CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209-963
Drug Name:	Topical cocaine (4%)
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:	Genus Lifesciences, Inc.
Date(s):	Received: November 23, 2016 PDUFA: December 23, 2017
Review Priority:	Standard
Biometrics Division:	II
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:	Diana Walker
Keywords:	NDA review, Clinical Studies

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1. EXECUTIVE SUMMARY

Genus Lifesciences, Inc. submitted a New Drug Application (NDA) for cocaine hydrochloride (HCl) topical solution 4%. 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. A single confirmatory phase 3 efficacy study, 2013011, was conducted to demonstrate the efficacy of cocaine HCl topical solution 4 % in comparison to placebo.

Study 2013011 was a multicenter, randomized, double-blind, placebo-controlled, parallel study that evaluated the efficacy and safety of two strengths of cocaine HCl topical solution, 4% and 8%, in subjects undergoing diagnostic procedures and surgeries through the accessible mucous membranes of the nasal cavities. However, the applicant only intends to market cocaine 4% strength. Efficacy was to be established if the analgesic success rate for the cocaine 4% arm was statistically greater than the placebo arm. Analgesic success was defined as reporting a pain score of 0 for the Von Frey filament test and did not request additional analgesic medication for subsequent surgery or diagnostic procedures.

Based on my review of study 2013011, there is evidence to support the analgesic efficacy of cocaine 4% over placebo based on the primary endpoint. Both the analgesic success rates of cocaine 4% and 8% were higher than that of placebo and reached statistical significance. The review team should consider overall benefit-risk profile while making approval decision. 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 this study.

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 without official approval from the agency. The applicant submitted a NDA for cocaine HCl topical solution 4% for use as a local anesthetic for diagnostic and surgical procedures on or through the mucous membranes of the nasal cavities. The clinical program for the cocaine solution was initiated (b) (4) under IND 118,527. The IND was transferred to the applicant in September 2016.

The clinical development program for cocaine was discussed with the division on several occasions. In an advice letter dated August 20, 2013, the division stated that a single clinical trial supported by a review of all available clinical literature may support approval. The division further stated that data from well-designed, double-blinded, randomized, controlled clinical trials carry the most weight in determinations of safety and efficacy. The applicant subsequently

proposed the phase 3 efficacy study (2013011) to support the efficacy and safety of cocaine HCl (4% or 8% topical solution). In the advice letter dated November 5, 2014, the division informed the applicant that the proposed single comparison between the combined cocaine groups (4% and 8%) and placebo in study 2013011 would not demonstrate the efficacy of the cocaine 4% strength and that the sample size and statistical analysis plan should be revised to test the 4% strength against placebo. At the pre-NDA meeting held on July 14, 2015, the division further stated that since the applicant only intends to seek approval of the 4% strength, the comparison between the cocaine 8% strength and placebo would be considered exploratory. Additionally, the division requested the sponsor report the time of unblinding for each subject in the study report.

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\NDA209963\0014\m5\datasets\2013011. An error due to a programming issue was identified in the originally submitted datasets. The datasets were then resubmitted after correction.

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, a critical error was identified during a clinical field inspection. The agency's inspector found that the treatment assignments of the cocaine 4% and 8% groups had been switched in the clinical study report. The subjects with treatment assignments indicated as cocaine 4% actually received cocaine 8% and subjects with treatment assignments indicated as cocaine 8% actually received cocaine 4%. On April 6, 2017, a teleconference between the division and the applicant was held to discuss this matter. The applicant subsequently submitted an explanation of this event along with supporting documents. According to the applicant, a definition error occurred during the creation of the database and the 4% and 8% group assignments had been transposed in the database. All the datasets and the Clinical Study Report (CSR) were then corrected and re-submitted to the division on May 1, 2017. Note that when the source is the CSR, it refers to the corrected CSR in this review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 2013011 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% or

8%) 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 consisted of a screening period within 14 days of a diagnostic procedure or surgery, a treatment period on the day of the diagnostic procedure or surgery (Day 1), and a follow-up visit (Day 8). The study was conducted at 17 sites in the United States.

Eligible subjects were randomized in a 3:3:1 ratio to receive cocaine 4%, cocaine 8% or placebo topical solution. The study drug was administered by placing medication-soaked cotton pledgets (two per side) into each of the nasal cavity and up against the septum for 20 minutes. The nasal mucous membranes were then tested for local analgesia using a Von Frey filament Test. The investigator/clinician chose the nostril for the pre-procedural testing based upon the scheduled procedure. 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 the worst pain.

