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21-359

MEDICAL REVIEW(S)

Clinical Review of Complete Response

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Reviewer Name(s) Neville A. Gibbs MD, MPH
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Established Name Nitroglycerin 0.4% Ointment
(Proposed) Trade Name Brandname (to be determined)
Therapeutic Class Nitrate
Applicant Prostrakan Inc

Formulation(s) NTG 0.4% (nitroglycerin) 0.4%
Dosing Regimen 1.5 mg bid intra-anally
Indication(s) Treatment of pain associated
with chronic anal fissure
Intended Population(s) Adults with Chronic Anal
Fissure

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The data submitted in this resubmission in response to a March 30th 2010 Complete Response letter, support the approval of NTG 0.4% (nitroglycerin, 0.4% ointment) for the indication of the treatment of pain associated with chronic anal fissure.

This recommendation is based on the review of the efficacy and safety data submitted by the Applicant, ProStrakan Inc, for this population of adult study participants with Chronic Anal Fissure (CAF).

NTG 0.4% has a long regulatory history that is summarized in Section 3 of the review.

With this resubmission, the efficacy of Trial REC-C-001, a randomized, double-blind, placebo-controlled, parallel-group study was reanalyzed, utilizing a hybrid LOCF/BOCF method of imputing missing data. A total of 123 patients were treated with nitroglycerin (NTG) 0.4%. Trial REC-C-001 initially failed to demonstrate efficacy because the study failed to meet the prospectively defined primary and secondary end points. The review of the safety data in this complete response to the March 30th 2010 CR Letter did not change the impression of the adverse event profile of this drug.

1.2 Risk Benefit Assessment

In the current submission, Prostrakan demonstrated that NTG 0.4% is effective in treating pain in patients with CAF.

The adverse events associated with use of the product are predominantly headache and slight decrease in systolic and diastolic blood pressure at the time of application of the ointment. These adverse events are self-limited, treatable (headache is treated with acetaminophen) and monitorable.

With the demonstration of effectiveness and the relative safe use of this product, the risk benefit relationship favors approval of this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Post approval Risk Evaluation and Mitigation Strategies (REMS) are not required to ensure safe use of this drug as trials have demonstrated that the drug is relatively safe to use, and without any serious adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no post-marketing requirements and commitment recommendations for this product

1.5 Summary of Clinical Findings

1.5.1 Brief Overview of Clinical Program

The applicant's Complete Response resubmission of NDA 21359, dated December 20th, 2010 contains a single efficacy and safety study, Trial REC-C-001 which was reviewed during the previous review cycle. No new clinical efficacy data was submitted; only the results of the two techniques for the imputation of missing data was proposed and submitted for approval.

The only new safety data was newer post marketing safety data received by the applicant during the period May 1st 2009 through October 23rd 2010.

Three additional studies NTG 98-03-01, NTG 00-03-01 and CP125 03-03-01 were performed earlier during the drug development. The results of these yielded an approvable action letter in 2006.

1.5.2 Efficacy

This Complete Response resubmission of NDA 21359, dated December 20th, 2010 contains a single efficacy and safety study, Trial REC-C-001 which was reviewed during the previous review cycle. No new clinical efficacy data was submitted; only the results of the two techniques for the imputation of missing data was proposed and submitted for approval.

The single efficacy and safety study REC-C-001 was a resubmission of NDA 21,359. Using the protocol-specified, conservative statistical analysis, the trial failed to show a statistically significant difference in pain intensity from baseline ($p=0.118$). A complete response letter was issued to the applicant.

(Full details of the efficacy analysis may be obtained by reviewing my March 2010 review)

Following discussions between the applicant and the Agency and after a Formal Dispute Resolution Request and appeal was denied by the ODE Director, two additional methods of imputing missing data were suggested to the applicant. The methodology and the results of these imputations formed the basis of the December 30th 2010 resubmission. These imputations included the Retrieved Drop-Out imputation method and the LOCF/BOCF hybrid imputation analysis method. The first method of imputation, the retrieved-dropout methodology, failed to demonstrate statistical significance. The second method, a hybrid of LOCF and BOCF method, demonstrated statistical significance. This latter method used LOCF imputation for patients who withdrew because of early effective pain relief, such that their condition did not require further therapy. With this imputation methodology, the Agencies Clinical-Statistical Team was able to retrieve the dropouts, and to determine that they their pain was successful treated.

However, the revised ANCOVA analysis approach for the primary efficacy endpoint using the LOCF/BOCF hybrid approach to imputation of data for 27 patients demonstrated that the effect of nitroglycerin ointment compared to placebo in reducing pain associated with CAF was statistically significant at the 5% level ($p=0.038$).

1.5.3 Safety

Details of the safety of 0.4% NTG in the treatment of CAF can be obtained by reviewing my prior report of March 2010. The only new safety data was newer post marketing safety data received by the applicant during the period May 1st 2009 through October 23rd 2010.

In Study REC-C-001, there were no deaths. There were a total of 3 serious adverse events (SAEs) which were not related to study drug. A total of 13 patients discontinued due to adverse events. The majority of these discontinuations were related to headache.

A total of 9 patients (7.3%) in the Cellegesic group and 4 patients (3.2%) in the placebo group had AEs that were classified as leading to treatment discontinuation. The most common AE leading to treatment discontinuation was headache.

The most common AEs in the NTG 0.4% group were headache and dizziness. Headaches in the NTG 0.4% group were mostly mild, and overall, were of a shorter duration than those in the placebo group. The incidence of other AEs

was similar in the 2 groups and there were no other obvious trends in the number of reported AEs.

The incidence of orthostatic hypotension occurred in similar proportions of patients in both groups after the first application of the study ointment at Visit 1 (12.3% of NTG 0.4%, 12.2% of placebo). The incidence of orthostatic hypotension was lower in both groups at the next visit approximately 7 days later.

There were no obvious trends in the shift from baseline or the actual and change from baseline results for hematology, serum chemistry, urinalysis, physical examination, or ECG results. Serum markers for hepatotoxicity were comparable between the NTG 0.4% and placebo groups.

The data from Study REC-C-001 were consistent with the safety profile characterized in prior review cycles.

No new safety information was submitted with the latest submission, except for the world-wide safety periodic safety update reports. NTG 0.4% is currently approved in 24 countries. The applicant submitted all safety information received during the period May 01, 2009 through October 23, 2010, with an estimated patient exposure of 44,748 patient treatment years.

During this review period, the applicant received a total of 43 case reports that were possibly associated with NTG ointment. The most common individual reactions were – headache (17), hypotension (5), off-label use (5), dizziness (4) and tachycardia. Headache was the most frequent adverse events were similar to recognized adverse events in the randomized, double-blind, parallel group confirmatory Trial REC-C-001.

The safety data submitted supports a favorable safety profile for topical NTG ointment. No new safety concerns have been identified since the resubmission of NDA 21-359 on September 30, 2009.

2. INTRODUCTION AND BACKGROUND

NTG 0.4% ointment includes the active ingredient nitroglycerin (NTG) at a concentration of 0.4%. The product is intended for administration as two 1.5 mg doses intra-anally, approximately 12 hours apart, resulting in a total daily dose of 3 mg.

The proposed indication is for the treatment of pain associated with chronic anal fissure in adult patients with this disease.

This 505(b) (2) application relies in part on FDA's findings of safety for the Reference Drug (RD), Nitro-Dur (Key Pharmaceuticals, NDA #020145).

Currently there are no approved prescription drugs in the United States for the treatment of pain associated with chronic anal fissure (CAF). Pharmacologic treatments are usually the first-line treatment for chronic fissures. Locally compounded formulations of topical NTG are currently used; however the quality of and concentration of NTG in these preparations are reported to be variable. Consequently, the applicant purports that NTG 0.4% has been developed to provide a standardized, optimal concentration NTG formulation intended for anodermal application for the treatment of pain associated with CAF.

Other pharmacological treatments and their mechanism of effecting relief include the following:

- o Calcium channel blockers – thought to reduce the pressure of the internal anal sphincter
- o Botulinium toxin (Botox), when injected into the anal sphincter- causing temporary paralysis of the muscle, which reduces muscle tension and helps to heal the anal fissure.

Surgery is typically performed when more conservative measures fail to heal the fissure. An undesired adverse effect of this surgery is fecal incontinence and recurrence of anal fissure.

This resubmission of NDA 21,359 and Response to Approvable letter, dated December 20th, 2010 contains a single efficacy and safety study, Trial REC-C-001. Trial REC-C-001 was conducted from August 2007 to July 2008 and reported in the prior NDA resubmission, dated September 30, 2009. A Complete Response was issued on March 30th 2010, as the trial failed to show statistical evidence of effectiveness.

A total of 123 patients were exposed to study medication in trial REC-C-001. The most common AE's were headache and dizziness. Adverse events are self-limited, treatable and monitorable. Evaluation of the post-marketing periodic safety reports confirmed the relative safety of this preparation and the tendency to cause headaches and a sensation of dizziness.

This December 20th 2010 resubmission proposes two new analyses for the primary end-point in this confirmatory Phase 3 trial, REC-C-001. No new clinical efficacy data was submitted; only the results of the two techniques for the imputation of missing data were submitted for approval. Based on the results of this analysis, a determination will be made on the effectiveness of NTG 0.4% for the treatment of CAF.

Further details on methodology and results of both imputation methods are discussed in the efficacy section of this report.

The clinical review of this complete response will focus on the clinical deficiencies listed in the March 30th 2010 CR letter. These are noted in tabular form below in Table 2.

All other issues for approval were addressed in the previous submission.

Therefore, this review will focus on the deficient areas identified in the areas identified in the table below.

TABLE 2: SHOWING DEFICIENCIES COMMUNICATED IN CR LETTER (3/30/10) AND RECOMMENDATIONS TO ADDRESS THE ISSUES

| DEFICIENCIES COMMUNICATED IN MARCH 30 th 2010 CR LETTER | RECOMMENDATIONS TO ADDRESS THE ISSUES |
|--|--|
| CLINICAL | |
| EFFICACY: Failure of REC-C-001 to demonstrate statistically significant evidence of efficacy using pre-specified conservative analysis | Use of modified strategies for the imputation of missing data in confirmatory trial REC-C-001. |
| SAFETY: Safety update to include data from all non-clinical and clinical trials | Provide summary of world-wide experience on the safety of this drug. |
| PROPOSED PEDIATRIC DRUG DEVELOPMENT PLAN is incomplete. | Pediatric studies must include an assessment of safety and tolerability, pharmacokinetics and efficacy |
| LABELING | Division reserved comment on labeling until the application is otherwise adequate |
| SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | |
| FAILURE to adequately demonstrate that NTG 0.4% when used in maximal dosing regimen produces plasma exposures of NTG and its metabolites which are within the same range as one or more reference listed Drug, Nitro-Dur. The requirement of Nonclinical bridging and repeat-dose toxicology studies was communicated to the sponsor. | Issue adequately addressed by reviewing trials within the public realm. Exposure levels produced by NTG 0.4% fall within the levels produced by other NTG products. The non-clinical deficiency was rescinded and the requirement to perform nonclinical bridging studies was withdrawn. |
| FAILURE to adequately demonstrate comparability of the drug product quality from proposed commercial manufacturing site to the clinical site and other CMC deficiencies pertaining to critical quality of drug product | Manufacturing issues are addressed in CMC report by Dr Olen Stephens |

Source: FDA Compilation from the March 30th 2010 CR Letter

This review will focus on the following areas identified:

- o The Pre-Submission Regulatory History (Section 3)
- o The methodology and the results of both imputation methods for the analysis of missing data in trial REC-C-001, for the determination of efficacy (Section 4)
- o Updated safety information, including post-marketing worldwide safety (Section 5)
- o Proposed pediatric drug development plan (Section 6)
- o Labeling Review (Section 7)

Additional significant efficacy/safety issues related to other review disciplines include:

- o Need for bridging studies (Section 8)
- o Manufacturing issues (Section 9)

These will be discussed in Section 8 and 9 of this report.

3. PRE-SUBMISSION REGULATORY HISTORY

NTG 0.4% ointment has a long regulatory history, dating back to June 2001, at the time of the initial IND submission. Early development was regulated by the Division of Cardio-Renal Products (DCRP); later development (after 2006) was regulated by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). Ownership of the NDA has also changed hands, and was transferred from Cellegy Pharmaceuticals Inc. to Strakan Pharmaceuticals Limited (part of the ProStrakan group of companies) in November 2006.

Earlier Studies 98-02-01, 00-02-01 and 03-02-01 failed to show efficacy of NTG 0.4% as a treatment for pain due to anal fissures. They received an approvable letter in July, 2006, with the provisory that an additional study was required to support efficacy of NTG 0.4% for the proposed indication; Trial REC-C-001 was designed in conjunction with advice offered by the Division, with the intent of confirming the effectiveness of NTG 0.4% in the treatment of the pain of chronic anal fissure.

A more detailed discussion of the early regulatory history (prior to March 30th 2010) can be obtained by reviewing my March 2010 Resubmission report).

The confirmatory trial REC-C-001 was submitted to the Division in September 30th 2009. In response to this submission, a Complete Response letter was issued on March 30th 2010. In the End-of-Review Meeting on June 17th 2010, an alternative statistical methodology for imputing missing data was suggested by the applicant. The proposed methodology had been used in the NDA for Ryzolt, an extended-release tramadol product. This imputation method was not accepted by the Division, as we felt that Ryzolt was not a product that was comparable to Nitroglycerin ointment.

A Formal Dispute Resolution Request (FDRR) was filed by the applicant and submitted to the Agency on August 24th 2010. After much deliberation, an Appeal Denied letter was issued by Dr Curtis Rosebraugh, Director of the Office of Drug Evaluation II. The letter noted that the short duration of chronicity for this indication warranted special consideration and proposed either of two new analyses for the primary endpoint.

Dr Rosebraugh's response to the FDRR may be summarized as follows:

- o The issues surrounding use of the Jenkins' Analysis for MDT3-005 were different from those of REC-C-001, and therefore, the Ryzolt action was

not an appropriate precedent by which use of the suggested alternative statistical imputation method would be applicable.

- o He commented on two other statistical imputations that may be an option for the applicant, if the applicant was able to procure the necessary data. These two other alternative methods of analysis for the imputation of missing data: a *Retrieved Dropout Analysis* and a *LOCF/BOCF Hybrid Analysis*. Both methods were described in a recent report on potential imputation strategies from the National Research Council.
- o DAAP has been willing to consider using LOCF for drop-outs that withdrew because of early effective pain relief such that their condition did not require further therapy thereby avoiding any potential adverse effects from further therapy, while applying BOCF to all other drop-outs.

Both missing data imputation analyses were performed on the REC-C-001 data. The latter imputation method yielded a statistically significant result. The methodology and the results of these analyses are further discussed in the efficacy section of this review.

4. IMPUTATION STRATEGIES USED IN EFFICACY RE-ANALYSIS OF REC-C-001

The data from Trial REC-C-001 was assessed by a panel of independent blinded reviewers forming a Data Review Committee (DRC). The DRC was provided with all relevant information on each of the 27 patients who withdrew from the study. The DRC was blinded as to patient study numbers and to treatment group allocation. The statisticians independently identified the patients for whom the balance of probabilities was in favor of early effective pain relief.

The first missing data imputation review strategy was the Retrieved drop out strategy.

4.1 Retrieved Drop-Out imputation

This imputation strategy identified patients who withdrew from the trial but had recorded at least one pain score during day 14 to day 18, and also had not recorded using any rescue therapy for their anal fissure pain before the end of day 18. These patients were identified from information recorded in the database.

For this group of patients, rather than imputing a zero change score for change since baseline (BOCF), the average of the actual recorded pain scores during day 14 to day 18 was used for the primary endpoint analysis. BOCF was used for the remaining withdrawals.

Results (by the FDA's analysis)

Following analysis using this Approach, the adjusted mean (SE) change from baseline VAS was -1.8 (3.08) mm for the Nitroglycerin Ointment group and -36 (3.0) mm for the placebo group.

The mean (95% CI) difference between treatment groups in the adjusted change from baseline VAS score was -6.0 (-12.8, 0.7) mm, i.e. in favor of Nitroglycerin 0.4% Ointment. The magnitude of pain response difference between the two arms was in favor of Nitroglycerin Ointment. However this analysis did not reach statistical significance and is presented in Table.4.1 below.

Table 4.1: Absolute Change from VAS Baseline in 24-hour Average

Pain for Days 14-18 (Intent to Treat Population) Approach

(a) Retrieved Drop-Out method

| VAS change from baseline | NTG 0.4% (N=123) | Placebo (N=124) |
|--|-------------------------|------------------------|
| LS Means (SE) | -42 (3.1) | -36 (3.0) |
| Difference from placebo (SE) 95% CI | -6 (3.4) (-13, 1) | |
| P-value | 0.079 | |

Source: FDA's Statistical analysis (Youngman Kim, PhD)

4.2 LOCF/BOCF Hybrid Imputation

The second approach is to use a hybrid LOCF/BOCF imputation.

The patient data were blinded to treatment and provided to three Independent Expert Clinical Reviewers. Using their clinical experience and knowledge of the disease they categorized the patients into two groups:

- (1) Patients with early effective pain relief as seen by sufficient clinical evidence
- (2) Patients with not enough clinical evidence of effective pain relief.

Once each of the 27 patients had been categorized by the Clinical Reviewers, the results were provided to the Statistician and this analysis was carried out as in the statistical analysis plan for REC-C-001 study for the primary endpoint using LOCF/BOCF Hybrid approach.

The following methodology was used:

- o If the patient had any VAS scores recorded during days 14 to 18, the average of those scores was used for the primary endpoint analysis.
- o If the patients had no VAS scores recorded during days 14 to 18, the last VAS score recorded prior to day 14 was carried forward (LOCF) for the primary endpoint analysis.

- o LOCF was used if the DRC concluded that early pain relief was the reason for withdrawal; otherwise BOCF was used.

Data were available on all 27 withdrawn patients for this method. Patients who withdrew but for whom there is evidence that they dropped out because of early effective pain relief AND did not require further therapy were identified.

Results

Following the independent clinical review 9 out of the 27 patients were determined to have early effective pain relief and were assigned LOCF pain values. The other 18 early withdrawing patients had the more conservative BOCF or zero value imputed. Six of these patients were from the NTG Ointment group and 3 in the placebo arm.

The adjusted mean (SE) change from baseline VAS was -43.7 (3.0) mm for the NTG 0.4% group and -37 (3.0) mm for the placebo group. The mean (95% CI) difference between treatment groups in the adjusted change from baseline VAS score was -7.0 (-13.6, -0) mm, i.e. in favor of NTG 0.4%. This difference was statistically significant at the 5% level (P=0.038).

By this hybrid method of imputation, one third of the withdrawn patients (9 out of 27) was deemed to have withdrawn because of early effective pain relief and did not record further therapy. This resulted in a greater adjusted mean difference between NTG 0.4% and placebo: -7.0 mm, original analysis: -5.4 mm) and the associated standard error was slightly smaller compared to the original analysis (hybrid approach: 3.3, original analysis: 3.5).

TABLE 4.2: Showing absolute change from VAS baseline in 24-hour average pain from day 14-18

B) LOCF/BOCF Hybrid

| VAS change from baseline | NTG 0.4% (N=123) | Placebo (N=124) |
|--|-------------------------|-----------------|
| LS Means (SE) | -44 (3.0) | -37 (3.0) |
| Difference from placebo (SE) 95% CI | -7 (3.3) (-14, -0.4) | |
| P-value | 0.038 | |

Source: FDA's Statistical analysis (Youngman Kim, PhD)

4.3 Discussion of Imputation Methods

Clinical trials for assessing interventions to relieve chronic pain are often subject to high rates of missing data because of inadequate efficacy and participant's inability to tolerate treatment.

The Division generally requires a high level of confidence before making a conclusion of safety and efficacy, and in ambiguous cases, the Division tends to err on the side of withholding approval. The issue of how best to handle missing data in clinical trials especially in regulatory submissions for trials intended to support efficacy and safety and marketing approval is not closed.

At present, the Division utilizes two main methods for treating missing data.

The **LOCF** implicitly assumes that a participant who had good pain control in the short term and then dropped out would have had good pain control in the long term. This assumption seems questionable in many settings.

The **BOCF** technique assumes that a participant's pain control is the same as that measured at the beginning of the trial. Since most patients in chronic pain studies, including those on placebos, improve substantially from the baseline over time, BOCF is likely to underestimate the effectiveness of any treatment.

Both imputation methods fail to properly reflect the uncertainty due to missing data.

However, the use of various *single* imputation methods for handling missing data is less than satisfactory. Additionally, there are no universally applicable methods of handling missing values that can be recommended.

In response to the FDRR submitted by the sponsor, Dr Rosebraugh's response suggested two additional methods of imputing missing data. The first method of imputation, the retrieved-dropout methodology, failed to demonstrate statistical significance. The second method, a hybrid of LOCF and BOCF method, demonstrated statistical significance. This method used LOCF imputation for patients who withdrew because of early effective pain relief, such that their condition did not require further therapy. There was a high rate of spontaneous resolution of pain due to the nature of the disease (CAF), as shown by the placebo response rate and the limited number of drop outs in the placebo groups, and the presence of drop outs with early effective pain relief.

I find that the hybrid LOCF/BOCF method of imputation is an acceptable method of approach and a fair imputation method for the determination of effectiveness in CAF.

Summary and Conclusion: Primary Endpoint Analysis

In the revised analysis, by the retrieved drop out method, the magnitude of the response difference between the two arms although favoring NTG ointment, did not reach statistical significance.

However, the revised ANCOVA analysis approach for the primary efficacy endpoint using the LOCF/BOCF hybrid approach to imputation of data for 27 patients demonstrated that the effect of nitroglycerin ointment compared to placebo in reducing pain associated with CAF was statistically significant at the 5% level ($p=0.038$).

Based on the collective evidence, I conclude that NTG ointment (0.4%) decreases the pain associated with anal fissure.

5. SAFETY- Periodic Safety Update Report

A full report of the safety of NTG 0.4% can be obtained by reviewing my prior resubmission report of March 2010.

No new safety information was submitted with the latest submission, except for the world-wide safety periodic safety update reports.

NTG 0.4% is currently approved in 24 countries.

The safety data submitted supports a favorable safety profile for topical NTG ointment. No new safety concerns have been identified since the resubmission of NDA 21-359 on September 30, 2009.

All safety information received during the period May 01, 2009 through October 23, 2010, with an estimated patient exposure during this period is 44,748 patient treatment years.

During this review period, the applicant received a total of 43 case reports that were possibly associated with NTG ointment.

Of these:

- o 29 spontaneous reports from Health Care professionals
- o 14 were non-medically confirmed reports from consumers.

A total of 77 adverse reactions were associated with 43 case reports.

The most common individual reactions were – headache (17), hypotension (5), off-label use (5), dizziness (4) and tachycardia. Headache was the most frequent adverse events were similar to recognized adverse events in the randomized, double-blind, parallel group confirmatory Trial REC-C-001.

5.1 Safety Conclusion

The safety data submitted with this submission supports a favorable safety profile for topical NTG 0.4% ointment. This impression is strengthened by the review of the world-wide periodic safety update reports.

With respect to the inclusion criteria, the Applicant

(b) (4)

(b) (4)

In order to discuss the design of the pediatric studies, a tele-conference call was held with the applicant on Wednesday, March 30th 2011, and the applicant was informed that their proposed pediatric development plan was inadequate. More specifically, the following details were highlighted:

- o We require information on the safety, tolerability, pharmacokinetics and efficacy of GTN 0.4% in three to sixteen year age group with chronic anal fissure. We advised that a controlled study rather than an (b) (4) study would be required for this age group.
- o The reliable measurement of pain in the pediatric population less than three years old is considered to be difficult to obtain, however information on the safety of GTN 0.4% would be required in this age group.

The applicant was advised that we would be taking their proposal to the Pediatric Review Committee (PeRC) for review and that we would be informing them of our decisions regarding study design after the PeRC committee meeting.

We are scheduled to meet with the PeRC on May 25th 2011.

We plan to request the following from the PeRC:

1. Waiver of pediatric studies involving patients, 0 to one month of age. This age group is considered to be too young to have chronic anal fissure.
2. Waiver of pediatric *efficacy* studies involving patients, one month to < 3 years. Patients in this age group are considered to be unable to differentiate between pain from headache (a common adverse event in patients exposed to NTG) and pain from anal fissure.
3. Deferral of safety and PK studies in patients one month to 3 years.
4. Deferral of efficacy, safety and PK studies in the 3 years to < 17 year old age group.

7. Labeling Recommendations

The applicant is relying on the Agency's findings of safety and efficacy as well as the pharmacology, pharmacokinetics and toxicology information in the label of Nitrodur, the reference drug. Past nitroglycerin products have been approved for intravenous, sublingual and transdermal administration; however this product was developed for intra-anal administration, and thus represents a new route of administration. Unlike other transdermals, application of this product is limited to the perianal and intraanal areas.

Based on the review of the data submitted in support of this application, I have the following recommendations for the product's label.

These recommendations will be discussed under the following headings:

- o Proprietary name

During earlier development of NTG 0.4% ointment was known as Cellegesic. After the drug was sold to Prostrakan, a further DMEPA review found the name of Cellegesic to be unacceptable because of the orthographic and phonetic similarities between Cellegesic and the already marketed products, Calagesic and Alagesic. The Cellegesic name was withdrawn, and the trade name of Rectogesic™ was submitted. DMEPA found the name Rectogesic to be unacceptable in OSE Review # 2010-278, dated April 15, 2010, due to the vulnerability to name confusion with the already marketed Rectagene, Relagesic and Rectacaine. The applicant withdrew the name Rectogesic on March 22, 2011 and submitted the name (b) (4) for primary consideration and (b) (4) for alternate consideration; both names were withdrawn by the applicant.

At the time of completing this clinical review, a new trade name has not yet been accepted by the Agency.

- o Drug Interactions

I concur with the Applicant's inclusion of the following drug interactions with 0.4% NTG include the following:

- Alcohol produces an additive vasodilatory effect
- PDE5 inhibitors such as sildenafil, vardenafil and tadalafil have been shown to potentiate the hypotensive effects
- Beta-adrenergic blockers producing a additive hypotensive effect

- Aspirin produces an increased nitroglycerin maximum concentration of approximately 70% when administered by a single dose.

- Dosage and administration

Sponsor's proposed wording under Dosage and Administration heading

"A 375 mg dose of ointment (equivalent to 1.5 mg of nitroglycerin) is to be applied intra-anally approximately every 12 hours. Treatment should be continued for up to three weeks.

A finger covering, such as plastic-wrap, disposable surgical glove or a finger cot, should be placed on the finger to apply the ointment. Hands should be washed after application of the ointment.

To obtain a 375 mg dose of ointment, the covered finger is laid alongside the 1.0 inch dosing line on the carton. The tube is gently squeezed until a line of ointment the length of the measuring line is expressed onto the covered finger.

The ointment is gently inserted into the anal canal using the covered finger no further than to the first finger joint and the ointment is applied around the side of the anal canal. If this cannot be achieved due to pain, application of the ointment should be made directly to the outside of the anus".

I believe that the wording noted below more clearly expresses the temporal sequence of the administration of the product.

DAAAP's proposed wording under Dosage and Administration

A 375 mg dose of ointment (equivalent to 1.5 mg of nitroglycerin) is to be applied intra-anally approximately every 12 hours. A finger covering, such as plastic-wrap, disposable surgical glove or a finger cot, should be placed on the finger to apply the ointment. To obtain a 375 mg dose of ointment, the covered finger is laid alongside the 1.0 inch dosing line on the carton. The tube is gently squeezed until a line of ointment the length of the measuring line is expressed onto the covered finger. The ointment is gently inserted into the anal canal using the covered finger no further than to the first finger joint and the ointment is applied around the side of the anal canal. If this cannot be achieved due to pain, application of the ointment should be made directly to the outside of the anus. Maximum daily dose should not exceed 21 days. Treatment may be continued for up to three weeks.

Hands should be washed after application of the ointment.

- o Description of Safety Findings as demonstrated in the label

The following safety Table 7.1 was submitted by the applicant. It consists of the four placebo-controlled trials submitted by the applicant in support of approval.



Although either table can report the treatment emergent adverse event by preferred term and treatment group, it would be preferable to utilize the data from Trial REC-C-001, the final randomized, placebo-controlled trial that formed the basis of approval.

Additionally, the patients in the previous three studies were dosed for 56 days, while patients in Trial REC-C-001 were dosed for 21 days. The latter duration of dosing more closely approximates the actual use of this product if it were to be approved. (See Table 7.2 below)

TABLE 7.2: SHOWING TREATMENT EMERGENT ADVERSE EVENTS BY PREFERRED TERM AND TREATMENT GROUP IN TRIAL REC-C-001

| System Organ Class Preferred Term | Cellegesic N = 123 | | Placebo N = 124 | |
|---|-----------------------|-------------|--------------------|-------------|
| | Patients n (%) | Events n | Patients n (%) | Events n |
| Number of patients with at least one AE | 96 (78.0) | 1056 | 67 (54.0) | 296 |
| Gastrointestinal disorders | 14 (11.4) | 17 | 11 (8.9) | 19 |
| Diarrhoea | 4 (3.3) | 4 | 4 (3.2) | 4 |
| Nausea | 2 (1.6) | 2 | 5 (4.0) | 5 |
| Infections and infestations | 8 (6.5) | 9 | 5 (4.0) | 5 |
| Sinusitis | 3 (2.4) | 3 | 1 (0.8) | 1 |
| Metabolism and nutrition disorders | 1 (0.8) | 1 | 3 (2.4) | 4 |
| Nervous system disorders | 90 (73.2) | 1001 | 59 (47.6) | 256 |
| Headache | 86 (69.9) | 972 | 59 (47.6) | 254 |
| Dizziness | 6 (4.9) | 26 | 2 (1.6) | 2 |
| Respiratory, thoracic, and mediastinal disorders | 3 (2.4) | 4 | 3 (2.4) | 3 |
| Skin and subcutaneous tissue disorders | 3 (2.4) | 3 | 1 (0.8) | 1 |

o Medication Guide

A Medication Guide is required if the one or more of the following "triggering criteria" or circumstances exist:

- o Patient labeling could help prevent serious risk
- o Serious risks could affect the patients decision to use a drug
- or
- o Patient adherence to directions is crucial to effectiveness of the drug.

Since there would be only minimal clinical consequences if the dosing is not exactly accurate, there have been no reports of serious adverse events that would affect the patient's decision to use the drug, and patient adherence to the directions is not crucial for the effectiveness, none of the above "triggering circumstances" have been identified with NTG 0.4%. Trials have demonstrated that the drug is relatively safe to use, and without any serious adverse events.

Since a medication guide is not needed, then neither will there be a need for a REMS. I do not believe that a Medication Guide and/or REMS are required to assure safe use of this drug, as this drug is considered to be relatively safe, without the incidence of serious adverse events.

We also consulted with the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) to determine whether a medication guide is required to assure safe use of NTG 0.4%. DMEPA concurred that, from a medication error perspective, the use of a Medication Guide for this product did not appear to be warranted as there did not appear to be a medication error risk that required mitigation.

8. Demonstration that NTG 0.4% bid produced plasma exposures similar to the reference listed drugs

Failure of applicant to adequately demonstrate that nitroglycerin 0.4% ointment when used at the maximal dosing regimen produces plasma exposures of nitroglycerin and its metabolites which are within the same range of Nitro Dur, a reference listed drug.

In earlier review cycles the Applicant did not provide acceptable support for establishing that systemic nitroglycerin and metabolite levels with NTG 0.4% is within those of the listed drug Nitro-Dur.

The data provided in the NDA submission compared systemic exposure levels attained with the ointment to levels reported in a Summary Basis of Approval (SBA) of the listed product (Nitro-Dur). It was conveyed to the Sponsor that information obtained from a SBA cannot be utilized for regulatory support. It was also uncertain whether C_{max} exposure levels of the Nitroglycerin 0.4% ointment subsequent to clinical dosing fell within levels of the listed drug or other nitroglycerin products approved for chronic use. Consequently, the following nonclinical deficiency was forwarded to the Applicant in the Complete Response letter of March 30th 2010.

The applicant submitted public literature data of currently marketed nitroglycerin products. The reviewing Clinical Pharmacologist, Dr David Lee reviewed the supplied references, and determined that 0.4% NTG ointment yielded levels of nitroglycerin and metabolites that are within levels reported with Nitro-Dur.

The non clinical deficiency was rescinded and the requirement to perform nonclinical bridging studies was withdrawn. (See Memo to file reports of Dr Newton Woo (8-19-10) and Dr David Lee (8-6-10).

9. Failure to adequately demonstrate comparability of the drug product quality from the proposed commercial manufacturing site to the clinical site and other CMC deficiencies pertaining to critical quality of drug product.

In previous review cycles, the applicant changed drug product manufacturers, but did not submit sufficient stability data to bridge the drug product registration batches to batches from previous drug. The applicant was asked to demonstrate comparability of drug product quality from the proposed commercial manufacturing site to the clinical site and to address critical quality attributes of drug product including establishing validation criteria, viscosity specification criteria and establishing current manufacturing process capabilities and stability data.

The current resubmission provides that bridging stability data, but proposes an increased commercial manufacturing scale that would require to bridge this larger manufacturing scale to the clinical and registration processes, the applicant submitted complete process comparisons, in vitro release rate comparisons and stability data.

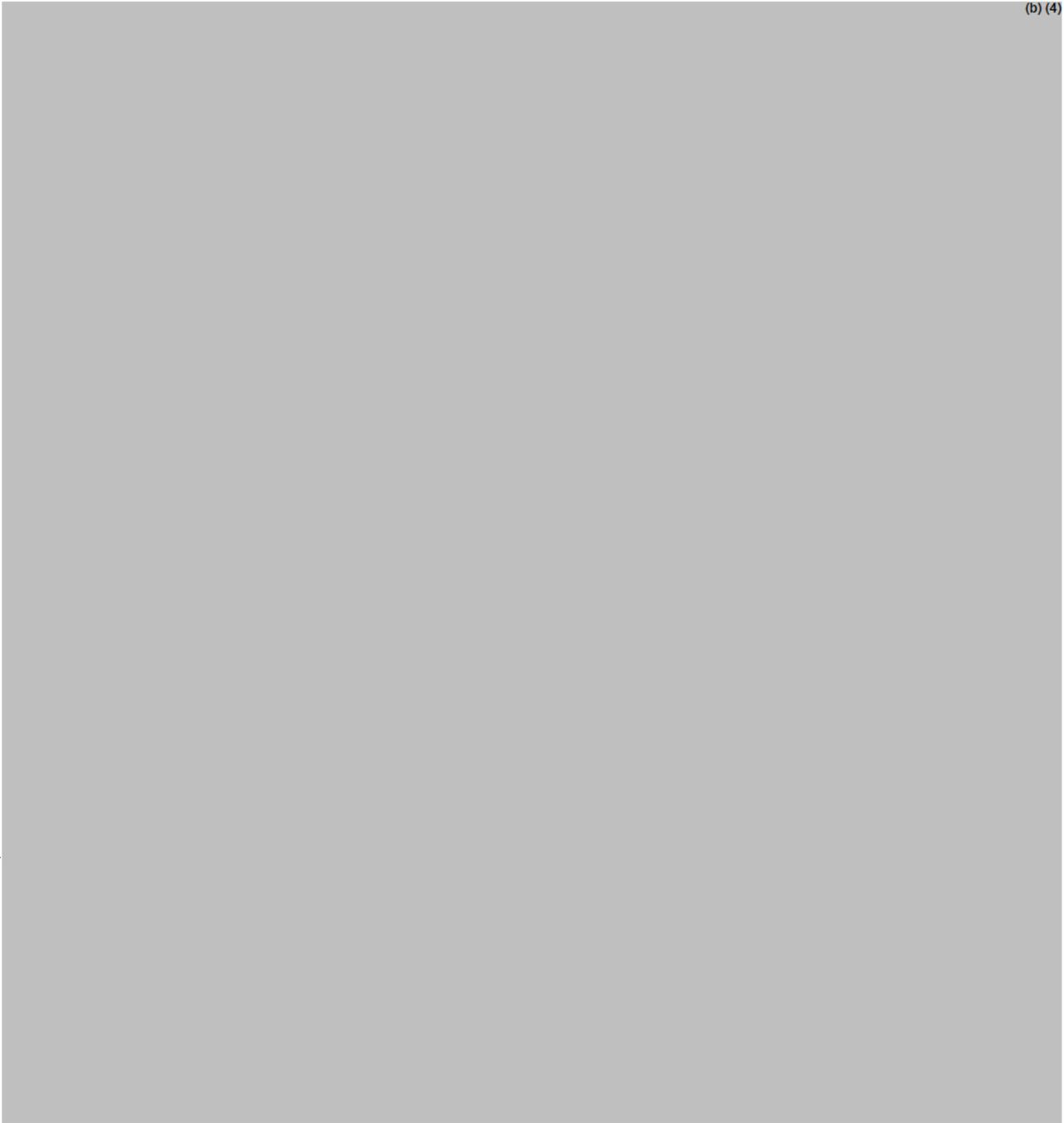
At the time of filing this review, the Biopharmaceutics Reviewer is awaiting additional data from the applicant concerning the in vitro release rate method development and computation method.

Details of the chemistry, manufacturing and control (CMC) process may be obtained by reviewing the report of Dr Olen Stephens.

Complete Response Clinical Review
Neville A. Gibbs, MD, MPH
CDER/ODEII/DAAP

NDA 21,359
Nitroglycerin (NTG 0.4%)
Prostrakan Inc

APPENDIX 1:
COPY OF PROPOSED LABEL AS SUBMITTED BY THE SPONSOR



(b) (4)

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

/s/

NEVILLE A GIBBS
05/20/2011

RIGOBERTO A ROCA
05/20/2011



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
 Division of Anesthesia and Analgesia Products
 10903 New Hampshire Ave.
 Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

| | |
|---|--|
| Date | March 30, 2010 |
| From | Rigoberto Roca, M.D. |
| Subject | Deputy Director Summary Review |
| NDA/Supplement No. | 21-359 |
| Applicant Name | ProStrakan, Inc. |
| Date of Original Submission | June 22, 2001 |
| Date of Complete Response | December 23, 2004; July 7, 2006 |
| Date of Re-Submission | September 30, 2009 |
| PDUFA Goal Date | March 30, 2010 |
| Proprietary Name / Established (USAN) Name | TRADENAME / Nitroglycerin 0.4% ointment |
| Dosage Forms / Strength | Ointment / 0.4% w/w |
| Proposed Indication | Treatment of moderate to severe pain associated with a chronic anal fissure. |
| Action | Complete response |

| | |
|---|--|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Medical Officer Review | Neville Gibbs, M.D., M.P.H. / Rob Shibuya, M.D. |
| Statistical Review | Yongman Kim, Ph.D. / Dionne Price, Ph.D. |
| Pharmacology Toxicology Review | L. Steven Leshin, Ph.D. / Adam Wasserman, Ph.D. |
| Chemistry, Manufacturing, and Controls Review | Olen Stephens, Ph.D. / Prasad Peri, Ph.D. |
| Clinical Pharmacology Review | David Lee, Ph.D. / Suresh Doddapaneni, Ph.D. |
| OSE/DMEPA | Kristina C. Arnwine, Pharm.D. / Denise Toyer, Pharm.D. |

CDTL = Cross-Discipline Team Leader
 DMEPA = Division of Medication Error and Analysis

OND = Office of New Drugs
 OSE = Office of Surveillance and Epidemiology

1. Introduction

The applicant, ProStrakan, Inc., has submitted the results of a Phase 3 study with a nitroglycerin ointment (0.4% w/w), in support of a 505(b)(2) application for the treatment of pain associated with chronic anal fissures. This submission actually constitutes a Complete Response to an Approvable action taken by the Agency on July 7, 2006. The regulatory history of this application involves several review cycles and changes in the application's sponsor, which will be elaborated further in this review. The current submission is the Applicant's attempt to address the concerns and deficiencies identified in the 2006 letter.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history and the adequacy of the data to support the application.

2. Background

Nitroglycerin is an organic nitrate with vasodilator properties that has been clinically used extensively for the treatment of angina. Its use in the treatment of pain in the anorectal region associated with anal fissures has been reported in many clinical journals. Although the immediate cause of anal fissures may differ, there is usually an associated spasm of the internal anal sphincter that at times is so severe that blood flow to the muscle may be impeded. The hypothesis that the perceived pain may be ischemic in nature offers a potential role for nitroglycerin therapy.

The regulatory history of this application spans almost nine years, and is well-documented in the reviews by the review team. In brief, the most important milestones are noted below.

- June 22, 2001 – the original application is submitted by Cellegy Pharmaceuticals to the Division of Cardio-Renal Products (DCRP), with two Phase 3 studies intended to demonstrate efficacy for pain relief and healing of anal fissures. The application was withdrawn on April 25, 2002, prior to the official Agency action.
- June 30, 2004 – the NDA was resubmitted to DCRP with the results of a new Phase 3 study. The application received a Not Approvable action on December 30, 2004.
- April 14, 2005 – Cellegy Pharmaceutical submitted a complete response to DCRP, consisting of a re-analysis of the data from the Phase 3 studies. An advisory committee meeting was held on April 26, 2006, and the final recommendation from the twelve voting members was an even split between approval and non-approval. The division took an Approvable action on July 7, 2006. Among the items cited in the action letter was the need for another Phase 3 study that would demonstrate the product's effectiveness.
- May 22, 2007 – a Type A meeting was held between ProStrakan, Inc., which had acquired the application from Cellegy Pharmaceutical the previous November, and the Division of Anesthesia, Analgesia, and Rheumatology Products, the division to which regulatory oversight for this application had been transferred. The major outcomes from this meeting were:

- The three previously conducted Phase 3 trials had failed to demonstrate the efficacy of the product as a treatment for pain due to anal fissures.
- An additional Phase 3 trial would be necessary.
- Patient selection, specifically enrollment of patients with moderate to severe pain secondary to chronic anal fissures, may address concerns about regression to the mean.
- The primary endpoint could be pain at a specific time point, or an integral of pain over time.

Additional advice conveyed during that meeting, and how the applicant incorporated that advice into the design and conduct of the new trial, are well-summarized in Dr. Kim's and Dr. Gibb's reviews. Of note, in addition to the patient population, the primary efficacy endpoint, and the baseline pain score required for enrollment, the Division recommended that, in order to reduce the use of acetaminophen as a confounding variable, acetaminophen should be given to all patients as part of a standard regimen or not at all. The Applicant opted to instruct all patients to take 650 mg of acetaminophen 30 minutes before each treatment; therefore, all placebo patients were being treated with acetaminophen. All other analgesics were prohibited, although low-dose aspirin (defined as 162 mg daily or 325 mg every other day) was permitted for cardiovascular prophylaxis.

The Applicant submitted the results of Study REC-C-001, which was initiated in August of 2007, on September 30, 2009. It is a multicenter, randomized, double-blind, parallel-group trial conducted in the United States and Latin America, in adult patients with moderate to severe pain (i.e., a score of at least 50/100 mm on a visual analog scale) due to a chronic anal fissure.

3. Chemistry, Manufacturing, and Controls (CMC)

The CMC reviews of the previous cycles had not identified any issues that would have precluded approval. However, since the last review cycle, the Applicant has changed the drug product manufacturer to (b) (4) and although technology transfer reports, validation data, and three batch analyses have been submitted in support of this change, the Applicant has not bridged the current drug product registration batches to batches from the previous drug product manufacturer. Therefore, as noted in Dr. Stephen's review, the submitted stability data does not support the registration batches.

I concur with the conclusions reached by the chemistry reviewers that the application can not be approved until these issues are addressed.

4. Nonclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology data submitted with this application. However, as noted in Dr. Leshin's and Dr. Wasserman's review, the majority of the nonclinical literature information supporting the marketing of nitroglycerin is based on dietary administration of nitroglycerin, which may not reflect the same exposure as topical administration due to the expected hepatic first-pass effect expected with oral administration of the product. Further, the referenced drug cited by the Applicant, Nitro-Dur, does not provide adequate coverage for the

exposure anticipated with the proposed formulation. The other issue identified during the review was whether the use of the nitroglycerin ointment for this indication could constitute “chronic use,” thereby necessitating the need for carcinogenicity studies.

Dr. Wasserman’s overall recommendation from a Pharmacology/toxicology perspective is that the Applicant had “...*not adequately demonstrated that nitroglycerin ointment 0.4% use under conditions of maximal indicated dosing and administration methods produces plasma exposures of nitroglycerin and metabolites which are within that of the Reference Listed Drug, Nitro-Dur, nor other approved nitroglycerin products approved for repeated use for which ...*” the Applicant can use as a reference.

In order to address this deficiency, Dr. Wasserman indicated that the Applicant would need to provide evidence that, under conditions of maximal administration as labeled, the product “...*produces exposure to nitroglycerin and metabolites that are within one or more Reference Listed Drugs approved for repeated or chronic use.*” If the Applicant was unable to provide this support, then Dr. Wasserman noted the potential need for the following requirements:

- Unless sufficient clinical experience is provided to support the local and systemic safety of the human exposure with maximum dosing regimen, repeat-dose toxicology studies using the intra-rectal route will be required in two species (one non-rodent) up to a chronic duration.
- Adequate nonclinical toxicokinetic bridging studies with dietary or topical exposure as appropriate to establish safety margins for animal reproductive toxicology and carcinogenicity studies described in the label.

Dr. Wasserman noted that if bridging studies were to fail to establish adequate exposure to nitroglycerin and metabolites to support a risk assessment, then the Applicant would need to conduct new reproductive toxicology studies with routes that produce sufficient exposures to allow a risk assessment to be made. Further, if the bridging studies were to fail to establish adequate exposure to nitroglycerin and metabolites to support a risk assessment and you do not provide usage data or other persuasive argument to indicate this product should not be considered a chronic use (i.e., greater than 6 months lifetime usage) product, then the Applicant would need to conduct a carcinogenicity evaluation with routes that produce sufficient exposures to allow a risk assessment to be made.

As noted in Dr. Wasserman’s review, the assessment as to whether the use of this product in the manner proposed can be considered “chronic use” is a determination that is dependent on various clinical factors. Dr. Gibbs has noted in his review his rationale why he does not believe that carcinogenicity studies would be required, primarily noting that even though anal fissures have a 40 to 50% recurrence rate after healing with conservative treatment, it is unlikely that someone would continue to use the nitroglycerin ointment for an extended period of time due to currently accepted treatment algorithms. Dr. Shibuya noted in his review that, if the product were to ever be approved for marketing, the number of patients that would be expected to use the product for chronic or repeated intermittent use for longer than six months would be small.

Citing from ICH E1: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, Dr. Shibuya noted that the guidance applies to "...drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases." Emphasizing that the *intention* of the therapy is the key point in the definition, he notes that the subset of patients that would meet this criteria would have to a) have multiply recurring episodes, b) be willing to tolerate the adverse events associated with the product, c) derive meaningful therapeutic benefit from the product each time it was used, and d) be poor surgical candidates or not willing to undergoing the surgical procedure.

Although I agree with Drs. Gibbs and Shibuya that the number of patients that may use the product in a chronic fashion may be small, I believe that the intended use of the product must be supported by data of what is the expected use, and that it is the Applicant that must provide the data to make the argument that indeed, the likelihood of chronic use is low, and that, therefore, carcinogenicity studies are not required.

Dr. Shibuya also noted in his review that guidance regarding the determination of whether a therapy can be considered chronic is also available in ICH S1A: *Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals*. Dr. Shibuya quoted from the guidance the following:

Certain classes of compounds may not be used continuously over a minimum of 6 months but may be expected to be used repeatedly in an intermittent manner. It is difficult to determine and to justify scientifically what time represents a clinically relevant treatment periods for frequent use with regard to carcinogenic potential, especially for discontinuous treatment periods. For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. Examples of such conditions include allergic rhinitis, depression, and anxiety.

Dr. Shibuya's final conclusion was that, given the natural history of anal fissures, the definition of "chronic use" identified in ICH S1A was being met. He indicated that the different wording in the two guidances could lead to different conclusions; however, in this case he would opt for the more conservative interpretation and deem that the therapy in this indication would likely result in "chronic use."

I concur with the conclusions reached by the pharmacology/toxicology reviewers that the product can not be approved until the Applicant has provided data that the product, under conditions of maximal indicated dosing and administration methods, produces plasma exposures of nitroglycerin and metabolites which are within that of the referenced drug(s). Further, adequate nonclinical toxicokinetic bridging studies between dietary or topical exposure, as appropriate to establish safety margins for animal reproductive toxicology and carcinogenicity studies described in the label or drugs, would need to be submitted.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology data submitted in this application. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval of this application.

6. Clinical Microbiology

The nitroglycerin ointment is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant submitted the results from a single Phase 3 trial, Study REC-C-001. The trial was a multicenter, randomized, double-blind, parallel-group trial in adult patients with moderate to severe pain (i.e., a score of at least 50/100 mm on a visual analog scale) due to a chronic anal fissure. It was conducted in clinical sites in the Argentina, Brazil, Mexico, and United States.

The details of the trial design are well-described in the reviews by the clinical and statistical members of the review team. In brief, the patient population was adults (age 18 to 75 years) with a single, chronic, posterior midline anal fissure with anal pain for at least six weeks prior to the screening visit. The 24-hour average pain assessment was to have been at least 50 mm on a 100 mm visual analog scale (0 mm was to be considered “no pain,” and 100 mm the “worst pain imaginable”), on the Randomization/Day 0 Visit, and for at least 2 of the 4 days prior to the Randomization/Day 0 Visit.

The primary efficacy endpoint of the trial was the change from baseline in the 24-hour average pain intensity, as determined by a patient-reported score using the visual analog scale (VAS), averaged over Days 14 to 18 of treatment. There were four secondary endpoints that were to be potentially considered for inclusion in the label:

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

The following secondary efficacy variables were considered exploratory:

- 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 scoring.
- Time to 10 mm and 50% improvement in VAS score.

A total of 247 patients were randomized and 219 completed the trial. The disposition of the patients is summarized in the table below, adapted from Dr. Kim's review.

| | Nitroglycerin 0.4% ointment N=123 n (%) | Placebo N=124 n (%) | Total N=247 n (%) |
|---|--|----------------------------------|--------------------------------|
| Total number of patients | | | |
| Completed | 106 (86.2) | 113 (91.1) | 219 (88.7) |
| Discontinued | 17 (13.8) | 11 (8.9) | 28 (11.3) |
| Primary reason for discontinuation | | | |
| Adverse event | 9 (7.3) | 3 (2.4) | 12 (4.9) |
| Voluntary withdrawal | 5 (4.1) | 4 (3.2) | 9 (3.5) |
| Protocol violation | 2 (1.6) | 0 | 2 (0.8) |
| Lost to follow up | 1 (0.8) | 4 (3.2) | 5 (2.0) |

The demographics and baseline characteristics between the two treatment groups were comparable, and are summarized in the table below, adapted from Dr. Kim's review.

| | Nitroglycerin 0.4% ointment N = 123 | Placebo N = 124 |
|---|---|---------------------------|
| Gender n (%) | | |
| Female | 65 (53%) | 66 (53%) |
| Male | 58 (47%) | 58 (47%) |
| Race n (%) | | |
| 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%) |
| Age (years) | | |
| Median | 46 | 43 |
| Range | 18 – 74 | 21 – 73 |
| Average Pain (VAS score) | | |
| Median | 73 | 72 |
| Range | 13 – 100 | 51 – 100 |

The results for the primary efficacy endpoint for the ITT population, defined as all randomized patients who had taken at least one dose, are summarized in the table below, adapted from Dr. Kim's review.

| LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain | Nitroglycerin 0.4% ointment (N=123) | Placebo (N=124) | P-value |
|--|--|------------------------|----------------|
| ANCOVA/BOCF* | -40 (3.1) | -35 (3.0) | 0.118 |

| | | | |
|------------------------------|----------|--|--|
| Difference from Placebo (SE) | -5 (3.5) | | |
| (95% CI) | (-12, 1) | | |

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

The prespecified analysis of the primary efficacy endpoint stipulated an imputation strategy of baseline-observation-carried-forward for missing data, as conveyed to the Applicant by the Division during the May 22, 2007 Type-A meeting. The Applicant also submitted results from two sensitivity analyses performed using a last-observation-carried-forward imputation strategy. The first, designated as LOCF 1, was pre-specified before unblinding of the randomization code, and imputed missing data from the last non-missing observation, whether it fell before Day 18 (last day of primary pain assessment) or not. The second analysis, designated as LOCF 2, was proposed after unblinding of the randomization code, and it restricted imputation from the last non-missing observation before Day 18.

