FDA Advisory Committee Briefing Document

Cellegesic™ Nitroglycerin Ointment 0.4%

NDA 21,359

Cardiovascular Renal Drug Advisory Committee

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. EXECUTIVE SUMMARY

1.1 Introduction

This briefing document provides an overview of the data that collectively provide the evidence that Cellegesic™ nitroglycerin (NTG) ointment 0.4% safely and effectively accelerates the relief of pain associated with a chronic anal fissure. There is currently no drug approved specifically for the treatment of chronic anal fissure in the United States.

1.2 Pathophysiology of Anal Fissure

An anal fissure is a linear tear in the thin epithelial layer (anoderm) lining the anal canal. It is a common, painful, but otherwise benign disorder that affects both men and women. The cardinal symptom of chronic anal fissure is severe, often disabling local pain that may interfere with the patient's daily activities, including work. Anal fissure pain is due primarily to the increased tone and spasm of the internal anal sphincter (IAS) that is frequently present in patients with a chronic anal fissure.[1,2] No direct correlation has been documented between pain severity and degree of tissue damage.

1.3 Current Treatment Practice

Pain is the complaint that brings the anal fissure patient to the physician's office, and relief of the pain is what the patient wants and needs most, with healing an important but secondary benefit. Reduction of anal fissure pain and anal fissure healing are not necessarily concordant.

Although standard treatment with dietary fiber supplements, bulk laxatives and sitz baths may provide temporary relief, these treatments are minimally effective and do not significantly affect long-term outcome in patients with a chronic anal fissure. Currently, the only available effective treatment is surgery with the potential for post-surgical complications, including fecal incontinence and other bowel disorders in up to 35% of patients.[3]

Medical treatment can also significantly reduce internal anal sphincter tone without risk of incontinence by anal canal application of nitroglycerin (NTG) ointment. NTG is converted in tissue to nitric oxide (NO), a neurotransmitter that relaxes smooth muscle of the internal anal sphincter and increases anodermal blood flow.[2] These pharmacodynamic effects form a rational basis for the use of NTG to treat the pain of chronic anal fissure.

1.4 Public Health Rationale

The incidence of anal fissure was estimated to be 765,000 during October 2003 to September 2004.[4] In the absence of an approved medical treatment some 84,000 uses have been recorded during this period for extemporaneously compounded nitroglycerin ointment for treating an anal fissure. A study by Cellegy Pharmaceuticals of nitroglycerin ointment extemporaneously compounded by 24 retail pharmacies found that 46% did not meet United States Pharmacopeial (USP) criteria for potency and or content uniformity.[5] In addition, the ointment was dispensed in jars and therefore not able to be dosed accurately.

Historically a chronic anal fissure has been treated with surgery, usually an internal lateral sphincterotomy (sectioning of internal anal sphincter muscle fibers) that may

have post- operative complications of up to 35% fecal incontinence.[3] Nitroglycerin is a medical treatment for anal fissure pain that does not result in fecal incontinence.

In the United Kingdom, where data are available, the incidence of anal fissure surgery has decreased approximately 50% since the usage of nitroglycerin ointment was recommended in 1999 whereas surgery for all other anal conditions has remained essentially constant.[6] The availability of a nitroglycerin ointment product has been estimated to significantly reduce the cost to the health care system[7]. Use of nitroglycerin is widely accepted in the management of chronic anal fissure and a number of clinical guidelines in the United Kingdom and United States endorse its use.[8-11] Initial use in United Kingdom was compounded nitroglycerin ointment; since May 2005, Rectogesic® rectal ointment (brand-name of Cellegesic in Europe) has been marketed. Even in the absence of an approved medical product in the United States, both the American Gastroenterological Association[12] and the American Society of Colon and Rectal Surgeons committee on anal fissures[13] have recommended a trial of nitroglycerin ointment before considering surgery.

1.5 Pharmacology of Cellegesic Nitroglycerin Ointment 0.4%

Cellegesic nitroglycerin ointment 0.4% contains nitroglycerin in a petrolatum base formulated for delivery to the anal canal.

Nitroglycerin is rapidly metabolized by most tissues to 1,2 and 1,3 dinitrates and to nitric oxide (NO) and other compounds.[14] At the cellular level, organic nitrates (including NTG) are metabolized to release nitric oxide (NO). Nitric oxide is also produced endogenously through the action of the enzymes, NO synthases, and has been shown to be an important signaling molecule with diverse physiologic functions. In the gastrointestinal tract endogenous NO is thought to be a neurotransmitter that mediates relaxation of smooth muscle and controls the anorectal inhibitory reflex in animals and man. The finding that exogenously administered NO mimics inhibitory nerve activation and mediates relaxation of the human internal anal sphincter supports this hypothesis. These pharmacodynamic effects form a rational basis for the use of NTG to treat the pain of a chronic anal fissure.

The mean bioavailability of 375 mg Cellegesic nitroglycerin 0.2% (0.75 mg nitroglycerin) applied intra-anally is approximately 50% with significant variability (NTG 98-02-02).

Unlike the vascular tissue effects of nitroglycerin, tolerance does not appear to occur in the internal anal sphincter.[15] Using internal anal canal pressure as a surrogate, measurements after the first dose and after daily anal treatment with 0.2% or 2.0% nitroglycerin ointment for 12 weeks in patients were similar.[16]

1.6 Efficacy, Including Regulatory History

The results of three well-controlled clinical trials provide the evidence that Cellegesic nitroglycerin ointment effectively and safely accelerate the relief of pain associated with a chronic anal fissure. The effective dose is 375 mg ointment (1.5 mg nitroglycerin) applied intra-anally every 12 hours for up to 56 days. In each study efficacy was determined as the rate of change in pain intensity by the subjects who kept a daily diary for eight weeks in which they recorded their 24-hour average pain and pain following a bowel movement any day one occurred. The rate of change in pain intensity stated clearly in the protocols and statistical analysis plans was the endpoint in each of the three studies, not the difference between active treatment and placebo at any specific

time point. The rate of change was determined using all the available data by a mixed-effects regression model.

NTG 98-02-01 (Study 1)
In this first study, healing of the chronic anal fissure was the primary endpoint of an eight arm dose response study (0.0, 0.375, 7.5 and 1.5mg nitroglycerin b.i.d. and t.i.d. every 12 hours). Although healing occurred in over 65 % of the Cellegesic nitroglycerin ointment treated group, it was not statistically better than placebo. However, the secondary endpoint, rate of change in pain intensity, in the active treatment group was markedly better than placebo. A difference among groups was seen as early as 4 days. The Division agreed that a study with rate of change in pain intensity as the primary endpoint was acceptable and study 1 would be considered supporting evidence for a pain relief indication.

NTG 00-02-01 (Study 2)
Study 1 provided the evidence that the rate of change in pain intensity, should be the primary endpoint. In study 2 rate of change in pain intensity, was the primary endpoint. The three arms of this study were placebo, 0.75 mg and 1.5 mg nitroglycerin dosed every 12 hours for 56 days. The acceleration of rate of change in pain intensity, was significantly better in the active treatment group (1.5 mg NTG) compared to placebo ($p < .05$) over 56 days. The Division would not accept the results because a quadratic term included in the mixed-effects regression model to compensate for the curved pain intensity data during the later half of the study had not been pre-specified in the protocol or statistical analysis plan. The Cellegy biostatisticians believe a quadratic term is an integral part of the mixed-effects regression model to address curvilinear results and is not necessary to be pre-specified. The assessors of Cellegy's marketing approval application at the United Kingdom Medicines and Healthcare Products Regulatory Agency agreed and approved the product for marketing in that country based on Studies 1 and 2 (1.5mg NTG every 12 hour dosage for up to 8 weeks of treatment).

NTG 03-02-01 (Study 3)
The results from Studies 1 and 2 demonstrated that the rate of change in pain intensity, was linear for the first 21 days of treatment. In discussions with the Division, the rate of change in pain intensity, over the first 21 days of treatment became the primary endpoint under a special protocol assessment in which the Division requested the last observation be carried forward (LOCF) for those subjects who dropped out due to a nitroglycerin headache. The acceleration of pain relief was statistically significantly better in the Cellegesic nitroglycerin group compared to placebo ($p < .05$) utilizing the last observation carried forward for the three subjects that dropped out due to a nitroglycerin-induced headache. To determine which subjects dropped as a result of developing a nitroglycerin headache, a nitroglycerin headache was defined in the protocol as one that occurs within 30 minutes of clinical trial material administration. Cellegy believes the addition of LOCF to the mixed effects regression model is statistically inappropriate. Utilizing all available pain intensity data with no imputation, the p value for the primary endpoint is $< .0309$.

After establishing the primary endpoint in study 3 as the rate of change in the 24-hour average pain intensity during the first 21 days of treatment, studies 1 and 2 were reanalyzed utilizing this endpoint and submitted to the NDA. The results are recorded below.

Table 1

Rate of Change in 24-Hour Pain Intensity over 21 and 56 Days

	Rate of change in 24-hour pain intensity Through Day 21	Through Day 56
Study 1	N=69 p < .0063	N=69 p< .0001
Study 2	N=141 p < .0388	N=141 p < .039
Study 3	N=187 p < .0309	N187 P < .0447
Studies 1,2 and 3	N=397 p < .0007	N=397 p < .0001

Further analysis of the results submitted to the NDA revealed that Cellegesic nitroglycerin ointment was most effective in those subjects whose baseline pain VAS rating was > 50mm (moderate to severe) in study 3 (p <.036) and study 2 (p <.040). The time to 50% improvement was also significantly better in the Cellegesic nitroglycerin ointment group compared to placebo.

Analyses of the results of study 3, clearly provide evidence that the effects of Cellegesic nitroglycerin ointment are not confounded by analgesic use, and that headache is not a significant predictor of drop-outs.

A dose response analysis was performed on the combined data from Studies 1 and 2 (where there were multiple doses). For 21 days, the dose by day interaction was significant (p<.0039), with the smallest effective dosage occurring at 0.4% NTG (p<.0040). Through 56 days, the dose by linear time interaction was significant (p<.0001), with smallest effective dosage occurring at 0.4% NTG (p<.0001).

1.7 Safety

In patients treated with Cellegesic nitroglycerin ointment 0.4%, the most common treatment related adverse event was dose-related headache that occurred with an incidence of 64%. Adverse reactions from clinical studies are displayed by system organ class in Table 2.

Table 2 Frequent Treatment Emergent Adverse Event

System Organ Class	Frequency	Adverse Reaction
Nervous system disorder	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhea, anal discomfort, vomiting, rectal bleeding, rectal disorder
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, anal burning and itching
Cardiovascular system disorders	Uncommon	Tachycardia

Within the system organ class, the adverse reactions are listed by frequency using the following groupings: very common (>1/10), common (>1/100<1/10), uncommon (>1/1000<1/100).

1.8 Risk Benefit Profile

The potential risks of Cellegesic nitroglycerin ointment 0.4% are related to the neurological, gastrointestinal and cardiovascular effects of nitroglycerin, primarily headache, dizziness, nausea, and hypotension. Headache may be managed with use of a mild analgesic[45] and concerns about dizziness and hypotension, well known nitroglycerin adverse effects, by precautions proposed in the labeling. The dosage of Cellegesic nitroglycerin ointment 0.4%, 3 mg NTG daily is smaller than the dosage of many of the nitroglycerin dosage forms approved in the United States for treating angina pectoris and congestive heart failure.

In Australia there have been 10 complaints of headache following sale of 200,000 tubes of Rectogesic® (brand name of Cellelgesic outside US) since 1999. There has been only one adverse event report, a headache, following sale of 28,000 tubes of Rectogesic rectal ointment in England since May 2005 even though the product bears a black triangle, the symbol urging physicians to report ALL adverse events.

Availability of Cellegesic nitroglycerin ointment 0.4% will provide the patient who has a painful, chronic anal fissure a safe, effective, good manufacturing practices (GMP) product with a definitive dose to ameliorate his/her pain.

Since the introduction in the United Kingdom of compounded nitroglycerin ointment for treating anal fissures, surgical intervention has decreased approximately 50%[4]

A medical treatment that reduces by 50% the need for surgery that has a post-operative incidence of fecal incontinence up to 35% in patients with a chronic anal fissure is a distinct benefit.

Cellegesic nitroglycerin ointment 0.4% is an effective medical treatment of a chronic anal fissure that accelerates a clinically useful reduction in pain compared to placebo without inducing fecal incontinence.

1.9 Overall Summary and Conclusions

- The efficacy data (rate of change in 24-hour average pain intensity) at 21 days for the third phase 3 trial meet the FDA requirements under a special protocol assessment.
- The efficacy of Cellegesic nitroglycerin ointment 0.4% at a dose of 375 mg (1.5 mg NTG) every 12 hours for up to 21 and 56 days of continuous use in accelerating the relief of pain has been demonstrated in three placebo-controlled trials in subjects with a chronic anal fissure.
- Cellegesic nitroglycerin ointment 0.4% is most effective in chronic anal fissure subjects with moderate to severe pain (baseline VAS >50mm).
- The reduction in anal fissure pain upon defecation supports and confirms the efficacy.
- Any improvement in pain is an essential component of the management of chronic anal fissure, with the rate of improvement being very important to the progress of treatment.

- Fissure healing occurred in 67% of subjects although not significantly different from placebo.
- The safety profile of nitroglycerin and Cellegesic nitroglycerin ointment 0.4% is well established.
- Headache, the primary side effect of nitroglycerin may be managed by use of a mild analgesic.
- The post marketing exposure in several countries is associated with very few complaints of headache. In the United Kingdom data are available that indicate the frequency of anal fissure surgery has been reduced approximately 50% since 1999 with the introduction of the recommendation to use nitroglycerin ointment to treat patients with an anal fissure. Surgery for all other anal disorders has remained essentially constant.
- Surgery with its cost and post-operative complications is the only effective treatment available at this time. There is no drug approved in the United States for the treatment of the pain associated with a chronic anal fissure
- Based on evidence in the medical literature and the clinical experiences of their members, both the American Gastroenterological Association and the American Society of Colon and Rectal Surgeons committee on anal fissure have recommended that pharmacological relaxation of the internal anal sphincter with a product, such as nitroglycerin ointment be considered before surgical treatment of a chronic anal fissure.
- The dosage of Cellegesic nitroglycerin ointment 0.4% demonstrated to safely and effectively accelerate the rate of pain relief in subjects with a chronic anal fissure is 3 mg nitroglycerin/day, smaller than many other approved nitroglycerin products.
- Based on the collective efficacy and safety results, 375 mg Cellegesic nitroglycerin ointment 0.4% every 12 hours for up to 8 weeks is suitable for prescribing by physicians and use by patients with a painful chronic anal fissure.

2. INTRODUCTION AND PUBLIC HEALTH

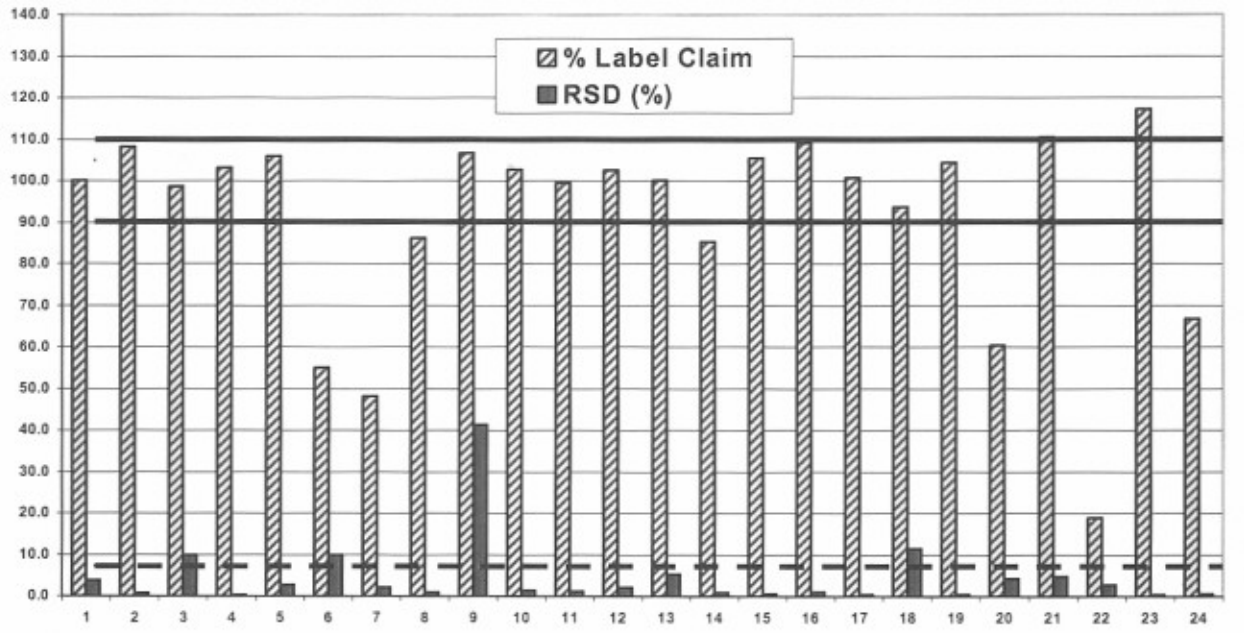
A chronic anal fissure is a lesion of the distal anal canal associated with increased tone of the internal anal sphincter that may be sufficiently painful to interfere with a person's daily activities.[17] A decrease in internal anal sphincter tone may be obtained by sphincterotomy, i.e. sectioning some of the muscle fibers of the sphincter, a surgical procedure that may result in incontinence in up to 35 % of subjects.[3] Relaxation may also be induced by medical treatment with nitroglycerin (NTG), a treatment not associated with incontinence.[1,18]

Pain is a significant symptom experienced by patients that is often inadequately treated by physicians. The most significant determinant for poor quality of life is pain associated with an anal fissure and evidence suggests that the worse the pain the poorer the health of the patient[17]. Griffin and his associates have shown that pain as assessed using a visual analog scale (VAS) correlated well with scores on the SF-36, a well-accepted quality of life instrument. Clearly, any improvement in pain is an essential component of the management of chronic anal fissure, with the rate of improvement being very

important to the progress of treatment.

Our most recent estimate of incidence in the United States is 765,000 probably an under reported number.[4] Based on Verispan diagnosis data for October 2003 – September 2004, 84,000 uses were recorded for compounded non-GMP NTG ointment to treat these patients. Cellegy has evaluated the ability of 24 retail pharmacies to extemporaneously compound 0.3% nitroglycerin ointment. The results (Figure 1) provide evidence that 46% did not meet USP requirements for potency and or content uniformity, posing a potential problem of safety and/or inadequate effectiveness.[5] In addition, the ointment was dispensed in jars, making accurate dosing impossible.

Figure 1
Quality of Extemporaneously Compounded Nitroglycerin Ointment



Label claim- USP specification 90-110%,
Content Uniformity- USP specification ≤ 6% RSD (relative standard deviation)

2.1 Rationale for the Treatment of Anal Fissure with Cellegesic Nitroglycerin Ointment

Nitroglycerin (NTG) has been used for more than a century to alleviate the pain of angina pectoris associated with coronary artery insufficiency. It has been administered to humans by oral, sublingual, buccal, intravenous, and transdermal routes. Nitroglycerin is approved for marketing by the U.S. Food and Drug Administration (FDA) for the relief of symptoms associated with coronary artery insufficiency (angina pectoris) and for intravenous use in congestive heart failure. Routes of administration include oral extended-release capsules [2.5, 6.5, and 9 mg], buccal tablets [2 and 3 mg], sublingual tablets [0.3, 0.4 and 0.6 mg], and metered sublingual aerosol spray [0.4 mg/spray], transdermal (patch [0.1-0.8 mg/hr], ointment [2%], and intravenous [10-40 mg/100 mL or 0.5 and 5.0 mg/mL solution]). The dosage of Cellegesic nitroglycerin ointment 0.4% demonstrated to safely and effectively accelerate the rate of pain relief in subjects with a

chronic anal fissure is 3 mg NTG /day, smaller than many of the approved products for the treatment of angina pectoris or congestive heart failure.

The clinical pharmacology and pharmacokinetics of NTG have been studied extensively, and the safety profile is well characterized.[14,19-21] Recent advances in our understanding of the mechanism(s) of action of NTG, particularly the role of its primary metabolite, nitric oxide (NO), in the physiology of both cardiac and non-cardiovascular systems has led to renewed interest in the use of this compound for a variety of disorders, including treatment of anal fissure.

At the cellular level, organic nitrates (including NTG) are metabolized to release nitric oxide (NO).[14] Nitric oxide is also produced endogenously through the action of the enzymes, NO synthases, and has been shown to be an important signaling molecule with diverse physiologic functions.[22-25] In the gastrointestinal tract endogenous NO is thought to be a neurotransmitter that mediates relaxation of smooth muscle and controls the anorectal inhibitory reflex in animals and man.[26-28] This hypothesis is supported by the finding that exogenously administered NO mimicked inhibitory nerve activation and mediated relaxation of the human internal anal sphincter (IAS).[26] These pharmacodynamic effects form a rational basis for the use of NTG to treat the pain of a chronic anal fissure.

Cellegy Pharmaceuticals has developed Cellegesic™ nitroglycerin ointment 0.4% for the relief of the pain associated with a chronic anal fissure. There is currently no drug approved by the FDA specifically for the treatment of an anal fissure.

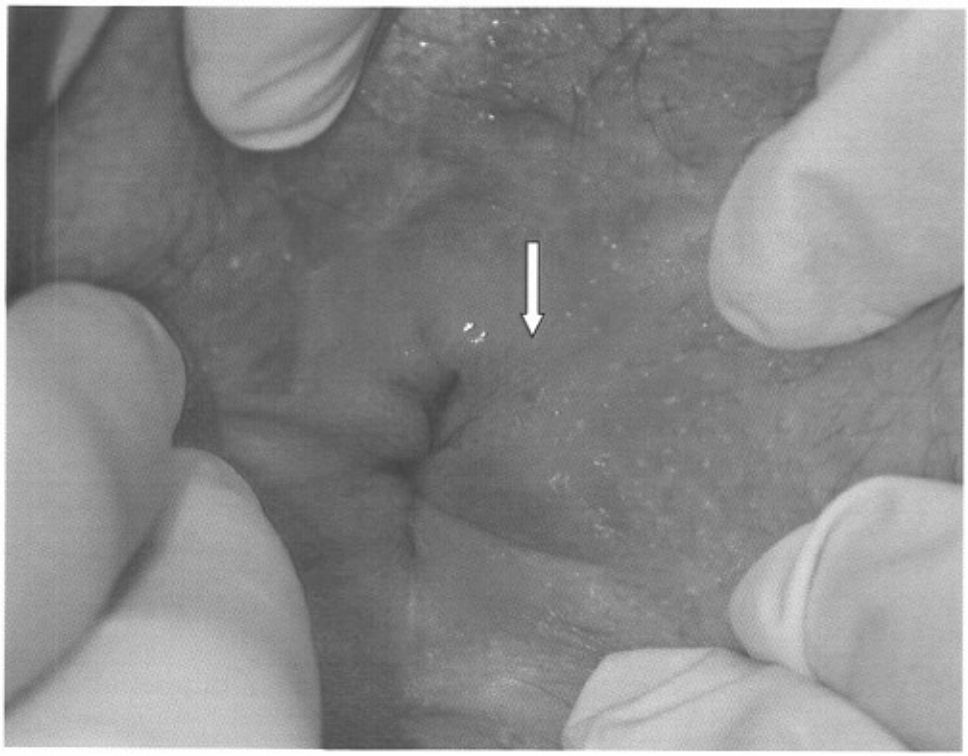
The Division has raised several concerns regarding the Cellegesic NDA, such as effect size and effect of acetaminophen on anal fissure pain. We will address these issues and summarize the trial designs and results that provide the evidence and support the conclusion that Cellegesic nitroglycerin ointment 0.4% is safe and effective for accelerating the relief of chronic anal fissure pain. These data were obtained from three phase 3, (NTG 98-02-01, NTG 00-02-01 & CP125 03-02-01) randomized, parallel groups, double blind and placebo controlled studies and one Phase 1 bioavailability study (NTG 98-02-02).

3. PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF ANAL FISSURE

An anal fissure is a linear tear in the thin epithelial layer (anoderm) lining the anal canal (Figure 2). It is a common, painful, but otherwise benign disorder that affects both men and women. The presence of an anal fissure is frequently associated with elevated intra-anal pressure (IAP) generated by hypertonicity of the IAS and a subsequent decrease in blood flow to the anoderm.[29-32] An anal fissure is usually located in the posterior midline. The posterior midline location may be due to the distribution of the inferior rectal artery. In approximately 85% of the population, the posterior commissure of the anal canal is less well perfused than the other parts of the anal canal. When sphincter tone is increased, the blood supply may be further compromised due to compression of the vessels passing vertically through the muscle fibers of the internal anal sphincter.