After the Von Frey filament testing for analgesia, the study blind was broken relative to placebo versus cocaine, that is, subjects in the cocaine arms did not know if they had received 4% or 8% cocaine. Subjects who received placebo were given the opportunity to receive an active anesthetic before undergoing the surgical or diagnostic procedure or to proceed without one. Cocaine-treated subjects proceeded with the diagnostic procedure or surgery. According to the protocol, cocaine-treated subjects who reported a pain score greater than 0 may continue with the diagnostic procedure or surgery or wait for no less than 24 hours if additional medication is required, based on the investigator's clinical judgment. However, based on the study report, no subject waited more than 24 hours even if additional medication was needed.

The primary efficacy endpoint was defined as the analgesic success immediately after study drug application and sustained analgesia through the diagnostic procedure or surgery. According to the CSR, a subject was considered 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 medication (with the exception of antibiotics or cardiac medications) during the diagnostic procedure or surgery.

Subjects who had a VNRS score > 0 or who needed additional medication during the procedure were considered treatment failures.

However, this was different from the original definition of analgesic success specified in the protocol and Statistical Analysis Plan (SAP). According to the final protocol and SAP, a placebo subject would be considered a treatment success if the subject had a 0 pain score based on the Von Frey filament challenge regardless whether further medication was needed for the diagnostic procedure or surgery. The division requested the applicant clarify this discrepancy. The applicant acknowledged this inconsistency and conducted a sensitivity analysis based on the

original definition of the primary endpoint (see Section 3.2.4). The study conclusion remained the same regardless of the definition used for analgesic success.

3.2.2 Statistical Methodologies

The primary efficacy endpoint was analyzed using a two-tailed Fisher's exact test. Efficacy analyses were carried out using the modified intent-to-treat (mITT) population, defined as all randomized patients who received study drug. The primary efficacy comparison was cocaine 4% versus placebo. The comparison between cocaine 8% and placebo was considered exploratory.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 648 subjects were randomized and received study drug, 95 to placebo, 275 to cocaine 8%, and 278 to cocaine 4%. All of the subjects completed the study, except for one subject in the cocaine 4% group who was lost to follow-up. The demographic and baseline characteristics were comparable across treatment groups (Table 2). The majority of the patients were female (60%) and white (79%).

Table 1: Patient Disposition

Population	Placebo	Cocaine 4%	Cocaine 8%
All randomized (ITT)	**N=95**	**N=278**	**N=275**
Completed, n (%)*	95 (100%)	277 (99.8%)	275 (100%)
Discontinued, n(%)*	0	1 (0.2%)	0
Lost to follow-up	0	1 (0.2%)	0

Source: Reviewer and Clinical Study Report, Table 14.1.2
*: Percentages are based on the total number of randomized patients.

Table 2: Summary of Demographics and Baseline Characteristics

	Placebo (N=95)	Cocaine 4% (N=278)	Cocaine 8% (N=275)
Age (days)			
Mean (SD)	45 (17)	43 (17)	45 (15)
Median	46	42	45
Min, Max	18, 80	18, 86	17, 83
Sex, n %)			
Female	55 (58%)	170 (61%)	167 (61%)
Male	40 (42%)	108 (39%)	108 (39%)
Race, n (%)			
American Indian or Alaska	0	0	1 (0%)
Asian	1 (1%)	1 (0.4%)	3 (1%)
Black or African American	16 (17%)	49 (18%)	51 (19%)
Other	3 (3%)	7 (3%)	4 (1%)
White	75 (79%)	220 (79%)	216 (79%)
Missing	0	1 (0.4%)	0
Height (cm)			
Mean (SD)	169 (10)	168 (11)	168 (11)
Median	170	168	168
Min, Max	145, 196	139, 213	132, 198
Weight at screening (kg)			
Mean (SD)	84 (23)	82 (21)	84 (23)
Median	81	80	80
Min, Max	46, 175	40, 189	45, 183
Baseline BMI (kg/m^2)			
Mean (SD)	29 (7)	29 (7)	30 (8)
Median	28	27	28
Min, Max	16, 57	17, 65	17, 70

Source: Reviewer and Clinical Study Report, Table 14.1.3; SD: standard deviation

3.2.4 Results and Conclusions

I reproduced the applicant's efficacy results in the corrected CSR. Both cocaine treatment groups had a higher analgesic success rate than the placebo group with statistical significance (Table 3). The analgesic success rates of the cocaine 4% and 8% groups were 77% and 81% respectively, whereas the success rate of the placebo group was about 9%. The analgesic success rate of the cocaine 8% group was numerically higher than that of the cocaine 4% group.

