

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-359**

**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 Serial Number:** NDA 21-359 Resubmission

**Drug Name:** Nitroglycerin Ointment 0.4%

**Indication(s):** Treatment of moderate to severe pain associated with chronic anal fissure

**Applicant:** Prostrakan Group, Ltd

**Date(s):** Submitted: December 20, 2010  
PDUFA: June 21, 2011

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Yongman Kim, Ph.D.

**Concurring Reviewers:** Dionne Price, Ph.D.

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Neville Gibbs, M.D.  
Rigoberto Roca, M.D.

**Project Manager:** Christopher Hilfiger

**Keywords:** Clinical studies, missing data, retrieved dropout, hybrid LOCF/BOCF analysis

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## 1. EXECUTIVE SUMMARY

Prostrakan has proposed nitroglycerin ointment 0.4% for the treatment of moderate to severe pain associated with a chronic anal fissure. Based on my overall review, I find that there is evidence of efficacy.

New analyses recommended by Dr. Curtis Rosebraugh in his response to a Formal Dispute Resolution Request (FDRR) were conducted and submitted for review. They are a “retrieved drop-out” analysis and a “hybrid last observation carried forward/baseline observation carried forward (LOCF/BOCF)” analysis. The second analysis demonstrated a statistically significant difference in pain intensity between nitroglycerin ointment 0.4% and placebo. However, the first analysis failed to demonstrate a statistically significant difference although the difference appeared to favor nitroglycerin ointment 0.4% over placebo.

In the July 2006 action letter, the Office of Drug Evaluation I stated that an additional study would be required because the results of the submitted three studies had failed to provide substantial evidence of the effectiveness of the drug. Among the concerns were the use of the last observation carried forward imputation procedure for patients who discontinued due to headaches, the use of acetaminophen, and the lack of a favorable trend in the United States population. In the September 2009 complete response, the applicant submitted an additional study. In the study, all patients received a standard dose of acetaminophen. The applicant employed a BOCF imputation method to handle missing data in their primary analysis, and the analysis failed to demonstrate a statistically significant difference. In the End-of-Review meeting and a subsequent FDRR, the applicant argued that the method could be unduly conservative since most anal fissures resolve within months. As such, some patients might withdraw because of early effective pain relief. Therefore the applicant surmised that imputing no improvement in pain for all dropouts could result in an overly conservative analysis.

Dr. Curtis Rosebraugh, in consultation with Dr. Robert Temple and Dr. Robert O’Neill, in his response to the FDRR recommended two approaches for handling missing data for this unique case. The first method was to retrieve pain scores assessed after discontinuation of the randomized treatment if patients used a limited amount of rescue medication. The second method was to impute good scores for patients with early effective pain relief before drop out. He based his recommendation on the fact that there was a high rate of spontaneous resolution of pain due to the nature of the disease as shown by the placebo response rate and the limited number of dropouts in the placebo group.

The results of the efficacy analyses varied when different methods of imputation were used to handle missing data. In the September 2009 complete response, the pre-specified primary analysis using BOCF failed to demonstrate statistical significance ( $p=0.118$ ). The difference in pain intensity between treatment groups was 5 mm. The study was conducted in the United States, Argentina, Brazil, and Mexico. An exploration of the US population demonstrated a statistically significant ( $p=0.048$ ) difference of 8 mm. The LOCF analysis, conducted as a

sensitivity analysis by the applicant, demonstrated statistical significance ( $p=0.033$ ) with a difference of 7 mm. In the current resubmission, the retrieved drop-out analysis failed to demonstrate statistical significance ( $p=0.079$ ), and the difference between groups was 6 mm. The hybrid LOCF/BOCF analysis demonstrated statistical significance ( $p=0.038$ ) with a difference between groups of 7 mm.

Effect sizes from the analyses using different imputation strategies are similar and consistently favor active treatment over placebo. As argued by the Applicant and considered by Dr. Rosebraugh, the BOCF analysis appears to be too conservative in this special case because it imputes bad scores even for patients with early effective pain relief before drop out. The retrieved dropout method, in principle, has merit in this case. However, the applicant did not originally plan to collect data on patients after withdrawal which resulted in a small amount of retrieved data (only 5 out of 28 dropouts). I find that the hybrid LOCF/BOCF analysis suggested by Dr. Rosebraugh is an acceptable approach in this unique setting where anal fissures resolve as evidenced by the sizeable placebo response and the presence of dropouts with early effective pain relief. The applicant formed a blinded review committee to objectively adjudicate dropouts with early effective pain relief.

Based on the collective evidence, I conclude that nitroglycerin ointment 0.4% decreases the pain intensity associated with anal fissures.

## 2. INTRODUCTION

### 2.1 Overview

The current resubmission includes two new analyses based on Dr. Rosebraugh's recommendations in his response to the FD RR. There is no change in statistical methods in the primary analysis including the statistical model, endpoint, and analysis population other than the methods used to handle missing data. The statistical analysis plan and analysis results can be found in the statistical review of the September 2009 complete response. This review has been formulated based on the submissions and discussions arising from numerous interactions outlined in the table below.

Timeline of Regulatory Interactions

Date	Correspondence
June 22, 2001	NDA 21-359 submitted to the Division of Cardio-Renal Drug Products.
April 25, 2002	The application was withdrawn.
June 30, 2004	The application was resubmitted.

December 24, 2004	The application received approvable status. Concerns included the lack of statistical significance using the pre-specified analysis, high rate of withdrawals for headache and other adverse events, and the concomitant use of acetaminophen (see appendix for relevant excerpts from the action letter).
April 14, 2005	A complete response to the Division's action was submitted.
April 25, 2006	Cardio-Renal Advisory Committee meeting was convened.
July 7, 2006	The application received approvable status. An additional study was required based on concerns regarding the use of acetaminophen, an unfavorable trend in the US population, and the use of a LOCF imputation strategy (see appendix for statistically relevant excerpts from the action letter).
May 22, 2007	The study design and statistical methods for an additional study were discussed during the May 22, 2007 Type A meeting. The applicant was advised to use a conservative imputation strategy (see Table 5 in appendix for statistical components).
September 30, 2009	A complete response to the Division's Action was submitted to the Division of Anesthesia, Analgesia and Rheumatology Products.
March 30, 2010	The application received 'Complete Response' status mainly due to failure of the pre-specified statistical analysis with BOCF imputation.
August 24, 2010	A Formal Dispute Resolution Request was submitted.
September 22, 2010	An Appeal Denial Letter was sent. Dr.

	Rosebraugh suggested two possible analyses as paths forward.
December 20, 2010	A complete response to the Division's action on March 30, 2010 was resubmitted.

## 2.2 Data Sources

In the current resubmission, the applicant provided the statistical analysis plan for the two new analyses and results. However, there was no new efficacy and safety data submitted. The new analyses were applied to the data submitted as part of the complete response received September 30, 2009.

## 3. STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

Since there were no issues on the quality or integrity of the data from the original submission and there is no new efficacy data from the current resubmission, we do not have such issues.

### 3.2 Evaluation of Efficacy

Study REC-C-001 was a 3-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of nitroglycerin ointment 0.4% in patients with pain associated with a chronic anal fissure. In REC-C-001, 248 eligible patients were randomized in a 1:1 ratio to nitroglycerin ointment 0.4% (n = 123) or placebo (n = 125) stratified by country, baseline VAS scores (<70 mm or ≥70 mm) and gender. The study was conducted at 45 centers in the United States, Argentina, Brazil, and Mexico. Patients were required to have a 24-hour average pain score of at least 50 mm.

The primary efficacy endpoint was the change from baseline in 24-hour average pain intensity, assessed by patient reported VAS, averaged over Days 14 to 18 of treatment. The endpoint was measured on the visual analog scale (VAS) ranging from 0 mm (no pain) to 100 mm (worst pain imaginable). The primary analysis used an analysis of covariance (ANCOVA) model including terms for treatment, region, and gender as factors and baseline VAS pain score as a covariate. The primary analysis was conducted on the intent-to-treat (ITT) population defined as all patients who were randomized and had applied the study medication at least once.

Patient demographic and baseline characteristics can be found in the appendix (Table 4).

The following table displays the patient disposition.

Patient Disposition

	Nitroglycerin ointment 0.4%	Placebo	Total
Randomized (ITT)	123 (100%)	124 (100%)	247 (100%)
Completed	106 (86%)	113 (91%)	219 (89%)
Reasons for dropout			
AE	9 (7%)	3 (2%)	12 (5%)
Voluntary Withdrawal	5 (4%)	4 (3%)	9 (3%)
Lost to Follow-Up	1 (1%)	4 (3%)	5 (2%)
Protocol Violation	2 (2%)	0 (0%)	2 (1%)

**Statistical Methodologies**

The two analyses recommended in the response to the FDRR were implemented by the applicant as follows:

- Retrieved-dropout analysis:
  - Patients who withdrew but had at least one pain score assessed during Days 14-18 and had not taken rescue medication were considered retrieved dropouts. The average score during Day14 to Day 18 was imputed for these patients.
  - The baseline scores were imputed for all other dropouts.
- LOCF/BOCF hybrid analysis:
  - A potentially “good” score (LOCF) was imputed for patients who withdrew but demonstrated an early effective pain relief.
  - If such patients were also retrieved-dropouts, then the average score during Day14 to Day 18 was imputed.
  - For other dropouts, baseline scores were imputed (BOCF).
  - Three blinded reviewers of the Data Review Committee independently evaluated dropouts and applied a majority rule to adjudicate dropouts with early effective pain relief.

## Results and Conclusions

The retrieved-dropout analysis failed to demonstrate a statistically significant difference between nitroglycerin ointment 0.4% and placebo (Table 1). There were 5 retrieved dropouts out of a total of 28 dropouts. The average scores during Days 14-18 were imputed for four patients. The baseline score was imputed for one because the patient took rescue medication.

**Table 1 Applicant's Retrieved-dropout Analysis (ITT)**

VAS	Nitroglycerin ointment 0.4% (N=123)	Placebo (N=124)
Actual Baseline Mean (SD)	73 (14.5)	73 (13.2)
Actual Day 14-18 Mean (SD)	32 (27.1)	38 (28.4)
Change from Baseline Adjusted Means (SE)	-42 (3.1)	-36 (3.0)
Difference from placebo (SE) 95% CI	-6 (3.4) (-13, 1)	
P-value	0.079	

Note: 1) Four subjects of retrieved-dropouts with pain scores assessed during days 14-18 were imputed with averages. Those four subjects were 1031771, 1211006, 2061309, and 2071554.

2) Adjusted means, confidence intervals, and p-values derived from ANCOVA model with terms for treatment, region, gender, and baseline score as covariate.

The hybrid LOCF/BOCF analysis demonstrated a statistically significant difference between Nitroglycerin ointment 0.4% and placebo (Table 2). There were nine patients who discontinued treatment and demonstrated early effective pain relief. Three of them were also retrieved-dropouts.

**Table 2 Applicant's Hybrid LOCF/BOCF Analysis (ITT)**

VAS	Nitroglycerin ointment 0.4% (N=123)	Placebo (N=124)
Actual Baseline Mean (SD)	73 (14.5)	73 (13.2)

Actual Day 14-18 Mean (SD)	31 (26.6)	38 (27.8)
Change from Baseline Adjusted Means (SE)	-44 (3.0)	-37 (3.0)
Difference from placebo (SE) 95% CI	-7 (3.3) (-14, -0.4)	
P-value	<b>0.038</b>	

Note: 1) Nine subjects with early effective pain relief before dropout were imputed with LOCF. Those nine subjects are 1031771, 1171054, 1261048, 2071554, 1091800, 2101837, 1211006, 1161770, and 1031543.

2) Adjusted means, confidence intervals, and p-values derived from ANCOVA model with terms for treatment, region, gender, and baseline score as covariate.

### 3.3 Evaluation of Safety

The evaluation of safety was conducted by the clinical reviewer, Neville Gibbs, M.D.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

The study was conducted in the United States, Argentina, Brazil, and Mexico. The applicant submitted an analysis of only the US population. The analysis demonstrated a statistically significant difference between nitroglycerin ointment 0.4% and placebo (Table 3).