The results from these two analyses are summarized in the two tables that follow, adapted from Dr. Kim's review.

LOCF 1: REC-C-001 (ITT Population)

| LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain | Nitroglycerin 0.4% ointment (N=123) | Placebo (N=124) | P-value |
|---|-------------------------------------|-----------------|---------|
| ANCOVA/LOCF 1* | -37 (3.0) | -30 (3.1) | 0.047 |
| Difference from Placebo (SE) (95% CI) | -7 (3.4) (-13, 0) | | |

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

LOCF 2: REC-C-001 (ITT Population)

| LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain | Nitroglycerin 0.4% ointment (N=123) | Placebo (N=124) | P-value |
|---|-------------------------------------|-----------------|---------|
| ANCOVA/LOCF 2* | -36 (2.9) | -29 (3.0) | 0.033 |
| Difference from Placebo (SE) (95% CI) | -7 (3.4) (-14, -1) | | |

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

As noted in Dr. Kim's review, a LOCF analysis may potentially provide supportive information only when a conservative analysis provides significant results. Since the conservative analysis utilizing a BOCF imputation strategy failed, the significance of a favorable LOCF analysis is questionable.

The Applicant also performed a mixed model repeated measure (MMRM) analysis as that resulted in a statistically significant difference between the nitroglycerin and placebo in terms of the change from baseline to Day 18 in 24-hour average pain. Dr. Kim was not able to exactly reproduce the numbers as submitted by the Applicant, however, his results were very close to the Applicant's analysis, which is summarized below.

| LS Mean Change (SE) from Baseline to average of Days 18 in 24-hour average pain | Nitroglycerin 0.4% ointment (N=123) | Placebo (N=124) | P-value |
|---|-------------------------------------|-----------------|---------|
| MMRM* | -48 (3.1) | -39 (3.0) | 0.008 |
| Difference from Placebo (SE) (95% CI) | -9 (3.4) (-16, -2) | | |

* 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.

Dr. Kim noted in his review that 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.

The Applicant indicated that since the first secondary efficacy endpoint, time to improvement in VAS score in the ITT population, failed to reject the null hypothesis all the other secondary endpoints were reported as exploratory analyses. From the Division's perspective, we can not formally test the first secondary endpoint once the primary endpoint fails, therefore, the results of the analyses of the secondary endpoints will not be discussed further in this review.

I concur with the conclusion reached by the review team that Study REC-C-001 failed to demonstrate that the Applicant's product, nitroglycerin 0.4% ointment, was effective compared to placebo in the treatment of moderate to severe pain associated with a chronic anal fissure.

8. Safety

The review of the safety data from Study REC-C-001 did not identify any new adverse event. There were no deaths in the trial, and three serious adverse events reported were reviewed and not felt to be attributable to the product.

The most common adverse events reported were headache, dizziness, diarrhea, and nausea. Among the patients that discontinued secondary to an adverse event, there were more patients in the nitroglycerin treatment group, and the most common reason within that group was "headache."

The rest of the safety profile for the product was consistent with the previously reported safety profile for nitrates.

9. Advisory Committee Meeting

An advisory committee hearing was held during the previous review cycle. There were no issues identified in this application that required presentation and discussion at an advisory committee meeting.

10. Pediatrics

There were no pediatric studies conducted for this application. The Applicant had requested a waiver of pediatric studies in patients in the (b) (4) years of age group. The rationale was that pain assessments in that age group would be unreliable, and that the patients would be not be able to reliably communicate whether the pain was due to the anal fissure or something else, like a headache. The Applicant proposed to conduct trials in patients (b) (4) years of age, but have requested a deferral for this age group at this time.

After internal discussions, the review team's conclusion was that, although pain assessments can be performed in patients less than (b) (4) years of age, it would be difficult to determine whether the patient was reliably reporting pain from the anal fissure or another anatomical site. The recommendation from the review team was that the drug development program should include safety and pharmacokinetic studies in the entire pediatric age range, with efficacy evaluation only in patients six years of age and older. In addition, the review team recommended that the request for deferral of these studies be denied, citing that there is no known safety reason why the pediatric studies should be delayed until further studies in adults are completed.

I agree that it might be difficult for a patient below a certain age group to reliably communicate the source of the pain; however, I think this would be more dependent on the communications skills of the child, both verbally and non-verbally, and in many children this would be adequate with patients as young as 2 or 3 years of age. Therefore, the Applicant will be expected to design a protocol that utilizes the expected communication skills of the patient as one of the determining factors when selecting the appropriate age cutoff. The Applicant should also provide an appropriate scientific justification for the age selected.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the name Cellegesic and felt that it was unacceptable due to name confusion with "Calagesic" and Alagesic." The name "Rectogesic" has been proposed by the Applicant and is under review by DMEPA.

There are no other unresolved relevant regulatory issues.

12. Labeling

The review of the proposed labeling was not warranted during this review cycle because the applicant did not submit sufficient information to support the proposed indication. Label review and discussions with the applicant will be initiated as appropriate.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Complete response.

- Risk Benefit Assessment

The Applicant has failed to submit substantial evidence of the effectiveness of nitroglycerin 0.4% ointment to treat moderate to severe pain associated with chronic anal fissures. I concur with the review team that the Applicant has not presented sufficient information to support their proposed indication.

In addition, the Applicant has to address the deficiencies identified by the pharmacology/toxicology and the CMC reviewers.

- Recommendation for Post-marketing Risk Management Activities

None.

- Recommendation for other Post-marketing Study Commitments

None.

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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/s/

RIGOBERTO A ROCA
03/30/2010

Cross-Discipline Team Leader Review

| | |
|--|--|
| Date | 15 March 2010 |
| From | Robert B. Shibuya, M.D., Clinical Team Leader |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 21-359 |
| Supplement# | |
| Applicant | ProStrakan |
| Date of Submission | 30 September 2009 |
| PDUFA Goal Date | 30 March 2010 |
| Proprietary Name / Established (USAN) names | Rectogesic (nitroglycerin 0.4% ointment) |
| Dosage forms / Strength | Ointment/0.4% |
| Proposed Indication(s) | "Treatment of pain associated with chronic anal fissure" |
| | |

| | |
|------------------------------------|---|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Primary Medical Officer Review | Neville Gibbs, M.D., MPH |
| Statistical | Yongman Kim, Ph.D. Dionne Price, Ph.D. |
| Pharmacology Toxicology Review | L. Steven Leshin, D.V.M, Ph.D. Adam Wasserman, Ph.D. |
| CMC Review | Olen Stephens, Ph.D. Prasad Peri, Ph.D. |
| Clinical Pharmacology Review | David Lee, Ph.D. Suresh Doddapaneni, Ph.D. |
| OSE/DMEPA | Kristina C. Arnwine, PharmD Denise Toyer, PharmD |

1. Introduction

The subject of this NDA resubmission, Rectogesic™ (0.4% nitroglycerin ointment), is an ointment containing nitroglycerin. This 505(b)(2) application references Nitro-Dur (NDA 20-145), a system that delivers nitroglycerin transdermally for the treatment of angina. Rectogesic contains a lower concentration of active drug compared to the topical ointments used for the indication of the prevention of angina (2%).

The Applicant, ProStrakan, seeks an indication of the treatment of pain due to chronic anal fissure. As detailed in the primary clinical review by Dr. Neville Gibbs, Rectogesic has a long regulatory history that dates to 2001. In previous review cycles, this application was reviewed in the Division of Cardio-Renal Products (DCRP). At this time, the single outstanding deficiency is a demonstration of efficacy.

In the current resubmission, the Applicant has submitted Study REC-C-001, a multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study in patients with moderate to severe pain due to chronic anal fissure. The study failed to reach statistical significance for its protocol-specified primary efficacy outcome variable. Safety data from this study are consistent with the known adverse event profile of Rectogesic and nitroglycerin (headache and dizziness). The Pharmacology/Toxicology team has also identified a deficiency related to whether the reference drug and data available in the public domain adequately address the potential for systemic nitroglycerin exposures likely to be observed with Rectogesic under maximal use conditions.

2. Background

Chronic anal fissure (CAF) is defined as a tear in the anoderm distal to the dentate line. The tear in the mucosa results in high levels of pain during and after defecation. The defect in the mucosa is thought to result in spasm of the internal anal sphincter which leads to mucosal ischemia which inhibits healing, a vicious cycle. Relevant textbooks (Current Diagnosis and Treatment in Surgery, 2010; Schwartz's Principles of Surgery, 2010; Current Medical Diagnosis and Treatment, 2010) indicate that the distinction between acute and chronic anal fissure is not based on the duration of symptoms. Rather the diagnosis is based on features such as a sentinel pile or direct visualization of the internal anal sphincter muscle fibers on physical examination.

The initial management of CAF is conservative and involves the use of bulk laxatives, increased dietary fiber, and sitz baths. There are no approved pharmacotherapies for CAF. However, meta-analyses (Cochrane) of clinical trials have supported the use of certain drugs in the treatment of CAF including local anesthetics, nitroglycerin, calcium channel blockers, and botulinum toxin. What is clear from the medical literature is that CAF is difficult to treat medically with a success rate of 50-80% and a recurrence rate in the range of 40-50%.

The most recent review of the surgical options for CAF (Cochrane) indicates that surgery (lateral sphincterotomy) is more than 90% effective at treating anal fissures and, more recent studies show a complication rate (incontinence) of <10%.

The current treatment algorithm (Up to Date – personal subscription) indicates that a one-month trial of locally compounded 0.2% topical nitroglycerin should be attempted early in therapy. If there is no response to nitroglycerin, an additional month of therapy may be attempted before changing to a therapy that is believed to be more efficacious such as an oral or topical calcium channel antagonist, botulinum toxin or surgery.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Olen Stephens, Ph.D. with concurrence from Prasad Peri, Ph.D..

After the last review cycle (2006), there were no CMC deficiencies. However, in the interim, the Applicant has changed the drug product manufacturer ((b) (4)). The Applicant supported this change with technology transfer reports, validation data, and 3 batch analyses. However, accelerated stability data were not provided and 2/3 of the stability batches exceeded the viscosity specification limit.

Because of these deficiencies, the CMC team has recommended against approval. Please see Dr. Stephens' excellent review for further details regarding the CMC aspects of this product.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by L. Steven Leshin, Ph.D., D.V.M. and a secondary review was conducted by Adam Wasserman, Ph.D.. As Dr. Wasserman notes, in 2002, the nonclinical team from DCRP recommended approval from the Pharmacology/Toxicology (P/T) perspective. Dr. Wasserman notes that this recommendation was based primarily upon the long history of use for the nitroglycerin moiety.

No new P/T data were submitted. However, after reviewing this application, Dr. Leshin noted that the nonclinical literature supporting the approval of nitroglycerin products is largely based on studies where nitroglycerin was administered in the diet. Because nitroglycerin has a very large first-pass effect, the dietary studies are likely to have resulted in very limited systemic exposure.

Dr. Wasserman notes that, by extrapolating clinical exposures for the 0.4% concentration of Rectogesic from the 0.2% strength of Rectogesic (dropped for lack of efficacy during development), the issue of systemic toxicities related to the overall exposure (AUC) is likely to be addressed with the Reference Drug. However, the C_{max} observed with even the low (0.2%) strength of Rectogesic is not addressed with the Reference Drug. Dr. Wasserman notes that certain nitroglycerin formulations for transmucosal administration are likely to cover the

Cmax of Rectogesic. However, the Applicant has not designated those products nor have they patent certified.

Thus, the P/T team has recommended against approval until the Applicant demonstrates that Rectogesic, under maximum use conditions, produces plasma exposures of nitroglycerin and its metabolites that are within those of the Reference Drug or other relevant approved products that can be used as a reference drug.

Please see Dr. Wasserman's supervisory memo for additional details.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by David Lee, Ph.D. with a secondary review by Suresh Doddapaneni, Ph.D.

There were no outstanding clinical pharmacology deficiencies; the Applicant submitted no new clinical pharmacology data.

6. Clinical Microbiology

Clinical microbiology is not applicable for this product.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Neville Gibbs, M.D., MPH and the primary statistical review was conducted by Yongman Kim, Ph.D. with secondary concurrence by Dionne Price, Ph.D..

In attempting to respond to the efficacy deficiency noted in the 2006 Approvable Letter, the Applicant submitted a single efficacy study, Study REC-C-001. This multicenter, randomized, double-blind, placebo-controlled, parallel-group study enrolled adults with moderate to severe [at least 50/100 mm on a visual analog scale (VAS)] pain due to a chronic anal fissure. Eligible patients were randomized 1:1 to receive Rectogesic, 1.5 mg (375 mg of ointment) BID or placebo BID. Patients were treated for 21 days. The primary efficacy endpoint was the absolute change from baseline to the average of Days 14-18 in the 24-hour average pain (assessed by a 100 mm VAS).

The Division provided advice to the Applicant regarding the design and statistical analysis of Study REC-C-001, as outlined in Dr. Gibbs' review. Missing data were handled conservatively (baseline observation carried forward).

Per Drs. Gibbs and Kim's reviews, Study REC-C001 was conducted to acceptable standards and the data were of adequate quality for review. The summary data for the primary efficacy endpoint, excerpted verbatim from Dr. Kim's review, are shown in Table 1, following.

Table 1: Primary Efficacy Endpoint Analysis

| 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/BOCF* Difference from Placebo (SE) (95% CI) | -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.

The Applicant submitted sensitivity analyses that showed that, via certain imputation schemes, (last observation carried forward), a statistically significant p-value could be calculated. The statistical team has concluded that these alternative imputation schemes are not conservative because they may assign a “good” score when a “bad” outcome (adverse event) was the result.

The Applicant also conducted a meta-analysis, assessing aggregate data from all efficacy studies. The Applicant asserts that the meta-analysis shows a statistically significant difference in favor of Rectogesic. As Dr. Gibbs notes in his review, a post-hoc meta-analysis would not support a finding of efficacy.

ProStrakan has failed to demonstrate efficacy in Study REC-C-001.

8. Safety

The review of clinical safety was conducted by Dr. Gibbs.

Dr. Gibbs limited his review to the new data from Study REC-C-001. Briefly, the use of Rectogesic is associated with headache (70%) and dizziness. While orthostasis was reported frequently as an adverse event in the clinical trial (~12%), the incidence of orthostasis was approximately equivalent in both active and placebo arms.

The adverse event profile in Study REC-C-001 was similar to that observed in previous review cycles.

The 120-day Safety Update, submitted on 11 March 2010 at the Division’s request, reported no new clinical or non-clinical development activities. The postmarketing data were updated.

There was a single case of interest (hypersensitivity). This is an 81-year-old woman with unknown medical history. Her concomitant medications included strontium ranelate, perindopril/indapamide, verapamil, and simvastatin. Approximately 12-hours post the first dose of Rectogesic, the patient “became prostrated” and subsequently developed lower extremity and hand edema. Apparently, there was a macular rash over the ankles. The patient was treated with parenteral corticosteroids and recovered within 24 hours. The Applicant notes that there was no pruritis or dyspnea. This appears to be drug hypersensitivity to

Rectogesic. According to the package insert for Nitro-BID, allergic reactions to organic nitrates are extremely rare but do occur.

To address what should be required to address questions about the systemic levels of nitroglycerin and its metabolites, the P/T team requested input from the clinical team regarding the probable duration of therapy for this product, if approved. It is important to note that DCRP did not perceive CAF as a chronic use indication; they did not require a carcinogenicity study from the Sponsor. I discussed this with a member of the DCRP clinical team; he responded that DCRP felt that patients would proceed to surgery before using this drug for a total of > 6 months.

I have reviewed the pertinent, available reference material. CAF is a very painful and symptomatic condition that adversely affects the quality of life of patients afflicted with the condition. There are no approved pharmacologic therapies at this time although the medical community uses certain drugs off-label with some success. CAF also has a high recurrence rate, in the range of 40-50%. There is a highly effective surgical therapy for CAF although it is fraught with a highly undesirable complication, incontinence of flatus and/or stool.

What has not been reported in textbooks or the literature is the incidence of multiple recurrences in a single patient. However, given what is known about this entity, multiple recurrences in a single patient appear to be likely.

In addressing the question posed by Drs. Lesbin and Wasserman, it is important to note how ICH E1 is worded. The pertinent section of this guidance that defines which drugs apply reads, "drugs intended [emphasis added] for the long-term treatment (chronic or repeated intermittent use for longer than 6 months)." I believe that, if Rectogesic is ever approved, some patients may ultimately use the drug for more than six months. However, that subset of patients would be expected to be very small. This subset would include those patients that: 1. Multiply recur, 2. Are willing to tolerate the adverse events associated with Rectogesic, 3. Derive meaningful therapeutic benefit from Rectogesic each time it is used, and 4. Either are poor surgical candidates or are not willing to undergo surgery. In the context of ICH E1, in my opinion, this potential subset of patients is not consistent with the ICH language in that this drug is not intended to be used in that manner.

However, in his supervisory memo, Dr. Wasserman cited language from ICH S1A that defines "chronic use." The operative part of that document reads:

Certain classes of compounds may not be used continuously over a minimum of 6 months but may be expected to be used repeatedly in an intermittent manner [emphasis added]. It is difficult to determine and to justify scientifically what time represents a clinically relevant treatment period for frequent use with regard to carcinogenic potential, especially for discontinuous treatment periods. For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. Examples of such conditions include allergic rhinitis, depression, and anxiety.

Given the natural history of anal fissure, I believe that the "chronic use" definition is met with the S1A definition. In this instance, subtle differences in the language between ICH E1 and S1A lead to a different conclusion regarding whether Rectogesic and its proposed indication of the treatment of pain due to chronic anal fissure meet the criteria for "chronic use." In this case, the more conservative interpretation should be employed. Rectogesic is a "chronic use" drug.

9. Advisory Committee Meeting

On this review cycle, there was no Advisory Committee Meeting held.

10. Pediatrics

In August 2004, DCRP sent a letter to Cellegy, the NDA holder at the time. In that letter, DCRP deferred pediatric studies until December 2007 because adult studies would be ready for approval before pediatric studies would be completed.

To date, ProStrakan and Cellegy have not started pediatric studies. In the current submission, ProStrakan requested a waiver of pediatric studies for ages (b) (4) years. ProStrakan asserted that pain assessments in that age range are unreliable and argued that the younger age strata would not be able to reliably communicate if pain experienced were due to anal fissure or headache. The Applicant proposed to conduct safety and tolerability studies in patients age (b) (4) years old.

Pediatricians in our Division were consulted. We do not necessarily agree that pain assessments are unreliable in patients (b) (4) years old. However, our pediatric staff felt that efficacy studies would not be feasible in patients under age 6 because the younger patients would not be able to reliably report anal pain versus headache. Per current Division policy, ProStrakan will have to conduct safety and pharmacokinetic studies for all age ranges and assess efficacy in patients age 6 years to 16 years.

I recommend that the lack of pediatric studies, given that more than two years have elapsed since their deferral date from DCRP, be listed as a deficiency in the Complete Response Letter.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to assess the tradename (Cellegesic). Cellegesic was found to be unacceptable due to name confusion with "Calagesic" and "Alagesic."

12. Labeling

No labeling review was conducted.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

- Risk Benefit Assessment

The Applicant has failed to demonstrate efficacy and this product causes a high rate of headache and some dizziness. The risk to benefit ratio does not favor approval.

- Recommendation for Postmarketing Risk Management Activities

Not applicable

- Recommendation for other Postmarketing Study Commitments

Not applicable.

- Recommended Comments to Applicant

1. Complete one adequate and well-controlled study to demonstrate that the drug is effective in the management of pain due to chronic anal fissure.
2. The P/T comments suggested by Dr. Wasserman should be included.
3. Submit completed pediatric studies with your response to this letter.
 - Study safety and pharmacokinetics in all pediatric age strata.
 - Study efficacy in patients age 6 years to 16 years.
4. The CMC deficiencies noted by Dr. Stephens should also be conveyed.

REFERENCES

Nelson R. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003431.

Nelson R. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002199.

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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/s/

ROBERT B SHIBUYA
03/15/2010

CLINICAL REVIEW

Application Type NDA
Application Number(s) 21359
Priority or Standard N/A

Submit Date(s) September 30, 2009
Received Date(s) September 30, 2009
PDUFA Goal Date March 30, 2010
Division / Office DAARP

Reviewer Name(s) Neville A Gibbs MD, MPH
Review Completion Date January 12, 2010

Established Name Nitroglycerin 0.4% Ointment
(Proposed) Trade Name Cellegesic
Therapeutic Class
Applicant ProStrakan Inc

Formulation(s) Cellegesic (nitroglycerin) 0.4%
Dosing Regimen 1.5 mg rectally bid
Indication(s) Treatment of pain associated
with chronic anal fissure
Intended Population(s) Adults with Chronic Anal
Fissure

Template Version: March 6, 2009

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{Neville A Gibbs, MD, MPH}
{NDA 21359}
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The data submitted in this resubmission in response to a 2006 Approvable Letter do not support the approval of Cellegesic (nitroglycerin, 0.4% ointment) for the indication of the treatment of pain associated with chronic anal fissure.

This recommendation is based on the review of the efficacy and safety data submitted by the Applicant, ProStrakan Inc, for this population of adult study participants with Chronic Anal Fissure (CAF).

Cellegesic has a long regulatory history that will be summarized in Section 2.5 of the review. However, at this time, there is a single outstanding deficiency. Following the last review cycle, the Applicant was told to provide substantial evidence of efficacy.

To address this deficiency, the Applicant conducted and submitted Study REC-C-001, a randomized, double-blind, placebo-controlled, parallel-group study. In this study, a total of 123 patients were treated with nitroglycerin (NTG) 0.4%. Study REC-C-001 failed to demonstrate efficacy because the study failed to meet the prospectively defined primary and secondary end points.

The review of the safety data in this complete response to the 2006 Approvable Letter did not change the impression of the adverse event profile of this drug.

1.2 Risk Benefit Assessment

In the current submission, ProStraken failed to demonstrate that Cellegesic is effective in treating pain in patients with CAF.

The adverse events associated with use of the product are predominantly headache and slight decrease in systolic and diastolic blood pressure at the time of application of the ointment. These adverse events are self-limited, treatable (headache is treated with acetaminophen) and monitorable.

Because there is no substantial evidence of efficacy, the risk-benefit relationship does not favor approval of this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Cellegesic™ ointment includes the active ingredient nitroglycerin (NTG) at a concentration of 0.4%. The product is intended for administration as two 1.5 mg doses approximately 12 hours apart, resulting in a total daily dose of 3 mg.

This 505(b)(2) application relies in part on FDA's findings of safety for the Reference Drug (RD), Nitro-Dur (Key Pharmaceuticals, NDA #020145).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there are no approved prescription drugs in the United States for the treatment of pain associated with chronic anal fissure (CAF).

Pharmacologic treatments are usually the first-line treatment for chronic fissures.

Locally compounded formulations of topical NTG are currently used; however the quality of and concentration of NTG in these preparations are reported to be variable. Consequently, the applicant purports that Cellegesic has been developed to provide a standardized, optimal concentration NTG formulation intended for anodermal application for the treatment of pain associated with CAF.

Calcium channel blockers such as nifedipine and diltiazem orally and as a compounded topical gel are also used by some practitioners, and are thought to reduce the pressure in the internal anal sphincter.

Botulinum toxin (Botox) may also be injected into the internal anal sphincter. This agent causes temporary paralysis of muscle, which can reduce muscle tension and help to heal the anal fissure.

Surgery is typically performed when more conservative treatments fail to heal an anal fissure. Although surgery is considered definitive, there is evidence that fissures can recur following surgery. Additionally, surgery may be associated with incontinence of flatus and fecal incontinence. These adverse events are generally infrequent but significant adverse effects of this surgical procedure. There is also concern that dividing the sphincter of younger patients may predispose them to further trauma during childbirth or continued weakening as the patient ages. The reported follow-up after sphincterotomy is short-term and this may underestimate the rates of incontinence.

2.3 Availability of Proposed Active Ingredient in the United States

Nitroglycerin is an organic nitrate. It is a vasodilator that is typically used to treat the symptoms of chest pain or angina.

Depending on the dosage and how it is taken, nitroglycerin may help prevent attacks of chest pain or relieve an attack that is occurring. It does this by increasing blood flow to the heart and by reducing the heart's workload.

Nitroglycerin is approved in several formulations:

- o Sublingual spray
- o Extended-release transdermal film
- o Injection
- o Transdermal ointment
- o Sublingual tablet

2.4 Important Safety Issues With Consideration to Related Drugs

The common adverse events associated with nitroglycerin administration include headache, low blood pressure, dizziness, lightheadedness, orthostasis and flushing of face and neck.

Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); blurred vision; fainting; increased chest pain; pounding in the chest; and slow heartbeat are rare adverse events.

Men are advised not to use nitroglycerin within 24 hours of taking erectile dysfunction medications such as sildenafil, tadalafil and vardenafil because of the possibility of significantly lowered blood pressure.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For most of the history of this product, the Division of Cardio-Renal Products (DCRP) has regulated the development of this product.

Cycle #1:

The NDA was submitted on June 22, 2001 and was withdrawn on April 25, 2002, prior to any official FDA action. At the time of withdrawal of the application, the Agency noted that one study, Study NTG 98-02-01, failed to demonstrate efficacy on anal fissure healing. A second study, Study NTG 00-02-01, failed to demonstrate pain relief using

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the pre-specified analysis at 56 days but there was a suggestion of an effect on CAF pain at 21 days.

Cycle #2:

The NDA was resubmitted on June 30, 2004 with a new efficacy study (Study 03-02-01).

DCRP found the submission Not Approvable (NA).

DCRP noted that the difference between the nitroglycerin ointment and placebo groups was 3 mm (out of 100) in 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 did not balance favorably against a high rate of withdrawals for headache and other adverse effects associated with nitroglycerin ointment.

The NA letter issued December 23, 2004 contained the following additional comments:

The first two studies only showed effects on anal pain that were nominally statistically significant using retrospective analyses.

The letter continued:

- o " 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.
- o 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 "
- o Concomitant use of acetaminophen was also more common with nitroglycerin than with placebo, which made it difficult to ascribe any small pain relief to nitroglycerin.

DCRP also requested that, in addressing the deficiencies, the Applicant responds to the issues of inadequately documented vital sign changes and withdrawals due to potential systemic cardiovascular effects.

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After a Type A Meeting on March 28, 2005, the NDA remained not approvable.

The Agency recommended that Cellegy consider the following:

- o Conduct a reanalysis of the available data for all subjects with no imputation censoring at the last observation.
- o Conduct an analysis of effects of open-label use of mild analgesics on anal pain.
- o Conduct an analysis of treatment effect by baseline pain, using full range of pain, not just a single value (>50 mm)

The Agency concluded that Cellegy Pharmaceuticals Inc could submit the information described above as a resubmission.

Cycle #3:

The Applicant submitted a Complete Response to the Approvable Letter on April 14, 2005. The April 14, 2005 submission constituted a complete response to the Agencies December 23, 2004 action letter. No new data was submitted.

An Advisory Committee Meeting held on April 26, 2006. The vote for approval was split: six members voted for approval and six voted that the NDA should be approvable pending another study showing effectiveness.

An Approvable action was taken in July 2006. The Approvable Letter contained a single deficiency which reads: "The results of the three randomized trials conducted to date do not provide substantial evidence of effectiveness." The Applicant was asked 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 ($p < 0.05$).

Other comments included:

- o The treated group had all the early withdrawals because of headache. In conjunction with the last observation carried forward (LOCF) imputation method and the fact that the study assessed the rate of change, DCRP felt that the results were biased.
- o DCRP specifically noted that the analysis was sensitive to the effects of imputation and changing the imputation for 3 subjects changed the p-value to 0.12.
- o The small treatment effect may be attributable to the unbalanced use of acetaminophen (necessary to manage headache in patients treated with nitroglycerin).
- o The favorable trend appeared to be confined to subjects Serbia and not in other participating countries

The Agency recommended an additional study to demonstrate effectiveness. Additional Agency suggestions for the additional study included enrolling a potentially more responsive population with a high qualifying score, a separate baseline and

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qualifying scores (to avoid regression to the mean), and the selection of a primary endpoint of pain at some time or pain over some time and not rate of change in pain. Additionally the applicant was advised to control analgesic background use "either by forbidding it or by mandating a standard regimen"

The NDA was transferred from Cellegy Pharmaceuticals Inc. to Strakan Pharmaceuticals Limited (part of the ProStrakan group of companies) in November 2006.

Following this ownership transfer, the FDA review division was changed to the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) from DCRP.

During a meeting between the Sponsor and DAARP on May 22, 2007 the DAARP confirmed that an additional study would be required to support efficacy.

In the meeting minutes of the 5-22-07 meeting, DAARP confirmed the previous conclusions of DCRP that:

- o Prior Studies 98-02-01, 00-02-01 and 03-02-01 failed to show efficacy of Cellegesic as a treatment for pain due to anal fissures.
- o An additional study was required to support efficacy of Cellegesic for the proposed indication.
- o Selection of patients with moderate-severe CAF pain may address concerns regarding regression to the mean.
- o Integral of pain over 14-18 days of treatment is acceptable for use as the "specific time-point" for primary analysis.

The Division also provided comments, summarized below about the sponsor's planned study (REC-C-001) that was submitted in the meeting packet.

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The Division's advice is shown in the left column, while the implementation of this advice into the final design Protocol of REC-C-001 is shown in the right column.

| FDA's advice | Implementation of advice in the design of Protocol REC-C-001 |
|--|--|
| 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 – 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 |
| Patients with a higher baseline pain score should be enrolled | Only patients with a baseline VAS score of 50 mm or greater were enrolled. A VAS score of 50 mm or greater was required on 2 of 4 days before baseline and at 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. | <p>Responder analysis has been performed defined as:</p> <ul style="list-style-type: none"> a) 50% and b) 10 mm reduction on the VAS scoring <p>A responder analysis has the advantage of not requiring any imputation for missing data as subjects who drop out of the study are considered non-responders</p> |
| The sponsor was told to use a conservative imputation method. The Division recommended the use of an imputation method which assigns a bad score to all patients who drop out since these patients will not be successfully treated. | Last observation carried forward (LOCF) was no longer being used for imputation |

2.6 Other Relevant Background Information

Nitroglycerin 0.4% Ointment (under the trade name Rectogesic) is licensed in 20 countries in the EU, and Switzerland. It was first marketed in the EU on 27 May 1995 (UK) and is currently marketed in 18 of the EU countries.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity were adequate. The integrity of analyses shown in the Integrated Summary of Safety and Integrated Summary of Efficacy was adequate and corresponded to the attached source tables. Random datasets were audited with their corresponding tables and the integrity of data was found to be satisfactory.

3.2 Compliance with Good Clinical Practices

The study submitted was certified as being conducted under acceptable ethical standards in accordance with the Declaration of Helsinki and with the approval of the appropriate Ethics Committee.

3.3 Financial Disclosures

All clinical investigators have certified that they have not entered into any financial arrangement with the sponsor whereby the value of compensation to the clinical investigators could have reasonably affected the outcome of the study. The clinical investigators have also certified that they did not have any proprietary interest in the product in the product. The investigators have also certified that they were not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the August 2004 resubmission of NTG 0.4%, and in his review, dated December 13, 2004, the CMC reviewer, Dr. Timmer stated that all CMC issues were satisfactorily resolved at that time. The Office of Compliance issued an acceptable recommendation to all manufacturing facilities.

In the current submission, the applicant has changed the drug product manufacturer. This change in drug product manufacturer is accompanied by technology transfer reports, validation data, and three batch analyses for registration batches manufactured at the new site ((b) (4)).

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However, the applicant has changed drug product manufacturers but has not bridged the current drug product registration batches to batches from the previous drug product manufacturer. Thus, the stability data do not support the registration batches.

The Office of Compliance recommendation is "acceptable" for all manufacturing facilities. However, the Office of New Drug Quality Assessment is recommending against approval until the issues related to the new drug product manufacturer are resolved.

Please see Dr. Olen Stephens' review for further details regarding the CMC issues for this application.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The resubmission of NDA 21-359 contains no new non-clinical pharmacology and toxicology studies requiring review. In his review dated August 9, 2004, Dr. Proakis stated that Cellegesic Nitroglycerin Ointment 0.4% remained approvable from a non-clinical perspective.

4.4 Clinical Pharmacology

There are no new clinical pharmacology data.

4.4.1 Mechanism of Action

Nitroglycerin acts to relax vascular smooth muscle. The Applicant asserts that nitric oxide, a metabolite of nitroglycerin, is a neurotransmitter that mediates relaxation of smooth muscle in the gastrointestinal system, including the internal anal sphincter, and controls the anorectal inhibitory reflex in animals and man. There is a strong association of elevated maximal anal resting pressure (MARP) with the presence of anal fissures. The applicant purports that reduction in the MARP after NTG applications may reduce pain and enhance healing rates.

4.4.2 Pharmacodynamics

There are no new clinical pharmacology data.

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(See 4.4.3 pharmacokinetics below).

4.4.3 Pharmacokinetics

There are no new clinical pharmacology data.

During the 2002 review cycle, the Office of Clinical Pharmacology and Biopharmaceutics reviewed NDA 21-359, Anogesic, for the treatment of chronic anal fissures and found that the clinical pharmacology and biopharmaceutics section was acceptable for approval provided that the assay validation be found acceptable.

The NDA holders for this product have not submitted carcinogenicity studies. Carcinogenic studies are required when a product is expected to be used for greater than six months over a lifetime.

If Cellegesic is ever approved for the treatment of CAF, I do not expect that the product will be used for six months in a lifetime.

Recurrence rates of CAF are high. In a randomized study published in J R Soc Med 1987 by Jensen et al that evaluated the recurrence rate of anal fissure by means of treatment with different doses of fiber versus placebo, a recurrence rate of 68% was noted. Another study showed recurrence rate of 50% after healing with use of conservative treatment. (Lock MR, Brit J of Surgery 1977, 64:355-358) Despite the fact that we have estimates of the recurrence rates, we do not know how many times the condition recurs. Given the high recurrence rate, it is possible that several episodes of CAF could be treated with Cellegesic.

However, it is important to note that CAF is a very painful condition and most patients are unlikely to tolerate the discomfort for long periods of time. While no pharmacologic therapies are currently approved for CAF, current treatment algorithms indicate that nitroglycerin is perceived as being fairly low efficacy, barely better than bulk laxatives and sitz baths; multiple newer and more effective treatments are recognized. For example, Botulinium toxin is believed to be more effective, producing better healing and with a low recurrence rate and calcium channel blockers, which is as effective as nitroglycerin, and without the bothersome adverse effect of headache.

Additionally, most current treatment algorithms utilize the use of nitroglycerin early in the course of treatment, and are followed by surgery if other chemical sphincterotomy measures (as described above) are not effective.

Lateral sphincterotomy, is considered to be the preferred surgical procedure, providing prompt and permanent relief. Surgery is a simple outpatient procedure, with a low recurrence rate.

Based on the reasons described above, we felt that if Cellegesic were approved for CAF, human exposure to this drug would likely be for less than six months duration continuously or intermittently.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1.1 shown below summarizes the salient features of the studies conducted in the development of NTG rectal suppository in the development of the treatment of pain of chronic anal fissure.

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TABLE 5.1.1 PHASE 3 EFFICACY STUDIES

| Report Number | Start Date | Patients Enrolled and Received CTM | Study Description | Study Dose | Treatment Frequency | Duration of Treatment | Primary Endpoint |
|-------------------------------------|-------------|------------------------------------|--|---------------------------------------|-----------------------------|---|--|
| Confirmatory Phase III Study | | | | | | | |
| REC-C-001 | August 2007 | 247 | Confirmatory study | Placebo, 0.4% NTG | b.i.d. | 21 days | Absolute change from VAS baseline (Day 0) in 24-hour average pain, averaged over Days 14-18 of treatment |
| Earlier Phase III Studies | | | | | | | |
| NTG 98-03-01 | July 1998 | 304 | Dose and dosing interval study | Placebo, 0.1% NTG, 0.2% NTG, 0.4% NTG | All doses b.i.d. and t.i.d. | 56 days or until fissure healed (< 56 days) | Complete fissure healing on or before Day 56 |
| NTG 00-03-01 | May 2000 | 229 | Dose ranging study | Placebo, 0.2% NTG, 0.4% NTG | b.i.d. | 56 days | Mean average pain intensity (as measured in mm on the VAS) due to anal fissure |
| CP125 03-03-01 | June 2003 | 188 | Effect on rate of change of pain intensity | Placebo, 0.4% NTG | b.i.d. | 56 days | Rate of change of the 24-hour average pain intensity over 21 days of treatment |

Cross-reference: Statistical Table 1.1 (Section 1.10.3)

KEY: CTM = clinical trial material

Source: p 31 of 263, ISE

5.2 Review Strategy

This Complete Response contains a single efficacy and safety study, Study REC-C-001 which was reviewed during this cycle.

5.3 Discussion of Individual Studies/Clinical Trials

TITLE OF STUDY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTINATIONAL STUDY TO DETERMINE THE EFFECT OF CELLEGESIC NITROGLYCERIN OINTMENT 0.4% (CELLEGESIC) ON THE PAIN ASSOCIATED WITH A CHRONIC ANAL FISSURE

Primary Objective: The primary objective was to have been to determine the effect of Cellegesic versus placebo on the absolute change in 24 hour average pain intensity (using visual analog scale (VAS) scoring) associated with a chronic anal fissure (CAF) averaged over Days 14 to 18 of treatment.

Secondary objectives of this study were to have been to determine the effect of Cellergesic versus placebo on the following parameters:

- o Patients' global assessment of treatment therapy at Day 21 (last assessed visit day)
- o The percentage of responders, defined as patients with a decrease in 24 hour average pain intensity
- o (VAS) scoring associated with a CAF averaged over Days 14 to 18 of treatment compared to baseline by (a) at least 10 mm and (b) at least 50%
- o The time to improvement in 24 hour average pain intensity (VAS) associated with a CAF defined as (a) a 10 mm and (b) a 50% decrease in VAS
- o Absolute change in 24 hour average pain intensity (VAS) associated with a CAF averaged over Days 14 to 18 of treatment, within each region represented in the study
- o Absolute change in 24 hour average pain intensity (VAS) associated with a CAF at Days 7, 14, and 21 (last assessed visit day)

Study Design: This was to have been a 3-week, multinational, Phase 3a, randomized, double-blind, placebo-controlled study.

Qualified patients were to have been assigned in a 1:1 ratio to Cellegesic or placebo ointment. All patients were instructed to take two 325 mg acetaminophen tablets approximately 30 minutes before application of the ointment into the anal canal twice daily. The patient's assessment of the 24-hour average pain intensity using a VAS was to have been carried out at the clinic on Day 0, then daily in the evening at bedtime until the evening before the Day 21 visit (last assessed visit day).

Patients were to have completed the final VAS and global assessment of therapy in the clinic at the Day 21 visit. Vital signs were recorded at every study visit; orthostatic hypotension was assessed from those data. Physical examinations, anal examinations,

and 12-lead electrocardiograms (ECGs) were performed at the screening and Day 21/End-of-study visits.

A total of 247 subjects were to have been randomized to treatment, 123 patients to the Cellegesic arm and 124 patients to placebo. All randomized subjects were to have been included in the intent-to-treat (ITT analysis).

Inclusion Criteria:

A patient was to have met the following criteria at Screening (except for criterion 4, which was checked at the Day 0 visit) to be enrolled in this study:

- 1) Was able to provide written informed consent;
- 2) Was male or female aged 18 to 75 years;
- 3) Had a single, chronic, posterior midline anal fissure defined as having anal pain for the 6 weeks prior to Screening and showing the presence of at least one of the following:
 - sentinel skin tag
 - hypertrophied anal papillae
 - exposed internal anal sphincter
 - fibrotic fissure marginsor
 - fibrotic anal sphincter
- 4) Had 24 hour average pain VAS of at least 50 mm at the time of the Randomization/Day 0 visit and for 2 of the 4 days before the Randomization/Day 0 visit;
- 5) Was willing to go without the use of non-prescription over-the-counter and prescription medicine for the treatment of anal fissure for the duration of the study (except fiber supplements and stool softeners);
- 6) Willing to go without the use of nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase 2 (COX-2) inhibitors (e.g. ibuprofen, naproxen, ketoprofen), and aspirin (except daily low-dose aspirin [162 mg] or up to 325 mg on alternate days for cardiovascular prophylaxis) or any other analgesic for the treatment of headache or any other condition; and
- 7) Was willing to go without the use of acetaminophen (other than that provided for use in the study at the permitted dose) and any other acetaminophen-containing product for the treatment of headache or any other condition.

Exclusion Criteria:

1. A patient meeting any of the following criteria at Screening was to have been excluded from the study:
2. Considered unlikely to comply with study visit schedule;

3. Had more than one anal fissure;
4. Had a fistula-in-ano or an anal abscess;
5. Had inflammatory bowel disease;
6. Had fibrotic anal stenosis;
7. Had an anal fissure secondary to an underlying condition, e.g. human immunodeficiency virus, tuberculosis, syphilis;
8. Had undergone any anal surgery;
9. Had severe intercurrent illness, which in the opinion of the Investigator, may have put the patient at risk when participating in the study or may have influenced the results of the study or affected the patient's ability to take part in the study;
10. Had acute or chronic renal and/or hepatic impairment;
11. Had clinically significant, abnormal, baseline study results, e.g. laboratory results, ECG and vital signs, which in the opinion of the Investigator affected the patient's suitability for the study, e.g. abnormal liver function tests;
12. Had previous or current pelvic radiation treatment;
13. Females who were of child-bearing potential but were not taking adequate contraceptive precautions or those who were pregnant or lactating;
14. Was known to be allergic to NTG, lanolin, white petroleum, paraffin wax, sorbitan sesquileate, propylene glycol, or acetaminophen;
15. Had hypotension or uncorrected hypovolemia, increased intracranial pressure (e.g. head trauma or cerebral hemorrhage) or inadequate cerebral circulation, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis or pericardial tamponade, marked anemia, or closed-angle glaucoma;
16. Had a history (going back 5 years) of migraine and chronic headaches or any other chronic pain that required treatment with analgesics;
17. Was taking NTG or any other NO donors (e.g. arginine), potassium channel blockers (e.g. nicorandil) or calcium channel blockers (e.g. nifedipine) by any route of administration for any indication;
18. Was taking any herbal remedies or homeopathic treatments for the treatment of a CAF.

Treatment:

Cellegesic or placebo was to have been applied twice daily for 3 weeks

Prohibited Medications

All patients, if not already on a regimen of conservative care, were advised about adopting a regimen of conservative care consisting of fiber supplementation, adequate fluid intake, and sitz baths. If a patient was on a stable dose of stool softener for the week before the Randomization visit/Day 0, he or she was instructed to continue on that daily dose for the duration of the study. Patients were asked to record their daily number of sitz baths on a diary card. Patients were instructed that they should not take a sitz bath until at least one hour after treatment application in order to allow absorption of the ointment.

A regimen of conservative care was maintained throughout the study. No other pharmacologic or non-pharmacologic therapies for anal fissure were permitted.

Prohibited medications were to have included the following:

- o Over-the-counter or prescription products for anorectal therapy including nitroglycerin (NTG) or any other nitric oxide donors (e.g. arginine).
- o Potassium channel blockers (e.g. nicorandil) or calcium channel blockers (e.g. nifedipine) by any route of administration.
- o Treatment with nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors (e.g. ibuprofen, naproxen, ketoprofen); aspirin (except low-dose aspirin (162 mg once daily or 325 mg every other day for cardiovascular prophylaxis) and other salicylates.
- o Acetaminophen, other than that provided for the study.
- o Phosphodiesterase type 5 inhibitors (e.g. sildenafil citrate).

Outcome Measures:

Primary Efficacy Endpoints:

The primary efficacy endpoint was to have been the absolute change from baseline VAS (defined as Day 0) in 24 hour average pain, as assessed by patient-reported VAS averaged over Days 14 to 18 of treatment.

Secondary Efficacy Measures:

The secondary efficacy measures were to have been:

- 1) Patients' global assessment of therapy at Day 21
 - a. Patients were to be asked to respond to the statement: "This treatment may have produced side effects. Please indicate whether you feel that the benefit of the treatment on anal pain outweighs any side effects you have experienced"

- b. Patient choice of responses: "yes" or "no".
- 2) Percentage of responders, defined as patients with decrease in 24-hour average pain intensity scoring over Days 14 to 18 of treatment compared to baseline by:
(a) at least 10 mm and (b) at least 50%
- 3) Time to 10 mm and 50% improvement in VAS
- 4) Primary endpoint analyzed separately for each country
- 5) Absolute change from baseline in 24-hour average pain as assessed by patient-reported VAS at Days 7, 14 and 21

Safety Outcome Measures:

- 1) Vital signs: Screening, Randomization and days 7, 14 and 21
- 2) ECG: Screening and day 21
- 3) Urinalysis: Screening and day 21
- 4) Laboratory evaluations: Screening and day 21
 - a. Hematology: CBC with differential, Hgb, Hct, Plat count
 - b. Chemistry – albumin, alkaline phosphatase, ALT, amylase, AST, BUN, chloride, creatine phosphokinase, creatinine, bilirubin (direct and total), GGT, glucose, LDH, lipid profile, phosphorus, potassium sodium, total protein and uric acid
 - c. Urine Pregnancy Testing done only at Randomization and day 21
- 5) Adverse Events: Randomization and days 7, 14 and 21

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Study Visit Schedule:

Study procedures were to have occurred according to the schedule of events in Table 5.3.1 noted below.

TABLE 5.3.1: STUDY VISIT SCHEDULE

| Visit | 0/Screening | 1/Randomization | 2 | 3 | 4 |
|---|-------------|---------------------|---------------|----------------|----------------|
| Day | -7 | 0 (Screening +7) | 7 ± 2 days | 14 ± 2 days | 21 ± 2 days |
| Informed consent | X | | | | |
| Demographics | X | | | | |
| Past/Current medical conditions | X | | | | |
| Physical examination | X | | | | X |
| Anal examination | X | | | | X |
| Vital signs | X | X | X | X | X |
| Orthostatic hypotension assessment | X | X | X | X | X |
| 12-lead Electrocardiogram | X | | | | X |
| Inclusion/Exclusion criteria | X | X | | | |
| Previous and current concomitant medication | X | X | X | X | X |
| Randomization | | X | | | |
| Adverse events | | X | X | X | X |
| Pain visual analog scale | X | X | X | X | X |
| Diary | | X | X | X | X |
| Global assessment of therapy | | | | | X |
| Drug dispensing | | X | | | |
| Treatment application at clinic | | X | X | | |
| Compliance check | | | X | X | X |
| Laboratory tests | X | | | | X |
| Urinalysis | X | | | | X |
| Urine pregnancy test | | X | | | X |

Source: Clinical Study Report REC-C-001 p 34/108

Statistical Analysis Plan and Definition of Analyzed Study Populations:

The analysis populations were defined as follows:

Intent-to-Treat (ITT)-defined as patients who are randomized to one of the treatment groups and have received study medication at least once

Per protocol (PP) - all patients who fully comply with the requirements of the protocol regarding inclusion and exclusion criteria, study medication compliance and have recorded all 24-hour average pain intensity assessments between Days 14 and 18.

The significant features of the Statistical Analysis Plan are as follows:

- The primary efficacy endpoint was the absolute change from VAS Baseline (Day 0) in 24 hour average pain, as assessed by patient-reported VAS averaged over Days 14 to 18 of treatment. Patients who withdrew from the study before Day 18 had a value of zero imputed for their change from baseline VAS score.
- The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment, region, and gender as factors and baseline VAS pain as a covariate.
- Imputation method
 - The sponsor agreed to conduct the primary analysis using a BOCF strategy
 - The sponsor stated that they would use a “zero change” imputation strategy for the primary efficacy analysis
- The mean VAS score and standard deviation from the mean at each time point up to the assessment made at the last visit day were to have been displayed graphically by treatment group.
- A sensitivity analysis was included to assess the effect of missing data and was performed using the intent-to-treat (ITT) population only.
- A second sensitivity analysis with modified rules was devised *after* the study was unblinded. Both analyses were conducted and reported. The primary endpoint was also analyzed by region.
- The primary analysis study population was set as the intent-to-treat (ITT) which includes all randomized subjects with at least one dose taken. Hierarchical testing was selected for secondary outcome variables.

Supportive Analysis

- A supportive analysis on absolute change from baseline VAS score was to have been carried out on the ITT population using repeated measures ANCOVA.

Analysis of Secondary Efficacy Data

- The time to improvement (a) for a 50% decrease and (b) for a 10 mm decrease in 24 hour average pain intensity (VAS) associated with a CAF were compared between the treatment groups using the log-rank test stratified by region, baseline VAS, and gender. Kaplan-Meier curves were also produced.
- The percentage of responders, defined as
 - (a) a 50% decrease

- and
- (b) a 10 mm decrease in 24 hour average pain intensity (VAS) from baseline to primary endpoint (average over Days 14 to 18 of treatment) was compared between the treatment groups using logistic regression with treatment, region, and gender as factors and baseline VAS pain as a covariate.
- Continuous Responder Analysis
A graph was to have been produced to show the proportion of patients who were responders, for levels of improvement in VAS pain measured in millimeters, for the 2 treatment groups. Another graph was produced, basing the improvement in VAS pain on percentage values.
 - Pain Intensity
Absolute change in 24 hour average pain (VAS) from baseline at scheduled visits on Days 7, 14, and 21 (last assessed visit day) was to have been analyzed separately, in a similar manner to the primary endpoint analysis (primary analysis only).
 - Patient's Global Assessment
The patients' global assessment of therapy at Day 21 (last assessed visit day) was compared between the treatment groups using logistic regression with treatment, region, and gender as factors and baseline VAS pain as a covariate.

Protocol Amendments:

Amendment 1 – 8 June 2007 (implemented before the start of recruitment)

- Removal of interim analysis
- Removal of Data Monitoring Committee. Revision of sample size calculations because of removal of the interim analysis. Last observation carried forward no longer being used for imputation.
- First doses of study medication on Day 0 and Day 7 were to be applied at the clinic. Baseline VAS obtained at the Day 0 visit and the final VAS obtained at the Day 21 visit. . Vital signs recorded in all patients at all visits, with additional measurements on Days 0 and 7. An electrocardiogram recorded in all patients at the beginning and end of the study.
- Addition of a continuous responder analysis as a study endpoint
- Definition of intent-to-treat population was amended, resulting in different requirements for replacement of patients

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Administrative Changes Letter - 3 July 2007

- Clarified that the screening period was up to 7 days' duration
- Provided corrected telephone and fax numbers to be used for serious adverse event reporting
- Provided a new name for the company that performed study drug packaging

Protocol amendment 2 included the addition of six investigator sites in Mexico.

