To: NDA 21359
From: Stephen Fredd, M.D and James Hung, Ph.D., HFD-110
Subject: Medical/Statistical Review

EXECUTIVE SUMMARY

Cellegy Pharmaceuticals submitted an NDA for nitroglycerin (NTG) ointment to relieve anal pain associated with anal fissures. Based on findings in the literature that NTG ointment relaxed the anal sphincter that could lead to anal fissure healing and relief of associated anal pain, the sponsor completed study NTG 98-02-01. The primary endpoint of that study was anal fissure healing. While that endpoint was NS, the secondary endpoint of relief of anal pain suggested a statistically significant effect in a linear mixed effects model for 0.4%BID NTG ointment compared to placebo. To prospectively test the pain relief hypothesis generated by that study, the sponsor performed study NTG 00-02-01. The primary hypothesis of efficacy was to be "tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects)." Using different parameters in a quadratic mixed effects model post-hoc, the sponsor found that NTG 0.4% BID average pain (primary endpoint) results were significantly different from placebo on linear trend and quadratic trend. The FDA statistician, Dr. Hung, using the linear model in the mixed effects model to evaluate the rate of change over time, as specified in the protocol and as used in the first study, found no significant difference for either active treatment group compared to placebo. Therefore using the mixed effects model with the methodology employed in the first study, the second study, the only confirmatory study provided, did not establish a significant difference between active drug and placebo.

Since the mixed effects model with the quadratic term gave somewhat different results, a hypothesis that the results differed over time was considered. To study this, Dr. Hung analyzed the rate of change in each weekly time period. For average pain, there seemed to be a difference in the rate of change for the 0.4% NTG group compared to placebo in the first week, but this was not sustained through the 56 days of treatment. At best there might have been a transient statistical difference, but even if this was the case, it would not translate into a meaningful clinical benefit for the patient since no benefit for NTG ointment could be found at the end of 56 days of therapy. In analyses of total pain relief or a difference in pain relief at the end of therapy, no differences comparing the active groups to placebo were found.

Importantly there were a large number of patients on active drug who developed headache. The headache was severe enough to lead to dropout in patients treated with NTG ointment, and those who remained in the study often required analgesic therapy. Headache should be considered a confounding element in the analysis of efficacy, since it led to more dropouts in the active treatment groups compared to placebo and might have influenced the anal pain results recorded by those patients who experienced headache on NTG ointment. Since no significant benefit on relief of anal pain was found in these clinical studies, and pain in the form of headache would be associated with NTG ointment treatment, a not approvable action is recommended

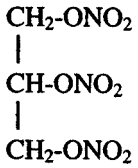
I. INTRODUCTION AND BACKGROUND

On June 22,2001 Cellegy Pharmaceuticals submitted an NDA for the use of nitroglycerin ointment (NTG) 0.2% and 0.4% to relieve pain associated with an anal fissure. The sponsor stated that there have been literature reports supporting the use of nitroglycerin ointment to treat anal fissures and use of currently available NTG products for such off label use. The proposed dose for Cellegy's product was 1.5 to 4.5 mg. The original NDA contained the results of one adequate and well-controlled study (NTG 98-02-01) in volumes 1.2 and 1.16-1.27. The application was amended on October 24, 2001 with the submission of all case reports forms per this reviewer's request. On November 30, 2001 the results of a second adequate and well-controlled study (NTG 00-02-01) was submitted. Datasets from that study were made available to the reviewers on 1/22/02.

II. CLINICALLY RELEVANT INFORMATION re CHEMISTRY AND NON-CLINICAL PHARMACOLGY AND TOXICOLGY

A. CHEMISTRY

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



The ointment is provided in 0.2 and 0.4% concentrations, and is formulated with propylene glycol in a base of lanolin, sorbitan sesquioleate, parafin wax and white petrolatum. A device and a metered dose dispenser are provided to measure out 374 mg of the ointment per dose. This provided 0.75mg per dose of the 0.2% formulation, and 1.5mg of the 0.4% formulation. The proposed treatment is for BID or TID applications of the ointment for two weeks after anal pain is gone or the anal fissure has healed. According to the proposed labeling, the treatment may be initiated with the 0.2% concentration, but after two weeks if the pain is not aleviated the 0.4% concentration should be used.