Table 3: Applicant's Primary Analysis on Analgesic Success

Event	Placebo (N=95)	Cocaine 4% (N=278)	Cocaine 8% (N=275)
Failure	86 (91%)	63 (23%)	52 (19%)
Success	9 (9%)	215 (77%)	223 (81%)
P-value*		<0.0001	<0.0001

Source: Reviewer and Clinical Study Report, Table 14.2.1
*Fisher's exact test for pairwise comparison on active drug to placebo.

The primary reason for analgesic failure in all treatment groups was failure to achieve a pain score of 0 for the Von Frey filament test. The percentage of subjects who reported a pain score greater than 0 was 85%, 22%, and 19% for the placebo group, the cocaine 4% group, and the cocaine 8% group, respectively (Table 4). The average of the non-zero pain scores was 4.1, 2.3, and 2.1 for the placebo group, the cocaine 4% group, and the cocaine 8% group, respectively.

The percentage of subjects who requested additional analgesic medication to complete the diagnostic or surgery procedures was lower in the cocaine groups than that in the placebo group (Table 4). One subject (0.4%) in the cocaine 8% group, 4 subjects (1.4%) in the cocaine 4% group, and 55 subjects (58%) in the placebo group were given additional analgesic medications. Note that a total of 40 (42%) placebo subjects went through the procedure without requesting any analgesic medication, which may indicate that most of the diagnostic procedures or surgeries were not painful. The most common diagnostic or surgical procedure in each of the groups was nasal endoscopy (Table 9, Appendix). Overall, approximately 59% of the subjects underwent nasal endoscopy (55%, 61%, and 60% in the placebo, cocaine 4%, and cocaine 8% groups, respectively). The second and third most common procedures were nasal laryngoscopy (14%) and nasopharyngeal laryngoscopy (8%).

Since treatment blinding was broken after the Von Frey filament test, the decision to administer additional analgesic medication for the subsequent diagnostic or surgery procedure might have been influenced by knowing the treatment assignment. A sensitivity analysis was conducted by considering placebo subjects who reported pain score of 0 as analgesic success regardless of subsequent administration of additional analgesic medication, which was actually the original definition of analgesic success in the protocol. The sensitivity analysis supported the primary analysis (Table 4). The placebo success rate was about 15%, which was still much lower than the success rates of the two cocaine groups with statistical significance. From hereafter in this review, I will use the protocol definition of analgesic success for my analyses.

Table 4: Sensitivity Analysis on Analgesic Success

Event	Placebo (N=95)		Cocaine 4% (N=278)		Cocaine 8% (N=275)	
Von Frey filament test	Pain=0	Pain>0	Pain=0	Pain>0	Pain=0	Pain>0
n (%)	14 (15%)	81(85%)	216 (78%)	62 (22%)	224 (81%)	51(19%)
P-value*			<0.0001		<0.0001	
Pain score mean (SD)		4.1 (2.4)		2.3(1.6)		2.1 (1.3)
Additional medication given n (%)	5 (5%)	50 (53%)	1 (0.4%)	3 (1%)	1 (0.4%)	0
Protocol defined failure	81 (85%)		63 (23%)		52 (19%)	
Protocol defined success	14 (15%)		215 (77%)		223 (81%)	
P-value*			<0.0001		<0.0001	

Source: Reviewer. *: Fisher's exact test.

The division requested at the pre-NDA meeting that the applicant submit the unblinding time of all subjects to confirm that treatment unblinding occurred after the Von Frey filament test. However, the applicant did not include the requested information in the initial submission. The unblinding time along with the corresponding dataset was submitted during the NDA review process in response to the division's information request.

Upon reviewing the unblinding time, it was found that 16 subjects were unblinded before the Von Frey filament test (Table 5), 2 (2%) in the placebo group, 8 (3%) in the cocaine 4% group, and 6 (2%) in the cocaine 8% group. In addition, for approximately 40% of the subjects, the recorded unblinding time was the same as the test time. So it is unclear which happened first since that the two tasks could be done within the same minute. Moreover, there were 19 subjects missing an unblinding time. Since almost half of the enrolled subjects may have known what treatment was administered, the study results may have been observer biased, both for the subject and clinician.