Figure 2

Photograph of a Chronic Anal Fissure



These 2 conditions predispose an individual to develop an anal fissure, especially in the posterior midline. An acute fissure that does not heal becomes a chronic fissure or anal ulcer. A chronic anal fissure is characterized by the persistence of the fissure accompanied by a hypertrophied anal papilla, a sentinel tag or pile, induration of the lateral margins of the fissure, and/or exposure of the IAS fibers. No direct correlation has been documented between pain severity and degree of tissue damage.

3.1 Current Treatment Practice

The cardinal symptom of chronic anal fissure is severe, often disabling local pain that may interfere with the patient's daily activities, including work. Anal fissure pain is due primarily to increased tone and spasm of the IAS, and in part to the passage of fecal matter over an open wound. Pain is the complaint that brings the anal fissure patient to the physician's office, and relief of the pain is what the patient wants and needs most, with healing an important but secondary benefit. Reduction of anal fissure pain and anal fissure healing are not necessarily concordant. It should be emphasized that the pain may be intermittent and varies daily, in part dependent on the number of bowel movements that may occur. Pain is a significant deterrent to well-being, and any relief is essential. For many physicians pain control ranks relatively low among patient care priorities.

Although standard treatment with dietary fiber supplements, bulk laxatives and sitz baths may provide temporary relief, these treatments are minimally effective and do not significantly affect long-term outcome in patients with a chronic anal fissure. Mild analgesics, such as aspirin, have little effect on the fissure pain and local anesthetics

effects are short lived and have the potential for inducing local hypersensitivity. Currently, no drug product has been approved in the US for treatment of chronic anal fissure, and the only established effective treatment is surgery.

Successful sphincterotomy is associated with a significant decrease in intra-anal pressure, relief of pain, and healing in up to 95% of cases.[31] However, the costs associated with the surgical procedure and the potential post-surgical complications, including fecal incontinence and other bowel disorders in up to 35% of patients, may limit this approach for many patients.[3] Multiple factors including multiparity, age, constipation, and previous surgery contribute to the occurrence of these complications; therefore, caution in the use of surgery is recommended, particularly in the elderly or individuals with diarrhea, irritable bowel syndrome, or recurrence of fissure after previous surgery.

Medical treatment can also significantly reduce internal anal sphincter tone without risk of incontinence by application of NTG ointment. NTG is converted in tissue to nitric oxide (NO), a neurotransmitter that relaxes smooth muscle of the internal anal sphincter and increases anodermal blood flow.[29] These pharmacodynamic effects form a rational basis for the use of NTG to treat the pain of chronic anal fissure.

Based on evidence in the medical literature and the clinical experiences of their members, both the American Gastroenterological Association[12] and the American Society of Colon and Rectal Surgeons committee[13] on anal fissure have recommended that pharmacological relaxation of the IAS be considered before surgical treatment of a chronic anal fissure. Nitroglycerin ointment has the required pharmacodynamic effect.

4. PHARMACOLOGY CELLEGESIC NTG OINTMENT 0.4%

4.1 The Product

Cellegesic nitroglycerin (NTG) ointment 0.4% has been developed for the topical treatment of anal fissures. It is formulated as an ointment containing 0.4% (w/w) NTG in white petrolatum, lanolin, propylene glycol, sorbitan sesquioleate, water, and paraffin wax. A dose of 375 mg of ointment contains 1.5 mg NTG.

4.2 Pharmacokinetics

4.2.1 Metabolism

Nitroglycerin is first metabolized to 1,2 and 1,3 glyceryl dinitrates and further to mono glycerol and nitric oxide. The elimination half life is 1-4 minutes.[14]

4.2.2 Bioavailability

The bioavailability of Cellegesic NTG ointment 0.2% (0.75 mg NTG) was determined in 6 healthy volunteers (study NTG 98-02-02) as a single dose and multiple doses of Cellegesic NTG ointment 0.2% compared to a constant rate infusion of NTG. Systemic bioavailability of NTG was approximately 50% following application of ointment to the anal canal mucosa. The mean AUCs for single and multiple dose applications were almost identical, as was the mean bioavailability and comparable mean absorption times. The ratio of 1,2-glyceryl dintrate to 1,3-glyceryl dinitrate was similar in both the intravenous and single dose phases but was approximately three times lower after the seventh dose in the multi-dose phase. Mean clearance of NTG following intravenous administration based on arterial plasma concentration was considerably lower than

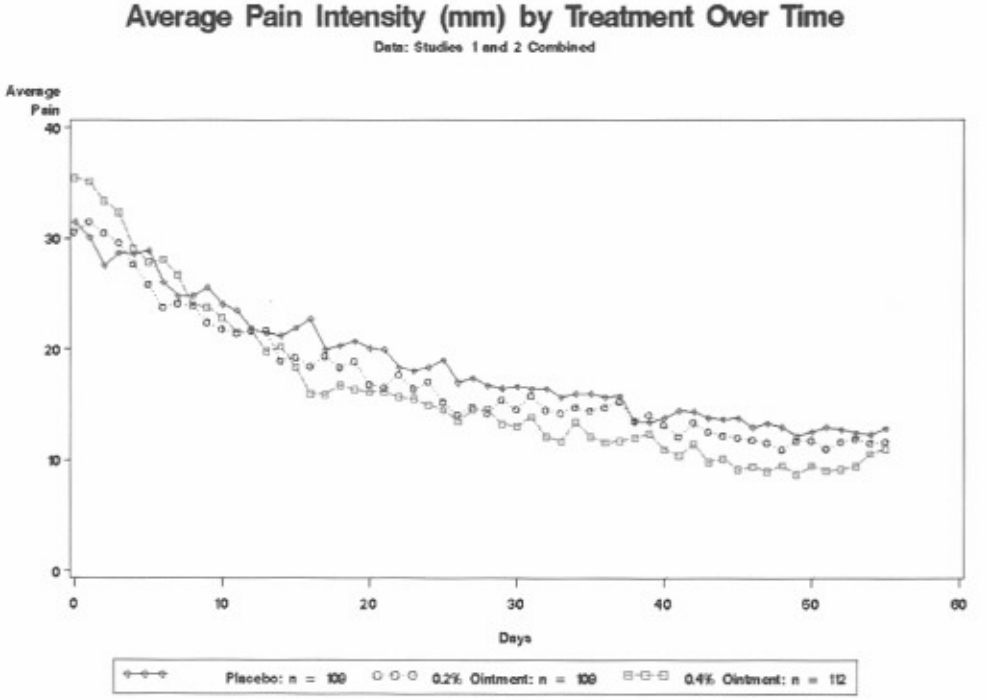
previously measured using venous plasma concentration. This may have been due to extensive extraction in the superficial tissues of the arm from which antecubital blood was collected.

Considerable inter-individual variability in mean absorption and bioavailability was noted and raised the possibility that absorption of NTG from the anal canal may not be a simple first- order process. This variability has also been noted in other studies of NTG absorption in normal volunteers.

4.2.3 Dose Response

A dose response analysis was performed on the combined data from Studies 1 and 2 (where there were multiple doses). For 21 days, the dose by day interaction was significant (p<.0039), with the smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0040). Through 56 days, the dose by linear time interaction was significant (p<.0001), with the smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0001). These effects are clearly seen in Figure 3.

Figure 3



4.3 Mechanism of Action

At the cellular level, NTG is metabolized to release nitric oxide (NO). NO interacts with the heme moiety of guanylyl cyclase,[23] enhancing guanylyl cyclase activity and increasing intracellular levels of cGMP.[23-25] The subsequent activation of cGMP-dependent protein kinase leads to muscle relaxation through a number of proposed pathways.

NO is synthesized endogenously from the amino acid L-arginine by the action of nitric oxide synthase (NOS). Three forms of NOS exist; constitutive or endothelial NOS,

inducible NOS, and neuronal NOS. Within the gut, there is evidence that NO is the neurotransmitter that mediates inhibitory reflexes. Nitric oxide synthase is found within enteric neurons. NO is released upon stimulation of enteric, nonadrenergic, noncholinergic nerves and exogenously applied NO mimics the action of nerve stimulation on smooth muscle relaxation.[25] The balance between stimulation (contraction) and inhibition (relaxation) controls the movement of the gastrointestinal tract contents.

4.4 Pharmacodynamics: Effects Relating to the Proposed Indications

NTG relaxes most smooth muscle, including bronchial, gastrointestinal tract, urethral, uterine, arteries and veins. It is well established that the pharmacological actions of NTG are mediated through the generation of NO, which is an endogenously produced signaling molecule with multiple functions in the body.[26,33]

As part of the role of NO in the gastrointestinal tract, there is evidence from investigations in humans that NO mediates the relaxation of the IAS.[35-36]

4.5 Tolerance

From the early use of NTG in myocardial ischaemia, it was known that repeated use of NTG resulted in a tolerance to the effects of the drug.[34] These mechanisms are incompletely understood, but include both physiological counter- regulation of nitrate-induced vasodilation as well as alterations in vascular biochemical pathways.[23-28]

Wang et al,[15] demonstrated that intra-anal administration of continuous doses of NTG (20 to 200 ug/hour or bolus doses of 20 to 200 ug/minute every 30 minutes) does not produce tolerance in the IAS of rats. *In vitro* data from rat IAS muscle bath experiments demonstrated reduced cGMP levels after pre-incubation and challenge with NTG in vascular smooth muscle tissue, but not in IAS smooth muscle, which suggested that tolerance to NTG does not develop in the IAS.

Using anal canal pressure as a surrogate for internal anal sphincter tone, Ciccaglione AF et al[16] found the anal pressure responses in humans were essentially the same after administration of 0.2% and 2.0% nitroglycerin ointment daily for 12 weeks, further evidence for the lack of tolerance developing in human internal anal sphincter.

5. CLINICAL PHASE 1 AND PHASE 3 STUDIES

5.1 Overview

The results from three multi-center, double-blind, parallel groups, placebo controlled, randomized studies provide the evidence that Cellegesic nitroglycerin ointment is safe and effective for the relief of the pain associated with a chronic anal fissure. These studies are: NTG 98-02-01, NTG 00-02-01 and CP125 03-02-01. These will be discussed as Study 1, Study 2 and Study 3 respectively to simplify their designation.

Studies 1, Study 2, and Study 3 evaluated intra-anal application of approximately 375 mg of Cellegesic NTG ointment for the treatment of chronic anal fissure. Three concentrations of Cellegesic NTG ointment were evaluated in these studies: 0.1% (0.375 mg NTG), 0.2% (0.75 mg NTG), and 0.4% (1.5 mg NTG). These studies provided the primary efficacy and safety data and are supplemented by the bioavailability and safety data from 6 healthy volunteer subjects in a phase 1, open-

label, 3-treatment, crossover study. All these studies were sponsored by Cellegy Pharmaceuticals, Inc.

An overview of the three well-controlled trials and combinations of these trials is recorded in Table 3. The subjects in these trials were to apply 375 mg of the designated Cellegesic™ nitroglycerin ointment concentration or placebo intra-anally every 12 hours. The dose of NTG applied was 375/1000 x the concentration of NTG in the ointment. Reports of studies in the literature contain the percentage of NTG but seldom the quantity of ointment; thus, the dose of NTG in most other studies cannot be precisely determined. Each evening at bed time the subject completed a diary containing 100 mm horizontal visual analog scales (VAS) marked no pain at the left end (0 mm) and worst pain imaginable at the right end (100 mm). The subject made a vertical hash mark on the horizontal line he or she estimated to be his or her 24 hour average pain. A similar VAS scale was used to estimate the intensity of pain during the last bowel movement any day one occurred. Intensity of the pain was determined as the distance in mm from 0 to the hash mark. The intensity of each day's estimation (24-hour average pain and defecation pain) was used in analyzing the results of these trials.

The differences among the three trials are recorded in Table 4. In Study 1, anal pain and or bleeding for at least 30 days plus the presence of a fissure on physical examination were the entry criteria. In Study 2, it was required that the anal pain occur at least three times a week for the 30 days prior to entry. In Study 3 each subject was also required to have a VAS pain intensity of at least 35mm and moderate or severe pain on defecation for two days prior to being enrolled. The subjects in Study 3 were also required to have a sentinel pile on physical examination, an accepted physical finding of chronicity of the fissure.

The subjects returned to the study site every two weeks until the fissure healed or for eight weeks in Study 1. The fissure was observed during these visits by a trained observer who was not privy to any information about the subject. Healing was considered complete reepithelialization of the fissure site. In Study 2 the subject returned to the study site every two weeks for eight weeks regardless of whether the fissure healed. In Study 3 the subject returned on days 1, 7, 21, 35 and 56.

The endpoints in the protocols of each study are recorded in Table 4. The first two trials produced the basis for the appropriate endpoint, the rate of change in 24-hour average pain intensity over the first 21 days of treatment. During this period the decrease in pain intensity in the NTG group was linear and curvilinear thereafter. Based on these results the primary endpoint was established with the Division via a special protocol assessment for Study 3.

To compensate for the curvilinearity a quadratic term was added to the mixed effects regression model analysis of Study 2 results. The Division would not accept the use of the quadratic term, since it was not stated specifically in the statistical analysis plan. However, the United Kingdom Medicines and Health Care Research Agency (MHRA) approved Cellegesic for marketing based on studies 1 and 2 using a quadratic term in the analyses for Study 2, accepting that a quadratic term's use was inherent and appropriate in the mixed-effects regression model.

5.2 Phase 3 Studies: Study Design and Evaluations

Study Design

Three randomized, double blind, placebo controlled, parallel groups phase 3 studies (Studies 1, 2 & 3) were conducted in subjects with a chronic anal fissure.

Study 1 was designed to determine the dose and dosing interval of Cellegesic NTG ointment that best promoted the complete healing of chronic anal fissure; relief of pain was originally considered a secondary endpoint. This multicenter study was conducted in the United States. Subjects were randomly assigned to 1 of 8 treatment groups, differing in the NTG dose (none, 0.1% [0.375 mg NTG], 0.2% [0.75 mg NTG], or 0.4% [1.5 mg NTG]) and the number of doses applied each day, either twice daily (b.i.d.) or 3 times daily (t.i.d.). Subjects were to self-administer the ointment to the anal canal until complete healing occurred or for 56 days, whichever occurred first. Bulk laxatives, sitz baths and acetaminophen were allowed *ad libitum.*

Study 2 was designed to determine the dose of Cellegesic NTG ointment that best promoted the relief of pain associated with chronic anal fissure. This multi-center study was conducted in the United States, Germany, the United Kingdom, and Israel. Subjects were randomly assigned to 1 of 3 treatments, differing in the NTG dose (none, 0.2% [0.75 mg NTG], or 0.4% [1.5 mg NTG]); all doses were applied on a b.i.d. schedule. Subjects were to self-administer the ointment to the anal canal for 56 days, regardless of healing status. Daily fiber intake was required and provided, and 1 sitz bath was allowed per day. Acetaminophen self-administered to control an headache was restricted to eight 650mg doses.

Study 3 was designed to determine the effect of Cellegesic NTG ointment 0.4% b.i.d. on the rate of change in the 24-hour average pain intensity associated with chronic anal fissure over a 21-day treatment period[1]. This multi-center study was conducted in the United States, Germany, Serbia and Montenegro, Russia, and Israel.

Subjects were randomly assigned to 1 of 2 treatments (placebo ointment or Cellegesic NTG ointment 0.4% [1.5 mg NTG]); all doses were applied approximately every 12 hours. Subjects were to self-administer the ointment to the anal canal for 56 days, regardless of healing status. If the subject used a dietary fiber supplement or stool softener for the week prior to enrollment, the subject was instructed to continue daily use with the same dose. Only 1 sitz bath was allowed per day. Fiber supplements, stool softeners, or sitz baths were not to be prescribed if the participant was not already using them. Acetaminophen was restricted to eight 650mg doses in US and eight 1000mg doses in Europe during the first 21 days and allowed *ad libitum* thereafter.

In bioavailability study NTG 98-02-02 the pharmacokinetics and bioavailability of single and multiple doses of intra-anal Cellegesic NTG ointment 0.2% (0.75 mg NTG) were compared to an intravenous infusion of NTG in healthy volunteers. The mean bioavailability was 50% with considerable inter-subject variation, a not uncommon finding for topically applied drugs.

[1] A nitroglycerin headache was defined in study 3 as one that occurs within 30 minutes of clinical trial material administration. The definition was put in the protocol. To allow determination of which if any subjects discontinued the trial due to a nitroglycerin headache.

6. BIOSTATISTICS AND EFFICACY RESULTS OF STUDIES 1, 2 AND 3

6.1 Mixed-Effects Regression Model

The mixed-effects regression model was the method used to determine the statistical significance of the effect of Cellegesic NTG ointment 0.4% on chronic anal fissure pain in Studies 1, 2 and 3.

The mixed-effects regression model uses all available data from each subject to compare rates of change in the outcome measure. The advantages of the model over traditional endpoint (e.g., LOCF) analyses are 1) it makes use of all data collected from each subject, thereby increasing statistical power; 2) eliminates bias due to exclusion of collected data from the analysis; 3) does not rely on a single measurement for each subject to characterize response to treatment, and 4) subjects leaving the trial early are not artificially assumed to have completed the trial. Relative to traditional "repeated measures" ANOVA, the advantages of the mixed-effects regression model are that 1) it does not assume an overly restrictive correlational structure in which variances and covariances are assumed to be constant over time, and 2) it can accommodate missing data and drop-outs. Relative to multivariate growth curve models, the advantage of the mixed-effects regression model is that it does not require any subject with missing data to be excluded from the analysis, a requirement that may produce a situation in which the subjects in the analysis are quite dissimilar to the subjects randomized to the treatment conditions, leading to biased statistical estimates and tests of hypotheses.

An important feature of generalized mixed-effects regression models is their treatment of missing data. Since there are no restrictions on the number of observations per individual, subjects who are missing data from a prescribed measurement occasion are not excluded from the analysis, nor do we need to impute a value for their missing observation(s). 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 similarly treated subjects. Thus, the model estimates the subject's trend across time based on whatever data that subject has, augmented by the time-trend that is estimated for subjects in that treatment group, and the effects of other covariates in the model.

As Laird[37] points out, random-effects models for longitudinal data using maximum likelihood estimation provide valid inferences in the presence of ignorable non-response. Ignorable non-response means that the probability of non-response is dependent on observed covariates and previous values of the dependent variable from the subjects with missing data. The notion here is that if subject attrition is related to previous performance, in addition to other observable subject characteristics, then the model provides valid statistical inferences for the model parameters. Since many instances of missing data are related to previous performance or other subject characteristics, the random-effects approach provides a powerful method for dealing with longitudinal datasets in the presence of missing data.

Table 3: Overview of Controlled Clinical Studies and Their Combined Analyses to Support the Efficacy of Cellegesic NTG Ointment 0.4% for the Treatment of Chronic Anal Fissures

Study No. (Sponsor) Investigators (Country)	Start Date	Study Design	Treatment Regimen (Dose)	Subjects Enrolled ITT Population	Sex (M/F) Race (C/B/O)[a]	Age Mean: ±SD (yr) (Range)[a]
Study 1 NTG 98-02-01 (Cellegy Pharmaceuticals, Inc.) Multicenter (USA)	07/98	Double-blind, randomized, placebo-controlled, parallel-groups. Subjects were discontinued when healed.	Approximately 375 mg of placebo or Cellegesic NTG ointment b.i.d. placebo 0.1 % NTG (0.375 mg) 0.2% NTG (0.75 mg) 0.4% NTG (1.5 mg) t.i.d. placebo 0.1 % NTG (0.375 mg) 0.2% NTG (0.75 mg) 0.4% NTG (1.5 mg) Duration: 56 consecutive days or until fissure healed	304/289[b]	55%/45% 82%/8%/10%	44.0±13.56 (19-81)
Study 2 NTG 00-02-01 (Cellegy Pharmaceuticals, Inc.) Multicenter (USA, Israel, United Kingdom, and Germany)	05/00	Double-blind, randomized, placebo-controlled, parallel-groups. Subjects were required to stay in study for 56 days even if healed or pain gone.	Approximately 375 mg of placebo or Cellegesic NTG ointment b.i.d. placebo 0.2% NTG (0.75 mg) 0.4% NTG (1.5 mg) Duration: 56 consecutive days	229/219	58%/42% 88%/6%/6%	43.4±13.43 (19-83)
Study 3 CP125 03-02-01 (Cellegy Pharmaceuticals, Inc.) Multicenter (USA, Germany, Serbia and Montenegro, Russia, & Israel)	06/03	Double-blind, randomized, placebo-controlled, parallel-groups. Subjects were required to stay in study for 56 days even if healed or pain gone.	Approximately 375 mg of placebo or Cellegesic NTG ointment b.i.d. placebo 0.4% NTG (1.5 mg) Duration: 56 consecutive days	193/187	36%/64% 95%/2%/3%	47.7±11.03 (20-76)
Combined Anaylsis of **Studies 1, 2 & 3**	NA	Double-blind, randomized, placebo-controlled, parallel-groups.	Approximately 375 mg of placebo or Cellegesic NTG ointment b.i.d. placebo 0.4% NTG (1.5 mg) Duration: 56 consecutive days, or until fissure healed in **Study 1**	421/407	45%/55% 90%/4%/5%	45.9±12.83 (19-78)
Combined Analysis of **Studies 2 & 3** Subjects with Sentinel Pile at Baseline	NA	Double-blind, randomized, placebo-controlled, parallel-groups.	Approximately 375 mg of placebo or Cellegesic NTG ointment b.i.d. placebo 0.4% NTG (1.5 mg) Duration: 56 consecutive days	263/255	40%/60% 93%/4%/3%	46.6±11.52 (19-76)

Table 4: Differences Among Studies 1, 2 and 3 in Designs and Endpoints

	Study 1	Study 2	Study 3
Primary Endpoints	Fissure healing	Rate of change of the 24-hour average pain intensity over a 56-day period	Rate of change of the 24-hour average pain intensity over a 21-day period
Secondary Endpoints	Rate of change of the 24-hour average pain intensity, worst pain and defecation pain over a 56-day period and safety	Rate of change of defecation pain over a 56-day period and safety, time to healing, safety, and gastrointestinal quality of life	Time to 50% improvement in the 3-day average of 24-hour average pain intensity
Tertiary Endpoints			Rate of change of the 24-hour average pain intensity over a 56-day period Rate of change of pain intensity during last bowel movement of the day over a 21-day treatment period Rate of change of pain intensity during last bowel movement of the day over a 56-day treatment period Complete healing of chronic anal fissures over a 56-day treatment period Safety **NTG headache occurs within 30 minutes of NTG administration**
Inclusion Criteria	Chronic anal fissure(s); pain and/or bleeding for at least 30 days prior to enrolment	A single anal fissure & pain after at least 50% of bowel movements each week for 30 days prior to enrolment	A single anal fissure and sentinel pile; pain especially on defecation ≥3 days a week for 30 days prior to enrolment; 24-hour average VAS pain score ≥35 mm for each of 2 days before study treatment, and defecation pain of moderate or severe intensity on at least 1 of the 2 days
Treatment Regimens	3 NTG concentrations (0.1%, 0.2%, & 0.4%) or placebo; 2 dosing frequencies (b.i.d. & t.i.d)	2 NTG concentrations (0.2%, & 0.4%) or placebo; 1 dosing frequency (b.i.d.)	1 NTG concentration (0.4%) or placebo 1 dosing frequency (b.i.d.)
Duration of Treatment	56 days or until fissure healing	56 days without regard to healing status	56 days without regard to healing status
Concomitant Anorectal Treatments	Subject was allowed to use dietary fiber supplement or stool softeners & sitz baths	Standard therapy (psyllium, 1 tablespoon in 8 oz. of water b.i.d., & sitz baths, no more than 1 per day if needed)	If a dietary fiber supplement or stool softener was used during the week before enrollment, the subject was allowed to continue their use at the same dose; no more than 1 sitz bath per day was allowed

In longitudinal studies, ignorable non-response falls under Rubin's[38] "missing at random" (MAR) assumption, in which the missingness depends only on observed data, and has also been termed "random dropout" by Diggle and Kenward[39]. It is important to distinguish MAR data from what Little[40] refers to as "covariate-dependent" dropout, in which the missing data can be explained by model covariates (the independent variables in a model), but does not depend on observed values of the dependent variable. Covariate-dependent drop-out is sometimes viewed as a special case of Rubin's[38] "missing completely at random" (MCAR) assumption, and has also been called "completely random drop-out" by Diggle and Kenward[39]. The essential distinction between MAR and covariate-dependent missing data, is that in addition to allowing dependency between the missing data and the model covariates, MAR allows the missing data to be related to observed values of the dependent variable. This distinction is important because longitudinal statistical procedures like Generalized Estimating Equations (GEE)[46] assume that the data are covariate-dependent, while full likelihood-based procedures like the random-effects models allow for MAR data. Thus, if the missing levels of the dependent variable are thought to be related to observed previous levels of the dependent variable (e.g., subjects with very bad or very good scores drop-out), then likelihood-based random-effects analysis may be valid, however GEE analysis, in general, is not.[46]

With respect to the proposed study, the MAR assumption is quite reasonable. One of the key concerns is drop-out due to headache. Headaches increase with increasing dosage of NTG ointment. Since treatment is in the model, the effect of treatment on drop-out due to headache is ignorable for the generalized mixed-effects regression model proposed in this study. Analysis of study 2 VAS-scores provided evidence that little or no remaining anal fissure pain was present in NTG-treated participants who dropped out of the study due to headache. This finding indicates that dropout due to headache was unrelated to the intensity of anal fissure pain, and if anything, patients dropped out of the study due to headache only after their anal fissure pain had remitted. There were 14 patients in the Cellegesic arm of study 2 who discontinued the study and experienced headaches. Random intercept and slope models were fitted to compare 1) linear time trends for patients with and without headache and 2) the effect of headache severity on 24-hour average pain intensity. The analyses indicate that neither incidence of headache nor headache severity is significantly related to rate of change of anal fissure pain. Patients with headache have lower average pain score compared to those without headache over time (Figure 4). Among participants who dropped out of the study, there was no association between severity of headache and anal fissure pain (Figure 5).

