjects in the placebo group. The cardiac disorders SOC had the second largest number of reported TEAEs, and included tachycardia, sinus tachycardia, and palpitations. Subjects treated with 10% cocaine consistently experienced a larger number of tachycardia, sinus tachycardia, and palpitation TEAEs compared to subjects treated with either 4% cocaine or placebo solutions. Please refer to Dr. Petit-Scott's review for more detailed information.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Age and Race

A summary of the analgesic success rate by sex, race and age are presented in Tables 8 and 9 for each study. Cocaine treated subjects had consistently higher analgesic success rates than placebo treated subjects in all subgroups. Note that the "other" race category included the races other than white and black.

Table 8: Analgesic Success Rates by Sex, Race and Age – Study 1

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

Source: Reviewer.

Table 9: Analgesic Success Rates by Sex, Race and Age – Study 2

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

Source: Reviewer.

4.2 Other Special/Subgroup Populations

No other special subgroup analyses were conducted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

One statistical issue in both studies was the uncertainty about the time of treatment unblinding as the unblinding time was not recorded in either study. If some subjects were unblinded before the Von Frey filament test was administered, knowing treatment assignment would likely affect the reported pain scores and potentially inflate the observed treatment effect. To explore the impact of this potential unblinding on the statistical significance of the comparison between cocaine and placebo, I performed a tipping point analysis for both studies.

My tipping analysis for study 1 showed that the statistical significance of cocaine 10% in comparison to placebo would be lost if the percentage of unblinding was more than 17%. My tipping point analysis for study 2 revealed that, to overturn the statistical significance in study 2, one needs to assume that more than 44% of the cocaine 4% group and more than 56% of the cocaine 10% had been accidentally unblinded before the Von Frey filament test, which seems unlikely.

Overall, the results from the tipping point analyses were considered supportive of the primary analysis. Thus, I am not overly concerned about the uncertainty of the unblinding time.

Another issue identified was (b) (4)

5.2 Collective Evidence

Overall, I think there was evidence from these two efficacy studies that both cocaine 4% and 10% were better than placebo in terms of the analgesic success rate as defined in the protocols. However, it should be noted that the diagnostic or surgery procedures performed in the two studies were mostly non-invasive procedures that are not considered very painful. Thus, it is unclear whether cocaine would work effectively for other more aggressive procedures or surgeries. (b) (4)

5.3 Conclusions and Recommendations

The two studies have provided evidence that cocaine 10% and 4% were better than placebo in terms of the analgesic success rate as defined in the protocols. However, there were limitations of the study that should be noted. The surgery or diagnostic procedures conducted in the studies were clinically considered not very painful. (b) (4)

(b) (4)

If this product is approved, I recommend that the indication be limited to the type of procedures like those conducted in the study.

5.4 Labeling Recommendations

The proposed labeling Section 14 contains the following:

(b) (4)

(b) (4)

The review of the labeling is still ongoing while this review is finalized. I have the following recommendations for consideration:

Study 1

- Remove p-values from the texts.
  It is sufficient to state that the treatment difference is statistically significant. Smaller p-values do not necessarily imply the presence of larger or more important effects. The medical division has consistently advised sponsors not to put p-values in labeling in the past.

- The sentence "(b) (4)." should be removed as not all randomized patients had surgeries performed.

- For study 1, based on the dataset, about 55.8% of the 120 subjects in the efficacy population were female and 83.3% were white, with a mean age of 37.8 years (18 to 70 years). Note that the applicant's corresponding numbers are based on the population in both phases of the study.

- The sentence (b) (4) should be removed as it is uncertain these were the only causes.

- Add the following sentences to the fourth paragraph: “The reason for analgesic failure in all treatment groups was failure to achieve a pain score of 0 for the Von Frey filament test. None subject who had surgery or diagnostic procedure performed requested additional analgesic medications. The most common diagnostic or surgical procedure was nasal endoscopy. Approximately 60% (34/57) of the performed procedures were nasal endoscopy. The second and third most common procedures were nasal laryngoscopy (21%) and nasal pharyngoscopy (16%).”

Study 2

- Remove p-values from the texts.

- Add the following sentences: “The primary reason for analgesic failure in all groups was failure to achieve a pain score of 0 for the Von Frey filament test. Two subjects in the cocaine 4% group and one subject in the cocaine 10% group reported pain score of 0 but requested additional analgesics for completing the scheduled surgery or procedure. All other subjects who had the surgery or procedure performed completed it without requesting additional analgesics. The most common diagnostic or surgical procedure was nasal endoscopy. Approximately 62% (247/398) of the performed procedures were nasal endoscopy. The next most common procedures were transnasal pharyngoscopy (24%).”