Table 5: Unblinding Time Relative to Administration of Von Frey Test

Relative time [n(%)]	**Placebo (N=95)**	**Cocaine 4% (N=278)**	**Cocaine 8% (N=275)**
Before test	2 (2%)	8 (3%)	6 (2%)
Same minute	36 (38%)	107 (38%)	122 (44%)
Missing	5 (5%))	6 (2%)	8 (3%)
After test	**52 (55%)**	**157 (57%)**	**139 (51%)**

Source: Reviewer

To address the concern statistically, I conducted two additional sensitivity analyses. I first analyzed the analgesic success rate among subjects who were clearly unblinded after the Von Frey filament test as they were not subject to any potential bias due to unblinding. The results were in favor of the cocaine treatments. Among these subjects, the analgesic success rate of each cocaine group was still higher than that of the placebo group with statistical significance (Table 6). The rate difference between the cocaine 4% and placebo groups was about 47%. The success rates are summarized by the unblinding time relative to the filament test time in Table 6 but the statistical comparison was performed only for subjects who were unblinded after the filament test.

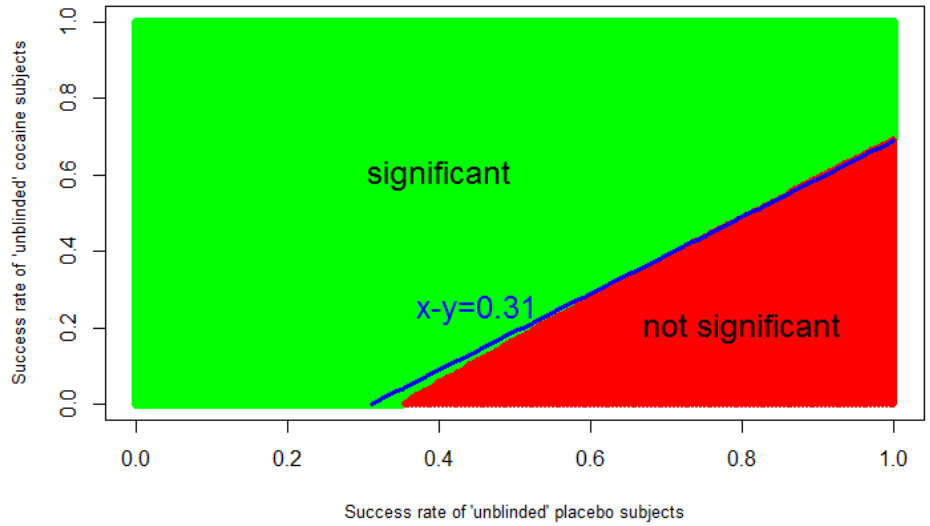
Table 6: Percentage of Analgesic Success by Unblinding Time

Unblinding time relative to Von Frey filament test	Placebo (N=95)	Cocaine 4% (N=278)	Cocaine 8% (N=275)
Before test	2	8	6
Success	0	7 (87.5%)	4 (67%)
Same minute	36	107	122
Success	1 (3%)	98 (92%)	110 (90%)
Missing	5	6	8
Success	2 (40%)	4 (67%)	6 (75%)
After test	**52**	**157**	**139**
Success	**11 (21%)**	**106 (68%)**	**103 (74%)**
P-value#		<0.0001	<0.0001

Source: Reviewer. A placebo subject is defined as a success if Von Frey filament test score is 0.
#: p-value is based on chi-square test with no multiplicity adjustment.

To further examine the impact of the potential unblinding, I considered the success rate of all subjects whose unblinding time was before or at the time of the Von Frey filament test as missing. I refer to these subjects along with the subjects whose recorded unblinding time was missing as potentially unblinded subjects for convenience. I then conducted a tipping point analysis by considering all possible values of the success rate of these potentially unblinded subjects and looking at under what scenarios the study conclusion would be overturned. For this analysis, I focus on the cocaine 4% and placebo groups only. The values of the success rates that render the superiority of cocaine 4% over placebo not statistically significant are highlighted in red in Figure 1. The tipping point analysis indicated that only when the success rate of the potentially unblinded placebo subjects was at least 31% higher than that of the potentially unblinded cocaine 4% subjects, the study conclusion would have been overturned. For example, if the success rate of the potentially unblinded cocaine 4% subjects were 50%, the success rate of the potentially unblinded placebo subjects had to be at least 81% to fail the study, which seems unlikely.