Amendment 2 - 18 June 2008

- Increase in total number of study sites from 30 to 45
- Initiation of study sites in Mexico in addition to Argentina, Brazil, and the US . The country stratification variables consist of Argentina, Brazil, Mexico, and the US
- Replacement of planned analysis by country with analysis by region (Latin America, US) as the number of patients in each of the Latin American countries was much smaller than originally expected

RESULTS

TABLE 5.3.2 DISPOSITION BY TREATMENT GROUP

| | CELLEGESIC N=123 n (%) | PLACEBO N=124 n (%) | TOTAL N=247 n (%) |
|---|-------------------------------------|----------------------------------|--------------------------------|
| Total number of patients | | | |
| Completed | 106 (86.2) | 113 (91.1) | 219 (88.7) |
| Discontinued | 17 (13.8) | 11 (8.9) | 28 (11.3) |
| Primary reason for discontinuation | | | |
| Adverse event | 9 (7.3) | 3 (2.4) | 12 (4.9) |
| Protocol Violation | 2 (1.6) | 0 | 2 (0.8) |
| Lost to follow up | 1 (0.8) | 4 (3.2) | 5 (2.0) |
| Patient death | 0 | 0 | 0 |
| Voluntary withdrawal | 5 (4.1) | 4 (3.2) | 9 (3.5) |

Source: p47 of 108 Clinical Study Report REC-C-001

Drop Outs and Discontinuations

Nine patients from the Cellegesic treatment arm withdrew from the trial because of an adverse event. Seven of the nine AE withdrawals were because of headache. Pt # 126/1305 withdrew because of skin fissures, and Pt #128/1286 withdrew because of osteomyelitis.

Three patients on the placebo control arm withdrew from the trial; Pt # 109/1800 because of diarrhea, Pt # 113/1527 because of celiac disease, and pt # 116/1807 because of headache.

Five patients on both the Cellegesic (4%) and the placebo arm (3%) withdrew voluntarily.

One patient on the Cellegesic arm were lost to follow up, while four patients on the placebo arm were lost to follow up.

Protocol Deviations

Table 5.3.3 show below shows the number and types of protocol violations

Approximately 29% of patients in each treatment arm had at least one protocol violation.

The proportion of active and placebo randomized patients in each category of protocol violations were similar.

TABLE 5.3.3: PROTOCOL VIOLATIONS IN CELLEGESIC AND PLACEBO ARMS

| | Cellegesic N = 123 n (%) | Placebo N = 125 n (%) | Total N = 248 n (%) |
|--|---------------------------------------|------------------------------------|----------------------------------|
| Number of patients with at least one protocol violation | 35 (28.5) | 36 (28.8) | 71 (28.6) |
| Total number of protocol violations | 78 | 65 | 143 |
| Protocol violation breakdown | | | |
| Did not satisfy inclusion/exclusion criteria | 2 (1.6) | 7 (5.6) | 9 (3.6) |
| Had an overall study drug compliance <80% up to Day 21 | 21 (17.1) | 14 (11.2) | 35 (14.1) |
| Had not recorded all 24 hour average pain assessments between Days 14 to 18 | 25 (20.3) | 20 (16.0) | 45 (18.1) |
| Received prohibited medications | 12 (9.8) | 9 (7.2) | 21 (8.5) |
| Had unsuitable medical history at Screening | 1 (0.8) | 1 (0.8) | 2 (0.8) |
| Withdrew before Day 19 (earliest allowed date for Visit 4/Withdrawal visit) | 17 (13.8) | 13 (10.4) | 30 (12.1) |
| Did not receive at least one application of study medication | 0 | 1 (0.8) | 1 (0.4) |
| <p>Note: Percentages were based on the number of patients (N) in each treatment group. The table summarizes patients who were excluded from the per-protocol population. No patients met the criteria of "received different treatment from the one randomized" or "unblinded prematurely." Source: Table 14.1.2.</p> | | | |

Source: p 49 of 108 Clinical Study Report REC-C-001

The most common violations reported were in the categories of excluded medications, ICF, and inclusion and exclusion criteria. There were also several violations noted in the categories of investigational product (study drug), laboratory, randomization error, procedure not done, and "other."

More than half of all reported deviations related to investigational product. These mostly related to the timing of the acetaminophen dose and ointment application. Less common violations were related to missed doses, tablet accountability, or other errors.

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Less common were deviations in the "other" category, which included a variety of errors in study conduct. Other deviations, in decreasing order of frequency, were out of visit window, procedure or assessment not done, inadequate source documents, laboratory errors, ICF, excluded medication, randomization error, and inclusion /exclusion criteria.

Deviations and violations reported for informed consent issues included the patient signing an incorrect ICF version, patient errors in signing or dating the ICF, the patient receiving an ICF not stamped by the IRB/IEC, the patient signing the ICF before the site initiation visit, or the patient not receiving and signing a revised ICF at the first study visit when it was available. In other cases, an examination was performed before the ICF was signed, the patient did not complete the page about primary care practitioner/specialist notification or the primary care practitioner/specialist was not notified as the patient had requested. In one case, the patient was provided a copy of the ICF instead of a second original signed ICF.

Overall, the proportion of protocol violations in each treatment group was similar, and was minor in nature. The protocol violations do not affect the quality of the inferences of the study analysis.

DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographics for the safety and ITT populations are shown in Table 5.3.4.

Distribution by age, gender and race was similar in the to treatment groups.

The mean age of study participants was 45 years; approximately 79% of the study population was Caucasian; and there was a slight male preponderance 53% versus 47% female.

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TABLE 5.3.4: DEMOGRAPHICS BY TREATMENT GROUP

| | Cellegesic N = 123 | Placebo N = 124 | Total N = 247 |
|---|-----------------------|--------------------|------------------|
| Age (years) | | | |
| N | 123 | 124 | 247 |
| Mean (SD) | 46.5 (12.61) | 43.4 (13.22) | 45.0 (12.99) |
| Median | 46.0 | 43.0 | 44.0 |
| Min, Max | 18, 74 | 21, 73 | 18, 74 |
| Age <65 years ^a , n (%) | 114 (92.7) | 117 (94.4) | 231 (93.5) |
| Age ≥65 years ^a , n (%) | 9 (7.3) | 7 (5.6) | 16 (6.5) |
| Gender, n (%) | | | |
| Male | 65 (52.8) | 66 (53.2) | 131 (53.0) |
| Female | 58 (47.2) | 58 (46.8) | 116 (47.0) |
| Race, n (%) | | | |
| White | 99 (80.5) | 96 (77.4) | 195 (78.9) |
| Black | 21 (17.1) | 16 (12.9) | 37 (15.0) |
| Asian | 0 | 2 (1.6) | 2 (0.8) |
| American Indian or Alaska Native | 0 | 3 (2.4) | 3 (1.2) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (0.8) | 1 (0.4) |
| Other | 3 (2.4) | 6 (4.8) | 9 (3.6) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 23 (18.7) | 31 (25.0) | 54 (21.9) |
| Not Hispanic or Latino | 100 (81.3) | 93 (75.0) | 193 (78.1) |
| Note: Percentages were based on the number of patients (N) in each treatment group. | | | |
| ^a Age categories were hand calculated from listing; counts are not represented in source tables. | | | |
| Source: Table 14.1.4.1, Listing 16.2.4. | | | |

Source: p 55 of 108- Clinical Study Report REC-C-001

PRIMARY EFFICACY RESULTS

Applicant's efficacy findings

The primary efficacy endpoint was the absolute change from VAS baseline (defined as Day 0) in 24-hour average pain, as assessed by patient-reported VAS averaged over Days 14-18 of treatment. These results were analyzed using ANCOVA and are summarized for the ITT population in Table 5.3.5.

The adjusted mean (standard error [SE]) change from baseline VAS was slightly greater in the Cellegesic™ group (-40.4 (3.12) mm) compared with the placebo group (-34.9 (3.04) mm). The mean (95% confidence interval [CI]) difference between treatment groups in the adjusted change from baseline VAS score was -5.4 (-12.3,1.4) mm in favor of Cellegesic™, the difference was not statistically significant (p = 0.118).

TABLE 5.3.5: ABSOLUTE CHANGE FROM VAS BASELINE IN 24-HOUR AVERAGE PAIN FOR DAYS 14 to 18 (ITT POPULATION)

| | Cellegesic™ N = 123 | | Placebo N = 124 | | Difference Change from Baseline ^a |
|-------------------------------|------------------------|-------------------------|--------------------|-------------------------|--|
| | Actual Result | Change from Baseline | Actual Result | Change from Baseline | |
| Day 0 | | | | | |
| Mean (SD) | 72.7 (14.5) | | 73.0 (13.21) | | |
| Median | 73.0 | | 71.5 | | |
| Range | 13 ^b -100 | | 51-100 | | |
| Days 14-18^c | | | | | |
| Mean (SD) | 33.3 (27.9) | -39.4 (27.7) | 38.8 (28.2) | -34.2 (27.8) | |
| Median | 24.4 | -43.6 | 39.0 | -33.8 | |
| Range | 0-94 | -91-18 | 0-97 | -95-12 | |
| Adjusted Mean (SE) | | -40.4 (3.12) | | -34.9 (3.04) | -5.4 (3.5) |
| 95% CI | | | | | -12.3, 1.4 |
| p-value | | | | | 0.118 |

Cross-reference: Statistical Table 14.2.2.1, REC-C-001 CSR (Module 5.3.5.1)

^a Difference between Cellegesic™ and placebo. Adjusted means, CIs and p-values were derived from an ANCOVA model with treatment, region, and gender as factors and baseline VAS pain as a covariate. Countries were pooled by region.

^b One patient in the Cellegesic™ group had a baseline VAS of 13 mm and was discontinued from the study because of a protocol violation.

^c Patients who withdrew before Day 18 had a zero change from baseline imputed. Imputations for missing values during Days 14-18 were performed according to the REC-C-001 CSR Statistical Analysis Plan (SAP; see Section 16.1.9, REC-C-001 CSR [Module 5.3.5.1]).

Source: page 26/88 Clinical Efficacy Summary

The applicant stated that since more than 10% of patients did not complete the study and had missing primary endpoints, two sensitivity analyses were performed to assess the effect of missing data.

The rules for the sensitivity analysis were proposed before the study began (original sensitivity analysis), but were later revised (after unblinding).

The applicant did not meet their prospectively defined primary efficacy endpoint goals.

SECONDARY EFFICACY RESULTS

The applicant states that since the first secondary endpoint (time to 50% decrease in VAS) analysis failed to reject the null hypothesis of no difference between treatments at the 5% significance level, all subsequent secondary efficacy analyses were reported as exploratory analyses.

1) Time to improvement in VAS Score (ITT Population)

The times to improvement in VAS score, defined as either a 50% decrease or a 10 mm decrease from baseline, are presented for the ITT population in Table 5.3.6.

The majority of patients in both treatment groups had an improvement of at least a 50% reduction from baseline VAS score (72.4% and 64.5% in the Cellegesic™ and placebo groups, respectively). The median (95% CI) time to a 50% decrease was longer in the placebo group (12.0 (11.0, 15.0) days) compared with the Cellegesic™ group (9.0 [7.0, 11.0] days). This difference was not statistically significant ($p = 0.071$).

A high proportion of patients in both treatment groups experienced at least a 10 mm decrease from baseline VAS (88.6% and 85.5% of patients in the Cellegesic™ placebo groups, respectively). The difference between groups in the time to achieve a 10 mm reduction in pain score was minimal (median (95% CI) was 3.0 (3.0, 4.0) and 4.0 (3.0,6.0) days for the Cellegesic™ and placebo groups, respectively). This difference was not statistically significant ($p=0.29$).

TABLE 5.3.6: TIME TO IMPROVEMENT IN VAS SCORE

| | Cellegesic™ N = 123 | Placebo N = 124 |
|---|--------------------------------|----------------------------|
| ≥ 50% Decrease in VAS Score | | |
| ≥ 50% decrease in VAS score, n (%) | 89 (72.4) | 80 (64.5) |
| Censored, n (%) | 34 (27.6) | 44 (35.5) |
| Time to improvement (days) ^a | | |
| Mean (SE) | 10.7 (0.6) | 13.2 (0.7) |
| Median (95% CI) | 9.0 (7.0, 11.0) | 12.0 (11.0, 15.0) |
| p-value ^b | 0.071 | - |
| 10 mm Decrease in VAS Score | | |
| 10 mm decrease in VAS score, n (%) | 109 (88.6) | 106 (85.5) |
| Censored, n (%) | 14 (11.4) | 18 (14.5) |
| Time to improvement (days) ^a | | |
| Mean (SE) | 6.1 (0.5) | 7.2 (0.6) |
| Median (95% CI) | 3.0 (3.0, 4.0) | 4.0 (3.0, 6.0) |
| p-value ^b | 0.287 | - |

Cross-reference: Statistical Table 14.2.5.1, REC-C-001 CSR (Module 5.3.5.1)

^a The summary statistics were based on the non-parametric estimates of the survivor function. The minimum and maximum time to improvement was based on uncensored data.

^b Comparison Cellegesic™ versus placebo. The p-value was obtained from a log-rank test stratified by region, baseline VAS pain and gender.

Source: p 28/88 Clinical Efficacy Summary

For the responder analyses of the proportions of patients who achieved a 50% or 10 mm reduction from baseline VAS score, no significant differences between treatment groups were observed. However, analysis of these parameters by logistic regression indicated that the odds of achieving these reductions in VAS scores were higher in the Cellegesic™ group versus the placebo group (odds ratios were 1.476 and 1.192 for 50% and 10 mm reductions in VAS scores, respectively).

2) Absolute Change from Baseline VAS at Scheduled Visits- Days 7, 14 and 21

The adjusted mean (SE) difference in change from baseline VAS between treatments was -5.2 (3.5) mm at Day 7, -6.8 (3.5) mm at Day 14, and -7.3 (3.7) mm at the final visit (Day 21/withdrawal visit) in favor of Cellegesic™. Thus, the difference between treatment groups in change from baseline VAS increased over time.

3) Global Assessment of Therapy

This assessment questioned patients' feelings about their therapy at a single timepoint.

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On the last assessed visit day (Day 21/withdrawal visit), 77.2% of patients in the Cellegesic™ group and 82.3% of patients in the placebo group answered that the benefit of the treatment outweighed any side effects they had experienced.

It is significant to note that the proportion of patients who subjectively experienced benefit from the treatment was similar in the placebo control and treatment arm.

4) Change from Baseline VAS in 24-Hour Average Pain by Region

The primary efficacy analysis was repeated by region (US and Latin America). An analysis by country had originally been planned, but this was amended as a result of Protocol Amendment 2 to an analysis by region since the number of patients in each of the Latin American countries was much smaller than originally expected. The results of this analysis were not consistent for the 2 regions.

The mean (95% CI) difference between treatment groups (using the zero-imputation method) in the adjusted change from baseline VAS score in the US was -7.5 (-14.9, -0.1) mm in favor of Cellegesic™ ($p = 0.048$), whereas in Latin America, the difference was 7.3 (-10.3, 25.0) mm ($p = 0.401$) in favor of placebo.

However, the number of Latin American patients (33) was small compared to the number of patients in the US (214).

5) Analyses by Baseline VAS Stratum

The absolute change from baseline VAS in 24-hour average pain was calculated by each baseline VAS stratum: 50 to 69 mm and 2: 70 mm. The larger mean change (SD) from baseline VAS occurred in the stratum with baseline VAS 2: 70 mm, which was -3.6 (30.08) mm and -36.4 (32.05) mm in the Cellegesic™ and placebo treatment groups, respectively. The mean change (SD) from baseline VAS in the stratum with baseline VAS of 50 to 69 mm was -34.5 (24.01) mm and -31.8 (22.37) mm in the Cellegesic™ and placebo treatment groups, respectively.

Similarly, the difference between the Cellegesic™ group and the placebo group in median values for time to a 50% decrease was greater in the subgroup with the higher baseline VAS scores. These results are presented in Table 5.3.6

TABLE 5.3.7: TIME TO IMPROVEMENT IN VAS SCORE BY BASELINE VAS STRATUM (ITT POPULATION)

| 50% Decrease in VAS score | Cellegesic™ N = 123 | Placebo N = 124 |
|---|--------------------------------|-----------------------------|
| Baseline VAS 50-69 mm | N = 57 | N = 59 |
| ≥ 50% decrease in VAS score, n (%) | 43 (75.4) | 44 (74.6) |
| Censored, n (%) | 14 (24.6) | 15 (25.4) |
| Time to improvement (days) ^a | | |
| Mean (SE) | 9.9 (0.9) | 12.2 (0.9) |
| Median (95% CI) | 8.0 (5.0, 10.0) | 11.0 (9.0, 14.0) |
| Baseline VAS ≥ 70 mm | N = 66 | N = 65 |
| ≥ 50% decrease in VAS score, n (%) | 46 (69.7) | 36 (55.4) |
| Censored, n (%) | 20 (30.3) | 29 (44.6) |
| Time to improvement (days) ^a | | |
| Mean (SE) | 11.2 (0.8) | 12.4 (0.8) |
| Median (95% CI) | 10.0 (8.0, 13.0) | 15.0 (11.0, not calculable) |

Cross-reference: Statistical Table 14.2.5.2, REC-C-001 CSR (Module 5.3.5.1)

^a The summary statistics were based on the non-parametric estimates of the survivor function.

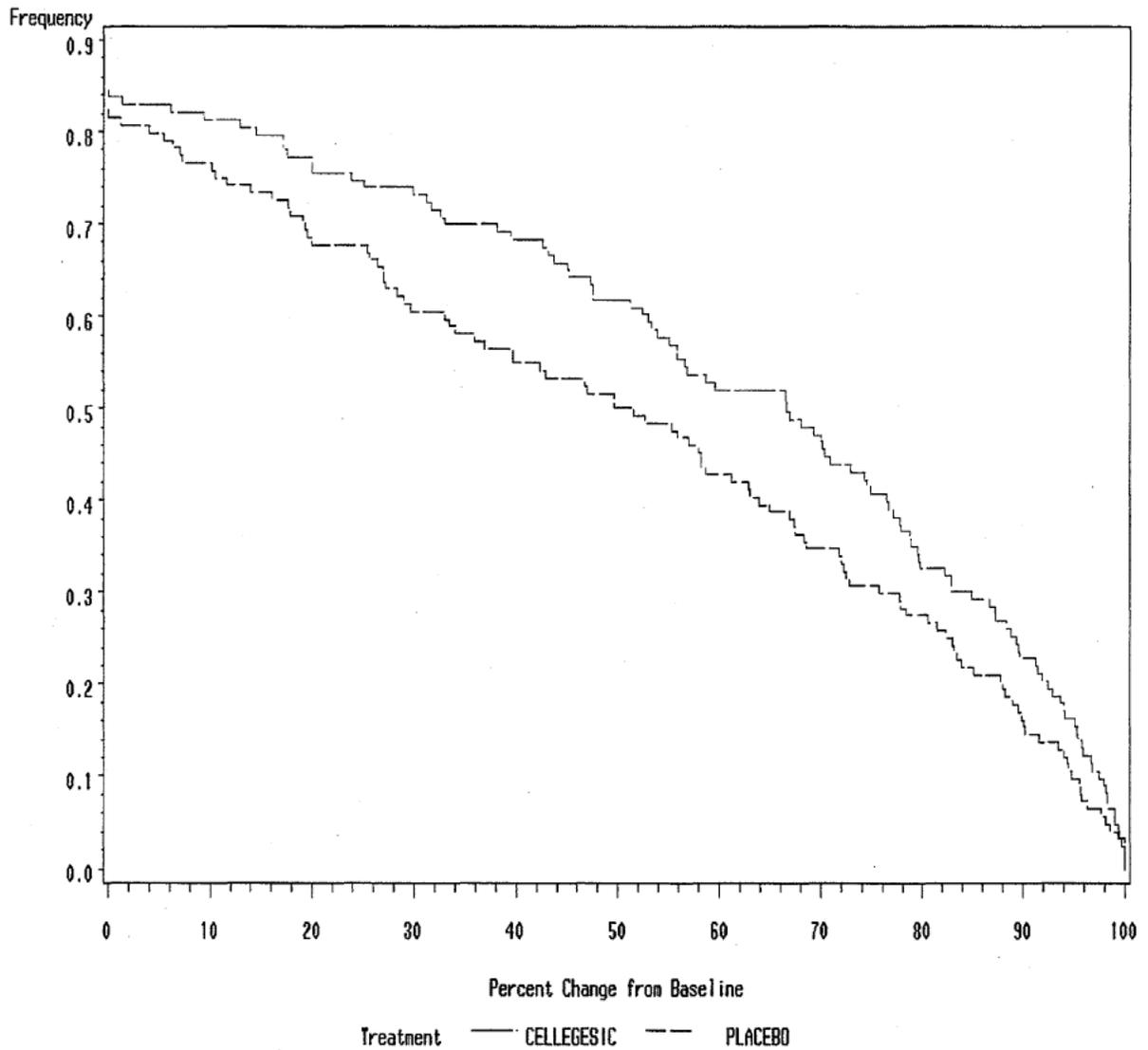
Source: p 29/88- Clinical Efficacy Summary

Continuous Responder Analysis

Figure 5.3.7 noted below is a plot of the proportion of patients who achieved each level of absolute improvement from baseline in VAS pain at the primary endpoint and as such provides a visual display of different responder definitions. Patients who worsened are not included in the figure. The plot (noted below) shows the proportions of patients who achieved each level of percentage change in VAS.

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FIGURE 5.3.7: Continuous Responder Analysis: Absolute Improvement in VAS Pain at the Primary Endpoint (Intent-to-Treat Population)



SAFETY RESULTS

Safety data collected included AEs, clinical laboratory data (hematology, serum chemistry, and urinalysis), vital sign measurements, orthostatic hypotension, physical examination, ECG, and anal examination. Data were summarized by treatment group.

In Study REC-C-001, there were no deaths. There were a total of 3 serious adverse events (SAEs) which were not related to study drug. A total of 13 patients discontinued due to adverse events. The majority of these discontinuations were related to headache.

Please see Section 7 for more information about the safety of this product.

DISCUSSION/CONCLUSION (EFFICACY)

Study REC-C-001 showed a small treatment effect that did not achieve statistical significance.

The adjusted mean (95% CI) treatment effect size for the protocol-specified analysis was -5.4 (-12.3, 1.4) mm ($p=0.118$). A larger proportion of patients in the Cellegesic group (17 of 123 [13.8%]) had discontinued before the primary endpoint, than in the placebo group (11 of 124 (8.9%)). These patients had a zero change from baseline imputed for the primary analysis. The sensitivity analysis imputed values based on actual VAS scores for the primary endpoint. The adjusted mean (95% CI) treatment difference in change from baseline 24 hour average pain at Days 14 to 18 was -7.2 (-13.8, -0.6) mm, ($p=0.033$).

The primary analysis endpoint was not met in Study REC-C-001 using the conservative zero-imputation method.

Withdrawals from NTG studies remain a design and analysis issue, and whether patients withdrew because of headache or due to early resolution of CAF pain, the effects of early discontinuation must be conservatively managed.

With regard to the secondary efficacy endpoints, the median (95% CI) time to a 50% improvement from baseline VAS was 9.0 (7.0, 11.0) days for the Cellegesic group and 12.0 (11.0, 15.0) days for the placebo group, although the difference was not statistically significant. More patients in the Cellegesic group (73 [59.3%]) experienced at least a 50% decrease in VAS score from baseline, than did patients in the placebo group (62 [50%]).

The applicant failed to meet the prospectively defined primary end point and most of the prospectively defined secondary efficacy endpoints. It is also interesting to note that the patient global assessment favored placebo over active drug.

6 Review of Efficacy

Efficacy Summary

This Complete Response consisted of a single efficacy study that met the criteria of an adequate and well-controlled study.

For the statistical analysis, after discussions with the Agency, the Applicant agreed to conduct the primary analysis using a conservative imputation strategy for the primary efficacy analysis. Using the protocol-specified, conservative statistical analysis plan, Study REC-C-001 failed to show a statistically significant difference in the difference in pain intensity from baseline.

Although subsequent primary efficacy analyses using LOCF and repeated post hoc analyses achieved statistical significance, the applicant failed to meet the prospectively defined primary efficacy end point.

Thus, the Applicant has failed to support this NDA with substantial evidence of efficacy.

6.1 Indication

Study REC-C-001 was submitted for the indication of Treatment of pain associated with chronic anal fissure in adults.

6.1.1 Methods

See Section 5.3

6.1.2 Demographics

See Section 5.3

6.1.3 Subject Disposition

See Section 5.3

6.1.4 Analysis of Primary Endpoint(s)

See Section 5.3

6.1.5 Analysis of Secondary Endpoints(s)

See Section 5.3

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Not applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

The Applicant also performed a meta-analysis on the integrated dataset (utilizing data from Study REC-C-001 in addition to three prior studies (Studies NTG 98-03-01, NTG 00-03-01 & CP125 03-03-01). The sponsor concluded that the meta-analysis showed a statistically significant difference in favor of NTG compared to placebo.

The results of the sponsor's post hoc meta-analysis are not acceptable for making a regulatory claim.

A meta-analysis of randomized trials is based on the assumption that each trial provides an unbiased estimate of the effect of an experimental treatment, with the variability of the results between the studies being attributed to random variation.

The sponsor's analysis was based on a cross-study comparison across different times and differing protocol designs and endpoints.

The trials differed in a number of ways:

- o Different primary and secondary end points- for example complete fissure healing versus re-epithelialization at site of fissure
- o Duration of trial & study day of measuring endpoint
- o Inclusion and exclusion factors
- o Concentration of nitroglycerin – 0.1% vs 0.2% vs 0.4%
- o Frequency of administering nitroglycerin agent- eg bid or tid
- o Concomitant anorectal Treatment - for example
 - Use of supplemental dietary fiber
 - Use of Sitz Baths
- o Use of concomitant analgesic medication eg acetaminophen

7 Review of Safety

Safety Summary

A total of 123 patients were exposed to study medication and were included in the analysis of the safety population of REC-C-001.

A total of 96 patients (78%) in the Cellegesic group and 67 patients (54%) in the placebo group experienced at least one AE during the study.

There were no deaths or serious adverse events related to study medication reported.

A total of 9 patients (7.3%) in the Cellegesic group and 4 patients (3.2%) in the placebo group had AE's that were classified as leading to treatment discontinuation. The most common AE leading to treatment discontinuation was headache.

The most common AE's in the Cellegesic group were headache and dizziness. Headaches in the Cellegesic group were mostly mild, and overall, were of a shorter duration than those in the placebo group. The incidence of other AE's was similar in the 2 groups and there were no other obvious trends in the number of reported AEs.

The incidence of orthostatic hypotension occurred in similar proportions of patients in both groups after the first application of the study ointment at Visit 1 (12.3% of Cellegesic, 12.2% of placebo). The Incidence of orthostatic hypotension was lower in both groups at the next visit approximately 7 days later.

There were no obvious trends in the shift from baseline or the actual and change from baseline results for hematology, serum chemistry, urinalysis, physical examination, or ECG results. Serum markers for hepatotoxicity were comparable between the Cellegesic and placebo groups.

The data from Study REC-C-001 were consistent with the safety profile characterized in prior review cycles.

At the time of finalization of this review, the 120-Day Safety Update does not appear to have been submitted. If, after reviewing the document, my impression of the adverse event profile changes, this will be addressed in an addendum to this review.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety and tolerability of Cellegesic has been reviewed in previous review cycles. For this Complete Response, the safety of the product was limited to a review of the new data from Study REC-C-001 which consisted of adverse events, vital signs (including orthostatics), physical examination, anal examination, and electrocardiogram data.

7.1.2 Categorization of Adverse Events

According to the applicant, treatment-emergent adverse events were coded using (Medical Dictionary for Regulatory Activities [MedDRA] Version 10.1) for the safety population. In my review the coding appeared acceptable and appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable

7.2 Adequacy of Safety Assessments

The safety assessments for Study REC-C-001 were considered to be acceptable and appropriate. All reasonably applicable tests were conducted to assess the safety of Cellegesic. A detailed description of the safety analysis is discussed in Section 7 of this report.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographics of target populations are discussed in Section 5.3. The duration of the trial was 21 days.

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

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7.2.4 Routine Clinical Testing

Not applicable

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the study.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

There were three SAE's reported in three subjects during the study. Two patients (1.6%) were randomized to the Cellegesic group and one patient was randomized to the placebo group (0.8%). The SAE's occurring in the cellegesic arm were in pt # 128/1286 (osteomyelitis), and anal sphincterotomy (pt # 302/1809), while the SAE occurring in the placebo group (pt # 104/1776) was related to iron deficiency anemia. All three SAE's were felt to be unrelated to study medication.

Narratives for the SAEs of patients on Cellegesic follow.

1) **Patient 128/1286** (Cellegesic 375 mg) was a 58 year old man with a past medical history that included diabetes mellitus, peripheral vascular disease, hypercholesterolemia and hypertension. He had undergone an amputation of the toes of the left foot because of complications related to diabetes mellitus.

Concomitant medications at study entry included pioglitazone, metformin, insulin, glargine, lisinopril, hydrochlorothiazide, siltvastatin, and acetylsalicylic acid (81 mg daily, oral).

He was assigned to the Cellegesic treatment arm. On Day 18 of the study, the patient was admitted to hospital with the diagnosis of severe osteomyelitis of the left foot and was treated with intravenous antibiotics, insulin and morphine and oxycodone for treatment of his pain, prior to his discharge.

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The patient was discharged from the hospital four days after hospitalization, and continued treatment with piperacilin and tazobactam and vancomycin for osteomyelitis for six weeks on an outpatient basis.

The event of osteomyelitis of the left foot was unrelated to Cellegesic.

2) **Patient 302/1809** (Cellegesic 375 mg) was a 64 year old woman with a past medical history significant for elevated blood cholesterol and triglyceride levels. Additionally, she was being treated with enalapril for hypertension.

On Day 6 of treatment with Cellegesic, she underwent an anal sphincterotomy. While being treated with Cellegesic she experienced headache which was felt to be related to Cellegesic. The need for sphincterotomy is unlikely directly related to study drug.

7.3.3 Dropouts and/or Discontinuations

Thirteen patients who had AE's were classified as experiencing AE's leading to treatment discontinuation. Of these discontinuations, nine events were treated with Cellegesic (7.3%). Seven of the nine discontinuations in the active arm were because of headache. Four subjects (3%) in the placebo arm experienced AE's that led to treatment discontinuation. Three patients assigned to the placebo group permanently discontinued the trial. One of the three placebo assigned patients discontinued because of headache, while the other two patients discontinued because of diarrhea and celiac disease.

See Table 7.3.3 noted below.

TABLE 7.3.3: ADVERSE EVENTS LEADING TO DISCONTINUATION OF TREATMENT

| Treatment | | | |
|--|----------------------|---|---|
| Patient Number | Adverse Event | Disposition Completed/Reason^a | Action Taken With Study Drug^b |
| Cellegesic | | | |
| 101/1301 | Headache | No/AE | Permanently discontinued |
| 103/1771 | Headache | No/AE | Permanently discontinued |
| 104/1294 | Headache | No/AE | Permanently discontinued |
| 117/1054 | Headache | No/AE | Permanently discontinued |
| 123/1531 | Headache | No/AE | Permanently discontinued |
| 126/1048 | Headache | No/AE | Permanently discontinued |
| 207/1554 | Headache | No/AE | Permanently discontinued |
| 126/1305 | Skin fissures | No/AE | Permanently discontinued |
| 128/1286 | Osteomyelitis | No/AE | None |
| 105/1039 | Palpitations | Yes/none | Permanently discontinued |
| Placebo | | | |
| 109/1800 | Diarrhoea | No/AE | Permanently discontinued |
| 113/1527 | Coeliac disease | No/AE | Permanently discontinued |
| 116/1807 | Headache | No/AE | Permanently discontinued |
| 116/1538 | Pain of skin | Yes/none | Permanently discontinued |
| Abbreviation: AE, adverse event. | | | |
| ^a Disposition Listing 16.2.3. | | | |
| ^b Adverse Eventa Listing 16.2.24. | | | |
| Source: Listings 16.2.3 and 16.2.24. | | | |

Source: Study REC-C-001 p 92 /108

7.3.4 Significant Adverse Events

The most common adverse event noted in the Cellegesic trial is headache. This adverse event is described in detail in Sections 7.3.5 and 7.4.1.

7.3.5 Submission Specific Primary Safety Concerns

The submission specific primary safety concerns were:

1) Headache

The incidence of headache, reported through patient diary cards, was relatively high in both groups. The Applicant believes that this finding suggests that inclusion of headache recording in a clinical trial prompted very sensitive reporting of these events.

More headache AEs were reported by patients in the Cellegesic group (70 %) than in the placebo group (40 %). Those headaches experienced were by subjects in the active treatment arm was on average, of a shorter duration and were more likely to be mild than those in the placebo group.

2) Orthostatic hypotension

A patient was defined as having orthostatic hypotension if he or she experienced either a 20 mm decrease in systolic blood pressure or a 10 mm decrease in diastolic blood pressure between lying and standing (either one or 3 minutes later). The incidence of orthostatic hypotension was 12% in both treatment arms. The incidence was lower in both groups at the next visit seven days later.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 96 patients (78%) in the Cellegesic group and 67 patients (54%) in the placebo group experienced at least one AE during the study.

The most common AE's were headache, dizziness, diarrhea, and nausea. (See Table 7.4.1)

{Neville A Gibbs, MD, MPH}
 {NDA 21359}
 {Cellegesic }

TABLE 7.4.1: TREATMENT EMERGENT ADVERSE EVENTS BY PREFERRED TERM AND TREATMENT GROUP

| System Organ Class Preferred Term | Cellegesic N = 123 | | Placebo N = 124 | |
|---|-----------------------|-------------|--------------------|-------------|
| | Patients n (%) | Events n | Patients n (%) | Events n |
| Number of patients with at least one AE | 96 (78.0) | 1056 | 67 (54.0) | 296 |
| Gastrointestinal disorders | 14 (11.4) | 17 | 11 (8.9) | 19 |
| Diarrhoea | 4 (3.3) | 4 | 4 (3.2) | 4 |
| Nausea | 2 (1.6) | 2 | 5 (4.0) | 5 |
| Infections and infestations | 8 (6.5) | 9 | 5 (4.0) | 5 |
| Sinusitis | 3 (2.4) | 3 | 1 (0.8) | 1 |
| Metabolism and nutrition disorders | 1 (0.8) | 1 | 3 (2.4) | 4 |
| Nervous system disorders | 90 (73.2) | 1001 | 59 (47.6) | 256 |
| Headache | 86 (69.9) | 972 | 59 (47.6) | 254 |
| Dizziness | 6 (4.9) | 26 | 2 (1.6) | 2 |
| Respiratory, thoracic, and mediastinal disorders | 3 (2.4) | 4 | 3 (2.4) | 3 |
| Skin and subcutaneous tissue disorders | 3 (2.4) | 3 | 1 (0.8) | 1 |

Abbreviation: AE, adverse event.
 Note: Adverse events refer to treatment-emergent AEs (TEAEs). The total number of TEAEs counts all TEAEs for patients. At each level of patient summarization, a patient was counted once if the patient reported one or more events. Percentages were based on the number of patients (N) in each treatment group.
 Source: Table 14.3.1.2.

Source: page 90/108 REC-C-001

Headaches occurred in 70% of patients randomized to the Cellegesic arm, and 48% of patients randomized to the placebo arm while dizziness occurred in 5% of patients randomized to Cellegesic, and 1.7 % patients randomized to placebo.

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{Cellegesic }

The incidence of headache, reported through patient diary cards, was relatively high in both groups. The Applicant believes that this finding suggests that inclusion of headache recording in a clinical trial prompted very sensitive reporting of these events.

More headache AEs were reported by patients in the Cellegesic group (70%) than in the placebo group (48%). The headaches experienced were by subjects in the active treatment arm was on average, of a shorter duration and were more likely to be mild than those in the placebo group.

Nausea was more common in the placebo group (4%) than in the Cellegesic group (1.6%). The incidence of diarrhea was the same for both groups (3%). The incidence of other AE's was similar in the two groups and there are no other obvious trends in the number of reported AE's.

7.4.2 Laboratory Findings

There were no obvious trends in the shift from baseline or the actual and change from baseline results for hematology, serum chemistry, urinalysis, physical examination, or ECG results. Markers for hepatotoxicity (alanine aminotransferase, aspartate aminotransferase, and bilirubin) were comparable between the Cellegesic and placebo groups.

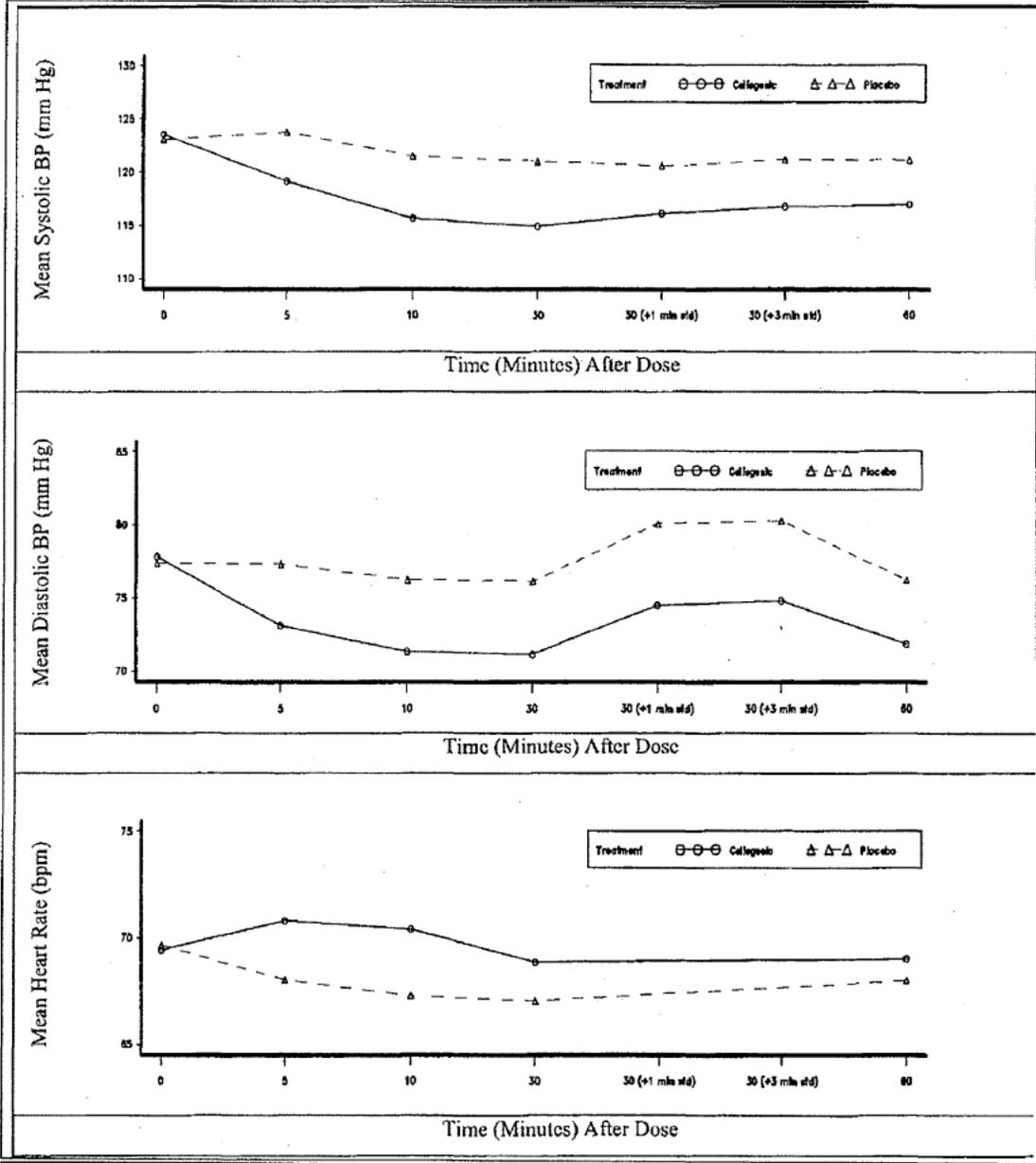
7.4.3 Vital Signs

Vital signs were measured before and for one hour after the initial application of study medication at Visit 1 and the morning application of study medication at Visit 2.

Vital signs were performed before the first dose, at 5, 10, and 30 minutes after dose (while supine); at 31 minutes (after standing one minute) and 33 minutes (after standing 3 minutes); and at 60 minutes after dose.

Figure 7.4.3 displays systolic and diastolic blood pressure and heart rate at Visit 1. Both systolic and diastolic blood pressure decreased in Cellegesic patients over the first 30 minutes after the dose, then increased upon standing. Placebo patients had smaller but similar changes. The heart rate in the Cellegesic group was higher than that of the placebo group, which shows the normal physiologic compensation for decreased blood pressure.

FIGURE 7.4.3: VITAL SIGNS AT VISIT 1- MEAN AT EACH TIME POINT



Source: REC-C-001 Study Report p 103/108

7.4.4 Electrocardiograms (ECGs)

There was no trend in the ECG interpretation from baseline to the end of study.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Not applicable

7.5.1 Dose Dependency for Adverse Events

Not applicable

7.5.2 Time Dependency for Adverse Events

Not applicable

7.5.3 Drug-Demographic Interactions

Not applicable

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

Not applicable

7.6 Additional Safety Evaluations

Not applicable

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

Not applicable

7.6.3 Pediatrics and Assessment of Effects on Growth

In a letter dated 26 August 2004, the Division of Cardio-Renal Products (DCRP) deferred pediatric studies because the application was ready for approval in adults before studies in children would be completed. The pediatric studies were deferred until December 2007. To date, the Applicant has not conducted any pediatric studies.

In the current submission, the Applicant has proposed the following:

- o Deferral request for children (ages (b) (4) years inclusive) and adolescents (age (b) (4) years inclusive)

- o  (b) (4)

The Division does not necessarily agree with the assertion that pain cannot be assessed reliably in younger patients. However, pediatricians in our Division agree that children under the age of 6 would not be expected to reliably communicate whether pain being experienced is due to the anal fissure or the frequent AE of headache experienced in the adult population.

Based on the above reason, we believe that an efficacy study is not feasible in pediatric patients under the age of 6 years.

The Division has determined that:

- o The pediatric Cellegesic developmental program should include safety and pharmacokinetics studies for the entire pediatric age range.
- o The evaluation of patients aged six to sixteen years should include an efficacy assessment.

The above Divisional requirements for pediatric studies will be communicated in the Complete Response Letter to the applicant.

Because neither our pediatricians nor DCRP believe that it would be unsafe to study Cellegesic in the pediatric population, no specific deferral should be granted. The Applicant should submit a completed pediatric program with the next resubmission.

As this application will not be approved this review cycle, the Pediatric Research Committee did not review the Applicant's Pediatric Plan.

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{Cellegesic }

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

Cellegesic™ 0.4% NTG ointment is currently approved in twenty EU member countries and one country outside the EU (Switzerland) under the trade name Rectogesic, and is currently marketed in eighteen EU countries.

Rectogesic and Cellegesic™ are identical products with the same composition. The first launch was in the UK in May 2005; the remaining launches followed from January 2007.

Since the launch in May 2005, Strakan Pharmaceuticals Limited received a total of 92 case reports possibly associated with Rectogesic. The most common single reaction was headache, recorded in 38 case reports.

The proportion of headache occurring with exposure to Cellegesic in the post marketing population of the European Union mirrored the incidence of occurrence of headache in the pre-approval population of the USA trials.

The foreign postmarketing experience is consistent with the safety profile of the submitted studies. There are no unexpected safety issues identified.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

Because we do not anticipate approval at this time, I have no labeling recommendations.

9.3 Advisory Committee Meeting

Not applicable

REFERENCES:

1. K McCallion et al. : Progress in the understanding and treatment of chronic anal fissure Postgrad Med J 2001;77:753-758
2. Minguez M et al. : Current Treatment Options in Gastroenterology; 2003 Jun:6 (3):257-262
3. Nelson R et al. : A Systematic Review of Medical Therapy for Anal Fissure, Diseases of Colon Rectum, April 2004; 422- 431
4. Nelson, R: Treatment of anal fissure; BMJ 2003;327:354-5
5. Lock MR et al.: Fissures-in-ano: the initial management and prognosis. Br J Surgery 1977, 64:355-358
6. Villalba, H et al. : Anal Fissure : A Common Cause of Anal Pain, The Permanente Journal, Fall 2007/Vol.11 No.4
7. Paper prepared for the American Gastroenterological Association Governing Board And Reported in Gastroenterology 2003; 124:235-245
8. Jensen, SL et al, Maintenance therapy with unprocessed bran in the prevention of acute anal fissure recurrence, Journal of the Royal Society of Medicine Volume 80 May 1987:286-298

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9. Bhardwaj, R et al, Modern Perspectives in the Treatment of Chronic Anal Fissures;
Annals of the Royal College of Surgery Engl. 2007 July; 89(5): 472-478
10. Acheson ,AG et al, Anal fissure: the changing management of a surgical condition,
Arch Surg (2005) 390:1-7

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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ROBERT B SHIBUYA
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW
Not Approvable Letter Response

NDA: 21-359

Name of Drug: nitroglycerin ointment 0.4%

Trade Name: Cellegesic

Formulation: ointment

Related Application:

Proposed Indications: relief of pain of anal fissure

Sponsor/Monitors: Cellegy Pharmaceuticals Inc.

Date of Submission: 4/14/05

Date Received by FDA: 4/15/05

Date Assigned: 4/19/05

Date Review Completed: 5/26/05

Reviewer: Thomas A. Marciniak, M.D.

Background:

This review critiques the sponsor's response to a not approvable letter for Cellegesic ointment. An NDA for Cellegesic for anal fissure was submitted in June 2004 and granted a priority review. A not approvable letter was sent to the sponsor on December 23, 2004. The Division discussed the issues with the sponsor at a meeting on March 28, 2005. This submission provides additional analyses based on the discussion at the meeting.

Not Approvable Letter Response:

The following analyses are presented in this response:

- Study 3 (CP125) was re-analyzed using a generalized mixed effects regression model with random intercept and linear time trend using all "relevant" data (no imputation by last-observation-carried-forward [LOCF] and no post-continuation data.) By this there was a statistically significant difference in the primary endpoint ($p < 0.0309$).
- A mixed-effects regression analysis using all available data from each subject (i.e., without LOCF imputation and post-discontinuation data) was performed using analgesic use (yes/no) as a time varying covariate, treatment, time, and treatment by time interaction. The outcome measure was 24 hour average pain through day 21. Analgesic use was not a

significant covariate ($p < 0.53$). Treatment by time interaction remained significant ($p < 0.032$).

- The data from all three trials were combined and subset into quintiles by baseline 24 hour average pain score. The 24 hour average pain scores at day 15 (maximal response) and day 21 were computed by quintile and treatment group. The drug/placebo group difference was greatest in quintile 4, 30-50% lower in quintile 5, and negligible in quintiles 1-3 (except in quintile 2 at day 15). Results from study 3 alone are similar.

Comments:

The first re-analysis of the primary endpoint for study 3 is not new. This analysis was also done by the FDA statistical reviewer and presented in his primary review and summarized in my primary review (my Table 25, analysis 7). I see no reason to change my interpretation of this post-hoc analysis discussed in my review. I still argue that by the appropriate, pre-specified analysis of this study the study failed.

Given that study 3 has failed for its primary endpoint, the analysis regarding analgesic use is interesting but not supportive by itself of approval. This analysis suggests that if there is a difference in pain, it is probably not related to analgesic use. The fundamental issue is that the data do not confirm conclusively that there is a difference in pain by treatment group.

The results by baseline pain quintile are not very convincing. If patients with more baseline pain respond better to treatment, why is the response in quintile 4 substantially better than in quintile 5? This analysis is merely hypothesis generating and would have to be confirmed conclusively with a new study.

Recommendations:

The NDA remains not approvable.

Thomas A. Marciniak, M.D.
Acting Deputy Director

cc:

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 23 December 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo is an addendum to two previous Divisional Memos (20 December 2004 and 22 December 2004), following up on an e-mail from the sponsor (22 December 2004).

The sponsor makes the following points.

- (1) *Concomitant pain medication was allowed.* On this point, there is no disagreement.
- (2) *"Since it was agreed that 8 doses would not confound the results, only those subjects consuming in excess of 8 doses could potentially affect the results."* Had there been a large difference between the treatment groups, one might be able to sustain an argument that differences in ancillary pain medication would have had little impact on the interpretation, but that is not the situation. The effect on anal pain is vanishingly small, and the differences in pain medications are not. Examination of the HEADACHE dataset reveals that, in the first 21 days of treatment, there were 208 episodes of treated headache on placebo and 384 such episodes on nitroglycerin ointment. From the CONMED dataset, 19 subjects on placebo reported use of acetaminophen for any reason in the first 21 days, compared with 30 subjects on nitroglycerin ointment. This certainly could have contributed to the 3-mm difference in the VAS for anal pain.

In summary, the sponsor's arguments do not alter my impression of these data. Whether there is a direct effect of treatment is not clear from study 03-02-01. Viewed most optimistically, the effect is, at best, a small fraction of the placebo effect. I remain of the opinion that these results make this application not approvable.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 22 December 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo is an addendum to a previous Divisional Memo (20 December 2004), following up on a discussion of review issues with the sponsor (21 December 2004) and a subsequent letter from the sponsor (also 21 December 2004).

The sponsor makes the following points.

- (1) *Pain associated with chronic anal fissures is a significant medical problem with currently inadequate medical treatment.* On this point, there is no disagreement.
- (2) *The effect of Cellegesic was consistent throughout the development program.* In support of this, the sponsor cites a subject-level pooled analysis of subjects in all three phase-3 studies, with $p < 0.0007$. The ISE says this analysis used the same end point as in study 03-02-01, but the letter clarifies that "LOCF was not utilized because NTG-related headaches were not recorded in the first two phase 2 studies." One can see what the effect of such a decision is in the only study in which both analyses are apparently possible—study 03-02-01. Dr. Hung's review describes 7 variations on the primary analysis, including the sponsor's preferred analysis (imputing only for withdrawals for treatment-related headache; $p = 0.0498$) and the one I believe is most reasonable and consistent with the protocol (imputing for all headache withdrawals; $p = 0.12$), but the very most favorable analysis ($p = 0.031$) comes from censoring at the time of withdrawal¹. There are other reasons to be cautious about interpreting the p-value for this combined analysis. (a) The first two studies were hypothesis-generating. There is no way to control the type-1 error rate for the set of studies by including these data. (b) The results of the three trials get smaller as the studies became larger and the hypothesis became more refined. (c) In the third trial, the disparity in concomitant pain medications can explain the small effect seem. None of these issues are addressed by the sponsor; " $p < 0.0007$ " greatly exaggerates the degree to which these datasets can be said to tell a consistent tale of benefit.
- (3) *The effect of Cellegesic was clinically meaningful.* Establishing an effect (statistical significance on some pre-specified end point) is a necessary but insufficient basis for approval. In this case, the effect is marginally significant and the p-value critically depends on the handling of a few subjects' data. What effect there may be in study 03-02-01 may be attributable to concomitant pain medication, rather than study drug. And what benefit there may be needs to offset headache so severe that it drives subjects out of trials and to offset risks (including those for which the database is too small to address in this patient population) of a variably absorbed and potent vasodilator. The sponsor cites a difference in time to 50% improvement in anal pain as evidence of clinical benefit ("as much as 7 days ... through the first

¹ This result is also noted on page 100 of the sponsor's ISE.