Figure 4

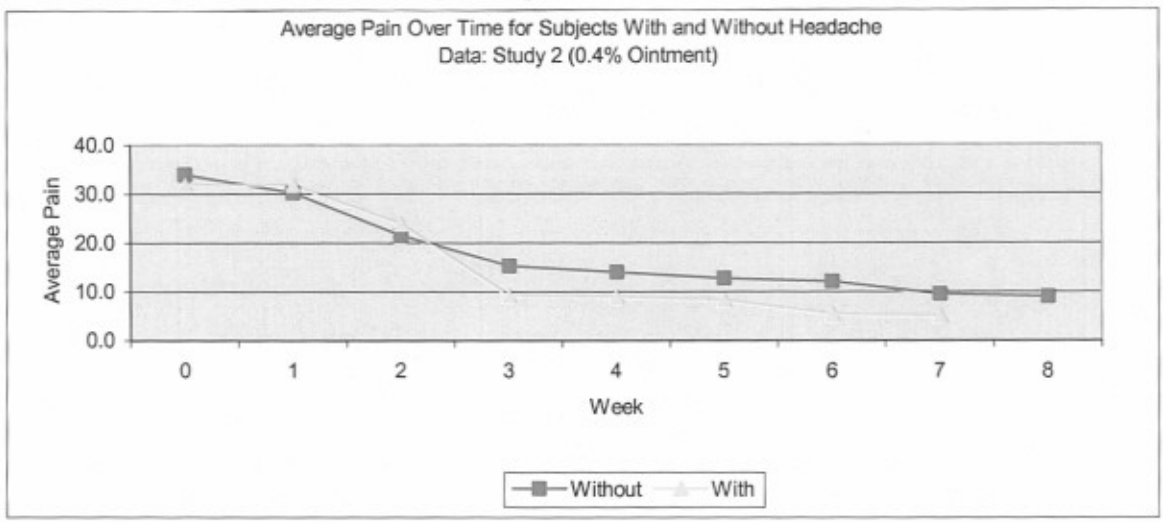
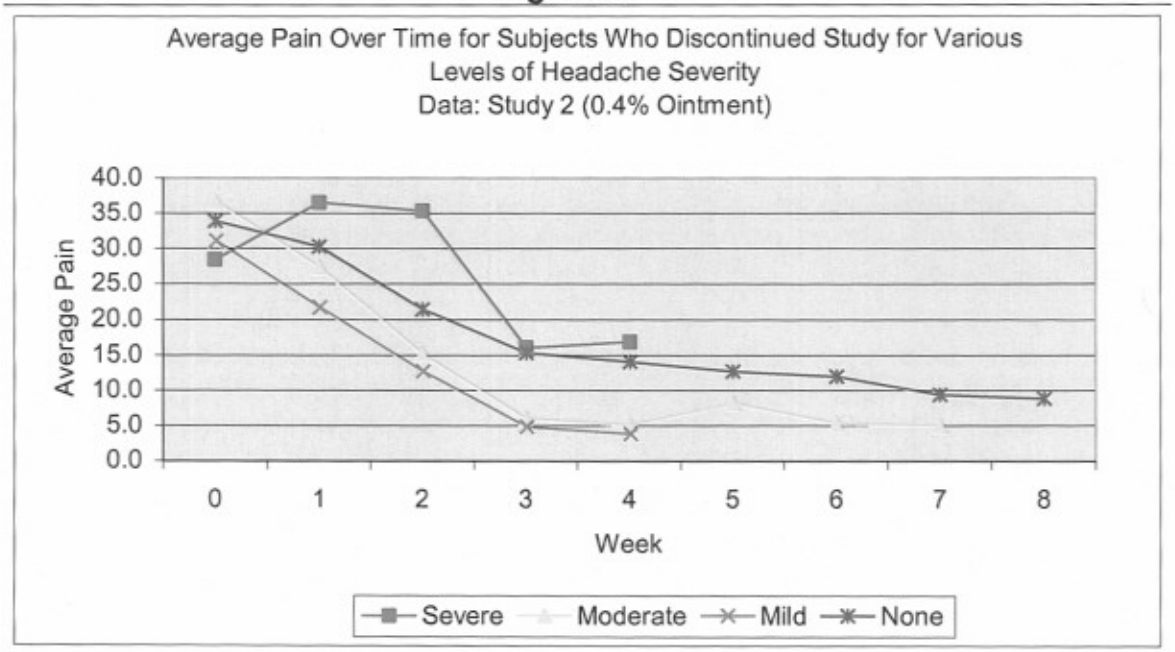


Figure 5



In light of these results we feel that the assumption of ignorable non-response (i.e., MAR) that is implicit in the generalized mixed-effects regression model is well justified. It should be noted that these assumptions are, in fact, far more general than the very restrictive assumptions which underlie the last observation carried forward (LOCF) end-point analysis. As proven by Mohlenberghs[41], LOCF methods are biased both under MCAR and MAR, whereas likelihood based methods (such as the methods used in the analyses of all three trials) are unbiased under both MCAR and MAR, and provide stable and reasonable results even when MAR is violated.

As a further demonstration of the robustness of our results to the assumption of missing data assumptions, we fit a missing not at random (MNAR) shared parameter model to the data in study 3, where headache, the random effects, and headache by

random effects interactions were shared between the response model and a model for drop-out. The treatment by linear time interaction for average VAS pain ratings remained statistically significant in this model. Interestingly, headache was not a significant predictor of drop-out.

6.2 Quadratic Terms

In terms of model specification, analyses were conducted with and without quadratic time trends; however in all cases, the treatment by linear time trend was the primary endpoint. The inclusion of this higher order polynomial term in the model allowed us to incorporate non-linearities in the time trends, particularly for the 56 day analysis. Inclusion of the quadratic term in the mixed-effects regression model was prespecified in the SAP for the 56 day analysis in study 3.

6.3 Requirement for Combining Sites

Finally, in Study 3, FDA required that we combine centers with fewer than six subjects. In addition, despite our objections, FDA required that for the primary endpoint, 21 day average VAS pain ratings, post-dropout data for subjects who dropped out of the study due to nitroglycerin induced headache (008-052, 037-159, and 037-380) be imputed as the last available measurement prior to dropout plus or minus normally distributed random error with mean zero and variance equal to the residual variance from a model fitted using all available data.

6.4 Efficacy Evaluations

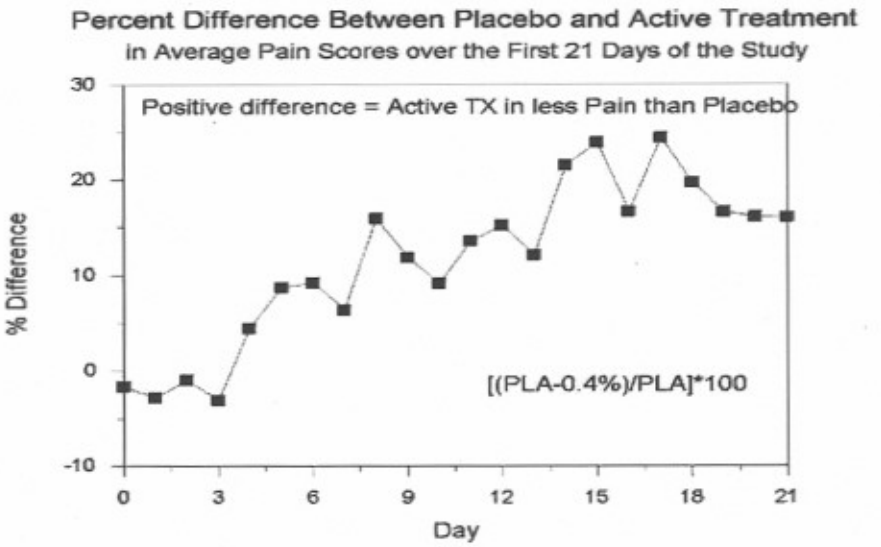
6.4.1 Study 3 Analyses

Three subjects dropped out of the study due to nitroglycerin-induced headache (008-052, 037-159, and 037-380). For the primary endpoint, 21 day 24-hour average VAS pain ratings, post-dropout data for these subjects were imputed as the last available measurement prior to dropout plus or minus normally distributed random error with mean zero and variance equal to the residual variance from a model fitted using all available data. Prior to analysis, centers with fewer than six subjects were combined as previously described. The new centers were 100, which is a combination of centers 22, 3, 17, and 29; 101, which is a combination of centers 14 and 8; 102, which is a combination of centers 19 and 39; 103, which is a combination of centers 25, and 5; 104, which is a combination of centers 34, 36, and 1; 105, which is a combination of centers 28, and 10; 106, which is a combination of centers 6, and 20; and 107, which is a combination of centers 30, and 27.

Statistical analysis of the primary endpoint, 24-hour average pain VAS ratings, over the first 21 days of the study, revealed statistically significant decreases in average pain ratings for Cellegesic NTG ointment 0.4% treated subjects relative to controls ($p<.05$). This was true for both the analysis that used all available data from each subject ($p<.0243$), as well as for the analysis that imputed the last observation plus random error for the subjects dropping out due to NTG related headache ($p<.0498$). Although not the primary endpoints, individual point in time contrasts revealed significant differences for the average of days 13-15 ($p<.003$), 16-18 ($p<.004$), and 19-21 ($p<.028$). Point in time contrasts for the average of days 7-9 ($p<.089$), and 10-12 ($p<.061$) approached statistical significance. Figure 6 presents the percent

difference in average pain between Cellegesic nitroglycerin ointment 0.4% and controls over the first 21 days of the study.

Figure 6



The percent mean differences in 24-hour average pain reached 20% or more by day 14 in study 3 (Figure 6). It is important to note that the analysis that uses all available data from each subject is unbiased under MAR, whereas the analysis that imputes LOCF for the missing data is biased both under MCAR and MAR.[41]

With respect to 24-hour average pain intensity over 56 days of the study, there were significant decreases in pain ratings for the Cellegesic nitroglycerin ointment 0.4% group relative to controls ($p<.0167$).

Significant decreases in the last defecation pain for Cellegesic NTG ointment 0.4% treated subjects relative to controls were found through 21 days ($p<.0504$), and through 56 days ($p<.0211$).

With respect to 50% improvement in average pain, no statistically significant between group differences were observed ($p<.3184$); however, results were in the hypothesized direction. Differences in the survival curves were as much as 7 days to 50% improvement through 21 days (i.e., 75% of the NTG treated subjects achieved 50% improvement 7 days earlier (day 10) than 75% of the control subjects achieved 50% improvement – day 17).

No statistically significant treatment related effects were observed in time to healing. Sixty eight and seven tenths% of Cellegesic NTG ointment 0.4% treated subjects healed whereas 62.9% of control subjects healed.

The statistically significant treatment related effects of Cellegesic NTG ointment 0.4% on 24-hour average pain over the first 21 days of the study were not significantly moderated by age ($p<.7321$), sex ($p<.6822$), or race ($p<.6975$). Analysis of the frequency of Sitz baths over the course of the study revealed no significant differences through 21 days ($p<.20$) or 56 days ($p<.50$); however, through 21 days, placebo patients took an average of 5.21 Sitz baths whereas Cellegesic nitroglycerin ointment 0.4% treated subjects took an average of 4.42

Sitz baths. Through 56 days, placebo patients took an average of 12.08 Sitz baths whereas Cellegesic nitroglycerin ointment 0.4% treated subjects took an average of 10.36 Sitz baths.

When subjected to the Holmes (1979) step down adjustment, none of the secondary endpoints reached the adjusted level of significance.

6.4.2 Results for Studies 1, 2 and 3 Pooled Analyses

Through 21 days significant Cellegesic NTG ointment 0.4% versus control differences were seen for 24-hour average pain in Study 1 ($p<.0063$), Study 2 ($p<.0388$), and Study 3 ($p<.0243$). Combination of patients with sentinel pile from Studies 2 and 3 was also significant ($p<.0002$). Pooling intent-to-treat (ITT) subjects from all three studies (0.4% b.i.d. and 0.0% b.i.d. only) also produced a significant difference between Cellegesic NTG ointment 0.4% versus control subjects ($p<.0003$). Through 56 days significant Cellegesic NTG ointment 0.4% versus control differences were seen for 24-hour average pain in Study 1 ($p<.0001$), Study 2 ($p<.0039$), and Study 3 ($p<.0167$). Combination of patients with sentinel pile from Studies 2 and 3 was also significant ($p<.0001$). Pooling ITT subjects from all three studies (0.4% b.i.d. and 0.0% b.i.d. only) also produced a significant difference between Cellegesic NTG ointment 0.4% versus control subjects ($p<.0001$). As an aid to examining the clinical magnitude of the effects, Figures 7-11 display % improvement in pain intensity (through 56 days) for each study individually, and for the two combined analyses.

Through 21 days, significant Cellegesic NTG ointment 0.4% versus control differences were not seen for pain at last defecation in Study 1 ($p<.1342$), and Study 2 ($p<.1308$), but were seen for Study 3 ($p<.0504$). Combination of patients with sentinel pile from Studies 2 and 3 was also significant ($p<.0096$). Pooling ITT subjects from all three studies (0.4% b.i.d. and 0.0% b.i.d only) also produced a significant difference between Cellegesic NTG ointment 0.4% versus control subjects ($p<.0048$). Through 56 days, significant Cellegesic NTG ointment 0.4% versus control differences were seen for pain at last defecation in Study 1 ($p<.0243$), Study 2 ($p<.0289$), and Study 3 ($p<.0211$). Combination of patients with sentinel pile from Studies 2 and 3 was also significant ($p<.0001$). Pooling ITT subjects from all three studies (0.4% b.i.d. and 0.0% b.i.d. only) also produced a significant difference between Cellegesic NTG ointment 0.4% versus control subjects ($p<.0001$).

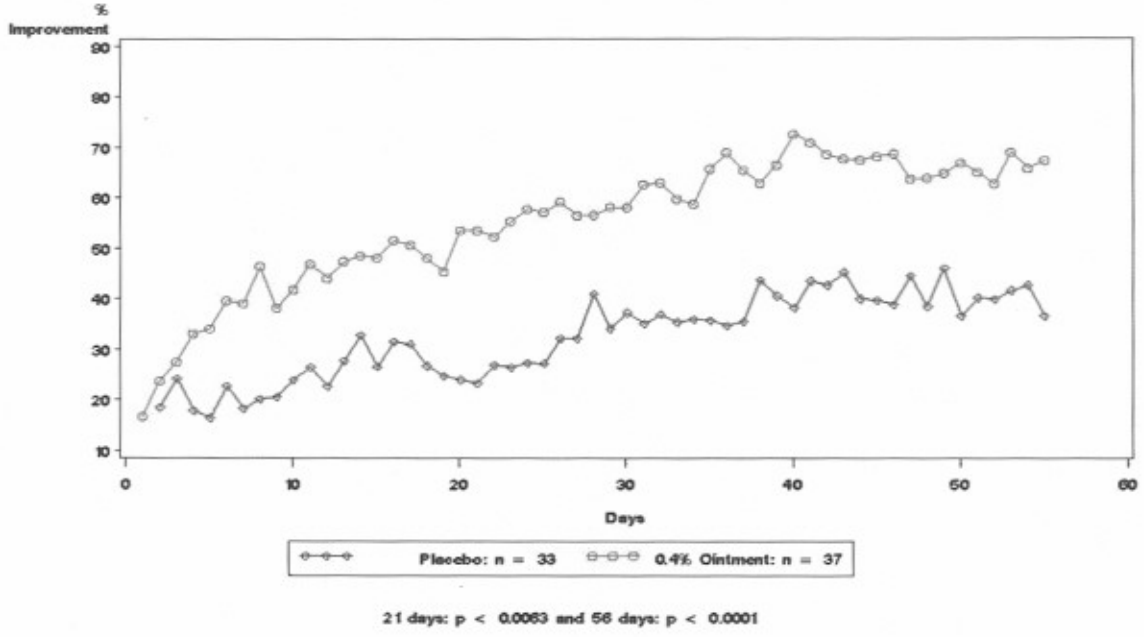
Through 56 days, significant NTG ointment 0.4% versus control differences were seen for time to 50% improvement in 24-hour average pain in Study 1 ($p<.0306$), approaching significance for Study 2 ($p<.1014$), but not for Study 3 ($p<.3184$). Combination of patients with sentinel pile from Studies 2 and 3 approached significance ($p<.0506$). Pooling ITT subjects from all three studies (0.4% b.i.d. and 0.0% b.i.d. only) did produce a significant difference between Cellegesic NTG ointment 0.4% versus control subjects ($p<.0117$). Figures 12-16 display time to 50% decrease in 24-hour average pain for each study individually, and for the two combined analyses.

No significant between group differences in terms of time to healing were observed for any individual study or combined analysis.