Figure 1: **Tipping Region of Success Rates of Potentially Unblinded Subjects**



Source: Reveiwer

Since the above sensitivity analyses support the primary analysis, my concern on the impact of the potential observer bias was alleviated.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Renee Petit-Scott. There were no major safety findings. Please refer to Dr. Petit-Scott's review for detailed information regarding the adverse event profile.

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 Table 7. 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 7: Analgesic Success Rates by Sex, Race and Age

		Placebo[#] (N=95)		Cocaine 4% (N=278)		Cocaine 8% (N=275)	
Subgroup		**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Sex	Male	40	5 (13%)	108	88 (81%)	108	89 (82%)
	Female	55	9 (16%)	170	127 (75%)	167	134 (80%)
Race	White	75	11 (15%)	220	166 (75%)	216	175 (81%)
	Black	16	2 (13%)	49	40 (82%)	51	43 (84%)
	Other	4	1 (25%)	9	9 (100%)	8	5 (63%)
Age	>=44	53	11 (21%)	134	99 (74%)	149	121 (81%)
	<44	42	3 (7%)	144	116 (81%)	126	102 (81%)

Source: Reviewer.
#: A placebo subject is defined as a success if Von Frey filament test score is 0.

4.2 Other Special/Subgroup Populations

The applicant also conducted a subgroup analysis by weight (Table 8). Weight was classified as 80 kg or greater or less than 80 kg. The analgesic success rates of both cocaine treatments were better than placebo regardless of weight.

Table 8: Analgesic Success Rates by Weight

		Placebo[*,#] (N=95)		Cocaine 4% (N=278)		Cocaine 8% (N=275)	
Subgroup		**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Weight	≥ 80 kg	49	3 (6%)	138	109 (79%)	138	112 (81%)
	<80 kg	46	11 (24%)	140	106 (76%)	136	110 (81%)

Source: reviewer.
#: One subject in the cocaine 8% group had missing weight.
*: A placebo subject is defined as a success if Von Frey filament test score is 0.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary statistical issue in study 2013011 was that some subjects were unblinded before the Von Frey filament test. Since a subject reporting a pain score greater than 0 was defined as an analgesic failure, knowing treatment assignment before the Von Frey filament test likely inflates the treatment effect. It doesn't appear to be a study integrity issue but raises a concern on the reliability and robustness of the conclusions.

To address the unblinding issue, I performed a subgroup analysis and a tipping point analysis. The subgroup analysis was conducted among subjects who were clearly blinded during the Von Frey filament test. These subjects, consisting of about 54% of all randomized subjects, were

more reliable for assessing the analgesic efficacy of cocaine in comparison to placebo than the other subjects, who were potentially unblinded for the Von Frey filament test. The subgroup analysis was supportive. The analgesic success rate in each cocaine group in this subgroup was still higher than that of the placebo group with nominal statistical significance.

A tipping point analysis was further performed by considering the success rate among subjects who were potentially unblinded for the filament test as missing and all possible values were tested. My tipping point analysis indicated that the superiority of cocaine 4% over placebo would only be not statistically significant, that is, the analysis tipped, if the success rate of those potentially unblinded placebo subjects was at least 0.31 higher than that of those potentially unblinded cocaine 4% subjects, which seems unlikely in this scenario.

My concern on the robustness of the study conclusions due to the unblinding issue was alleviated as the results from my subgroup and tipping point analyses were both supportive to the primary analysis.

5.2 Collective Evidence

Notwithstanding the programming error that resulted in the treatment assignments of cocaine groups transposed and the unblinding issue, I think there was evidence in Study 2013011 that cocaine 4% was better than placebo in terms of the analgesic success rate as defined in the protocol. However, it should be noted that the diagnostic or surgery procedures performed in this study were procedures that may not require anesthesia. The treatment difference was primarily attributed to the differential response to the Von Frey filament test. Thus it is unclear whether cocaine 4% would work effectively for other more aggressive procedures or surgeries. Moreover, there was a lack of characterization of some analgesic properties such as time to onset of anesthesia and duration of effect, which I think are very important to describe in the labeling. Additionally, the clinical reviewer indicated that the cocaine is typically administered as a vasoconstrictor rather than an anesthetic.

5.3 Conclusions and Recommendations

Study 2013011 has provided evidence that cocaine 4% was better than placebo in terms of the analgesic success rate as defined in the protocol. However, the limitation of the study design should be noted. The surgery or diagnostic procedures conducted in the study were mostly not very painful. Moreover, there was a lack of characterization of time to onset of anesthesia and duration of effect. Information from clinical pharmacology studies might be helpful in this regard.