21 days of treatment²), but this difference is not even nominally statistically significant ($p=0.3$)². A similar analysis of all three studies is described as nominally statistically significant ($p=0.01$), but there the nominal effect is only 3 days, and this analysis has same problems as the pooled analysis discussed above.

In summary, the sponsor's arguments do not alter my impression of these data. Whether there is a direct effect of treatment is not clear from study 03-02-01. Viewed most optimistically, the effect is, at best, a small fraction of the placebo effect. I remain of the opinion that these results make this application not approvable.

² And the median difference is only about 2 days.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-359 (Cellegesic; nitroglycerin ointment)

Sponsor: Cellegy Pharmaceuticals

Review date: 20 December 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

These comments are based on reviews of Drs. Marciniak (clinical; 17 December 2004), Hung (statistics; 17 December 2004), Timmer (chemistry; 13 December 2004), and Proakis (pharmacology). Dr. Beasley (biopharmaceutics; 25 October 2004) issued a memo acknowledging that this resubmission contained no information not previously reviewed. In addition, I have taken into consideration the sponsor's response (14 December 2004) to the Division's discipline review letter of 10 December 2004.

The pertinent regulatory history is that an initial study (study 98-02-01) of efficacy of nitroglycerin ointment was targeted at healing anal fissures. This study was unsuccessful, but the sponsor performed unplanned analyses of anal pain, the results of which encouraged the sponsor to conduct a confirmatory study for anal pain (study 00-02-01). The second study was successful ($p < 0.05$) only when a post-hoc analysis different from the one applied to study 98-02-01 was used. The Division appeared to be headed toward an unfavorable regulatory action when the originally submitted NDA was withdrawn by the sponsor. A third study was the subject of a Special Protocol Assessment (1 November 2002) and attendant discussions. The various interactions with the sponsor are summarized in Dr. Marciniak's review.

The sponsor has now resubmitted the NDA with the results of study 03-02-01, and this resubmission has been given a priority review.

The primary end point of study 03-02-01 was the rate of change in anal pain over 21 days. What p-value to assign the results is a matter of some dispute, since, in this small study, the results depend critically upon how a few withdrawn subjects' data are utilized. The sponsor's favorite assessment gives $p = 0.0498$, and most other treatments result in larger values, including one apparently most consistent with the protocol which gives $p = 0.12$. What is undeniable is that small studies with, at best, marginally significant results are not comforting.

The sponsor cites a meta-analysis of the three studies to obtain $p = 0.0007$, but this result is largely the product of the first two retrospective analyses and is not particularly reassuring. I note, too, that as the studies have gotten larger, the magnitude of effects has gone down and the associated p-value has gone up.

The fundamental problem is likely to be that the effect of treatment is very small. By the sponsor's generous interpretation of the findings in 03-02-01, the reduction in anal pain corresponded to a 3-mm shift in the 100-mm VAS for anal pain after 3 weeks of treatment. The placebo effect is 7- to 8-fold larger than this.

This reduction in anal pain is bought at the expense of headache. Follow-up was 100% at 21 days in the placebo group and 90% on nitroglycerin. Five of the 9 withdrawals are attributed to adverse events, the others to patient choice ($n = 3$) or loss to follow-up

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(n=1). Ignoring 4 subjects (2 from each arm) from an excluded site, the withdrawal rates at 56 days were 6% on placebo and 14% on nitroglycerin.

The nitroglycerin group had a higher use of concomitant pain medication, chiefly acetaminophen (40% vs 27%), and it is difficult to know whether this alone may account for the small apparent effect on anal pain.

Part of the advice given to the sponsor in discussions of the third study was to use a global pain index, rather than anal pain. Given the marginal overall results and the evident imbalance in headache, it is quite clear that any analysis of global pain would not have favored Cellegesic.

I conclude that the appropriate regulatory action is not approval (NA). These data cannot be made more compelling by further analysis and further study is unlikely to change one's impression of the overall magnitude of effect. If there is an effect of Cellegesic on anal pain, it is too small to be of clinical interest and comes with too high a cost—intolerable headache pain.

I see no evidence in the available data of a greater safety risk associated with the use of nitroglycerin ointment, although, as Dr. Marciniak points out in his review, the available database is pretty small. The sponsor asserts that one can rely upon the safety of nitroglycerin as used in the treatment of angina and myocardial infarction, and this is true, up to a point. However, the different clinical setting is pertinent for at least two reasons. First, the risks may be different. Systemic vasodilation likely contributes to the benefits in angina and myocardial infarction, but it is unlikely to contribute anything but risk in the current setting. Second, the same risks might lead to different risk-benefit decisions in the different clinical settings. The issue of risk is not a significant one in the decision being made here, but the sponsor's assertion that all the required information on safety could be inherited through a 505(b)(2) process is simply untenable.

The sponsor also (14 December 2004) makes reference to the terrible burden of anal pain ("disabling pain", "diminished quality of life", and "[interference] with ... daily activities", but the sponsor's development program did not demonstrate effects on any of these things.

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CLINICAL REVIEW

Application Type NDA
Submission Number 21-359
Submission Code N-000 RS

Letter Date 06/30/04
Stamp Date 07/01/04
PDUFA Goal Date 01/01/05

Reviewer Name Thomas A. Marciniak, M.D.
Review Completion Date 12/14/04

Established Name nitroglycerin ointment
(Proposed) Trade Name Cellegesic
Therapeutic Class vasodilators
Applicant Cellegy Pharmaceuticals Inc.

Priority Designation P

Formulation ointment
Dosing Regimen 375 mg intra-anal every 12 hours
Indication relief of pain associated with
chronic anal fissure
Intended Population patients with chronic anal fissure

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective I do not recommend approval of Cellegesic nitroglycerin (NTG) ointment for the relief of pain associated with chronic anal fissure. The submission includes data and reports for three clinical efficacy studies in support of this indication. These studies do not provide substantial evidence of efficacy of NTG ointment for this indication. The first failed on its primary endpoint of improving anal fissure healing but the sponsor interpreted secondary analyses as suggesting that NTG ointment relieves pain. 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 prespecified in the protocol. By the analysis prespecified in the protocol the result was not statistically significant. The third study had a primary endpoint of improvement in the rate of decrease of pain over a 21-day period that showed a nominally statistically significant result ($p < 0.0498$) when the sponsor analyzed the data not carrying forward the last observation for some patients who discontinued due to headache as the protocol specified. When the data are analyzed by the protocol-specified methodology, the p value is 0.12. This study has additional weaknesses of a tiny treatment effect (about 3 mm on a 100 mm visual analog pain scale), excessive dropouts in the NTG group, possible confounding by partial unblinding due to NTG-induced headaches and use of acetaminophen for them, and reasonable improvement demonstrated only in one country.

The size of the safety database in this application is small (only 167 patients completing the regimen proposed to be marketed) and monitoring for adverse effects was not optimal. While there are no safety findings that alone preclude approval, the uncertainty about safety contributes to the negative risk vs. benefit assessment.

1.2 Recommendation on Postmarketing Actions

Because I do not recommend approval of this application, I can not recommend any postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cellegesic NTG ointment is a formulation of nitroglycerin (NTG) 0.4% (w/w) in a white petrolatum and lanolin base compatible with a USP monograph. It is intended for use as a self-administered treatment to be applied intra-anally at the site of a chronic anal fissure for relief of pain. The proposed dosing is 375 mg every 12 hours. Because NTG is a drug in widespread use

for many years in approved sublingual and topical formulations, the sponsor did not perform preclinical studies but relied upon literature reports of such studies.

The three clinical efficacy trials reported in the application and mentioned in Section 1.1 were randomized, double-blind, placebo-controlled, parallel group studies. The first study was conducted in the US, while the other two were international studies. All studies enrolled adults with anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Anal fistulas and fissures secondary to recent anal surgery were excluded. For the first study anal pain was not required, but anal pain was mandatory for the second two studies. For the third study a confirmed sentinel pile was also mandatory. While the first study had a primary endpoint of fissure healing at 28 days, average anal pain was recorded daily by the patient on a 100 mm visual analog scale (VAS) in all three studies.

The first study, NTG 98-02-01, enrolled 360 patients and tested regimens of 0.1%, 0.2%, and 0.4% BID and TID versus placebo. The second study, NTG 00-02-01, enrolled 229 patients and tested regimens of 0.2% and 0.4% BID versus placebo. The third study, CP125 03-02-01 compared 0.4% BID to placebo. I summarize the results of these efficacy studies in the next section.

The application also includes the results of one small pharmacokinetic study in six normal subjects comparing single dose intra-anal NTG, repeated dose intra-anal NTG, and IV NTG. This study estimated a mean bioavailability of intra-anal NTG of about 50% with a wide variability (standard deviation of 30%). These numbers suggest that intra-anal NTG may lead to systemic adverse effects (as the clinical efficacy studies confirmed) and that the occurrence of these adverse effects could be erratic.

1.3.2 Efficacy

Study NTG 98-02-01 did not show a favorable effect of NTG ointment for the primary endpoint, fissure healing. Healing was observed in 49% of placebo, 40% of 0.1% NTG, 33% of 0.2% NTG, and 44% of 0.4% NTG patients (pooling the BID and TID regimens). Using a mixed effects regression model that was not pre-specified the sponsor found a significant effect of 0.4% NTG ointment on average daily pain but no significant differences for the two lower doses. The significance of the results depends upon the precise definition of the regression model, e.g., changing the definition of the residuals eliminates the statistical significance of the 0.4% NTG effect. The results are also not internally consistent, e.g., 0.4% NTG BID appears better than TID but for lower dosages TID is better. These results did justify doing a second study targeting pain relief.

Study NTG 00-02-01 targeted improving the rate of change in daily average pain through 56 days evaluated by a mixed-effects regression model as was done for the first study. By a regression model also incorporating center and quadratic components (not pre-specified and not done for the first study) the sponsor found a significant treatment by linear time interaction for the 0.4% NTG group ($p=0.005$) but not for the 0.2% NTG group. However, besides the issue of lack of pre-specification, the treatment by linear time interaction is not the rate of change.

Evaluating the rate of change by the linear mixed-effects regression model without the center and quadratic components produces statistically insignificant results ($p = 0.85$ for 0.2% NTG and $p = 0.24$ for 0.4% NTG).

The sponsor had submitted the first two studies in an initial NDA submission. When informed about the Division's interpretation of the two studies, the sponsor withdrew the NDA. The Division and sponsor discussed the performance of a third study to show convincing results. The sponsor incorporated most, but not all, of the Division's recommendations into the third study.

Study CP125 03-02-01 targeted improving the rate of change in daily average pain through 21 days evaluated by a mixed-effects regression model without the quadratic component. NTG patients discontinuing the study due to headache were to have their last observation carried forward (LOCF). For this endpoint the sponsor reports a p value of <0.0498 . The mean changes calculated by the sponsor are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale. However, the sponsor's handling of some patients' data for its primary analysis is not consistent with the protocol specification. The sponsor did not use LOCF for two patients who discontinued due to headache. For the analysis that matches the description of the primary analysis in the protocol the p value is 0.12.

The evidence for efficacy of NTG ointment from this study is even weaker than the p value of 0.12 implies. The effect size estimate, even with the sponsor's liberal analysis, is small. This study is plagued by a high dropout rate only in the NTG ointment arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21. The Division warned the sponsor in advance that a high dropout rate would make this study uninterpretable. My confidence in any suggestion of a benefit for NTG ointment is weakened further by the potential for partial unblinding because of headaches with NTG ointment and confounding by acetaminophen use and because reasonable improvement with NTG ointment was demonstrated only in one country.

The sponsor also performed analyses combining data from the 0.4% NTG ointment groups of the three studies. The fundamental problem with these analyses is that they were not pre-specified. They are subject to unstated selection criteria that may be used to produce positive results and misleadingly high p values. The great variation in p values depending upon how the analyses are done is shown by the discussions above of the three individual study results. For the combined analyses this variability is also present. If the 0.2% BID groups are included, then 0.2% NTG appears as worse than placebo as 0.4% appears better. There is no evidence for a dose-response relationship that would help to confirm efficacy.

All three of these studies fail to show statistical significance for their primary endpoint analyses. The estimated magnitude of a benefit, if any, of NTG in relieving pain of anal fissure is small, e.g., a mean improvement of about 3 mm on a 100 mm visual analog scale at day 21 even with the sponsor's liberal analysis, and is confounded by many issues regarding analyses not prespecified, data exclusions, excessive dropouts with NTG, acetaminophen use, and benefit limited to one country. These studies do not provide substantial evidence of efficacy of NTG ointment in relief of pain associated with chronic anal fissure.

1.3.3 Safety

The size of the safety database in this application is small. Only 475 patients received any dose of NTG ointment, 206 patients received any dose of NTG ointment 0.4% BID (the regimen proposed to be marketed), and 167 of these patients completed a treatment period of 56-days. Of the latter only 19 patients were age 65 or older. The most frequent reason for withdrawal was adverse event in 20 (10%, typically headache), but another 13 (6%) withdrew for "patient choice".

No deaths occurred during the clinical trials. Ten patients experienced serious adverse events (SAEs) during the trials, four placebo, two 0.4% NTG BID, and four other NTG dosing. There is no pattern to the SAEs.

Overall 45 NTG (22 0.4% BID patients) and 7 placebo patients discontinued treatment due to an adverse event (AE). Headache was the most common AE leading to discontinuation in 29 NTG patients (about 8% of the 0.4% BID patients) compared to 2 (about 1%) of the placebo patients. For any NTG use vomiting was the cause for discontinuation in 4 patients, nausea in 3 patients, and burning sensation, tachycardia, dizziness, and vertigo in 2 patients.

The most frequent AEs were headache (38% placebo and 67% NTG 0.4% BID) and nausea (1% placebo and 6% NTG). In the third study alone headache was reported by 67% of placebo and 86% of NTG patients, indicating a low threshold for reporting. More NTG patients reported severe headaches (34% vs. 3.4%), took medication for it (48% vs. 28%), and had longer symptoms (mean 8 hours vs. 4.3 hours). The second most common AE in this study was upper abdominal pain, reported by 11% of placebo patients and 18% of NTG patients.

There were no reports of hypotension or low blood pressure. However, there were withdrawals for tachycardia, bradycardia, and dizziness. Vital signs are not reported for these patients. Vital signs were typically measured pre-dose (except 10-20 minutes post-dose at day 1 in the first two studies) and showed no pattern.

In addition to the small size of the safety database, there are two other limitations worth noting: (1) Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure. It would be helpful to know how much blood pressure is affected and the variability of it. (2) The case report forms provided minimal information on the adverse events. For example, tachycardia and bradycardia were reported for several patients but no information is provided on heart rate, heart rhythm, or blood pressure.

The potential or lack of potential of NTG ointment for causing dangerous cardiovascular AEs is not well explored in the limited exposure in the Cellegesic development program with limited information on blood pressure changes and AEs. While the available data don't confirm that NTG ointment is a dangerous drug, they also don't provide sufficient reassurance that it is safe.

1.3.4 Dosing Regimen and Administration

The dosing regimen was selected based on the first study examining a range of doses (0.1, 0.2, and 0.4%) and BID and TID dosing and the second study testing 0.2 and 0.4% BID. While the regimen proposed to be marketed was selected based on the suggestion of best pain relief, the evidence was weak and the efficacy of 0.4% BID was not supported by the third study. The rate of headaches with the 0.4% BID regimen suggests that higher doses would not be acceptable. I believe that the failure of this development program lies not with an inappropriate regimen but with inadequate efficacy of NTG for this condition.

The sponsor proposes marketing CELLEGESIC nitroglycerin ointment 0.4% in both a metered dose canister and in a tube. The canister has a metered dose-dispensing pump for dispensing of 375 mg of ointment; the tube's carton has a line for measuring a 375 mg dose. In the pharmacokinetic study bioavailability was highly variable (8% to 99%) and overdosing was common at the sites audited by DSI (possibly to fourfold). For average bioavailability numbers the 375 mg dose of 0.4% NTG ointment delivers about 0.4 mg/hour, comparable to rates of systemic NTG delivery from NTG patches for angina. For the highest extremes of bioavailability the proposed dose delivers about 1.7 mg in the first hour, substantially higher than the usual antianginal dosages. I am concerned that a delivery rate of 1.7 mg or higher in the first hour could be dangerous in vulnerable patients and that the size of the safety database is too small to exclude such problems.

1.3.5 Drug-Drug Interactions

The sponsor did not perform any drug-drug interaction studies but relied upon the published literature regarding NTG. This approach is acceptable for pharmacokinetic interaction studies.

1.3.6 Special Populations

The sponsor did not study any special populations except that both genders were adequately represented in the clinical trials. Blacks and the elderly are sparsely represented in the clinical studies. Children were not studied and the Division granted a deferral of pediatric studies in a letter dated August 26, 2004, because the drug would be ready for approval in adults before studies in children would be completed.

NTG use has not been associated with varying efficacy or safety issues in either gender or specific ethnic groups. The elderly, who have a higher burden of chronic disease such as hypertension, coronary heart disease, and heart failure, are a population for whom adverse effects of NTG are more problematic.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cellegesic NTG ointment is a formulation of nitroglycerin (NTG) 0.4% (w/w) in a white petrolatum and lanolin base. It is intended for use as a self-administered treatment to be applied intra-anally at the site of a chronic anal fissure for relief of pain. The proposed dosing is 375 mg every 12 hours.

2.2 Currently Available Treatment for Indications

There are no approved treatments for anal fissure. Various topical agents (including diltiazem, nifedipine, and corticosteroids) as well as injection of botulinum toxin have been tried, but well-controlled trials documenting their effectiveness have not been done. (Nelson 2003) Accepted conservative treatment for anal fissure is dietary modification, i.e., increased fiber, and stool softeners. For fissures not healing with conservative treatment various surgical procedures have been advocated, with internal lateral sphincterotomy being the standard. (Nelson 2002) Surgery, however, produces fecal incontinence in some patients.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient nitroglycerin has long been available in the U.S. in IV, sublingual, and topical formulations (ointment, patches) for the treatment of angina pectoris.

2.4 Important Issues with Pharmacologically Related Products

Nitroglycerin by sublingual or topical administration has been safely used with recognized adverse effects of hypotension and headaches related to the pharmacodynamic action. With topical use contact dermatitis and fixed drug eruptions have been reported infrequently.

One relevant phenomenon of nitroglycerin use is tolerance. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

2.5 Presubmission Regulatory Activity

The sponsor met with the Division on January 12, 2001, to discuss the disappointing results of the first trial targeting anal fissure healing and problems with recruitment for a second trial targeting pain relief. The Division informed the sponsor that they would need convincing results from the ongoing trial to support approval. The Division and sponsor also discussed that any interim looks at efficacy in the ongoing trial would need to be prespecified and would require adjustment of the p value for the primary analysis.

The sponsor originally submitted an NDA for the use of NTG ointment 0.2% and 0.4% to relieve pain associated with an anal fissure on June 22, 2001. The original NDA contained the results of one pivotal study, NTG 98-02-01. The sponsor amended the application on November 30, 2001, with the results of a second pivotal study, NTG 00-02-01. The Division reviewed this submission. The Division concluded that each of these trials showed a statistical significant benefit of the product only when analyzed by post-hoc analyses, the first study in healing and the second in pain relief. The Division reviewers also questioned whether the marginal benefit of reduced anal pain was offset by the headaches produced by systemic absorption of the NTG. The Division discussed these observations with the sponsor at a teleconference on April 5, 2002. At that teleconference the Division informed the sponsor that a non-approval action was likely and that further clinical studies were needed. The Division also requested that full validation information for an assay used in a pharmacokinetic (PK) study be provided. The sponsor met with the Division on April 22, 2002, and presented its arguments why NTG ointment was effective. The sponsor discussed that NTG was being used in extemporaneous preparations and that the formulation should be uniform and surgery avoided. The Division agreed with these latter statements but maintained that the two trials did not prove efficacy of NTG ointment. The Division Director noted that the application would receive a not approvable action by the April 26, 2002 goal date, unless the sponsor decides to withdraw their application by that date. The Division confirmed at a teleconference on April 24, 2002, that pain would be an acceptable endpoint for another study. The sponsor formally withdrew its application on April 26, 2002.

The Division met with the sponsor again on June 11, 2002, to discuss future development. The sponsor reiterated its belief that the first two trials supported efficacy of the drug and the Division and Office Director disagreed. The Division maintained that the primary analyses need to be pre-specified and that post-hoc adjustments yielding marginal significance were not convincing. The Office Director confirmed that another trial was needed and that it should be long term, although a short term primary endpoint time of 2-3 weeks was acceptable. He also stated that focusing on a subset of patients with anal fissure, such as those with sentinel pile, was acceptable and that standards of care could be specified. The Division Director advised that the sponsor try to establish a clearer temporal relationship between drug use and the frequency and severity of headaches in the next study and suggested using a global pain score.

The sponsor submitted request for a special protocol assessment for a third study on September 16, 2002. The Division's letter dated November 1, 2002, providing the assessment stated that one additional trial convincingly supporting efficacy of the product for pain relief would be sufficient to support approval. The letter advised that restricting standard therapy would not be

acceptable, the specifics of the pain relief question and the timing of the pain evaluated need to be detailed, the timing and relationship of headaches to therapy and timing and use of analgesics should be captured, handling of dropouts should be prespecified to the Division in writing, the details of the proposed complex primary analysis need to be prespecified but that a simple categorical analysis would be preferable and easier to describe in labeling, and the use of diaries is less desirable than a daily evaluation by a blinded assessor.

The sponsor met with the Division on January 31, 2003, to discuss the special protocol assessment. The Division statisticians expressed concern about the sponsor's last observation carried forward (LOCF) approach for handling dropouts and cautioned that a large number of dropouts would make interpretation of the study results impossible. The Division requested that the sponsor submit data on the time course of pain relief with the product prior to starting the trial so that the issue of evaluating the pain at peak (bedtime) could be resolved.

The sponsor submitted revisions to the protocol on February 13 and 27, 2003. The sponsor and the Division had teleconferences on March 20 and April 1, 2003, to discuss the revisions. The relevant issues discussed were the LOCF approach, handling secondary endpoints, and the temporal relationship between product use and pain relief. The Division also sent a letter to the sponsor dated May 16, 2003, explaining the appropriate statistical approaches for controlling alpha for the five secondary endpoints.

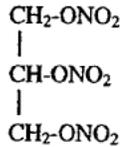
2.6 Other Relevant Background Information

Cellegesic NTG ointment is not currently marketed anywhere. A MAA for Rectogesic NTG ointment 0.4% was submitted to the United Kingdom Committee on Safety of Medicines (CSM) on February 7, 2003. On March 31, 2004, the CSM assessors notified Cellegy UK Ltd that they recommended approval pending responses to some CMC and labeling questions. A NDS for Cellegesic NTG ointment as an over-the-counter product was submitted to the Canadian Therapeutic Products Directorate (CTPD) on March 19, 2002. The CTPD notified Cellegy that the product will be reviewed as a prescription drug. Recently the CTPD sent a notice of deficiency to Cellegy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The active ingredient is nitroglycerin (1,2,3-propanetriol trinitrate) with the following structural formula:



The ointment is provided in a 0.4% concentrations and is formulated with propylene glycol in a base of lanolin, sorbitan sesquioleate, parafin wax and white petrolatum. A device and a metered dose dispenser are provided to measure out 374 mg of the ointment per dose.

The Division chemistry review dated December 7, 2004, states that the Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections. All other CMC approvability issues have been satisfactorily resolved at this time. This review also notes that a USP monograph is available for NTG ointment. This product is compliant with the monograph.

3.2 Animal Pharmacology/Toxicology

The sponsor did not perform any animal pharmacology or toxicology studies. The NDA provides literature references regarding the preclinical pharmacology and toxicology of NTG, i.e., a 505(b)(2) submission. The Division pharmacology and toxicology reviewer's memo dated August 4, 2004, states that the non-clinical pharmacology and toxicology studies that were included in the June, 2001 original submission were reviewed (Pharmacology/Toxicology Review, 3/14/02). The product was deemed approvable from a non-clinical perspective provided that statements in the sponsor's draft labeling that refer to results of animal toxicity studies be made consistent with labeling used for other nitroglycerin containing products. The resubmission of NDA 21,359 contains no new non-clinical pharmacology and toxicology studies requiring review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the NDA submission dated June 30, 2004. This submission included paper study reports for all three pivotal studies as well as electronic SAS data sets for them and case report forms (CRFs) in Adobe Acrobat PDF files. In addition, I and other reviewers asked questions to which the sponsor responded with supplemental submissions. The sponsor also submitted additional information regarding extended follow-up and other issues. I've listed all of these submissions in Table 1.

Table 1: NDA 21-359 Submissions Reviewed

| Date | Description |
|--------------------|--|
| June 30, 2004 | Primary resubmission |
| September 21, 2004 | Answers to questions regarding randomization |

| Date | Description |
|--------------------|---|
| September 30, 2004 | Six month follow-up for Study 03-02-01 |
| October 5, 2004 | Data submission of corrected CP125 data file |
| October 22, 2004 | Compounding problems with extemporaneous NTG ointment |
| October 26, 2004 | Additional answers on randomization |
| December 14, 2004 | Responses to discipline review letter |

4.2 Tables of Clinical Studies

Table 2: Table of Clinical Studies

| # | Description | N | Endpoint | Comment |
|----------------|--|-----|----------------------|--|
| NTG 98-02-02 | 3-way crossover: 0.2% ointment, IV, placebo | 6 | PK | 50% bioavailable; high variability |
| NTG 98-02-01 | RCT 0.1%, 0.2%, & 0.4% BID or TID (0.75, 1.1., 1.5, 2.3, 3, & 4.5 mg) vs placebo | 360 | Healing through 56 d | P>.1; pain relief suggested |
| NTG 00-02-01 | RCT 0.2% & 0.4% BID (0.75 & 1.5 mg) vs. placebo | 229 | Pain through 56 d | Trend significant only with quadratic term |
| CP125 03-02-01 | RCT 0.4% BID (1.5 mg) vs. placebo | 193 | Pain slope to 21 d | 150 planned; 193 analyzed |

RCT = randomized controlled trial; PK = pharmacokinetics

4.3 Review Strategy

I depended primarily upon the raw data (SAS data sets and CRFs) for my review with the analysis plans as stated in the protocols. I and the FDA statistical reviewer analyzed the data for the latest study CP125 03-02-01 in depth. I used the Division clinical and statistical reviews from the original NDA submission for the first studies, confirming that I agreed with their analyses. I compared my results to those presented by the sponsor in the study reports and in the sponsor's integrated summary of efficacy (ISE) and integrated summary of safety (ISS).

4.4 Data Quality and Integrity

I recommended sites to be audited from the latest study. I observed that the results at the two sites with the highest enrollments (16 and 20 patients) had among the more favorable results. If these two sites are excluded, then the pain difference between the NTG ointment and placebo groups is virtually nil. The Division of Scientific Investigations (DSI) audited these two sites and judged their data to be acceptable.

Randomization was sloppy as I describe in Section 9.6.1.2.8.1 Number of Subjects, Randomization, and Blinding. The data provided in the SAS data sets corresponded to the

tabulations and analyses in the study report and NDA summaries and in the case report forms (CRFs), although the quality of the copying on some of the CRFs was poor. Copies of the patient diaries were not provided. One limitation of the CRFs is that the amount of information regarding adverse events is very limited.

4.5 Compliance with Good Clinical Practices

I scrutinized only the new submission, CP125 03-02-01. This study was supposed to be conducted following Good Clinical Practices. The protocol was to be reviewed and approved by a local IRB. Each participant was to have provided written consent. Please see the detailed review of this study for comments on two study deviations: (1) The sponsor excluded data from one site in Russia following an unsatisfactory audit. (2) The planned sample size was 150 but 193 subjects were included in the analyses.

4.6 Financial Disclosures

The financial disclosures for NTG 98-02-01 and NTG 98-02-02 were reviewed in association with the original NDA submission and described in a memo filed in DFS dated March 26, 2002. The financial disclosures for these trials as well as NTG 00-02-01 and CP125 03-02-01 are provided in this submission. The sponsor was unable to contact ten investigators for NTG 98-02-01 and NTG 98-02-02 and four investigators for NTG 00-02-01. None of the other investigators had a financial conflict of interest. There is no evidence provided that financial conflicts of interest could have influenced the conduct or outcomes of the trials.

5 CLINICAL PHARMACOLOGY

The sponsor did not provide any new clinical pharmacology studies in this submission. The sponsor provided one pharmacokinetic study, NTG 98-02-02, in the original NDA submission, and the Division biopharmacist reviewed it in conjunction with that submission. I summarize the Division biopharmacist's review below.

5.1 Pharmacokinetics

The sponsor performed one PK study, NTG 98-02-02, to elucidate the bioavailability and PK of NTG administered intra-anally. The sponsor studied six healthy subjects (four males and two females), ages 25 to 45 years. Five subjects were white and one was Hispanic. The subjects were treated in a random order with single dose intra-anal NTG, repeated dose intra-anal NTG, and IV NTG with seven days washout between phases and dosing as given in Table 3.

Table 3: Treatment phases for PK study

| Phase | Concentration | Frequency | Total NTG | Total amount | Route |
|-------|---------------|--|-----------|--------------|------------|
| I | 0.2% | qd x1 | 0.75 mg | ~374 mg | Intra-anal |
| II | 0.2% | tid x 7 doses | 5.25 mg | ~2618 mg | Intra-anal |
| III | 10 µg/mL | 1 mL/min constant infusion over 30 minutes | 0.3 mg | 30 mL | IV |

Blood samples for glyceryl trinitrate (NTG) and two principal metabolites, 1, 2-glyceryl dinitrate and 1, 3-glyceryl dinitrate, were collected at the times shown in Table 4.

Table 4: Drug level collection times for PK study

| Phase | Blood collection times |
|--------|---|
| I & II | predose, & at 15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes post dose |
| III | predose, & at 1, 2, 4, 6, 10, 15, 20, 30, 31, 32, 34, 36, 40, 45, 50, 60, 70, 90, 150, 210, and 270 minutes after the start of the infusion |

The plasma NTG levels in the study subjects are shown in Figure 1.

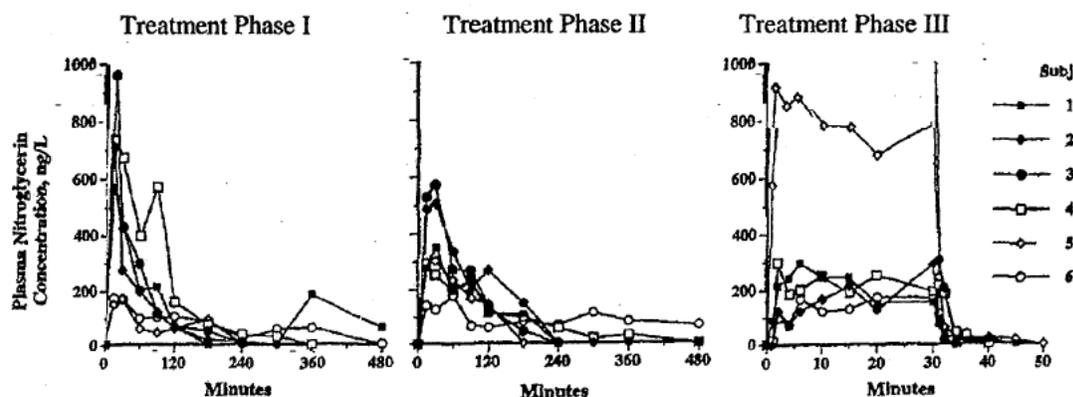


Figure 1: Sponsor's Plasma NTG levels in PK Study

The bioavailability of intra-anal NTG was approximately 50% as shown in Table 5.

Table 5: Sponsor's Bioavailability of Intra-anal NTG in PK study

| Subject ID | Mean Absorption Time (min) | | Bioavailability | |
|-------------|----------------------------|------------|-----------------|---------------|
| | Phase | | Phase | |
| | I | II | I | II |
| 1100 | 192 | 84 | 0.77 | 0.40 |
| 1101 | 56 | 84 | 0.47 | 0.99 |
| 1102 | 53 | 64 | 0.20 | 0.23 |
| 1103 | 79 | 120 | 0.77 | 0.47 |
| 1104 | 98 | 65 | 0.084 | 0.13 |
| 1105 | 167 | 245 | 0.49 | 0.61 |
| Mean (± SD) | 108 (± 59) | 110 (± 69) | 0.46 (± 0.28) | 0.47 (± 0.31) |

Please see the Division biopharmaceutist's review for other details of the study results, including levels of metabolites.

COMMENT:

- The Division biopharmacist reviewer considered the information submitted on the assay used in this study to be inadequate and requested the sponsor to submit full validation information for the assay at a teleconference on April 5, 2002. The current resubmission contains acceptable assay information per the Division biopharmacist reviewer's memo dated October 22, 2004.
- Note that this study was performed with the 0.2% formulation rather than the 0.4% formulation now proposed for marketing.
- Table 5 indicates a substantial amount of both inter- and intra-subject variability in the bioavailability of intra-anal NTG. While its effects upon efficacy are difficult to project, it is a safety issue.
- The sponsor also provided a submission dated October 24, 2004, of a report entitled "A Study to Determine Whether Pharmacy Extemporaneous Compounding of Nitroglycerin Ointment Provides a Safe and Effective Treatment of Anal Fissures." This study did not examine safety or efficacy but whether 24 pharmacies compounded 0.3% nitroglycerin ointment appropriately. The report states that 50% of the compounded products did not meet the relevant USP standards for potency and/or content uniformity. About 29% of the compounded products tested did not fall into the range 90-115% of labeled content. This study does not provide data on the safety or efficacy of Cellegesic.

5.2 Pharmacodynamics

Nitroglycerin (NTG) is converted in tissue to nitric oxide. Nitric oxide relaxes smooth muscle, including smooth muscle in arteries and veins. The sponsor proposes that the mechanism of action of NTG ointment is to relax the internal anal sphincter and to increase anoderm blood flow. The sponsor did not provide study reports documenting these actions in this NDA submission but does provide a published reference to a study that used isosorbide dinitrate.

5.3 Exposure-Response Relationships

The sponsor's justification for the proposed dosage and dose schedule is based on its interpretation of the results of the first two pivotal clinical trials. Study NTG 98-02-01 used total daily dosages of 0.75, 1.1, 1.5, 2.3, 3, and 4.5 mg given either BID or TID. The sponsor interprets the results as indicating that pain relief did not differ between those dosed BID or TID (although the primary clinical reviewer of this study expressed concern about lack of sensitivity of the sponsor's ANOVA test supporting this conclusion.) Study NTG 00-02-01 used BID dosing and compared the 0.2% (0.75 mg) and 0.4% (1.5 mg) concentrations. Pain relief was greater with the 0.4% concentration. The primary clinical reviewer found that a greater effect of the 0.4% concentration was evident only for the first week or two. Please see the detailed reviews of the studies in the Appendix.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor's proposed indication is relief of pain associated with chronic anal fissure.

6.1.1 Methods

This submission is a resubmission of an earlier submission that was withdrawn. The earlier submission included the results of two clinical efficacy trials that the Division judged did not provide substantial evidence of efficacy. This submission provides the results of a third clinical efficacy trial. I did not re-analyze the results of the first two trials but used the Division clinical and statistical reviews of them from the earlier submission. I analyzed the data from the third trial and report the details in Section 9.6.1. I summarize my interpretations of all three studies below.

Of the three studies, the latest is the most critical for approval because the Division judged the earlier studies to have nonsignificant results and recommended to the sponsor to perform a third study with convincing results. Also, the first study had a primary endpoint of fissure healing rather than pain relief and all studies had peculiarities in analysis as discussed in the next section.

6.1.2 General Discussion of Endpoints

The primary endpoint for the third study was anal pain relief as evaluated by daily patient diary recordings of average anal pain over the past 24 hours on a 100 mm visual analog scale (VAS). Visual analog scales are commonly used to evaluate subjective entities such as pain. However, the Division advised the sponsor in a pre-study letter that the use of diaries is less desirable than a daily evaluation by a blinded assessor. The Division also expressed concern about evaluating the pain at peak (bedtime). Another concern was that, regardless of whether NTG ointment may relieve anal pain, it causes another type of pain, i.e., headache. The Division suggested to the sponsor to include a global pain assessment at a meeting on June 11, 2002.

Of the two earlier studies, the first had a primary endpoint of anal fissure healing rather than pain relief. The first study failed to demonstrate efficacy of NTG ointment for pain relief. A post hoc analysis suggested a possible benefit of pain relief, so the sponsor performed a second study using anal pain relief (average daily pain evaluated by a 100 mm VAS over 56 days) as the primary endpoint. This second study showed a statistically significant benefit only when analyzed by a quadratic mixed effects model that was not pre-specified. The ambiguities regarding the second study results led to the recommendation to perform a third study. The sponsor decided to perform this third study with the primary endpoint of rate of change of average daily pain over a 21 day period.

COMMENT: Ultimately the Division accepted the sponsor's proposed primary endpoint for the third study in a special protocol assessment.

6.1.3 Study Designs

All three studies were randomized, double-blind, placebo-controlled, parallel group trials. The dosages tested, total enrollments, and endpoints are shown in Table 2. The first study was conducted in the US, while the other two were international studies. All studies enrolled adults with anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Anal fistulas and fissures secondary to recent anal surgery were excluded. For the first study anal pain was not required, but anal pain was mandatory for the second two studies. For the third study a confirmed sentinel pile was also mandatory.

For the first study the primary endpoint was fissure healing at 56 days evaluated by the investigator. To maintain the blind the investigator was not to ask about headache while evaluating fissure healing. In all three studies average anal pain was recorded daily by the patient on a 100 mm VAS. Pain on defecation and worst pain (for the first two studies) were also recorded. For the second study the primary pain relief endpoint was evaluated through 56 days, while for the third study the primary pain endpoint was evaluated through 21 days with a secondary endpoint through 56 days. All three studies attempted to limit use of acetaminophen for headache relief. The first study did not control dietary fiber supplement or sitz bath use, the second specified psyllium 1 tbsp in 8 oz of water BID and limited sitz baths to one per day, and the third allowed continuation of baseline dietary fiber supplements and also limited sitz baths to one per day.

Randomization in all three studies was by computer-generated schedule. In the third study I noted various randomization errors: one site used a higher block prior to using a lower block, another site assigned a block starting with the highest number, and two patients were assigned randomization numbers but never treated.

COMMENT: While all three studies were on paper double-blinded, the occurrence of headache secondary to NTG ointment use introduces the potential for partial unblinding. The use of acetaminophen for headache is a potential confounder of anal pain relief. The randomization errors in the third study suggest some sloppiness in study conduct. All of these factors reduce my confidence in the validity of any positive results. However, as presented below, the results of each of the three studies is negative for other reasons.

6.1.4 Efficacy Findings

6.1.4.1 Study NTG 98-02-01: A Study to Determine the Nitroglycerin Ointment Dose and Dosing Interval That Best Promote the Complete Healing of Chronic Anal Fissures

The primary endpoint for this study was anal fissure healing. The sponsor provided various analyses of anal fissure healing and the FDA statistical reviewer confirmed these results. None

suggested a benefit of NTG ointment to heal the fissures. The results for the analyses pooling the BID and TID dosing groups are shown in Table 6.

Table 6: Sponsor's Study NTG 98-02-01 Anal Fissure Healing Rates

| Treatment Group* | Healing Rate | | p-value |
|------------------|--------------|-------|---------|
| | n | (%) | |
| 0.1% NTG (N=76) | 30 | (40%) | p=0.63 |
| placebo (N=70) | 34 | (49%) | |
| 0.2% NTG (N=78) | 26 | (33%) | p=0.12 |
| placebo (N=70) | 34 | (49%) | |
| 0.4% NTG (N=80) | 35 | (44%) | p=0.64 |
| placebo (N=70) | 34 | (49%) | |

* Results from b.i.d. and t.i.d. dose frequency groups combined.

Pain relief was a secondary endpoint in this study. The sponsor provided a pain analysis pooling the BID and TID dose groups using a mixed effects model. The exact model used and the pooling of the groups were not pre-specified. By this analysis "In the ITT population, linear time by treatment interactions were significant for the 0.4% NTG group relative to placebo for average pain ($p < 0.0002$), defecation pain ($p < 0.003$) and worst pain ($p < 0.0002$). No overall significant differences were observed for the two lower doses relative to the placebo control." These analyses used only 267 of the 304 randomized patients because of missing data. In addition, the FDA reviewers noted imbalances in baseline pain scores among the groups and that the results of the mixed effects model were dependent upon the precise nature of the model used. The FDA statistical reviewer produced the results shown in Table 7 for the mixed effects models.

Table 7: Statistical Reviewer's Study NTG 98-02-01 Slope of Change in Average Daily Pain over Time

| | Mean slope (average daily pain) | | Nominal P-value* | |
|---------------------|------------------------------------|-------|------------------|--------|
| | indep | AR(1) | indep | AR(1) |
| Placebo BID (N=34) | -0.21 | -0.21 | --- | --- |
| 0.1% NTG BID (N=39) | -0.23 | -0.24 | 0.86 | 0.78 |
| 0.2% NTG BID (N=39) | -0.27 | -0.25 | 0.62 | 0.68 |
| 0.4% NTG BID (N=38) | -0.52 | -0.52 | 0.005 | 0.0004 |
| Placebo TID (N=36) | -0.21 | -0.19 | --- | --- |
| 0.1% NTG TID (N=37) | -0.37 | -0.36 | 0.12 | 0.049 |
| 0.2% NTG TID (N=39) | -0.32 | -0.33 | 0.27 | 0.093 |
| 0.4% NTG TID (N=42) | -0.37 | -0.36 | 0.14 | 0.059 |

* for comparison with the corresponding placebo regimen

Indep: model with independent residuals

AR(1): model with AR(1) residuals

The prior medical reviewer tabulated mean change from baseline to last available daily average pain score in Table 8.

Table 8: Prior Reviewers' Study NTG 98-02-01 Mean Change in Last Available Visit Daily Average Pain from Baseline

| | Baseline Mean | Mean change | Nominal p-value [§] | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|------------------------------|-------------------|------------------------------|
| 0.1% NTG BID | 26.4 | -9.9 | 0.85 | -12.0 | 0.46 |
| 0.1% NTG TID | 35.3 | -21.7 | 0.076 | -18.3 | 0.61 |
| 0.2% NTG BID | 25.8 | -14.9 | 0.51 | -17.4 | 0.52 |
| 0.2% NTG TID | 29.9 | -23.7 | 0.031 | -23.3 | 0.059 |
| 0.4% NTG BID | 39.2 | -27.9 | 0.003 | -21.0 | 0.10 |
| 0.4% NTG TID | 30.8 | -18.9 | 0.19 | -17.9 | 0.66 |
| Placebo BID | 25.7 | -11.0 | --- | -14.9 | --- |
| Placebo TID | 23.4 | -11.6 | --- | -16.3 | --- |

* adjusted for baseline daily average pain

§ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change

NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Please see the combined medical/statistical review of the original NDA submission for more details on this study's results.

COMMENT: This study failed on its primary endpoint, healing of anal fissure. The analyses of pain relief do suggest the possibility that 0.4% NTG ointment may improve anal pain. However, because of the failure of the primary endpoint, the lack of complete pre-specification of the pain analyses, and some inconsistencies in the results (e.g., 0.4% NTG BID appears better than TID but for lower dosages TID is better), the pain analyses of this study must be viewed as exploratory rather than confirmatory.

6.1.4.2 Study NTG 00-02-01: A Study to Determine the Nitroglycerine Ointment Dose that Best Promotes the Relief of Pain Associated with Anal Fissures

The primary endpoint for this study was daily average pain through 56 days evaluated by a mixed-effects regression model using all values recorded for each subject in the ITT population (defined as subjects with baseline and some post-treatment data) The study report states that the effects of center and a quadratic effect of time were included in the model. The center and quadratic components of the model used for analysis were not pre-specified, and these parameters were not used to analyze study NTG 98-02-01. The sponsor concluded that in the ITT population, for comparisons with the placebo group, a significant treatment by linear time interaction for average pain intensity was observed for the 0.4% NTG group (p=0.005), but not for the 0.2% NTG group as shown in Table 9.

Table 9: Sponsor’s Primary Endpoint Analysis for Study NTG 00-02-01 (Mixed Effects Regression Model with Center and Quadratic Components)

| | Linear trend | p-value for linear* | Quadratic trend | p-value for quadratic* |
|------------------------|--------------|---------------------|-----------------|------------------------|
| 0.2% NTG minus placebo | -0.055 | 0.57 | 0.0013 | 0.20 |
| 0.4% NTG minus placebo | -0.27 | 0.005 | 0.0040 | < 0.0001 |

The mixed-effects analysis results depend on the regression model used. Based on the plan of estimating sample size, the model the sponsor intended to use at the time of planning the study was a linear model in which the trend of average pain intensity is linear over time. The previous study NTG98-02-01 also suggested that the linear model was the model to use. In the linear model, the rate of change in pain is the slope of the linear trend that does not change over time. Using the linear model (excluding sites, using a simple covariance matrix for random-effects components and for residual as the sponsor used in Study NTG 98-02-01), the prior reviewer performed the mixed-effects analysis with results summarized in Table 10. Adding sites or using an unstructured covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference. Based on the linear model, there was no significant difference in slope (rate of change of average pain intensity over time) between either of the NTG groups and the placebo group.

Table 10: Prior Reviewer’s Primary Endpoint Analysis for Study NTG 00-02-01 (Slope of Change in Average Daily Pain Over Time Using Linear Model)

| | Mean slope | Nominal p-value* |
|-----------------|------------|------------------|
| Placebo (N=75) | -0.37 | --- |
| 0.2% NTG (N=70) | -0.385 | 0.85 |
| 0.4% NTG (N=74) | -0.466 | 0.24 |

* for comparison with the placebo group

the model the sponsor used in Study NTG 98-02-01 (excluding sites, using a simple covariance matrix for random-effects components and for the residual)

The mixed effects regression models are somewhat difficult to visualize. The prior reviewer also performed an analysis of the mean change from baseline to the last available visit of the average daily pain. The results are shown in Table 11. There is little difference among the groups in the mean change in average daily pain at the last available visit.

Table 11: Prior Reviewer’s Mean Change from Baseline to Last Available Visit of the Average Daily Pain for Study NTG 00-02-01

| | Baseline Mean | Mean change | Nominal p-value [§] | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|------------------------------|-------------------|------------------------------|
| 0.2% NTG BID | 33.8 | -18.9 | 0.78 | -19.0 | 0.73 |
| 0.4% NTG BID | 34.1 | -21.3 | 0.80 | -21.2 | 0.77 |
| Placebo BID | 34.0 | -20.2 | --- | -20.2 | --- |

* adjusted for baseline daily average pain

§ NTG bid vs. placebo bid, based on mean change

NTG bid vs. placebo bid, based on adjusted mean change

For the secondary efficacy endpoint of anal fissure healing there was no benefit versus placebo noted in either the percentage of patients healed (59% placebo, 59% 0.2% NTG, 54% 0.4% NTG, $p = 0.571$) or time to healing by Cox regression ($p = 0.9984$ 0.2% NTG, $p = 0.7227$ 0.4% NTG vs placebo).

The prior reviewers also identified problems with missing data. For example, the 0.4% NTG group had a greater percent of the patients who did not complete the pain study compared to placebo (11% for placebo and 24% for 0.4% NTG). Please see the combined medical/statistical review of the original NDA submission for the details on this issue and other results.

COMMENT: The prior reviewer made this cogent comment on these results: While the mixed effects model analyses may suggest a transient difference in the shape of the 0.4% NTG ointment compared to placebo, it is not clear whether this difference would be clinically perceived transiently. At the end of a course of 56 days no difference in pain relief was found. No difference in the number of patients totally relieved of pain was noted. Whatever arguments might be made concerning statistical significance, there do not appear to be meaningful clinical benefits provided.

6.1.4.3 Study CP125 03-02-01: A Study to Determine the Effect of CP125 Ointment on the Pain Associated with a Chronic Anal Fissure

The primary efficacy endpoint for this study was rate of change of the 24-hour average pain intensity over a 21-day treatment period evaluated by a generalized mixed-effects regression model. NTG patients discontinuing the study due to headache were to have their last observation carried forward (LOCF). For this endpoint the sponsor reports a p value of <0.0498 (Table 13 of the study report). The mean changes calculated by the sponsor are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale.

However, the sponsor's handling of some patients' data for its primary analysis is not consistent with the protocol specification. The sponsor did not use LOCF for two patients who discontinued due to headache. For the analysis that matches the description of the primary analysis in the protocol the p value is 0.12. If one argues that post-discontinuation data should be used when available, then the p value is 0.15. For more detail on these analyses see Table 25 and for a complete discussion see the FDA statistical review.

The one secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. By the sponsor's calculation there was no statistically significant difference between the two groups ($p < 0.3$). Fissure healing at 56 days, a tertiary endpoint, was similar in the two groups (placebo 63%, NTG 69%, $p = 0.42$).

The mean change in pain score from baseline to day 21 was similar in the two groups (placebo -31, NTG -32, see Table 27). Response did not vary significantly by age or gender and race was

predominantly white (95%), making race comparisons impossible. The one subgroup difference I found is that the only country with a substantial improvement in pain scores with NTG is Serbia (see Table 28). US patients fared better with placebo. Serbia had three sites, two of which were among the largest sites and showed substantial improvement with NTG.

COMMENT: By the primary analysis this study fails to show efficacy of NTG ointment for relief of pain with anal fissure. The evidence for efficacy of NTG ointment from this study is even weaker than the p value of 0.12 implies. This study is plagued by a high dropout rate only in the NTG ointment arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21 (see Table 20). The Division warned the sponsor that a high dropout rate would make this study uninterpretable. My confidence in any suggestion of a benefit for NTG ointment is weakened further by the potential for partial unblinding because of headaches with NTG ointment and confounding by acetaminophen use and because reasonable improvement with NTG ointment was demonstrated only in one country.

6.1.4.4 Sponsor's Integrated Summary of Efficacy

In its Integrated Summary of Efficacy the sponsor provides two sets of analyses combining data from the three studies: (1) a "combined ITT analysis population" consisting of patients treated with 0.4% NTG ointment or placebo BID (206 placebo and 201 NTG patients); and (2) a "sentinel pile ITT population subgroup" as for (1) but having a sentinel pile, a "well-accepted marker of chronicity" (137 placebo and 118 NTG patients, excluding patients from the first study who did not have sentinel piles recorded). The main results for the combined ITT analysis population are shown in Table 12. The results for the sentinel pile subgroup show similar high statistical significance.