Appendix

Table 10: Summary of Performed Procedure - Study 1

Event	Cocaine 4% (N=39)	Cocaine 10% (N=41)	Total
Procedure performed	24	33	57
Procedure type			
Ear, nose throat exam	1	0	1 (2%) *
Laryngoscopy	3	9	12 (21%)
Nasal polypectomy	1	0	1 (2%)
Nasoendoscopy	13	21	34 (60%)
Pharyngoscopy	6	3	9 (16%)

Source: Reviewer. *: percentages are based on number of subjects who had procedure performed

Table 11: Summary of Performed Procedure - Study 2

Event	Cocaine 4% (N=258)	Cocaine 10% (N=254)	Total
Procedure performed	186	212	398
Procedure type			
Biopsy	1	0	1*(0.25%)
Epistaxis control and treatment	1	0	1 (0.25%)
Nasal chemical cautery	0	1	1 (0.25%)
Nasal endoscopy	118	129	247 (62%)
Nasal polyp removal	0	1	1 (0.25%)
Office-based sinonasal procedure	1	0	1 (0.25%)
Postoperative care (debridement of other minor procedure)	9	10	19 (5%)
Sinus endoscopy	11	13	24 (6%)
Sinus ostial dilation	0	2	2 (0.5%)
Transnasal laryngoscope	45	51	96 (24%)
Transnasal pharyngoscope	0	4	4 (1%)
Turbinate reduction using radiofrequency, cryogenic or other technique	0	1	1 (0.25%)

Source: Reviewer. *: percentages are based on number of subjects who had procedure performed

Figure 1: Tipping point analysis on percentage of unblinding for Study 1

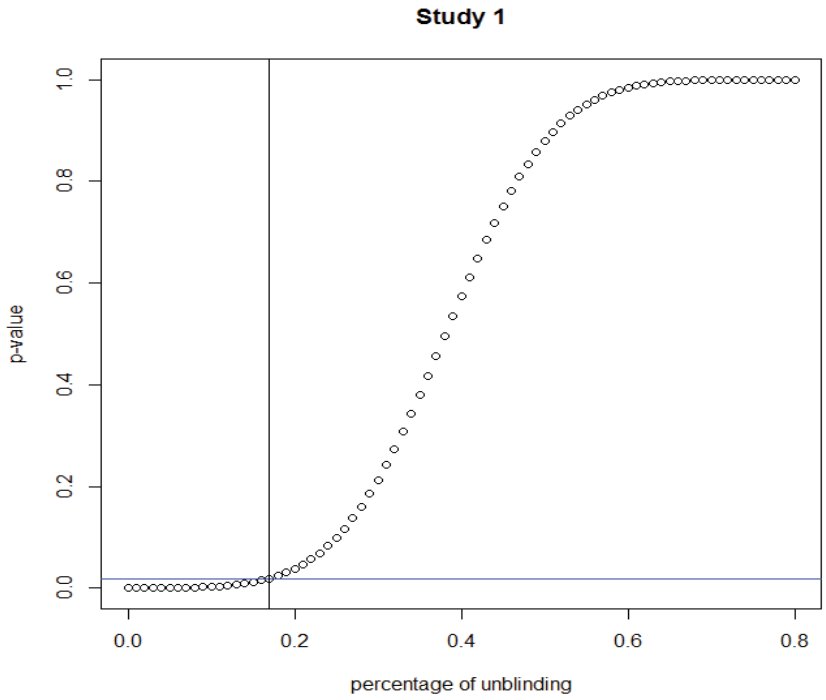
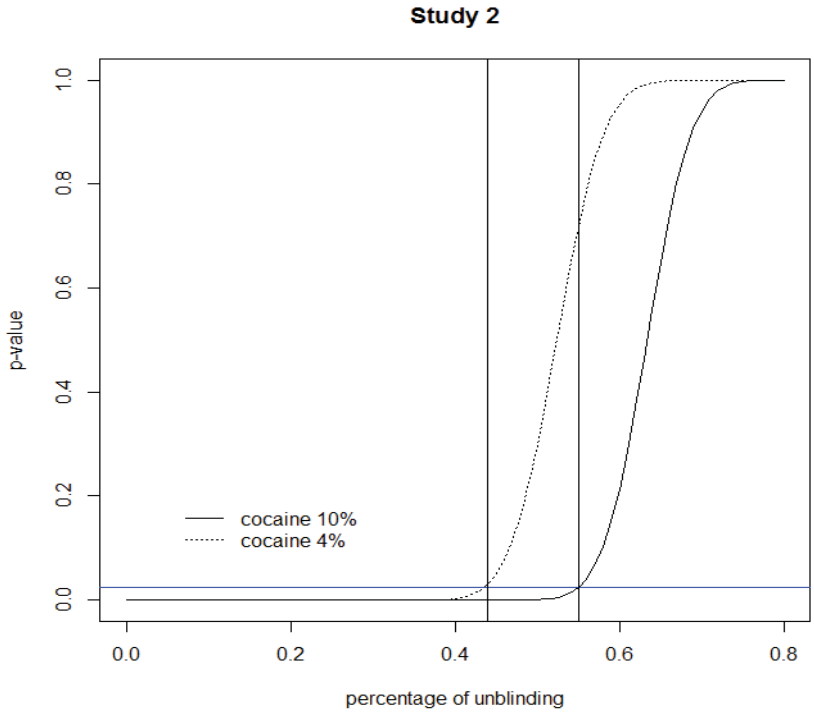


Figure 2: Tipping point analysis on percentage of unblinding for Study 2



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

/s/

FENG LI
06/18/2018

DAVID M PETULLO
06/18/2018
I concur.