See Chemistry review.

B. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

The sponsor notes that the proposed doses of 1.5mg to 4.5mg daily are lower than generally used doses of NTG for angina, however it should be noted that administration rectally decreases first pass metabolism and increases systemic bioavailability of an administered dose. Available literature was pharmacology and toxicology was provided, and skin sensitivity tests with the final product and vehicle were performed.

See Pharmacology review.

III. HUMAN PK AND PD

Study NTG 98-02-02 was a three-way, three period, open PK study of the 0.2% NTG formulation and IV NTG (0.01mg/min constant rate infusion for 30 minutes) in 6 normal subjects (4 males, 2 females), aged 25 to 45 years. Single and multiple dose administrations were studied. The sponsor provided the results as follows:

Table 2: Mean Values ± S.D. for Primary Pharmacokinetic Parameters for Intra-anal Application of 0.2% NTG Ointment versus i.v. Infusion: All Subjects (Protocol 98-02-02)

Bioavailability [a] (F)		Mean Absorption Time (min)	
Treatment Phase		Treatment Phase	
I	II	I	II
0.46 (± 0.28)	0.47 (± 0.31)	108 (± 59)	110 (± 69)

AUC[b] for Arterial Plasma NTG; Single and Multiple Dose 0.2% NTG Ointment

Treatment Phase I (Single)	Treatment Phase II (Multiple)
41.3 (± 18.9)	41.8 (± 8.8)

Ratio of AUC(m)[b,c] Values (Treatment Phase II/Treatment Phase I) for 1,2- and 1,3-GDN

1,2-glyceryl dinitrate	1,3-glyceryl dinitrate
1.00 (± 0.57)	3.36 (± 2.44)

Ratio of AUC(m)[b,c] Values (1,2-glyceryl dinitrate/ 1,3-glyceryl dinitrate)

Treatment Phase III	Treatment Phase I	Treatment Phase II
8.54 (± 2.67)	5.41 (± 2.51)	1.84 (± 1.05)

Clearance[d] of NTG in Treatment Phase III (L/min)

7.0 (± 3.6)

[a] $F = \frac{AUC_{anal}}{AUC_{inf}} \times \frac{Dose_{inf}}{Dose_{anal}}$

where AUC_{anal} and AUC_{inf} were the areas under the curve following intra-anal application and infusion, respectively.

[b] AUCs up to 270 min (Treatment Phase III) and 480 min (Treatment Phases I and II).

[c] AUC(m) = Area under the plasma level versus time curve for the mean values.

[d] Calculated as $Dose_{inf}/AUC_{inf}$

NOTE: Treatment Phase I = Single Dose
Treatment Phase II = Multiple Dose
Treatment Phase III = i.v. Infusion

Headache was reported in 5 out of 6 subjects, and 1 subject had two abnormal urinalyses that resolved 17 days later.

The sponsor summarized the published literature relevant to the pharmacodynamics of NTG. They note that NTG releases NO that leads to smooth muscle relaxation and also has CNS and peripheral nervous system effects. Onset and duration of action of various NTG doses and routes are provided by the sponsor in the following chart:

Table 2: Summary of Typical NTG Preparations Used for the Treatment of Angina Pectoris

Dosage Form	Dosage	Onset of Action	Duration of Action
i.v injection	5 to 10 µg/min for 3 to 5 min	1 to 2 min	3 to 5 min
Sublingual tablets	0.3 to 0.6 mg/tablet	1 to 3 min	10 to 30 min
Translingual spray	0.4 to 0.8 mg/spray	2 to 4 min	10 to 30 min
Oral extended release tablets	2.5-9 mg/tablet 2 to 4 times daily	20 to 45 min	4 to 8 hours
Topical ointment	2% 1.25 to 5 cm (6 to 30 mg NTG applied every 4-8 hours	30 to 60 min	3 to 6 hours
Transdermal patch	1 disc (2.5--15 mg) every 24 hours	30 to 60 min	4 to 8 hours