If the division decides to approve, I would recommend that the indication be restricted to type of procedures similar to those conducted in the study such as endoscopy.

5.4 Labeling Recommendations

The proposed labeling Section 14 contains the following:

14 CLINICAL STUDIES

A double-blind, multicenter, single-dose, placebo- and dose-controlled, parallel-group study was conducted in 648 subjects undergoing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. Subjects were randomized to receive (b) (4)

(b) (4)

(b) (4)

In addition, results from the Von Frey filament test and the usage of additional medication during the procedures or surgeries should be described. Moreover, the percentages should be rounded to integer.

Appendix

Table 9: Diagnostic or Surgical Procedures

Procedure	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8% RX0041-002 (N=275) n (%)
Nasal Endoscope Alone			
Nasal Endoscopy	52 (54.7)	169 (60.8)	164 (59.6)
Other Procedures			
Nasal Laryngoscopy	14 (14.7)	43 (15.5)	33 (12.0)
Nasopharyngeal Laryngoscopy	12 (12.6)	18 (6.5)	23 (8.4)
Nasal Debridement	3 (3.2)	15 (5.4)	19 (6.9)
Nasal Endoscopy with Debridement	0 (0.0)	9 (3.2)	11 (4.0)
Intraturbinate DepoMedrol Injection	5 (5.3)	7 (2.5)	7 (2.5)
Laryngoscopy	3 (3.2)	6 (2.2)	5 (1.8)
Transnasal Esophagoscopy	2 (2.1)	2 (0.7)	1 (0.4)
Turbinate Reduction	1 (1.1)	2 (0.7)	3 (1.1)
Nasal Endoscopy with Polypectomy	0 (0.0)	2 (0.7)	2 (0.7)
Sinuplasty	0 (0.0)	0 (0.0)	2 (0.7)
Nasal Endoscopy and Stroboscopy	0 (0.0)	0 (0.0)	1 (0.4)
Nasal Cauterization	0 (0.0)	0 (0.0)	1 (0.4)
Nasal Endoscopy and Nasal Laryngoscopy	0 (0.0)	1 (0.4)	0 (0.0)
Nasal Stroboscopy	1 (1.1)	0 (0.0)	0 (0.0)

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
09/07/2017

DAVID M PETULLO
09/07/2017
I concur.

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209-963
Related IND #:	IND 118,527
Product Name:	Cocaine hydrochloride topical solution, 4%
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:	(b) (4)
Dates:	Received: November 23, 2016 PDUFA: September 23, 2017
Review Priority:	Standard
Biometrics Division:	II
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. Medical Team Leader: Leah Crisafi, M.D.
Project Manager:	Diana Walker

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
2013011	MC, R, DB, PG, PC trial	Cocaine 4%/ 275 Cocaine 8%/278 Placebo/ 95	Primary: analgesic success Key Secondary: None	Both cocaine 4% and 8% were superior to placebo with statistical significance.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes.**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes.**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**Not applicable.**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Not applicable.**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes.**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\Cdsesub1\evsprod\NDA209963\0000\m5\datasets\2013011
Were analysis datasets provided?	Yes.
Dataset structure (e.g., SDTM or ADaM)	Indicated as SDTM and ADaM.
Are the define files sufficiently detailed?	Yes.
List the dataset(s) that contains the primary endpoint(s)	ADQS
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No.
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Not applicable.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	x			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		x		The ISE is a link to the Summary of Efficacy. There is no separate ISE report.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	x			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None.

5.2. Information Requests/Review Issues

The following information requests should be conveyed to the applicant.

- In the Clinical Study Report for Study 2013011, a subject was considered an analgesic success if the subject both reported a score of 0 on visual numeric rating scale (VNRS) based on a Von Frey Filament Test prior to the diagnostic procedure or surgery, and had no need for additional nasal analgesic medication during the diagnostic procedure or surgery. However, this definition of analgesic success is different from what was pre-specified in the study protocol and Statistical Analysis Plan (SAP). According to the protocol and SAP, a placebo subject would be an analgesic success if the subject reported a score of 0 on VNRS based on the Von Frey Filament Test. Clarify this discrepancy.

- At the pre-NDA meeting held on July 14, 2015, the agency requested that the time of unblinding for each subject be reported in the clinical study report. However, this information could not be located. If the report was submitted, indicate the location in the current submission otherwise submit this information.

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/s/

FENG LI
01/13/2017

DAVID M PETULLO
01/13/2017
I concur.