**Table 3 Applicant's Subgroup Analysis (US population with BOCF)**

VAS	Nitroglycerin ointment 0.4% (N=108)	Placebo (N=106)
Actual Baseline Mean (SD)	73 (13.4)	73 (13.4)
Actual Day 14-18 Mean (SD)	33 (28.2)	40 (28.9)
Change from Baseline Adjusted Means (SE)	-40 (2.7)	-33 (2.7)

Difference from placebo (SE)	-8 (3.8)	
95% CI	(-15, -0.1)	
P-value	<b>0.048</b>	

1) Adjusted means, confidence intervals, and p-values derived from ANCOVA model with terms for treatment, region, gender, and baseline score as covariate.

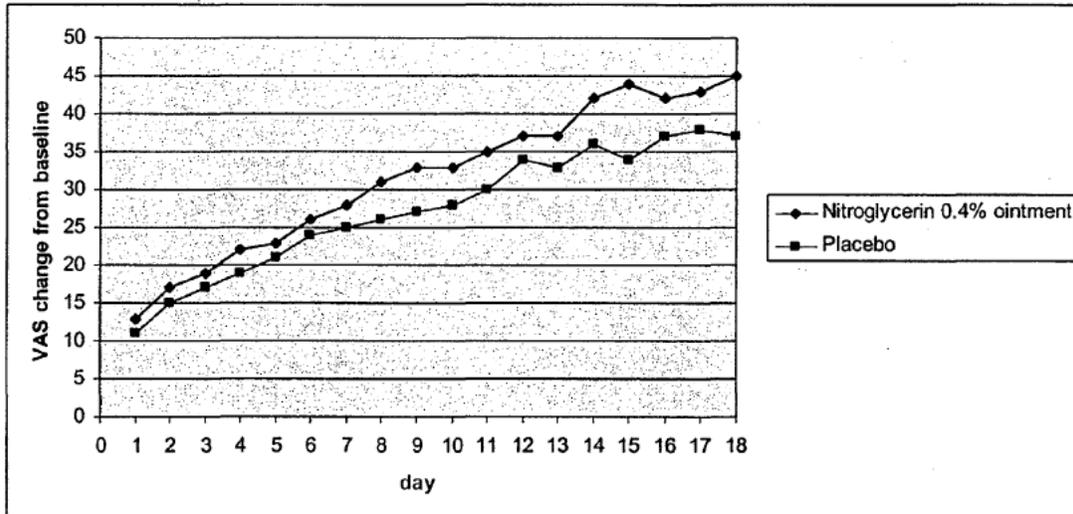
## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

There were conflicts in efficacy analyses with different methods of imputation for missing data. In the original complete response, the BOCF analysis failed to demonstrate a statistical significance with difference of 5 mm between treatment groups. The BOCF analysis on US population demonstrated a statistical significance with difference of 8 mm. The LOCF analysis demonstrated a statistical significance with difference of 7 mm. In the current resubmission, the retrieved drop-out analysis failed to demonstrate a statistical significance with difference of 6 mm. The hybrid LOCF/BOCF analysis demonstrated a statistical significance with difference of 7 mm.

Although the successful analysis using a hybrid LOCF/BOCF strategy was post-hoc and therefore was subject to inherent multiple analysis issues, the use was justified in the current resubmission based on Dr. Rosebraugh's assessment of the uniqueness of chronic anal fissures. His rationale for recommending the method was based on a high rate of spontaneous resolution of pain as evidenced by "an impressive placebo response, despite a very low dropout rate from the placebo group." The figure below depicts the placebo response.

VAS Difference by Day (ITT with BOCF)



Therefore based on the nature of the disease, missing pain scores from patients who dropped out for various reasons including adverse events who had early effective pain relief were imputed with good scores. There were nine such patients – three dropouts due to headache, one due to other adverse event, two due to voluntary withdrawal, one due to lost to follow-up, and one due to protocol violation.

The applicant formed a post-hoc blinded data review committee with three clinicians to objectively define a group of patients with early effective pain relief. Blinding was critical to minimize the potential bias and the majority rule out of three reviewers increased the credibility of the final adjudication.

Although the retrieved-dropout analysis did not demonstrate a statistically significant difference, the magnitude of the effect supported the conclusion based on the hybrid LOCF/BOCF analysis. Also, 87% (214/247) of the population was from US sites. The successful BOCF analysis on the US population further supported the efficacy of nitroglycerin ointment 0.4%.

## 5.2 Conclusions and Recommendations

A chronic anal fissure is a special case since the pain resolves as evidenced by the sizeable placebo effect and dropouts with early effective pain relief.

Thus, I find that the hybrid LOCF/BOCF analysis is an acceptable approach in this setting where there is a sizeable placebo effect and there are dropouts with early effective pain relief. The finding of efficacy is further supported by the similar effect sizes across the various analyses and the finding of statistical significance in the US population.

Based on my overall review, I find that there is evidence of efficacy.

### **5.3 Review of Clinical Studies of Proposed Label**

The applicant updated the original clinical study section in the original proposed label. I agree with the proposed label. However, I recommend deletion of the phrase regarding statistical significance and some changes to clarify the study design and primary endpoint.

BRANDNAME ointment was evaluated in a 3-week double-blind, randomized, multi-center, placebo-controlled study. Patients with a painful anal fissure for at least 30 days and moderate or severe pain prior to treatment ( $\geq 50$  mm on the 100mm visual analog scale, VAS) were randomized to receive 0.4% (1.5mg) nitroglycerin or placebo ointment applied to the anal canal every 12 hours. Pain as assessed by the change in VAS from baseline to Days 14-18 was lower in patients receiving 0.4% ointment compared to placebo. The difference in the mean change in pain between BRANDNAME and placebo was -7.0mm (95% CI -13.6 to -0.4mm).

## APPENDICES

**Table 4 Patient Demographic and Baseline Characteristics**

	Nitroglycerin ointment 0.4% (n=123)	Placebo (n=124)
<b>Gender n (%)</b>		
Female	65 (53%)	66 (53%)
Male	58 (47%)	58 (47%)
<b>Race n (%)</b>		
White	99 (81%)	96 (77%)
Black	21 (17%)	16 (13%)
Asian	0 (0%)	2 (2%)
American Indian or Alaska Native	0 (0%)	3 (2%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1%)
Other	3 (2%)	6 (5%)
<b>Age (years)</b>		
Median	46	43
Range	18 – 74	21 – 73
<b>Average VAS Pain</b>		
Median	73	72
Range	13 – 100	51 – 100

**Table 5 Study Design Advice from DAARP and Implementation**

<b>Advice</b>	<b>Study design</b>
Primary endpoint of pain at a specific time or an integral of pain over time.	Primary endpoint was 24 hour average pain intensity averaged over Days 14 to Day 18 of treatment.
Because of possible confounding, acetaminophen should be given to all patients as a standard regimen or not at all.	All patients were instructed to take a standard dose of 650 mg acetaminophen 30 minutes before each treatment; other analgesics were prohibited, except for low-dose aspirin (162 mg daily or 325 mg every other day) for cardiovascular prophylaxis.
Patients with a higher baseline pain score should be enrolled.	Only patients with baseline VAS scores of 50 mm or greater were enrolled.
Separate baseline and qualifying pain scores should be obtained.	A VAS score of 50 mm or greater was required on 2 of 4 days before Baseline and at the baseline visit.
A responder analysis should be performed. In this analysis, a zero change from baseline is imputed for patients who do not complete the study.	Responder analysis has been performed defined as a) 50% and b) 10 mm reduction on the VAS scoring. This analysis evaluates individual patterns of pain.
Collection of data on "worst pain" in 24 hours as a secondary measure.	As this parameter is linked to defecation, which may not occur daily, it was not considered appropriate for the study.
The reason for "dropout" should be captured in the CRF.	This information was captured in the CRF.
The ITT population should include all randomized patients who took at least one dose of study medication.	This definition was used for the ITT population in the study.
Before and after treatment vital signs should be obtained on all patients at least during initial visits. Vital signs should be measured at 5, 10, 30 and 60 minutes after dosing. Orthostatic hypotension assessments should be performed during all clinic visits.	Vital signs were measured at all study visits. At the Day 14 and 21 visits following supine blood pressure measurement, blood pressure was also measured one and 3 minutes after standing. At Days 0 and 7, vital signs were measured before application and at 5, 10, 30 and 60 minutes after treatment application. At the 30 minute time point blood pressure was measured at one and 3 minutes after standing. Symptoms of hypotension were recorded in the AE CRF, with the timing of the event noted.

A continuous responder analysis should be performed.	A continuous responder analysis has been performed.
A conservative approach to the analysis should be employed, i.e. use of zero change from baseline, as opposed to use of LOCF, for missing data for subjects who withdrew early	This strategy was employed for the primary and secondary analysis.

This table is excerpted from Table 4 in pages 24 – 25 of the study report. The advice on missing data handling described here is not accurate. DAARP advised that the primary approach for addressing missing data should be more conservative than a last observation carried forward strategy. Use of zero change from baseline was proposed by the applicant.

**Excerpts from the July 7th 2006 action letter:**

Before the application may be approved, however, it will be necessary for you to perform another trial with Cellegesic Ointment in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ( $p < 0.05$ ). We are requiring the additional study because we believe the results of the three randomized trials conducted to date do not provide substantial evidence that the drug is effective. The first study clearly failed to show an effect on its primary endpoint of improving anal fissure healing. The second study had a primary endpoint of improvement in the rate of decrease of pain over a 56-day period but this endpoint showed statistically significant improvement only with an analysis not clearly specified in the protocol.

The evidence of benefit thus depends very much on the results of the third study. The first two studies could provide some support, but only if the third study is “strongly supportive”. The following considerations render the third study even less persuasive in our view than your calculated  $p = 0.0498$  would convey.

1. The treated group had all of the early withdrawals because of headaches. Ordinarily, in a study that uses a last observation carried forward analysis, the group with more early withdrawals for adverse effects is disadvantaged because the early values do not benefit from late spontaneous improvement. This study examined the rate of change in pain, but this analysis too, would give a **disadvantage to the group with more dropouts, if the dropouts’ slope were based on the last measured value carried forward**, again because the late slope would not reflect the observed spontaneous improvement. There is one analysis, however, that gives great advantage to the group **with early dropouts—a rate of change analysis that uses observed values up to the time of dropout**. In this case, the slope for the dropouts is dominated by the early rapid changes seen in both the drug and placebo, which probably represents regression to the mean, but in any case does not represent drug effect. For your third study, only analyses that treat some or all NDA 21-359 dropouts this way give nominally significant results. We consider this a biased analysis inevitably favoring the treatment group, which had all the early dropouts, whether or not the decision to use this analysis was made in a blinded state.

2. We interpret the protocol specified analysis as calling for all subjects who discontinued because of headache to have their last observation carried forward. This changes the handling of 3 subjects’ data and results in  $p = 0.12$ .

3. We are also concerned that the small nominal treatment effect may be attributable to unbalanced use of acetaminophen.

4. Finally, we note that the favorable trend appears to be confined to the subjects in Serbia, with no favorable trend at all in the other participating countries, a major problem given that this is the most critical study and that the drug is intended for use in the United States.

Thus, we do not believe the results of this study support the effectiveness of Cellegesic when it is appropriately analyzed. We believe an additional study is needed.

#### **Excerpts from the December 23, 2004 action letter**

1. At best, the difference between the nitroglycerin ointment and placebo groups was 3 mm (out of 100) mean change from baseline in the average anal pain visual analog scale in study 03-02-01, only about 13% of the placebo effect. This small effect estimate does not balance favorably against a high rate of withdrawals for headache and other adverse effects with nitroglycerin ointment.

2. Several observations suggest that even this modest effect may be an overestimate of the effectiveness of nitroglycerin ointment.