Figure 7

Percent Improvement in Average Pain Intensity (mm) by Time Period

Data: Study 1

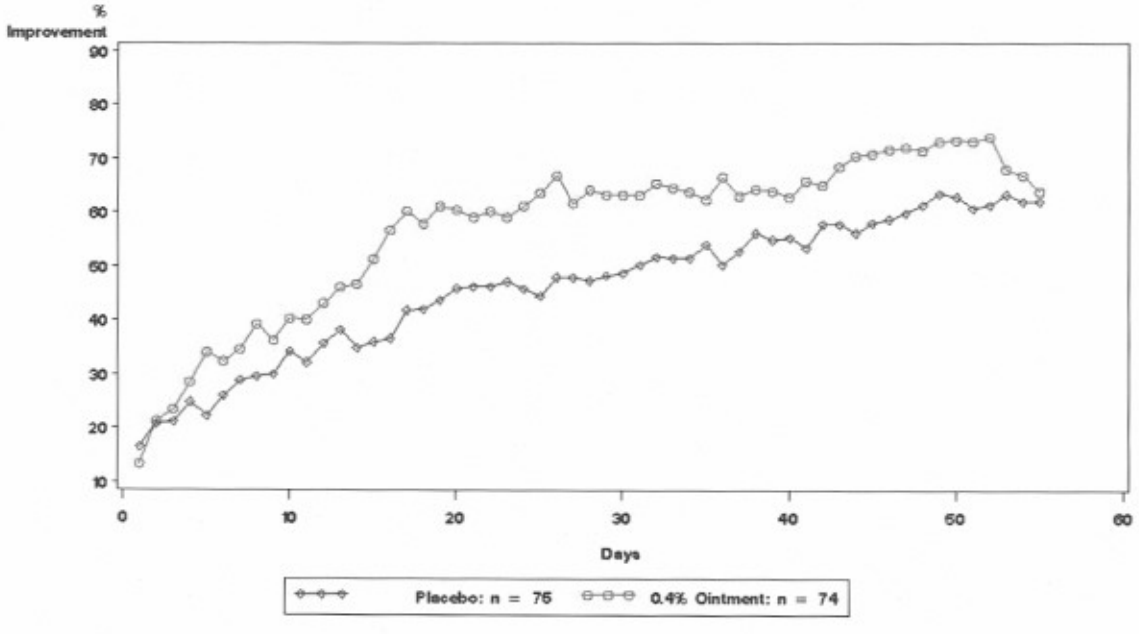


21 days: $p < 0.0063$ and 56 days: $p < 0.0001$

Figure 8

Percent Improvement in Average Pain Intensity (mm) by Time Period

Data: Study 2

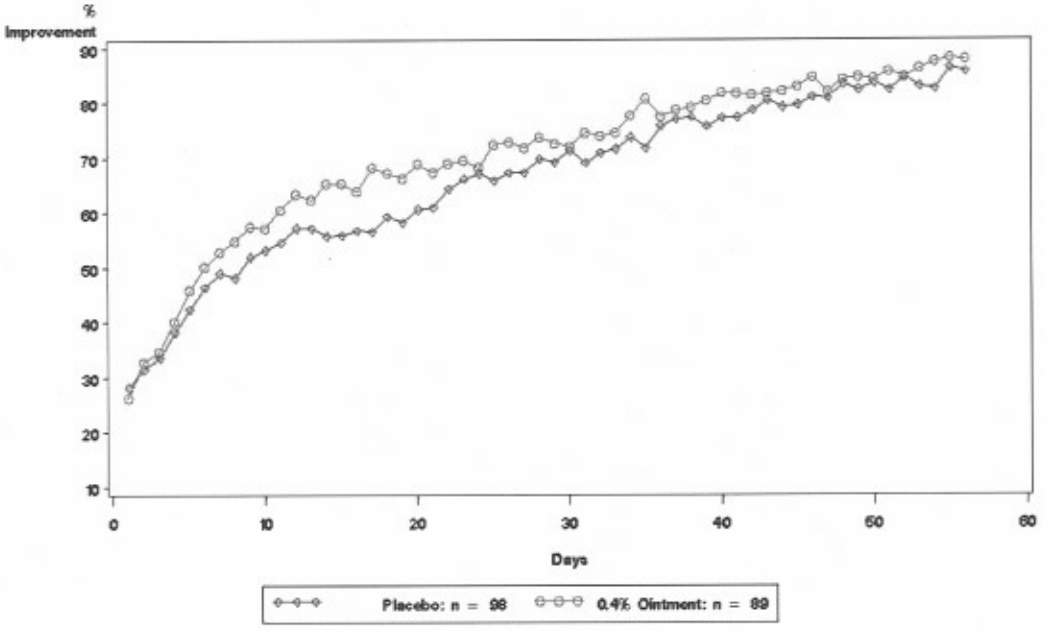


21 days: $p < 0.0388$ and 56 days: $p < 0.0039$

Figure 9

Percent Improvement in Average Pain Intensity (mm) by Time Period

Data: Study 3

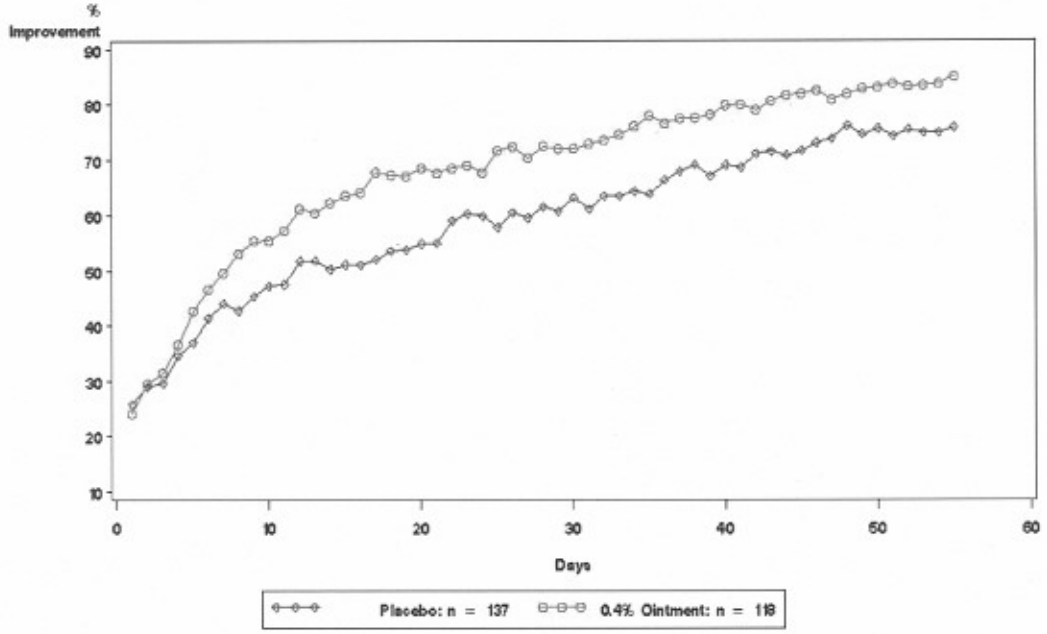


21 days: $p < 0.0498$ and 56 days: $p < 0.0167$

Figure 10

Percent Improvement in Average Pain Intensity (mm) by Time Period

Data: Studies 2 and 3 sentinel pile patients combined

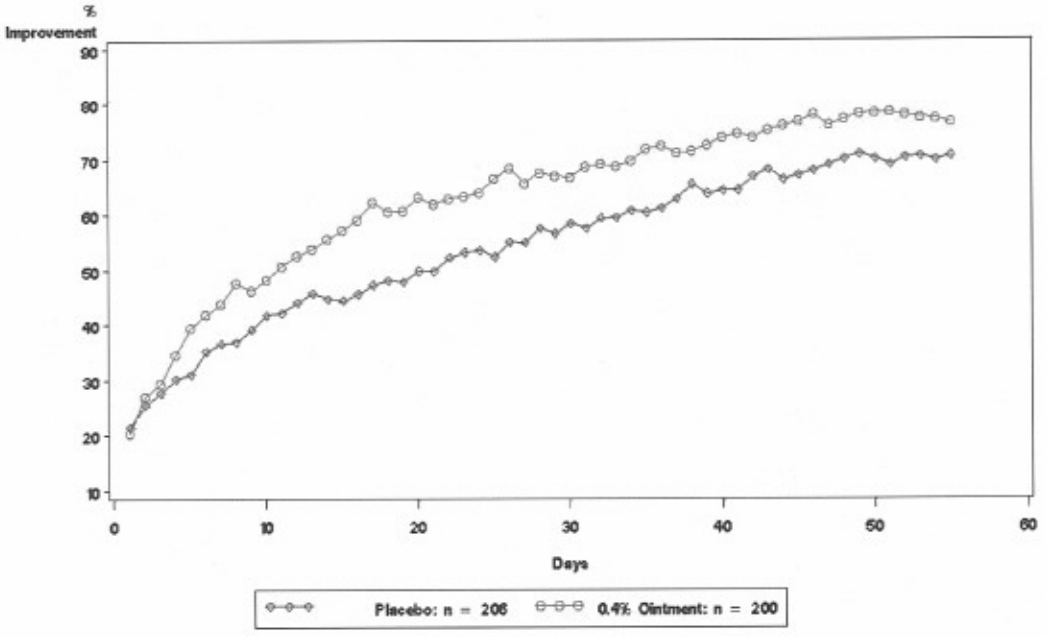


21 days: $p < 0.0098$ and 56 days: $p < 0.0001$

Figure 11

Percent Improvement in Average Pain Intensity (mm) by Time Period

Data: Studies 1, 2 and 3 combined

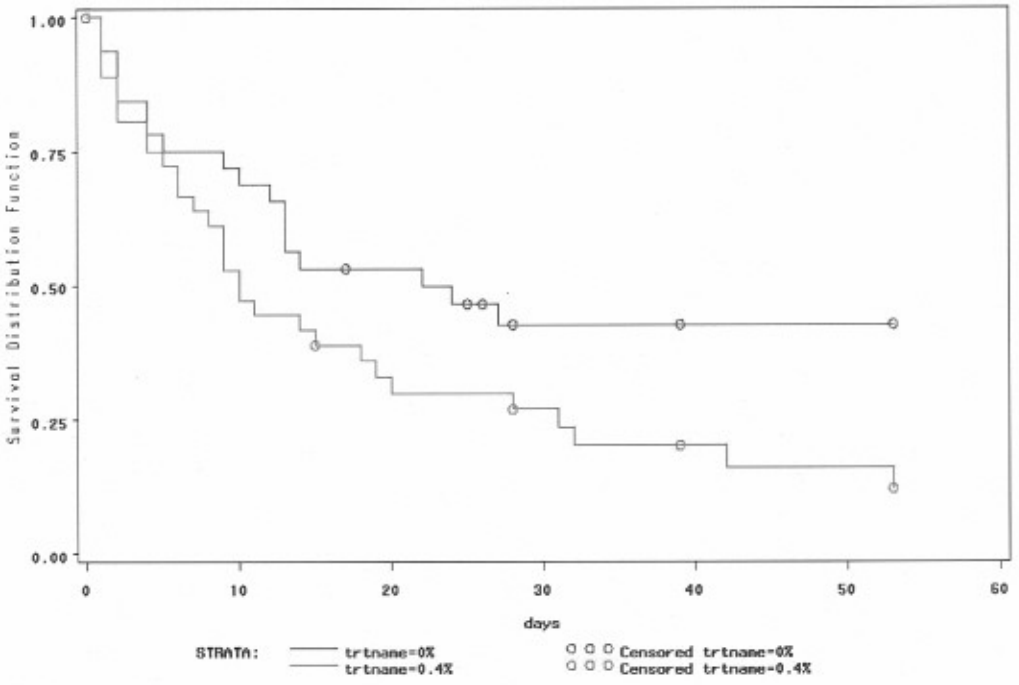


21 days: $p < 0.0048$ and 56 days: $p < 0.0001$

Figure 12

Survival Curve – Time to Reach 50% Improvement

Data: Study 1



Placebo: n = 33, 0.4% Ointment: n = 37, $p < 0.0306$

Figure 13

Survival Curve – Time to Reach 50% Improvement

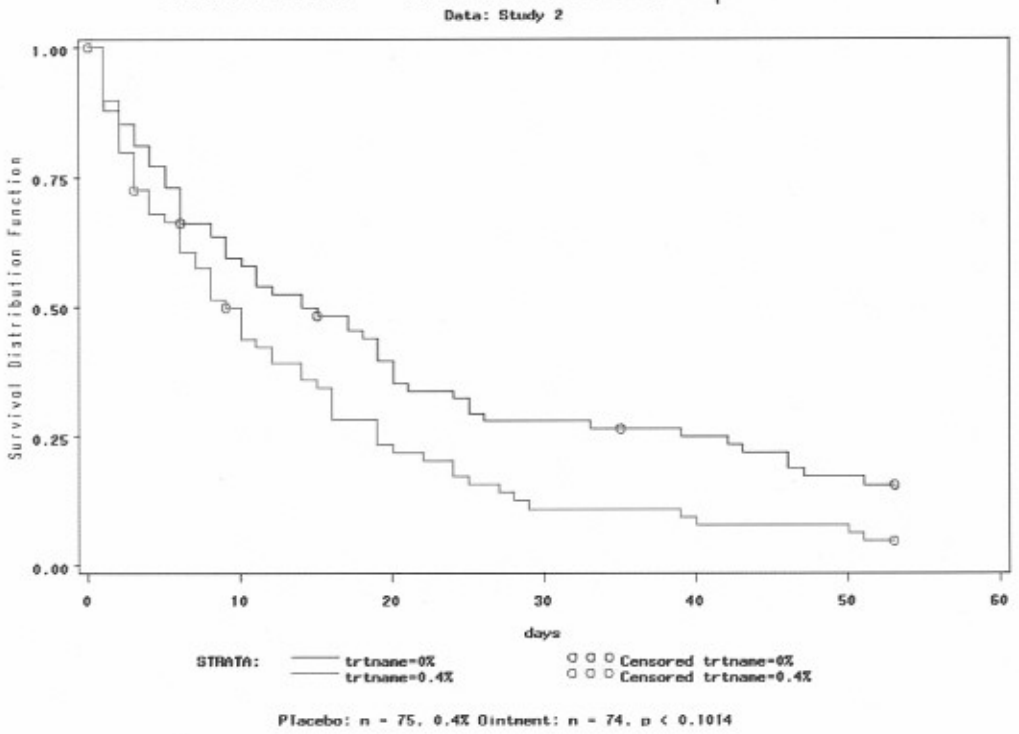


Figure 14

Survival Curve – Time to Reach 50% Improvement

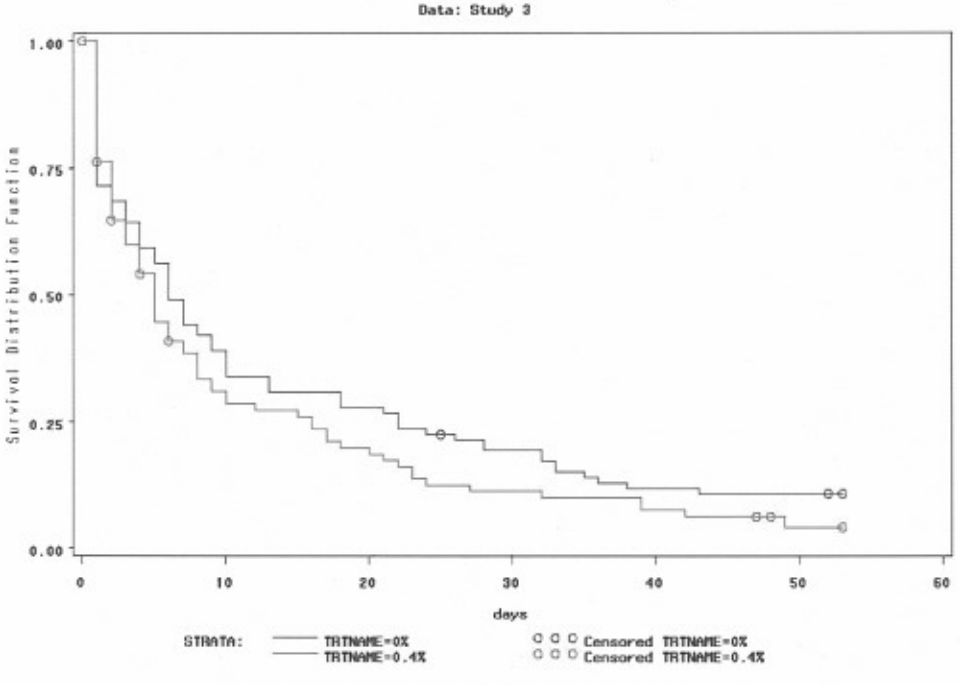


Figure 15

Survival Curve – Time to Reach 50% Improvement

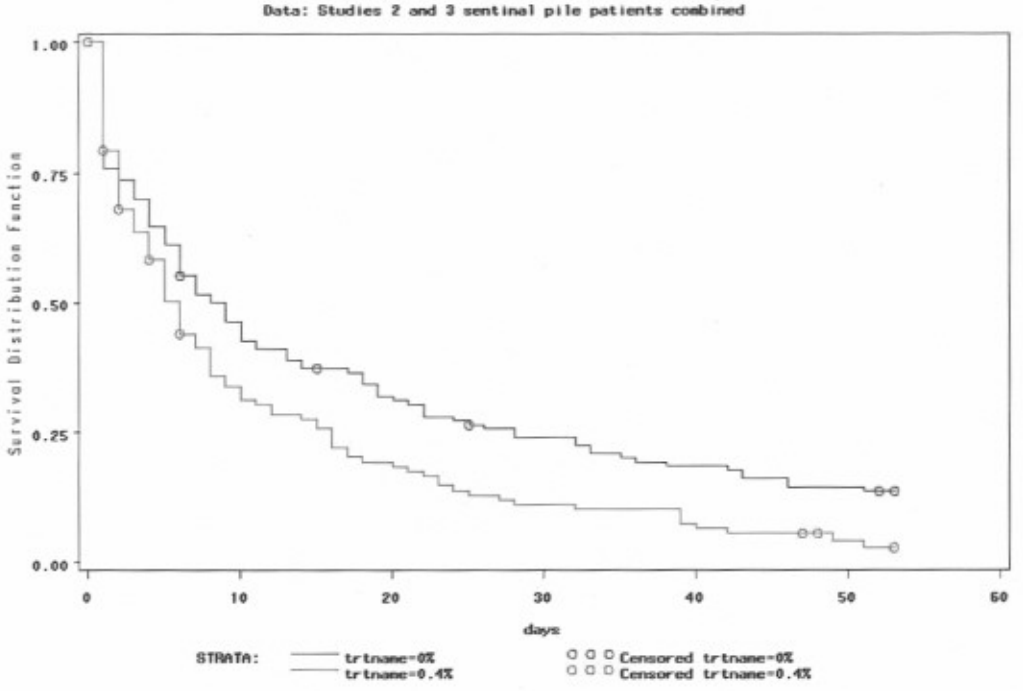
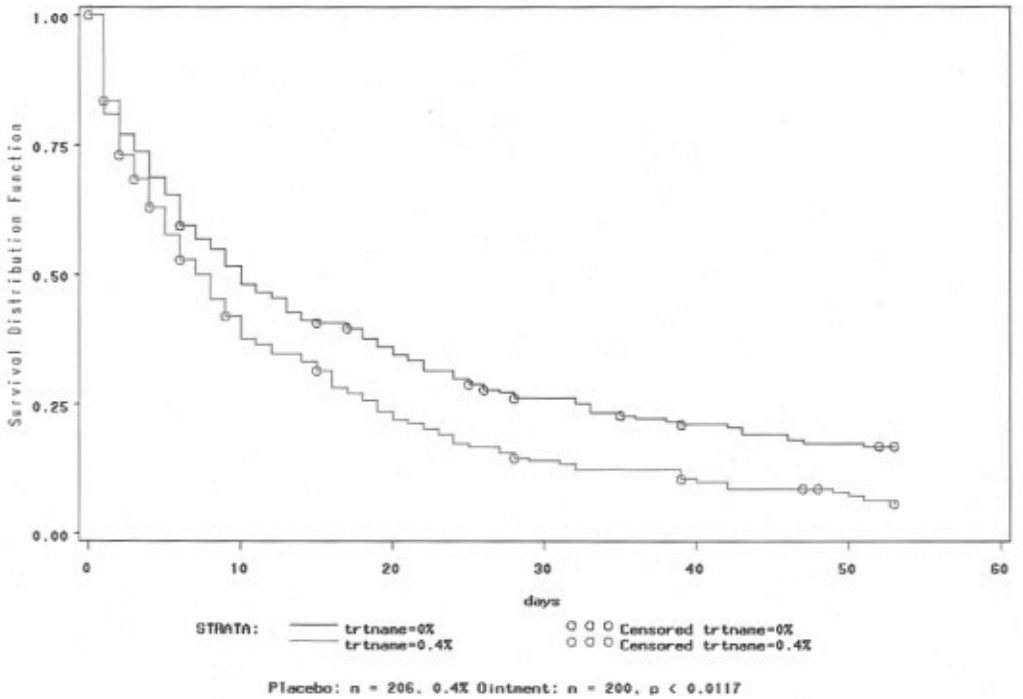


Figure 16

Survival Curve – Time to Reach 50% Improvement



6.5 Analysis of Patients in Moderate and Severe Pain (24-hour average pain VAS >50mm)

There were 17 subjects from Study 1, 35 subjects from Study 2, and 92 subjects from Study 3 that met criteria for baseline VAS > 50mm (24-hour average pain intensity), for a total of 144 subjects available for the combined analysis. The larger number of subjects meeting this criterion in Study 3 is based on the fact that the entrance criterion to this study required a baseline 24-hour average pain intensity of ≥35mm (as measured by VAS).

Table 5 provides the results of the analyses of subjects with baseline 24-hour average VAS-scores greater than 50mm.

The sample sizes are marginal for analysis of each study individually, but adequate for the combined analysis. Nevertheless, we provide results of individual and combined analyses for completeness. The combined analysis of studies 1, 2, and 3 revealed statistically significant treatment by linear time interactions for the rate of change of the 24-hour average pain intensity ($p<.004$) and defecation pain ($p<.0148$) over the first 21-days of treatment, indicating significantly greater rate of pain relief for the Cellegesic NTG ointment 0.4% treated subjects. The observed means are displayed in Figure 17 for the rate of change of the 24-hour average pain intensity and Figure 16 for defecation pain. The peak 24-hour average pain effects were on Day 15. At day 15, the difference between placebo and active treatment was 13.5mm. On day 21, the difference between placebo and active treatment was 10.3mm. Figure 18 reveals that for defecation pain, at day 15, the difference between placebo and active treatment was 5.6mm. On day 21, the difference in defecation pain between placebo and active treatment was 8.0mm.

Analysis of Study 3 revealed statistically significant treatment by linear time interactions for the rate of change of the 24-hour average pain intensity ($p<.036$) and approaching significance for defecation pain ($p<.062$) providing evidence for significantly greater rate of pain relief for the Cellegesic NTG ointment 0.4% treated subjects. On day 15 the 24-hour average pain difference between placebo and active treatment was 13.3mm. On day 21, the 24-hour average pain difference between placebo and active treatment was 9.5mm. On day 15 the defecation pain difference between placebo and active treatment was 5.4mm. On day 21, the difference in defecation pain between placebo and active treatment was 6.1mm (Table 5).

Analysis of Study 2 revealed statistically significant treatment by linear time interactions for the rate of change of the 24-hour average pain intensity ($p<.040$) and approaching significance for defecation pain ($p<.089$) indicating a significantly greater rate of pain relief for the Cellegesic NTG ointment 0.4% treated subjects. Table 3 reveals that for 24-hour average pain on day 15 the difference between placebo and active treatment was 18.0mm. On day 21, the average pain difference between placebo and active treatment was 16.0mm. On day 15 the defecation pain difference between placebo and active treatment was 9.0mm and on day 21, the difference was 16.5mm (Table 5).

Table 5: Cellegesic Nitroglycerin Ointment 0.4% Minus Placebo 24-Hour Average Pain and Defecation Pain Intensity Differences in Subjects with Moderate to Severe Pain

Study	N >50 mm for 2 days preceding treatment	Cellegesic nitroglycerin ointment 0.4% Minus Placebo					
		24-hr Average Pain Intensity			Defecation Pain Intensity		
		Rate of change through Day 21	Day 15 (mm)	Day 21 (mm)	Rate of change through Day 21	Day 15 (mm)	Day 21 (mm)
Studies 1, 2 & 3	144	p<0.004	13.5	10.3	p<0.0148	5.6	8.0
Study 3	92	p<0.036	13.3	9.5	p<0.062	5.4	6.1
Study 2	35	p<0.040	18.0	16.0	p<0.089	9.0	16.5
Study 1	17	NS	22.7	11.7	NS	26.5	21.0

Analysis of Study 1 revealed no statistically significant treatment by linear time interactions for the rate of change of the 24-hour average pain intensity or for defecation pain due to the small number of subjects in this study with baseline 24-hour average pain VAS scores greater than 50mm. However, the large numerical differences favor Cellegesic NTG ointment 0.4% as seen in Table 5. On day 15 the 24-hour average pain difference between placebo and active treatment was 22.7mm; on day 21, the average pain difference between placebo and active treatment was 11.7mm. On day 15 the defecation pain difference between placebo and active treatment was 26.5mm and on day 21 the difference was 21.0mm.

These findings provide evidence that there is statistically significant treatment related effects for those subjects with moderate to severe pain that we believe are clinically relevant.

Figure 17

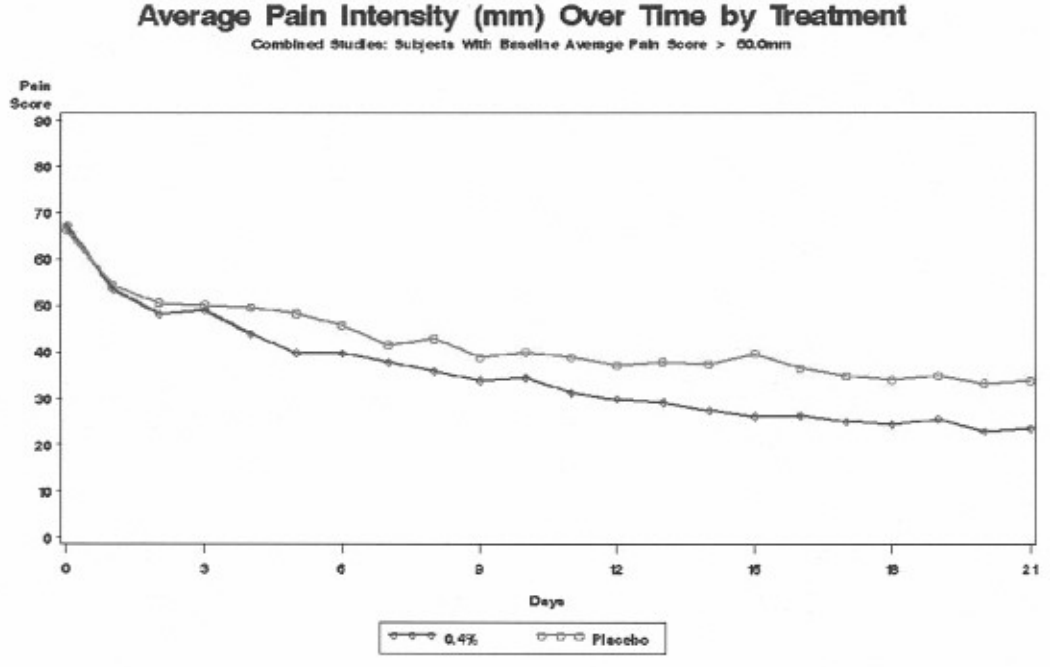
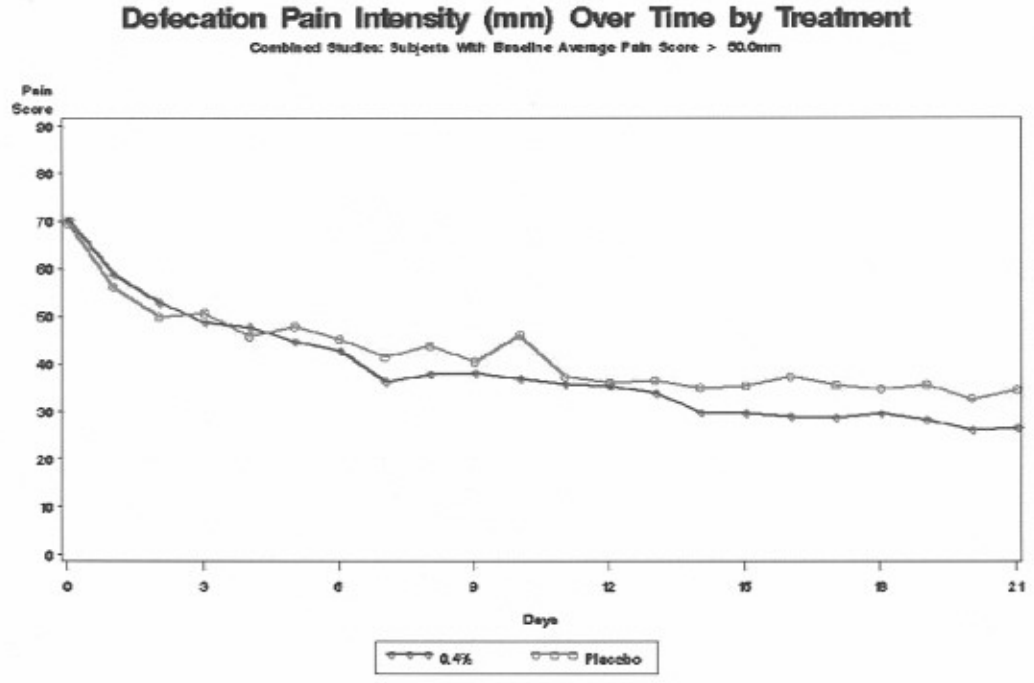


Figure 18



6.6 Dose Response Analysis

A dose response analysis was performed on the combined data from Studies 1 and 2 (where there were multiple doses). For 21 days, the dose by day interaction was significant (p<.0039), with the smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0040). Through 56 days, the dose by linear time interaction was significant (p<.0001), with smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0001). These results are clearly displayed in Figure 3, Section 4.2.3.

6.7 FDA Requests for Additional Analyses

Based on Cellegy's meeting with FDA on 3/28/2005, two additional analyses were requested by the Division of Cardio-Renal Drug Products. The first was to evaluate the effect of analgesic use on pain, and the effect of analgesic use on treatment related effect of Cellegesic on pain. The second was to evaluate the magnitude of the treatment versus control difference as a function of baseline pain intensity. To evaluate these requests the following analyses were performed.

6.7.1 Analgesic Effects

A mixed-effects regression analysis using all available data from each subject was performed to evaluate the effects of analgesic use (yes or no as a time varying covariate), treatment, time (linear), and the treatment by time (linear) interaction. The outcome measure was 24 hour average pain through day 21. No relationship between analgesic use and 24 hour average anal fissure pain was found (p<.53). When adjusted for analgesic use, the treatment by linear time interaction was still significant (p<.032).