Adapted from Robertson and Robertson, 1996

The direct application of NTG to the internal anal sphincter results in a relaxation of that sphincter measured by anal manometry. Maximal anal resting pressure(MARP) has been studied by multiple investigators. Lund and Scholefeld, Lancet, 1997, 349:11-14 Compared manometry results 20 minutes before and 40 minutes after 0.5g NTG and placebo. There was a significant decrease in MARP in the NTG treated patients, but not in the placebo treated patients. Ciccaglione et al, DDS, vol.45 #12, 12/2000. pp.2352-2256 compared 0.2% NTG and 2%NTG on MARP over an 8 week period and found significant and comparable reductions from baseline in MARP for both concentrations that continued thoughout the 8 week treatment period. Schouten et al, Gut 1996; 39; 465-469 determined that the onset of MARP reduction was within 5 minutes after NTG application and lasted 41 minutes. The pressure drop was associated with an increase in anodermal blood flow. While tolerance is a known problem with NTG actions, the sponsor suggests that this may not be as much of a problem with NTG action on the internal anal sphincter. Noting the published studies of Munzel et al, JCI, 1995; 95:187-194 suggesting that endothelium-free aortic tissue demonstrated less NTG tolerance led to the idea that the internal anal

sphincter (IAS) which lacks an endothelial layer might also exhibit less NTG tolerance. Wang et al, Br. J.Pharm, in press and Grayson et al, data developed by Cellegy pharmaceuticals, demonstrated that high dose NTG given frequently to rats did not lessen the MARP lessening over time, and isolated IAS rat smooth muscle did not show less cGMP levels over time. The sponsor also points to the results of the clinical studies to support the hypothesis that tolerance does not develop to NTG when it is applied repetitively to the IAS as would have been expected.

See Biopharmaceutics review.

IV. DESCRIPTION OF CLINICAL DATA

Two controlled studies were provided to support the benefit of NTG ointment to heal anal fissures and to relieve the pain of anal fissures..

NTG 98-02-01 was a randomized, multicenter controlled study in 360 patients to evaluate the safety and efficacy of 6 doses (0.75, 1.1, 1.5, 2.3, 3.0,and 4.5 mg) of NTG ointment versus placebo given daily for 56 days or until fissure healing. The primary endpoint was anal fissure healing. Secondary endpoints were relief of anal fissure pain and safety.

Study NTG 00-02-01 was a randomized, multicenter controlled study of two doses (7.5 and 1.5 mg) of NTG ointment versus placebo in 229 patients with anal pain due to fissures. The “primary outcome endpoint” was relief of pain associated with the fissure. Secondary endpoints were time to anal fissure healing, quality of life, and safety.

A literature review of controlled studies evaluating the use of NTG ointment in the healing and relief of pain was also provided.

V. CLINICAL AND STATISTICAL REVIEW

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

The protocol was finalized on May 18, 1998, and amended on August 6, 1998 and November 5, 1998. The study was conducted between July 29, 1998 and September 15, 1999 by 18 investigators at 18 centers.

The protocol stated that a minimum of 360 adult patients with chronic anal fissures would be randomized to one of eight treatments: placebo, 0.1%NTG, 0.2%NTG, 0.4%NTG given BID, and placebo. 0.1%NTG, 0.2%NTG, 0.4%NTG given TID for 56 days or until the fissures were healed. The total daily dose of NTG to be applied was 0.75 mg, 1.1 mg, 1.5 mg, 2.3 mg, 3.0 mg and 4.5 mg. A computer generated randomized program was to be employed, and the study was double-blind by design.

The primary endpoint was complete anal fissure healing. The rate of recurrence 4 weeks after healing was also to be determined. Secondary endpoints were relief of anal pain (not required for admission to the study) and safety. To maintain the blind, the investigator was not to ask about headache while evaluating fissure healing.