Table 12: Sponsor's Change from Baseline in 21- and 56-Day Measurements of 24-Hour Average Pain Intensity (mm) – Combined Analysis

| Time Period | Statistics ^a | Placebo (N=206) | Cellegesic Nitroglycerin Ointment 0.4% (N=201) | P-value ^b |
|-------------|-------------------------|--------------------|---|----------------------|
| Baseline | N | 204 | 198 | N/A |
| | Mean (SD) | 42.3 (22.53) | 44.2 (22.38) | |
| | Median | 44.0 | 44.0 | |
| | Min, Max | 0.0, 98.0 | 1.0, 100.0 | |
| Days 1-21 | N | 203 | 194 | <0.0007 |
| | Mean (SD) | -15.4 (19.33) | -19.3 (20.53) | |
| | Median | -12.7 | -17.7 | |
| | Min, Max | -77.0, 24.0 | -76.6, 63.5 | |
| Days 1-56 | N | 203 | 194 | <0.0001 |
| | Mean (SD) | -22.4 (20.80) | -25.8 (21.96) | |
| | Median | -22.9 | -27.9 | |
| | Min, Max | -88.2, 20.2 | -75.8, 57.3 | |

Combined analysis includes all ITT subjects who applied Cellegesic NTG ointment 0.4% b.i.d. or placebo b.i.d. in studies NTG 98-02-01, NTG 00-02-01, and CP125 03-02-01.

^a Summary statistics displayed at the above intervals are calculated by using the mean of daily change from baseline in 24-hour average pain intensity assessments recorded for each subject during the indicated interval.

^b Analysis of the raw daily pain intensity assessments from Baseline through Day 21 or 56 used a mixed-effects regression model. The P-values are from the test of the linear component of the treatment-by-day interaction (i.e., the rate of change in pain is different between placebo and Cellegesic-treated subjects).

Note: The N's in the column headers are the number of subjects in the ITT population.
 The N's in the time period rows are the number of ITT subjects having data for the descriptive statistics for that time period

COMMENT: The fundamental problem with these analyses is that they were not pre-specified. They are subject to unstated selection criteria that may be used to produce positive results and misleadingly low p values. The Division statistical reviewer shows in his review the great variations in p values resulting from inclusion or exclusion of a few data values in the analyses of the most recent study. The prior reviewers have discussed in their review the variations in p values resulting from variations in how the mixed effects regression model is run for the second study. The variability of the results is also demonstrated by examining the results for the patients that the sponsor excluded from these analyses, i.e., the patients treated with 0.2% NTG ointment. One would like to see a dose response relationship to confirm that NTG is showing an effect rather than a chance outcome. I show in Table 13 the mean change from baseline to day 21 in pain score for BID dosing in all three studies, including the 0.2% NTG patients.

Table 13: Reviewer's Mean Change from Baseline to Day 21 in Pain Score for BID Dosing in All Three Studies

| Dose | N | Mean | SD |
|---------|-----|-------|------|
| Placebo | 203 | -20.4 | 23.1 |
| 0.2 | 97 | -13.5 | 25.6 |
| 0.4 | 189 | -26.1 | 25.8 |

Note that there is no suggestion of a dose response for NTG ointment—0.2% NTG appears as worse than placebo as 0.4% appears better. I also note that the absolute differences in the pain

scores are small, e.g., < 6 mm or < 6% for 0.4% NTG vs. placebo, compared to the variability (SD about 25 mm). These studies, whether analyzed individually or collectively, provide little suggestion and no substantial evidence that NTG ointment relieves the pain of anal fissure.

6.1.5 Clinical Microbiology

This section is not applicable because this drug is not an antimicrobial.

6.1.6 Efficacy Conclusions

All three of these studies fail to show statistical significance for their primary endpoint analyses. The estimated magnitude of a benefit, if any, of NTG in relieving pain of anal fissure is small, e.g., a mean improvement of about 3 mm on a 100 mm visual analog scale at day 21 even with the sponsor's liberal analysis, and is confounded by many issues regarding analyses not prespecified, data exclusions, excessive dropouts with NTG, acetaminophen use, and benefit limited to one country. These studies do not provide substantial evidence of efficacy of NTG ointment in relief of pain associated with chronic anal fissure.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

For the evaluation of safety issues related specifically to NTG ointment I relied upon the data and tabulations provided in this submission for the four studies identified in Table 2. For safety issues related to systemic absorption of NTG I used the safety information in the approved labeling for other NTG formulations.

7.1.1 Deaths

No deaths occurred during the clinical trials.

7.1.2 Other Serious Adverse Events

Ten patients experienced serious adverse events (SAEs) during the trials, four placebo, two 0.4% NTG BID, and four other NTG dosing. The SAEs are listed in Table 14.

Table 14: Sponsor's Serious Adverse Events

| Treatment Group Study Number Subject Number | Age (Yrs) | Serious Adverse Event (Preferred Term) | D/C Study Drug ^a | Study Day of Onset ^b | Intensity | Relationship to Study Drug ^c | Duration of Event (Days) |
|---|--------------|---|-----------------------------------|---------------------------------------|-----------|---|--------------------------------|
| Placebo ointment b.i.d. | | | | | | | |
| NTG 00-02-01 | | | | | | | |
| 007-123 | 19 | Pain exacerbated | Yes | 22 | Moderate | None | 22 |
| 015-106 | 46 | Hepatitis C | No | 3 | Moderate | None | Ongoing |
| CP125 03-02-01 | | | | | | | |
| 025-109 | 52 | Vein pain | No | 1 | Moderate | None | 5 |
| 033-340 | 41 | Perianal abscess | No | 60 | Moderate | None | 14 |
| Cellegesic nitroglycerin ointment (0.1%) t.i.d. | | | | | | | |
| NTG 98-02-01 | | | | | | | |
| 312-113 ^d | 42 | Cholelithiasis | No | 23 | Moderate | None | 23 |
| Cellegesic nitroglycerin ointment (0.2%) b.i.d. | | | | | | | |
| NTG 98-02-01 | | | | | | | |
| 322-146 ^d | 24 | Perirectal abscess | Yes | 8 | Severe | None | 2 |
| NTG 00-02-01 | | | | | | | |
| 009-110 | 41 | Migraine NOS | Yes | 1 | Severe | Related | 1 |
| Cellegesic nitroglycerin ointment (0.2%) t.i.d. | | | | | | | |
| NTG 98-02-01 | | | | | | | |
| 320-103 ^d | 63 | Chest pain | No | 34 | Severe | None | 3 |
| | | Dyspnea NOS | No | 34 | Severe | None | 3 |
| Cellegesic nitroglycerin ointment (0.4%) b.i.d. | | | | | | | |
| NTG 98-02-01 | | | | | | | |
| 317-115 ^e | 72 | Hip fracture | Yes | 48 | Severe | None | 1 |
| CP125 03-02-01 | | | | | | | |
| 019-045 | 69 | Abdominal distension | No | 50 | Mild | None | 42 |
| | | Abdominal pain NOS | No | 46 | Severe | None | 46 |
| | | Anorexia | No | 50 | Moderate | None | 42 |
| | | Dyspnea NOS | No | 51 | Moderate | None | 39 |
| | | Dysuria | No | 50 | Mild | None | Ongoing |
| | | Hemoglobin decreased | No | 53 | Moderate | None | 25 |
| | | Hypercalcaemia | No | 53 | Severe | None | Ongoing |
| | | Loose stools | No | 47 | Moderate | None | Ongoing |
| | | Nausea | No | 52 | Moderate | None | 33 |
| | | Night sweats | No | 50 | Mild | None | 2 |
| | | Pyrexia | No | 48 | Mild | None | 44 |
| | | Rigors | No | 50 | Mild | None | 3 |
| | | Small intestinal obstruction NOS | No | 50 | Severe | None | 42 |
| | | Weakness | No | 50 | Moderate | None | Ongoing |

^a Subject discontinued therapy due to this adverse event.

^b Relative to start of therapy.

^c Based on investigator's assessment.

^d For these 3 subjects, the duration of event was reported incorrectly in Table 19 Subjects with Serious Adverse Events in Report NTG 98-03-01, 8:v05:p079. For Subject 312-113 (duration 23 days) and Subject 322-146 (duration 2 days), durations of event were reported as 1 day. For Subject 320-103 (duration 3 days), duration was reported as 2 days.

^e For Subject 317-115, onset of event (Day 48) was reported as Day 47 in Table 19 Subjects with Serious Adverse Events in Report NTG 98-03-01, 8:v05:p079.

The patient with the chest pain and dyspnea SAE was a 63 year-old white male with a history of coronary artery disease, hypertension, and angioplasty. He was hospitalized on day 37 with chest pain and dyspnea, underwent catheterization and angioplasty, and was discharged after three days. He subsequently completed the study.

COMMENT: The SAEs were infrequent, uncorrelated, and not suggestive of any unusual problem with anal administration of NTG.

7.1.3 Dropouts and Other Significant Adverse Events

Overall 45 NTG (22 0.4% BID patients) and 7 placebo patients discontinued treatment due to an adverse event (AE). Headache was the most common AE leading to discontinuation in 29 NTG patients (about 8% of the 0.4% BID patients) compared to 2 (about 1%) of the placebo patients. For any NTG use vomiting was the cause for discontinuation in 4 patients, nausea in 3 patients, and burning sensation, tachycardia, dizziness, and vertigo in 2 patients. Other AEs led to discontinuation in only 1 patient each.

One AE in a 0.4% BID patient was coded as syncope but the CRF records "faintness following cream application" of mild intensity lasting several days. Another 0.4% BID patient had nausea, vomiting, and vertigo leading to moderate tachycardia and discontinuation. A 0.2% BID patient had moderate dizziness, faintness, and palpitations and another one had worsening vertigo of moderate intensity. A 0.2% TID patient also had moderate vertigo along with headache. Other details and blood pressure measurements are not available for these patients.

COMMENT: The withdrawal AEs confirm that the systemic absorption of NTG from the ointment can cause systemic effects. The headaches may not be dangerous, but they do confound the interpretation of the pain scores. Was anal pain rated less intense because the patient was more concerned with the headache? This problem was the reason why the Division recommended to the sponsor to capture a global assessment of pain, but the sponsor ignored this suggestion. The dizziness and faintness suggest that the systemic absorption of NTG may also be causing hypotension. Whether this AE could lead to more serious problems in more vulnerable patients or those taking other medications is not determinable from this small safety data base.

7.1.4 Other Search Strategies

For this small safety data base no other search strategies were employed or are needed.

7.1.5 Common Adverse Events

The AES occurring at a frequency $\geq 2\%$ in any treatment group are shown in Table 15. Severe headaches were reported in about 20% of NTG 0.4% BID patients but only 6% of placebo patients.

COMMENT: Note the higher rate of headaches, dizziness, and nausea in the NTG patients.

Table 15: Sponsor's Adverse Events =2% Frequency in Any Treatment Group

| Body System Preferred Term | Placebo ^a (N=246) | Cellegesic Nitroglycerin Ointment | |
|---|---------------------------------|-----------------------------------|-------------------------------|
| | | 0.4% b.i.d. (N=206) | Total ^b (N=475) |
| | n (%) | n (%) | n (%) |
| Subjects With Any Adverse Events | 149 (60.6) | 162 (78.6) | 315 (66.3) |
| Nervous system disorders | 95 (38.6) | 138 (67.0) | 243 (51.2) |
| Headache NOS | 93 (37.8) | 131 (63.6) | 229 (48.2) |
| Dizziness | 0 | 9 (4.4) | 17 (3.6) |
| Gastrointestinal disorders | 39 (15.9) | 36 (17.5) | 78 (16.4) |
| Nausea | 2 (0.8) | 12 (5.8) | 21 (4.4) |
| Diarrhea NOS | 8 (3.3) | 6 (2.9) | 12 (2.5) |
| Hemorrhoids | 0 | 5 (2.4) | 6 (1.3) |
| Anal discomfort | 6 (2.4) | 1 (0.5) | 1 (0.2) |
| Infections and infestations | 31 (12.6) | 17 (8.3) | 36 (7.6) |
| Upper respiratory tract infection NOS | 7 (2.8) | 2 (1.0) | 6 (1.3) |
| Influenza | 6 (2.4) | 1 (0.5) | 4 (0.8) |
| Respiratory, thoracic and mediastinal disorders | 13 (5.3) | 9 (4.4) | 21 (4.4) |
| Pharyngitis | 5 (2.0) | 2 (1.0) | 6 (1.3) |
| Skin and subcutaneous tissue disorders | 10 (4.1) | 6 (2.9) | 9 (1.9) |
| Pruritus NOS | 6 (2.4) | 1 (0.5) | 1 (0.2) |

^a Includes all subjects receiving placebo (b.i.d. or t.i.d.).

^b Includes all subjects receiving any concentration of Cellegesic ointment (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.

7.1.6 Less Common Adverse Events

The safety database is too small to evaluate less common AEs.

7.1.7 Laboratory Findings

Routine safety labs (hematology, clinical chemistry, and urinalysis) were measured at baseline and at day 56 or study exit. Shifts from normal at baseline to abnormal at day 56 were infrequent and similar between placebo and NTG patients. The most frequent abnormality was a high blood glucose (12-15% of all patients at day 56 in all groups), but samples were not necessarily collected fasting. There were also similar frequencies of increased creatinines (6-7%) and increased SGOT or SGPT (3-6%). Follow-up on abnormalities judged clinically significant did not document any abnormalities clearly related to study drug.

COMMENT: NTG use sublingually or topically has not been associated with laboratory abnormalities other than methemoglobinemia with overdose.

7.1.8 Vital Signs

Vital signs were measured at baseline (prior to the first study drug use) and post-baseline at days 1 (10-20 minutes post-dose for this visit only), 14, 28, 42, and exit visits in studies NTG 98-02-01 and NTG 00-02-01 and at the day 7, 21, 35, and exit visits in study CP125 03-02-01. The NDA comments that there were no time- or dose-related trends in DBP, SBP, or pulse. The sponsor also examined decreases in DBP of ≥ 20 mm Hg as shown in Table 16.

Table 16: Sponsor's Decreases in Sitting DBP of ≥ 20 mm Hg

| Visit ^a | Cellegesic Nitroglycerin Ointment | | | | | |
|--------------------|-----------------------------------|------------------------------|------------------------------|-------------------|-------------------------------|-------------------------------|
| | Placebo ^b n/N (%) | 0.1% ^b n/N (%) | 0.2% ^b n/N (%) | 0.4% | | Total ^d n/N (%) |
| | | | | b.i.d. n/N (%) | Total ^e n/N (%) | |
| Day 1 | 2/147 (1.4) | 5/ 74 (6.8) | 2/151 (1.3) | 7/115 (6.1) | 9/157 (5.7) | 16/382 (4.2) |
| Day 7-14 | 10/237 (4.2) | 5/ 65 (7.7) | 5/136 (3.7) | 5/184 (2.7) | 9/219 (4.1) | 19/420 (4.5) |
| Day 21-28 | 12/226 (5.3) | 6/ 60 (10.0) | 7/123 (5.7) | 8/178 (4.5) | 11/208 (5.3) | 24/391 (6.1) |
| Day 35-42 | 7/211 (3.3) | 6/ 41 (14.6) | 6/107 (5.6) | 3/165 (1.8) | 6/190 (3.2) | 18/338 (5.3) |
| Exit | 9/227 (4.0) | 5/ 64 (7.8) | 2/131 (1.5) | 9/187 (4.8) | 11/225 (4.9) | 18/420 (4.3) |
| Any Post-baseline | 24/246 (9.8) | 13/ 76 (17.1) | 10/151 (6.6) | 21/203 (10.3) | 30/245 (12.2) | 53/472 (11.2) |

^a Baseline is the last measurement taken prior to the first CTM application. Post-baseline vital signs were to be collected at the Day 1 (10-20 minutes post-dose), 14, 28, 42, and exit visits in Studies NTG 98-02-01 and NTG 00-02-01, and at the Day 7, 21, 35, and exit visits in study CP125 03-02-01.

^b Includes all subjects receiving the indicated treatment (b.i.d. or t.i.d.).

^c Includes all subjects receiving any Cellegesic 0.4% (b.i.d. or t.i.d.).

^d Includes all subjects receiving any concentration of Cellegesic (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.

NOTE: n = number of subjects with a decrease from baseline at the indicated visit

N = number of subjects with a diastolic blood pressure at baseline and the indicated visit.

COMMENT: Because vital sign measurements were not timed for peak drug effect after the first visit, most of the measurements are not helpful.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were recorded only in study CP125 03-02-01. One NTG patient withdrew because of bradycardia and extrasystoles, the only abnormality considered "clinically significant". Between 72 and 82% of ECGs were considered normal at any time, and the rates of "not clinically significant" abnormalities in both groups decreased slightly from screening to last visit.

COMMENT: ECGs were only evaluated qualitatively and QTc and other interval measurements at peak drug effect were not done. Given the vast experience with oral and topical NTG, a thorough QTc study is not needed.

7.1.10 Immunogenicity

Immunogenicity was not evaluated.

COMMENT: Topical NTG use has been associated with contact dermatitis or fixed drug eruptions. The safety database is too small to rule out rare problems with anal NTG administration.

7.1.11 Human Carcinogenicity

The safety database is too small and of limited duration to provide any information regarding human carcinogenicity.

7.1.12 Special Safety Studies

No special safety studies were done.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal studies were done.

COMMENT: Rebound hypertension has been reported with withdrawal of NTG. Given the unpleasant adverse effect (headache), the abuse potential is low.

7.1.14 Human Reproduction and Pregnancy Data

There have been no clinical studies of the effects of NTG in pregnant women.

7.1.15 Assessment of Effect on Growth

Only adult patients were studied.

7.1.16 Overdose Experience

There were no overdoses in the clinical studies.

7.1.17 Postmarketing Experience

Cellegesic has not been marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The three randomized, placebo-controlled trials and the one small pharmacokinetic study that provide the safety data for this NDA are identified in Table 2. Of the 726 patients enrolled in the three trials, 475 received any dose of NTG (0.1%, 0.2%, or 0.4%) BID or TID and 206 patients received 0.4% BID, the regimen proposed to be marketed. Of these 206, 167 (81%) completed a 56-day treatment period. The most frequent reason for withdrawal was adverse event in 20 (10%), but another 13 (6%) withdrew for "patient choice".

7.2.1.2 Demographics

The demographics of the safety population are shown in Table 17.

Table 17: Sponsor's Demographics of Safety Population

| | Cellegesic Nitroglycerin Ointment | | | Overall Total (N=721) n (%) |
|-----------------------------|--|---------------------------------|--|-----------------------------------|
| | Placebo ^a (N=246) n (%) | 0.4% b.i.d. (N=206) n (%) | Total ^b (N=475) n (%) | |
| Sex | | | | |
| Male | 119 (48.4) | 90 (43.7) | 246 (51.8) | 365 (50.6) |
| Female | 127 (51.6) | 116 (56.3) | 229 (48.2) | 356 (49.4) |
| Race | | | | |
| Caucasian | 219 (89.0) | 187 (90.8) | 408 (85.9) | 627 (87.0) |
| Black | 13 (5.3) | 8 (3.9) | 29 (6.1) | 42 (5.8) |
| Asian | 5 (2.0) | 1 (0.5) | 4 (0.8) | 9 (1.2) |
| Hispanic/American or Latino | 8 (3.3) | 9 (4.4) | 26 (5.5) | 34 (4.7) |
| Native American | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Other | 1 (0.4) | 1 (0.5) | 7 (1.5) | 8 (1.1) |
| Age (years) | | | | |
| ≤45 | 128 (52.0) | 99 (48.1) | 264 (55.6) | 392 (54.4) |
| 46-64 | 96 (39.0) | 87 (42.2) | 173 (36.4) | 269 (37.3) |
| 65-74 | 17 (6.9) | 17 (8.3) | 30 (6.3) | 47 (6.5) |
| ≥75 | 5 (2.0) | 2 (1.0) | 7 (1.5) | 12 (1.7) |
| N | 246 | 205 | 474 | 720 |
| Mean±SD | 45.2±13.01 | 46.2±12.95 | 44.3±13.09 | 44.6±13.06 |
| Range | 19.0-81.0 | 19.0-76.0 | 19.0-83.0 | 19.0-83.0 |
| Missing | 0 | 1 | 1 | 1 |

COMMENT: Note that the safety population has a reasonable gender split but is predominantly white (90%) and middle aged (mean 46). The one subgroup representation for which more exposure would be desirable is the elderly, because they have a higher rates of chronic cardiovascular disease for which adverse effects such as hypotension would be more

troublesome. Only 19 patients 65 or older were exposed to the regimen proposed to be marketed. However, given the widespread use of sublingual and topical NTG, the extent of safety exposure to anal NTG is not critical.

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure is shown in Table 18.

Table 18: Sponsor's Extent of Exposure

| | Placebo (N=246) n (%) | Cellegesic Nitroglycerin Ointment | |
|---|-----------------------------|-----------------------------------|---------------------------|
| | | 0.4% b.i.d. (N=206) n (%) | Total (N=475) n (%) |
| Duration of Therapy (days) | | | |
| 1-7 | 1 (0.4) | 9 (4.4) | 18 (3.8) |
| 8-21 | 11 (4.5) | 8 (3.9) | 28 (5.9) |
| 22-35 | 8 (3.3) | 12 (5.8) | 42 (8.8) |
| 36-56 | 95 (38.6) | 85 (41.3) | 138 (29.1) |
| >56 | 109 (44.3) | 76 (36.9) | 195 (41.1) |
| Missing | 22 (8.9) | 16 (7.8) | 54 (11.4) |
| Total Amount of CTM Administered (grams) | | | |
| N | 224 | 188 | 419 |
| Mean±SD | 42.6±15.20 | 39.8±17.65 | 38.7±19.04 |
| Range | 1.5-86.9 | 0.4-83.8 | 0.4-102.1 |
| Missing | 22 | 18 | 56 |
| Percent compliance | | | |
| N | 223 | 187 | 418 |
| Mean±SD | 101.2±31.60 | 104.9±36.26 | 94.3±35.28 |
| Range | 24.1-254.6 | 1.3-244.4 | 1.3-252.8 |

COMMENT: The extent of exposure in terms of patient exposure years is low (about 28). The safety evaluation of this drug depends upon the vast experience with NTG by sublingual and topical administration. However, some potential problems of this new preparation, e.g., variable systemic absorption by the anal route, can not be addressed by the sublingual and topical administration experiences.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

I also used the descriptions of adverse events included in the approved labels for sublingual and topical NTG.

7.2.2.1 Other studies

In addition to the three clinical efficacy trials the safety data from one small pharmacokinetic study in healthy volunteers is provided.

7.2.2.2 Postmarketing experience

Cellegesic has not been marketed anywhere.

7.2.2.3 Literature

The sponsor provided a summary of uncontrolled and controlled studies of anal application of medications containing a nitric oxide donor. The published studies reported AEs similar to those in the NDA studies, e.g., headache was the most frequent AE. No unusual toxicities were reported.

7.2.3 Adequacy of Overall Clinical Experience

For NTG ointment 475 patients were exposed to some dosage, 206 started the regimen proposed to be marketed (0.4% BID), 167 completed a 56-day treatment period with this regimen, and only 19 patients of the latter patients were age 65 or older. This is fairly limited exposure for a new route of administration. I am most concerned about exposures for vulnerable patients with other cardiovascular diseases.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal studies were submitted or are needed for NTG.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing had two limitations:

- Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure. It would be helpful to know how much blood pressure is affected and the variability of it.
- The case report forms provided minimal information on the adverse events. For example, tachycardia was reported for several patients but no information is provided on heart rate, heart rhythm, or blood pressure.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Because NTG has had widespread clinical use, no workup was done for metabolism, clearance, or drug interaction and none is indicated.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The potential for cardiovascular AEs in individuals with existing cardiovascular disease has not been adequately evaluated and should be studied further. The effects of intra-anal administration on heart rate and blood pressure are not documented adequately and should be studied further.

7.2.8 Assessment of Quality and Completeness of Data

Please see the two comments in Section 7.2.5.

7.2.9 Additional Submissions, Including Safety Update

The sponsor provided a submission dated September 30, 2004, with the first six-month follow-up data from study CP125 03-02-01. Data were provided for 175 subjects (89 placebo and 86 NTG). This supplement provided information on subsequent treatments rather than safety data.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

NTG administered intra-anally is systemically absorbed—bioavailability about 50% with a wide SD of about $\pm 30\%$. Not surprisingly, NTG ointment causes AEs typical of systemic administration of NTG such as headaches. While the headaches may be considered more of a nuisance AE, other effects of systemic administration of NTG, such as hypotension, may be troublesome in patients with existing cardiovascular disease. The potential or lack of potential of NTG ointment for causing dangerous cardiovascular AEs is not well explored in the limited exposure in the Cellegesic development program with limited information on blood pressure changes and AEs. While the available data don't confirm that NTG ointment is a dangerous drug, they also don't provide sufficient reassurance that it is safe.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor pooled data for the regimen proposed to be marketed (0.4% BID) and for all NTG ointment use as well as presented the individual regimen's data. The sponsor also reported each study's data individually. All of these analyses are appropriate.

COMMENT: Despite the pooling the size of the safety database is small.

7.4.2 Explorations for Predictive Factors

The size of the safety database is too small to facilitate exploration for predictive factors.

7.4.3 Causality Determination

The most frequent AE, headache, is a recognized side effect of systemic NTG exposure.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen was selected based on the first study examining a range of doses (0.1, 0.2, and 0.4%) and BID and TID dosing and the second study testing 0.2 and 0.4% BID. The regimen selected for the third study and proposed to be marketed was selected based on the suggestion of best pain relief and a rate of adverse effects (i.e., headache) considered tolerable. The evidence for efficacy of the 0.4% BID regimen was weak and not supported by the third study. The rate of headaches with the 0.4% BID regimen suggests that higher doses would not be acceptable.

The sponsor proposes marketing CELLEGESIC nitroglycerin ointment 0.4% in both a metered dose canister and in a tube. The canister has a metered dose-dispensing pump that delivers approximately 375 mg ointment each time the piston is fully depressed. To obtain a 375 mg dose of ointment with the tube, a finger cot or plastic food wrapped finger is laid alongside the dosing line on the carton. The tube is gently squeezed until a ribbon of ointment the length of the line is expressed onto the covered finger. Once the dose is dispensed the finger is gently inserted into the anal canal to the first knuckle (joint) to apply the ointment around the side of the anal canal.

The 375 mg dose of 0.4% NTG ointment contains about 1.5 mg of NTG. The bioavailability of NTG from the NTG ointment varied widely even in the small pharmacokinetic study in normal volunteers (e.g., range 8% to 99% intersubject and as high as 40% to 77% intrasubject, with a mean absorption time of about 110 minutes and a range of 53 to 245 minutes--see Table 5.) For average bioavailability numbers the 375 mg dose of 0.4% NTG ointment delivers about 0.4 mg/hour, comparable to rates of systemic NTG delivery from NTG patches for angina. For the highest extremes of bioavailability the proposed dose delivers about 1.7 mg in the first hour, substantially higher than the usual antianginal dosages.

COMMENT: I believe that the failure of this development program lies not with an inappropriate regimen but with inadequate efficacy of NTG for this condition. The 0.4% BID regimen has been tested in three studies, produces a substantial rate of severe headaches, and has consistently failed to show substantial efficacy.

The estimates on the variability of NTG systemic variability above are likely low. As can be judged from the description of the dispensing, patients are likely to administer higher or lower doses than prescribed because of measuring error. In the two sites that were audited the DSI inspector found substantial overdosage by patients, as high as fourfold. I am concerned that a delivery rate of 1.7 mg or higher in the first hour could be dangerous in vulnerable patients and that the size of the safety database is too small to exclude such problems.

8.2 Drug-Drug Interactions

The sponsor did not perform any drug-drug interaction studies but relied upon the published literature regarding NTG. This approach is acceptable.

8.3 Special Populations

The sponsor did not study any special populations except both genders were adequately represented in the clinical trials. Blacks and the elderly are sparsely represented in the clinical studies (see Table 17).

COMMENT: NTG use has not been associated with varying efficacy or safety issues in either gender or specific ethnic groups. The elderly, who have a higher burden of chronic disease such as hypertension, coronary heart disease, and heart failure, may be a population for whom adverse effects of NTG may be more problematic.

8.4 Pediatrics

The Division granted a deferral of pediatric studies in a letter dated August 26, 2004, because the drug would be ready for approval in adults before studies in children would be completed. The Division also requested that the sponsor submit a general plan and timeline for their pediatric development program by December 27, 2004

8.5 Advisory Committee Meeting

This NDA has not been and is not planned to be discussed at an advisory committee meeting.

8.6 Literature Review

The sponsor provided a literature review of NTG and related nitric oxide donors used for the treatment of anal fissure. I searched Medline for references regarding NTG ointment use for treating anal fissure. In addition to references cited in the NDA expressing positive results for NTG ointment I found the following references raising questions about the efficacy of NTG ointment in anal fissure:

- A prospective, double-blind study published in 2004 randomized 48 patients to placebo, 0.2%, or 0.4% NTG ointment. (Weinstein, Halevy et al. 2004) The study found no benefit regarding healing or pain relief in treating patients suffering from an anal fissure with

NTG ointment in combination with stool softeners and sitz baths, compared to the same treatment without NTG ointment.

- A Cochrane review examined non-surgical therapy for anal fissure. (Nelson 2003) Excluding two studies with quality concerns, NTG ointment was not significantly better than placebo in curing anal fissure. This meta-analysis did not address pain relief.

8.7 Postmarketing Risk Management Plan

The sponsor did not propose a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

All three of the major clinical studies submitted to support this NDA fail to show a statistically significant and clinically meaningful benefit of NTG ointment in the relief of pain associated with chronic anal fissure. The first study, NTG 98-02-01, failed for its primary endpoint of fissure healing, but the sponsor interpreted some secondary analyses as suggesting a beneficial effect upon pain. The second study, NTG 00-02-01, showed a statistically significant result only when analyzed with a quadratic term included in the mixed effects regression model that was not specified in the protocol. Using a linear model the p value is 0.24 for 0.4% NTG ointment. The third study, CP125 03-02-01, showed a statistically significant effect ($p < 0.0498$) in a sponsor's analysis selectively apply last observation carried forward (LOCF) to some NTG patients discontinuing for headache. When LOCF is applied to all NTG patients discontinuing for headache as specified in the protocol, the p value is 0.12.

Study CP125 03-02-01 also has other weaknesses. The estimated magnitude of a benefit, if any, of NTG in relieving pain of anal fissure is small, e.g., a mean improvement of about 3 mm on a 100 mm visual analog scale even with the sponsor's liberal analysis. Other problems are excessive dropouts with NTG, greater acetaminophen use for headache in the NTG group, and benefit limited to one country.

These studies do not provide substantial evidence of efficacy of NTG ointment in relief of pain associated with chronic anal fissure.

The data supporting safety are also weak. The numbers of patients initially exposed (206) and completing (167) a typical treatment period with the regimen proposed to be marketed are low.

Only 19 of the latter patients were age 65 or older. The monitoring in the clinical trials also had some weaknesses: Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure so that effects upon blood pressure are known. The case report forms provided minimal information on the adverse events so that the severity and criticality of some events, e.g., tachycardia, is difficult to assess.

The Division sent the sponsor a discipline review letter dated December 10, 2004, summarizing the critical issues regarding efficacy and safety. The critical issues were the following, and I have summarized the sponsor's responses to them dated December 14, 2004, and my comments on the responses:

1. *The protocol says that imputation would be applied to subjects who withdrew for reasons of headache, but in the analysis of study 03-02-01, imputation was restricted to subjects whose headaches were attributed to study drug. How is this justified?*

The sponsor quotes the protocol section regarding AEs, which does specify a criterion that only headaches occurring within 30 minutes of NTG administration will be considered a NTG-related AE, and the protocol section on the primary analysis, which does not impose such a restriction. We consistently maintain that attributions of causality, such as the 30-minute limit, are futile and that the more appropriate approach is to include all headaches for the LOCF analyses. We believe that the protocol and our discussions with the sponsor are consistent with that position.

2. *Four subjects randomized to nitroglycerin ointment (NTG) in study 03-02-01 have no data post randomization. Seven more NTG subjects discontinued prior to 21 days. No placebo subjects did. What are the implications on the interpretability of the findings of study 03-02-01 of having the observed imbalance between groups in the number of subjects withdrawn in the first 21 days?*

The sponsor responded that the assertion that four subjects randomized to NTG have no data is not correct. The sponsor is neglecting to count the two subjects that were assigned randomization numbers but allegedly failed to start treatment. These subjects were identified by the sponsor in an earlier response and are accounted for in Table 20.

The sponsor goes on to claim that the generalized mixed-effects regression model supports validity regardless of missing data. The sponsor ignores the possibility that "The assumption of the model is that the data that are available for a given subject are representative of that subject's deviation from the average trend lines that are observed for the whole sample" is not true. The latter is an assumption, not a fact.

3. *What is the plausible clinical significance of a 3-mm mean difference in the anal pain visual analog scale, when this magnitude of effect is 13% of the placebo effect, and how does this difference balance against a high rate of withdrawal for headache and other adverse events?*

The sponsor responded that the agreement from the special protocol assessment was for a primary endpoint for rate of change, not for the mean difference. The sponsor does not consider

that this rate of change was not significant if the pre-specified analysis is followed. The sponsor also does not consider that confidence in this small effect is weakened by the withdrawals (as the Division warned the sponsor during discussions) and must be weighed in a risk-benefit analysis against the adverse effects. The sponsor also does not consider that the Division advised that the third study would have to show substantial benefit if it was to stand alone as a single significant study. The sponsor in its response does quote its selective analyses of data from the three studies, but these analyses are “not part of the agreed upon analyses” (i.e., not pre-specified.)

- 4. In study 03-02-01 one NTG patient withdrew because of dizziness, bradycardia, and extrasystoles and another withdrew because of tachycardia, both adverse events suggestive of systemic cardiovascular effects of NTG absorption. Your pharmacokinetic study documented about 50% bioavailability of NTG with wide variability ($\pm 30\%$). How well does your clinical safety database characterize the variability in systemic cardiovascular effects of NTG ointment, e.g., time course of vital signs post administration in patients and during adverse events? How much assurance does your clinical safety database provide of cardiovascular safety, particularly for patients with underlying cardiovascular disease? How do these potentially serious adverse effects balance against a minimal symptomatic benefit?*

The sponsor expresses dismay in its opening remarks that the Division is considering safety. Apparently the sponsor believes that filing as a 505(b)(2) transfers the burden of establishing safety to the Division: “Our NDA was filed as a 505 (b)(2) which we understand relies upon existing safety information, much of which is in the form of a very large database available to the Agency for NTG.” Regarding the two patients withdrawing because of possible cardiovascular events the sponsor qualifies the first as “moderate” bradycardia and second as no explanation for the recording of tachycardia. This lack of information about potentially serious adverse events remains disturbing. The sponsor provides estimates of plasma NTG levels that ignore the variability shown both in its PK study and in the clinical trials.

- 5. Only 19 patients aged 65 or older completed treatment with 0.4% NTG BID in your studies. Your proposed label suggests that ‘Clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.’ How does the exposure in your studies support safe administration in the elderly?*

The sponsor admitted that only 19 patients aged 65 or older completed treatment with 0.4% NTG BID. Its response is that “There are ample data available to the Agency on the safety of NTG in the elderly and other special populations.” This response ignores the problem that the variability in systemic availability from their product creates additional safety concerns.

9.2 Recommendation on Regulatory Action

I do not recommend approval of this application until the following deficiencies are addressed:

1. The sponsor must demonstrate substantial evidence of efficacy of NTG ointment in relieving pain from chronic anal fissure in a new trial of convincing statistical significance ($p < 0.01$) or two trials at the usual level of significance ($p < 0.05$).
2. For trials the primary endpoint analysis must be pre-specified operationally such that no variations are determined after any trial data are available. An analysis plan for secondary endpoints should also be pre-specified that preserves an overall alpha of 0.05 for all secondary analyses.
3. Randomization should be done centrally. Dropouts after randomization but prior to initiating treatment should be avoided entirely.
4. Patients should be followed for endpoint evaluation until the time of the primary endpoint evaluation regardless of discontinuing treatment. The handling of missing data must be unambiguously specified in the protocol.
5. A global assessment of pain (all pain, including headache and anal fissure pain) must be included in the evaluation.
6. For patients with tachycardia or bradycardia, dizziness, or lightheadedness, vital signs should be obtained preferably when the patient is symptomatic and, if abnormal, followed until the abnormality resolved. Detailed information must be collected regarding all serious adverse events corresponding to Medwatch reporting requirements.
7. Vital signs should be recorded around the time of estimated peak effect after chronic administration. To estimate intra-individual variability, these measurements should be repeated on a different day in a subset of patients. The administration of the study drug should be performed by the patient without special coaching.
8. Recruitment for any new trials should include reasonable representation of the elderly and patients with chronic diseases such as hypertension and heart failure.

9.3 Recommendation on Postmarketing Actions

Because I do not recommend approval I can not recommend postmarketing actions.

9.4 Labeling Review

Because I do not recommend approval I have not done a labeling review.

9.5 Comments to Applicant

The deficiencies listed in Section 9.2 should be communicated to the sponsor.

Appendices

9.6 Review of Individual Study Reports

9.6.1 Study CP125 03-03-01, A Study to Determine the Effect of CP125 Ointment on the Pain Associated with a Chronic Anal Fissure

9.6.1.1 Protocol, Amendment and Post Hoc Changes

The initial protocol for this study is numbered CP125 03-02-01 and dated April 2, 2003. This study was not amended. The NDA submission does not identify any post hoc changes to the protocol.

COMMENT:

- I note that the protocol states the planned study size as 150 while data from 193 subjects were analyzed. The NDA submission did not comment on this discrepancy. The sponsor explained in a letter that the protocol synopsis indicates that "at least 150 subjects" will be enrolled (I confirmed) and that the trial was proceeding rapidly so that it was difficult to tell investigators not to enroll subjects who had already started screening procedures. Note that randomization was done locally and not through a central randomization center or system.
- I discuss in the Results section the post hoc interpretations of variations in the data analysis that were not completely specified in the protocol.
- The study did not follow exactly the protocol description of study number assignments. I describe the variation in Section 9.6.1.2.8.1 Number of Subjects, Randomization, and Blinding.

9.6.1.2 Study Design

This was an international, multi-site, randomized, double-blind, placebo-controlled parallel group study.

9.6.1.2.1 Objectives

The primary objective was to determine the effect of NTG ointment vs. placebo on pain associated with anal fissure. Another objective was to determine the effect of NTG ointment on healing of anal fissure. The safety and tolerability of NTG ointment was to be elucidated, particularly with regard to headache.

9.6.1.2.2 *Inclusion and Exclusion Criteria*

The inclusion criteria were the following (note the qualifying entry criteria in 1 and 4 below):

1. single anal fissure
2. informed consent
3. aged 18-75
4. history of anal pain at least three days a week for at least 30 days, confirmed sentinel pile, visual analog score (VAS) =35 mm and historical categorical pain score of moderate or severe for each of 2 days prior to treatment
5. willingness to forego other anal treatment drugs during study
6. willingness to limit sitz baths to one per day
7. practicing birth control if female of child-bearing potential
8. willingness to provide blood and urine samples

The exclusion criteria were the following:

1. more than one anal fissure
2. fistula-in-ano
3. anal surgery within 30 days
4. any other experimental study within 30 days
5. lacking suitability to participate per investigator
6. positive urine screen for illicit drug
7. allergy to NTG or vehicle constituents
8. hypotension, hypovolemia, increased intracranial pressure, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis or tamponade, marked anemia, or closed angle glaucoma
9. receiving NTG by any route
10. pregnant or nursing female
11. anal abscess
12. inflammatory bowel disease
13. pelvic radiation
14. fixed anal stenosis
15. immunocompromise
16. unwillingness to discontinue PDE5 inhibitor

9.6.1.2.3 *Study Plan*

Patients were to be screened for eligibility over five days and then randomized to double-blind active treatment or matching placebo. Study medication was to be applied intra-anally every 12 hours as described in the next section. Patients were to record in a daily diary of the following:

- 24-hour average pain and pain on defecation on a visual analog scale (VAS)
- times when study medication was applied
- number of sitz baths
- headache start time, stop time, and severity
- time and number of acetaminophen tablets consumed
- all concomitant medications including fiber

Patients were to be treated for 56 days with clinic visits at days 7, 21, 35, and 56. Anal fissure healing was to be determined at each study visit by a trained observer blinded to other study aspects. Follow-up was to continue by phone every 3 months for 12 months.

9.6.1.2.4 Dosage, Duration, and Adjustment of Therapy

The ointment was to be applied about every 12 hours for 56 days. Patients were provided with a measuring device. The contents of the measuring device were to be delivered onto the tip of a finger covered with a finger cot. That finger was to be inserted into the anal canal up to the first interphalangeal joint and the ointment applied to the anoderm. No adjustments to therapy were specified.

9.6.1.2.5 Concomitant Therapy

Patients on dietary fiber supplements or stool softeners could continue them at their usual dose but new use was prohibited. Acetaminophen 650 mg PO could be used as rescue medication for a headache occurring within 30 minutes of NTG ointment use but not more than 8 doses during the first 21 days. Sitz baths were limited to one per day. Other NTG, NSAID, and aspirin (except low dose aspirin for cardiovascular prophylaxis) use was prohibited.

9.6.1.2.6 Efficacy Endpoints

9.6.1.2.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of change of the 24-hour average pain intensity over a 21-day treatment period. See the Statistical Considerations section below for more details on the analytic approach and handling of missing data. Patients were asked to record at bedtime their pain symptoms on a visual analog scale (VAS). The VAS was a 100 mm line marked "no pain" at the left end and "worst pain imaginable" at the right end. Patients were to complete two scales each bedtime, one for the average amount of pain experienced during the preceding 24-hour period and another for the amount of pain experienced during the last bowel movement.

9.6.1.2.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. Tertiary endpoints included rate of change of pain intensity over a 56-day treatment period, rate of change of pain intensity during the last bowel movement over the 21-day period, rate of change of pain intensity during the last bowel movement over the 56-day period, and complete healing over the 56-day period.

COMMENT: The need to use a statistical method, such as Holm's stepdown method, to maintain Type I error at 0.05 for the secondary endpoints was communicated to the sponsor in a letter dated May 16, 2003.

9.6.1.2.7 Safety Endpoints

Safety was evaluated through adverse events (AEs), routine safety labs, vital signs, physical examinations, and ECGs. Headache start time, stop time, and severity were to be recorded in the patient's daily diary.

9.6.1.2.8 *Statistical Considerations*

9.6.1.2.8.1 *Number of Subjects, Randomization, and Blinding*

The planned study size was 150 (75 per group). The sample size was calculated using a mixed-effects regression model, with type 1 error of 5%, power of 80%, residual variance of 102.53, projected placebo mean at 21 days of 24.95 and SD 18.61, and projected NTG ointment mean of 15.59 and SD 15.79. With these parameters 53 completer participants per group were estimated. A group size of 75 was selected to allow for dropouts.

Patients were randomized based on a computer-generated randomization schedule prepared by (b) (4). Randomization was stratified by center and balanced using permuted blocks of size 4. Blinded labeling of study drug and matching placebo (vehicle ointment without NTG) was prepared by (b) (4). The label included a tear-off portion having a concealed area containing the drug identity.

Principal investigators were to be assigned a three number identification code. Subject numbers were to be issued sequentially in the order subjects were enrolled starting at 001. The case report forms were to be numbered with the combination of the investigator code and sequential subject number, e.g., 301-001.

To check whether unblinding had occurred patients and investigators were to be asked verbatim the following questions (from page 36 [original numbering] of the protocol) on day 21±2:

- Patient: "During your participation in the study, which treatment do you think you received nitroglycerin ointment or placebo ointment?"
- Investigator: "Which treatment do you think the participant received during the study, nitroglycerin ointment or placebo ointment?"

COMMENT: See comments on numbers of patients in Section 9.6.1.1 Protocol, Amendment and Post Hoc Changes and on how patient numbers were really assigned and randomization done in Section 9.6.1.3.1.2 Good Practice, Monitoring, and Protocol Deviations.

9.6.1.2.8.2 *Analysis Cohorts and Missing Data*

The protocol does not define an analysis cohort. It states that "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." It states further that "for 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... 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."

COMMENT: This approach for insuring appropriate variance for last observation carried forward (LOCF) was suggested to the sponsor in a teleconference on March 20, 2003.

9.6.1.2.8.3 Primary Analysis

The primary outcome measure proposed was the rate of change of the 24-hour average pain intensity over a 21-day treatment period. The measure was to be tested as the linear component (slope) of the treatment-by-week interaction in a generalized mixed-effects regression model, with random intercept and linear time-trend, using SAS MIXED.

9.6.1.2.8.4 Secondary Analyses

Secondary analyses of rates of change also were to use the mixed-effects regression model as for the primary analysis. However, for the secondary analyses a quadratic term was to be added. Analysis of the secondary endpoint time to 50% improvement was to be tested using a "Cox log rank test."

COMMENT: The protocol does not specify how the secondary analyses will be adjusted for multiplicity.

9.6.1.3 Results

9.6.1.3.1 Conduct

9.6.1.3.1.1 Sites, Investigators, and Study Dates

Twenty-nine sites in five countries enrolled 193 patients: US (19%), Germany (13%), Israel (0.5%), Russia (41%), and Serbia (26%). The enrollment on the arms was balanced within countries with the exception of the US, in which 21 patients received placebo and 16 received NTG ointment. The first patient was enrolled on June 16, 2003, and the study was completed on December 16, 2003.

COMMENT: Two (024 with 20 patients and 041 with 16 patients) of the three largest sites had better than average results with NTG ointment. Eliminating them from the analyses eliminated the small benefit from NTG ointment found by the sponsor. I recommended to DSI to audit these sites. Both of them were located in Serbia.

9.6.1.3.1.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices. The sponsor audited three sites in Serbia and Montenegro, five sites in Russia, and one site in Germany. The sponsor closed site 043 in Russia after the first monitoring visit revealed a large number of protocol violations. Screening assessments were incomplete and no drug exposure, efficacy, or safety information was collected. The sponsor classified the four subjects (two per arm) at this site as withdrawn for administrative reasons.

Most of the other protocol deviations were minor other than a few documented in the next section regarding Disposition of Subjects. The most frequent deviation (74 placebo and 56 NTG) were study visits outside of the protocol-specified window. Inclusion/exclusion criteria not being met was reported in 17 instances for placebo patients and 20 instances for NTG patients. The most frequent of these deviations was a lab test result outside of the normal range (23 of the 37 instances). Noncompliance (<70% or >130% by weight or missed doses) was reported in 52 instances for placebo patients and 49 instances for NTG patients. Acetaminophen was used for headache by 24 placebo patients and 34 NTG patients.

Randomization was not done centrally but at each individual site. Study drug in blocks of four numbered sequentially was distributed to each site. The sites were to select the next available sequential number for the next patient randomized. One site (033) appears to have used a higher block prior to using a lower block and another site (035) appears to have assigned a block starting with the highest number and working down. For the highest subject number (296) for this block from site 035 the randomization date is reported as August 31 but the date of first treatment is reported as July 31—other dates in the data files are consistent with July 31. Two entries (block 13, subject 49, site 008; and block 82, subject 326, site 26) were assigned to patients but results for these patients are not reported. For the first the sponsor reported that the inclusion criteria were not met and the study drug was retrieved. For the second the sponsor reported that the entry was “reserved” for a patient but the patient was not enrolled because lab tests were incomplete and were not completed prior to enrollment closing. Both of these entries were NTG study drugs.

At about day 21 the patients and investigators were asked questions regarding whether the patient was receiving NTG ointment or placebo. The sponsor’s analysis of these questions is shown in Table 19: Sponsor’s Analysis of Unblinding Questions.

Table 19: Sponsor’s Analysis of Unblinding Questions

| Assessment | | Cellegesic NTG Ointment 0.4% | |
|---|------------------------|------------------------------|-----------|
| | | Placebo N=98 | N=89 |
| | | n (%) | n (%) |
| Subject: “During the study did you receive nitroglycerin ointment or placebo?” | Nitroglycerin Ointment | 64 (65.3) | 64 (71.9) |
| | Placebo | 19 (19.4) | 9 (10.1) |
| | Unable to Decide | 12 (12.2) | 9 (10.1) |
| | Missing Assessment | 3 (3.1) | 7 (7.9) |
| Investigator: “During the study do you believe the participant received nitroglycerin ointment or placebo?” | Nitroglycerin Ointment | 42 (42.9) | 56 (62.9) |
| | Placebo | 34 (34.7) | 12 (13.5) |
| | Unable to Decide | 19 (19.4) | 14 (15.7) |
| | Missing Assessment | 3 (3.1) | 7 (7.9) |

DSI audited two sites in Serbia. The DSI inspector judged data from both sites to be acceptable. The inspector noted minor problems at both sites with dosage (dosage exceeded probably because of inadequate instruction) and at one site with recordkeeping accuracy. At one site investigator records for patient dose compliance indicate that doses varied from 375mg by 20% or more at 44 visits of the total of 80 evaluation visits. At the other site the compliance was as high as 252%, 330%, and 397% in three patients.

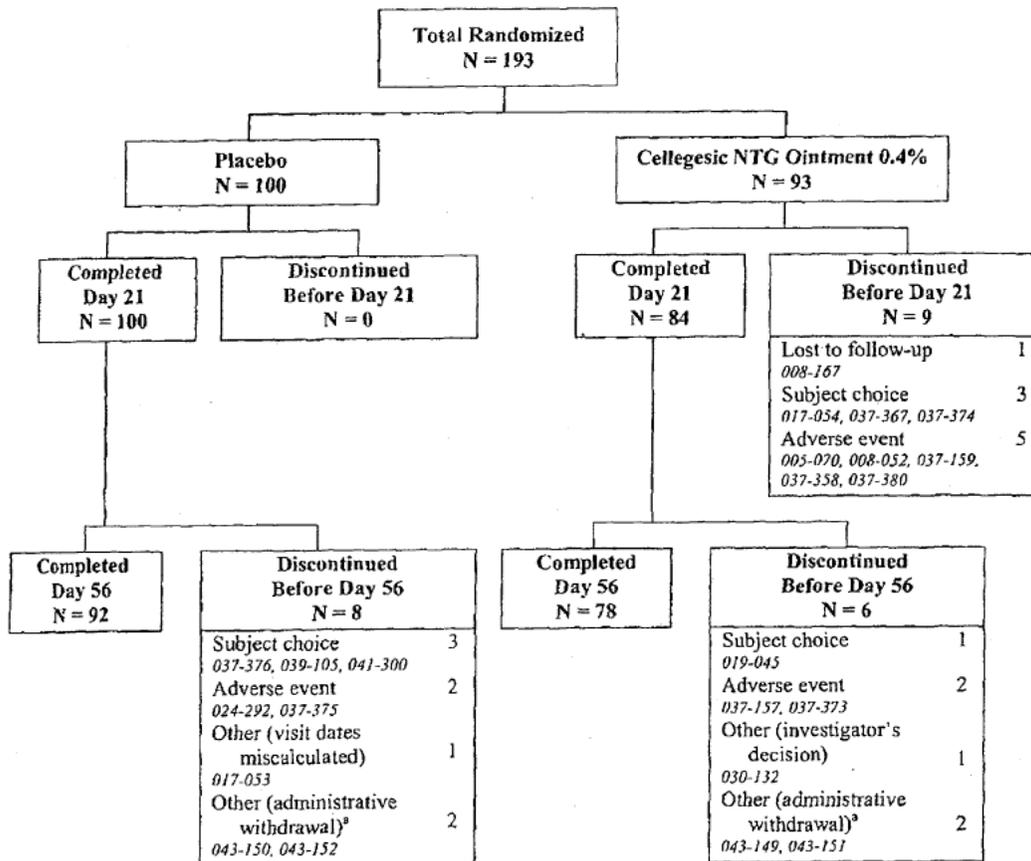
The DSI inspector asked the investigators why there was such a dramatic improvement in some subjects' pain, sometimes within 24 hours of enrollment. The investigators did not have any explanations other than they did see this happen and that it could be a placebo effect. .