6.7.2 Baseline Severity

To examine the relationship between baseline pain intensity and the treatment versus placebo difference in 24 hour average pain scores (in mm), we combined the data from all three trials, subset the data into quintiles based on baseline 24 hour average pain scores, and computed mean 24 hour average pain scores by quintile and treatment group at day 15 (point of maximal response) and day 21. The means for 24-hour average pain are displayed in Table 6.

Table 6
24-hour Average Pain Scores at Days 15 and 21 by Quintiles of Baseline Score
(Studies 1, 2, and 3 Combined)

		Average Pain				
		0.40%		Placebo		NTG - PLA
Quintile	Days	n	Mean	n	Mean	Difference
BL <= 21	0	40	11.2	43	9.9	1.3
BL <= 21	15	33	10.1	40	10.8	-0.7
BL <= 21	21	33	10.2	38	9.9	0.3
21 < BL <= 40	0	40	34.4	45	32.8	1.6
21 < BL <= 40	15	35	12.8	43	19.8	-7.0
21 < BL <= 40	21	34	12.8	42	14.4	-1.6
40 < BL <= 48	0	35	43.8	39	44.5	-0.7
40 < BL <= 48	15	30	18.2	39	17.3	0.9
40 < BL <= 48	21	29	17.1	38	18.4	-1.3
48 < BL <= 63	0	41	55.2	41	55.9	-0.7
48 < BL <= 63	15	38	18.7	39	34.8	-16.1
48 < BL <= 63	21	36	16.2	39	29.4	-13.2
BL > 63	0	42	74.6	36	75.0	-0.4
BL > 63	15	41	33.4	35	43.1	-9.7
BL > 63	21	39	29.9	34	38.0	-8.1

Inspection of Table 6 reveals that in the first three quintiles (<=48 mm) there is little drug effect. By contrast, in the fourth and fifth quintiles there are clinically significant drug effects, with the largest being in quintile 4 (48-63mm). In quintile 4, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for 24-hour average pain on day 15 was 16.1mm (46%) and on day 21 it was 13.2mm (45%). In quintile 5, the difference between 0.4% NTG and Placebo for 24 hour average pain on day 15 was 9.7mm (23%) and on day 21 it was 8.1mm (21%).

Table 7 displays the means for defecation pain.

Table 7
Defecation Pain Scores at Days 15 and 21 by Quintiles of Baseline Score
(Studies 1, 2, and 3 Combined)

		Defecation Pain				
		0.40%		Placebo		NTG-PLA
Quintile	Days	n	Mean	n	Mean	Difference
BL <= 21	0	35	29.4	39	23.3	6.1
BL <= 21	15	32	14.2	39	14.2	0.0
BL <= 21	21	30	12.3	37	13.1	-0.8
21 < BL <= 40	0	38	39.0	43	45.3	-6.3
21 < BL <= 40	15	35	17.4	38	21.7	-4.3
21 < BL <= 40	21	33	16.2	38	17.3	-1.1
40 < BL <= 48	0	31	43.5	35	37.1	6.4
40 < BL <= 48	15	28	16.3	36	19.7	-3.4
40 < BL <= 48	21	26	16.4	37	18.0	-1.6
48 < BL <= 63	0	38	55.3	37	53.5	1.8
48 < BL <= 63	15	36	20.4	39	30.2	-9.8
48 < BL <= 63	21	33	18.6	36	30.5	-11.9
BL > 63	0	38	65.5	35	62.3	3.2
BL > 63	15	39	36.6	32	40.8	-4.2
BL > 63	21	35	33.7	32	39.5	-5.8

In quintile 4, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for defecation pain on day 15 was 9.8mm (33%) and on day 21 it was 11.9mm (39%). In quintile 5, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for defecation pain on day 15 was 4.2mm (10%) and on day 21 it was 5.8mm (15%). In general, baseline levels of 24 hour average pain intensity were quite similar across quintiles and treated and control subjects.

A similar, but even larger difference was observed when this analysis was repeated for Study 3 alone (using quintiles derived from the Study 3 data only), see Tables 8 and 9.

Table 8
Average Pain Score at Days 15 and 21 by Quintiles of Baseline Score
(Study 3)

		0.40%		Placebo		NTG – PLA
Quintile	Days	n	mean	n	Mean	Difference
BL <= 41.5	0	20	38.9	18	38.7	0.2
BL <= 41.5	15	19	11.7	18	15.2	-3.5
BL <= 41.5	21	19	13.7	16	12.5	1.2
41.5 < BL <= 46	0	13	43.9	25	44.1	-0.2
41.5 < BL <= 46	15	11	24.2	25	19.6	4.6
41.5 < BL <= 46	21	11	23.7	25	16.7	7.0
46 < BL <= 55	0	20	50.3	17	50.9	-0.6
46 < BL <= 55	15	19	18.8	17	17.5	1.3
46 < BL <= 55	21	19	15.1	17	15.7	-0.6
55 < BL <= 66	0	16	61.4	21	61.3	0.1
55 < BL <= 66	15	15	12.7	21	38.6	-25.9
55 < BL <= 66	21	14	12.4	20	35.5	-23.1
BL > 66	0	20	77.8	17	79.2	-1.4
BL > 66	15	20	34.7	17	46.1	-11.4
BL > 66	21	18	32.4	16	35.5	-3.1

Inspection of Table 8 reveals that in the first three quintiles (<=55 mm) there is little drug effect. By contrast, in the fourth and fifth quintiles there are clinically significant drug effects, with the largest being in quintile 4 (55-66mm). In quintile 4, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for 24-hour average pain on day 15 was 25.9mm (67%) and on day 21 it was 23.1mm (65%). In quintile 5, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for 24 hour average pain on day 15 was 11.4mm (25%) and on day 21 it was 3.1mm (9%). Table 9 presents results of a similar analysis for defecation pain. In quintile 4, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for defecation pain on day 15 was 12.5mm (42%) and on day 21 it was 9.9mm (31%). In quintile 5, the difference between Cellegesic nitroglycerin ointment 0.4% and Placebo for defecation pain on day 15 was 7.8mm (20%) and on day 21 it was 8.5mm (22%). In general, baseline levels of 24 hour average pain intensity were quite similar across quintiles and treated and control subjects. A single exception was for defecation pain in quintile 3, where the NTG treated patients had greater pain intensity (9.7mm greater at baseline), making the day 15 and 21 differences even more clinically significant.

Table 9
Defecation Pain Score at Days 15 and 21 by Quintiles of Baseline Score
(Study 3)

		0.40%		Placebo		NTG – PLA
Quintile	Days	n	Mean	n	Mean	Difference
BL <= 41.5	0	20	29.9	18	29.6	0.3
BL <= 41.5	15	19	13.3	17	13.5	-0.2
BL <= 41.5	21	18	11.8	16	14.1	-2.3
41.5 < BL <= 46	0	10	35.3	23	37.3	-2.0
41.5 < BL <= 46	15	9	21.3	24	21.6	-0.3
41.5 < BL <= 46	21	8	26.0	25	16.5	9.5
46 < BL <= 55	0	18	49.4	14	39.7	9.7
46 < BL <= 55	15	17	20.8	17	18.8	2.0
46 < BL <= 55	21	17	14.8	17	18.9	-4.1
55 < BL <= 66	0	15	47.7	20	46.9	0.8
55 < BL <= 66	15	14	17.4	20	29.9	-12.5
55 < BL <= 66	21	13	21.8	19	31.7	-9.9
BL > 66	0	18	62.4	16	63.9	-1.5
BL > 66	15	19	31.9	15	39.7	-7.8
BL > 66	21	16	30.6	15	39.1	-8.5

Similarly, we observe substantial decreases in time to 50% improvement in NTG treated subjects relative to Placebo controls particularly in quintiles 4 and 5 through 21 days (see Figures 19 and 20). These differences, which favor NTG over Placebo, are on the order of 10 days at various points along the cumulative time to 50% improvement distributions.

Figure 19

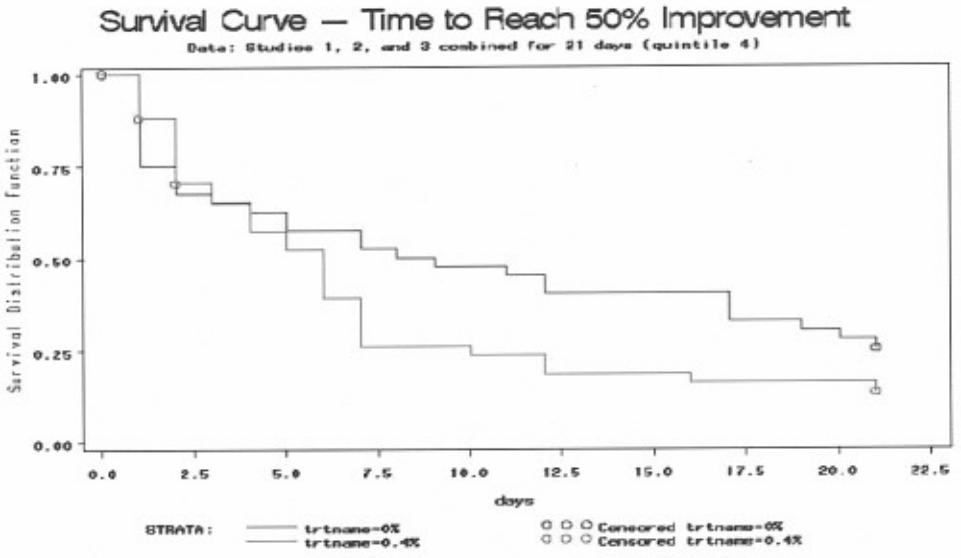
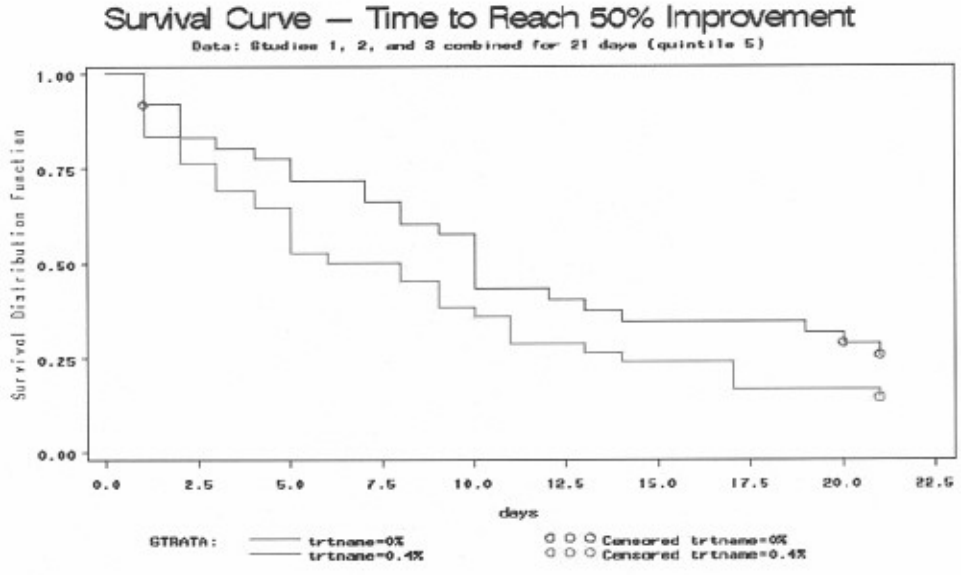


Figure 20



6.8 Additional Analyses Based on FDA NDA 21-359 Discipline Review Letter (1/31/06)

FDA provided a discipline review letter to Cellegy on 1/31/06. In the following, we address the key issues and concerns raised in that letter.

6.8.1 Acetaminophen Effect on Anal Fissure Pain

A key concern of FDA's is that the increased number of headaches observed in the NTG group led to an increase use of analgesics in the NTG group, which could have accounted for the significant decrease in pain observed in that group. Based on Cellegy's analysis of the data, we do not find any evidence of this effect. First, of 89 NTG subjects, 25 (28%) took acetaminophen and of 98 Placebo subjects 23 (23%) took acetaminophen. This finding indicates that there was essentially no difference in the rate of analgesics taken between NTG and Placebo groups. Second, inspection of Figure 21 reveals that the NTG subjects who took acetaminophen actually did a bit worse than those NTG subjects that did not take an analgesic. This effect is even larger in Placebo subjects (see Figure 22). These results indicate that taking an analgesic did not reduce anal fissure pain. Interestingly, if we compare those patients who took an analgesic in NTG and Placebo arms of the study, we observe a very large effect of the NTG (see Figure 23). Again, this difference is not an effect of the analgesic on anal fissure pain, since (a) both NTG and Placebo patients took analgesics, and (b) within both Placebo and NTG patients, there was no beneficial effect of taking an analgesic on anal fissure pain (in fact the patients who took the analgesic had worse anal fissure pain compared to those that did not).

These findings clearly provide evidence that the effects of Cellegesic nitroglycerin ointment are not confounded by analgesic use.

Figure 21

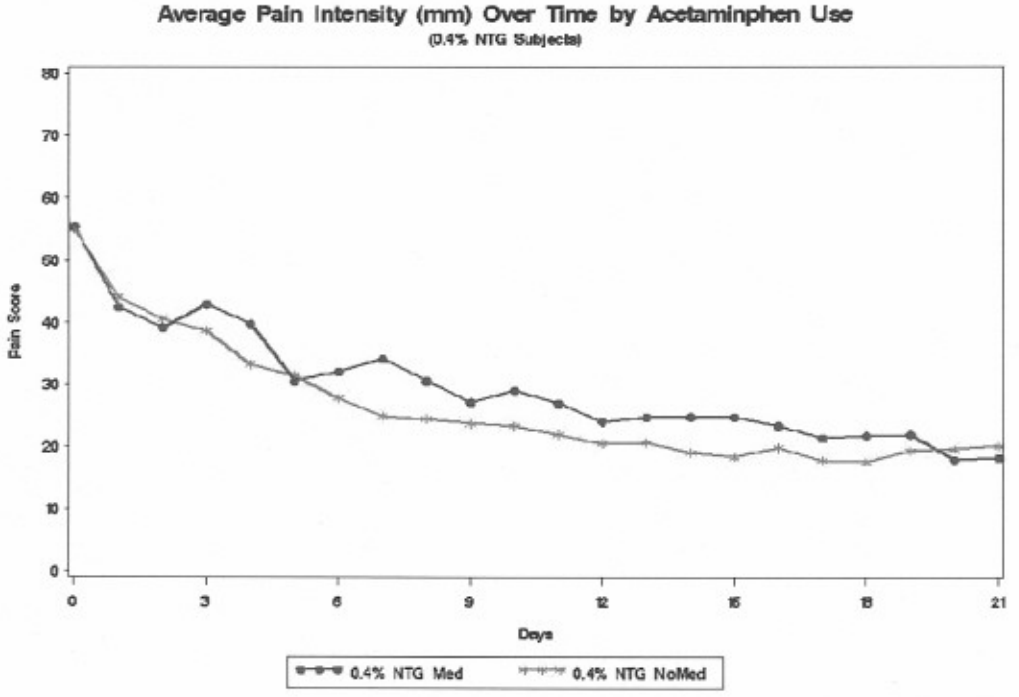


Figure 22

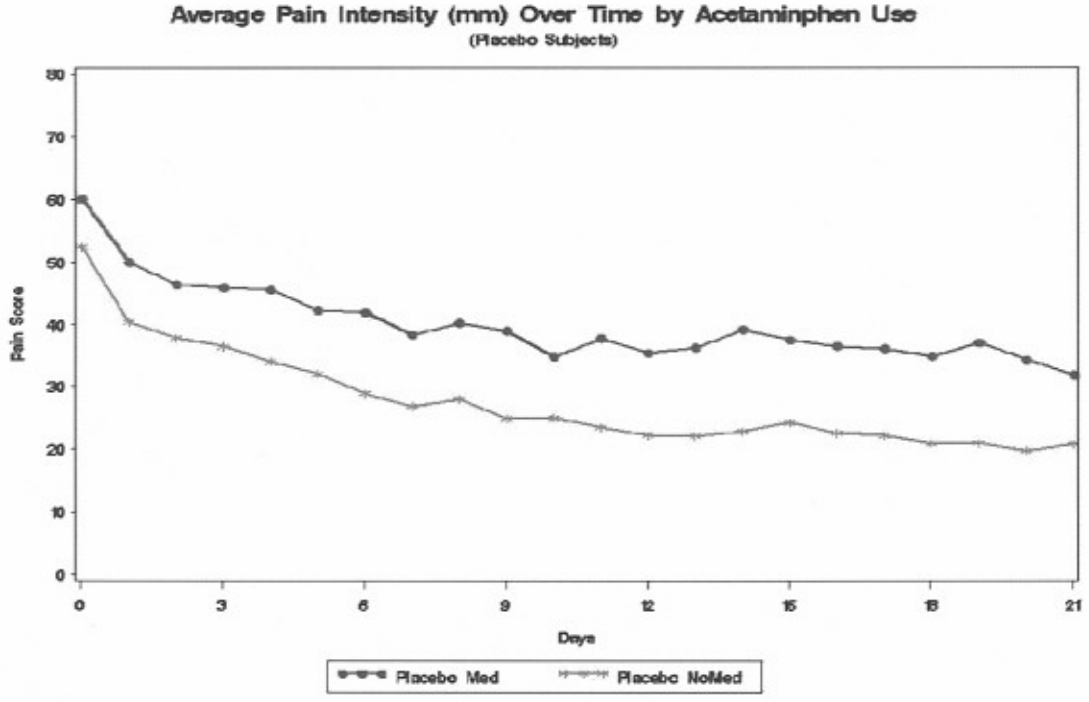
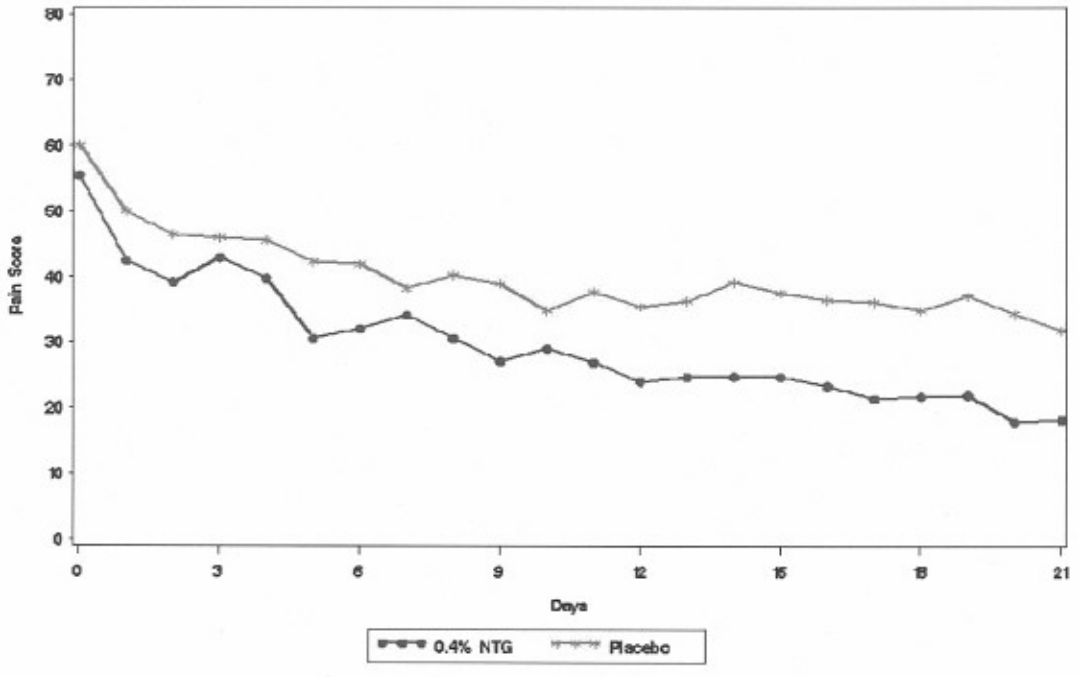


Figure 23



6.8.2 No Evidence of a Dose Response Relationship

As previously discussed, a dose response analysis was performed on the combined data from Studies 1 and 2 (where there were multiple doses). For 21 days, the dose by day interaction was significant (p<.0039), with the smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0040). Through 56 days, the dose by linear time interaction was significant (p<.0001), with the smallest significant dosage occurring at Cellegesic nitroglycerin ointment 0.4% (p<.0001). These effects are clearly seen in Figure 4 of section 4.2.3.

6.8.3 Non-Ignorable Non-Response

The mixed-effects regression model used in the analysis of these data assumes that the missing data (i.e., following drop-out) are ignorable conditional on the covariates in the model and the available outcomes (VAS scores) for each subject. Another way of stating this is that the available data from each subject and other similarly treated subjects provide an estimate of the rate of change over time for that subject, that would accurately predict the missing data if they were available. Of course, we do not have the missing data, so it is not really possible to prove that the missing data are ignorable under MAR. For example, it might be that headaches lead to dropout and the missing data in those subjects who dropped out of the study due to headache are not predictable based on the observable data. While this assumption is difficult if not impossible to verify, Mohlenberghs[41] suggest that (a) models based on MAR are generally robust to the presence of MNAR, and (b) MNAR models can be used as sensitivity analyses to verify the robustness of the findings under MAR. To this end, we followed the method described by Hedeker and Gibbons[42] and fit an MNAR model (shared parameter model) based on jointly fitting a model for drop-out (complementary log-log person-time survival model) and mixed-effects regression model for response (AVG VAS score) to treatment. For this purpose, the data were aggregated to the week level and average VAS scores per week and drop-out rates per week were jointly modeled.

The drop-out model included headache, and the random intercept and slope (shared parameters from the outcome model), and the headache by intercept and headache by slope interactions. This analysis was conducted using SAS NLMIXED. None of the terms related to headache were significantly associated with drop-outs. The treatment by time interaction was significant (p<.0131). Note that this probability value is even smaller than the probability value obtained under the MAR assumption (P< .0243). These findings clearly reveal that the assumption of MAR is not biasing the significance of the treatment by time interaction (since it remains significant under MNAR), and that headache is not related to drop-out or treatment efficacy.

7. SUMMARY OF CLINICAL SAFETY

7.1 Overview

This summary presents safety data from three phase 3, placebo-controlled, double-blind clinical studies (Study 1, Study 2, and Study 3) that evaluated intra-anal application of approximately 375 mg of Cellegesic NTG ointment for the treatment of

chronic anal fissure. Three concentrations of Cellegesic NTG ointment were evaluated in these studies: 0.1% (0.375 mg NTG), 0.2% (0.75 mg NTG), and 0.4% (1.5 mg NTG). These studies provided the primary safety data for Cellegesic NTG ointment 0.4% and are supplemented by the safety data from 6 healthy volunteer subjects in a phase 1, open-label, 3-treatment, crossover study (NTG 98-02-02).

Demographics, extent of exposure, and treatment-emergent adverse events are presented from the four Cellegy-sponsored clinical studies. Serious adverse events, adverse events that led to discontinuation, clinical laboratory test results, and other safety information are described or summarized for the phase 3 studies. The baseline demographic results are recorded in Table 10.

Table 10 Demographic and Baseline Characteristics (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

	Cellegesic Nitroglycerin Ointment			
	Placebo[a] (N=246) n (%)	0.4% b.i.d. (N=206) n (%)	Total[b] (N=475) n (%)	Overall Total (N=721) 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
Weight (kg)				
N	246	206	465	711
Mean±SD	79.9±19.64	78.9±17.84	80.7±19.58	80.4±19.59

	Cellegesic Nitroglycerin Ointment			
	Placebo[a] (N=246) n (%)	0.4% b.i.d. (N=206) n (%)	Total[b] (N=475) n (%)	Overall Total (N=721) n (%)
Range	47.0-188.4	43.8-158.9	43.8-172.7	43.8-188.4
Missing	0	0	10	10
Height (cm)				
N	246	205	466	712
Mean±SD	169.4±9.81	170.4±9.84	171.2±10.06	170.6±10.00
Range	142.0-193.0	146.0-203.2	144.8-203.2	142.0-203.2
Missing	0	1	9	9
Systolic Blood Pressure (mmHg)				
N	245	206	471	716
Mean±SD	124.8±17.89	125.8±17.78	123.3±16.24	123.8±16.82
Range	88.0-188.0	90.0-190.0	90.0-190.0	88.0-190.0
Missing	1	0	4	5
Diastolic Blood Pressure (mmHg)				
N	245	206	471	716
Mean±SD	76.8±10.63	77.6±10.34	76.4±10.81	76.6±10.74
Range	40.0-104.0	50.0-120.0	34.0-120.0	34.0-120.0
Missing	1	0	4	5
Pulse (bpm)				
N	244	206	471	715
Mean±SD	73.1±9.77	73.5±9.83	72.6±10.25	72.8±10.09
Range	50.0-111.0	50.0-110.0	46.0-110.0	46.0-111.0
Missing	2	0	4	6
Current Alcohol Use				
Yes	81 (32.9)	69 (33.5)	200 (42.1)	281 (39.0)
No	165 (67.1)	137 (66.5)	275 (57.9)	440 (61.0)
Current Tobacco Use				
Yes	45 (18.3)	31 (15.0)	73 (15.4)	118 (16.4)
No	201 (81.7)	175 (85.0)	402 (84.6)	603 (83.6)

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

7.2 Safety Evaluations

Safety evaluations were based on the collection of data on treatment-emergent adverse events, and changes between the screening and exit visits in clinical laboratory (hematology, serum chemistry, and urinalysis) test results, physical examination findings, and electrocardiogram (ECG) results, as well as changes from baseline to each visit for vital signs measurements. Clinical laboratory testing and physical examinations were performed at the screening and exit visits. Vital signs were measured at baseline and at each on-therapy visit (approximately Days 1, 14, 28, 42, and 56 for studies 1 & 2, and approximately Days 7, 21, 35, and 56 for study 3). Electrocardiograms were recorded only

in study 3 at the screening and exit visits.