The sample size was based on estimates of placebo and NTG anal fissure healing (8% and 68% respectively) from the literature where 0.2%NTG ointment was used. The sample size estimate was also controlled for the effects of 6 primary statistical comparisons. With 36 patients per group it was estimated that a healing rate difference of 43% could be detected.

Regarding pain assessments, the protocol specified use of a visual analog scale (vas) from 0-100 with 0 being no pain and 100 the most severe pain. Three pain estimates were to be made in a diary each day; the average intensity, the worst intensity, and the intensity during defecation. For patients whose fissure healed, the study evaluations were terminated. Statistically it was recognized that the unequal numbers of evaluations due to dropouts and healing would produce a highly unbalanced design. Rather than a mixed-model ANOVA, the sponsor proposed use of mixed-effects regression models without prespecifying a particular model.

For entrance male or female patients 18 years of age or older had to have an anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Exclusion criteria included fistula-in-ano, fissures associated with anal surgery within 30 days of enrollment, class IV cardiovascular disease especially hypotension, pregnant or nursing female, anal abscess, IBD, or requiring NSAID or other pain medication. It was noted that headache occuring during the study could be treated with acetominophen 650 mg q 6h for up to three doses daily.

The schedule of procedures was as follows:

Treatment Days

	-1 Base-line	1	14	28	42	56	4 Week Follow -up
		TREATMENT PHASE					
History	X						
Physical Examination	X					X	
Anal Exam	X[b]		X[a,b]	X[a,b]	X[a,b]	X[a,b]	X
Hematology	X					X[a]	
Clinical Chemistry	X					X[a]	
Urinalysis	X[c]					X[a]	
Vital Signs	X		X	X	X	X	X
Vital Signs 10 and 20min		X[d]					
Review Adverse Events	X	X	X	X	X	X	X
NTG Application		X					
Visual Analog Scales VAS Intensity	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	

a) Patient removed from study when healing complete at which time all Day 56 studies (physical examination, clinical chemistry and urinalysis) should be obtained and patient instructed to return in one month for follow-up.
b) A digital/anoscopic examination may be performed, as is the Investigator's standard of practice.
c) Including pregnancy test on all pre-menopausal females.
d) Blood pressure and pulse determined at indicated times following first application of NTG.
e) VAS each evening for average pain intensity for the day, the maximum pain intensity that day and the pain intensity at most recent defecation.

The 8/6/1998 protocol amendment involved details of administration of the ointment to the anus. The 11/5/1998 amendment provided for an open-label treatment period for those patients who completed the double-blind study but whose fissure had not healed.
The study was performed at 18 centers and involved 304 subjects, 93 of these entered the open-label evaluation phase.
The active drug was Nitroglycerin (NTG) in an ointment composed of propylene glycol, lanolin, white petrolatum, parafin wax and sorbitan sesquioleate. Placebo contained the same ingredients minus the NTG.
The numbers of patients randomized to each treatment are provided in the following chart.

RX daily dose	Placebo BID	NTG 0.75mg	NTG 1.1mg	NTG 1.5mg	Placebo TID	NTG 2.3mg	NTG 3.0mg	NTG 4.5mg
N	34	39	39	38	36	37	39	42

The sponsor provided some baseline demographic characteristics (confirmed by the FDA reviewer) as follows:

Table 3: Demographic and Baseline Characteristics: ITT Population (Study NTG-98-02-01)