- **The first two studies only showed effects on anal pain that were nominally statistically significant using retrospective analyses.** Your confirmatory study, when analyzed by the protocol-specified linear mixed-effects regression model using last observation carried forward for all nitroglycerin patients who withdrew because of headache, failed to demonstrate a statistically significant improvement in the rate of change of average daily pain through 21 days, the primary endpoint.
- **Not counting the two patients in each treatment group at the disqualified site, eleven patients randomized to nitroglycerin ointment in the third study failed to complete 21 days while no patients randomized to placebo failed to complete 21 days.** This large imbalance in withdrawals between the two groups makes it difficult to interpret any differences in results between the two groups over the primary endpoint evaluation period of 21 days.
- **Concomitant use of acetaminophen was also more common with nitroglycerin than with placebo, making it difficult to ascribe any small pain relief to nitroglycerin.**

## SIGNATURES/DISTRIBUTION LIST

An example of this optional documentation is as follows:

Primary Statistical Reviewer: Yongman Kim  
Date: May 20, 2011

Concurring Reviewer(s): Dionne Price

Statistical Team Leader: Dionne Price

Biometrics Division Director: Thomas Permutt

cc:

Christopher Hilfiger

Neville Gibbs

Rigoberto Roca

Yongman Kim

Dionne Price

Thomas Permutt

Lillian Patrician

c:\NDA\statreview.doc

## CHECK LIST

Number of Pivotal Studies: 1

### Trial Specification

Specify for each trial:

**Protocol Number (s):** REC-C-001

**Protocol Title (optional):** A randomized, double-blind, placebo-controlled, multi-national study to determine the effect of Nitroglycerin 0.4% ointment nitroglycerin ointment 0.4% (Nitroglycerin 0.4% ointment) on the pain associated with chronic anal fissure

**Phase:** 3

**Control:** Placebo Control

**Blinding:** Double-Blind

**Number of Centers:** 45

**Region(s) (Country):** US, Argentina, Brazil, Mexico

**Duration:** 3 Weeks

**Treatment Arms:** Nitroglycerin 0.4% ointment

**Treatment Schedule:** 375mg applied into the anal canal twice daily

**Randomization:** Yes

Ratio: 1:1

Method of Randomization: stratification, Central via IVRS

If stratified, then the Stratification Factors: country, baseline VAS score, gender

**Primary Endpoint:** mean change from baseline in VAS pain scores averaged over days 14 -18

**Primary Analysis Population:** ITT

**Statistical Design:** Superiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data?

Margin =

%Retained =

Adaptive Design: No

**Primary Statistical Methodology:** ANCOVA

**Interim Analysis:** No

If yes:

No. of Times:

Method:

$\alpha$  Adjustment: Yes/No

$\alpha$  Spending Function:

**DSMB:** Yes/No

**Sample Size:** 250

**Sample Size Determination:** Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?

Statistic = t-test

**Power**= 90%

**Δ**= 10 mm

**α** = 5%

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? Center, baseline VAS score, and gender
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? BOCF
- Was there a **Multiplicity** involved? No  
If yes,  
Multiple Arms (Yes/No)? No  
Multiple Endpoints (Yes/No)? No  
Which method was used to control for type I error? No
- **Multiple Secondary Endpoints:** Are they being included in the label? No. If yes, method to control for type 1 error.
- **Were Subgroup Analyses Performed (Yes/No)?** Yes
- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?  
No
- Overall, was the study positive (Yes/No)? Yes

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/s/

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YONGMAN KIM  
05/19/2011

DIONNE L PRICE  
05/19/2011  
concur



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/Serial Number:** NDA 21-359

**Drug Name:** Cellegesic (nitroglycerin) 0.4% Ointment

**Indication(s):** Treatment of moderate to severe pain associated with chronic anal fissure

**Applicant:** Prostrakan Group, Ltd

**Date(s):** Submitted: September 30, 2009  
PDUFA: March 31, 2010

**Review Priority:** Standard

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**Medical Division:** Division of Anesthesia, Analgesia, and Rheumatology Products

**Clinical Team:** Neville Gibbs, M.D.  
Robert Shibuya, M.D.

**Project Manager:** Christopher Hilfiger

**Keywords:** Clinical studies, missing data, sensitivity analyses

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

Study REC-C-001, submitted as a complete response, failed to demonstrate a statistically significant difference between Cellegesic and placebo in terms of the change in pain intensity from baseline to Day 14 through Day 18 of treatment.

### 1.2 Brief Overview of Clinical Studies

The original NDA was submitted to the Division of Cardio-Renal Drug Products on June 22, 2001 and subsequently withdrawn. It was resubmitted June 30, 2004. The December 24, 2004 action letter stated that the application was 'approvable'. A complete response was submitted April 14, 2005. The resulting July 7, 2006 action letter stated that the application was again 'approvable'. In the letter, the Division explained that one study failed to demonstrate an effect on its primary endpoint. A second study utilized a less desirable primary endpoint and an analysis that was not clearly pre-specified. A concern with the third study was that statistical significance was only achieved as a result of an analysis that inappropriately handled withdrawals from the study. The Division concluded that the effectiveness of Cellegesic had not been demonstrated and that an additional study was necessary. Study REC-C-001 was submitted in response to the July 7, 2006 'approvable' action letter. Following a re-organization within the Center for Drug Evaluation and Research (CDER), the review of Cellegesic fell under the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP).

Study REC-C-001 was a 3-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of Cellegesic ointment in patients with pain associated with a chronic anal fissure. In the study, 248 patients were randomized to Cellegesic (n = 123) or placebo (n = 125). The primary efficacy variable was the change from baseline in 24 hour average pain intensity averaged over Days 14 to 18. Secondary efficacy measures included Patient Global Assessment of treatment therapy and the percentage of responders defined as patients with a decrease in 24 hour average pain intensity averaged over Days 14 to 18 from baseline by (a) a 10 mm and (b) a 50% decrease in VAS.

### 1.3 Statistical Issues and Findings

Study REC-C-001 failed to demonstrate a significant analgesic effect of Cellegesic compared to placebo using the pre-specified ANCOVA model with a BOCF imputation strategy. Sensitivity analyses employing the last observation carried forward (LOCF) imputation strategy for missing data and a supportive analysis employing mixed model repeated measures (MMRM) demonstrated statistical significance. However, there were several concerns with the sensitivity and supportive analyses of the data. In chronic pain trials where the goal is to treat a symptom, patients who withdraw before the end of the

study should be treated as non-responders, and little to no benefit should be assigned based on the pain scores before dropout. The applicant used the two LOCF methods to assess the impact of missing data on the primary analysis. Since the LOCF methods may have assigned 'good' scores to 'bad' outcomes, the methods were not considered conservative. Moreover in a chronic pain setting, a LOCF analysis may potentially provide supportive information only when a conservative analysis provides significant results. In my opinion, the successful LOCF analyses do not negate the failure of the more appropriate conservative analyses. Similarly, the MMRM analysis used pain data from patients who withdrew before the study ended thereby attributing some benefit to dropouts. Also in order for the MMRM method to be valid, missing at random (MAR) should be assumed as the mechanism generating missing data. However in chronic pain trials, missing data is often informative and therefore the MAR assumption is not supported.

## 2. INTRODUCTION

### 2.1 Overview

#### 2.1.1 Drug class and regulatory history

The original NDA was submitted to the Division of Cardio-Renal Drug Products on June 22, 2001 and withdrawn April 25, 2002. It was resubmitted June 30, 2004. The December 24, 2004 action letter stated that the application was 'approvable'. The NDA was resubmitted April 14, 2005 as a complete response to the action letter. The July 7, 2006 action letter stated that the application was "approvable". Relevant excerpts from the action letter are as follows:

Before the application may be approved, however, it will be necessary for you to perform another trial with Cellegesic Ointment in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ( $p < 0.05$ ). We are requiring the additional study because we believe the results of the three randomized trials conducted to date do not provide substantial evidence that the drug is effective. The first study clearly failed to show an effect on its primary endpoint of improving anal fissure healing. The second study had a primary endpoint of improvement in the rate of decrease of pain over a 56-day period but this endpoint showed statistically significant improvement only with an analysis not clearly specified in the protocol.

The evidence of benefit thus depends very much on the results of the third study. The first two studies could provide some support, but only if the third study is "strongly supportive". The following considerations render the third study even less persuasive in our view than your calculated  $p = 0.0498$  would convey.

1. The treated group had all of the early withdrawals because of headaches. Ordinarily, in a study that uses a last observation carried forward analysis, the group with more early withdrawals for adverse effects is disadvantaged because the early values do not benefit from

late spontaneous improvement. This study examined the rate of change in pain, but this analysis too, would give a disadvantage to the group with more dropouts, if the dropouts' slope were based on the last measured value carried forward, again because the late slope would not reflect the observed spontaneous improvement. There is one analysis, however, that gives great advantage to the group with early dropouts—a rate of change analysis that uses observed values up to the time of dropout. In this case, the slope for the dropouts is dominated by the early rapid changes seen in both the drug and placebo, which probably represents regression to the mean, but in any case does not represent drug effect. For your third study, only analyses that treat some or all NDA 21-359 dropouts this way give nominally significant results. We consider this a biased analysis inevitably favoring the treatment group, which had all the early dropouts, whether or not the decision to use this analysis was made in a blinded state.

2. We interpret the protocol specified analysis as calling for all subjects who discontinued because of headache to have their last observation carried forward. This changes the handling of 3 subjects' data and results in  $p = 0.12$ .

3. We are also concerned that the small nominal treatment effect may be attributable to unbalanced use of acetaminophen.

4. Finally, we note that the favorable trend appears to be confined to the subjects in Serbia, with no favorable trend at all in the other participating countries, a major problem given that this is the most critical study and that the drug is intended for use in the United States.

Thus, we do not believe the results of this study support the effectiveness of Cellegesic when it is appropriately analyzed. We believe an additional study is needed.

Following a re-organization within CDER, the review of the product fell within the purview of the DAARP. The study design and statistical methods for an additional study were discussed during the May 22, 2007 Type A meeting between Prostrakan and DAARP. Specific design elements recommended by DAARP, and the way in which they were addressed, are summarized in the appendix (Table 1 excerpted from the study report). The current NDA is resubmitted as a complete response to the action letter.

### **2.1.2 Proposed Indication**

The proposed indication is for the treatment of moderate to severe pain associated with chronic anal fissure.

### **2.2 Data Sources**

NDA 21-359 was submitted on September 30, 2009. Data are located in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The electronic SAS data sets were also provided in the EDR using the following path:

\\FDSWA150\NONECTD\N21359\N\_000\2009-09-30

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy of Study REC-C-001

##### 3.1.1 Study Design and Endpoints

Study REC-C-001 was a 3-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of Cellegesic in patients with pain associated with a chronic anal fissure. In REC-C-001, 248 eligible patients were randomized in a 1:1 ratio to Cellegesic (n = 123) or placebo (n = 125) stratified by country, baseline VAS scores (<70 mm or ≥70 mm) and gender at 45 centers in United States, Argentina, Brazil, and Mexico. Patients were required to have a 24-hour average pain score of at least 50 mm.

The primary efficacy endpoint was the change from baseline in 24-hour average pain intensity, assessed by patient reported VAS, averaged over Days 14 to 18 of treatment. The endpoint was measured on the visual analog scale (VAS) ranging from 0 mm (no pain) to 100 mm (worst pain imaginable).

The secondary endpoints proposed for possible inclusion in the label were:

- Time to improvement for a 50% decrease in 24-hour average pain intensity (VAS)
- Time to improvement for a 10 mm decrease in 24-hour average pain intensity (VAS)
- Percentage of responders, defined as 50% decrease in 24-hour average pain intensity (VAS)
- Percentage of responders, defined as 10 mm decrease in 24-hour average pain intensity (VAS).

Other exploratory secondary efficacy variables included the following:

- Patient Global Assessment of therapy at Day 21
- Percentage of responders defined as patients with a decrease in 24 hour average pain intensity averaged over Days 14 to 18 from baseline by (a) a 10 mm and (b) a 50% decrease in VAS.
- Time to 10 mm and 50% improvement in VAS score.

##### 3.1.2 Disposition and Demographics

Approximately 11% of the patients discontinued before the end of study (Table 1). However, more patients from the Cellegesic group discontinued compared to the placebo group. Fourteen percent of Cellegesic patients discontinued while 9 % of placebo patients discontinued. As expected, the majority of the Cellegesic dropouts were due to adverse events. Seven percent of Cellegesic patients discontinued due to adverse events. However, unexpectedly, the placebo dropouts were not due to lack of efficacy, but due to AE, voluntary withdrawal, or lost to follow-up. Three percent of placebo patients discontinued due to adverse events, 3% due to voluntary withdrawal, and 3% due to lost to follow-up.