Subjects were evaluable for safety if they took at least 1 dose of study medication and had any safety information obtained for them.

7.3 Adverse Events

Treatment-emergent adverse events were defined as events that began during the double-blind treatment phase or were present at baseline but worsened in severity. For studies 1 & 2, non serious adverse events were considered treatment-emergent through 14 days following the date of study completion or discontinuation. For study 3, non-serious adverse events were considered treatment-emergent through the exit visit, or if an exit visit was not performed, through 24 hours after the last dose of study medication. If timing of the adverse event onset was not available, the adverse event was assumed to be treatment-emergent.

A serious adverse event was defined as any event that was fatal or immediately life-threatening, resulted in or prolonged inpatient hospitalization, caused persistent or significant disability or incapacity, represented an important new medical event, or was a congenital anomaly in the offspring of a subject who received drug. A serious adverse event was treatment-emergent if it occurred within 30 days after the last dose of study medication.

In studies 1 and 2, an adverse event included any symptom whether thought to be related or unrelated to the condition under study; any clinically significant laboratory test result abnormality; or any abnormality detected during physical examination. In study 3, an adverse event was defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which did not necessarily have a causal relationship with this treatment. An adverse event could therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of study treatment, whether or not related to the study treatment. Abnormal results from diagnostic procedures such as laboratory test abnormalities were considered adverse events if they resulted in study discontinuation, required treatment or therapeutic intervention, required further diagnostic evaluation, or were associated with clinical signs or symptoms judged by the investigator to have significant clinical effect.

For all 3 studies, pain resulting from anal fissure and anal bleeding were to be considered part of the subject's disease process, and not to be recorded as adverse events; however, these were inadvertently reported by some investigators as adverse events for some subjects.

The investigator assessed the relationship between an adverse event and the study medication as not related, possibly related, or related in studies 1 and 2, and as not related, possibly related, probably related, or related in study 3. The probably related and related categories in study 3 were combined for summaries where data were integrated from all 3 studies.

Adverse events were graded by the investigator in all 3 studies as mild (causing no limitation of usual activities), moderate (causing some limitation of usual activities), or severe (causing inability to carry out usual activities).

7.3.1 Clinical Laboratory Data

Blood and urine samples were to be obtained at screening before study drug administration and at the exit visit for the following clinical laboratory tests:

Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count;

- Serum chemistry: albumin, alkaline phosphatase, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphorus, potassium, serum glutamic-oxaloacetic transaminase/aspartate aminotransferase (SGOT/AST), serum glutamic-pyruvic transaminase/alanine aminotransferase (SGPT/ALT), sodium, total bilirubin, total protein, triglycerides, and uric acid;
- Urinalysis: color/appearance, pH, specific gravity, bilirubin, blood, glucose, ketones, protein, and microscopy.

7.4 Phase 3 Studies: Analysis of Safety Data

Safety data are presented for the subjects who were enrolled in the three completed phase 3 studies and who were evaluable for safety (defined as those applying at least 1 dose of study medication and having safety information recorded). In the 3 studies, subjects applied 1 of 6 total daily doses of Cellegesic NTG ointment (0.75, 1.1, 1.5, 2.3, 3.0, or 4.5 mg of NTG, depending on the concentration and dosing interval) or vehicle (placebo) alone. In most of the tables summarizing the safety data from these studies, the results are presented for subjects who applied Cellegesic NTG ointment 0.4% b.i.d. (3.0 mg NTG total daily dose) and also for all subjects who applied Cellegesic NTG ointment regardless of the assigned dose. Results are also pooled across studies for all subjects who applied vehicle only. Selected safety data are presented for subgroups of subjects treated with Cellegesic NTG ointment, categorized by NTG concentration or by the dose and frequency of Cellegesic NTG ointment they used.

7.4.1 Demographic and Baseline Characteristics

Subject disposition is summarized, and the demographic characteristics (age, sex, and race) and baseline characteristics (weight, height, vital signs, alcohol use, and tobacco use) are provided for the subjects evaluable for safety in the phase 3 studies (Table 9).

7.4.2 Extent of Exposure to Study Medication

In the completed phase 3 studies, the subjects were to apply Cellegesic NTG ointment or placebo (vehicle only) 2 or 3 times a day to the anal canal for a maximum of 56 days. Subjects in study 1 could complete the study in less than 56 days if complete healing occurred. The distribution of all subjects by number of days on therapy is provided using the visit intervals of study 3.

Tubes containing study medication were weighed before they were dispensed and when they were returned at each clinic visit. The amount of ointment expressed from the tube by a subject between clinic visits was calculated as the difference between the tube weights recorded on the case report forms (CRFs). Summary statistics (mean, standard deviation [SD], and range) for the amount of ointment used by subjects over the entire study period are provided for the completed phase 3 studies.

Percent compliance for each subject was calculated by dividing the total amount of ointment (in grams) expressed from the tube by the total amount expected to be expressed and multiplying by 100. The amount of ointment expected to be expressed was based on the dosing regimen assigned to the subject. Summary statistics (mean, SD, and range) for percent compliance are presented.

7.4.3 Adverse Events

Treatment-emergent adverse events reported during the phase 3 studies were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 5.0.

The incidence of frequently reported (≥2.0%) adverse events are presented by body system and preferred term. In addition, the incidence of frequently reported adverse events by highest relationship to study drug (none, possibly, or related) and by maximum intensity (mild, moderate, or severe) are displayed overall and by body system and preferred term. The incidence of frequently reported adverse events are also reported by body system and preferred term for subgroups of subjects based on sex, age group (<65 years versus ≥65 years), and race.

The incidence of headache across all studies is presented by maximum intensity, dose, and frequency, as well as by maximum intensity and history of migraine or recurrent headaches. NTG-related headache was defined as a headache that occurred within 30 minutes of study drug application in study 3 and not defined in the others by a 30-minute window. To determine those subjects who dropped-out due to a NTG headache. Because of this difference in definition, separate summaries of treatment-related and not treatment-related headaches are also provided for study 3 alone, including summaries by intensity, concomitant medication treatment, and duration of headache.

Deaths, other serious adverse events, and discontinuations due to adverse events are summarized.

7.4.4 Clinical Laboratory Data

According to the phase 3 protocols, non fasting blood and urine samples for clinical laboratory tests were to be obtained at screening before study drug administration and at the exit visit. All clinical laboratory data are provided as part of the clinical study reports. This summary presents only those results that shifted from normal at baseline to abnormal at the exit visit and those that were considered clinically significant by the investigator.

7.4.5 Other Safety Observations

For the phase 3 studies, vital signs (pulse and sitting blood pressure) are summarized for each visit using descriptive statistics (mean, SD, median, and range). Changes from baseline at each visit are also summarized. In addition, the number and percentage of subjects who had clinically significant decreases (≥20 mm Hg) from baseline in diastolic blood pressure are presented for each visit.

Subjects with abnormal physical examination findings at the exit visit that were not recorded as abnormal at baseline are summarized. Electrocardiograms were performed only in study 3, and the number and percentage of subjects with normal, clinically significant abnormal, and not clinically significant abnormal ECGs at screening and exit visits are presented.

7.5 Phase 3 Studies: Results

7.5.1 Disposition of Subjects

The disposition of the 726 subjects who participated in the three phase 3 double-blind studies is summarized in Table 11. Most subjects in the Cellegesic NTG ointment 0.4% b.i.d. group (81.1%), the overall Cellegesic NTG ointment group (78.3%), and the

placebo group (89.4%) completed the studies. The most common reason for premature discontinuation in the Cellegesic NTG ointment 0.4% b.i.d group was adverse event (9.7%); (2.8% of the placebo group and 7.8% of the overall Cellegesic NTG ointment group). The most common reason for discontinuation across all safety-evaluable subjects was subject choice (6.5%). A total of 721 subjects applied at least 1 dose of study medication and had safety information; these subjects constituted the safety-evaluable population for this summary. A total of 475 subjects of the safety-evaluable population applied at least 1 dose of Cellegesic NTG ointment.

Table 11: Subject Disposition (All Subjects in Completed Phase 3 Studies)

	Cellegesic Nitroglycerin Ointment			
	Placebo[a] n (%)	0.4% b.i.d. n (%)	Total[b] n (%)	Overall Total n (%)
Enrolled	248	209	478	726
Evaluable for Safety	246 (100.0)	206 (100.0)	475 (100.0)	721 (100.0)
Completed Study	220 (89.4)	167 (81.1)	372 (78.3)	592 (82.1)
Withdrew Prematurely	26 (10.6)	39 (18.9)	103 (21.7)	129 (17.9)
Reason for Premature Withdrawal				
Adverse Event	7 (2.8)	20 (9.7)	37 (7.8)	44 (6.1)
Inadequate Response	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Patient Choice	10 (4.1)	13 (6.3)	37 (7.8)	47 (6.5)
Protocol Violation	0 (0.0)	2 (1.0)	2 (0.4)	2 (0.3)
Patient Non-Compliance	1 (0.4)	0 (0.0)	8 (1.7)	9 (1.2)
Lost to Follow-up	6 (2.4)	2 (1.0)	13 (2.7)	19 (2.6)
Other	2 (0.8)	2 (1.0)	4 (0.8)	6 (0.8)

[a] Includes all subjects receiving placebo (b.i.d. or t.i.d.)
[b] Includes all subjects receiving any concentration of Cellegesic (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.
NOTE: Study completion and withdrawl summaries are based on subjects evaluable for safety.

7.5.2 Demographic and Baseline Characteristics

721 subjects were evaluable for safety. The subjects who applied Cellegesic NTG ointment 0.4% b.i.d. and those who applied any dose of Cellegesic NTG ointment were generally comparable to the subjects who applied vehicle (placebo) with regard to sex, race, age, weight, height, vital signs, and current tobacco use. The mean age of all subjects was 44.6 years. Most of the subjects (87%, 627/721) were Caucasian, and the number of males and females were near-equal (365 and 356, respectively). The mean height was 170.6 cm, and mean weight was 80.4 kg. The mean systolic and diastolic blood pressure measurements recorded after the subjects were sitting for 10 minutes were 123.8 and 76.6 mm Hg, respectively. The mean heart rate was 72.8 bpm.

A higher percentage of subjects in the overall Cellegesic ointment group (42.1%) than in the Cellegesic NTG ointment 0.4% b.i.d. group (33.5%) or in the placebo group (32.9%) identified themselves as drinkers of alcoholic beverages. The protocols for the phase 3 studies recommended that all subjects control their alcohol intake in order to minimize the risk of vasodilatation and hypotension.

Demographic and baseline characteristics for subgroups of the safety population were based on sex, age (<65 years or ≥65 years), and race (Caucasian, Black, or other). For

most characteristics, no noteworthy differences by sex, age, or race were evident among subjects who applied Cellegesic NTG ointment 0.4% b.i.d., any dose of Cellegesic ointment, or placebo. The percentage of males ≥65 years was at least twice that of females in this age group; about 10-15% of all males compared with approximately 5% of all females were ≥65 years; these proportions were seen similarly in the treatment groups. The dominance of males compared to females in the subgroup of subjects ≥65 years (about 70% to 30%) is evident; in contrast, the percentages of males and females are similar in the subgroup of subjects <65 years. Black subjects in the Cellegesic NTG ointment 0.4% b.i.d. group had a mean blood pressure consistent with mild hypertension compared to mean normotension in Blacks of the other 2 treatment groups and in the other racial subgroups. Because the elderly and Blacks were a small proportion of the overall study populations (each <10%), the differences observed in these small subgroups were unlikely to affect the results. There was essentially no difference in alcohol use between the Cellegesic 0.4% group and placebo group. The higher alcohol use in the overall Cellegesic ointment group was contributed by the larger proportion of both males and females admitting to current alcohol use compared to those in the placebo group.

7.5.3 Extent of Exposure

Extent of exposure is reflected by duration of therapy, which was determined from the dates of first dispensing and last return of study medication. The duration of exposure was similar for both active and placebo groups.

Exposure is also reflected by the amount of study medication each subject used, which was determined by weighing the tubes of assigned study drug when they were dispensed and when they were returned, and calculating the difference in weight. The mean total amount of medication used was similar in the Cellegesic NTG ointment 0.4% b.i.d. group, the overall Cellegesic ointment group, and the placebo group (40 g, 39 g, and 43 g, respectively).

Treatment compliance was determined by comparing the amount of study medication used with the expected amount of use. Mean percentage compliance with the prescribed dosage was comparable for the Cellegesic NTG ointment 0.4% b.i.d. group (104.9%) and the placebo group (101.2%), and somewhat lower for the overall Cellegesic ointment group (94.3%).

7.5.4 Frequently Reported Adverse Events

Frequently reported adverse events are presented by body system and preferred term in Table 12. The most frequently reported adverse event was headache NOS in all 3 treatment groups: 131/206 (63.6%) subjects in the Cellegesic NTG ointment 0.4% b.i.d. group, 229/475 (48.2%) subjects in the overall Cellegesic ointment group, and 93/246 (37.8%) subjects in the placebo group. Other adverse events that occurred in ≥2.0% of the subjects who applied Cellegesic NTG ointment 0.4% b.i.d. were nausea (5.8%), dizziness (4.4%), diarrhea NOS (2.9%) and hemorrhoids (2.4%). These adverse events occurred at slightly lower rates in the overall Cellegesic ointment group. Events other than headache that occurred in ≥2.0% of the placebo group were as follows: diarrhea (3.3%); upper respiratory tract infection NOS (2.8%); anal discomfort, influenza, and pruritus (2.4% each); and pharyngitis (2.0%).

Table 12: Incidence of Frequently Reported Treatment-Emergent Adverse Events (≥2.0% of Subjects in Any Treatment Group) Summarized by Body System and Preferred Term (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

		Cellegesic Nitroglycerin Ointment	
	Placebo[a] (N=246)	0.4% b.i.d. (N=206)	Total[b] (N=475)
Body System Preferred Term	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.

7.5.5 Frequently Reported Adverse Events: Relationship to Treatment

Frequently reported adverse events and their relationship to study treatment based on the investigators' assessments are displayed in Table 13. In this table, each subject is counted once, according to the strongest relationship of any event reported for the subject. In addition to "possibly related" and "related," study CP125 03-02-01 included the category, "probably related;" events considered probably related from this study were pooled with the "related" adverse events in Table 14

Of the 131 subjects who had at least 1 event that was considered treatment-related after applying Cellegesic NTG ointment 0.4% b.i.d., 33 had at least 1 event with the strongest level of relatedness as "possibly" and 98 had at least 1 event with the strongest level of relatedness as "related." Therefore, a total of 131/206 (64%) subjects in the Cellegesic NTG ointment 0.4% b.i.d. group had possibly-related or related adverse events, compared with 50% in the overall Cellegesic group and 30% in the placebo group. Headache was considered treatment-related in 118/206 (57.3%) subjects who applied Cellegesic NTG ointment 0.4% b.i.d., 210/475 (44.2%) subjects who applied any dose of Cellegesic ointment, and 55/246 (22.4%) subjects in the placebo group. While treatment relatedness was determined by the investigators in studies 1 and 2, all headaches that occurred within 30 minutes of study drug application were recorded as treatment-related in study 3. Use of this criterion in the 90 subjects who applied Cellegesic NTG ointment 0.4% b.i.d. in study 3 contributed to the high incidence of treatment-related headache for this dose group. Events other than headache that were considered treatment-related at an incidence of ≥2.0% in the Cellegesic NTG ointment 0.4% group and overall Cellegesic ointment group were dizziness (4.4% and 3.4%, respectively) and nausea (4.4% and 3.2%, respectively). Pruritus was the only treatment-related adverse event reported in ≥2.0% of the placebo group.

Table 13: Incidence of Frequently Reported Treatment-Emergent Adverse Events (≥2.0% of Subjects in Any Treatment Group) Summarized by Strongest Relationship to Study Drug (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

	Placebo[a] (N=246)				Cellegesic Nitroglycerin Ointment 0.4% b.i.d. (N=206)				Total[b] (N=475)			
Body System Preferred Term	None n	Possibly n	Related[c] n	Total Related[d] n (%)	None n	Possibly n	Related[c] n	Total Related[d] n (%)	None n	Possibly n	Related[c] n	Total Related[d] n (%)
Subjects With Any Adverse Events	76	33	40	73 (29.7)	31	33	98	131 (63.6)	76	99	140	239 (50.3)
Nervous system disorders	39	18	38	56 (22.8)	12	30	96	126 (61.2)	20	87	136	223 (46.9)
Headache NOS	38	18	37	55 (22.4)	13	26	92	118 (57.3)	19	79	131	210 (44.2)
Dizziness	0	0	0	0	0	8	1	9 (4.4)	1	15	1	16 (3.4)
Gastrointestinal disorders	21	16	2	18 (7.3)	23	9	4	13 (6.3)	46	25	7	32 (6.7)
Nausea	0	2	0	2 (0.8)	3	6	3	9 (4.4)	6	11	4	15 (3.2)
Anal discomfort	2	3	1	4 (1.6)	0	1	0	1 (0.5)	0	1	0	1 (0.2)
Diarrhea NOS	7	1	0	1 (0.4)	6	0	0	0	8	4	0	4 (0.8)
Hemorrhoids	0	0	0	0	5	0	0	0	6	0	0	0
Infections and infestations	31	0	0	0	16	1	0	1 (0.5)	35	1	0	1 (0.2)
Influenza	6	0	0	0	1	0	0	0	4	0	0	0
Upper respiratory tract infection NOS	7	0	0	0	2	0	0	0	6	0	0	0
Skin and subcutaneous tissue disorders	4	4	2	6 (2.4)	5	0	1	1 (0.5)	6	2	1	3 (0.6)
Pruritus NOS	1	3	2	5 (2.0)	0	0	1	1 (0.5)	0	0	1	1 (0.2)
Respiratory, thoracic and mediastinal disorders	13	0	0	0	9	0	0	0	21	0	0	0
Pharyngitis	5	0	0	0	2	0	0	0	6	0	0	0

[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.
[c] Includes all Probably and Related adverse events in study CP125 03-02-01. For headaches in study CP125 03-02-01, only those that occurred within 30 minutes of study drug administration were considered treatment related.
[d] Subjects having Total Related (Possibly Related or Related) adverse events in the treatment group.
Note: Frequently reported adverse events are defined as preferred terms reported by ≥2.0% of subjects in any treatment group regardless of relationship.
Subjects who reported multiple occurrences of the same preferred term or body system with different relationship assessments are categorized according to the strongest relationship for the event.

7.5.6 Frequently Reported Adverse Events: Maximum Intensity

Frequently reported adverse events categorized by their maximum severity (mild, moderate, severe) are presented in Table 13. A subject who had multiple episodes of the same event is counted once, according to the most severe episode.

The maximum intensity of any adverse event was mild or moderate for the majority of subjects who had at least 1 adverse event during treatment with Cellegesic NTG ointment 0.4% b.i.d., any dose of Cellegesic ointment, or placebo. However, events were assessed as severe in more subjects who applied Cellegesic NTG ointment 0.4% b.i.d. (22.8%, 47/206) and any dose of Cellegesic ointment (16.4%, 78/475) than those who applied placebo (7.3 %, 18/246). In all 3 treatment groups, headache was the event most frequently assessed as severe. Severe headache was reported in 20.4% (42/206) subjects who applied Cellegesic NTG ointment 0.4% b.i.d. Severe headache was reported in 5.7% (14/246) subjects who applied placebo. No other event was assessed as severe in more than 1 subject of any group.

Most of the severe headaches in subjects who applied placebo were assessed as not related to study medication. For studies NTG 98-02-01 and NTG 00-02-01, all severe headaches in subjects who received any dose of Cellegesic NTG ointment 0.4% were considered by the investigator to be related or possibly related to study drug administration. In study 3, 32% (29/90) subjects who applied CP125 ointment (0.4%) b.i.d. had severe headache and 22/29 (76%) met the criterion for NTG-related headache based on their occurrence within 30 minutes of drug application. The remaining 7 subjects were determined to have severe headaches unrelated to study treatment since their occurrence was not within 30 minutes of application. All headaches with known outcomes resolved either upon discontinuation of study drug or treatment with concomitant medication, except headache of 1 subject (007-102) that was unchanged at the final study visit despite concomitant medication.

7.5.7 Frequently Reported Adverse Events: Subgroups of Subjects

The influence of sex, age, and race on the incidence of frequently reported adverse events are summarized for the safety-evaluable subjects.

Sex

Treatment-emergent adverse events were reported for a larger proportion of female subjects than male subjects in all treatment groups, with the percentage being about 10% higher for females than males in the Cellegesic NTG ointment groups and almost 30% higher for females than males in the placebo group. These higher rates in females than males were similarly seen for the incidences of headache in these groups, where the rates in males and females were 56% and 70%, respectively, in the Cellegesic NTG ointment 0.4% b.i.d. group, 46% and 51%, respectively, in the overall Cellegesic group, and 27% and 48%, respectively, in the placebo group. Nausea and diarrhea also occurred at a lower incidence in males than females in the Cellegesic NTG ointment 0.4% b.i.d. group (4% versus 7% for nausea and 2% versus 3% for diarrhea), in the overall Cellegesic group (3% versus 6% for nausea and 2% versus 4% for diarrhea), and the placebo group (0 versus 2% for nausea and 1% versus 6% for diarrhea).

Table 14: Incidence of Frequently Reported Treatment-Emergent Adverse Events (≥2.0% of Subjects in Any Treatment Group) Summarized by Maximum Intensity (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

					Cellegesic Nitroglycerin Ointment							
	Placebo[a] (N=246)				0.4% b.i.d. (N=206)				Total[b] (N=475)			
Body System Preferred Term	Mild n	Moderate n	Severe n	Total[c] n (%)	Mild n	Moderate n	Severe n	Total[c] n (%)	Mild n	Moderate n	Severe n	Total[c] n (%)
Subjects With Any Adverse Events	59	71	18	149 (60.6)	53	61	47	162 (78.6)	122	114	78	315 (66.3)
Nervous system disorders	34	45	15	95 (38.6)	42	53	43	138 (67.0)	89	87	67	243 (51.2)
Headache NOS	33	45	14	93 (37.8)	37	52	42	131 (63.6)	82	82	65	229 (48.2)
Dizziness	0	0	0	0	7	2	0	9 (4.4)	14	3	0	17 (3.6)
Gastrointestinal disorders	26	13	0	39 (15.9)	24	11	1	36 (17.5)	51	19	8	78 (16.4)
Nausea	1	1	0	2 (0.8)	8	4	0	12 (5.8)	16	4	1	21 (4.4)
Diarrhea NOS	5	3	0	8 (3.3)	4	2	0	6 (2.9)	8	4	0	12 (2.5)
Hemorrhoids	0	0	0	0	3	2	0	5 (2.4)	4	2	0	6 (1.3)
Anal discomfort	4	2	0	6 (2.4)	1	0	0	1 (0.5)	1	0	0	1 (0.2)
Infections and infestations	14	17	0	31 (12.6)	8	7	2	17 (8.3)	15	19	2	36 (7.6)
Upper respiratory tract infection NOS	2	5	0	7 (2.8)	1	1	0	2 (1.0)	2	4	0	6 (1.3)
Influenza	2	4	0	6 (2.4)	0	1	0	1 (0.5)	1	3	0	4 (0.8)
Respiratory, thoracic and mediastinal disorders	10	3	0	13 (5.3)	7	2	0	9 (4.4)	16	4	1	21 (4.4)
Pharyngitis	4	1	0	5 (2.0)	2	0	0	2 (1.0)	5	1	0	6 (1.3)
Skin and subcutaneous tissue disorders	6	4	0	10 (4.1)	4	2	0	6 (2.9)	5	4	0	9 (1.9)
Pruritus NOS	3	3	0	6 (2.4)	0	1	0	1 (0.5)	0	1	0	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.
[c] Subjects with adverse events with an unknown intensity on every record are included in the appropriate treatment group Total column.
Note: Frequently reported adverse events are defined as preferred terms reported by ≥2.0% of subjects in any treatment group regardless of intensity.
Subjects who reported multiple occurrences of the same preferred term or body system with different intensity assessments are categorized according to the worst intensity for the event.