COMMENT: The randomization was sloppy. Randomization at the site with a small block size increases susceptibility of breaking of the blinded allocation. There were at least 195 patients randomized rather than 193 as reported by the sponsor.

The analysis of the unblinding questions suggests that there was partial unblinding of the study, particularly from the appraisals by the investigators.

9.6.1.3.2 Disposition of Subjects

The sponsor's figure showing disposition of subjects is given in Figure 2.



* Subjects were withdrawn because the site was closed for administrative reasons.

Figure 2: Sponsor's Subject Disposition

My accounting of subject disposition differs from that shown in Figure 2. I count two more patients randomized to NTG as described in the last section and note that one of the patients discontinuing for "patient choice" prior to day 21 did so for increased anal pain. I also believe that it is crucial to show the accounting for the sponsor's primary analysis set of 187 patients and for data completeness. I show my accounting through day 21 in Table 20.

Table 20: Reviewer's Subject Disposition and Data Completeness to Day 21

| Category | Placebo | | NTG | |
|------------------------|---------|------------------|-----|------------------|
| | N | Subject IDs | N | Subject IDs |
| 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 |

| Category | Placebo | | NTG | |
|--------------------------------------|---------|-------------|-----|------------------|
| | N | Subject IDs | N | Subject IDs |
| 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

COMMENT: Note that, in addition to the two patients in each group excluded from the Russian site who failed an audit, 11 patients in the Cellagesic group discontinued before day 21 (the primary endpoint period) but none in the placebo group. (Two of these 11 patients do have diary data complete through day 21.) The Division cautioned the sponsor at a meeting on January 31, 2003, that a large number of dropouts would make interpretation of the study results impossible.

The sponsor's handling of these discontinuations is not entirely consistent with the protocol. The sponsor restricted using LOCF to patients who dropped out for headaches judged to be related to study drug. The protocol states that LOCF will be used for patients discontinuing for headache without qualifying the headache as related to study drug.

I am also concerned that the patient lost to follow-up and the two who discontinued for "subject choice" also had efficacy failure or adverse events. For the primary analysis LOCF must be used for all NTG patients discontinuing for headache as specified in the protocol.

9.6.1.3.3 Demographics and Baseline Characteristics

Demographics and selected baseline characteristics are shown in Table 21. The majority of the patients were white females under the age of 65. The findings on the baseline anal exam are shown in Table 22.

COMMENT: There do not appear to be any substantial demographic or baseline characteristic imbalances.

Table 21: Sponsor's Demographics and Baseline Characteristics

| Characteristic | | Value | Placebo (N=98) | Cellegesic NTG Ointment 0.4% (N=89) |
|---|-----------------------------|-------|-------------------|---|
| Sex, n (%) | Male | | 37 (37.8) | 30 (33.7) |
| | Female | | 61 (62.2) | 59 (66.3) |
| Race, n (%) | Caucasian | | 94 (95.9) | 84 (94.4) |
| | Black | | 1 (1.0) | 3 (3.4) |
| | Asian | | 0 (0.0) | 0 (0.0) |
| | Hispanic-American or Latino | | 3 (3.1) | 2 (2.2) |
| | Native American | | 0 (0.0) | 0 (0.0) |
| | Other | | 0 (0.0) | 0 (0.0) |
| Age n (%) | ≤ 45 years | | 34 (34.7) | 43 (48.3) |
| | 46-64 years | | 57 (58.2) | 38 (42.7) |
| | ≥ 65 years | | 7 (7.1) | 8 (9.0) |
| (years) | N | | 98 | 89 |
| | Mean (SD) | | 47.7 (10.67) | 47.7 (11.48) |
| | Median | | 49.0 | 47.0 |
| | Min - Max | | 20 - 70 | 25 - 76 |
| Weight (kg) | N | | 98 | 89 |
| | Mean (SD) | | 78.6 (15.49) | 77.5 (16.65) |
| | Median | | 76.5 | 76.0 |
| | Min - Max | | 50 - 120 | 44 - 128 |
| | Missing | | 0 | 0 |
| Height (cm) | N | | 98 | 89 |
| | Mean (SD) | | 168.3 (9.18) | 169.5 (8.96) |
| | Median | | 166.5 | 168.0 |
| | Min - Max | | 150 - 191 | 154 - 201 |
| | Missing | | 0 | 0 |
| Body Mass Index (kg/m ²) | N | | 98 | 89 |
| | Mean (SD) | | 27.76 (5.084) | 26.90 (5.096) |
| | Median | | 27.36 | 25.93 |
| | Min - Max | | 18.9 - 43.0 | 16.5 - 41.1 |
| | Missing | | 0 | 0 |
| Current Alcohol Use | Yes | | 25 (25.5) | 16 (18.0) |
| | No | | 73 (74.5) | 73 (82.0) |
| Current Tobacco Use | Yes | | 25 (25.5) | 16 (18.0) |
| | No | | 73 (74.5) | 73 (82.0) |

Table 22: Sponsor's Baseline Anal Exam Findings

| Characteristic | Value | Placebo | Cellegesic NTG |
|--|----------------------------|--------------|-------------------------|
| | | (N=98) | Ointment 0.4% (N=89) |
| Anal Fissure, ^a n (%) | Single Anal Fissure | 97 (99.0) | 89 (100.0) |
| | More than 1 Anal Fissure | 1 (1.0) | 0 (0.0) |
| | Absent | 0 (0.0) | 0 (0.0) |
| Fissure Features, ^{a,b} n (%) | Visible Fibers | 47 (48.0) | 54 (60.7) |
| | Indurated Edges | 69 (70.4) | 68 (76.4) |
| | Sentinel Pile | 97 (99.0) | 89 (100.0) |
| | Hypertrophied Anal Papilla | 42 (42.9) | 40 (44.9) |
| Fissure Length (cm) ^c | N | 98 | 88 |
| | Mean (SD) | 1.06 (0.774) | 1.08 (0.627) |
| | Median | 1.00 | 1.00 |
| | Min - Max | 0.3 - 5.0 | 0.2 - 4.0 |

^a Subjects had to have a single anal fissure and a sentinel pile to be eligible for enrollment.

^b Subjects are counted in all applicable categories.

^c Estimated length, not measured length.

9.6.1.3.4 Dosing

Compliance, assessed by weighing the study medication, was slightly higher in the placebo group. The percent of subjects who used from 70 to 130% of the required quantity was 84% in the placebo group and 72% in the NTG group.

9.6.1.3.5 Concomitant Therapy

More patients in the NTG group used acetaminophen (paracetamol) than in the placebo group as shown in Table 23.

Table 23: Sponsor's Concomitant Medications Taken by =5% of Subjects

| WHO Preferred Term | Placebo | Cellegesic NTG |
|--------------------------|-----------|-----------------------|
| | N=98 | Ointment 0.4% N=89 |
| | n (%) | n (%) |
| acetylsalicylic acid | 9 (9.2) | 6 (6.7) |
| diazepam | 6 (6.1) | 6 (6.7) |
| paracetamol ^a | 26 (26.5) | 36 (40.4) |

^a United States Pharmacopoeia Dictionary of U.S. Adopted Names and International Drug Names (USAN) name is acetaminophen.

Sitz bath use was similar in the two groups as shown in Table 24. The numbers of patients starting dietary fiber or stool softeners during the study was low, one patient in each group during the first 21 days and one additional patient in the NTG ointment group after day 21.

Table 24: Sponsor's Sitz Bath Use

| Time Period ^a | Statistics | Placebo (N=98) | Cellegesic NTG Ointment 0.4% (N=89) | P-value ^b |
|--------------------------|------------|-------------------|---|----------------------|
| Days 1 through 21 | N | 98 | 89 | 0.2031 |
| | Mean (SD) | 5.2 (7.74) | 4.4 (7.37) | |
| | Median | 0.5 | 0.0 | |
| | Min - Max | 0 - 21 | 0 - 26 | |
| Days 1 through 56 | N | 98 | 89 | 0.4986 |
| | Mean (SD) | 12.0 (19.77) | 10.3 (17.83) | |
| | Median | 1.0 | 0.0 | |
| | Min - Max | 0 - 56 | 0 - 64 | |

^a Summary statistics were calculated by using the total number of sitz baths recorded for each subject during the indicated time period.

^b P-values were calculated by using a Wilcoxon rank-sum test.

COMMENT: The greater use of acetaminophen in the NTG ointment group is another confounder of the relationship between NTG ointment use and symptomatic relief.

9.6.1.3.6 Primary Efficacy Endpoint

For the primary efficacy endpoint, rate of change of the 24-hour average pain intensity over a 21-day treatment period evaluated by a generalized mixed-effects regression model, the sponsor reports a P value of <0.0498 (Table 13 of the study report). The mean changes calculated by the sponsor are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale.

However, the sponsor's handling of some patients' data for its primary analysis is not consistent with the protocol specification. The sponsor did not use LOCF for two patients (005-070, 037-358) who discontinued due to headache. For another patient (037-380) the sponsor carried forward the last pain score prior to discontinuing study drug rather than using the pain scores recorded after discontinuing study drug. (See Table 20 for my accounting of subject disposition and data completeness to day 21.) Dr. Hung, the FDA statistical reviewer, performed analyses avoiding these analytic problems. The results of his analyses are shown in Table 25.

Table 25: Statistical Reviewer's Primary Efficacy Analysis – 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)

| # | Data Inclusion | Placebo (N=98) | NTG (N=89) | NTG - placebo in slope (± SE) | p- value |
|---|--|-------------------|---------------|----------------------------------|-------------|
| 1 | Sponsor's primary analysis: LOCF for discontinuation only due to drug-related headache | -31.0 | -34.6 | -0.29 ± 0.15 | 0.0498 |

| # | Data Inclusion | Placebo (N=98) | NTG (N=89) | NTG - placebo in slope (\pm SE) | p- value |
|---|---|-------------------|---------------|---------------------------------------|-------------|
| 2 | Same as 1 except using all available data for subject 037-380 | -31.0 | -34.5 | -0.26 \pm 0.15 | 0.0843 |
| 3 | LOCF for discontinuation due to all reasons except using all available data for 037-374 | -31.0 | -34.6 | -0.25 \pm 0.15 | 0.0943 |
| 4 | Same as 3 except also using all available data for subject 037-380 | -31.0 | -34.5 | -0.22 \pm 0.15 | 0.15 |
| 5 | Protocol-defined primary analysis: LOCF for discontinuation due to headache | -31.0 | -34.5 | -0.24 \pm 0.15 | 0.12 |
| 6 | Use all available data and do not impute missing data | -31.0 | -34.6 | -0.30 \pm 0.15 | 0.0489 |
| 7 | Delete post discontinuation data and do not impute missing data | -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

COMMENT: The analysis from Table 25 that matches the description of the primary analysis in the protocol and the discussions with the sponsor prior to the NDA submission is #5, with a p value of 0.12. I would argue that the more appropriate analysis is to use all available data, including post-study drug discontinuation data. The analysis corresponding to the latter is #4, with a p value of 0.15. Regardless, by the primary analysis this study fails to show efficacy of Cellegesic NTG ointment for relief of pain with anal fissure.

The evidence for efficacy of NTG ointment from this study is even weaker than the p value of 0.12 implies. This study is plagued by a high dropout rate only in the NTG arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21. The Division warned the sponsor that a high dropout rate would make this study uninterpretable. If one does a true ITT analysis, i.e., all randomized patients, and classifies the four patients whom the sponsor excluded from its analysis (excluding the two NTG patients from the Russian site who may be considered legitimate exclusions) as failures (i.e., zero slope pain curves), then the p value would be substantially worse than 0.12. Please see also the FDA statistician's review for a further discussion of the dropouts and their effect upon the interpretation of the study results.

9.6.1.3.7 Secondary Efficacy Endpoints

The one secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. By the sponsor's calculation there was no statistically significant difference between the two groups ($p < 0.295$).

The protocol defined four tertiary endpoints (although it did not specify how the analyses of them would be adjusted for multiplicity). Given the statistical insignificance of the primary and secondary endpoints, I did not re-analyze them. I've listed in Table 26 a summary of the sponsor's analyses of the tertiary endpoints.

Table 26: Reviewer's Summary of Sponsor's Tertiary Analyses

| Endpoint | Summary | P# |
|---------------------------|---|--------|
| Pain change for 56 days | NTG marginally better by sponsor's analysis | 0.0447 |
| Last BM* pain for 21 days | No significant difference | 0.0719 |
| Last BM* pain for 56 days | NTG marginally better by sponsor's analysis | 0.0306 |
| Healing at 56 days | Placebo 63% vs. NTG 69% † | 0.4166 |

*BM = bowel movement; †Data missing for 1 placebo, 6 NTG patients; # no multiplicity adjustment

COMMENT: The sponsor's secondary analyses are consistent with the primary endpoint results and do not suggest efficacy of NTG ointment. Even the results marginally statistically significant by the sponsor's report would not be with multiplicity adjustment or with including all cases and data rather than the sponsor's selective inclusion as with the primary analysis. Noteworthy is that neither pain nor healing were improved.

9.6.1.3.8 Subgroup Analyses

Because the sponsor's primary endpoint analysis is complex and produces a statistic that is hard to visualize, for subgroup analyses I used a simpler approach of examining the mean change in the pain scores at day 21 with missing data replaced by LOCF or, for patients dropping out for increased pain, an average increase of 25 (the increase for the one patient dropping out for increased pain with a recorded increased score.) For comparison I've listed the overall results for this statistic in Table 27. By the ranksum test the differences in changes in pain scores at day 21 are insignificant ($p = 0.58$).

Table 27: Reviewer's Mean Changes from Baseline to Day 21 in Pain Score

| Arm | N | Baseline | Change from Baseline | | |
|---------|----|----------|----------------------|----|--------|
| | | | Mean | SD | Median |
| Placebo | 98 | 54 | -31 | 22 | -34 |
| NTG | 91 | 55 | -32 | 25 | -35.5 |

COMMENT: The above analysis shows how little difference in pain scores is evident at day 21.

9.6.1.3.8.1 Region and Country

The mean changes from baseline to day 21 in pain score by country are shown in Table 28.

Table 28: Reviewer’s Mean Changes from Baseline to Day 21 in Pain Score by Country

| Country | Placebo | | NTG | |
|---------|---------|--------|-----|--------|
| | N | Change | N | Change |
| Germany | 12 | -28 | 13 | -12 |
| Israel | 1 | 6 | 0 | |
| Russia | 40 | -38 | 39 | -40 |
| Serbia | 26 | -25 | 25 | -36 |
| US | 21 | -29 | 16 | -21 |

COMMENT: Note that the only country with a substantial improvement in pain scores with NTG is Serbia. US patients fared better with placebo. Serbia had three sites, two of which showed substantial improvement with NTG.

9.6.1.3.8.2 Age and Gender

The mean changes from baseline to day 21 in pain score by age are shown in Table 29 and by gender in Table 30.

Table 29: Reviewer’s Mean Changes from Baseline to Day 21 in Pain Score by Age

| | Placebo | NTG |
|-------|---------|-----|
| ≤40 | -33 | -34 |
| 41-50 | -26 | -35 |
| 51-60 | -36 | -30 |
| >60 | -25 | -25 |

Table 30: Reviewer’s Mean Changes from Baseline to Day 21 in Pain Score by Gender

| | Placebo | NTG |
|--------|---------|-----|
| Female | -31 | -32 |
| Male | -31 | -32 |

COMMENT: There do not appear to be any significant differences in response by age or gender.

9.6.1.3.8.3 Race

The vast majority of patients were white (95%). There are two few patients of other race or ethnic groups to provide meaningful statistics on efficacy by race.

9.6.1.3.8.4 Other Subgroups

There are no other subgroups of particular interest.

9.6.1.3.9 Safety

9.6.1.3.9.1 Exposure

The exposure to NTG in this study was 89 initially, decreasing to 81 at 21 days, and 61 at 56 days. All dosing was the same.

9.6.1.3.9.2 *Serious Adverse Events*

9.6.1.3.9.2.1 Deaths

There were no deaths during the study.

9.6.1.3.9.2.2 Hospitalizations

One NTG and one placebo patient were hospitalized due to AEs. The NTG patient was a 69-year-old male with a history of T-cell lymphoma treated by surgery and chemotherapy. After treatment with NTG for 23 days he withdrew because of rectal pain. On day 46 he developed abdominal pain, then loose stools and pyrexia. On day 50 he was hospitalized with ascites and partial bowel obstruction due to an abdominal mass. The diagnosis was lymphoma.

9.6.1.3.9.2.3 Other SAEs

The only SAE in the NTG group was the one hospitalization described above.

9.6.1.3.9.3 *Withdrawals*

Seven NTG and two placebo patients withdrew because of AEs per the sponsor. The reasons for withdrawal of the NTG patients included headache in five (vs. no placebo patients) and burning sensation in two (vs. one placebo patient). One NTG patient (008-052) also had dizziness, bradycardia, and extrasystoles and another (037-380) had tachycardia.

Patient 008-52 who withdrew because of dizziness, bradycardia, and extrasystoles was a 54-year-old Hispanic female with a history of hypertension and dyspepsia taking atenolol/chlorthalidone (?) and Nexium. She developed headache and dizziness starting day 1 and the bradycardia and extrasystoles starting day 8, at which time she withdrew. The bradycardia and extrasystoles are recorded as ended by day 20. There are no other details on these AEs.

Patient 037-380 who withdrew with tachycardia was a 52-year old white female with a history of colon cancer and nephrolithiasis who developed headache and "mild" tachycardia on day 1 and withdrew on day 7. The heart rate and rhythm are not recorded.

COMMENT: The sponsor's analysis for withdrawals does not include patients who withdrew for increased anal pain or those who withdrew for "subject choice".

9.6.1.3.9.4 *Other Adverse Events*

Overall 81% of the placebo and 90% of NTG patients reported at least one AE. The most common AE was headache, reported by 67% of the placebo patients and 86% of NTG patients. More NTG patients reported severe headaches (34% vs. 3.4%), took medication for it (48% vs. 28%), and had longer symptoms (mean 8 hours vs. 4.3 hours). The second most common AE was upper abdominal pain, reported by 11% of placebo patients and 18% of NTG patients. Cardiac disorders were reported in one placebo and five NTG patients. In addition to the withdrawals for bradycardia and for tachycardia, one other NTG patient experienced bradycardia, one experienced multifocal ventricular extrasystoles, and one experienced "heart pain". There were no reports of hypotension or low blood pressure.

COMMENT: The headache rate was high in the placebo group, although even higher in the NTG group. The higher rate of cardiac symptoms in the NTG group suggests some effect of systemic absorption and bears scrutinizing in the other trials.

9.6.1.3.9.5 Vital Sign Changes

There were no significant changes in SBP or DBP, pulse, or temperature from day 0 to day 21 or day 56.

COMMENT: The protocol does not specify taking vital signs following administration of study drug, so changes at peak drug effect were not captured.

9.6.1.3.9.6 Laboratory Test Value Changes

There were no significant changes or differences between the two groups from screening to last visit for CBC, chemistry panel, and routine urinalysis values.

9.6.1.3.9.7 Electrocardiographic Changes

One NTG patient withdrew because of bradycardia and extrasystoles, the only abnormality considered "clinically significant". Between 72 and 82% of ECGs were considered normal at any time, and the rates of "not clinically significant" abnormalities in both groups decreased slightly from screening to last visit.

COMMENT: ECGs were only evaluated qualitatively and QTc and other interval measurements at peak drug effect were not done. Given the vast experience with oral and topical NTG, a thorough QTc study is not needed.

9.6.1.3.9.8 Events of Special Interest

The one event of special interest that occurred was headache as discussed above. Another event of special interest, hypotension, was not reported.

9.6.1.3.9.9 Safety Subgroup Analyses

The sponsor did not include subgroup analyses of AEs, e.g., by age, gender, race, etc., in the study report. They will be examined in the ISS.

9.6.1.4 Summary

9.6.1.4.1 Efficacy Summary

This study fails to demonstrate efficacy of NTG ointment for reducing anal pain in patients with anal fissure. By the protocol-specified primary analysis the difference in the rate of change in pain through day 21 compared to placebo is statistically insignificant ($p = 0.12$) even for a modified ITT analysis set excluding four randomized NTG patients. The study also failed to show a beneficial effect upon healing of anal fissure.

9.6.1.4.2 *Safety Summary*

NTG ointment produces headaches, particularly severe headaches, at rates exceeding placebo. NTG ointment also produces more GI symptoms, predominantly upper abdominal pain. There were two withdrawals for cardiac AEs which, while not alarming, have inadequate characterization to be completely reassuring about cardiac safety. The small size of this study precludes a definitive answer regarding cardiac safety.

9.6.1.5 Conclusions

This study does not support approval of NTG ointment for relief of pain of anal fissure.

9.7 **Line-by-Line Labeling Review**

Because I do not recommend approval of this application, I have not provided a line-by-line labeling review.

REFERENCES

- Nelson, R. (2002). "Operative procedures for fissure in ano." Cochrane Database Syst Rev(1): CD002199.
- Nelson, R. (2003). "Non surgical therapy for anal fissure." Cochrane Database Syst Rev(4): CD003431.
- Weinstein, D., A. Halevy, et al. (2004). "[A prospective, randomized double-blind study on the treatment of anal fissures with Nitroglycerin ointment]." Harefuah **143**(10): 713-7, 767, 766.

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/s/

Thomas Marciniak
12/17/04 08:20:37 AM
MEDICAL OFFICER



Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 4.29.02

FROM: Douglas C. Throckmorton, M.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvability of Nitroglycerin ointment (Cellegesic) for anal fissures

NAME OF DRUG: Nitroglycerin Ointment

TRADE NAME: Cellegesic

IND/NDA: 21-359

FORMULATION: Ointment for topical administration

RELATED APPLICATIONS: Multiple oral and topical preparations of nitrates.

APPROVED INDICATIONS: None

SPONSOR: Cellegy Pharmaceuticals, Inc.

DOCUMENTS USED FOR REVIEW:

1. Division of Scientific Investigations Review by Antoine El-Hage, Ph.D., dated 3.15.02.
2. Medical and Statistical Review by Stephan Fredd, M.D., and James Hung, Ph.D., dated 2.27.02.
3. Clinical Pharmacology and Biopharmaceutics Review by B. Nhi Nguyen, Pharm.D., dated 3.12.02.
4. Pharmacology Review by Anthony G. Proakis, Ph.D., dated 4.10.02.
5. Chemistry Review by William C. Timmer, Ph.D., dated 4.19.02.
6. NDA 21-359 volumes 4.011 and 4.012.

CONCLUSIONS

This memorandum represents the Secondary Medical Review and the Divisional Memorandum regarding the approvability of Cellegesic for the treatment of anal fissures. At this time this memorandum is submitted, the product has been withdrawn, and no action is necessary; the intent of this memorandum instead is to summarize the thinking of the Division at the time of the withdrawal. As discussed below, this application was considered not approvable. The deficiencies are discussed by discipline in the following paragraphs.

PHARMACOLOGY TOXICOLOGY

It is clear that nitroglycerin (NTG) is effective at relaxing the anorectal smooth muscle in animals, providing the basis for a possible effect in patients with anal fissures, where chronic spasm of the anal sphincter is posited to lead to tissue hypoxia, pain and poor wound healing. There is also an effect of NTG to cause vasodilation, although the relative contribution of this mechanism to possible healing is unknown. In rats, administration of nitroglycerin produced a dose-dependent reduction in anal pressures, with no evidence of the development of tolerance. Regarding the pharmacology, toxicology, carcinogenicity of nitroglycerin, the sponsor submitted the NDA under the provisions of section 505 (b)(2), and referenced the Agency's previous findings related to nitroglycerin. Here, while the literature suggests some animal toxicological findings (*e.g.*, mutagenesis in one bacterial strain, testicular tumors in rats) there is evidence that the systemic exposure following topical anal administration is substantially lower than that seen using currently approved topical nitrate creams for angina. No deficiencies related to the pre-clinical Pharmacology or Toxicology were identified.

MEDICAL/STATISTICAL

On the basis of extensive published literature suggesting a robust, albeit variable, effect of topical nitrates in promoting both healing and reduction in pain associated with anal fissures, the sponsor conducted two clinical trials in sequence.

The first trial, NTG 98-02-01, evaluated 360 patients with anal fissures, who were administered one of six doses of nitroglycerin (NTG) ointment or placebo. The primary endpoint of the study was anal fissure healing, and the sponsor failed to demonstrate a significant effect of Cellegesic compared with placebo. There was a nominally significant effect of Cellegesic to reduce the pain associated with the anal fissure when analyzed using a post-hoc statistical method.

On the basis of the secondary analysis, the sponsor conducted a second pivotal trial of NTG ointment, NTG 00-02-01, that randomized 229 patients to receive either placebo or NTG ointment (0.75 mg or 1.5 mg total dose per day). The primary endpoint of the trial was pain relief, assessed using a visual analogue scale (VAS) ranging from zero (no pain) to 100 (most severe imaginable). The protocol pre-specified a mixed regression model as the statistical analysis to be conducted on the ITT population for the primary endpoint. When this model was used, incorporating the parameters used in the first trial (98-02-01), no significant effect of Cellegesic on pain was demonstrated. While the incorporation of additional factors, including a quadratic effect of time and the effect of center, results in a nominally significant effect on pain, this analysis suggests an effect of Cellegesic on pain that is significant, at most for 1-2 weeks.

Unfortunately, there are no additional clinical benefits of the use of Cellegesic that were demonstrated (or strongly suggested) by the studies (see the Medical/Statistical review for details). For instance, no effect on anal fissure healing was demonstrated in either trial. There are also no available data on the possible effects of Cellegesic on the need for surgery for anal fissure (which is apparently the final procedure when necessary) or on any Quality of Life indices. The latter measure would be useful in defining the overall changes in functional status that are associated with the use of Cellegesic, and help to understand the balance between the proposed effects on the pain associated with anal fissures and the headache pain associated with the pharmacologic effect of nitroglycerin use.

The safety review raised no new issues of clinical safety relative to the extensive safety database available for topical nitrates. The major 'safety' issue that impacts the approvability decision is the need to understand the clinical consequences of the headaches caused by nitrates, as discussed above.

Based on the reviewed data, then, two Clinical/Statistical deficiencies were identified: insufficient evidence of effectiveness in the treatment of patients with anal fissures, and insufficient data on the relative balance between the potential therapeutic effect of Cellegesic on anal fissure pain and the documented headache pain resulting from systemic absorption of NTG.

CHEMISTRY AND MICROBIOLOGY

The drug substance is commercially available, as (b) (4), and consists of (b) (4) nitroglycerin (glyceryl trinitrate, NTG) in (b) (4). This mixture complies with the current USP monograph. The drug product is described in the Chemistry review (page 12 of 36) and consists of (b) (4) combined with white petrolatum, lanolin, propylene glycol, paraffin and sorbitan sequeolate. Per the review Chemist, the acceptance criteria are appropriate to ensure the identity, strength, quality, potency and purity of the drug product as formulated. The drug product is to be packaged with two unique container-closure systems: one a collapsible aluminum tube, the second a metered-dose pump. No issues related to this packaging were identified in the Chemistry review (see section II.6). Two microbiology-related tests of the drug product were conducted: anti-microbial effectiveness test and total aerobic microbial count. As the product is (b) (4).

On the basis of the submitted stability data, the approved shelf life for Cellegesic ointment is 24 months for the NTG ointment in the aluminum tubes and is 12 months for the NTG ointment packaged in the metered-dose pump.

The following deficiencies were noted in the Chemistry review of the NDA submission:

1. The retest date for the drug substance needs to be specified.
2. Regarding test (b) (4) the impurities in the quantitative analysis of the nitroglycerin ointment are reported with no acceptance criteria. One set of all-encompassing physico-chemical tests should be developed for the finished dosage form to function as regulatory specifications as well as stability specifications. The tests should include an assay that reports the percentage of drug substance as well as impurities/degradation products. A limit needs to be developed for each impurity, as well as for the total impurity limit. These limits apply to impurity testing of the drug substance, release testing after manufacture of the ointment, and stability of the drug product.
3. As a part of the stability program (In-Process Controls and Tests), a numerical acceptance criterion needs to be developed for the viscosity test.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor referenced the Agency's previous findings related to nitroglycerin under the provisions of section 505 (b)(2) for the clinical pharmacology of NTG. The clinical pharmacology of nitroglycerin has been described in other products using various dosage forms. These literatures adequately support an effect of NTG to dilate both arterial and venous systems and to relax smooth muscle. In the present submission a single study (98-02-02) of the absorption of nitroglycerin following intra-anal administration. Study 98-02-02 was conducted in 6 healthy subjects (4 men, 2 women) and measured concentrations of glyceryl trinitrate (NTG) and two active metabolites. As the full details validating the measurement of NTG concentrations was not submitted in the NDA, the Biopharm reviewer was unable to draw final conclusions about the pharmacokinetics of NTG in the 6 patients, but there was clear evidence of systemic absorption of NTG. The bioavailability of NTG was approximately 50% following single and multiple dosing (page 25 of 28). The lack of analytic validation was identified as a deficiency.

COMPLIANCE

At the time of this letter the inspections by the Office of Compliance have not yet been completed. Given the length of time anticipated until the sponsor can obtain and submit a complete response to the deficiencies noted above, the request for inspections has been withdrawn.

SUMMARY

The overall weight of the evidence suggests, but does not demonstrate, that Cellegesic has some effect to ameliorate the pain of anal fissures. This impression is based on a series of post-hoc analyses of the data from the two pivotal trials conducted by the sponsor; analyses that require clinical confirmation through the conduct of additional clinical trialing using pre-specified endpoints and methods of analysis. No data on more durable clinical endpoints (e.g., anal fissure healing, need for surgical intervention) are available to buttress the case for approval, although such data would be supportive and should be collected in any future trials. The case for approval of Cellegesic is made more difficult by the presence of a prominent side-effect of systemic nitrates: headache. Without direct data (e.g., Quality of Life scales), the sponsor has asserted that relief of anal fissure pain more than offsets the >50% observed rate of headaches in the patients taking Cellegesic. Such data would add materially to the case for approval. Finally, a number of issues have been raised by the Chemistry, Biopharmaceutics reviewers that must be addressed by the sponsor. Given the uncertainty of the clinical effects, and these deficiencies, this NDA submission cannot be approved without additional clinical data.

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/s/

Doug Throckmorton
4/29/02 01:43:17 PM
MEDICAL OFFICER

To: NDA 21359
From: Stephen Fredd, M.D and James Hung, Ph.D., HFD-110
Subject: Medical/Statistical Review

EXECUTIVE SUMMARY

Cellegy Pharmaceuticals submitted an NDA for nitroglycerin (NTG) ointment to relieve anal pain associated with anal fissures. Based on findings in the literature that NTG ointment relaxed the anal sphincter that could lead to anal fissure healing and relief of associated anal pain, the sponsor completed study NTG 98-02-01. The primary endpoint of that study was anal fissure healing. While that endpoint was NS, the secondary endpoint of relief of anal pain suggested a statistically significant effect in a linear mixed effects model for 0.4% BID NTG ointment compared to placebo. To prospectively test the pain relief hypothesis generated by that study, the sponsor performed study NTG 00-02-01. The primary hypothesis of efficacy was to be "tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects)." Using different parameters in a quadratic mixed effects model post-hoc, the sponsor found that NTG 0.4% BID average pain (primary endpoint) results were significantly different from placebo on linear trend and quadratic trend. The FDA statistician, Dr. Hung, using the linear model in the mixed effects model to evaluate the rate of change over time, as specified in the protocol and as used in the first study, found no significant difference for either active treatment group compared to placebo. Therefore using the mixed effects model with the methodology employed in the first study, the second study, the only confirmatory study provided, did not establish a significant difference between active drug and placebo.

Since the mixed effects model with the quadratic term gave somewhat different results, a hypothesis that the results differed over time was considered. To study this, Dr. Hung analyzed the rate of change in each weekly time period. For average pain, there seemed to be a difference in the rate of change for the 0.4% NTG group compared to placebo in the first week, but this was not sustained through the 56 days of treatment. At best there might have been a transient statistical difference, but even if this was the case, it would not translate into a meaningful clinical benefit for the patient since no benefit for NTG ointment could be found at the end of 56 days of therapy. In analyses of total pain relief or a difference in pain relief at the end of therapy, no differences comparing the active groups to placebo were found.

Importantly there were a large number of patients on active drug who developed headache. The headache was severe enough to lead to dropout in patients treated with NTG ointment, and those who remained in the study often required analgesic therapy. Headache should be considered a confounding element in the analysis of efficacy, since it led to more dropouts in the active treatment groups compared to placebo and might have influenced the anal pain results recorded by those patients who experienced headache on NTG ointment. Since no significant benefit on relief of anal pain was found in these clinical studies, and pain in the form of headache would be associated with NTG ointment treatment, a not approvable action is recommended

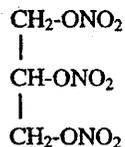
I. INTRODUCTION AND BACKGROUND

On June 22, 2001 Cellegy Pharmaceuticals submitted an NDA for the use of nitroglycerin ointment (NTG) 0.2% and 0.4% to relieve pain associated with an anal fissure. The sponsor stated that there have been literature reports supporting the use of nitroglycerin ointment to treat anal fissures and use of currently available NTG products for such off label use. The proposed dose for Cellegy's product was 1.5 to 4.5 mg. The original NDA contained the results of one adequate and well-controlled study (NTG 98-02-01) in volumes 1.2 and 1.16-1.27. The application was amended on October 24, 2001 with the submission of all case reports forms per this reviewer's request. On November 30, 2001 the results of a second adequate and well-controlled study (NTG 00-02-01) was submitted. Datasets from that study were made available to the reviewers on 1/22/02.

II. CLINICALLY RELEVANT INFORMATION re CHEMISTRY AND NON-CLINICAL PHARMACOLGY AND TOXICOLGY

A. CHEMISTRY

The active ingredient is nitroglycerin (1,2,3-propanetriol trinitrate) with the following structural formula:



The ointment is provided in 0.2 and 0.4% concentrations, and is formulated with propylene glycol in a base of lanolin, sorbitan sesquioleate, parafin wax and white petrolatum. A device and a metered dose dispenser are provided to measure out 374 mg of the ointment per dose. This provided 0.75mg per dose of the 0.2% formulation, and 1.5mg of the 0.4% formulation. The proposed treatment is for BID or TID applications of the ointment for two weeks after anal pain is gone or the anal fissure has healed. According to the proposed labeling, the treatment may be initiated with the 0.2% concentration, but after two weeks if the pain is not alleviated the 0.4% concentration should be used.

See Chemistry review.

B. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

The sponsor notes that the proposed doses of 1.5mg to 4.5mg daily are lower than generally used doses of NTG for angina, however it should be noted that administration rectally decreases first pass metabolism and increases systemic bioavailability of an administered dose. Available literature was pharmacology and toxicology was provided, and skin sensitivity tests with the final product and vehicle were performed.

See Pharmacology review.

III. HUMAN PK AND PD

Study NTG 98-02-02 was a three-way, three period, open PK study of the 0.2% NTG formulation and IV NTG (0.01mg/min constant rate infusion for 30 minutes) in 6 normal subjects (4 males, 2 females), aged 25 to 45 years. Single and multiple dose administrations were studied. The sponsor provided the results as follows:

Table 2: Mean Values ± S.D. for Primary Pharmacokinetic Parameters for Intra-anal Application of 0.2% NTG Ointment versus i.v. Infusion: All Subjects (Protocol 98-02-02)

| Bioavailability * (F) | | Mean Absorption Time (min) | |
|---|-------------------|-------------------------------|------------|
| Treatment Phase | | Treatment Phase | |
| I | II | I | II |
| 0.46 (± 0.28) | 0.47 (± 0.31) | 108 (± 59) | 110 (± 69) |
| AUC* for Arterial Plasma NTG; Single and Multiple Dose 0.2% NTG Ointment | | | |
| Treatment Phase I (Single) | | Treatment Phase II (Multiple) | |
| 41.3 (± 18.9) | | 41.8 (± 8.8) | |
| Ratio of AUC(m) ³ Values (Treatment Phase II/Treatment Phase I) for 1,2- and 1,3-ODN | | | |
| 1,2-glyceryl dinitrate | | 1,3-glyceryl dinitrate | |
| 1.00 (± 0.57) | | 3.36 (± 2.44) | |
| Ratio of AUC(m) ³ Values (1,2-glyceryl dinitrate/ 1,3-glyceryl dinitrate) | | | |
| Treatment Phase III | Treatment Phase I | Treatment Phase II | |
| 8.54 (± 2.67) | 5.41 (± 2.51) | 1.84 (± 1.05) | |
| Clearance ^d of NTG in Treatment Phase III (L/min) | | | |
| 7.0 (± 3.6) | | | |

$$F = \frac{AUC_{oral} \times Dose_{iv}}{AUC_{iv} \times Dose_{oral}}$$

where AUC_{oral} and AUC_{iv} were the areas under the curve following intra-anal application and infusion, respectively.

* AUCs up to 270 min (Treatment Phase III) and 480 min (Treatment Phases I and II).

^b AUC(m)³ = Area under the plasma level versus time curve for the mean values.

^d Calculated as Dose_{iv}/AUC_{iv}.

NOTE: Treatment Phase I = Single Dose
Treatment Phase II = Multiple Dose
Treatment Phase III = i.v. Infusion

Headache was reported in 5 out of 6 subjects, and 1 subject had two abnormal urinalyses that resolved 17 days later.

The sponsor summarized the published literature relevant to the pharmacodynamics of NTG. They note that NTG releases NO that leads to smooth muscle relaxation and also has CNS and peripheral nervous system effects. Onset and duration of action of various NTG doses and routes are provided by the sponsor in the following chart:

| Dosage Form | Dosage | Onset of Action | Duration of Action |
|-------------------------------|--|-----------------|--------------------|
| i.v injection | 5 to 10 µg/min for 3 to 5 min | 1 to 2 min | 3 to 5 min |
| Sublingual tablets | 0.3 to 0.6 mg/tablet | 1 to 3 min | 10 to 30 min |
| Translingual spray | 0.4 to 0.8 mg/spray | 2 to 4 min | 10 to 30 min |
| Oral extended release tablets | 2.5-9 mg/tablet 2 to 4 times daily | 20 to 45 min | 4 to 8 hours |
| Topical ointment | 2% 1.25 to 5 cm (6 to 30 mg NTG applied every 4-8 hours) | 30 to 60 min | 3 to 6 hours |
| Transdermal patch | 1 disc (2.5-15 mg) every 24 hours | 30 to 60 min | 4 to 8 hours |

Adapted from Robertson and Robertson, 1996

The direct application of NTG to the internal anal sphincter results in a relaxation of that sphincter measured by anal manometry. Maximal anal resting pressure(MARP) has been studied by multiple investigators. Lund and Scholefeld, Lancet, 1997, 349:11-14 Compared manometry results 20 minutes before and 40 minutes after 0.5g NTG and placebo. There was a significant decrease in MARP in the NTG treated patients, but not in the placebo treated patients. Ciccaglione et al, DDS, vol.45 #12, 12/2000. pp.2352-2256 compared 0.2% NTG and 2%NTG on MARP over an 8 week period and found significant and comparable reductions from baseline in MARP for both concentrations that continued throughout the 8 week treatment period. Schouten et al, Gut 1996; 39; 465-469 determined that the onset of MARP reduction was within 5 minutes after NTG application and lasted 41 minutes. The pressure drop was associated with an increase in anodermal blood flow. While tolerance is a known problem with NTG actions, the sponsor suggests that this may not be as much of a problem with NTG action on the internal anal sphincter. Noting the published studies of Munzel et al, JCI, 1995; 95:187-194 suggesting that endothelium-free aortic tissue demonstrated less NTG tolerance led to the idea that the internal anal

sphincter (IAS) which lacks an endothelial layer might also exhibit less NTG tolerance. Wang et al, Br. J.Pharm, in press and Grayson et al, data developed by Cellegy pharmaceuticals, demonstrated that high dose NTG given frequently to rats did not lessen the MARP lessening over time, and isolated IAS rat smooth muscle did not show less cGMP levels over time. The sponsor also points to the results of the clinical studies to support the hypothesis that tolerance does not develop to NTG when it is applied repetitively to the IAS as would have been expected.

See Biopharmaceutics review.

IV. DESCRIPTION OF CLINICAL DATA

Two controlled studies were provided to support the benefit of NTG ointment to heal anal fissures and to relieve the pain of anal fissures..

NTG 98-02-01 was a randomized, multicenter controlled study in 360 patients to evaluate the safety and efficacy of 6 doses (0.75, 1.1, 1.5, 2.3, 3.0, and 4.5 mg) of NTG ointment versus placebo given daily for 56 days or until fissure healing. The primary endpoint was anal fissure healing. Secondary endpoints were relief of anal fissure pain and safety.

Study NTG 00-02-01 was a randomized, multicenter controlled study of two doses (7.5 and 1.5 mg) of NTG ointment versus placebo in 229 patients with anal pain due to fissures. The "primary outcome endpoint" was relief of pain associated with the fissure. Secondary endpoints were time to anal fissure healing, quality of life, and safety.

A literature review of controlled studies evaluating the use of NTG ointment in the healing and relief of pain was also provided.

V. CLINICAL AND STATISTICAL REVIEW

STUDY NTG 98-02-01: A Study to Determine the Nitroglycerin Ointment Dose and Dosing Interval That Best Promote the Complete Healing of Chronic Anal Fissures.

The protocol was finalized on May 18, 1998, and amended on August 6, 1998 and November 5, 1998. The study was conducted between July 29, 1998 and September 15, 1999 by 18 investigators at 18 centers.

The protocol stated that a minimum of 360 adult patients with chronic anal fissures would be randomized to one of eight treatments: placebo, 0.1%NTG, 0.2%NTG, 0.4%NTG given BID, and placebo. 0.1%NTG, 0.2%NTG, 0.4%NTG given TID for 56 days or until the fissures were healed. The total daily dose of NTG to be applied was 0.75 mg, 1.1 mg, 1.5 mg, 2.3 mg, 3.0 mg and 4.5 mg. A computer generated randomized program was to be employed, and the study was double-blind by design.

The primary endpoint was complete anal fissure healing. The rate of recurrence 4 weeks after healing was also to be determined. Secondary endpoints were relief of anal pain (not required for admission to the study) and safety. To maintain the blind, the investigator was not to ask about headache while evaluating fissure healing.

The sample size was based on estimates of placebo and NTG anal fissure healing (8% and 68% respectively) from the literature where 0.2%NTG ointment was used. The sample size estimate was also controlled for the effects of 6 primary statistical comparisons. With 36 patients per group it was estimated that a healing rate difference of 43% could be detected.

Regarding pain assessments, the protocol specified use of a visual analog scale (vas) from 0-100 with 0 being no pain and 100 the most severe pain. Three pain estimates were to be made in a diary each day; the average intensity, the worst intensity, and the intensity during defecation. For patients whose fissure healed, the study evaluations were terminated. Statistically it was recognized that the unequal numbers of evaluations due to dropouts and healing would produce a highly unbalanced design. Rather than a mixed-model ANOVA, the sponsor proposed use of mixed-effects regression models without prespecifying a particular model.

For entrance male or female patients 18 years of age or older had to have an anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Exclusion criteria included fistula-in-ano, fissures associated with anal surgery within 30 days of enrollment, class IV cardiovascular disease especially hypotension, pregnant or nursing female, anal abscess, IBD, or requiring NSAID or other pain medication. It was noted that headache occurring during the study could be treated with acetaminophen 650 mg q 6h for up to three doses daily.

The schedule of procedures was as follows:

| | Treatment Days | | | | | | |
|--------------------------|---------------------|-----------------|------------------|------------------|------------------|------------------|----------------------------|
| | -1 Base- line | 1 | 14 | 28 | 42 | 56 | 4 Week Follow -up |
| | | TREATMENT PHASE | | | | | |
| History | X | | | | | | |
| Physical Examination | X | | | | | X | |
| Anal Exam | X ^a | | X ^{a,b} | X ^{a,b} | X ^{a,b} | X ^{a,b} | X |
| Hematology | X | | | | | X ^a | |
| Clinical Chemistry | X | | | | | X ^a | |
| Urinalysis | X ^c | | | | | X ^a | |
| Vital Signs | X | | X | X | X | X | X |
| Vital Signs 10 and 20min | | X ^d | | | | | |
| Review Adverse Events | X | X | X | X | X | X | X |
| NTG Application | | X | | | | | |
| Visual Analog Scales | X ^e | X ^e | X ^e | X ^e | X ^e | X ^e | |
| VAS Intensity | | | | | | | |

- a) Patient removed from study when healing complete at which time all Day 56 studies (physical examination, clinical chemistry and urinalysis) should be obtained and patient instructed to return in one month for follow-up.
- b) A digital/anoscopic examination may be performed, as is the Investigator's standard of practice.
- c) Including pregnancy test on all pre-menopausal females.
- d) Blood pressure and pulse determined at indicated times following first application of NTG.
- e) VAS each evening for average pain intensity for the day, the maximum pain intensity that day and the pain intensity at most recent defecation.

The 8/6/1998 protocol amendment involved details of administration of the ointment to the anus. The 11/5/1998 amendment provided for an open-label treatment period for those patients who completed the double-blind study but whose fissure had not healed.

The study was performed at 18 centers and involved 304 subjects, 93 of these entered the open-label evaluation phase.

The active drug was Nitroglycerin (NTG) in an ointment composed of propylene glycol, lanolin, white petrolatum, parafin wax and sorbitan sesquioleate. Placebo contained the same ingredients minus the NTG. The numbers of patients randomized to each treatment are provided in the following chart.

| RX daily dose | Placebo BID | NTG 0.75mg | NTG 1.1mg | NTG 1.5mg | Placebo TID | NTG 2.3mg | NTG 3.0mg | NTG 4.5mg |
|---------------|-------------|------------|-----------|-----------|-------------|-----------|-----------|-----------|
| N | 34 | 39 | 39 | 38 | 36 | 37 | 39 | 42 |

The sponsor provided some baseline demographic characteristics (confirmed by the FDA reviewer) as follows:

Table 3: Demographic and Baseline Characteristics: ITT Population
(Study NTG-98-02-01)

| | Placebo ^a (N=70) | | NTG ^b (N=234) | | Overall Total (N=304) | |
|--------------------|--------------------------------|--------|-----------------------------|--------|--------------------------|--------|
| | n | (%) | n | (%) | n | (%) |
| Sex | | | | | | |
| Male | 39 | (55.7) | 127 | (54.3) | 166 | (54.6) |
| Female | 31 | (44.3) | 107 | (45.7) | 138 | (45.4) |
| Race | | | | | | |
| Caucasian | 58 | (82.9) | 189 | (80.8) | 247 | (81.3) |
| Black | 7 | (10.0) | 18 | (7.7) | 25 | (8.2) |
| Asian ^c | 4 | (5.7) | 9 | (3.9) | 13 | (4.3) |
| Hispanic | 1 | (1.4) | 17 | (7.3) | 18 | (6.0) |
| Native American | 0 | (0.0) | 1 | (0.4) | 1 | (0.3) |
| Age (years) | | | | | | |
| ≤45 | 48 | (68.6) | 136 | (58.1) | 184 | (60.5) |
| 46-64 | 13 | (18.6) | 76 | (32.5) | 89 | (29.3) |
| ≥65 | 9 | (12.9) | 22 | (9.4) | 31 | (10.2) |
| N | 70 | | 234 | | 304 | |
| Mean | 44.13±14.62 | | 43.59±13.40 | | 43.71±13.67 | |
| Range | 23.00-81.00 | | 19.00-81.00 | | 19.00-81.00 | |
| Median | 41 | | 42 | | 42 | |
| Weight (kg) | | | | | | |
| N | 70 | | 229 | | 299 | |
| Mean | 173.4±49.92 | | 179.5±46.10 | | 178.1±47.00 | |
| Range | 106.0-415.0 | | 101.0-350.0 | | 101.0-415.0 | |
| Median | 167 | | 175 | | 175 | |
| Missing | 0 | | 5 | | 5 | |
| Height (in) | | | | | | |
| N | 70 | | 230 | | 300 | |
| Mean | 66.80±4.37 | | 67.48±4.04 | | 67.32±4.13 | |
| Range | 56.00-76.00 | | 57.00-80.00 | | 56.00-80.00 | |
| Median | 67 | | 68 | | 67.5 | |
| Missing | 0 | | 4 | | 4 | |

- ^a Includes all subjects receiving placebo (b.i.d. and l.i.d. combined).
- ^b Includes all subjects receiving ointment containing any concentration of NTG (b.i.d. and l.i.d. combined).
- ^c Seven subjects of Asian race were listed incorrectly as "other" in database, but are included here.