**Table 1 Subject Disposition: REC-C-001**

	Number of Patients	
	Cellegesic	Placebo
<b>Randomized</b>	123 (100%)	125 (100%)
<b>ITT</b>	123	124
<b>Completed</b>	106 (86%)	113 (91%)
<b>Reasons for dropout</b>		
<b>AE</b>	9 (7%)	3 (3%)
<b>Voluntary Withdrawal</b>	5 (4%)	4 (3%)
<b>Lost to Follow-Up</b>	1 (1%)	4 (3%)
<b>Protocol Violation</b>	2 (2%)	0 (0%)

Patient demographics are presented by treatment groups in the appendix (Table 9). There were no noticeable imbalances between treatment groups with respect to demographic variables of age, race, and sex.

Table 9 also shows baseline values for the efficacy variable of 24-hour average pain score by treatment groups. Distributions of the efficacy variable at baseline were comparable between treatment groups.

### 3.1.3 Statistical Methodologies

The primary analysis used an analysis of covariance (ANCOVA) model including terms for treatment, region, and gender as factors and baseline VAS pain score as a covariate. Missing data due to dropouts were imputed employing the baseline observation carried forward (BOCF) strategy in the primary analysis.

The applicant stated that sensitivity analyses would be conducted if “an appreciable number of patients, i.e. 5%,” had missing data. To assess the impact of missing data on the primary analysis, the ANCOVA analysis was conducted with a last observation carried forward (LOCF) imputation strategy. As a sensitivity analysis, a continuous responder analysis was conducted treating dropouts as non-responders. A graph with two responder curves was generated without statistical comparison between two responder curves. I conducted the continuous responder analysis with van der Warden test comparing the responder curves.

As a supportive analysis, a mixed-model repeated measures (MMRM) model was fit on the change from baseline to each day in 24-hour average pain score. The model included terms for treatment, region, gender, day and treatment-by-day interactions, and baseline VAS pain score as a covariate. The contrast at Day 18 comparing treatments was used to test if Cellegesic was superior to placebo. This model assumed that, first, any missing data were missing at random, and, second, an autoregressive first order variance-covariance structure should be used.

The primary analysis was conducted on the intent-to-treat (ITT) population defined as all patients who were randomized and had applied the study medication at least once.

For the analysis of the time to improvement for a 50% decrease and for a 10 mm decrease in 24 hour average pain intensity, the log-rank test stratified by region, baseline VAS pain, and gender was used. For the analysis of Patient Global Assessment of therapy, a logistic regression model with terms for treatment, region, gender, and baseline VAS pain was used.

In order to adjust for multiple testing on the secondary endpoints, a hierarchical test procedure was performed in the following order:

1. Time to response (50% pain reduction)
2. Time to response (10 mm pain reduction)
3. Response proportions (50% pain reduction)
4. Response proportions (10 mm pain reduction).

### **3.1.4 Results and Conclusions**

Study REC-C-001 failed to demonstrate a statistically significant difference between Cellegesic and placebo in the pre-specified primary analysis (Table 2).

**Table 2 Applicant's Primary Efficacy Analysis: REC-C-001 (ITT)**

<b>LS Mean Change (SE) from Baseline to average of Days 14 - 18 in 24-hour average pain</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>	<b>P-value</b>
<b>ANCOVA/BOCF* Difference from Placebo (SE) (95% CI)</b>	-40 (3.1) -5 (3.5) (-12, 1)	-35 (3.0)	0.118

\*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

As sensitivity analyses, the applicant conducted two LOCF analyses, both of which demonstrated statistical significances (Tables 3 & 4). However because the pre-specified primary BOCF analysis failed, the fact that the LOCF analyses were significant is not informative in assessing the sensitivity of the conclusion from the failed primary analysis. The original LOCF method (LOCF1) was pre-specified before unblinding the randomization code. The second LOCF method (LOCF2) was proposed after unblinding the randomization code. The main difference between the two methods is that LOCF1 imputed missing data from the last non-missing observation whether it fell before Day 18 (last day of primary pain assessment) or not. In contrast, the LOCF2 method restricted imputation from the last non-missing observation before Day 18. Because I could not exactly reproduce their least squares means in LOCF2 analysis, I presented my analysis. However, my analysis and applicant's analysis gave the same conclusion.

**Table 3 Reviewer's Sensitivity Analysis using LOCF1: REC-C-001 (ITT)**

<b>LS Mean Change (SE) from Baseline to average of Days 14 - 18 in 24-hour average pain</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>	<b>P-value</b>
<b>ANCOVA/LOCF1* Difference from Placebo (SE) (95% CI)</b>	-37 (3.0) -7 (3.4) (-13, 0)	-30 (3.1)	0.047

\*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

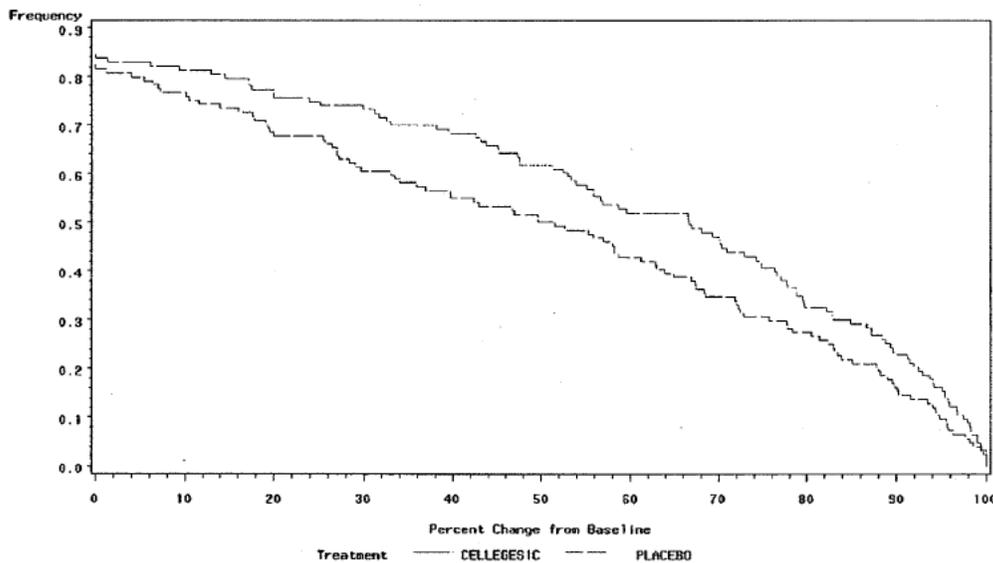
**Table 4 Reviewer's Sensitivity Analysis using LOCF2: REC-C-001 (ITT)**

LS Mean Change (SE) from Baseline to average of Days 14 - 18 in 24-hour average pain	Cellegesic (N=123)	Placebo (N=124)	P-value
ANCOVA/LOCF2* Difference from Placebo (SE) (95% CI)	-36 (2.9) -7 (3.4) (-14, -1)	-29 (3.0)	<b>0.033</b>

\*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

Although the continuous responder curves between Cellegesic and placebo appear to separate, the van der Waerden test did not result in statistical significance (Figure 1).

**Figure 1 Reviewer's Continuous Responder Analysis on Primary Efficacy Variable: REC-C-001 (ITT)**



Note: P-value of 0.138 is generated by van der Waerden test.

As a supportive analysis, the applicant conducted an MMRM analysis which resulted in a statistically significant difference between Cellegesic and placebo in terms of the change from baseline to Day 18 in 24-hour average pain. Because I could not exactly reproduce their numbers, I conducted the same analysis and found that my results were very close to the results from applicant's analysis (Table 5).

**Table 5 Reviewer’s “Supportive” Analysis: REC-C-001 (ITT)**

<b>LS Mean Change (SE) from Baseline to Day18 in 24-hour average pain</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>	<b>P-value</b>
<b>MMRM* Difference from Placebo (SE) (95% CI)</b>	-48 (3.1) -9 (3.4) (-16, -2)	-39 (3.0)	<b>0.008</b>

\* P-value calculated from repeated measures ANCOVA (MMRM) model with terms for treatment, day, treatment\*day, region, gender, and baseline score as covariate and AR(1) covariance structure.

The secondary efficacy analyses on the time to VAS pain 50% improvement, the rate of response defined as VAS pain 50% improvement, and the patient global assessment of therapy failed to demonstrate statistically significant differences (Tables 6 - 8).

**Table 6 Applicant’s Analysis of Secondary Efficacy Variables: REC-C-001 (ITT)**

<b>-Time to VAS pain 50% improvement (days)</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>
<b>Median (95% CI)</b>	9 (7, 11))	12 (11, 15))
<b>p-value vs. Placebo*</b>		0.071

\*P-value calculated from log-rank test stratified by region, gender, and baseline VAS pain.

**Table 7 Applicant’s Analysis of Secondary Efficacy Variables: REC-C-001 (ITT)**

<b>VAS pain 50% improvement</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>
<b>Proportion for affirmative response</b>	59%	50%
<b>p-value vs. Placebo*</b>		0.131

\*P-value calculated from logistic regression model with terms for treatment, region, and gender, and baseline VAS pain as a covariate.

**Table 8 Applicant's Analysis of Secondary Efficacy Variables: REC-C-001 (ITT)**

<b>Patient Global Assessment</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>
<b>Proportion for affirmative response</b>	77%	82%
<b>p-value vs. Placebo*</b>		0.277

Note: The proportion for patient's affirmative response to question "*Do the benefits of the treatment outweigh any side effects?*"

\* P-value calculated from logistic regression with treatment, region, and gender as factors and baseline VAS pain as a covariate.

In summary, the primary analysis based on an ANCOVA model with conservative BOCF imputation strategy failed to demonstrate a statistically significant difference between Cellegesic and placebo. In addition, the continuous responder analysis treating dropouts as non-responders also failed to demonstrate a statistically significant separation between responder curves. LOCF analyses and a MMRM analysis demonstrated a statistically significant difference between treatments. However, these analyses are not informative because the pre-specified BOCF analysis failed and, in these two methods, dropouts resulting from a 'bad' outcome may artificially be assigned some benefit from treatment. In addition, the MMRM analysis is based on an untenable MAR assumption.

### 3.2 Evaluation of Safety

The evaluation of safety was conducted by the clinical reviewer, Neville Gibbs, M.D.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

I explored the heterogeneity of the treatment effect across age, race, and sex by inclusion of interaction terms in the ANCOVA model. In the analyses of primary efficacy variables, there were no statistically significant interactions between treatment and age group ('<55 yr.' or '≥55 yr. '), sex, or race group ('White' or 'Other'). I also conducted subgroup analyses, and my results can be found in the appendix (Tables 10).

## 5. SUMMARY AND CONCLUSIONS

## **5.1 Statistical Issues and Collective Evidence**

### **5.1.1 Statistical Issues**

Study REC-C-001 failed to demonstrate a significant analgesic effect of Cellegesic compared to placebo using the pre-specified ANCOVA model with a BOCF imputation strategy. Sensitivity analyses employing the last observation carried forward (LOCF) imputation strategy for missing data and a supportive analysis employing mixed model repeated measures (MMRM) demonstrated statistical significance. However, there were several concerns with the sensitivity and supportive analyses of the data. In chronic pain trials where the goal is to treat a symptom, patients who withdraw before the end of the study should be treated as non-responders, and little to no benefit should be assigned based on the pain scores before dropout. The applicant used the two LOCF methods to assess the impact of missing data on the primary analysis. Since the LOCF methods may have assigned 'good' scores to 'bad' outcomes, the methods were not considered conservative. Moreover in a chronic pain setting, a LOCF analysis may potentially provide supportive information only when a conservative analysis provides significant results. In my opinion, the successful LOCF analyses do not negate the failure of the more appropriate conservative analyses. Similarly, the MMRM analysis used pain data from patients who withdrew before the study ended thereby attributing some benefit to dropouts. Also in order for the MMRM method to be valid, missing at random (MAR) should be assumed as the mechanism generating missing data. However in chronic pain trials, missing data is often informative and therefore the MAR assumption is not supported.

### **5.1.2 Collective Evidence**

The applicant previously submitted three studies that were reviewed by the Division of Cardio-Renal Drug Products. Sufficient evidence of an analgesic effect was not found; therefore, the Division stated that an additional study was needed. Specifically, the action letter stated, "Before the application may be approved, however, it will be necessary for you to perform another trial with Cellegesic Ointment in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ( $p < 0.05$ )."