Age

A smaller percentage of elderly subjects (≥65 years) than younger subjects had adverse events; the rates were about 10% lower for elderly in all 3 treatment groups. These differences were similarly seen specifically for headache for the 3 groups, where the rates of headache in the elderly versus younger subjects were 47% versus 66% in the Cellegesic NTG ointment 0.4% b.i.d. group, 32% versus 50% in the overall Cellegesic group, and 23% versus 39% in the placebo group. Although the elderly were a small proportion of the study subjects, nausea tended to occur in a larger percentage of elderly subjects than younger subjects who received Cellegesic NTG ointment 0.4% b.i.d. (21% versus 4%) or any dose of Cellegesic (11% versus 4%); nausea was reported in only 2 placebo-treated subjects, both of whom were <65 years.

Race

Adverse events were reported for a larger percentage of Caucasian subjects than other races. The larger percentage of Caucasians than other races was evident for headache: 66% versus 42% in the Cellegesic NTG ointment 0.4% b.i.d. group, 50% versus 37% in the overall Cellegesic group, and 40% versus 22% in the placebo group. Relatively small numbers of non-Caucasian subjects were in these studies, and no other trends by race were evident.

Headache

In the 3 studies, headache was the most commonly reported adverse event in subjects who applied Cellegesic NTG ointment 0.4% b.i.d. intra-anally, subjects who applied any dose of Cellegesic ointment and those who applied placebo. The incidence of headache was 64% with Cellegesic NTG ointment 0.4% b.i.d., 48% with any dose of Cellegesic ointment, and 38% with placebo, as shown in Table 12. The overall incidence of headache and the incidences of mild, moderate, and severe headaches during treatment with placebo ointment were higher than the incidences during treatment with Cellegesic NTG ointment 0.1%; they were slightly lower than the incidences with Cellegesic NTG ointment 0.2%, except moderate headaches were higher in the placebo group. Table 15 also indicates that the incidences of headache and the intensity of headaches tended to increase with increased daily doses of Cellegesic NTG ointment. As the NTG concentration and dosing frequency increased, the extent of increase in the percentage of subjects with moderate and severe headaches was greater than the extent seen for mild headaches. Headaches generally occurred more often on a t.i.d. than a b.i.d schedule, which is consistent with a higher daily dose, but this trend was less evident at the 0.4% concentration.

Throbbing frontal headache of relatively short duration is the most common side effect of NTG administration in any dosage form, by any route, or for any indication. Appropriate warnings and precautions are included in the labeling of approved NTG products. The labelling of oral NTG tablets cautions the patient that headaches may be a marker of drug activity, indicating the high likelihood for headache, although headache frequencies are not specified. Headache incidence is about 50% with NTG oral spray. Headache was reported in 63% with all doses of NTG patch compared to 18% with placebo patch.[43] In evaluating 5.10 & 15mg/24hr patches, Santoro[44] found headache incidences of 72,100 & 94% respectively. Based on the reported incidences of headache with these dosage forms, the 48% incidence of headache with all doses of Cellegesic NTG ointment was lower than, and the 64% incidence with specifically the 0.4% b.i.d. dose was similar to the incidence[43] or less than NTG patches.[44]

Of note is the high incidence of headache with placebo in the Cellegesic studies. The incidence of headache with placebo treatment for the combined studies (38%) was much higher than reported with placebo in the labeling for NTG patch (18%).[6] The high placebo rate in the Cellegesic studies suggests that the subjects may have been sensitive to the potential for headaches due to the requirement that they record headache data in a daily diary. In study 3, headache was reported in 85.6% of subjects treated with Cellegesic NTG ointment 0.4% and a notably high incidence of 67.3% of subjects treated with placebo.

Also, the incidence of headache in these studies is in context with the protocol restrictions on the use of concomitant medications to treat headache during the study period. In study 3, subjects who developed headache were allowed to take 2 tablets of acetaminophen (total 650 mg per dose at U.S. study sites; total 1000 mg at European study sites) for no more than 8 doses during the first 21-days. Acetaminophen use for headaches was limited to 650 mg every 6 hours for no more than 3 doses a day in study 1 and limited to 650 mg every 12 hours for no more than 4 days in study 2. Headache could be anticipated to be a lesser problem in clinical practice, when mild analgesics could be used prophylactically as well as reactively. Headaches associated with NTG respond well to mild analgesics (e.g., acetaminophen). Clinical experience with a transdermal NTG system, for example, reported that headaches in patients receiving 5-20 mg NTG patches plus sublingual tablet supplementation were satisfactorily managed with mild analgesics.[45]

Headache data were collected during visits in studies 1 and 2 and in daily diaries in study 3. Using the more detailed data collected in study 3, the incidence of headache by week was examined; headache was reported with decreasing incidence during the study and the decrease was seen in both treatment groups. While some decrease may reflect subjects who discontinued treatment due to headache, the incidence of headache tended to decrease to a greater extent than could be explained by discontinuations due to headache alone, which was relatively low in this study (5.6%, 5/90). An alternative explanation may be that subjects reported less headache as treatment continued due to increased tolerance to this effect.

Of the 71 subjects who applied Cellegesic NTG ointment 0.4% and reported headache in the first week, less than 50% of the 65 subjects who remained in the study through the fourth week also reported headache, further suggesting that many subjects who initially experienced headache did not have headache later during the study.

In study 3, 85.6% of subjects developed a headache at anytime during the study and placebo subjects 67.3% in NTG group.

An interesting trend in the change in incidence of headache intensity by week was observed for all safety subjects in study 3 for those subjects who had headache during the first week. While the incidence of moderate and severe headaches decreased by week, the incidence of mild headaches in the Cellegesic NTG ointment 0.4% increased for a couple weeks after the first week, then decreased; this transient increase was not seen in the placebo group. These results suggest that in some subjects, severe or moderate intensity headaches may have diminished over time to mild headaches (resulting in the transient rise in mild headaches), with a general trend towards no headache over the study period. These observations further suggest increased tolerance to headache over the treatment period.

Because headaches following administration of NTG have been reported to more

likely occur in patients with a history of migraine, cluster, or tension headaches,[8] the incidence of headaches and the intensity were examined based on the presence or absence of a history of headache (Table 14). Headache generally occurred at a similar rate in subjects with and without a history of headache. The results suggest that mild and moderate headaches occurred at a higher rate in subjects without a history. However, among subjects with a history of headaches, the headaches reported during treatment were more often of severe intensity.

Table 15: Incidence of Treatment-Emergent Headache by Maximum Intensity and History of Migraine or Recurrent Headaches (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

	History of Migraine or Recurrent Headaches					
	Placebo[a] (N=246)		Cellegesic Nitroglycerin Ointment 0.4% b.i.d (N=206)		Total[b] (N=475)	
On-Study Headache Maximum Intensity	Yes (N=16) n (%)	No (N=230) n (%)	Yes (N=19) n (%)	No (N=187) n (%)	Yes (N=43) n (%)	No (N=432) n (%)
Mild	1 (6.3)	32 (13.9)	2 (10.5)	35 (18.7)	6 (14.0)	76 (17.6)
Moderate	1 (6.3)	44 (19.1)	3 (15.8)	49 (26.2)	4 (9.3)	78 (18.1)
Severe	2 (12.5)	12 (5.2)	6 (31.6)	36 (19.3)	11 (25.6)	54 (12.5)

[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.

In study 3, headaches that occurred within 30 minutes of study drug administration were considered NTG-related. Because this criterion was not used in the other 2 studies, headaches by NTG relatedness were examined for study 3 separately. By meeting the criterion of occurrence within 30 minutes of study drug application, 64/90 (71%) subjects in the Cellegesic NTG ointment 0.4% b.i.d. group had at least 1 treatment-related headache, compared with 29/98 (30%) subjects in the placebo group. Most headaches were of moderate or severe intensity in the subjects reporting headache in the Cellegesic NTG ointment 0.4% b.i.d. group, whereas headaches were more often of mild or moderate intensity in the placebo group. Also, headaches in subjects in the Cellegesic NTG ointment 0.4% b.i.d. group generally lasted longer (mean 8 hours) compared with the placebo group (mean 4 hours). About 48% of subjects used concomitant medication to treat headache in the Cellegesic NTG ointment 0.4% b.i.d. group compared with 38% in the placebo group.

The incidence of non-treatment related headaches in the placebo group was 57%, which is higher than the 30% incidence of treatment-related headaches in this group. The distribution of the intensity of non-treatment-related headache was similar for the Cellegesic NTG ointment 0.4% b.i.d. and placebo groups, with more mild or moderate than severe headaches. Interestingly, while the mean duration of non-treatment-related headaches was similar to that of treatment-related headaches for the Cellegesic NTG ointment 0.4% b.i.d. group, the mean duration of non-treatment-related headaches was about 3 times longer in the placebo group than in the Cellegesic NTG ointment 0.4% b.i.d., and 5 times longer than treatment-related headaches for the placebo group. The percentage of subjects who used concomitant medications to treat headache was about 10% lower in the Cellegesic NTG ointment 0.4% group (33%) compared with the placebo group (46%).

7.6 Deaths, Other Serious Adverse Events, and Discontinuations Due to Adverse Events Deaths

No deaths were reported during the three phase 3 studies sponsored by Cellegy Pharmaceuticals, Inc.

7.7 Other Serious Adverse Events

A total 10 subjects had serious adverse events during the three phase 3 studies: 4 subjects applied placebo ointment and 6 subjects applied Cellegesic NTG ointment, 2 of whom applied the 0.4% b.i.d. dose. Two subjects had serious perianal or perirectal abscess; all other subjects had unique events. The events began from 1 to 60 days after the start of therapy. The 4 placebo-treated subjects had serious events that were considered to be of moderate intensity; 1 subject treated with Cellegesic NTG ointment 0.1% had a serious event of moderate intensity; the remaining 5 subjects who received Cellegesic ointment had an event of severe intensity. One placebo-treated subject (007-123) and 3 Cellegesic ointment-treated subjects (322-146, 009-110, and 317-115) discontinued study treatment due to their events. The only serious event judged to be related to study medication was severe migraine headache that began on the first day of treatment with Cellegesic NTG ointment 0.2% (Subject 009-110). This subject had a history of migraine headaches. Headaches following administration of NTG have been reported to more likely occur in patients with a history of migraine, cluster, or tension headaches.

Details of the serious adverse events are provided in the narrative descriptions that follow.

Subject 007-123 (Pain exacerbated): This 19-year-old Caucasian female had a medical history that included anal fissure for 1.5 months and glucose-6-phosphate dehydrogenase deficiency. The subject was randomly assigned to receive placebo ointment b.i.d for 56 days for treatment of an anal fissure. On Day 22 of therapy, the subject reported worsening of the anal fissure pain, which was assessed by the investigator as moderate in intensity. The subject was withdrawn from the study due to the event and hospitalized. During the hospitalization, a lateral internal sphincterotomy was performed and the pain resolved. The investigator determined the event of worsening anal fissure pain to be unrelated to study medication. Concomitant medications at the time of the event included psyllium (Metamucil®) and combination gestodene plus ethinyl estradiol oral contraceptive (Minulet®).

Subject 015-106 (Hepatitis C): This 46-year-old Caucasian male had a medical history that included anal fissure for about 1 month, allergies to seafood and bee stings, intermittent peripheral edema, alopecia, intermittent ringing in the left ear, tonsillectomy, hemachromatosis, fatigue and tiredness, intermittent heartburn, recurrent blood in stool, kidney infections, pyeloplasty, congenital narrowing of the right ureter, hydronephrosis, erectile dysfunction, leg cramps, chronic leg pain, degenerative disc disease, tremors, hyperopia, pain disorder, sleeplessness, anxiety, depression, recurrent acute bronchitis, alcoholism (recovering alcoholic), elevated liver enzymes, and unspecified liver problems (including pain). The subject was randomly assigned to receive placebo ointment b.i.d. for 56 days for treatment of an anal fissure. On Day 3, hepatitis C was diagnosed. Study drug was continued and the subject completed the 56-day double-blind treatment phase, with the event of hepatitis C ongoing at the exit visit. Although the subject completed the 56-day treatment phase, he was withdrawn from the study at the exit visit due to the event. The

investigator determined the hepatitis C to be moderate in intensity and unrelated to study medication. Concomitant medications at the time of the event included propranolol (Inderal®), trazodone (Desyrel®), dronabinol (Marinol®), amitriptyline (Elavil®), hydrochlorothiazide plus triamterene (Dyazide®), fluoxetine (Prozac®), cyclobenzaprine (Flexeril®), and oxazepam (Serax®).

Subject 025-109 (Vein pain): This 52-year-old female with diabetes had a diagnosis of diabetic angiopathy at screening. On Day 1 of study treatment she developed left femoral pain (vein pain) and was hospitalized for observation. Study drug was interrupted from Day 2 until Day 7. The subject's pain resolved, and she was discharged. She resumed study treatment and completed the study according to protocol. The investigator attributed the pain to "changing of the weather." The investigator and sponsor agreed that this subject's vein pain was not related to study medication.

Subject 033-340 (Perianal abscess): This 41-year-old female completed study treatment according to protocol on Day 54. On Day 55 she developed left anal pain (a non-serious AE). Examination on Day 60 revealed a left perianal abscess that was treated with incision and drainage. The subject recovered. The investigator and sponsor agreed that this subject's perianal abscess was not related to study medication.

Subject 312-113 (Cholelithiasis): This 42-year-old Caucasian female had a medical history that included chronic anal fissure, irritable bowels, loose stools, gas, intermittent stitch after eating, and a foot disorder (possible bone spur). The subject was randomly assigned to receive Cellegesic NTG ointment 0.1% t.i.d. for 56 days for treatment of a chronic anal fissure. Baseline laboratory results revealed elevated alkaline phosphatase (279 U/L) and SGPT of 47 U/L. Subsequent clinical evaluation resulted in the diagnosis of cholelithiasis. The subject completed the study with the anal fissure completely healed by Day 42. On Day 44, during the posttreatment follow-up phase of the study, the subject underwent an elective cholecystectomy, and was hospitalized overnight for surgical recovery. The investigator determined the event of cholelithiasis to be unrelated to study medication. Concomitant medications at the time of the event included loperamide, psyllium, oxycodone, acetaminophen, ondansetron, ketorolac tromethamine, metoclopramide, lactated Ringer's solution, morphine, "triple antibiotic ointment", cefotetan, fentanyl, propofol, naloxone, sevoflurone, rocuronium, neostigmine, and glycopyrrolate.

Subject 322-146 (Perirectal abscess): This 24-year-old Caucasian male had a medical history that included eczema, chronic anal fissure with pain and bleeding. The subject was randomly assigned to receive Cellegesic NTG ointment 0.2% b.i.d. for 56 days for treatment of chronic anal fissure. Therapy was discontinued on Day 8, after the subject was hospitalized for surgical drainage of a severe perirectal abscess. The subject was discharged from the hospital and recovered 2 days later. The investigator determined the perirectal abscess to be severe and unrelated to study medication. Concomitant medications at the time of the event included metronidazole, ciprofloxacin and hydrocodone-acetaminophen.

Subject 009-110 (Migraine NOS): This 41-year-old Caucasian male had a medical history that included anal fissure for about 7 months, hypertension, and migraines. The subject was randomly assigned to receive Cellegesic NTG ointment 0.2% b.i.d. for 56 days for treatment of an anal fissure. Following the first dose of study drug on Day 1, the subject experienced mild facial flushing, mild headache, and a severe migraine headache thought

to be exacerbated by Cellegesic NTG ointment 0.2%. The subject visited an emergency room because of the migraine headache. Intramuscular prochlorperazine (Compazine®) and intravenous metoclopramide (Reglan®) were used to treat the migraine headache, which resolved the same day. The subject was withdrawn from the study due to the event on Day 2. The investigator assessed the migraine headache as severe in intensity and related to study drug. The only concomitant medication at the time of the event was propranolol.

Subject 320-103 (Chest pain and dyspnea NOS): This 63-year-old Caucasian male had a medical history that included coronary artery disease, hypertension, angioplasty, reflux disease, benign anal fissure with pain and bleeding, allergy to penicillin and sulfa, benign prostate hypertrophy, and a removal of a testicular cyst. The subject was randomly assigned to receive Cellegesic NTG ointment 0.2% t.i.d. for 56 days for treatment of a chronic anal fissure. On Day 37, the subject was hospitalized after developing shortness of breath and chest pain. Cardiac catheterization and angioplasty were completed, and the subject recovered and was discharged from the hospital after 3 days. The subject completed the study. The investigator determined the adverse event of dyspnea and chest pain to be severe and unrelated to study medication. Concomitant medications at the time of the event included lansoprazole, cisapride, terazosin, atorvastatin, aspirin, and ramipril.

Subject 317-115 (Hip fracture): This 72-year-old Caucasian female had a medical history that included allergy to morphine, hypothyroidism, diabetes mellitus, chronic fatigue, chronic anal fissure, spastic bowel, urinary incontinence, water retention, right leg and knee surgery, and the wearing of eyeglasses. The subject was randomly assigned to receive Cellegesic NTG ointment 0.4% b.i.d. for 56 days for treatment of a chronic anal fissure. On Day 47, therapy was discontinued after the subject was hospitalized for a fractured hip and surgical replacement of the head of the femur resulting from a fall. The outcome of the event was unknown. The investigator determined the fractured hip to be severe and unrelated to study medication. Concomitant medications at the time of the event included levothyroxine, glyburide, metformin, amitriptyline, bumetanide, methylcellulose, and calmospeptine ointment.

Subject 019-045 (Abdominal distension, abdominal pain NOS, anorexia, dyspnea NOS, dysuria, decreased hemoglobin, hypercalcemia, loose stools, nausea, night sweats, pyrexia, rigors, small intestinal obstruction NOS, weakness): This 69-year-old male had a history of T-cell lymphoma treated by surgery and chemotherapy. This subject was a protocol violation and should not have been enrolled in the study. The subject received study medication for 23 days and withdrew (reason = "Subject Choice") because of rectal pain. The subject developed severe abdominal pain on Day 46, moderately loose stools on Day 47, and mild pyrexia on Day 48. On Day 50 he presented to the emergency department with complaints of abdominal pain, distention, and loose stools; and he was hospitalized after an abdominal CT scan showed increasing ascites, lymphadenopathy, and partial obstruction due to an abdominal mass in the root of the small bowel mesentery. He was treated with nasogastric tube decompression and discharged. The investigator and sponsor agreed that the subject's small bowel obstruction resulted from lymphoma and was not related to study medication.

7.8 Discontinuations Due to Adverse Events

Overall, 45 subjects who applied Cellegesic ointment, 22 of whom applied the 0.4% b.i.d. dose, and 7 subjects who applied placebo discontinued study treatment due to an adverse

event. Headache was the most common adverse event leading to discontinuation in 29 subjects in the Cellegesic ointment group; 7.8% (16/206) of subjects who applied Cellegesic NTG ointment 0.4% b.i.d. discontinued due to headache. In the overall placebo group, 0.8% (2/246) subjects discontinued due to headache. In subjects who applied any dose of Cellegesic ointment, vomiting was the cause for withdrawal in 4 subjects, nausea was the cause for withdrawal in 3 subjects, and burning sensation NOS, tachycardia NOS, dizziness, and vertigo were each causes for withdrawal of 2 subjects. Pruritus NOS was a cause for withdrawal in 2 subjects treated with placebo. The remaining adverse events led to discontinuation in only 1 subject each.

The 52 subjects who discontinued study participation due to adverse events are listed in Table 22. Four of these subjects (007-123, 322-146, 009-110, and 317-115) had events that met the criteria for serious. Most of the subjects had events leading to treatment discontinuation that were assessed as at least possibly related to study treatment (39/45 Cellegesic-treated; 5/7 placebo-treated).

Headache was the event or among the events leading to treatment discontinuation in 29 subjects who applied Cellegesic NTG ointment, 16 of whom applied the 0.4% b.i.d. dose, the dose proposed in this NDA application. These 16 discontinuations by study were as follows: 5.6% (5/90) of subjects who applied Cellegesic NTG ointment 0.4% b.i.d. in study 3, 11.5% (9/78) subjects who applied this dose in study 2 and 5.3% (2/38) subjects who applied this dose in study 1. One might speculate from these percentages that baseline anal fissure pain may have played a role in treatment discontinuation.

The possible role of fissure pain intensity was examined for the 16 subjects who discontinued treatment with Cellegesic NTG ointment 0.4% b.i.d. due to headache. Of these 16 subjects, 56% (9/16) had pain improvement during study treatment and 56% (9/16) subjects had relatively low VAS scores (<30 mm) at the time of treatment discontinuation. Overall, 62.5% (10/16) had either improved pain scores or low scores at the time of discontinuation, suggesting that subjects may have been more likely to discontinue treatment due to headache when fissure pain improved or became tolerable.

7.9 Other Safety Observations Clinical Laboratory Evaluations

Laboratory test results for the hematology, clinical chemistry, and urinalysis parameters were measured at baseline and on Day 56 (or day of exit from the study). To assess the safety of Cellegesic NTG ointment 0.4% b.i.d. and of all doses of Cellegesic ointment with regard to routine laboratory tests, the number and percentage of subjects whose laboratory values changed from normal at baseline to outside the normal range at the exit visit were determined.

The percentages of subjects who had normal baseline values and abnormally high or low exit-visit values for hematology analytes were small in all treatment groups, as shown in Table 16. The largest percentage of subjects with shifts occurred in the placebo group, where 5.7% of subjects shifted from normal to low neutrophil counts. Shift in any particular hematology laboratory test occurred in less than 5% of subjects who applied Cellegesic NTG ointment 0.4% b.i.d. or any dose of Cellegesic ointment.

Table 16: Hematology Laboratory Values within Normal Range at Baseline and Outside Normal Range at Exit (All subjects in completed phase 3 studies evaluable for safety)

	Placebo[a]		Cellegesic Nitroglycerin Ointment 0.4% b.i.d.		Total[b]	
Analyte	Low n/N (%)	High n/N (%)	Low n/N (%)	High n/N (%)	Low n/N (%)	High n/N (%)
Basophils	0/211 (0.0)	6/211 (2.8)	1/171 (0.6)	3/171 (1.8)	1/391 (0.3)	8/391 (2.0)
Eosinophils	0/211 (0.0)	5/211 (2.4)	0/171 (0.0)	3/171 (1.8)	1/392 (0.3)	7/392 (1.8)
Hematocrit	5/205 (2.4)	0/205 (0.0)	2/166 (1.2)	0/166 (0.0)	12/388 (3.1)	2/388 (0.5)
Hemoglobin[c]	5/212 (2.4)	0/212 (0.0)	6/172 (3.5)	0/172 (0.0)	16/394 (4.1)	0/394 (0.0)
Lymphocytes	4/211 (1.9)	10/211 (4.7)	4/172 (2.3)	6/172 (3.5)	10/393 (2.5)	17/393 (4.3)
Monocytes	3/211 (1.4)	2/211 (0.9)	0/172 (0.0)	0/172 (0.0)	9/393 (2.3)	1/393 (0.3)
Neutrophils[c]	12/211 (5.7)	8/211 (3.8)	3/172 (1.7)	2/172 (1.2)	15/393 (3.8)	11/393 (2.8)
Platelet Count	3/211 (1.4)	2/211 (0.9)	0/172 (0.0)	0/172 (0.0)	4/394 (1.0)	0/394 (0.0)

a Includes all subjects receiving placebo (b.i.d. or t.i.d.).
b Includes all subjects receiving any concentration of Cellegesic (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.
c The normal ranges for neutrophils and hemoglobin (female) were different from those used in Report NTG 98-03-01, resulting in different shift data for subjects from that study.
Note: n=number of subjects with a normal baseline value and abnormal exit value in that category; N=number of subjects in the treatment group with a baseline and exit value for that analyte.

