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

Review file: c:\data\my ocuments\review\nda\cellegesic_3.doc

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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 nitroglycern 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 nitroglycern 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 ≥ 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:

"A*ll 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[a]
	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[b] < 0.0498[c]
Day 1-56	98	-33.8	89	-35.2	< 0.0447[b]

[a] p-value determined by using a mixed-effect regression analysis
[b] Analysis using all available data from each subject up until the time of the exit visit or early withdrawal
[c] 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 (placebo score – NTG score)/placebo score x 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 (± SE)	p-value
Sponsor's primary analysis: LOCF for discontinuation only due to drug-related headache [1]	-31.0	-34.6	-0.29 ± 0.15	0.0498
Same as [1], except using all available data for subject 037-380 [2]	-31.0	-34.5	-0.26 ± 0.15	0.0843
LOCF for discontinuation due to all reasons, except using all available data for 037-374 [3]	-31.0	-34.6	-0.25 ± 0.15	0.0943
Same as [3], except also using all available data for subject 037-380 [4]	-31.0	-34.5	-0.22 ± 0.15	0.15
Protocol-defined primary analysis: LOCF for discontinuation due to headache [5]	-31.0	-34.5	-0.24± 0.15	0.12
Use all available data and do not impute missing data [6]	-31.0	-34.6	-0.30 ± 0.15	0.0489
Delete post discontinuation data and do not impute missing data [7]	-31.0	-34.4	-0.32 ± 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 0374-380) who had post discontinuation data up to Day 21

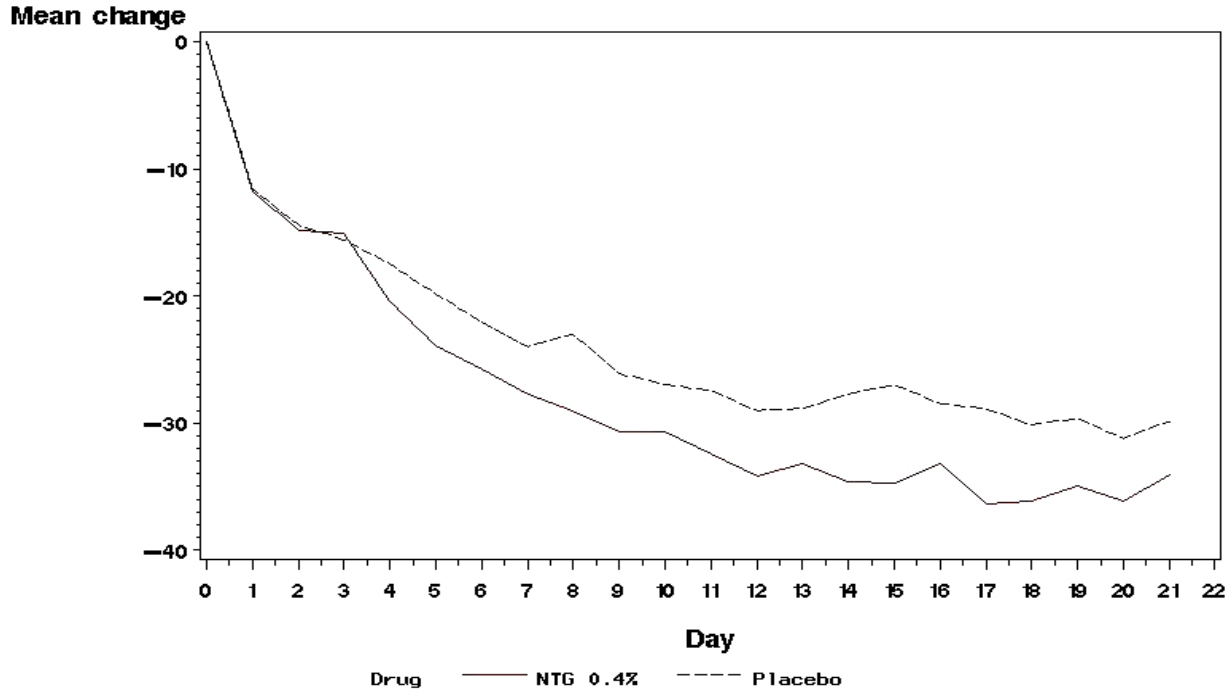

Figure 2. 24-hour Average Pain Intensity of Dropouts up to Day 21
[subject 037-374 discontinued on Day 5 and subject 037-380 discontinued on Day 9]