In response, the applicant submitted Study REC-C-001. In reviewing the evidence from the applicant's primary and sensitivity analyses as well as my additional analyses, I conclude that the data from Study REC-C-001 do not provide evidence of the efficacy of Cellegesic for treating moderate to severe pain associated with chronic anal fissure.

## **5.2 Conclusions and Recommendations**

Study REC-C-001, submitted as a complete response to an 'approvable' action, failed to demonstrate a statistically significant difference between Cellegesic and placebo. When considering the totality of the evidence, I find that there is not sufficient evidence to

conclude that Cellegesic Ointment is effective in treating pain associated with chronic anal fissures.

### **5.3 Review of Clinical Studies of Proposed Label**

The following portion of the Clinical Study section from the proposed label includes the applicant's results of data analyses from studies in the previous and current submissions. Only pooled analyses from studies in the previous and current submissions are presented and the failed result from the REC-C-001 is not presented. The pooled analyses are unacceptable. Based on my conclusions and the lack of clarity of a path forward for the product, I recommend that a thorough review of the label not be conducted.



(b) (4)



APPENDIX

Table 9 Patient Demographic and Baseline Characteristics: REC-C-001

	Cellegesic (n=123)	Placebo (n=124)
<b>Gender n (%)</b>		
Female	65 (53%)	66 (53%)
Male	58 (47%)	58 (47%)
<b>Race n (%)</b>		
White	99 (81%)	96 (77%)
Black	21 (17%)	16 (13%)
Asian	0 (0%)	2 (2%)
American Indian or Alaska Native	0 (0%)	3 (2%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1%)
Other	3 (2%)	6 (5%)
<b>Age (years)</b>		
Median	46	43
Range	18 – 74	21 – 73
<b>Average VAS Pain</b>		
Median	73	72
Range	13 – 100	51 – 100

**Table 10 Subgroup Analyses on Primary Efficacy Endpoint: REC-C-001**

<b>LS Mean Change (SE) from Baseline to average of Days 14 - 18 in 24-hour average pain *</b>	<b>Cellegesic (N=123)</b>	<b>Placebo (N=124)</b>
<b>White</b>	-40 (3.8)	-38 (3.9)
<b>Non-White</b>	-43 (6.0)	-27 (5.2)
<b>Age &lt;55</b>	-41 (3.7)	-34 (3.6)
<b>Age &gt;=55</b>	-38 (6.4)	-36 (5.8)
<b>Female**</b>	-41 (4.9)	-39 (4.9)
<b>Male**</b>	-40 (3.9)	-32 (3.8)

\*LSMeans calculated from ANCOVA/BOCF model with terms for treatment, region, and gender, and baseline VAS pain score as a covariate.

\*\*LSMeans calculated from ANCOVA/BOCF model with terms for treatment and region, and baseline VAS pain score as a covariate.

**Table 11 Study Design Advice from DAARP and Implementation**

<b>Advice</b>	<b>Study design</b>
Primary endpoint of pain at a specific time or an integral of pain over time.	Primary endpoint was 24 hour average pain intensity averaged over Days 14 to Day 18 of treatment.
Because of possible confounding, acetaminophen should be given to all patients as a standard regimen or not at all.	All patients were instructed to take a standard dose of 650 mg acetaminophen 30 minutes before each treatment; other analgesics were prohibited, except for low-dose aspirin (162 mg daily or 325 mg every other day) for cardiovascular prophylaxis.
Patients with a higher baseline pain score should be enrolled.	Only patients with baseline VAS scores of 50 mm or greater were enrolled.
Separate baseline and qualifying pain scores should be obtained.	A VAS score of 50 mm or greater was required on 2 of 4 days before Baseline and at the baseline visit.
A responder analysis should be performed. In this analysis, a zero change from baseline is imputed for patients who do not complete the study.	Responder analysis has been performed defined as a) 50% and b) 10 mm reduction on the VAS scoring. This analysis evaluates individual patterns of pain.
Collection of data on “worst pain” in 24 hours as a secondary measure.	As this parameter is linked to defecation, which may not occur daily, it was not considered appropriate for the study.
The reason for “dropout” should be captured in the CRF.	This information was captured in the CRF.
The ITT population should include all randomized patients who took at least one dose of study medication.	This definition was used for the ITT population in the study.
Before and after treatment vital signs should be obtained on all patients at least during initial visits. Vital signs should be measured at 5, 10, 30 and 60 minutes after dosing. Orthostatic hypotension assessments should be performed during all clinic visits.	Vital signs were measured at all study visits. At the Day 14 and 21 visits following supine blood pressure measurement, blood pressure was also measured one and 3 minutes after standing. At Days 0 and 7, vital signs were measured before application and at 5, 10, 30 and 60 minutes after treatment application. At the 30 minute time point blood pressure was measured at one and 3 minutes after standing. Symptoms of hypotension were recorded in the AE CRF, with the timing of the event noted.

A continuous responder analysis should be performed.	A continuous responder analysis has been performed.
A conservative approach to the analysis should be employed, i.e. use of zero change from baseline, as opposed to use of LOCF, for missing data for subjects who withdrew early	This strategy was employed for the primary and secondary analysis.

This table is excerpted from Table 4 in pages 24 – 25 of the study report.

**SIGNATURES/DISTRIBUTION LIST**

**Primary Statistical Reviewer:** Yongman Kim, Ph.D.  
Mathematical Statistician  
**Date:** February 23, 2010

**Concurring Reviewer:** Dionne Price, Ph.D.  
Team Leader

**cc:**

DAARP/Christopher Hilfiger  
DAARP/Neville Gibbs, M.D.  
DAARP/Robert Shibuya, M.D.  
HFD-715/Yongman Kim, Ph.D.  
HFD-715/Dionne Price, Ph.D.  
HFD-715/Thomas Permutt, Ph.D.  
HFD-700/Edward Nevius, Ph.D.  
HFD-700/Ram Tiwari, Ph.D.  
HFD-700/Lillian Patrician

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-21359

ORIG-1

PROSTRAKAN INC

CELLEGESIC NITROGLYCERIN  
OINTMENT 0.4%

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

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YONGMAN KIM  
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03/02/2010  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA #/Serial #:** 21-359  
**DRUG NAME:** Cellegesic Nitroglycerin Ointment 0.4% (Nitroglycerin)  
**INDICATION:** Relieve pain associated with chronic anal fissure  
**APPLICANT:** Cellegy Pharmaceuticals, Inc.  
**DATE:** July 7, 2004  
**REVIEW PRIORITY:** P  
**BIOMETRICS DIVISION:** Division of Biometrics I  
**STATISTICAL REVIEWER:** H.M. James Hung, Ph.D. (HFD-710)  
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**CLINICAL TEAM:** Tom Marciniak, M.D. (HFD-110)  
**PROJECT MANAGER:** Daryl Allis (HFD-110)

**KEY WORDS:** LOCF, generalized mixed effects model, rate of change, logrank, Kaplan-Meier, slope

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

The previously submitted placebo-controlled clinical study NTG 00-02-01 seems to give a hint of a possible benefit of relief of pain associated with chronic anal fissure with nitroglycerin ointment 0.4% bid for a short term use. Study CP 125 03-02-01 was completed to confirm this hypothesis. Based on the reviewer's evaluation, this study does not provide sufficient evidence in support of this hypothesis. The additional analyses for integrated summary of efficacy in the study report also add little to help conclude the claimed effect of pain relief.

### 1.2 Brief Overview of Clinical Studies

In the previous NDA Cellegy submitted two placebo-controlled clinical studies NTG 98-02-01 and NTG 00-02-01 to show NTG's efficacy. As reported in the joint medical/statistical review dated February 27, 2002, Study NTG 98-02-01 fails to demonstrate the benefit of anal fissure healing (the primary endpoint) with NTG. The secondary endpoint of anal pain relief seemed to suggest a possible effect for NTG ointment 0.4% BID, based on a post hoc analysis with a linear mixed effects model. Study NTG 00-02-01 was then conducted using anal pain relief as the primary endpoint. A mixed effects model analysis to evaluate the rate of change over time was specified in this study, but without details of the model terms to be used. The sponsor using a quadratic mixed effects model and evaluating the shapes of the curves claimed that there was a statistically significant difference in linear component coefficient for the 0.4% NTG compared to placebo. But, as argued in the Agency's review, the linear component coefficient in the quadratic mixed effects model is not the rate of change – the efficacy parameter in the hypothesis to be tested. In addition, some other issues of concern were raised in the review. Consequently, it could not be concluded that there is sufficient evidence to support the claimed benefit of anal pain relief associated with chronic anal fissure with the nitroglycerin ointment 0.4% bid. The NDA was withdrawn. It is noted by the sponsor that based on the data of NTG 00-02-01 and NTG 98-02-01, the pain decrease is linear over the first 21 days and there may be a real early treatment difference. So Study CP 125 03-02-01 was completed to demonstrate this possible early treatment effect on anal pain relief with nitroglycerin ointment 0.4% administered bid as compared to placebo in patients with chronic anal fissure. The sponsor concluded that nitroglycerin ointment 0.4% bid produces a statistically significantly greater decrease than placebo in pain associated with a chronic anal fissure for 21 days, based on a modified analysis that gives a p-value of 0.0498.

### 1.3 Statistical Issues and Findings

In Study CP 125 03-02-01, excluding two patients per treatment group in Russian site, all other placebo randomized patients completed the study up to Day 21. The NTG group had seven dropouts and additional four patients who were randomized but did not have any data. NTG appeared to relieve pain faster than the placebo, based on the data of the completers and the two dropouts (037-374, 037-380) who had complete data up to Day 21. If there were no bias, the p-

value of this analysis would be 0.059. One subject (#037-380) discontinued the drug due to drug-related headache but had post-discontinuation data. In the sponsor's primary analysis (p=0.0498), the actual observed data for this subject were replaced by the LOCF imputed data. The actual observed data and the LOCF imputed data are very different. If the actual observed data were used for this subject, then the p-value would be 0.0843. Moreover, protocol-defined primary analysis that imputes missing post discontinuation data due to headache (not just drug-related headache) gives p = 0.12, not statistically significant. Depending on how the post discontinuation data or missing data are handled, the reviewer's analyses show that p-value can range from 0.0309 to 0.15. The results of the analysis of completers and the two dropouts and any of the analyses presented in Table 6 (page 11) may have been substantially biased in favor of NTG for the following reasons. All the dropouts for Day 1-21 are in the NTG group. In six of the seven NTG dropouts, the average pain intensity seemed to trend toward worsening one or more days before discontinuation (Figure 2, page 13). For subjects 037-374 and 037-380 who had post discontinuation data after discontinuation, the pain scores of subject 037-380 got worse fast for at least a week immediately after discontinuation at Day 9. These response profiles imply that the proposed LOCF method even with variability added to the imputed pain scores might still overestimate the slope of the average pain change in these subjects. That is, the p-values of these analyses are likely to be smaller than what the unbiased p-value should be. Furthermore, it is not possible to guess how the additional four randomized NTG subjects who did not have data and were excluded from analysis would have performed had they been in the study. This uncertainty adds more difficulty to the analysis and the interpretation of the treatment comparisons. In summary, Study CP 125 03-02-01 does not provide sufficient evidence in support of the hypothesis that NTG reduces pain due to anal fissure to a larger extent than placebo during the first 21 days of the treatment.

For the integrated summary of efficacy, the sponsor presented a number of additional analyses in the study report. First, analyses of the three studies combined were performed. Second, new analyses of Study NTG 98-02-01 and Study NTG 00-02-01 were also performed to evaluate the possible pain relief effect for Day 1-21 in these studies. I'd argue that these analyses did not produce additional evidence in support of the claimed effect of pain relief with NTG ointment 0.4% bid for the following reasons. These analyses are not pre-specified and post hoc. These retrospective analyses performed on Study NTG 98-02-01 and Study NTG 00-02-01 that failed on the primary efficacy endpoint or produced uninterpretable treatment differences for Day 1-21 gave  $p < 0.0063$  for NTG 98-02-01 (with  $n = 32, 37$  for placebo, NTG) and  $p < 0.0388$  for NTG 00-02-01 (with  $n = 73, 68$  for placebo, NTG). It is not clear whether the missing values in these two studies were handled in the same way as in Study CP 125 03-02-01. Regardless, at best, these retrospective analyses may suggest a possible short-term pain relief effect. If NTG has a substantial effect on pain relief and the patient population remains the same, Study CP 125 03-02-01 with a larger sample size ( $n = 98, 89$  for placebo, NTG) should be able to demonstrate the effect with much larger power and achieve high statistical significance. On the contrary, CP 125 03-02-01 does not provide sufficient evidence in support of the claimed effect. Such inconsistency highlights the problem with interpretation of these analyses. The post hoc analyses for Day 1-56 have the same problem in addition to other problems discussed in this review and in the joint medical/statistical review dated 02/27/2002.