Shifts from normal baseline to abnormally high or low clinical chemistry values at exit visit are shown in Table 17. The largest percentage of subjects with shifts occurred in the overall Cellegesic ointment group, where 15.4% of subjects shifted from normal to high blood glucose values; 14.7% of the Cellegesic NTG ointment 0.4% b.i.d. group and 12.3% of the placebo group had such shifts. Creatinine values shifted to abnormally high values in a similar percentage of subjects (6-7%) of each group. A smaller proportion of subjects in the Cellegesic NTG ointment 0.4% b.i.d. group (3%) had shifts to abnormally high ALT or AST values compared with 5 to 6% of subjects in the overall Cellegesic ointment group or the placebo group. Shifts for alkaline phosphatase and BUN occurred in a small percentage of subjects (<5%) in all 3 groups.

Table 17: Clinical Chemistry Laboratory Values Within Normal Range at Baseline and Outside Normal Range at Exit (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

	Placebo[a]		Cellegesic Nitroglycerin Ointment 0.4% b.i.d.		Total[b]	
Analyte	Low n/N (%)	High n/N (%)	Low n/N (%)	High n/N (%)	Low n/N (%)	High n/N (%)
Alkaline Phosphatase	1/220 (0.5)	2/220 (0.9)	2/180 (1.1)	0/180 (0.0)	5/407 (1.2)	5/407 (1.2)
Blood Glucose	8/212 (3.8)	26/212 (12.3)	3/170 (1.8)	25/170 (14.7)	10/397 (2.5)	61/397 (15.4)
BUN	0/220 (0.0)	3/220 (1.4)	0/181 (0.0)	8/181 (4.4)	1/410 (0.2)	14/410 (3.4)
Creatinine	2/220 (0.9)	13/220 (5.9)	2/181 (1.1)	12/181 (6.6)	2/406 (0.5)	28/406 (6.9)
SGOT (AST)	0/209 (0.0)	11/209 (5.3)	1/173 (0.6)	5/173 (2.9)	2/400 (0.5)	22/400 (5.5)
SGPT (ALT)	0/217 (0.0)	13/217 (6.0)	0/177 (0.0)	5/177 (2.8)	0/405 (0.0)	18/405 (4.4)

[a]Includes all subjects receiving placebo (b.i.d. or t.i.d.).
[b]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 normal baseline value and abnormal exit value in that category; N=number of subjects in the treatment group with a baseline and exit value for that analyte.

Forty-four subjects judged by investigator to be clinically significant; 25 either had clinically significant laboratory values for 1 or more laboratory analytes at baseline only (16 subjects), at both baseline and follow-up (7 subjects), or at baseline alone and at baseline and follow-up (2 subjects). The remaining 19 subjects (4 applied Cellegesic NTG ointment 0.4% b.i.d., 10 applied other doses of Cellegesic NTG ointment, and 5 applied placebo), had analyses

whose values were assessed as not clinically significant at baseline and clinically significant at the exit visit.

The laboratory abnormalities were reported as adverse events for 10 of the 19 subjects. In 1 of these 10 subjects (015-106), the elevated liver enzymes were associated with hepatitis C that was reported as a serious adverse event for this placebo-treated subject. In another subject (019-108), the abnormally high liver enzymes were considered to be possibly related to study treatment (Cellegesic NTG ointment 0.2%).

7.10 Vital Signs

Summary statistics (mean, SD, median, range) for vital signs measured at every evaluation visit for the placebo group and for each concentration of Cellegesic NTG ointment used in the three phase 3 studies; diastolic blood pressure, 9 (systolic blood pressure) and 10 (pulse). There were no time- or dose-related trends in diastolic blood pressure, systolic blood pressure, or pulse. Mean values were generally similar at all time points for all treatment categories. Summary statistics for the change from baseline at each evaluation for these 3 parameters further indicate stable vital signs during the study, with mean changes in diastolic and systolic blood pressures less than ±6 mm Hg and mean changes in pulse less than ±3.5 bpm at any visit for any of the treatment groups.

A few subjects in the phase 3 studies had vasodilatation or hypotension, a known side effects of NTG. To evaluate this potential effect during use of Cellegesic ointment, the proportion of subjects with clinically significant decreases in diastolic blood pressure (≥20 mm Hg), based on change compared to baseline at each clinic visit, is summarized for placebo and all concentrations of Cellegesic ointment in Table 18. Overall, 24/246 subjects (9.8%) who applied placebo ointment and 53/472 subjects (11.2%) who applied any dose of Cellegesic ointment had clinically significant decreases in diastolic blood pressure compared to baseline during at least 1 clinic visit. Clinically significant blood pressure decreases occurred in the largest proportion of subjects who applied the 0.1% concentration of Cellegesic NTG ointment and in the smallest proportion of subjects who applied the 0.2% concentration. No dose-related trends were evident.

Table 18: Decreases of ≥20 mm Hg From Baseline in Sitting Diastolic Blood Pressure by Visit (All Subjects in Completed Phase 3 Studies Evaluable for Safety)

		Cellegesic Nitroglycerin Ointment				
				0.4%		
Visit[a]	Placebo[b] n/N (%)	0.1%[b] n/N (%)	0.2%[b] n/N (%)	b.i.d. n/N (%)	Total[c] n/N (%)	Total[d] 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.

7.11 Physical Examination

Of the total 721 subjects in the phase 3 studies who were evaluable for safety, 21 subjects had abnormalities noted during physical examinations at the exit visit that were not noted at the pre-study physical examination or on the medical history. None of the physical examination abnormalities at exit visit were clinically significant in the 7 placebo-treated subjects. Of the 14 subjects who applied Cellegesic ointment and had physical examination abnormality at exit visit, the abnormality was determined to be clinically significant by the investigator in 6 subjects. These 6 subjects are briefly summarized below.

- **Subject 005-104:** This subject had a medical history of constipation, rectocele, and appendectomy. Abdominal pain was reported as an adverse event for this subject during Week 4 of treatment with Cellegesic NTG ointment 0.2%; the event was mild and considered unrelated to the study medication. This event was treated with concomitant medication and resolved during the study. There was no apparent association between study medication and the exit visit finding of lower abdominal pain.
- **Subject 008-052** developed bradycardia and extrasystole about 1 week after starting treatment with Cellegesic NTG ointment 0.4% b.i.d. These abnormalities were considered probably related to study, and the subject discontinued treatment due to these events.
- **Subjects 007-105 (**hemorrhoids), 024-291 (glaucoma), and 024-302 (inflammation of external and middle ear) each had these abnormal physical findings reported as adverse events during the study. These events were of mild or moderate intensity and considered not related to study treatment. The subjects were able to complete the study.
- **Subject 310-106** had an anal fistula with purulent drainage that was identified at the exit physical examination. The fistula was located well above the admission fissure site. The physical examination occurred 38 days late for the Day 56 clinic visit. At that time, the anal fissure was completely healed. The fistula was considered by the investigator to be unrelated to the original anal fissure. The anal fistula was reported as an adverse event of mild severity which resolved after drainage of the fistula.

7.12 Electrocardiogram

Electrocardiograms were recorded only in study CP125 03-02-01. Over 70% of subjects had normal ECGs at baseline and at exit visit in both the placebo and Cellegesic NTG ointment 0.4% b.i.d. groups. Most abnormal ECGs were not clinically significant. One subject (008-052) had a normal ECG at baseline and a clinically significant ECG (bradycardia and extrasystoles) during the study. This subject was withdrawn from treatment due to these abnormalities

7.13 Safety Information from Other Sources

7.13.1 Phase 1 Study Data

Safety data from one phase 1 study (Report NTG 98-03-02) follow. This pharmacokinetic study was an open-label, 3-treatment, 3-period, cross-over study conducted at 1 site in the United States. Six healthy volunteers participated in each of the 3 treatment phases. In

Treatment Phase I, a single application of Cellegesic NTG ointment 0.2% (approximately 375 mg containing approximately 0.75 mg of NTG) was applied to the anal canal. In Treatment Phase II, approximately 375 mg of Cellegesic NTG ointment 0.2% was applied intra-anally 3 times daily for 2 days followed by 1 application on the third day, for a total of 7 doses. In Treatment Phase III, NTG was infused intravenously at a constant rate of 0.01 mg NTG/minute over 30 minutes.

Headache was the adverse event reported most frequently and occurred during all study phases. Five subjects experienced headaches (1 per subject) in the single-dose phase of the study, 4 subjects experienced a total of 17 headaches in the multiple-dose phase of the study, and 2 subjects experienced headaches (1 per subject) in the intravenous administration phase of the study. Only 1 subject experienced a severe headache. All headaches were considered by the investigator to be possibly related or related to study treatment. Four headaches required treatment with acetaminophen; 3 headaches were experienced by Subject 001-103 (1 headache on each day of multiple-dose phase of the study), and 1 headache was experienced by Subject 001-100 (Day 1 of the multiple-dose phase).

One subject (001-102) reported a stomachache on Days 2 and 3 of multiple dose application that was considered by the investigator to have no relationship to the study drug. One subject (001-105) did not report any adverse events during the study.

No subject withdrew from the study due to an adverse event. There were no serious adverse events reported during the study.

All laboratory values were considered by the investigator to be within normal limits. There were no clinically significant changes in hematology or blood chemistry values during the study. One subject (001-101) had leukocyte esterase (2+) and WBC (10-25 cells/HPF) in the poststudy urinalysis results that were considered clinically significant by the investigator. This subject had normal urinalysis results 17 days later.

There were no clinically significant changes in heart rate, temperature, or in systolic, diastolic, or mean arterial blood pressure over time following NTG administration in the 3 treatment phases. One subject (001-102) had an increase in diastolic blood pressure from 54 mm Hg at 210 minutes to 98 mm Hg at 270 minutes during the intravenous infusion phase.

All post-study physical examination findings were within normal limits. Results from the 12-lead ECG were within normal limits at screening for all subjects. No further ECG information is available.

8. RISK BENEFIT PROFILE

The efficacy of Cellegesic nitroglycerin ointment, acceleration of rate of change in 24-hour average pain intensity, has been established in three well controlled studies.

The safety profile in the three studies is essentially the same as the adverse events observed in other trials of nitroglycerin.

8.1 Supporting and Post Marketing Data

8.1.1 Patient Headache Complaints

Cellegesic nitroglycerin ointment is branded Rectogesic outside the United States.

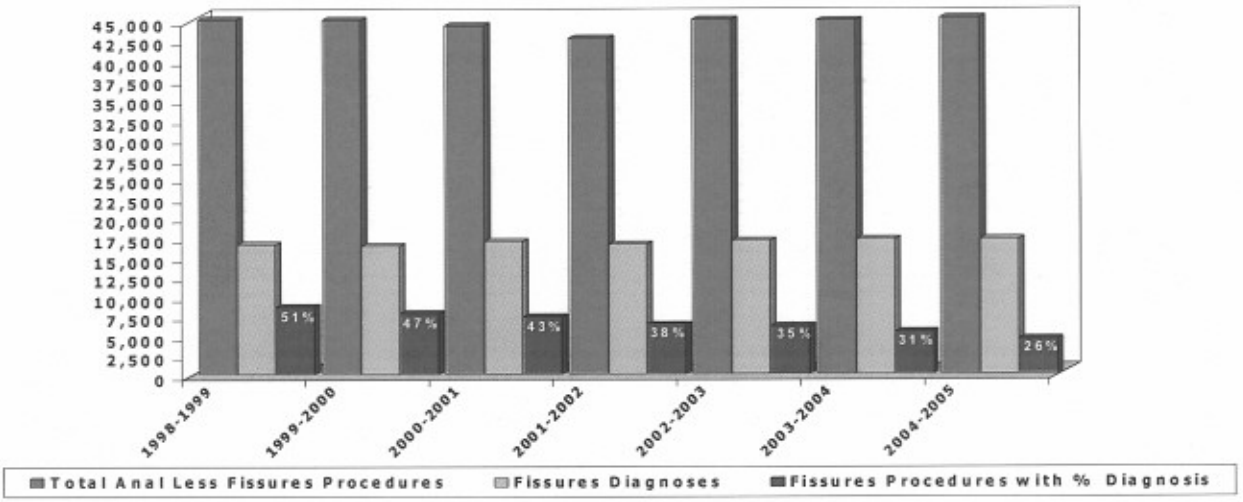
Rectogesic® rectal ointment 0.2% is marketed in Australia, New Zealand, South Korea and Singapore. Rectogesic rectal ointment 0.4% has been marketed in the United Kingdom since May 2005. In Australia approximately 200,000 tubes have been sold since 1999 and the company has received only 10 complaints of headache. In the United Kingdom the product carries a black triangle, a symbol urging physicians to report ALL adverse events via the country's yellow card system. To date, approximately 28,000 tubes have been sold and there has been only one adverse event report, a patient with a headache.

8.1.2 Decreased Need for Anal Fissure Surgery Associated with Nitroglycerin Ointment Usage

Via the health care system in the United Kingdom, the type and frequency of surgical procedures can be determined. Compounded nitroglycerin ointment was recommended for treating patients with an anal fissure in 1999. As seen in figure 24, the frequency of surgical treatment of an anal fissure has decreased approximately 50% since 1999 while the number of diagnosed cases has remained essentially constant, as has the frequency of surgery for all other anal conditions.

Figure 24

Surgical Procedures of the Anus



If the patient is satisfactorily treated medically without the need for surgery, he or she is spared the pain, inconvenience & cost of surgery.

8.1.3 Improvement in Quality of Life

In study 2, subjects completed a gastrointestinal quality of life questionnaire that had very few questions related to symptoms of a chronic anal fissure. The range of scores was wide in all groups (placebo, 0.2%, 0.4%) leading to non-statistical significance; the results however favored subjects having a relatively high quality of life which improved during the course of the study. It did not suggest that the frequency and severity of headache had a detrimental effect on Quality of Life.

The most significant determinant for poor quality of life is pain associated with the fissure and evidence suggests that the worse the pain the poorer the health of the patient.[17] Griffin and his associates have shown that pain as assessed using a VAS correlated well with scores on the SF-36, demonstrating that higher levels of pain were associated with more bodily pain ($p<.001$), poorer general health ($p<.03$), and mental health ($p<.001$), less vitality ($p<.006$), decreased physical ($p<.02$) and social functioning ($p<.001$) and greater role limitations due to physical ($p<.02$) and emotional problems ($p<.04$). Clearly then, any improvement in pain is an essential component of the management of chronic anal fissure, with the rate of improvement being very important to the progress of treatment.

8.1.4 Trials of Nitroglycerin Ointment Treatment of Anal Fissure in the Medical Literature

Controlled clinical studies in the literature reported the peri- or intra-anal use of NTG ointment in the treatment of over 700 anal fissure subjects. The vast majority of these studies demonstrated efficacy of NTG ointment. The most common adverse event reported in the published controlled studies was headache that was often mild and transient and did not interfere with treatment. Headache was the most common reason for discontinuing treatment in the published controlled studies. In many subjects headache was treated effectively with acetaminophen or other mild analgesics. Adverse events other than headache reported in the published controlled studies of peri- or intra-anal use of NTG-containing products included gastrointestinal effects, anal burning or discomfort. Orthostatic hypotension was reported in 5 subjects and dizziness in 1 subject.

8.1.5 Poor Quality of Extemporaneously Compounded Nitroglycerin Ointment

As reported in section 2.1, 46% of compounded nitroglycerin ointment does not meet USP standards for potency and or content uniformity. Dispensing in jars also does not allow accurate dosing. These observations raise concerns of potential efficacy or safety problem in patients using compounded ointment.

8.2 Conclusion

The benefit of accelerating the rate of pain intensity decrease and potentially decreasing the need for surgery by intra-anal application of Cellegesic nitroglycerin ointment 0.4% in patients with a chronic anal fissure clearly out weighs any safety concerns.

9. SUMMARY AND CONCLUSIONS

Nitroglycerin has been used extensively for the treatment of myocardial ischemia and has been shown to be safe and effective for this condition

Cellegesic NTG ointment 0.4% is intended to be self-applied intra-anally to relieve the pain of a chronic anal fissure. Three randomized, double-blind, placebo-controlled, phase 3 studies (NTG 98-02-01, NTG 00-02-01, and CP125 03-02-01) providing the largest reported body of controlled clinical experience have demonstrated the efficacy and safety of Cellegesic NTG ointment 0.4% applied intra-anally approximately every 12 hours. In these 3 studies, 475 subjects applied any dose of Cellegesic NTG ointment, of whom 206 applied Cellegesic NTG ointment 0.4% b.i.d. Safety was also documented in 6 healthy volunteers who participated in an open-label, 3-way, 3-period, cross-over phase 1 study (NTG 98-02-02) that characterized the bioavailability of NTG and 2 primary metabolites (1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate) after a dose of 375 mg Cellegesic NTG ointment 0.2% (0.75 mg NTG) applied topically to the anal canal compared to 0.3 mg NTG

administered as a single intravenous dose over 30 minutes.

Adverse events were reported for 66.3% of subjects who applied any dose of Cellegesic ointment and in 78.6% of subjects who applied Cellegesic NTG ointment 0.4% applied approximately every 12 hours. Of the placebo-treated subjects of the three phase 3 studies, 60.6% reported adverse events.

Headache was the most common adverse event with Cellegesic NTG ointment. The incidence of headache was 64% in subjects who applied Cellegesic NTG ointment 0.4% approximately every 12 hours and 38% in subjects who applied placebo at any frequency in the three phase 3 studies. The incidence of headache with Cellegesic NTG ointment 0.4% applied approximately every 12 hours is similar to that reported in the labeling for all doses of the NTG patch (63%), although the placebo rate is higher in the Cellegesic studies than reported with placebo patch (18%), suggesting a high sensitivity to the potential for headache in the phase 3 studies of Cellegesic NTG ointment. Headache incidence decreased during the study, suggesting the development of tolerance to this effect.

While the investigators in Studies 1 and 2 were asked to determine treatment relatedness, all headaches that occurred within 30 minutes of study drug application were recorded as treatment-related in Study 3. For all 3 studies combined, headache was considered treatment-related in 57.3% subjects who applied Cellegesic NTG ointment 0.4% approximately every 12 hours and 22.4% subjects who applied placebo at any frequency.

Headache was considered to be severe in 20.4% of the subjects who applied Cellegesic NTG ointment 0.4% approximately every 12 hours and in 5.7% in the overall placebo group. Most of the severe headaches in subjects who applied placebo were assessed as not related to study medication. All severe headaches in subjects who received any dose of Cellegesic NTG ointment 0.4% in studies 1 and 2 were considered by the investigator to be related or possibly related to study drug administration. For study 3, 32% (29/90) subjects had severe headaches during treatment with Cellegesic NTG ointment 0.4% approximately every 12 hours and 22 of these 29 (76%) met the criterion for NTG-related headache based on their occurrence within 30 minutes of drug application. The remaining 7 subjects had severe headaches that were determined to be unrelated to study treatment since they did not occur within 30 minutes of application. All severe headaches with known outcomes resolved either upon discontinuation of study drug or treatment with concomitant medication, except headache of 1 subject was unchanged at the final study visit despite concomitant medication.

In general, headache following administration of any dosage form of NTG is more common in patients with a history of migraine, cluster, or tension headache. In the three phase 3 studies, the overall incidence of headache was no different or slightly higher in those without a history of migraine or recurrent headaches; however, severe headache was more often reported in subjects with a history. Increasing doses of Cellegesic ointment were associated with higher incidences of headache.

Of the subjects who applied Cellegesic NTG ointment 0.4% b.i.d. approximately every 12 hours and had treatment-related headaches, about 48% used concomitant medication to treat headache compared with 38% in the placebo group. Dose and frequency of acetaminophen to treat headaches was restricted in the phase 3 studies.

Ten serious events were reported in the three phase 3 studies; 4 were placebo-treated and 6 received Cellegesic ointment. The only treatment-related serious adverse event was a single case of severe migraine headache. There have been no deaths reported during the Cellegy-sponsored clinical studies of Cellegesic NTG ointment.

In the phase 3 studies, headache was the event, or among the events, that led to discontinuation of 29 of 475 (6%) of subjects treated with any dose of Cellegesic ointment; 16 of these subjects applied Cellegesic NTG ointment 0.4% approximately every 12 hours, giving an incidence of 7.8% (16/206) of all subjects applying this dose. Headache led to discontinuation in 0.8% (2/246) placebo-treated subjects. Treatment discontinuation by study was 5.6% (5/90) of subjects who applied Cellegesic NTG ointment 0.4% approximately every 12 hours in study CP125 03-02-01, compared with 11.5% (9/78) subjects who applied this dose in study NTG 00-02-01 and 5.3% (2/38) subjects who applied this dose in study NTG 98-02-01. The low discontinuation rate in study CP125 03-02-01 may in part be related to the higher baseline fissure pain intensity in these subjects. Subjects who applied Cellegesic NTG ointment 0.4% in study CP125 03-02-01 had a mean baseline VAS scores of 55 mm compared with a mean of 33.4 mm for subjects who applied Cellegesic NTG ointment 0.4% approximately every 12 hours in study NTG 00-02-01. Subjects in study CP125 03-02-01 may have elected to not discontinue treatment in order to achieve the benefit of pain relief with Cellegesic NTG ointment 0.4%.

Of the 16 subjects who discontinued treatment from the three phase 3 studies due to headache during treatment with Cellegesic NTG ointment 0.4% b.i.d., 62.5% were observed to have improvement in pain scores or have low pain scores at the time of treatment discontinuation, suggesting that subjects tended to discontinue treatment due to headache when fissure pain become more tolerable or had resolved.

Most other adverse events were mild or moderate in severity. In the controlled phase 3 studies, adverse events other than headache that occurred in ≥2.0% of the subjects who used Cellegesic NTG ointment 0.4% b.i.d. and the respective rates for the placebo group were nausea (5.8% and 0.8%), dizziness (4.4% and 0%), diarrhea NOS (2.9% and 3.3%) and hemorrhoids (2.4% and 0%).

No consistent, clinically significant changes in laboratory test values, physical examination findings, blood pressure, heart rate, or 12-lead ECG have been reported following Cellegesic NTG ointment application. There were no time- or dose-related trends in diastolic or systolic blood pressure or pulse rate. A few subjects in the phase 3 studies experienced vasodilatation or hypotension, known pharmacologic effects of NTG. Postural hypotension was not specifically evaluated during the studies; however sitting blood pressure was assessed during clinic visits. Overall, 10% of subjects who applied placebo and 11% of subjects who applied any dose of Cellegesic ointment had diastolic blood pressure decreases of at least 20 mm Hg at at least one clinic visit. The highest incidence of blood pressure decrease was seen with the lowest dose of NTG, and no dose-related trends were evident.

In the phase 1 study, headache was the most frequently reported adverse event after administration of Cellegesic NTG ointment 0.2%. No subject withdrew due to headache in this study, and only 1 subject had a severe headache.

- The efficacy of Cellegesic nitroglycerin ointment 0.4% at a dose of 375 mg (1.5 mg NTG) every 12 hours for up to 8 weeks of continuous use has been demonstrated in three placebo-controlled trials in subjects with a chronic anal fissure.
- Cellegesic nitroglycerin ointment 0.4% is most effective in chronic anal fissure subjects with moderate to severe pain.
- The efficacy data (rate of change in 24-hour average pain) at 21 days for the third phase 3 trial meet the FDA requirements under a special protocol assessment.
- The reduction in anal fissure pain upon defecation supports and confirms the efficacy.
- Any improvement in pain is an essential component of the management of chronic anal fissure, with the rate of improvement being very important to the progress of treatment.
- Fissure healing occurred in 67% of subjects although not significantly different from placebo.
- The safety profile of nitroglycerin and Cellegesic nitroglycerin ointment 0.4% is well established.
- Headache, the primary side effect of nitroglycerin may be ameliorated by use of a mild analgesic.
- The post marketing exposure in several countries is associated with very few complaints of headache. In the United Kingdom data are available that indicate the frequency of anal fissure surgery has been reduced approximately 50% since 1999 with the introduction of the recommendation to use nitroglycerin ointment to treat patients with an anal fissure. Surgery for all other anal disorders has remained essentially constant.
- Surgery with its cost and post-operative complications is the only effective treatment available at this time. There is no drug approved in the United States for the treatment of the pain associated with a chronic anal fissure
- Based on evidence in the medical literature and the clinical experiences of their members, both the American Gastroenterological Association and the American Society of Colon and Rectal Surgeons committee on anal fissure have recommended that pharmacological relaxation of the internal anal sphincter with a product, such as nitroglycerin ointment be considered before surgical treatment of a chronic anal fissure.
- The dosage of Cellegesic nitroglycerin ointment 0.4% demonstrated to safely and effectively accelerate the rate of pain relief in subjects with a chronic anal fissure is 3 mg nitroglycerin/day, smaller than other approved products.
- Based on the collective efficacy and safety results, 375 mg Cellegesic nitroglycerin ointment 0.4% every 12 hours for up to 8 weeks is suitable for prescribing by physicians and use by patients with a painful chronic anal fissure.

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