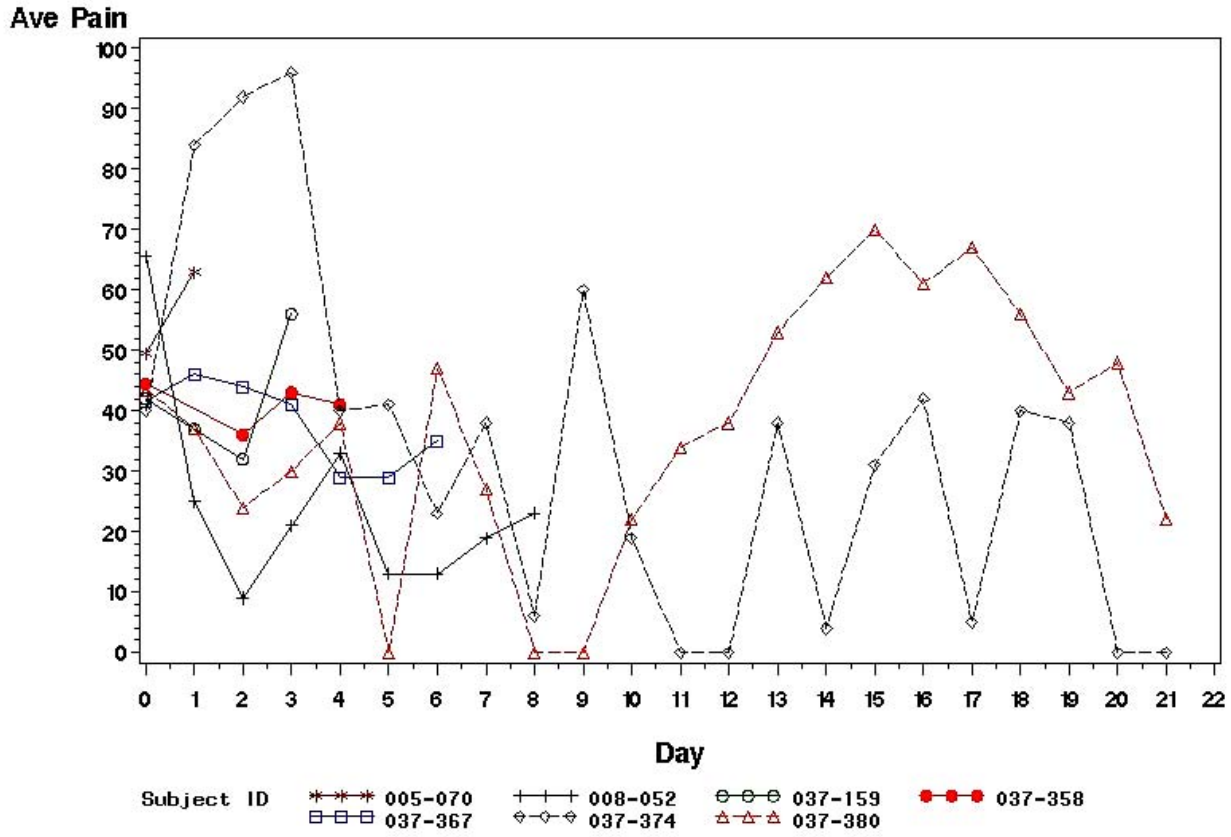

Table 7 provides the mean change from baseline in average pain intensity score at Day 21 by site, based on the protocol-specified primary analysis (i.e., impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 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 basline 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]

	Placebo (N=98)		NTG (N=89)	
Site #	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 curvilineariy 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[a]
	N	Mean change	N	Mean change	
Average pain Day 1-56	98	-33.8	89	-35.2	< 0.0447[b]
Pain during the last bowel movement Day 1-21 Day 1-56	98 98	-14.1 -22.4	89 89	-19.2 -27.9	< 0.0719 < 0.0306

[a] p-value determined by using a mixed-effect regression analysis
[b] 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 (± SE)
	n	Mean change	n	Mean change	
Male	37	-31.1	30	-39.1	-0.37 ± 0.23
Female	61	-30.9	59	-32.1	-0.16 ± 0.20
Caucasian	94	-31.4	84	-34.8	-0.25 ± 0.16
Black		9.0		-34.5	NE
Others	1 3	-31.2	3 2	-20.3	NE
Age < 65	91	-31.5	81	-33.5	-0.22 ± 0.16
Age ≥ 65	7	-24.5	8	-47.6	-0.60 ± 0.41

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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/s/

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