## 2. INTRODUCTION

### 2.1 Overview

In the previous NDA, Cellegy submitted two placebo-controlled clinical studies NTG 98-02-01 and NTG 00-02-01 to show NTG's efficacy. A joint medical/statistical review was completed on February 27, 2002. Study NTG 98-02-01 fails to demonstrate the benefit of anal fissure healing (the primary endpoint) with NTG. The secondary endpoint of anal pain relief seemed to suggest a possible effect for NTG ointment 0.4% BID, based on a post hoc analysis using a linear mixed effects model. Study NTG 00-02-01 was then performed using anal pain relief as the primary endpoint. A mixed effects model analysis to evaluate the rate of change over time was specified in this study, but without details of the model terms to be used. The sponsor using a quadratic mixed effects model and evaluating the shapes of the curves claimed that there was a statistically significant difference in linear component coefficient for the 0.4% NTG compared to placebo. The Agency's review argued that the linear component coefficient in the quadratic mixed effects model is not the rate of change – the efficacy parameter in the hypothesis to be tested. In addition, some other issues of concern were raised in the review. Consequently, it could not be concluded that there is sufficient evidence to support the claimed benefit of anal pain relief associated with chronic anal fissure with the nitroglycerin ointment 0.4% bid. The NDA was withdrawn. It is noted by the sponsor that based on the data of NTG 00-02-01 and NTG 98-02-01, the pain decrease is linear over the first 21 days and there may be a real early treatment difference. So Study CP 125 03-02-01 was launched to demonstrate this possible early effect on anal pain relief with nitroglycerin ointment 0.4% administered bid as compared to placebo in patients with chronic anal fissure. This review pertains to Study CP 125 03-02-01.

### 2.2 Data Sources

SAS datasets in \\CDSESUB1\N\_000\2004-06-30, \\CDSESUB1\N\_000\2004-09-21,  
\\CDSESUB1\N\_000\2004-10-05

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

Study CP125 03-02-01 was a multicenter, double-blind, parallel-group, randomized, placebo (vehicle)-controlled trial to evaluate the effect of Cellegesic NTG ointment 0.4% (375 mg bid) on the pain associated with chronic anal fissure. Subjects applied Cellegesic NTG ointment 0.4% or placebo ointment intra-anally b.i.d. for 56 days. Subjects recorded their 24-hour average pain intensity and pain intensity during the last bowel movement of the day (if any) using 100-mm visual analog scale (VAS) at bedtime for 21 days (primary efficacy endpoint) and continued daily through Day 56. At the visit on Day 21, the subject and investigator performed a global assessment in which they stated their opinion as to whether the subject had received study medication containing NTG or placebo. A subset (20 subjects) was asked to complete a more detailed diary on approximately Days 8 and 9 to assess pain relief and duration of pain relief between the morning and evening doses of study medication. Subjects withdrawing from the

study before the Day 56 close-out visit were asked to continue to record their 24-hour average pain intensity and pain intensity during the last bowel movement of the day through Day 56. Following the 56-day study period, all subjects were to be contacted by telephone every 3 months for 12 months to determine whether they received any subsequent treatments for their anal fissure. This 12-month follow-up phase of this study is ongoing.

According to the study report, a total of 150 subjects were planned for the study at 40 sites, and 193 subjects were enrolled at 29 sites and randomized to treatment (100 placebo subjects, 93 NTG subjects). The patient disposition is summarized in Table 1. Of the 193 subjects, 2 placebo patients and 4 NTG patients were lacking drug exposure information and had no efficacy assessments. So the ITT cohorts consists of 187 patients (98 in placebo, 89 in NTG). One Russia site (Site 043) was closed for cause after the first monitoring visit revealed a large number of egregious protocol violations. These patients were counted as withdrawals. Medical Reviewer's table (Table 5 of this review) gives a more detailed summary on subject disposition and data completeness to Day 21.

Table 1. Study Completion/Withdraw Information

[Source: Sponsor's Table 4, Tab 6.1, page 95, Volume 2.20, green jacket document]

Subject disposition	Placebo (N=100)	NTG (N=93)
Number of subjects completing 21-day treatment	100 (100%)	84 (90%)
Premature withdrawals before Day 21	0 ( 0%)	9 (10%)
Adverse event	0 ( 0%)	5 ( 5%)
Protocol violation	0 ( 0%)	0 ( 0%)
Non-compliance	0 ( 0%)	0 ( 0%)
Subject choice	0 ( 0%)	3 ( 3%)
Lost to follow-up	0 ( 0%)	1 ( 1%)
Other	0 ( 0%)	0 ( 0%)
Number of subjects completing 56-day treatment	92 ( 92%)	78 (84%)
Premature withdrawals before Day 56	8 ( 8%)	15 (16%)
Adverse event	2 ( 2%)	7 ( 8%)
Protocol violation	0 ( 0%)	0 ( 0%)
Non-compliance	0 ( 0%)	0 ( 0%)
Subject choice	3 ( 3%)	4 ( 4%)
Lost to follow-up	0 ( 0%)	0 ( 0%)
Other	3 ( 3%)	2 ( 3%)

The number and percent of subjects who received the most frequently used concomitant medications, taken by at least 5% of subjects in a treatment group, are in Table 2. Numerically, a larger proportion of placebo patients than NTG patients used analgesics through Day 21 and Day 56 (Table 3).

Table 2. Number (%) of subjects receiving concomitant medications taken by  $\geq 5\%$  of subjects  
 [Source: Sponsor's Table 6, Tab 3, page 45, Volume 2.20, green jacket document]

WHO Preferred Term	Placebo (N=98)	NTG (N=89)
Acetylsalicylic acid	9 ( 9%)	6 ( 7%)
diazepam	6 ( 6%)	6 ( 7%)
paracetamol	26 (27%)	36 (40%)

Table 3. Number (%) of subjects receiving analgesics in excess of the allowed amount during the study (ITT population)

[Source: Sponsor's Table 9, Tab 3, page 47, Volume 2.20, green jacket document]

	Placebo (N=98)	NTG (N=89)	p-value
Days 1 through 21	27 (28%)	20 (23%)	0.42
Days 1 through 56	29 (30%)	25 (28%)	0.82

The two treatment groups appeared comparable in demographic and baseline characteristics (Sponsor's Table 10, Tab 3, page 49, Volume 2.20, green jacket document). All subjects except one in the placebo group had an anal fissure. Overall, the treatment groups had similar results for their baseline assessment; however, the NTG group consistently had a greater proportion of subjects with additional fissure features, most notably visible internal anal sphincter fibers (61% of NTG subjects versus 48% of placebo subjects). The number of sitz baths over the course of study revealed no significant differences through 21 days ( $p = 0.20$ ) or 56 days ( $p=0.50$ ). Numerically, the NTG subjects took fewer sitz baths than the placebo patients.

#### Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of change of the 24-hour average pain intensity associated with chronic anal fissure over the first 21-day treatment period. It is noted in the study report that based on the data of Studies NTG 00-02-01 and NTG 98-02-01, the rate of pain decrease is linear over the first 21 days and the data are sufficiently Gaussian to apply a normal theory statistical method. The protocol pre-specified primary analysis for the primary efficacy variable will use a generalized mixed-effects regression model with a random intercept and linear time-trend. The primary hypothesis is tested via the linear component (i.e., slope) of the treatment-by-week interaction. This reviewer agrees that when the pain decrease follows a straight line model, the slope is the rate of change.

With respect to missing data, the protocol stated:

*“With respect to missing data, all available data from each placebo participant and each treatment participant who drops out for a reason other than headache will be used in the analysis. This assumes that the missing data before or after dropout are ignorable conditional on the available data and fixed-effects in the model (i.e., treatment). Since treatment is in the model, the effect of treatment on dropout due to headache is ignorable for the generalized mixed-effects regression model proposed in this study. It was determined by analysis of our prior*

*study (NTG 00-02-01) that VAS scores provide evidence that neither incidence of headache nor headache severity is statistically significantly related to the average rate of change in pain. This finding indicates that dropout due to headache was unrelated to the intensity of anal fissure pain, and if anything, participants drop out of the study due to headache once their anal fissure pain had remitted. There were 14 participants in Study NTG 00-02-01 (0.4% ointment) who discontinued the study and experienced headaches.”*

The sponsor determined that the participants who complained of headache had lower average pain scores over time compared to those without headache, and that there was no association between severity of headache and anal fissure pain for participants who dropped out of the study (the sponsor’s Figure 2 and Figure 3, Appendix 1.1, pages 350-351, Volume 2.21, green jacket document).

The protocol further stated:

*“Nevertheless, to eliminate any potential bias, for the participants treated with active CTM who leave the study due to headache, the last available observation (plus a simulated random error component based on the variance components structure from the model) will be carried forward to all subsequent measurement occasions. By adding the random error component, the imputed values will not be constant. The random error component will be simulated from a normal distribution with mean zero and variance equal to the residual variance from the model estimated from all available data. The CP125-treated subjects who drop out for reasons other than headache and placebo subjects who drop out regardless of reason will be treated as censored (i.e., all available data will be used in the analysis). Note that in all cases, we will make every attempt to obtain valid pain ratings from all subjects, including who dropped out. Where available, the post-dropout pain ratings will be used in the secondary analyses.”*

The study report stated that there were no amendments to the protocol. In Section 2.10.3.2 of the study report (Tab 2, Volume 2.20, green jacket document), it was stated:

*“All available data from each subject who dropped out for a reason other than headache were be used in the analysis. This procedure was based upon the assumption that the missing data before or after dropout could be ignorable conditional on the available data and fixed-effects in the model (i.e., treatment). Since treatment was in the model, the effect of treatment on dropout due to headache could be ignorable for the generalized mixed-effects regression model used in this analysis. However, to eliminate any potential bias, for subjects treated with Cellegesic NTG ointment 0.4% who discontinued due to NTG-related headache, a second analysis was performed in which the last available observation (plus a simulated random error component based on the variance components structure from the model) will be carried forward to all subsequent measurement occasions. Addition of the random error component resulted in imputed values that were not be constant. The random error component was simulated from a normal distribution with mean zero and variance equal to the residual variance from the model, estimated from all available data. Subjects who dropped out for reasons other than a NTG-related headache were treated as censored (i.e., all available data will be used in the analysis).”*

**Reviewer's comments**

Both analysis of all available data without imputation and analysis of all available data with imputation are planned in the protocol. According to Attachment #7 (page 9) of the document submitted on 9/21/2004, the analysis with imputation is primary and the analysis without imputation is secondary. In addition, according to the protocol, subjects who discontinued due to any headache were to have their last observation carried forward to impute the missing data. However, according to the study report, only subjects who discontinued due to NTG-related headaches (defined as a headache starting within 30 minutes of NTG administration) were to have their last observation carried forward for the missing data.

According to the study report, the NTG group had a numerically greater decrease in 24-hour average pain score than the placebo group over all time intervals; the difference between groups decreased as the trial continued. Subjects treated with NTG had a significantly greater decrease in average pain score than subjects treated with placebo over Days 1 to 21 ( $p < 0.0498$ ) and Days 1 to 56 ( $p < 0.0447$ ); see Table 4.