	Placebo[a] (N=70)		NTG[b] (N=234)		Overall Total (N=304)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	39	(55.7)	127	(54.3)	166	(54.6)
Female	31	(44.3)	107	(45.7)	138	(45.4)
Race						
Caucasian	58	(82.9)	189	(80.8)	247	(81.3)
Black	7	(10.0)	18	(7.7)	25	(8.2)
Asian[c]	4	(5.7)	9	(3.9)	13	(4.3)
Hispanic	1	(1.4)	17	(7.3)	18	(6.0)
Native American	0	(0.0)	1	(0.4)	1	(0.3)
Age (years)						
≤45	48	(68.6)	136	(58.1)	184	(60.5)
46-64	13	(18.6)	76	(32.5)	89	(29.3)
≥65	9	(12.9)	22	(9.4)	31	(10.2)
N	70		234		304	
Mean	44.13±14.62		43.59±13.40		43.71±13.67	
Range	23.00-81.00		19.00-81.00		19.00-81.00	
Median	41		42		42	
Weight (kg)						
N	70		229		299	
Mean	173.4±49.92		179.5±46.10		178.1±47.00	
Range	106.0-415.0		101.0-350.0		101.0-415.0	
Median	167		175		175	
Missing	0		5		5	
Height (in)						
N	70		230		300	
Mean	66.80±4.37		67.48±4.04		67.32±4.13	
Range	56.00-76.00		57.00-80.00		56.00-80.00	
Median	67		68		67.5	
Missing	0		4		4	

[a] Includes all subjects receiving placebo (b.i.d. and t.i.d. combined).
[b] Includes all subjects receiving ointment containing any concentration of NTG (b.i.d. and t.i.d. combined).
[c] Seven subjects of Asian race were listed incorrectly as "other" in database, but are included here.

Withdrawals were outlined by the sponsor as follows:

	Patients Randomized								
Patient Status	Placebo BID n(%)	0.1% NTG BID n(%)	0.2% NTG BID n(%)	0.4% NTG BID n(%)	Placebo TID n(%)	0.1% NTG TID n(%)	0.2% NTG TID n(%)	0.4% NTG TID n(%)	Total n(%)
Randomized(N)	34	39	39	38	36	37	39	42	304
Completed Study	29(85.29)	22(56.41)	29(74.36)	32(84.21)	32(88.89)	33(89.19)	34(87.18)	30(71.43)	241(79.28)
Early Termination	5(14.71)	17(43.59)	10(25.64)	6(15.79)	4(11.11)	4(10.81)	5(12.82)	12(28.57)	63(20.72)
Reasons for Early Termination									
Inadequate Response	0(0.00)	1(2.56)	0(0.00)	0(0.00)	0(0.00)	1(2.70)	0(0.00)	0(0.00)	2(0.66)
Adverse Event	0(0.00)	1(2.56)	2(5.13)	1(2.63)	1(2.78)	2(5.41)	0(0.00)	6(14.29)	13(4.28)
Protocol Violation	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Patient Non-Compliance	1(2.94)	4(10.26)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(2.56)	0(0.00)	6(1.97)
Patient Choice	3(8.82)	8(20.51)	2(5.13)	4(10.53)	1(2.78)	1(2.70)	3(7.69)	6(14.29)	28(9.21)
Lost to Follow-up	1(2.94)	3(7.69)	5(12.82)	1(2.63)	2(5.56)	0(0.00)	0(0.00)	0(0.00)	12(3.95)
Other	0(0.00)	0(0.00)	1(2.56)	0(0.00)	0(0.00)	0(0.00)	1(2.56)	0(0.00)	2(0.66)
Randomized(N)	0	1	1	1	1	1	1	1	7
Completed Study	0(0.00)	1(2.56)	1(2.56)	1(2.63)	1(2.78)	1(2.70)	0(0.00)	1(2.38)	6(85.71)
Early Termination	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(2.56)	0(0.00)	1(14.29)
Reasons for Early Termination									
Inadequate Response	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Treatment Group Subject Number	Age (yrs)	Adverse Event (Primary Term)	Study Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
0.1% NTG b.i.d.						
315121	55	Respiratory disorder	14	Moderate	None	35
		Headache[d]	2	Severe	Possibly	35
		Flu syndrome	14	Moderate	None	35
0.2% NTG b.i.d.						
315104	29	Dizziness[d]	2	Moderate	Possibly	5
		Palpitation[d]	2	Moderate	Possibly	5
322146	24	Rectal disorder[c]	8	Severe	None	10
0.4% NTG b.i.d.						
317115	72	Headache	2	Mild	Possibly	197[e]
		Nausea	2	Mild	Possibly	197
		Pruritus	27	Moderate	Possibly	197
		Accidental injury[c,d]	48	Severe	None	197
Placebo t.i.d.						
323107	41	Headache[d]	1	Moderate	Related	12
0.1% NTG t.i.d.						
317114	41	Headache[d]	1	Severe	Possibly	5
		Vomiting[d]	1	Severe	Possibly	5
		Hypertension[d]	1	Moderate	Possibly	5
323102	71	Vertigo[d]	2	Moderate	Possibly	8
0.4% NTG t.i.d.						
315105	26	Headache[d]	1	Severe	Possibly	3
317127	35	Nausea	1	Mild	Possibly	39
		Headache	1	Severe	Possibly	39
		Headache	4	Severe	Possibly	39
		Headache	21	Severe	Possibly	39
		Headache[d]	24	Severe	Possibly	39
		Hypernatremia	39	Mild	None	39
317138	37	Headache[d]	1	Severe	Related	15
		Vomiting[d]	1	Moderate	Possibly	15
		Sweating[d]	1	Moderate	Possibly	15
319108	21	Headache[d]	1	Severe	Related	6
		Nausea[d]	1	Severe	Related	6
323101	50	Headache[d]	1	Severe	Related	9
		Sweating[d]	1	Moderate	Possibly	9
		Anxiety[d]	2	Moderate	Possibly	9
323111	29	Headache[d]	Unknown[f]	Moderate	Related	11