Withdrawals were outlined by the sponsor as follows:

| Patient Status | Patients Randomized | | | | | | | | Total n(n) |
|--------------------------------------|------------------------|-------------------------|-------------------------|-------------------------|------------------------|-------------------------|-------------------------|-------------------------|---------------|
| | Placebo NID n(n) | 0.1% NTG NID n(n) | 0.2% NTG NID n(n) | 0.4% NTG NID n(n) | Placebo TID n(n) | 0.1% NTG TID n(n) | 0.2% NTG TID n(n) | 0.4% NTG TID n(n) | |
| Randomized (N) | 34 | 38 | 39 | 38 | 36 | 37 | 38 | 42 | 304 |
| Completed Study | 29 (85.29) | 22 (58.41) | 29 (74.36) | 32 (84.21) | 32 (88.89) | 33 (89.19) | 34 (87.18) | 30 (71.43) | 241 (79.29) |
| Early Termination | 5 (14.71) | 17 (43.59) | 10 (25.64) | 6 (15.79) | 4 (11.11) | 4 (10.81) | 4 (10.82) | 12 (28.57) | 63 (20.72) |
| Reasons for Early Termination | | | | | | | | | |
| Inadequate Response | 0 (0.00) | 1 (2.56) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (2.70) | 0 (0.00) | 0 (0.00) | 2 (0.64) |
| Adverse Event | 0 (0.00) | 1 (2.56) | 2 (5.13) | 1 (2.63) | 1 (2.78) | 2 (5.41) | 0 (0.00) | 4 (14.29) | 13 (4.28) |
| Protocol Violation | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Patient Non-Compliance | 1 (2.94) | 4 (10.26) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (2.56) | 0 (0.00) | 6 (1.97) |
| Patient Choice | 1 (2.94) | 8 (20.51) | 2 (5.13) | 4 (10.53) | 1 (2.78) | 1 (2.70) | 3 (7.49) | 4 (14.29) | 28 (9.21) |
| Lost to Follow-up | 1 (2.94) | 3 (7.49) | 5 (12.82) | 1 (2.63) | 2 (5.56) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 12 (3.95) |
| Other | 0 (0.00) | 0 (0.00) | 1 (2.56) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (2.56) | 0 (0.00) | 2 (0.64) |
| Randomized (N) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Completed Study | 0 (0.00) | 1 (2.56) | 1 (2.56) | 1 (2.63) | 1 (2.78) | 1 (2.70) | 0 (0.00) | 1 (2.38) | 6 (85.71) |
| Early Termination | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (2.54) | 0 (0.00) | 1 (14.29) |
| Reasons for Early Termination | | | | | | | | | |
| Inadequate Response | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |

| Treatment Group Subject Number | Age (yrs) | Adverse Event (Primary Term) | Study Day of Onset ^a | Severity | Relationship to Study Drug ^b | Duration of Therapy (Days) |
|-----------------------------------|--------------|----------------------------------|------------------------------------|-----------------------|--|----------------------------------|
| 0.1% NTG b.i.d. | | | | | | |
| 315121 | 55 | Respiratory disorder | 14 | Moderate | None | 35 |
| | | Headache ^c | 2 | Severe | Possibly | 35 |
| | | Flu syndrome | 14 | Moderate | None | 35 |
| 0.2% NTG b.i.d. | | | | | | |
| 315104 | 29 | Dizziness ^d | 2 | Moderate | Possibly | 5 |
| | | Palpitation ^d | 2 | Moderate | Possibly | 5 |
| 322146 | 24 | Rectal disorder ^e | 8 | Severe | None | 10 |
| 0.4% NTG b.i.d. | | | | | | |
| 317115 | 72 | Headache | 2 | Mild | Possibly | 197 ^f |
| | | Nausea | 2 | Mild | Possibly | 197 |
| | | Pruritus | 27 | Moderate | Possibly | 197 |
| | | Accidental injury ^{e,d} | 48 | Severe | None | 197 |
| Placebo t.i.d. | | | | | | |
| 323107 | 41 | Headache ^d | 1 | Moderate | Related | 12 |
| 0.1% NTG t.i.d. | | | | | | |
| 317114 | 41 | Headache ^d | 1 | Severe | Possibly | 5 |
| | | Vomiting ^d | 1 | Severe | Possibly | 5 |
| | | Hypertension ^d | 1 | Moderate | Possibly | 5 |
| 323102 | 71 | Vertigo ^d | 2 | Moderate | Possibly | 8 |
| 0.4% NTG t.i.d. | | | | | | |
| 315105 | 26 | Headache ^d | 1 | Severe | Possibly | 3 |
| 317127 | 35 | Nausea | 1 | Mild | Possibly | 39 |
| | | Headache | 1 | Severe | Possibly | 39 |
| | | Headache | 4 | Severe | Possibly | 39 |
| | | Headache | 21 | Severe | Possibly | 39 |
| | | Headache ^d | 24 | Severe | Possibly | 39 |
| | | Hypernatremia | 39 | Mild | None | 39 |
| | | 317138 | 37 | Headache ^d | 1 | Severe |
| 319108 | 21 | Vomiting ^d | 1 | Moderate | Possibly | 15 |
| | | Sweating ^d | 1 | Moderate | Possibly | 15 |
| | | Headache ^d | 1 | Severe | Related | 6 |
| 323101 | 50 | Nausea ^d | 1 | Severe | Related | 6 |
| | | Headache ^d | 1 | Severe | Related | 9 |
| 323101 | 50 | Sweating ^d | 1 | Moderate | Possibly | 9 |
| | | Anxiety ^d | 2 | Moderate | Possibly | 9 |
| 323111 | 29 | Headache ^d | Unknown ^f | Moderate | Related | 11 |

^a Relative to start of therapy.

^b Based on investigator's assessment.

^c Serious adverse event.

^d Subject discontinued therapy due to this adverse event.

^e Subject 317115 discontinued the study due to a broken hip on 3/06/99. The clinical summary page of the CRF was completed on 9/22/99.

^f The first day of study drug administration for Subject 323111 was April 20, 1999. The onset of headache was an unknown date in April, 1999.

The chart above lists 13 patients as having terminated early for an adverse event, but the patient listing of adverse events leading to early termination (volume 1.21,p1711-1713) lists 14 patients. Subject 314120 was assigned to 0.2% NTG TID, and was listed in the "other" category withdrew after 27 days of treatment for increasing anal pain due to the fissure.

A review of case report forms for patients without any pain data, only baseline pain data or less than 7 days of pain data revealed in this reviewer's judgment 9 additional patients withdrawn for adverse events:

- 0.1% NTG TID patient 314105 for anal surgery.
- 0.1% NTG TID patient 315113 for anal pain necessitating surgery,
- 0.2% NTG BID patient 322112 for headache,
- 0.2% NTG TID patient 310101 for headache and vertigo,
- 0.2% NTG TID patient 317130 for headache,
- 0.4% NTG TID patient 317117 for headache,
- 0.4% NTG TID patient 317121 for headache and short arms,
- 0.4% NTG TID patient 320124 for vomiting,
- 0.4% NTG TID patient 322123 for headache.

At least 23 patients withdrew for an adverse event; 10 were in the highest dose NTG TID group versus 1 in the placebo TID group.

ANAL FISSURE HEALING

The sponsor provided various analyses of anal fissure healing. Dr. Hung confirmed these results. None suggested a benefit of NTG ointment to heal the fissures.

**Table 5: Percent Fissure Healing: ITT Population
(Study NTG 98-02-01)**

| Dose Frequency | Study Treatment | | | |
|----------------|------------------|-------------------|-------------------|-------------------|
| | Placebo n (%) | 0.1% NTG n (%) | 0.2% NTG n (%) | 0.4% NTG n (%) |
| b.i.d. (N=150) | 17 (50%) | 12 (31%) | 10 (26%) | 15 (39%) |
| t.i.d. (N=154) | 17 (47%) | 18 (49%) | 16 (41%) | 20 (48%) |

**Table 6: Individual Between-Group Comparison of Healing Rates:
ITT Population
(Study NTG 98-02-01)**

| Treatment Group ^a | Healing Rate | | p-value |
|------------------------------|--------------|--|---------|
| | n (%) | | |
| 0.1% NTG (N=76) | 30 (40%) | | p=0.63 |
| placebo (N=70) | 34 (49%) | | |
| 0.2% NTG (N=78) | 26 (33%) | | p=0.12 |
| placebo (N=70) | 34 (49%) | | |
| 0.4% NTG (N=80) | 35 (44%) | | p=0.64 |
| placebo (N=70) | 34 (49%) | | |

^a Results from b.i.d. and t.i.d. dose frequency groups combined.

An analysis of fissure recurrence after healing was also done, and demonstrated no benefit.

**Table 12: Recurrence Rates of Fissures: Subjects with a Follow-Up
Examination
(Study NTG 98-02-01)**

| Frequency and Dose | Healed Subjects at End of Study | Subjects Who Relapsed at Follow-Up | Recurrence Rate |
|--------------------|---------------------------------------|--|--------------------|
| b.i.d. | | | |
| Placebo | 18 | 4 | 0.222 |
| 0.1% NTG Ointment | 12 | 2 | 0.167 |
| 0.2% NTG Ointment | 10 | 1 | 0.100 |
| 0.4% NTG Ointment | 15 | 3 | 0.200 |
| t.i.d. | | | |
| Placebo | 17 | 3 | 0.176 |
| 0.1% NTG Ointment | 18 | 2 | 0.111 |
| 0.2% NTG Ointment | 16 | 5 | 0.313 |
| 0.4% NTG Ointment | 19 | 7 | 0.368 |

As previously noted, the protocol specified that the statistical analysis of anal fissure healing involved 6 active treatment groups, and some consideration for multiple comparisons was proposed. No plan was presented for handling secondary endpoints for multiple comparisons and multiple endpoints, particularly where the primary endpoint was NS.

PAIN ASSESSMENTS

Three pain assessments were to be made daily by each patient; average pain for the day, worst pain, and pain on defecation. Assessments were to continue to day 56 or anal fissure healing.

Patient assessment of pain on the 0-100mm VAS was made daily and written into a diary which was brought to the clinical visits. At those visits "study site personnel" measured the responses as noted by the patient, and put the result (# of mm between the left end, i.e. no pain, and the patient's mark) on the CRF. The pain data reported was noted to have been "finalized from a database specified and approved by Cellegy."

The sponsor provided a pain analysis pooling the BID and TID dose groups using a mixed effects model. The exact model used was not pre-specified. This pooling was not pre-specified. The analysis of the primary endpoint, anal fissure healing, was by randomized group. The pooling was justified by the sponsor based on their finding that "No significant main effects or interactions involving dosage frequency were found." It must be noted that increased dose frequency provided higher doses of the active drug, so that pooling frequency of administration also pooled different doses of active.

An analysis using data from 267 of the 304 randomized patients as well as an analysis of those patients with baseline pain >25 mm on the VAS were provided as follows:

Table 11: Percent Pain Decrease From Baseline as a Function of Percent Nitroglycerin Content of Ointment: All Subjects and Subjects With Baseline Average Pain >25 mm (Study NTG 98-02-01)

| Type of Pain Day | All Subjects | | | | Baseline AVG Pain >25 mm | | | |
|------------------------|--------------|-----------------|-----------------|-----------------|--------------------------|-----------------|-----------------|-----------------|
| | Placebo | 0.1% | 0.2% | 0.4% | Placebo | 0.1% | 0.2% | 0.4% |
| Average Pain | | | | | | | | |
| 4 | 22 | 37 ^a | 32 ^b | | | | | |
| 7 | 26 | 30 | 42 ^c | 40 ^e | 32 | 37 | 52 ^c | 44 ^d |
| 14 | 42 | 37 | 46 | 49 ^e | 46 | 43 | 55 ^d | 58 ^d |
| 21 | 39 | 48 ^d | 51 ^a | 58 ^a | 47 | 55 | 60 ^d | 65 ^e |
| 28 | 52 | 51 | 58 ^d | 60 ^a | 55 | 53 | 65 ^d | 68 ^c |
| 35 | 50 | 57 | 57 ^d | 66 ^a | 57 | 59 | 66 | 75 ^a |
| 42 | 54 | 58 | 63 | 65 ^a | 56 | 60 | 70 | 71 ^c |
| 49 | 54 | 62 | 67 ^c | 69 ^a | 57 | 67 | 74 ^d | 78 ^c |
| 56 | 51 | 62 | 65 ^c | 72 ^a | 57 | 66 | 76 ^c | 80 ^c |
| Defecation Pain | | | | | | | | |
| 7 | 42 | 42 | 43 | 51 | 38 | 37 | 49 | 53 |
| 14 | 56 | 43 | 44 | 59 | 46 | 40 | 44 | 60 |
| 21 | 53 | 56 | 47 | 64 ^c | 50 | 54 | 46 | 67 |
| 28 | 57 | 60 | 55 | 68 ^c | 46 | 58 | 58 | 68 ^d |
| 35 | 58 | 62 | 58 | 72 ^a | 52 | 58 | 62 | 77 ^a |
| 42 | 61 | 65 | 61 | 72 ^c | 53 | 62 | 66 | 72 ^c |
| 49 | 61 | 65 | 66 | 77 ^a | 52 | 64 ^d | 74 ^c | 81 ^a |
| 56 | 61 | 67 | 67 | 80 ^c | 55 | 65 | 78 ^a | 83 ^c |
| Worst Pain | | | | | | | | |
| 7 | 39 | 39 | 46 | 48 ^d | 39 | 38 | 49 | 48 |
| 14 | 55 | 46 | 52 | 59 ^d | 49 | 47 | 53 | 59 |
| 21 | 56 | 60 | 56 | 65 ^a | 53 | 63 | 59 | 68 ^d |
| 28 | 61 | 61 | 61 | 71 ^a | 55 | 58 | 65 | 73 ^c |
| 35 | 62 | 66 | 61 | 74 ^a | 57 | 63 | 66 | 78 ^c |
| 42 | 64 | 67 | 67 | 74 ^a | 58 | 65 | 72 ^d | 74 ^c |
| 49 | 61 | 71 | 70 ^d | 77 ^a | 57 | 71 | 77 ^c | 79 ^c |
| 56 | 60 | 71 | 69 | 79 ^a | 57 | 70 | 79 ^c | 82 ^c |

^a p < 0.001

^b p < 0.02

^c p < 0.01

^d p < 0.05

NOTE: Significance levels based on mixed model analysis

As can be noted from Dr. Hung's chart of available data (see below), 20 patients had neither baseline nor follow-up data and 8 had only baseline data. There are data from 276 patients who had baseline and some follow-up data. The sponsor's mixed effects analysis used patients only if they had follow-up data including day 7, and used only data at time points baseline, days 7, 14, 21, 28, 35, 42, 49, and 56 as shown above.

While the sponsor stated that secondary analyses were performed to consider the relationship between use of analgesics on pain relief, and that those analyses did not show a different result for those who took more than 6 days of analgesic medication versus those who took less or none, no data were provided.

Dr. Hung, using SAS diskettes from the sponsor, provided independent analyses that clarify the sponsor's summary report.

Distribution of missing pain data followed by baseline average daily pain data per Dr. Hung was:

Table R1-1. Distribution of the patients with incomplete pain data

| | No baseline pain data and no post randomization pain data | Have baseline pain data only | Have baseline and post randomization pain data |
|---------------------|---|------------------------------|--|
| 0.1% NTG BID (N=39) | 6 (15%) | 2 (5%) | 31 (79%) |
| 0.1% NTG TID (N=37) | 1 (3%) | 1 (3%) | 35 (95%) |
| 0.2% NTG BID (N=39) | 5 (13%) | 2 (5%) | 32 (82%) |
| 0.2% NTG TID (N=39) | 1 (3%) | 1 (3%) | 37 (95%) |
| 0.4% NTG BID (N=38) | 1 (3%) | 0 | 37 (97%) |
| 0.4% NTG TID (N=42) | 3 (7%) | 1 (2%) | 38 (90%) |
| Placebo BID (N=34) | 1 (3%) | 1 (3%) | 32 (94%) |
| Placebo TID (N=36) | 2 (6%) | 0 | 34 (94%) |

The sponsor did not provide baseline pain data per group. Dr. Hung has provided that data.

Table R1-2. Distribution of baseline measurement on daily average pain

| | Mean | SD | Range | 1 st quartile | Median | 3 rd quartile |
|--------------|------|------|---------|--------------------------|--------|--------------------------|
| 0.1% NTG BID | 26.4 | 20.9 | 0 - 66 | 11 | 18 | 45 |
| 0.1% NTG TID | 35.3 | 23.4 | 0 - 84 | 13 | 36 | 52 |
| 0.2% NTG BID | 25.8 | 20.4 | 0 - 72 | 11 | 22 | 38 |
| 0.2% NTG TID | 29.9 | 27.4 | 0 - 95 | 5 | 18 | 50 |
| 0.4% NTG BID | 39.2 | 25.5 | 0 - 97 | 15 | 42 | 55 |
| 0.4% NTG TID | 30.8 | 24.6 | 0 - 100 | 9 | 27 | 48 |
| Placebo BID | 25.7 | 24.0 | 0 - 81 | 4 | 21 | 43 |
| Placebo TID | 23.4 | 22.1 | 0 - 79 | 4 | 19 | 35 |

There appeared to be some imbalance in the baseline daily average pain measurement (Table R1-2, $p = 0.081$, ANOVA F-test; $p = 0.10$, Kruskal-Wallis test); in particular, among the bid groups ($p = 0.032$, ANOVA F-test; $p = 0.07$, Kruskal-Wallis test). This is apparently due to the 0.4% bid group. Other endpoints were explored to consider the nature of any clinical benefit that NTG ointment might provide in relieving pain.

Percent of patients with zero pain score at last visit

Of the patients who had pain at baseline, 3%-19% had zero pain at the last visit in the bid groups and 16%-38% in the tid groups; see Table R1-3. Only the 0.2% and 0.4% NTG TID groups appeared to have more patients with zero pain at the last visit.

Table R1-3. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

| | Zero average pain | Zero worst pain | Zero defecation pain |
|---------------------|-------------------|-----------------|----------------------|
| Placebo BID (N=34) | 2/29 (7%) | 2/30 (7%) | 2/27 (7%) |
| 0.1% NTG BID (N=39) | 4/29 (14%) | 5/30 (17%) | 5/27 (19%) |
| 0.2% NTG BID (N=39) | 1/30 (3%) | 1/31 (3%) | 1/29 (3%) |
| 0.4% NTG BID (N=38) | 4/37 (11%) | 5/37 (14%) | 2/33 (6%) |
| | | | |
| Placebo TID (N=36) | 5/29 (17%) | 5/32 (16%) | 8/30 (27%) |
| 0.1% NTG TID (N=37) | 6/34 (18%) | 7/35 (20%) | 6/33 (18%) |
| 0.2% NTG TID (N=39) | 11/33 (33%) | 12/36 (33%) | 9/31 (29%) |
| 0.4% NTG TID (N=42) | 10/36 (28%) | 10/38 (26%) | 12/32 (38%) |

While only descriptive and exploratory, this analysis suggests that NTG ointment, 2% and 4% TID, may relieve pain due to anal fissures.

Last Available Visit Analysis

Average daily pain

As mentioned above, a total of 28 patients did not have any pain data after randomization. Thus, the last available visit analysis can be performed only on 276 patients.

Numerically, 0.2% and 0.4% NTG seemed to have a greater improvement on pain measurement, but statistical significance is not conclusive. Only 0.4% NTG bid appeared to give a greater improvement, but TID did not, thereby weakening any inference. After adjusting for imbalance in baseline daily average pain, the apparently greater improvement with 0.4%NTG BID disappeared.

Table R1-4. Mean change in last available visit daily average pain from baseline (Reviewer's analysis)

| | Baseline Mean | Mean change | Nominal p-value ^{\$} | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|-------------------------------|-------------------|------------------------------|
| 0.1% NTG BID | 26.4 | -9.9 | 0.85 | -12.0 | 0.46 |
| 0.1% NTG TID | 35.3 | -21.7 | 0.076 | -18.3 | 0.61 |
| 0.2% NTG BID | 25.8 | -14.9 | 0.51 | -17.4 | 0.52 |
| 0.2% NTG TID | 29.9 | -23.7 | 0.031 | -23.3 | 0.059 |
| 0.4% NTG BID | 39.2 | -27.9 | 0.003 | -21.0 | 0.10 |
| 0.4% NTG TID | 30.8 | -18.9 | 0.19 | -17.9 | 0.66 |
| Placebo BID | 25.7 | -11.0 | --- | -14.9 | --- |
| Placebo TID | 23.4 | -11.6 | --- | -16.3 | --- |

* adjusted for baseline daily average pain

\$ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change

NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Worst pain and defecation pain

There was no evidence of a significant difference in last visit change from baseline in daily worst pain or defecation pain between the treatment groups (Tables R1-5 and R1-6).

Table R1-5. Mean change in last available visit daily worst pain from baseline (Reviewer's analysis)

| | Baseline Mean | Mean change | Nominal p-value [§] | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|------------------------------|-------------------|------------------------------|
| 0.1% NTG BID | 35.4 | -17.9 | 0.14 | -22.3 | 0.053 |
| 0.1% NTG TID | 51.4 | -41.2 | 0.041 | -37.7 | 0.15 |
| 0.2% NTG BID | 43.6 | -31.1 | 0.74 | -32.2 | 0.94 |
| 0.2% NTG TID | 41.8 | -32.0 | 0.46 | -34.6 | 0.42 |
| 0.4% NTG BID | 54.4 | -43.5 | 0.034 | -37.4 | 0.24 |
| 0.4% NTG TID | 51.4 | -36.0 | 0.18 | -32.0 | 0.80 |
| Placebo BID | 41.6 | -28.7 | --- | -31.8 | --- |
| Placebo TID | 40.8 | -26.9 | --- | -30.8 | --- |

* adjusted for baseline daily worst pain

§ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change

NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Table R1-6. Mean change in last available visit daily defecation pain from baseline (Reviewer's analysis)

| | Baseline Mean | Mean change | Nominal p-value [§] | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|------------------------------|-------------------|------------------------------|
| 0.1% NTG BID | 38.0 | -16.6 | 0.60 | -19.0 | 0.39 |
| 0.1% NTG TID | 46.1 | -31.2 | 0.27 | -27.7 | 0.53 |
| 0.2% NTG BID | 40.2 | -25.0 | 0.54 | -25.5 | 0.67 |
| 0.2% NTG TID | 31.9 | -23.1 | 0.97 | -29.1 | 0.35 |
| 0.4% NTG BID | 49.4 | -36.1 | 0.031 | -29.6 | 0.20 |
| 0.4% NTG TID | 43.9 | -29.0 | 0.43 | -26.6 | 0.70 |
| Placebo BID | 37.8 | -20.5 | --- | -23.4 | --- |
| Placebo TID | 38.8 | -23.4 | --- | -24.7 | --- |

* adjusted for baseline daily defecation pain

§ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change

NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Mixed-Effects Analysis for Rate of Change in Pain

According to the study protocol, the pain relief was a secondary endpoint in this study. Generalized mixed-effects regression models were to be used in analyses of the pain data because the repeated evaluation of pain over time induces correlation among the residual model deviations and the unequal number of measurements per subject (due to subject withdrawal and early healing) produces a highly unbalanced design. However, the mixed-effects model was not specified. The computer output in Appendix 2, Statistical Documentation (pages 442-490, Volume 1.30) gave quite different p-values from those reported in the study report.

Average daily pain

In response to Dr. Hung's request for details of the mixed-effect analyses utilized, the sponsor faxed the results of mixed-effects analyses on the daily average pain data (dated October 26, 2001). In their mixed-effects analyses, the model included the main effects of day 0 (baseline), 7, 14, 21, 28, 35, 42, 49, and 55, dose (three dummy coded contrasts where contol = 0 0 0), frequency (0=bid, 1=tid), and all 3 two-way interactions and all 3 three-way interactions. Day was treated as a continuous variable. Intercept and day were specified as random and the residuals were specified as independent. The model provided in the faxed 10/26/01 document was different from the models that were used to generate the computer output of Appendix 2, Statistical Documentation mentioned above.

According to the study report, no significant main effects or interactions involving dosage frequency were found, therefore the data for the two frequencies (bid and tid) were pooled for the subsequent analyses. It must be emphasized that differences in frequency of administration of NTG resulted in different daily doses to the patient. For example a dose of 0.4% NTG BID provided 3 mg of drug versus 4.5 mg when given TID. The sponsor concluded in the study report that in the ITT population, linear time by treatment interactions were significant for the 0.4% NTG group relative to placebo for average pain ($p < 0.0002$). The mixed-effects analysis in the faxed 10/26/01 document gives $p = 0.00018$. With stationary AR(1) residuals, the p-value for this interaction becomes 0.00019. In addition, the sponsor reported that analyses performed on all 56 days of pain yielded similar results. However, the reviewer's analysis of all 56 days of pain gave a $p = 0.0052$, different in an order of magnitude, with independent residuals, but $p = 0.0004$ with AR(1) residuals.

As noted there are concerns about pooling dose frequencies. Not only would the effect, if any, of different doses be ignored, but is inconsistent with the analysis of anal fissure healing, the primary endpoint which was done for each dose group and frequency of administration per protocol. Additionally, the ANOVA method used to detect differences between BID and TID dosing is relatively insensitive, and pairwise comparisons between groups reveals differences than may not be detected by this method. One would be concerned about the analysis of a secondary endpoint by methods selected post-hoc. To provide an analysis preserving the randomized groups, utilizing all available data, Dr. Hung has provided the following. Table R1-7 presents the results of slope of change in average daily pain without pooling. All daily measurements are incorporated in the analyses. The mixed-effects model is identical to the one used by the sponsor. The results suggest that only 0.4% NTG bid appear to reduce average daily pain in a greater rate over time than placebo. The models with AR(1) residuals appear to be better in terms of likelihood and give better sensitivity in showing statistical significance.

Table R1-7. Slope of change in average daily pain over time (Reviewer's analysis)

| | Mean slope (average daily pain) | | Nominal P-value* | |
|---------------------|------------------------------------|-------|------------------|--------|
| | indep | AR(1) | indep | AR(1) |
| Placebo BID (N=34) | -0.21 | -0.21 | --- | --- |
| 0.1% NTG BID (N=39) | -0.23 | -0.24 | 0.86 | 0.78 |
| 0.2% NTG BID (N=39) | -0.27 | -0.25 | 0.62 | 0.68 |
| 0.4% NTG BID (N=38) | -0.52 | -0.52 | 0.005 | 0.0004 |
| | | | | |
| Placebo TID (N=36) | -0.21 | -0.19 | --- | --- |
| 0.1% NTG TID (N=37) | -0.37 | -0.36 | 0.12 | 0.049 |
| 0.2% NTG TID (N=39) | -0.32 | -0.33 | 0.27 | 0.093 |
| 0.4% NTG TID (N=42) | -0.37 | -0.36 | 0.14 | 0.059 |

* for comparison with the corresponding placebo regimen

Indep: model with independent residuals

AR(1): model with AR(1) residuals

Worst pain and defecation pain

The mixed-effects analysis using the same models were also performed on worse pain and defecation pain. The results are summarized in Tables R1-8 and R1-9. The results give the essentially the same suggestion that 0.4% NTG bid appear to reduce pain in a greater rate over time than placebo. Again the models with AR(1) residuals appear to be better in terms of likelihood and give better sensitivity in showing statistical significance. The 0.1% and 0.4% tid doses of NTG give a nominal p-value < 0.05. However, they are difficult to interpret because 1) 0.2% showed no significantly large slope, 2) awkward dose slope relationship, and 3) multiple comparisons and multiple choices of models. In my view, these p-values have not attained statistical significance.

Table R1-8. Slope of change in worst daily pain over time (Reviewer's analysis)

| | Mean slope (worst daily pain) | | Nominal P-value* | |
|---------------------|----------------------------------|-------|------------------|-------|
| | indep | AR(1) | indep | AR(1) |
| Placebo BID (N=34) | -0.39 | -0.41 | --- | --- |
| 0.1% NTG BID (N=39) | -0.35 | -0.37 | 0.80 | 0.79 |
| 0.2% NTG BID (N=39) | -0.45 | -0.45 | 0.70 | 0.72 |
| 0.4% NTG BID (N=38) | -0.71 | -0.71 | 0.025 | 0.007 |
| | | | | |
| Placebo TID (N=36) | -0.31 | -0.31 | --- | --- |
| 0.1% NTG TID (N=37) | -0.64 | -0.59 | 0.022 | 0.012 |
| 0.2% NTG TID (N=39) | -0.45 | -0.46 | 0.32 | 0.16 |
| 0.4% NTG TID (N=42) | -0.60 | -0.59 | 0.042 | 0.011 |

* for comparison with the corresponding placebo regimen

Indep: model with independent residuals

AR(1): model with AR(1) residuals

Table R1-9. Slope of change in defecation pain over time (Reviewer's analysis)

| | Mean slope (defecation pain) | | Nominal P-value* | |
|---------------------|---------------------------------|-------|------------------|-------|
| | indep | AR(1) | indep | AR(1) |
| Placebo BID (N=34) | -0.39 | -0.36 | --- | --- |
| 0.1% NTG BID (N=39) | -0.38 | -0.38 | 0.96 | 0.87 |
| 0.2% NTG BID (N=39) | -0.41 | -0.41 | 0.84 | 0.65 |
| 0.4% NTG BID (N=38) | -0.66 | -0.66 | 0.056 | 0.007 |
| | | | | |
| Placebo TID (N=36) | -0.27 | -0.27 | --- | --- |
| 0.1% NTG TID (N=37) | -0.53 | -0.50 | 0.064 | 0.037 |
| 0.2% NTG TID (N=39) | -0.36 | -0.38 | 0.50 | 0.30 |
| 0.4% NTG TID (N=42) | -0.52 | -0.50 | 0.075 | 0.041 |

* for comparison with the corresponding placebo regimen

Indep: model with independent residuals

AR(1): model with AR(1) residuals

The mixed-effects analyses in this study are purely exploratory. The mixed-effects models chosen for final analyses to generate p-values suggesting potential signals were not pre-specified; thus, there are many possible models that might be used. For instance, the residuals could be modeled to follow an independent covariance structure, AR(1), or some others. From the comparison of residuals, this study seems to suggest that the stationary AR(1) residuals are more likely to show a signal.

Numerically, the bid and tid regimens showed different dose slope relationships, though the differences were not statistically significant (no statistically significant frequency by time interaction). The tid regimen showed an awkward dose slope relationship. These observations have established a ground for doubt of whether pooling the dosage frequencies is sensible. For reasons enumerated above, this study does not

provide convincing support for the efficacy of NTG ointment to relieve anal pain due to fissures, but does not establish a hypothesis for study NTG 00-02-01 which tests prospectively the efficacy of NTG ointment for that indication.

SAFETY

304 patients were included in the safety analyses: 70 assigned to placebo; 234 on NTG. No deaths occurred.

The sponsor reported that 13 patients withdrew for an adverse event as follows:

| Treatment Group Subject Number | Age (yrs) | Adverse Event (Primary Term) | Study Day of Onset ^a | Severity | Relationship to Study Drug ^b | Duration of Therapy (Days) |
|-----------------------------------|--------------|----------------------------------|------------------------------------|----------|--|----------------------------------|
| 0.1% NTG b.i.d. | | | | | | |
| 315121 | 55 | Respiratory disorder | 14 | Moderate | None | 35 |
| | | Headache ^c | 2 | Severe | Possibly | 35 |
| | | Flu syndrome | 14 | Moderate | None | 35 |
| 0.2% NTG b.i.d. | | | | | | |
| 315104 | 29 | Dizziness ^d | 2 | Moderate | Possibly | 5 |
| | | Palpitation ^e | 2 | Moderate | Possibly | 5 |
| 322146 | 24 | Rectal disorder ^f | 8 | Severe | None | 10 |
| 0.4% NTG b.i.d. | | | | | | |
| 317115 | 72 | Headache | 2 | Mild | Possibly | 197 ^g |
| | | Nausea | 2 | Mild | Possibly | 197 |
| | | Pruritus | 27 | Moderate | Possibly | 197 |
| | | Accidental injury ^{h,i} | 48 | Severe | None | 197 |
| Placebo t.i.d. | | | | | | |
| 323107 | 41 | Headache ^d | 1 | Moderate | Related | 12 |
| 0.1% NTG t.i.d. | | | | | | |
| 317114 | 41 | Headache ^d | 1 | Severe | Possibly | 5 |
| | | Vomiting ^d | 1 | Severe | Possibly | 5 |
| | | Hypertension ^d | 1 | Moderate | Possibly | 5 |
| 323102 | 71 | Vertigo ^d | 2 | Moderate | Possibly | 8 |
| 0.4% NTG t.i.d. | | | | | | |
| 315105 | 26 | Headache ^d | 1 | Severe | Possibly | 3 |
| 317127 | 35 | Nausea | 1 | Mild | Possibly | 39 |
| | | Headache | 1 | Severe | Possibly | 39 |
| | | Headache | 4 | Severe | Possibly | 39 |
| | | Headache | 21 | Severe | Possibly | 39 |
| | | Headache ^e | 24 | Severe | Possibly | 39 |
| | | Hypernatremia | 39 | Mild | None | 39 |
| 317138 | 37 | Headache ^d | 1 | Severe | Related | 15 |
| | | Vomiting ^d | 1 | Moderate | Possibly | 15 |
| | | Sweating ^d | 1 | Moderate | Possibly | 15 |
| 319108 | 21 | Headache ^d | 1 | Severe | Related | 6 |
| | | Nausea ^d | 1 | Severe | Related | 6 |
| 323101 | 50 | Headache ^d | 1 | Severe | Related | 9 |
| | | Sweating ^d | 1 | Moderate | Possibly | 9 |
| | | Anxiety ^d | 2 | Moderate | Possibly | 9 |
| 323111 | 29 | Headache ^d | Unknown ^f | Moderate | Related | 11 |

^a Relative to start of therapy.

^b Based on investigator's assessment.

^c Serious adverse event.

^d Subject discontinued therapy due to this adverse event.

^e Subject 317115 discontinued the study due to a broken hip on 3/06/99. The clinical summary page of the CRF was completed on 9/22/99.

^f The first day of study drug administration for Subject 323111 was April 20, 1999. The onset of headache was an unknown date in April, 1999.

A review of case report forms for patients without any pain data, only baseline pain data or less than 7 days of pain data revealed in this reviewer's judgment 9 additional patients withdrawn for adverse events:

- 0.1% NTG TID patient 314105 for anal surgery.
- 0.1% NTG TID patient 315113 for anal pain necessitating surgery,
- 0.2% NTG BID patient 322112 for headache,
- 0.2% NTG TID patient 310101 for headache and vertigo,
- 0.2% NTG TID patient 317130 for headache,
- 0.4% NTG TID patient 317117 for headache,
- 0.4% NTG TID patient 317121 for headache and short arms,
- 0.4% NTG TID patient 320124 for vomiting,
- 0.4% NTG TID patient 322123 for headache.

At least 23 patients withdrew for an adverse event; 10 were in the highest dose NTG TID group versus 1 in the placebo TID group.

A listing of patients reporting severe adverse events was provided as follows:

Table 17: Subjects With Severe Adverse Events Considered to be Severe: Safety Population
(Study NTG-98-02-01)

| Treatment Group | Subject Number | Age | Adverse Event (Primary Term) | Relationship to Study Drug ^a | Action Taken | Outcome |
|-----------------|----------------|-----|------------------------------|---|---------------------------------|-------------------|
| placebo b.i.d. | | | | | | |
| | 316105 | 55 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 319109 | 38 | Rectal disorder | None | Procedure | Resolved |
| 0.1% NTG b.i.d. | | | | | | |
| | 312108 | 45 | Rectal disorder | None | Procedure | Resolved |
| | | | Rectal Hemorrhage | None | Procedure | Resolved |
| | 315121 | 55 | Headache | Possibly | Rx or OTC drug | Resolved |
| 0.2% NTG b.i.d. | | | | | | |
| | 313115 | 37 | Headache | Possibly | None | Resolved |
| | 317118 | 29 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 322112 | 36 | Headache | Possibly | D/C Study drug | Resolved |
| | 322146 | 24 | Rectal disorder | None | Procedure | Resolved |
| 0.4% NTG b.i.d. | | | | | | |
| | 313111 | 55 | Headache | Related | None | Resolved |
| | 317115 | 72 | Accidental injury | None | D/C study drug and hospitalized | Hospitalized |
| | 317117 | 26 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 317142 | 23 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 320105 | 30 | Headache | Related | None | Resolved |
| | | | Headache | Related | D/C study drug | Lost to follow-up |
| | 322150 | 32 | Gastroenteritis | None | Rx or OTC drug | Resolved |
| placebo t.i.d. | | | | | | |
| | 312104 | 31 | Headache | Possibly | None | Resolved |
| | 317123 | 41 | Menstrual disorder | None | Rx or OTC drug | Resolved |
| | | | Menstrual disorder | None | Rx or OTC drug | Resolved |
| 0.1% NTG t.i.d. | | | | | | |
| | 317114 | 41 | Headache | Possibly | D/C Study drug | Resolved |
| | | | Vomiting | Possibly | D/C Study drug | Resolved |
| 0.2% NTG t.i.d. | | | | | | |
| | 313109 | 26 | Headache | Related | None | Resolved |
| | 317109 | 59 | Headache | Possibly | Rx or OTC drug | Resolved |
| | | | Palpitation | Possibly | D/C study drug | Resolved |
| | 317119 | 41 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 317130 | 51 | Headache | Related | Rx or OTC drug | Resolved |
| | 317132 | 38 | Gastrointestinal disorder | None | Rx or OTC drug | Improved |
| | 320103 | 63 | Dyspnea ^b | None | Procedure | Resolved |
| | | | Chest pain ^b | None | Procedure | Resolved |
| 0.4% NTG t.i.d. | | | | | | |
| | 313105 | 52 | Headache | Related | Rx or OTC drug | Resolved |
| | | | Headache | Possibly | None | Resolved |
| | 315105 | 26 | Headache | Possibly | Rx or OTC drug | Resolved |
| | 316102 | 34 | Headache | Related | Rx or OTC drug | Resolved |
| | 317127 | 35 | Headache | Possibly | Rx or OTC drug | Resolved |
| | | | Headache | Possibly | Rx or OTC drug | Resolved |
| | | | Headache | Possibly | Rx or OTC drug | Resolved |
| | | | Headache | Possibly | D/C study drug | Resolved |
| | 317138 | 37 | Headache | Related | D/C study drug | Resolved |
| | 319108 | 21 | Headache | Related | D/C study drug | Resolved |
| | | | Nausea | Related | D/C study drug | Resolved |
| | 320124 | 19 | Vomiting | Related | None | Resolved |
| | | | Vomiting | Related | D/C study drug | Resolved |
| | 323101 | 50 | Headache | Related | Rx or OTC drug | Resolved |
| | 325101 | 41 | Headache | Related | Rx or OTC drug | Resolved |

^a Based on investigator's assessment

^b Serious adverse event

^c Subjects discontinued therapy due to this adverse event

KEY: Rx = prescription medication; OTC = over-the-counter; D/C = discontinue

Checking the 0.4% NTG TID group against the listing of patients who withdrew for adverse events (see chart above) raises questions of consistency and accuracy in the safety reporting. For example, patient 315105 is listed as headache treated with some RX, but this patient was listed as withdrawn for severe headache. The same situation exists for patients 323101 and 323111. Patient 320124 is said to have discontinued the study drug for vomiting, but is not listed on the chart of those withdrawn. This problem is not confined to the 0.4%NTG TID group. For example, patient 320105 from the 0.4%BID group is noted to have withdrawn for headache on the severe adverse events chart above, but not on the withdrawal chart. As noted above when the additional patients withdrawn for adverse events as noted by this reviewer, and inconsistencies resolved at least 23 patients were withdrawn for an adverse event with 10 of these in the highest dose NTG group.

Headache was the most frequent cause of patient withdrawal, as well as the most frequently experienced adverse event, mostly in those treated with NTG and with increasing incidence as the NTG dose increases.

| Dosage Frequency/ Dose | All Reported (N=97) | | Treatment-Related ^a (N=36) | | Severe (N=23) | |
|---------------------------|------------------------|--------|--|--------|------------------|--------|
| | n | (%) | n | (%) | n | (%) |
| b.i.d. | | | | | | |
| placebo | 3 | (3.1) | 0 | (0.0) | 1 | (4.3) |
| 0.1% | 7 | (7.2) | 1 | (2.8) | 1 | (4.3) |
| 0.2% | 13 | (13.4) | 6 | (16.7) | 3 | (13.0) |
| 0.4% | 14 | (14.4) | 5 | (13.9) | 4 | (17.4) |
| l.i.d. | | | | | | |
| placebo | 10 | (10.3) | 4 | (11.1) | 1 | (4.3) |
| 0.1% | 7 | (7.2) | 0 | (0.0) | 1 | (4.3) |
| 0.2% | 18 | (18.6) | 7 | (19.4) | 4 | (17.4) |
| 0.4% | 25 | (25.8) | 13 | (36.1) | 8 | (34.8) |

^a Includes headaches that were possibly related and related to study drug.

214 patients took medication for pain relief during the study. Of these it was noted that 67 took acetaminophen for headache and 5 took additional pain medication for headache. 36 patients took NSAIDs or salicylates for chronic pain or inflammation.

Other severe adverse events leading to withdrawal were rectal pain, and one case of dizziness, faint felling and heart palpitations (patient 315104, 0.2%NTG BID) where the blood pressure readings were 102/64 predose to 90/58 20 minutes postdose. While the hypotensive effects of nitroglycerin are described in the approved labeling, no severe adverse events other than possibly that noted for patient 315104 might be ascribed to a hypotensive effect of anogestic therapy. The mean, median and extreme blood pressure readings over time do not reveal significant differences between groups. 31 patients had a 20 mm Hg or greater drop in systolic blood pressure predose to 10 or 20 minutes postdose.

STUDY NTG 00-02-01: A Study to Determine the Nitroglycerine Ointment Dose that Best Promotes the Relief of Pain Associated with Anal Fissures.

This multicenter, multinational (USA, UK, Israel and Germany), randomized, placebo controlled, double-blind parallel study of two doses of NTG ointment (0.75mg and 1.5 mg daily for 56 days) to relieve the pain of anal fissures was initiated May 30,2000 and completed August 27, 2001.

229 patients were randomized to placebo (vehicle), NTG 0.2% BID (0.75mg total daily dose), or NTG 0.4% BID (1.5mg total daily dose). To enter a patient had to have an anal fissure with pain. The pain had to have been present after at least 50% of bowel movements for 30 days prior to enrollment and be present at enrollment. Patients could be male or female, 18 years or older, and if female, on an approved method of birth control. Exclusion criteria included fistulo-in-ano, anal surgery within the preceeding 30 days, allergy to any of the medications, require NSAID therapy but for cardiac uses, anal abscess, IBD, anal stenosis, or unwilling to discontinue use of Viagra.

The primary objective was stated in the title of the study. Pain was assessed at baseline and daily on a VAS going from zero (none) to 100 (most severe imaginable). Average daily pain, worst daily pain and pain on defecation were rated. Every two weeks subjects returned with their diaries that were transcribed by the investigators onto the CRFs. Statistically, it was pre-specified in the protocol that a mixed-effects regression model using all values recorded for each subject would be used for the ITT population (defined elsewhere as subjects with baseline and some post-treatment data). In the study report it is stated that the effects of center and a quadratic effect of time were included in the model. The center and quadratic components of the model used for analysis were not pre-specified, and these parameters were not used to analyze study NTG 98-02-01. The study report goes on to note that, if the overall analysis was significant, treatment comparisons at each timepoint would be made. Average daily pain was the primary parameter to be analyzed, but worst pain and defecation pain were also to be analyzed. Secondary endpoints were time to anal fissure healing, safety and Gastrointestinal Quality of Life Index results. Statistically, the study was sized based on effect size estimates for daily average pain (primary endpoint) from the initial clinical study. For a power of 0.8 and an alpha of .05, adjusting for two active comparisons, it was estimated that 55 patients per group were needed. An attrition rate of 2.5% per week was factored into the proposed sample size.

The schedule of procedures with detailed footnotes was provided in the study report as follows:

Table 1: Schedule of Study Procedures
(Study NTG 00-02-01)

| Assessment/Procedure | Screening ^a | Baseline (Day 1) | On-Therapy Evaluation ^b | Exit Visit Evaluation ^c | Open-label ^d | Follow-up |
|--|------------------------|------------------|------------------------------------|------------------------------------|-------------------------|----------------|
| Consent Form Signed | X | | | | | |
| Physical Examination | X | | | X | | |
| Medical History | X | | | | | |
| Medication History | X | | | | | |
| Clinical Laboratory Tests ^e | X | | | X | | |
| Anal Examination/Assessment ^f | X | | X | X | X ^g | |
| Vital Signs ^h | X | X ^b | X | X | | |
| CTM Weight Assessment ⁱ | | X | X | X | | |
| Subject Instruction | | X | | | | |
| Pain Intensity Assessment ^j | | X | X | X | X ^g | |
| Gastrointestinal Quality of Life Index | X | | X ^k | X | | |
| Daily Sitz Bath Recorded | X | | | X | X ^g | |
| Study Drug Application | | X | | | X | |
| Concomitant Medications Recorded | | X | | X | | |
| Adverse Events Recorded | | X | | | X | |
| Telephone contact | | | | | | X ^m |

^a Screening was to occur from before Day 1 and was to end just prior to dosing on Day 1; Screening and Baseline could occur on Day 1.

^b Clinic visits on Days 14, 28, 42, and 56 ±3 days.

^c Final (exit) clinic visit (whether due to early withdrawal or on Day 56).

^d For subjects for whom the anal fissure was not completely healed during the 56-day study period.

^e Including blood chemistry, hematology, and urinalysis; a urine pregnancy test was required to be performed for all women of child-bearing potential (Section 3.8.4.3).

^f A digital/anoscopic examination could be performed, depending on the investigator's standard of practice, once only during the eighth week.

^g Baseline and exit visits included measurement of height (baseline visit only), weight, temperature, sitting blood pressure, and pulse. Day 1 and on-therapy visits included measurement of pulse and sitting blood pressure only.

^h Sitting blood pressure and pulse were to be measured immediately prior to and 15 minutes after administration of first dose of study drug.

ⁱ The individual CTM (tube with study medication) was to be weighed (to nearest 0.1 g) before being given to the subject and again when returned by the subject at each 2-week visit.

^j Record of VAS scores for average pain intensity for the day, maximum pain intensity that day, and pain intensity at most recent defecation reported prior to first dose of study medication and on each evening during the study were to be transcribed onto the CRF by study site personnel.

^k Gastrointestinal Quality of Life Index was to be completed at the Week 2 and Week 4 on-therapy assessments only.

^l Only for subjects who participated in the open-label phase.

^m Applicable only for those subjects who healed during either the double-blind or open-label phase of the study. These subjects were contacted every 12 weeks to determine if sphincterotomy had been performed.

Key: CTM = clinical trial material; VAS = visual analog scale

The disposition of patients randomized and included in various analyses were:

Figure 1: Subject Disposition

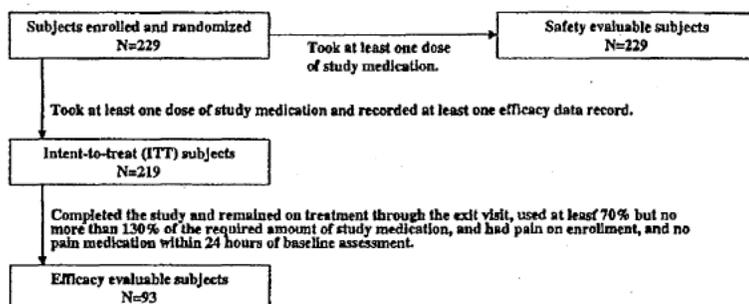


Table 2 presents the number of subjects in each treatment group for each analysis population.

Table 2: Number of Subjects in Each Population (Study NTG 00-02-01)

| Treatment Group | ITT (N=219) | | Efficacy Evaluable (N=93) | | Safety (N=229) | |
|-------------------|-------------|------------------|---------------------------|------------------|----------------|------------------|
| | n | (%) ^a | n | (%) ^a | n | (%) ^a |
| Placebo | 75 | (34.25) | 34 | (36.56) | 78 | (34.06) |
| 0.2% NTG Ointment | 70 | (32.00) | 29 | (31.18) | 73 | (31.88) |
| 0.4% NTG Ointment | 74 | (33.79) | 30 | (32.26) | 78 | (34.06) |

^a Percentages represent the portion (n) of subjects from the total population (N).

Table 3: Study Completion/Withdrawal Information: Intent-to-Treat Population (Study NTG 00-02-01)

| Subject Disposition | Placebo | | 0.2% NTG Ointment | | 0.4% NTG Ointment | |
|--|---------|---------|-------------------|---------|-------------------|---------|
| | n | (%) | n | (%) | n | (%) |
| Number of Subjects Randomized | 75 | | 70 | | 74 | |
| Number of Subjects Completing 56-day Treatment Phase | 67 | (89.33) | 57 | (81.43) | 56 | (75.68) |
| Number of Subjects Who Prematurely Withdrew From Treatment Phase | 8 | (10.67) | 13 | (18.57) | 18 | (24.32) |
| Reason for Premature Withdrawal | | | | | | |
| Adverse Event | 2 | (2.67) | 3 | (4.29) | 10 | (13.51) |
| Protocol Violation/Deviation | 0 | | 0 | | 2 | (2.70) |
| Subject Non-Compliance | 0 | | 3 | (4.28) | 0 | |
| Subject Choice | 3 | (4.00) | 4 | (5.71) | 4 | (5.41) |
| Lost to Follow-up | 3 | (4.00) | 3 | (4.29) | 1 | (1.35) |
| Other ^a | 0 | | 0 | | 1 | (1.35) |

^a The subject who withdrew for "Other" reasons was taking an unexpected holiday.

According to the sponsor, the ITT population for efficacy analysis contained 219 out of 229 randomized patients. In the sponsor's statistical report the following patients were excluded from the ITT population. According to the report, all exclusions were for no baseline data.

PLACEBO

007-111
022-107
048-105

NTG 0.2%

007-110
009-110
028-110

NTG 0.4%

009-105
028-109
030-101
048-107

Review of the case report tabulations for pain response revealed 6 types of problems raising questions of who should be included in the analyses. These were: dropouts(pain data not recorded to endpoint), no pain data, no baseline data, only baseline data, zero pain at entrance, and missing days of pain data in the middle of the treatment period.

The dropouts identified were:

PLACEBO

007-114
007-123
008-102
009-101
019-101
028-107

NTG 0.2%

001-103
001-114
002-101
005-114
008-103
009-103
010-102
014-102
019-108
022-102
048-108

NTG 0.4%

002-103
002-104
007-102
007-107
007-115
008-101
008-104
008-114
010-106
012-104
015-105
021-101
028-105
028-106
048-102

The case report forms were reviewed for these patients. All but two were reported as having not completed the study. Various choices for the primary reason for early termination were provided, i.e. adverse event, protocol violation, patient non-compliance, patient choice, lost to follow-up, and other. While a choice such as protocol violation may have been made, no detail was provided to support the choice, and often other factors such as treatment failure or adverse events seemed probable influences. Adverse events such as headache were frequently present in the NTG ointment groups, and will be discussed in the safety section. Some data recording problems were found. Patient 002-101 had zero recorded for defecation pain when no defecation occurred. Patient 048-108 was called a completer by the investigator, but no pain data was recorded after day. Pain data of patient 028-106 was correct by date but not by days in the study. Such errors were not frequent or systematic, though it must be noted that we do not have the original diaries to correlate with the case report form data.

Adding these withdrawals to those listed by the sponsor, there were 11 in the placebo group, 17 in the 0.2%NTG group and 21 in the 0.4% NTG group.

Some patients had no pain data recorded at all.

PLACEBO

007-111
022-107
048-105

NTG 0.2%

007-110
009-110
028-110

NTG 0.4%

009-105
028-109
030-101
048-107

This list accord with the sponsor's list of exclusions.

Those with no baseline data were:

PLACEBO

022-108

029-110

NTG 0.2%

008-116

048-104 (average pain data not recorded)

NTG 0.4%

009-106

013-102

There were patients with only baseline data.

PLACEBO

None

NTG 0.2%

008-108

010-111

010-112

010-117

NTG 0.4%

007-108

010-109

010-115

011-101

There were patients with no pain at entrance.

PLACEBO

009-109

010-118

NTG 0.2%

None

NTG 0.4%

None

Some patients had missing pain data for considerable lengths of time in the middle of the study with pain data resuming after the hiatus. Centers 007 and 010 had the same PI (Dr. Ziv, Israel).

PLACEBO

007-121

009-102

010-116

010-120

015-106

NTG 0.2%

007-101

007-122
010-113
028-102
NTG 0.4%
007-115
007-120
010-123

According to the sponsor the efficacy ITT analysis should include patients with baseline and some post treatment data. To accord with this definition, patients with no baseline data and only baseline data should also be excluded. This would lead to an additional 2 patients on placebo, 6 on NTG 0.2%, and 6 on NTG 0.4% being excluded. Additionally, the two patients on placebo who had no pain at entrance should be excluded, since they did not have the condition of primary interest.

This would lead to 71 patients on placebo, 64 on NTG 0.2%, and 68 on NTG 0.4% being included in the analysis of the ITT. Since those who withdrew and those with missing data in the middle of the study had anal pain at entrance, baseline and follow-up pain data they should be included in the analyses.