Table 4. Change in average VAS score for pain intensity by time period (ITT population)  
[Source: Sponsor's Table 13, Tab 3, page 51-52, Volume 2.20, green jacket document]

Time period	Placebo (N=98)		NTG (N=89)		p-value <sup>a</sup>
	N	Mean change	N	Mean change	
Baseline					
Day 7	93	-25.3	85	-28.0	< 0.31
Day 8	96	-23.5	84	-29.5	< 0.038
Day 9	98	-26.1	84	-30.7	< 0.12
Day 10	98	-27.0	84	-30.7	< 0.19
Day 11	98	-27.5	84	-32.4	< 0.071
Day 12	98	-29.0	84	-34.1	< 0.053
Day 13	98	-28.9	84	-33.2	< 0.091
Day 14	98	-27.7	84	-34.7	< 0.006
Day 15	98	-27.0	84	-34.8	< 0.002
Day 16	98	-28.5	83	-33.6	< 0.025
Day 17	98	-28.9	84	-36.3	< 0.003
Day 18	98	-30.1	84	-36.1	< 0.019
Day 19	98	-29.6	84	-35.0	< 0.042
Day 20	98	-31.2	84	-36.2	< 0.055
Day 21	94	-31.2	81	-35.3	< 0.053
Day 1-21	98	-24.9	89	-28.1	< 0.0309 <sup>b</sup> < 0.0498 <sup>c</sup>
Day 1-56	98	-33.8	89	-35.2	< 0.0447 <sup>b</sup>

<sup>a</sup> p-value determined by using a mixed-effect regression analysis

<sup>b</sup> Analysis using all available data from each subject up until the time of the exit visit or early withdrawal

<sup>c</sup> Analysis using LOCF for subjects clinically identified as withdrawing due to NTG-related headache

The average percent improvement appeared to rise over time in both treatment groups (Sponsor's Figure 3, Tab 3, page 54, Volume 2.20, green jacket document). The percent difference between placebo and NTG, defined as  $(\text{placebo score} - \text{NTG score}) / \text{placebo score} \times 100\%$ , in average pain intensity rose over time but appeared to start leveling off after Day 13 (Sponsor's Figure 4, Tab 3, page 55, Volume 2.20, green jacket document).

### Reviewer's analysis

In Table 5 provided by Dr. Tom Marciniak – Medical Reviewer, 195 (not 193) patients were randomized. Of them, two NTG patients were ineligible. The sponsor's randomized set has 100 subjects in the placebo group and 93 in the NTG groups. Of the 193 patients, two subjects per treatment group from the Russian site and one lost to follow up and one not dosed (both are in the NTG group) were excluded from the sponsor's analysis set. The sponsor's analysis data set contains 98 placebo subjects and 89 NTG subjects. Of the 89 NTG subjects, one (subject 037-367) discontinued due to subject choice, two (008-052, 037-159) discontinued due to headache and their post discontinuation data were imputed by the LOCF described above, and another two (005-070, 037-358) discontinued due to headache but they were censored at the time of discontinuation. In addition, two NTG subjects, 037-374 and 037-380, had post discontinuation data. Subject 037-380 had post discontinuation data and also the imputed data using the specified LOCF algorithm; the two data are quite different.

Table 5: Medical Reviewer's Subject Disposition and Data Completeness to Day 21

Category	Placebo		NTG	
	N	Subject ID	N	Subject ID
Randomized	100		95	
Ineligible	0		-2	008-049, 026-326
Sponsor's "randomized"	100		93	
Excluded Russian site	-2	043-149, 043-151	-2	043-150, 043-152
Lost to follow-up	0		-1	008-167
Subject choice D/C, not dosed	0		-1	017-054
Sponsor's analysis set	98		89	
Subject choice D/C, sponsor censored	0		-1	037-367
Headache D/C, sponsor LOCF	0		-2	008-052, 037-159
Headache D/C, sponsor censored	0		-2	005-070, 037-358
Data complete to day 21	98		84	
*Headache D/C, sponsor LOCF	0		-1	037-380
*More pain D/C, all data used	0		-1	037-374
Sponsor's "completed day 21"	98		82	

\* Diary to day 21; D/C = discontinued study drug

Table 6 presents a number of the reviewer's analyses performed because of differential dropouts between the two treatment groups. Note that subject 037-380 discontinued the drug due to drug-related headache but had post-discontinuation data. In the sponsor's primary analysis (p=0.0498), the actual observed data for this subject were replaced by the LOCF imputed data. The actual observed data and the LOCF imputed data are very different. It was said in Attachment #7 (page

9) of the 9/21/2004 document that from a statistical perspective it is preferable to use the actual observed data following study discontinuation, when available, as opposed to simply assuming that the missing data are consistent with the data prior to study discontinuation. If the actual observed data were used for this subject, then the p-value would be 0.0843. Moreover, protocol-defined primary analysis that imputes missing post discontinuation data due to headache (not just drug-related headache) gives  $p = 0.12$ , not statistically significant. Depending on how the post discontinuation data of the dropouts are handled, the p-value changes substantially from analysis to analysis, ranging from 0.0309 to 0.15.

Table 6. Primary efficacy endpoint – rate of change and mean change from baseline in average VAS score for pain intensity due to anal fissure at Day 21 (the sponsor's ITT patient population) [Source: Reviewer's analysis]

	Placebo (N=98)	NTG (N=89)	NTG - placebo in slope ( $\pm$ SE)	p-value
<b>Sponsor's primary analysis:</b> LOCF for discontinuation only due to drug-related headache <sup>1</sup>	-31.0	-34.6	$-0.29 \pm 0.15$	0.0498
Same as <sup>1</sup> , except using all available data for subject 037-380 <sup>2</sup>	-31.0	-34.5	$-0.26 \pm 0.15$	0.0843
LOCF for discontinuation due to all reasons, except using all available data for 037-374 <sup>3</sup>	-31.0	-34.6	$-0.25 \pm 0.15$	0.0943
Same as <sup>3</sup> , except also using all available data for subject 037-380 <sup>4</sup>	-31.0	-34.5	$-0.22 \pm 0.15$	0.15
<b>Protocol-defined primary analysis:</b> LOCF for discontinuation due to headache <sup>5</sup>	-31.0	-34.5	$-0.24 \pm 0.15$	0.12
Use all available data and do not impute missing data <sup>6</sup>	-31.0	-34.6	$-0.30 \pm 0.15$	0.0489
Delete post discontinuation data and do not impute missing data <sup>7</sup>	-31.0	-34.4	$-0.32 \pm 0.15$	0.0309

1 sponsor's primary analysis: impute post discontinuation data only for 008-052, 037-159, 037-380, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374

2 impute post discontinuation data only for 008-052, 037-159, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374, 037-380

3 impute post discontinuation data for 008-052, 037-159, 037-380, 005-070, 037-358, 037-367, use all available data for 037-374

4 impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, 037-367, use all available data for 037-374, 037-380

5 impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380

6 use all available data for 037-380 and 037-374, do not impute missing data for remaining five dropouts

7 delete post discontinuation data, do not impute

The NTG appeared to relieve pain faster than the placebo; see Figure 1 for completers plus the two dropouts (037-374, 037-380) who had complete data up to Day 21. If there were no bias, the p-value of this analysis (completers plus these two dropouts) would be 0.059. However, the results of this analysis and any of the analyses presented in Table 6 may have been substantially biased in favor of NTG for the following reasons. The placebo group did not have a dropout. All seven dropouts are in the NTG group; their average pain intensity profiles are plotted in Figure 2. In six of the seven dropouts, the average pain intensity seemed to trend toward worsening one or more days before discontinuation. For subjects 037-374 and 037-380 who had post discontinuation data after discontinuation, only subject 037-374 had pain score trending flat after discontinuation. The pain scores of subject 037-380 got worse fast for at least a week immediately after discontinuation at Day 9. These response profiles imply that the proposed LOCF method even with variability added to imputed pain scores might still overestimate the slope of the average pain change for these subjects. That is, the p-values as given in Table 6 are likely to be smaller than what the unbiased p-value should be. In addition, the NTG group has four randomized subjects who were declared ineligible, lost to follow up or not dosed. These four patients had no data and were excluded from analysis. It is certainly not possible to guess how these subjects would have performed had they been in the study. This uncertainty adds difficulty to the analysis and the interpretation of the treatment comparisons. In sum, this study fails to provide sufficient evidence in support of the hypothesis that NTG reduces pain due to anal fissure during the first 21 days of the treatment.

Figure 1. Mean change from baseline in average pain intensity in the completers and the two dropouts (037-374 and 037-380) who had post discontinuation data up to Day 21

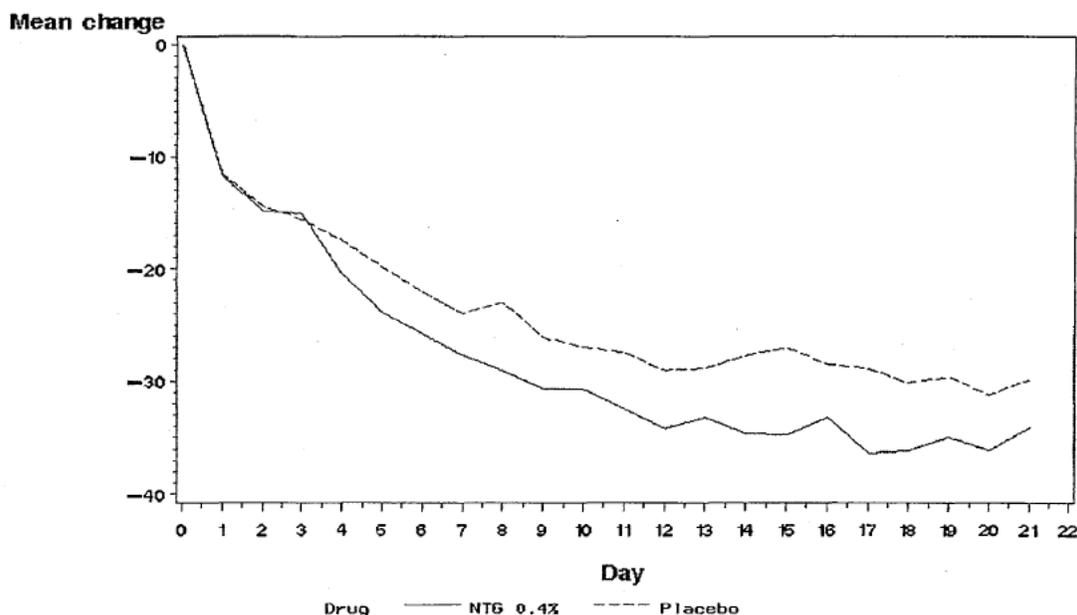


Figure 2. 24-hour Average Pain Intensity of Dropouts up to Day 21  
 [ subject 037-374 discontinued on Day 5 and subject 037-380 discontinued on Day 9 ]

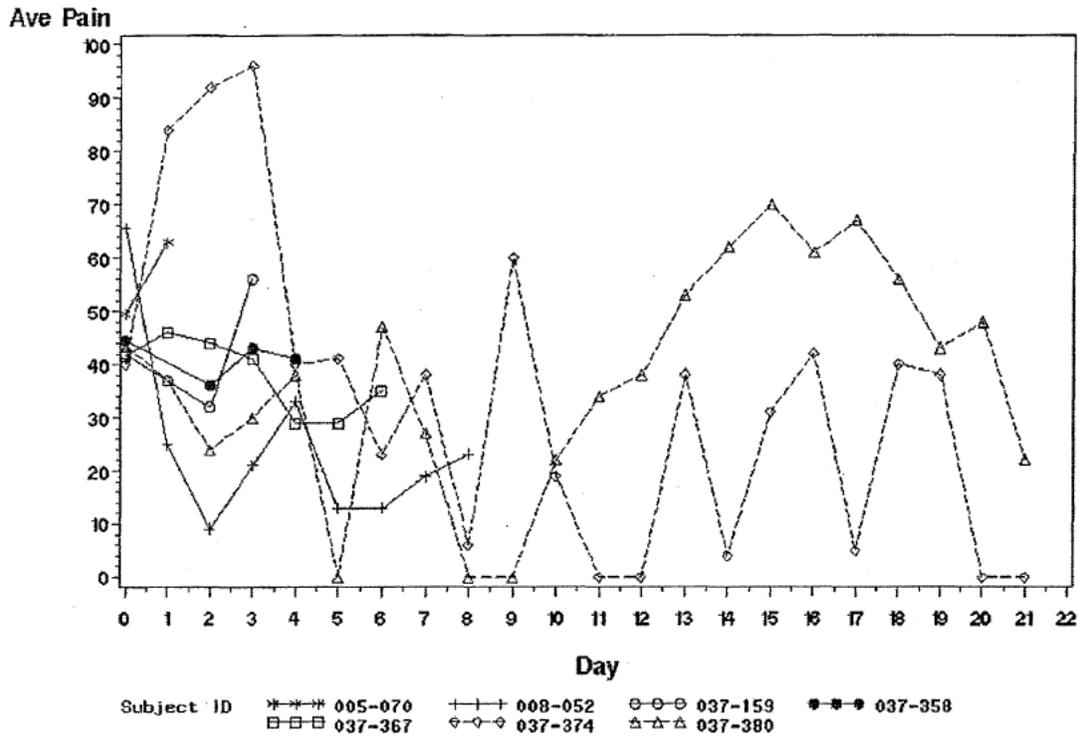


Table 7 provides the mean change from baseline in average pain intensity score at Day 21 by site, based on the protocol-specified primary analysis (i.e., impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380 and completers). Of the 17 sites, as compared to placebo, NTG was numerically substantially worse in 6 sites, not much different in 3 sites (difference is less than one), substantially better in 8 sites. This by-site result adds little to support NTG on potential pain relief effect.

Table 7. Mean change from baseline in average pain intensity score at Day 21 by site – protocol specified primary analysis (i.e., impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380 and completers)

[Source: Reviewer's analysis]

Site #	Placebo (N=98)		NTG (N=89)	
	n	Mean change	n	Mean change
24	10	-31.5	10	-44.4
26	4	-42.5	3	-38.2
32	6	-30.7	6	-48.4
33	6	-41.6	6	-27.8
35	8	-26.6	7	-26.4
37	10	-26.4	10	-10.9
41	8	-16.2	8	-35.1
42	4	-44.6	4	-43.9
44	4	-28.8	4	-38.6
100	6	-19.3	3	-39.3
101	6	-28.2	3	-34.6
102	4	-26.0	4	-43.9
103	4	-36.8	4	-27.3
104	3	-49.0	4	-39.5
105	4	-30.5	3	-25.0
106	5	-32.2	4	-32.5
107	6	-41.7	6	-47.6

### Secondary Efficacy Endpoint

The secondary efficacy endpoint was time to 50% improvement in the three-day average (i.e., moving window) of 24-hour average pain intensity measurements associated with a chronic anal fissure. This variable was analyzed using a Cox log rank test comparing the Kaplan-Meier survival curves. According to the study report, no statistically significant between-group differences were observed ( $p = 0.29$ ), though numerically the difference seems to trend in favor of the NTG group (75% of the NTG treated subjects achieved 50% improvement 7 days earlier than 75% of the placebo patients achieved 50% improvement (the sponsor's Figure 5, page 56, Tab 3, Volume 2.20, green jacket document).

### Tertiary Endpoints

The protocol lists the following four tertiary endpoints:

- rate of change of the 24-hour average pain intensity associated with a chronic anal fissure over a 56-day treatment period
- rate of change of the pain intensity during the last bowel movement of the day (if any) associated with a chronic anal fissure over a 21-day treatment period

- rate of change of the pain intensity during the last bowel movement of the day (if any) associated with a chronic anal fissure over a 56-day treatment period
- complete healing of chronic anal fissure over a 56-day treatment period

There was virtually no difference between the NTG group and the placebo group in average number of days to complete healing of chronic anal fissure over a 56-day treatment period (46 days for NTG versus 47 days for placebo).

Table 8 summarizes the sponsor's results on other tertiary endpoints. For pain intensity variables for Day 1 through Day 56, a quadratic term was added to the model to incorporate the curvilinearity of the temporal response curves, due to the suggestion from the longitudinal response patterns in the previous two studies. And indeed, the quadratic term was also highly nominally significant in Study C0 125 03-02-01. However, there are several reasons why the results of Table 8 for the Day1-56 analyses are difficult to interpret. Firstly, the parameter associated with the reported nominal p-value is not the rate of change in pain intensity over 56 days. As the sponsor reported, the p-values in Table 8 are for the treatment differences in the linear component coefficient of the quadratic mixed-effect model (this is in contrast with the Day 1-21 analysis where the mixed-effect model is linear and thus the treatment difference in the linear component coefficient is indeed the treatment difference in the rate of change in pain density). This point was elaborated in the joint medical/statistical review of 2/27/2002 for Studies NTG 98-02-01 and NTG 00-02-01. Secondly, there were additional 14 subjects (6 in placebo, 8 in NTG) who discontinued between Day 21 and Day 56. The Sponsor's analyses that generate the nominal p-values in Table 8 used all available data from each subject up to the time of the exit visit or early withdrawal; no imputation was performed. Like the Day 1-21 analyses in Table 6, these all-available-data analyses would give a smaller p-value than the imputed analysis. Thirdly, there is no pre-specified statistical significance criterion for any of these tertiary endpoints in the protocol. Therefore, statistical significance of the nominal p-value cannot be assessed in the context that the overall type I error of these endpoints needs to be controlled at a level much less than two-sided 0.05. No primary analysis is specified, either. Nor is specified the way of how to handle missing values occurring between Day 21 and Day 56. Thus, these results are purely exploratory and at best to generate hypotheses for future studies. In Section 2.10.3.2 of the study report (Tab 2, Volume 2.20, green jacket document), it was stated:

*“To adjust for the multiple comparisons, all secondary and tertiary analyses (time to 50% pain reduction, rate of change in pain over 56 days, proportion healed) were tested by using Holm's 1979 stepdown method.”*

Based on this method, none of the secondary and tertiary endpoint reached statistical significance.

Table 8. Change in VAS score for pain intensity due to anal fissure in 56 days (ITT population)  
 [Source: excerpted from Sponsor's Tables 13,15, Tab 3, pages 51, 57, Volume 2.20, green jacket document]

Time period	Placebo (N=98)		NTG (N=89)		nominal p-value <sup>a</sup>
	N	Mean change	N	Mean change	
Average pain					
Day 1-56	98	-33.8	89	-35.2	< 0.0447 <sup>b</sup>
Pain during the last bowel movement					
Day 1-21	98	-14.1	89	-19.2	< 0.0719
Day 1-56	98	-22.4	89	-27.9	< 0.0306

<sup>a</sup> p-value determined by using a mixed-effect regression analysis

<sup>b</sup> Analysis using all available data from each subject up until the time of the exit visit or early withdrawal

### 3.2 Evaluation of Safety

Please read Dr. Marciniak's review for safety assessment.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

Numerically, there seems to be a larger mean reduction and a larger reduction in rate of decrease in average pain score in males than in females (Table 98).

Table 9. Subgroup results on primary efficacy endpoint – rate of change and mean change from baseline in average VAS score for pain intensity due to anal fissure at Day 21

[Source: Reviewer's analysis]

	Placebo (N=98)		NTG (N=89)		NTG - placebo in slope ( $\pm$ SE)
	n	Mean change	n	Mean change	
Male	37	-31.1	30	-39.1	-0.37 $\pm$ 0.23
Female	61	-30.9	59	-32.1	-0.16 $\pm$ 0.20
Caucasian	94	-31.4	84	-34.8	-0.25 $\pm$ 0.16
Black		9.0		-34.5	NE
Others	1	-31.2	3	-20.3	NE
	3		2		
Age < 65	91	-31.5	81	-33.5	-0.22 $\pm$ 0.16
Age $\geq$ 65		-24.5		-47.6	-0.60 $\pm$ 0.41
	7		8		

NE: not estimable

## 4.2 Other Special/Subgroup Populations

None.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

Study NTG 98-02-01 failed to demonstrate the benefit of anal fissure healing (the primary endpoint) with NTG. The secondary endpoint of anal pain relief seemed to suggest a possible effect for NTG ointment 0.4% BID, based on a post hoc analysis with a linear mixed effects model. So the sponsor performed Study NTG 00-02-01 using anal pain relief as the primary endpoint. A mixed effects model analysis to evaluate the rate of change over time was specified in this study, but without details of the model terms to be used. The sponsor using a quadratic mixed effects model and evaluating the shapes of the curves claimed that there was a statistically significant difference in linear component coefficient for the 0.4% NTG compared to placebo. But the linear component coefficient in the quadratic mixed effects model is not the rate of change – the efficacy parameter in the hypothesis to be tested.

The sponsor noted that based on the data of NTG 00-02-01 and NTG 98-02-01, the rate of pain decrease is linear over the first 21 days (so the rate of pain decrease is indeed the linear component coefficient) and there may be a real early treatment difference. So Study CP 125 03-02-01 was set out to demonstrate this early treatment effect on anal pain relief.

In Study CP 125 03-02-01, excluding two patients per treatment group in Russian site, all other placebo randomized patients completed the study up to Day 21. The NTG group had seven dropouts and additional four patients who were randomized but did not have any data. NTG appeared to relieve pain faster than the placebo, based on the data of the completers and the two dropouts (037-374, 037-380) who had complete data up to Day 21. If there were no bias, the p-value of this analysis would be 0.059. One subject (#037-380) discontinued the drug due to drug-related headache but had post-discontinuation data. In the sponsor's primary analysis (p=0.0498), the actual observed data for this subject were replaced by the LOCF imputed data. The actual observed data and the LOCF imputed data are very different. If the actual observed data were used for this subject, then the p-value would be 0.0843. Moreover, protocol-defined primary analysis that imputes missing post discontinuation data due to headache (not just drug-related headache) gives p = 0.12, not statistically significant. Depending on how the post discontinuation data or missing data are handled, the reviewer's analyses show that p-value can range from 0.0309 to 0.15. The results of the analysis of completers and the two dropouts and any of the analyses presented in Table 6 (page 11) may have been substantially biased in favor of NTG for the following reasons. All the dropouts for Day 1-21 are in the NTG group. In six of the seven NTG dropouts, the average pain intensity seemed to trend toward worsening one or more days before discontinuation (Figure 2, page 13). For subjects 037-374 and 037-380 who had post discontinuation data after discontinuation, the pain scores of subject 037-380 got worse fast for at least a week immediately after discontinuation at Day 9. These response profiles imply that the

proposed LOCF method even with variability added to the imputed pain scores might still overestimate the slope of the average pain change in these subjects. That is, the p-values of these analyses are likely to be smaller than what the unbiased p-value should be. Furthermore, it is not possible to guess how the additional four randomized NTG subjects who did not have data and were excluded from analysis would have performed had they been in the study. This uncertainty adds more difficulty to the analysis and the interpretation of the treatment comparisons. In summary, Study CP 125 03-02-01 does not provide sufficient evidence in support of the hypothesis that NTG reduces pain due to anal fissure to a larger extent than placebo during the first 21 days of the treatment.

For the integrated summary of efficacy, the sponsor presented a number of additional analyses in the study report. First, analyses of the three studies combined were performed. Second, new analyses of Study NTG 98-02-01 and Study NTG 00-02-01 were also performed to evaluate the possible pain relief effect for Day 1-21 in these studies. I'd argue that these analyses did not produce additional evidence in support of the claimed effect of pain relief with NTG ointment 0.4% bid for the following reasons. These analyses are not pre-specified and post hoc. These retrospective analyses performed on Study NTG 98-02-01 and Study NTG 00-02-01 that failed on the primary efficacy endpoint or produced uninterpretable treatment differences for Day 1-21 gave  $p < 0.0063$  for NTG 98-02-01 (with  $n = 32, 37$  for placebo, NTG) and  $p < 0.0388$  for NTG 00-02-01 (with  $n = 73, 68$  for placebo, NTG). It is not clear whether the missing values in these two studies were handled in the same way as in Study CP 125 03-02-01. Regardless, at best, these retrospective analyses may suggest a possible short-term pain relief effect. If NTG has a substantial effect on pain relief and the patient population remains the same, Study CP 125 03-02-01 with a larger sample size ( $n = 98, 89$  for placebo, NTG) should be able to demonstrate the effect with much larger power and achieve high statistical significance. On the contrary, CP 125 03-02-01 does not provide sufficient evidence in support of the claimed effect. Such inconsistency highlights the problem with interpretation of these analyses. The post hoc analyses for Day 1-56 have the same problem in addition to other problems discussed in this review and in the joint medical/statistical review dated 02/27/2002.

## 5.2 Conclusions and Recommendations

The previous placebo-controlled clinical study NTG 00-02-01 seems to give a hint of a possible benefit of relief of pain associated with chronic anal fissure with nitroglycerin ointment 0.4% bid for a short term use (21 days). Study CP 125 03-02-01 was completed to confirm this hypothesis. Based on the reviewer's evaluation, this study does not provide sufficient evidence in support of this hypothesis. The additional analyses for integrated summary of efficacy in the study report also add little to help conclude the claimed effect of pain relief.

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