Using their ITT population, the sponsor provided the following demographic information:

Table 4: Demographic and Baseline Characteristics: Intent-to-Treat Population
(Study NTG 00-02-01)

| | Placebo | 0.2% NTG Ointment | 0.4% NTG Ointment |
|---|--------------|-------------------|-------------------|
| | (N=75) | (N=70) | (N=74) |
| | n (%) | n (%) | n (%) |
| Sex | | | |
| Female | 34 (45.33) | 27 (38.57) | 31 (41.89) |
| Male | 41 (54.67) | 43 (61.43) | 43 (58.11) |
| Race | | | |
| Asian | 2 (2.67) | 1 (1.43) | 0 |
| Black | 5 (6.67) | 3 (4.29) | 5 (6.76) |
| Caucasian | 64 (85.33) | 62 (88.57) | 67 (90.54) |
| Hispanic/American or Latino | 4 (5.33) | 3 (4.29) | 2 (2.70) |
| Other | 0 | 1 (1.43) | 0 |
| Age (years) | | | |
| ≤45 | 44 (58.67) | 41 (58.57) | 39 (52.70) |
| 46-64 | 25 (33.33) | 25 (35.71) | 33 (44.59) |
| ≥65 | 6 (8.00) | 4 (5.71) | 2 (2.70) |
| Age (years) | | | |
| N | 75 | 70 | 74 |
| Mean (SD) | 43.1 (13.93) | 43.4 (13.74) | 43.6 (12.72) |
| Min. - Max. | 19.0-78.0 | 20.0-83.0 | 19.0-71.0 |
| Median | 42.0 | 44.5 | 45.0 |
| Missing | 0 | 0 | 0 |
| Weight (kg) | | | |
| N | 75 | 68 | 74 |
| Mean (SD) | 82.8 (21.53) | 79.7 (20.05) | 81.7 (17.23) |
| Min. - Max. | 47.0-157.3 | 45.5-172.7 | 50.0-131.8 |
| Median | 79.5 | 78.0 | 81.3 |
| Missing | 0 | 2 | 0 |
| Height (cm) | | | |
| N | 75 | 69 | 73 |
| Mean (SD) | 170.4 (9.46) | 171.8 (10.75) | 172.5 (9.97) |
| Min. - Max. | 142.0-190.0 | 147.0-198.1 | 146.0-193.0 |
| Median | 170.0 | 174.0 | 174.0 |
| Missing | 0 | 1 | 1 |
| Body Mass Index (kg/m²) | | | |
| N | 75 | 68 | 73 |
| Mean (SD) | 28.4 (6.84) | 26.8 (5.53) | 27.3 (4.70) |
| Min. - Max. | 17.9-48.5 | 15.5-53.1 | 18.8-41.6 |
| Median | 26.7 | 25.9 | 26.2 |
| Missing | 0 | 2 | 1 |
| Alcohol Use | | | |
| No | 54 (72.00) | 43 (61.43) | 44 (59.46) |
| Yes | 21 (28.00) | 27 (38.57) | 30 (40.54) |
| Tobacco Use | | | |
| No | 65 (86.67) | 56 (80.00) | 60 (81.08) |
| Yes | 10 (13.33) | 14 (20.00) | 14 (18.92) |

Cross-reference: Appendix 3.1.3

To enter patients had to have an anal fissure with pain at entrance and a history of at least 50% of days in the preceding 30 days of pain on defecation.

According to the sponsor, anal fissure baseline data was:

**Table 5: Baseline Anal Exam/Assessment:
Intent-to-Treat Population
(Study NTG 00-02-01)**

| | Placebo (N=75) | | 0.2% NTG Ointment (N=70) | | 0.4% NTG Ointment (N=74) | |
|-------------------------------------|-------------------|----------|--------------------------------|----------|--------------------------------|----------|
| | n | (%) | n | (%) | n | (%) |
| Anal Fissure^a | | | | | | |
| Present | 75 | (100.00) | 70 | (100.00) | 74 | (100.00) |
| Fissure Features^b | | | | | | |
| Visible Fibers | 49 | (65.33) | 43 | (61.43) | 52 | (70.27) |
| Indurated edges | 47 | (62.67) | 41 | (58.57) | 56 | (75.68) |
| Sentinel pile | 39 | (52.00) | 31 | (44.29) | 29 | (39.19) |
| Hypertrophied Papilla present | 20 | (26.67) | 15 | (21.43) | 14 | (18.92) |
| No. of Fissure Features | | | | | | |
| <3 features | 49 | (65.33) | 53 | (75.71) | 52 | (70.27) |
| ≥3 features | 26 | (34.67) | 17 | (24.29) | 22 | (29.73) |
| Fissure Length (cm) | | | | | | |
| Mean (SD) | 1.0 | (0.73) | 1.0 | (0.38) | 1.1 | (0.73) |
| Min. - Max. | 0.2-6.0 | | 0.4-2.0 | | 0.1-4.5 | |
| Median | 1.0 | | 1.0 | | 1.0 | |
| Missing | 0 | | 0 | | 0 | |

^a To be eligible for enrollment, subjects were to have a single anal fissure.
^b Subjects are included in all applicable categories.

Average pain was the primary parameter for the efficacy analysis. Per the sponsor the baseline data for average pain was:

**Table A-1.1
Mean Average Pain Intensity (mm) Due to Anal Fissure by Time Period:
Intent to treat population**

| Time Period | Statistics | Placebo (N=75) | 0.2% NTG Ointment (N=70) | 0.4% NTG Ointment (N=74) |
|-------------|-------------|-------------------|--------------------------------|--------------------------------|
| Baseline | N | 73 | 68 | 72 |
| | Mean (SD) | 34.0(22.5) | 32.9(20.7) | 33.4(22.2) |
| | Median | 31.0 | 30.0 | 30.5 |
| | Min. - Max. | 0.0 - 93.0 | 2.0 - 87.0 | 1.0 - 84.0 |

As previously noted, two placebo patients had recorded zero average pain at entrance.

Worst pain at entrance was:

**Table A-1.2
Mean Worst Pain Intensity (mm) Due to Anal Fissure by Time Period:
intent to treat population**

| Time Period | Statistics | Placebo (N=75) | 0.2% NTG Ointment (N=70) | 0.4% NTG Ointment (N=74) |
|-------------|-------------|-------------------|--------------------------------|--------------------------------|
| Baseline | N | 73 | 69 | 72 |
| | Mean (SD) | 51.4(27.3) | 51.8(23.7) | 53.0(25.8) |
| | Median | 52.0 | 55.0 | 53.0 |
| | Min. - Max. | 0.0 - 100 | 8.0 - 100 | 7.0 - 100 |

Defecation pain was:

**Table A-1.3
Mean Defecation Pain Intensity (mm) Due to Anal Fissure by Time Period:
Intent to treat population**

| Time Period | Statistics | Placebo (N=75) | 0.2% NTG Ointment (N=70) | 0.4% NTG Ointment (N=74) |
|-------------|-------------|-------------------|--------------------------------|--------------------------------|
| Baseline | N | 68 | 65 | 63 |
| | Mean (SD) | 48.1(28.2) | 46.6(26.1) | 47.5(26.0) |
| | Median | 50.0 | 44.0 | 46.0 |
| | Min. - Max. | 0.0 - 100 | 0.0 - 100 | 0.0 - 100 |

Some patients on NTG ointment and placebo had no baseline defecation pain recorded. It should also be noted that mean and median worst and defecation pain were more severe than average pain. That would be an expected finding, not only because the intensity would vary throughout the day, but because one of the pain requirements for entrance was pain on defecation in the previous 30 days before randomization.

Dr. Hung provided the following analyses of missing pain data and baseline demographics:
 A total of 10 patients had no pain data at all. In addition, six patients had no baseline pain data but had pain data after baseline; 8 patients had baseline pain data but no pain data recorded after this.

Distribution of the patients with incomplete pain data

| | 0.2% NTG BID (N=73) | 0.4% NTG BID (N=78) | Placebo BID (N=78) |
|---------------------------------|------------------------|------------------------|-----------------------|
| No pain data recorded at all | 3 | 3 | 4 |
| No baseline pain data | 2 | 2 | 2 |
| No post randomization pain data | 4 | 4 | 0 |

Baseline Pain Data

The three treatment groups appeared to be comparable with respect to baseline pain.

Distribution of baseline measurement on daily average pain

| | Mean | SD | Range | 1 st quartile | Median | 3 rd quartile |
|-------------------------|------|------|---------|--------------------------|--------|--------------------------|
| Average Pain | | | | | | |
| 0.2% NTG BID (N=68) | 32.9 | 20.7 | 2 - 87 | 16 | 30 | 46.5 |
| 0.4% NTG BID (N= 72) | 33.4 | 22.2 | 1 - 84 | 14 | 30.5 | 48 |
| Placebo BID (N= 73) | 34.0 | 22.5 | 0 - 93 | 15 | 31 | 50 |
| Worst Pain | | | | | | |
| 0.2% NTG BID (N=69) | 51.8 | 23.7 | 8 - 100 | 33 | 55 | 69 |
| 0.4% NTG BID (N= 72) | 53.0 | 25.8 | 7 - 100 | 31 | 53 | 75 |
| Placebo BID (N= 73) | 51.4 | 27.3 | 0 - 100 | 31 | 52 | 76 |
| Defecation Pain | | | | | | |
| 0.2% NTG BID (N=65) | 46.6 | 26.1 | 0 - 100 | 25 | 44 | 64 |
| 0.4% NTG BID (N= 63) | 47.5 | 26.0 | 0 - 100 | 26 | 46 | 68 |
| Placebo BID (N= 68) | 48.1 | 28.2 | 0 - 100 | 20.5 | 50 | 72 |

RESULTS
EFFICACY
I. PAIN

The protocol specified that a mixed-effects regression model would be used to analyze pain response throughout the trial. Dr. Hung provided the following analysis of these data:

Mixed effects analysis

In the protocol, mixed-effects analysis was proposed as the primary analysis to test whether there is a difference in rate of change of average pain during the course of the trial. A general mixed-effects regression model would be used but the form of the model, i.e., a linear model or a quadratic model, was not specified, nor were the covariance structure of the random-effects components and the covariance structure of the residual pre-specified.

According to the protocol, the primary hypothesis would be tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects). Thus the rate of change in the average pain score is the primary efficacy parameter. There is no specific definition of rate of change in the protocol.

Depending on the model, the rate of change is defined differently. In a linear model (straight line model that the sponsor used in the first study), the rate of change is the slope of the linear trend. In a quadratic model (linear trend plus quadratic trend over time), the rate of change is no longer the slope of the linear trend. Mathematically, it is the first-order derivative of the quadratic function in the model, i.e. the slope of the response curve. Consequently, the rate of change varies over time. According to the sample size plan in the protocol, intercept and slope and their variability were used to project the treatment difference at the end of treatment (day 56) and calculate the sample size. This indicates that the linear model was the model the sponsor had in mind for design and analysis of the study. The linear model was the model used in the sponsor's exploratory analysis to suggest that 0.4% NTG may have a greater rate of change in pain over time in the previous study, NTG 98-02-01.

In Study NTG 00-02-01, the sponsor's analyses and statistical inference were based on the quadratic model with an unstructured covariance matrix for the random-effects component (intercept and slope) and a simple covariance matrix for the residual. This differs from the model used in Study NTG 98-02-01, which is a linear model with a simple covariance matrix for the random-effects component and a simple covariance matrix for the residual. In addition, the model in NTG 00-02-01 contains sites for adjustment and the model in NTG 98-02-01 does not. Adjustment for sites in statistical analysis was not pre-specified in the protocol of either study.

Sponsor's Results

Average Pain

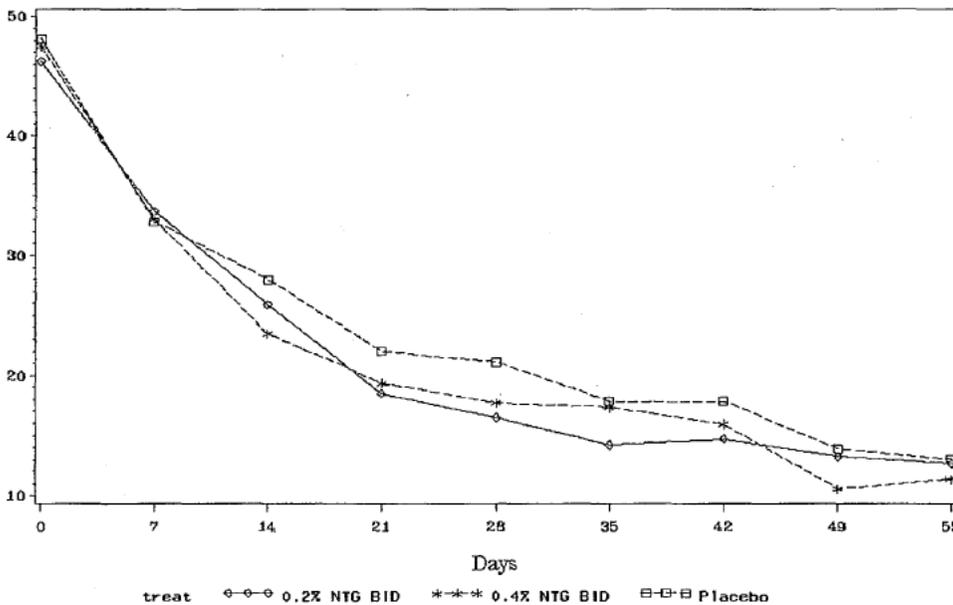
In response to the reviewer's request, the sponsor provided the results of the mixed-effects analyses for average pain, worst pain and defecation pain (dated 1/22/02). Average pain intensity was the primary efficacy parameter. In their analyses, week was the unit of analysis in the primary analysis. The sponsor concluded that in the ITT population, for comparisons with the placebo group, a significant treatment by linear time interaction for average pain intensity was observed for the 0.4% NTG group ($p=0.005$), but not for the 0.2% NTG group; see Table S2-1 which summarizes the sponsor's results from the computer output. In addition, a significant treatment by quadratic time interaction was observed for the 0.4% NTG group. Mean average pain for 0.2% NTG group was also numerically lower than the placebo group throughout the eight weeks of treatment (Sponsor's Table 9, Table A-1.1). To aid in interpretation, the sponsor presented percent improvement from baseline in Figure A-1 to show the quadratic trend. The mean average daily pain score versus days 0, 7, 14, 21, 28, 35, 42, 49, 55 is illustrated in Figure R2-1.

Table S2-1. Testing the differences in linear trend and quadratic trend parameters between treatments on average pain score (Sponsor's results summarized by Reviewer)

| | Linear trend | p-value for linear* | Quadratic trend | p-value for quadratic* |
|------------------------|--------------|---------------------|-----------------|------------------------|
| 0.2% NTG minus placebo | -0.055 | 0.57 | 0.0013 | 0.20 |
| 0.4% NTG minus placebo | -0.27 | 0.005 | 0.0040 | < 0.0001 |

* nominal p-value

Figure R2-1. Mean average daily pain score versus Days 0, 7, 14, 21, 28, 35, 42, 49, 55 (Reviewer's analysis)



Worst Pain and Defecation Pain

Worst pain and defecation pain intensities were secondary efficacy parameters. The sponsor reported that similar patterns seen for these variables when compared to the patterns seen for mean average pain (Sponsor's Tables A-1.2, A-1.3). Individual dosage group versus the placebo group by linear time interactions were observed for both 0.2% and 0.4% groups for worst pain (0.2% $p < 0.04$; 0.4% $p < 0.005$), and defecation pain (0.2% $p < 0.01$; 0.4% $p < 0.04$); see Table S2-2 in the following. In all these comparisons, significant treatment by quadratic time interactions were observed (see also Sponsor's Figures A-2 and A-3, for percent improvement from baseline over weeks).

Table S2-2. Testing the differences in linear trend and quadratic trend parameters between treatments on worst pain and defecation pain (Sponsor's results summarized by Reviewer)

| | Linear trend | p-value for linear* | Quadratic trend | p-value for quadratic* |
|------------------------|--------------|---------------------|-----------------|------------------------|
| Worst pain | | | | |
| 0.2% NTG minus placebo | -0.22 | 0.040 | 0.0035 | 0.005 |
| 0.4% NTG minus placebo | -0.30 | 0.005 | 0.0044 | 0.0004 |
| Defecation pain | | | | |
| 0.2% NTG minus placebo | -0.26 | 0.013 | 0.0030 | 0.012 |
| 0.4% NTG minus placebo | -0.22 | 0.039 | 0.0031 | 0.009 |

* nominal p-value

Reviewer's Analysis and Evaluation

Average Pain

The mixed-effects analysis results depend on the regression model used. As mentioned above, based on the plan of estimating sample size, the model the sponsor intended to use at the time of planning the study was a linear model in which the trend of average pain intensity is linear over time. The previous study NTG98-02-01 also suggested that the linear model was the model to use. In the linear model, the rate of change in pain is the slope of the linear trend that does not change over time. Using the linear model (excluding sites, using a simple covariance matrix for random-effects components and for residual as the sponsor used in Study NTG 98-02-01), the reviewer performed the mixed-effects analysis and the results are summarized in Table R2-1. Adding sites or using an unstructured covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference. Based on the linear model, there was no significant difference in slope (rate of change of average pain intensity over time) among the treatment groups, though the 0.4% NTG group had a numerically greater rate of decrease of average pain intensity compared to the placebo group.

Table R2-1. Slope of change in average daily pain over time
(Reviewer's analysis, using linear model[#])

| | Mean slope | Nominal p-value* |
|-----------------|------------|------------------|
| Placebo (N=75) | -0.37 | --- |
| 0.2% NTG (N=70) | -0.385 | 0.85 |
| 0.4% NTG (N=74) | -0.466 | 0.24 |

* for comparison with the placebo group

[#] the model the sponsor used in Study NTG 98-02-01 (excluding sites, using a simple covariance matrix for random-effects components and for the residual)

The results of the sponsor's mixed-effects analysis, using a quadratic model with the unstructured covariance matrix for the random-effects components and the simple covariance matrix for the residual, were confirmed by the reviewer. The results suggest that the mean average pain intensity over time behaved differently in the 0.4% NTG group as compared to the placebo group. The treatment differences quantified by the differences in the linear and quadratic trends were suggested by the data ($p = 0.005$ for linear trend; $p < 0.0001$ for quadratic trend; Table S2-1 and Figure R2-1). Adding sites or using a simple covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference.

The primary parameter to be tested, however, was the rate of change according to the protocol. As explained above, with the quadratic model, the rate of change (or decrease) in average pain score over time should be the first-order derivative of the quadratic model, i.e. the slope of the mean average pain curve. Consequently the rate of decrease changes over time. This reviewer performed mixed-effects analysis to estimate the differences between 0.4% NTG and placebo in the rate of change of average pain at Days 7, 14, 21, 28, 35, 42, 49 and 55 using the quadratic model the sponsor used. The results of the reviewer's analyses are summarized under Model 1 in Table R2-2 and suggest that the 0.4% NTG group seemed to have a significantly larger rate of decrease in average pain intensity than the placebo group in the first week or possibly two. Thereafter, no statistical significant difference in rate of change favoring 0.4% NTG was found. The numerical differences in the rate of change decreased in days and showed a reversed trend favoring placebo in last few weeks. That is, numerically, the 0.4% NTG group had a smaller rate of decrease in average pain intensity than the placebo group in the last few weeks. Using simple covariance for random effects or excluding the 16 patients who had zero pain at baseline, no baseline pain score

recorded, or no post-randomization pain score recorded (Model 2 or 3), the mixed-effects analyses gave similar results (Table R2-2). Including sites in the model made little change on the results.

Table R2-2. Differences (0.4% NTG minus placebo) in the rate of change of average pain score over weeks (Reviewer's Analysis, using quadratic model)

| | NTG (N=74) | Placebo (N=75) | Model 1 | | Model 2 | | Model 3 | |
|--------|---------------|-------------------|---------|---------|---------|---------|---------|---------|
| | N | n | Diff | p-value | Diff | p-value | Diff | p-value |
| Day 7 | 65 | 72 | -0.22 | 0.014 | -0.23 | 0.008 | -0.24 | 0.009 |
| Day 14 | 62 | 72 | -0.16 | 0.053 | -0.19 | 0.031 | -0.18 | 0.031 |
| Day 21 | 59 | 69 | -0.10 | 0.20 | -0.12 | 0.12 | -0.13 | 0.11 |
| Day 28 | 57 | 69 | -0.045 | 0.56 | -0.067 | 0.40 | -0.076 | 0.35 |
| Day 35 | 57 | 67 | 0.011 | 0.89 | -0.011 | 0.89 | -0.021 | 0.80 |
| Day 42 | 56 | 63 | 0.068 | 0.42 | 0.045 | 0.60 | 0.033 | 0.71 |
| Day 49 | 53 | 67 | 0.12 | 0.17 | 0.10 | 0.27 | 0.088 | 0.35 |
| Day 55 | 46 | 63 | 0.18 | 0.068 | 0.16 | 0.11 | 0.14 | 0.17 |

n= number of patients having average pain score

Diff = difference in the rate of change of average pain score

Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual

Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual

Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain

Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Worst Pain and Defecation Pain

Analyses of worst pain and defecation pain showed a similar pattern as the average pain intensity did; see Tables R2-3, R2-4 and R2-5.

Table R2-3. Slope of change in worst pain and defecation pain over time (Reviewer's analysis, using linear model[#])

| | Mean slope | Nominal p-value* |
|------------------------|------------|------------------|
| Worst Pain | | |
| Placebo (N=75) | -0.51 | --- |
| 0.2% NTG (N=70) | -0.59 | 0.44 |
| 0.4% NTG (N=74) | -0.63 | 0.21 |
| Defecation Pain | | |
| Placebo (N=75) | -0.45 | --- |
| 0.2% NTG (N=70) | -0.60 | 0.12 |
| 0.4% NTG (N=74) | -0.57 | 0.19 |

* for comparison with the placebo group

[#] the model the sponsor used in Study NTG 98-02-01 (excluding sites, using a simple covariance matrix for random-effects components and for the residual)

Table R2-4. Differences (0.4% NTG minus placebo) in the rate of change of worst pain score over weeks (Reviewer's Analysis, using quadratic model)

| | NTG (N=74) | Placebo (N=75) | Model 1 | | Model 2 | | Model 3 | |
|--------|---------------|-------------------|---------|---------|---------|---------|---------|---------|
| | n | n | Diff | p-value | Diff | p-value | Diff | p-value |
| Day 7 | 65 | 72 | -0.25 | 0.010 | -0.25 | 0.012 | -0.26 | 0.009 |
| Day 14 | 62 | 72 | -0.19 | 0.035 | -0.19 | 0.042 | -0.20 | 0.030 |
| Day 21 | 59 | 69 | -0.13 | 0.13 | -0.12 | 0.16 | -0.14 | 0.11 |
| Day 28 | 57 | 69 | -0.068 | 0.42 | -0.062 | 0.47 | -0.081 | 0.36 |
| Day 35 | 57 | 67 | -0.007 | 0.94 | -0.000 | 1.00 | -0.020 | 0.83 |
| Day 42 | 56 | 63 | 0.055 | 0.56 | 0.062 | 0.51 | 0.041 | 0.67 |
| Day 49 | 53 | 67 | 0.12 | 0.25 | 0.12 | 0.23 | 0.10 | 0.33 |
| Day 56 | 46 | 63 | 0.18 | 0.11 | 0.19 | 0.10 | 0.16 | 0.16 |

n= number of patients having worst pain score

Diff= difference in the rate of change of worst pain score

Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual

Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual

Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain

Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Table R2-5. Differences (0.4% NTG minus placebo) in the rate of change of defecation pain score over weeks (Reviewer's Analysis, using quadratic model)

| | NTG (N=74) | Placebo (N=75) | Model 1 | | Model 2 | | Model 3 | |
|--------|---------------|-------------------|---------|---------|---------|---------|---------|---------|
| | n | n | Diff | p-value | Diff | p-value | Diff | p-value |
| Day 7 | 65 | 72 | -0.21 | 0.028 | -0.18 | 0.062 | -0.22 | 0.027 |
| Day 14 | 62 | 72 | -0.17 | 0.060 | -0.14 | 0.13 | -0.18 | 0.054 |
| Day 21 | 59 | 69 | -0.13 | 0.14 | -0.096 | 0.27 | -0.14 | 0.12 |
| Day 28 | 57 | 69 | -0.086 | 0.32 | -0.053 | 0.54 | -0.098 | 0.28 |
| Day 35 | 57 | 67 | -0.043 | 0.63 | -0.010 | 0.91 | -0.056 | 0.54 |
| Day 42 | 56 | 63 | 0.0005 | 1.00 | 0.034 | 0.72 | -0.014 | 0.89 |
| Day 49 | 53 | 67 | 0.044 | 0.67 | 0.077 | 0.45 | 0.028 | 0.79 |
| Day 56 | 46 | 63 | 0.087 | 0.44 | 0.12 | 0.28 | 0.070 | 0.54 |

n= number of patients having worst pain score

Diff= difference in the rate of change of worst pain score

Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual

Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual

Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain

Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Effect of Dropouts

The 0.4% NTG group had a greater percent of the patients who did not complete the pain study compared to placebo (11% for placebo and 24% for 0.4% NTG). Most of the 0.4% NTG group dropped out because of headache compared to placebo. This difference might have an impact on the interpretation of the statistical results from both LOCF analysis and mixed-effects analysis. If anal pain perception is independent of headache perception, then both LOCF analysis and mixed-effects analysis may be valid in

the sense that statistical significance based on p-values can be correctly interpreted. If that is not the case, the p-values of both LOCF analysis and mixed-effects analysis may be biased in either direction for assessing statistical significance. If the patients dropping out of the study because of headache had worsening pain, then the degree of the quadratic trend for the 0.4% NTG group might be greater than that the current data showed. Consequently, this NTG group might show a much worse trend than the placebo group in the later weeks.

Last Available Visit Analysis

Average pain

The last available visit analysis of average pain can be performed only on 205 patients due to exclusion of 14 patients with no baseline average pain or with no post randomization pain data. As in Table R2-6, there was virtually no difference between treatment groups in mean change from baseline of last available visit average pain. Excluding the two placebo patients with zero baseline average pain had little change of the result.

Table R2-6. Mean change in last available visit daily average pain from baseline (Reviewer's analysis)

| | Baseline Mean | Mean change | Nominal p-value ^{\$} | Adj. mean change* | Nominal p-value [#] |
|--------------|---------------|-------------|-------------------------------|-------------------|------------------------------|
| 0.2% NTG BID | 33.8 | -18.9 | 0.78 | -19.0 | 0.73 |
| 0.4% NTG BID | 34.1 | -21.3 | 0.80 | -21.2 | 0.77 |
| Placebo BID | 34.0 | -20.2 | --- | -20.2 | --- |

* adjusted for baseline daily average pain

\$ NTG bid vs. placebo bid, based on mean change

NTG bid vs. placebo bid, based on adjusted mean change

Worst pain and defecation pain

There was no significant difference between the treatment groups with respect to change from baseline to last available visit worst pain or defecation pain (Table R2-7).

Table R2-7. Mean change baseline to last available visit: worst pain and defecation pain (Reviewer's analysis)

| | Baseline Mean | Mean change | Nominal p-value ^{\$} | Adj. mean change* | Nominal p-value [#] |
|------------------------|---------------|-------------|-------------------------------|-------------------|------------------------------|
| Worst Pain | | | | | |
| 0.2% NTG BID | 52.1 | -35.3 | 0.70 | -35.4 | 0.70 |
| 0.4% NTG BID | 53.0 | -35.4 | 0.69 | -34.8 | 0.82 |
| Placebo BID | 51.4 | -33.3 | --- | -33.9 | --- |
| Defecation Pain | | | | | |
| 0.2% NTG BID | 46.0 | -33.6 | 0.60 | -34.8 | 0.17 |
| 0.4% NTG BID | 47.4 | -34.2 | 0.53 | -34.2 | 0.23 |
| Placebo BID | 48.6 | -30.8 | --- | -29.8 | --- |

* adjusted for baseline daily average pain

\$ NTG bid vs. placebo bid, based on mean change

NTG bid vs. placebo bid, based on adjusted mean change

Percent of patients with zero pain at last visit

NTG 0.4% BID group appeared to have fewest patients that had zero average or worst pain at last visit; see Table R2-8.

Table R2-8. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

| | Zero average pain | Zero worst pain | Zero defecation pain |
|--------------|-------------------|-----------------|----------------------|
| 0.2% NTG BID | 14/68 (21%) | 14/68 (21%) | 13/63 (21%) |
| 0.4% NTG BID | 8/72 (11%) | 10/68 (14%) | 13/62 (21%) |
| Placebo BID | 14/71 (20%) | 14/71 (20%) | 12/67 (18%) |

Complete Pain Relief

The number of patients in each group who had pain (average) at baseline and were completely relieved (zero average pain) at last visit. NTG 0.4% BID group appeared to have fewest patients that had zero average or worst pain at last visit; see Table R2-9.

Table R2-9. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

| | Zero average pain | Zero worst pain | Zero defecation pain |
|--------------|-------------------|-----------------|----------------------|
| 0.2% NTG BID | 14/68 (21%) | 14/68 (21%) | 13/63 (21%) |
| 0.4% NTG BID | 8/72 (11%) | 10/68 (14%) | 13/62 (21%) |
| Placebo BID | 14/71 (20%) | 14/71 (20%) | 12/67 (18%) |

While the mixed effects model analyses may suggest a transient difference in the shape of the 0.4% NTG ointment compared to placebo, it is not clear whether this difference would be clinically perceived transiently. At the end of a course of 56 days no difference in pain relief was found. No difference in the number of patients totally relieved of pain was noted. Whatever arguments might be made concerning statistical significance, there do not appear to be meaningful clinical benefits provided.

II. ANAL FISSURE HEALING

For the secondary efficacy endpoint of anal fissure healing there was no benefit versus placebo noted in either the percentage of patients healed:

Comparison of Proportion of Subjects With Healed Anal Fissure in Each Treatment Group Intent-to-Treat Population

| | Placebo (N=75) | 0.2% NTG Ointment (N=70) | 0.4% NTG Ointment (N=74) | P-value |
|--|----------------|--------------------------|--------------------------|--|
| Number (%) of Subjects with Healed Fissure | 44(59%) | 41(59%) | 40(54%) | 0.571 [p = 0.587 (w/ controlling center)] |

or the time to healing:

Time to Healing of Anal Fissures-Results of Cox Regression: Intent-to-Treat Population

| Prognostic Variables | Regression Coefficients (S.E.) | P-value |
|-------------------------------|--------------------------------|---------|
| 0.2% NTG ointment vs. Placebo | 0.0004604 (0.22357) | 0.9984 |
| 0.4% NTG ointment vs. Placebo | -0.07905 (0.22275) | 0.7227 |

III. QUALITY OF LIFE

No benefit of drug to placebo in quality of life assessments were found:

**Table 17: Gastrointestinal Quality of Life Index-Total Score by Study Day:
Intent-to-Treat Population
(Study NTG 00-02-01)**

| Study Day | Statistics | Placebo (N=75) | 0.2% NTG Ointment (N=70) | 0.4% NTG Ointment (N=74) |
|-----------|-------------|-------------------|--------------------------------|--------------------------------|
| Day 1 | N | 75 | 70 | 73 |
| | Mean (SD) | 109.0 (24.47) | 114.9 (18.06) | 112.9 (20.08) |
| | Min. - Max. | 24-140 | 62-141 | 57-142 |
| | Median | 116.0 | 119.5 | 122.0 |
| | Missing | 0 | 0 | 1 |
| Day 14 | N | 73 | 66 | 65 |
| | Mean (SD) | 116.4 (20.77) | 119.7 (17.15) | 117.7 (14.72) |
| | Min. - Max. | 60-144 | 72-141 | 82-139 |
| | Median | 124.0 | 124.0 | 121.0 |
| | Missing | 2 | 4 | 9 |
| Day 28 | N | 69 | 59 | 62 |
| | Mean (SD) | 118.2 (19.47) | 125.1 (14.08) | 121.3 (16.22) |
| | Min. - Max. | 65-144 | 80-144 | 68-140 |
| | Median | 126.0 | 128.0 | 126.0 |
| | Missing | 6 | 11 | 12 |
| Day 56 | N | 66 | 57 | 55 |
| | Mean (SD) | 121.3 (22.66) | 126.8 (14.04) | 125.8 (15.43) |
| | Min. - Max. | 63-144 | 86-144 | 86-144 |
| | Median | 131.5 | 131.0 | 132.0 |
| | Missing | 9 | 13 | 19 |

Total score could range for 0 (least desirable score) to 144 (most desirable score).

SAFETY

No deaths occurred. The sponsor stated that 23 patients withdrew for adverse events and provided the following table.

Table 27: Subjects Who Discontinued Due to Adverse Events: Safety Population (Study NTG 00-02-01)

| Subject No. | Age (Yr) | Sex | Preferred Term | Day of Onset | Severity | Relationship to Study Drug | Duration (Days) | Day of Discontinuation |
|-------------------------------------|----------|--------|-----------------------------------|--------------|----------|----------------------------|-----------------|------------------------|
| Treatment: Placebo | | | | | | | | |
| 007-111 | 33 | Female | Headache ^b | 1 | Severe | Related | 5 | 5 |
| 007-123 | 19 | Female | Pain ^{b,c} | 22 | Moderate | None | 22 | 23 |
| 015-106 | 46 | Male | Hepatitis C ^{b,d} | 3 | Moderate | None | Ongoing | 61 |
| | | | Hemorrhage Rectal | 42 | Mild | None | 3 | 61 |
| | | | Pain Abdominal | 43 | Moderate | None | 5 | 61 |
| 022-107 | 44 | Male | Asthenia ^b | 13 | Moderate | Possibly | 1 | 13 |
| | | | Libido Decreased ^b | 13 | Severe | Possibly | 1 | 13 |
| | | | Pruritus ^b | 13 | Moderate | Possibly | 1 | 13 |
| 028-104 | 48 | Female | Allergic Reaction ^b | 7 | Moderate | None | 9 | 15 |
| Treatment: 0.2% NTG Ointment | | | | | | | | |
| 007-110 | 34 | Female | Headache ^b | 1 | Severe | Related | 8 | 8 |
| 008-108 | 35 | Female | Headache ^b | 1 | Severe | Related | 3 | 44 |
| 009-110 | 41 | Male | Vasodilator Headache ^b | 1 | Mild | Related | 1 | 2 |
| | | | Headache ^b | 1 | Severe | Related | 1 | 2 |
| | | | Headache ^b | 1 | Mild | Related | 1 | 2 |
| 010-112 | 36 | Male | Headache ^b | 1 | Severe | Related | 6 | 6 |
| 010-117 | 36 | Male | Headache ^b | 1 | Severe | Related | 8 | 8 |
| 028-110 | 53 | Female | Constipation ^b | 6 | Mild | None | 7 | 12 |
| | | | Pain ^b | 6 | Mild | Related | 7 | 12 |
| Treatment: 0.4% NTG Ointment | | | | | | | | |
| 001-101 | 60 | Female | Headache | 1 | Moderate | Related | 1 | 57 |
| | | | Headache | 14 | Moderate | Possibly | 1 | 57 |
| | | | Pain ^b | 32 | Mild | Possibly | 1 | 57 |
| | | | Hemorrhage Rectal | 56 | Mild | None | 1 | 57 |
| | | | Pain | 56 | Mild | Possibly | 1 | 57 |
| 002-104 | 53 | Female | Headache | 1 | Moderate | Related | 6 | 57 |
| | | | Headache | 7 | Mild | Related | 41 | 57 |
| | | | Cough Increased | 24 | Mild | None | 3 | 57 |
| | | | Sinusitis | 24 | Mild | None | 3 | 57 |
| | | | Dizziness | 28 | Mild | Possibly | 20 | 57 |
| | | | Twitching | 28 | Mild | Possibly | 20 | 57 |
| | | | Thinking Abnormal ^b | 32 | Moderate | Possibly | 16 | 57 |
| 007-107 | 19 | Female | Headache ^b | 1 | Severe | Related | 11 | 15 |
| | | | Vaginitis | 1 | Mild | None | 3 | 15 |
| 007-108 | 38 | Male | Headache ^b | 1 | Moderate | Related | 8 | 8 |
| 008-101 | 55 | Male | Headache ^b | 1 | Severe | Possibly | 6 | 8 |
| 009-105 | 25 | Female | Vertigo ^b | 2 | Mild | Related | 12 | 15 |
| | | | Nausea | 3 | Mild | Related | 11 | 15 |
| | | | Voices ^b | 3 | Mild | Related | 11 | 15 |
| | | | Tachycardia ^b | 7 | Moderate | Related | 7 | 15 |
| 010-106 | 25 | Male | Headache ^b | 1 | Moderate | Related | 40 | 40 |
| 010-115 | 29 | Male | Headache ^b | 1 | Severe | Related | 3 | 3 |
| 015-105 | 28 | Female | Headache | 1 | Severe | Related | 12 | 15 |
| | | | Rectal Disorder ^b | 9 | Moderate | None | Ongoing | 15 |
| 016-103 | 71 | Female | Headache ^b | 1 | Severe | Related | 2 | 2 |
| | | | Nausea | 1 | Moderate | Possibly | 2 | 2 |
| | | | Pain ^b | 1 | Moderate | Possibly | 2 | 2 |
| 021-101 | 52 | Male | Headache ^b | 1 | Mild | Related | 25 | 29 |
| 028-109 | 40 | Male | Dizziness ^b | 2 | Mild | Related | 3 | 4 |

^a Relative to first dose of study drug (Day 1).
^b Subject discontinued therapy due to this adverse event.
^c Serious adverse event.

The sponsor noted that only 1 of 6 placebo withdrew for headache compared to 5 of 6 intermediate NTG dose and 8 of 12 high dose NTG patients. As previously noted there were 11 placebo, 17 0.2% NTG ointment patients and 21 0.4% NTG ointment patients who terminated early. Review of the case reports shows that many not noted by the sponsor terminated early for headache. For example patient 005-114 (0.2% NTG) terminated for severe headaches as did patients 007-102 and 008-104 (0.4% NTG). Headache was present as an adverse event in 3 other 0.2% NTG patients and 4 other 0.4% NTG patients. This analysis leads to the finding that in this study of those who terminated early 1 out of 11 (9%) placebo patients, 9 out of 17 (53%) 0.2% NTG, and 16 out of 21 (76%) 0.4% NTG patients had headache associated with that early withdrawal. Of those randomized 11 of 73 (15%) placebo patients, 17 of 78 (22%) of 0.2% NTG patients, and 21 of 78 (27%) of 0.4% NTG patients did not complete the study. It should also be noted that while patient 019-108 (0.2%NTG) and patient 008-114 (0.4% NTG) withdrew for “patient choice”, both had elevated liver enzymes at termination. Therefore it appears that treatment with NTG ointment to relieve anal pain associated with anal fissures is not well tolerated and is associated with a high incidence of headache severe enough to lead to discontinuation of that treatment. While no orthostatic hypotension or interaction with drugs such as sildenafil (use was an exclusion criterion) was found in this study, these would be concerns with any nitroglycerin product.

According to the sponsor, the incidence of headache in each randomized group was:

Table 25: Incidence of Adverse Event of Headache: Safety Population (Study NTG 00-02-01)

| | Placebo (N=78) | 0.2% NTG Ointment (N=73) | 0.4% NTG Ointment (N=78) |
|---|-------------------|--------------------------------|--------------------------------|
| Subjects Reporting Headache | 14 (17.95%) | 31 (42.47%) | 40 (51.28%) |
| Subjects Reporting Treatment-Related Headache | 14 (17.95%) | 30 (41.10%) | 40 (51.28%) |
| Subjects Reporting Severe Headache | 1 (1.28%) | 7 (9.59%) | 9 (11.54%) |
| Subjects Treated with Concomitant Medication for Headache | 8 (10.26%) | 11 (15.07%) | 16 (20.51%) |
| Subjects Withdrawn Due to Headache | 1 (1.28%) | 5 (6.85%) | 8 (10.26%) |

Cross-reference: Appendix 3.7.1

Headache is clearly more prevalent in the NTG ointment treated patients versus those on placebo with some suggestion that an increased incidence of headache occurs with increasing NTG dose.

A listing of frequently reported adverse events were provided by the sponsor as follows:

Table 22: Incidence of Frequently Reported (≥1%) Adverse Events* by Body System and Preferred Term – Possibly-Related or Related to Study Drug: Safety Population (Study NTG 00-02-01)

| | Placebo (N=78) | | 0.2% NTG Ointment (N=73) | | 0.4% NTG Ointment (N=78) | |
|-------------------------------------|-------------------|---------|--------------------------------|---------|--------------------------------|---------|
| | n | (%) | n | (%) | n | (%) |
| Subjects With Adverse Events | 18 | (23.08) | 33 | (45.21) | 48 | (61.54) |
| Any Event | | | | | | |
| Body as a Whole | | | | | | |
| Any Event | 16 | (20.51) | 32 | (43.84) | 41 | (52.56) |
| Abscess | | | | | 1 | (1.28) |
| Asthenia | 1 | (1.28) | | | | |
| Headache | 14 | (17.95) | 30 | (41.10) | 40 | (51.28) |
| Pain | 1 | (1.28) | 1 | (1.37) | 4 | (5.13) |
| Pain Abdominal | | | 1 | (1.37) | | |
| Cardiovascular System | | | | | | |
| Any Event | | | 2 | (2.74) | 5 | (6.41) |
| Migraine | | | | | 1 | (1.28) |
| Tachycardia | | | 1 | (1.37) | 2 | (2.56) |
| Vasodilator | | | 1 | (1.37) | 2 | (2.56) |
| Digestive System | | | | | | |
| Any Event | 3 | (3.85) | 5 | (6.85) | 6 | (7.69) |
| Diarrhea | 1 | (1.28) | 2 | (2.74) | | |
| Flatulence | 1 | (1.28) | 1 | (1.37) | | |
| Hemorrhage Rectal | | | | | 2 | (2.56) |
| Nausea | 2 | (2.56) | 1 | (1.37) | 5 | (6.41) |
| Rectal Disorder | 1 | (1.28) | 1 | (1.37) | | |
| Vomit | | | | | 2 | (2.56) |
| Metabolic and Nutritional Disorders | | | | | | |
| Any Event | | | 1 | (1.37) | | |
| Phosphatase Alkaline Increase | | | 1 | (1.37) | | |
| SGOT Increased | | | 1 | (1.37) | | |
| SGPT Increased | | | 1 | (1.37) | | |
| Musculoskeletal System | | | | | | |
| Any Event | | | | | 1 | (1.28) |
| Twitching | | | | | 1 | (1.28) |
| Nervous System | | | | | | |
| Any Event | 1 | (1.28) | 1 | (1.37) | 12 | (15.38) |
| Amnesia | | | | | 1 | (1.28) |
| Dizziness | | | 1 | (1.37) | 8 | (10.26) |
| Intracranial Hypertension | | | | | 1 | (1.28) |
| Libido Decreased | 1 | (1.28) | | | | |
| Nervousness | | | | | 1 | (1.28) |
| Thinking Abnormal | | | | | 1 | (1.28) |
| Vertigo | | | | | 2 | (2.56) |
| Skin and Appendages | | | | | | |
| Any Event | 3 | (3.85) | | | | |
| Pruritis | 1 | (1.28) | | | | |
| Pruritus | 1 | (1.28) | | | | |
| Rash | 1 | (1.28) | | | | |
| Special Senses | | | | | | |
| Any Event | | | 1 | (1.37) | | |
| Pain Ear | | | 1 | (1.37) | | |
| Urogenital System | | | | | | |
| Any Event | | | | | 1 | (1.28) |
| Urination Frequency | | | | | 1 | (1.28) |

* Number and percent of subjects reporting one or more adverse events.

PUBLISHED CLINICAL STUDIES

Five placebo controlled published studies, which evaluated NTG ointment for the relief of anal pain were submitted. These are:

1. Altomare et al, Dis. Colon Rectum 2000; 43: 174-181.
2. Carapeti et al, GUT, 1999; 44; 727-730.
3. Kennedy et al, Dis. Colon Rectum, 1999, 42; 1000-1006.
4. Lund and Scholefield, Lancet, 1997, 349, 11-14.
5. Tander et al, J. Pediatric Surgery, 1999, 34; 1810-1812.

1. Altomare et al.

This study was a multicenter, randomized, placebo-controlled study to compare chronic anal fissure healing with NTG or placebo. Pain relief and safety were also evaluated. Pain on defecation was recorded on a 0-10 scale, zero being no pain. 132 patients were randomized to 0.2% glycerol trinitrate or placebo BID for 4 weeks. Of the 132 randomized patients, 13 dropped out (9 on active, 4 on placebo), leaving 119 to be analyzed.

Anal fissure healing occurred in 29 (49%) NTG treated patients and 31 (52%) of the placebo treated patients. Pain scores decreased from 7.56 ± 1.8 to 4.13 ± 2.7 in the NTG group and from 6.9 ± 2.3 to 3.97 ± 2.8 in the placebo group. While change from baseline was significant in both groups, no statistical difference was found between groups. Pain relief was significantly greater in patients who healed versus those who did not.

Concerning safety, headache was noted in 34% of the NTG patients versus 8% of the placebo patients. Orthostatic hypotension was documented in 4 of the NTG treated patients.

2. Carapeti et al.

This was a randomized, double-blind study of two doses of glycerol trinitrate ointment and placebo to assess healing and pain relief in patients with chronic anal fissure. 70 patients were randomized to placebo, 0.2% NTG TID, and 0.2% TID increasing by 0.1% to a maximum concentration of 0.6% GTN. Treatment was to be continued for 8 weeks followed by a 2 week off treatment observation period. Pain was recorded on daily diary cards using a 0-10 scale. 24 patients were randomized to each of the active groups, while 22 were assigned to placebo.

After 10 weeks the anal fissures had healed in 32% of the placebo patients, compared to 65% and 70% of those on 2% and escalating dose NTG. The comparison of placebo versus both active groups gave a $p=0.008$ by Fisher's Exact test. Pain reduction occurred in all groups, but there were no significant differences in pain relief comparing placebo to the actives ($p=0.4$).

Headache occurred in 72% of patients on NTG and in 27% of those on placebo ($p<0.001$), but no significant difference comparing the rate of headache in the actives. No data on orthostatic hypotension or BP effect are provided.

3. Kennedy et al.

This was a randomized, double-blind study of 0.2% NTG ointment versus placebo for 4 weeks in 43 patients with anal fissures severe enough to warrant sphincterotomy. The primary endpoints were fissure healing and pain relief. 24 patients received NTG and 19 placebo, and 39 patients completed treatment (4 patients discontinued NTG because of headache). At the end of treatment 46% of the fissures had healed in the NTG group compared to 16% in the placebo group (p=0.001). Pain was significantly reduced from baseline in both NTG and placebo treated patients, but no between group significant differences are mentioned for this parameter. Headache was noted in 7 NTG treated patients, and, as mentioned, was severe enough to cause discontinuation of treatment by 4 NTG patients.

4. Lund and Scholefield.

This was a randomized double-blind study of 80 patients with anal fissures to compare 0.2% NTG ointment versus placebo BID for 8 weeks in healing the fissures and relieving pain. 38 patients received NTG as allocated, and 40 received placebo. Healing occurred in 68% of those who received NTG versus 8% of those on placebo (p<0.001). At 2 weeks pain was significantly relieved in both treatment groups, but it was noted that the pain relief was sustained in those receiving NTG, not those on placebo. At 8 weeks pain relief from baseline was reported to be significantly greater in the NTG group compared to placebo. Headache occurred in 22 NTG treated patients versus 7 in the placebo group (p<0.05), and 1 patient on NTG withdrew due to headache.

5. Tander et al.

This was a randomized, double-blind single center study of 0.2% NTG ointment, 10% lidocain ointment or placebo BID for 8 weeks in 62 children with anal fissure to assess healing and pain relief. 31 patients received NTG, 14 lidocain, and 17 placebo. Results were provided in the following chart:

Table 2. Summary of Results

| | No. | Total Healing of the Fissure, (%) | | Relief of Symptoms, (%) | |
|----------------------|-----|-----------------------------------|-------------------|-------------------------|------------|
| | | (+) Responders | (-) Nonresponders | (+) | (-) |
| Group I (NTG) | 31 | 28 (90.32)* | 5 (16.13)* | 29 (93.55)* | 2 (6.45)* |
| Group II (Lidocaine) | 14 | 3 (21.43)†† | 11 (78.57)†† | 7 (50)†† | 7 (50)†† |
| Group III (placebo) | 17 | 8 (47.06) | 11 (64.71) | 9 (52.94) | 11 (64.71) |
| Total | 62 | 39 (62.90) | 27 (43.55) | 45 (72.58) | 19 (30.65) |

*P < .001 NTG treatment compared with lidocaine and placebo treatments.
 ††P > .05 Lidocaine treatment compared with placebo treatment.

No patient experienced headache during the trial. One NTG treated patient had transient fecal incontinence.

The publications do not consistently demonstrate a benefit of NTG ointment compared to placebo in the healing or relief of pain of anal fissures. The finding of a benefit of NTG ointment to heal anal fissures is not confirmed by the sponsor's studies.

VI: DISCUSSION AND RECOMMENDATIONS

The sponsor provided two clinical studies to demonstrate efficacy. The first study (NTG 98-02-01) examined a dose range from 0.75 mg to 4.5 mg daily for 56 days. The primary endpoint was anal fissure healing, and presumably the duration of treatment was thought to be sufficient to heal. However, no significant benefit on healing was found. A secondary endpoint was relief of anal fissure pain (average pain, worst pain, and defecation pain), but pain was not required at entrance. Noting that it was likely that there would be missing pain data, the sponsor selected a mixed effects model to analyze the pain data available. No specific model was pre-specified, and, rather than analyze per randomized group, the sponsor post-hoc pooled the active dose groups in their analysis. Given the surprising null result on anal fissure healing and a possible statistical active drug effect on anal fissure pain, the sponsor performed a second study (NTG-00-02-01) using relief of anal fissure pain as the primary endpoint. The doses of active were limited to 0.75 mg and 1.5 mg given daily in divided doses for 56 days. Healing and quality of life were secondary endpoints. No difference of active drug versus placebo in the last available observation analysis or in those with no pain at the end of 56 days of therapy was found. No benefit of anal fissure healing or quality of life was found.

A mixed effects analysis to evaluate the rate of change over time was pre-specified in the second study, but without details of the model terms to be used. The sponsor using a quadratic term in the model and evaluating the shapes of the curves, found statistically significant difference in linear trend and quadratic trend for the 1.5 mg dose compared to placebo. Dr. Hung, using the linear mixed effects model that was used by the sponsor in the first study to evaluate the rate of change as specified in the protocol, found no significant difference between active drug and placebo.

Since the quadratic model gave somewhat different results, Dr. Hung found that the quadratic model results suggested an early difference in the rate of change, but no sustained difference. If one considered this early difference real and due to active therapy, tachyphylaxis to nitroglycerin might provide a rationale. It is not clear that any early difference in the shape of the curves could be perceived clinically. Even if an early clinical benefit could be established, the lack of a sustained benefit and no difference in total relief of pain at the end of therapy would raise questions of clinical efficacy. Directions for use would be hard to write, since the 56 days of therapy were not needed for any purported benefit. Also undercutting the significance of any difference found was the fact that many patients withdrew from active therapy because of headache. It is unclear what effect headache had on anal pain perception in these patients. It is unclear how a treatment to relieve anal pain can be considered effective if it produces pain such as headache.

What was clear from the sponsor's studies was that NTG ointment was not well tolerated. Of those who withdrew from the active treatment, most did so for headache. A larger number of patients remained in the study, but had headache, often requiring analgesics. More serious adverse reactions, such as postural hypotension and interactions with drugs like sildenafil, were not noted, but remain concerns with any NTG product.

In conclusion, we find that no benefit of NTG ointment to relieve anal pain associated with anal fissures was established by the studies provided. The studies did confirm that the drug was not well tolerated, producing an amount of frequent and severe headache, not acceptable in a drug purported to relieve pain. Consequently we recommend that a not approvable action be taken.

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