[a] Relative to start of therapy.
[b] Based on investigator's assessment.
[c] Serious adverse event.
[d] Subjects discontinued therapy due to this adverse event.
[e] Subject 317115 discontinued the study due to a broken hip on 3/06/99. The clinical summary page of the CRF was completed on 9/22/99.
[f] The first day of study drug administration for Subject 323111 was April 20, 1999. The onset of headache was an unknown date in April, 1999.

The chart above lists 13 patients as having terminated early for an adverse event, but the patient listing of adverse events leading to early termination (volume 1.21,p1711-1713) lists 14 patients. Subject 314120 was assigned to 0.2% NTG TID, and was listed in the "other" category withdrew after 27 days of treatment for increasing anal pain due to the fissure.

A review of case report forms for patients without any pain data, only baseline pain data or less than 7 days of pain data revealed in this reviewer's judgment 9 additional patients withdrawn for adverse events:
0.1% NTG TID patient 314105 for anal surgery.
0.1% NTG TID patient 315113 for anal pain necessitating surgery,
0.2% NTG BID patient 322112 for headache,
0.2% NTG TID patient 310101 for headache and vertigo,
0.2% NTG TID patient 317130 for headache,
0.4% NTG TID patient 317117 for headache,
0.4% NTG TID patient 317121 for headache and short arms,
0.4% NTG TID patient 320124 for vomiting,
0.4% NTG TID patient 322123 for headache.
At least 23 patients withdrew for an adverse event; 10 were in the highest dose NTG TID group versus 1 in the placebo TID group.

ANAL FISSURE HEALING

The sponsor provided various analyses of anal fissure healing. Dr. Hung confirmed these results. None suggested a benefit of NTG ointment to heal the fissures.

Table 5: Percent Fissure Healing: ITT Population
(Study NTG 98-02-01)

	Study Treatment			
	Placebo	0.1% NTG	0.2% NTG	0.4% NTG
Dose Frequency	n (%)	n (%)	n (%)	n (%)
b.i.d. (N=150)	17 (50%)	12 (31%)	10 (26%)	15 (39%)
t.i.d. (N=154)	17 (47%)	18 (49%)	16 (41%)	20 (48%)

Table 6: Individual Between-Group Comparison of Healing Rates: ITT Population
(Study NTG 98-02-01)

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

[a] Results from b.i.d. and t.i.d. dose frequency groups combined.

An analysis of fissure recurrence after healing was also done, and demonstrated no benefit.

Table 12: Recurrence Rates of Fissures: Subjects with a Follow-Up Examination
(Study NTG 98-02-01)

Frequency and Dose	Healed Subjects at End of Study	Subjects Who Relapsed at Follow-Up	Recurrence Rate
b.i.d			
Placebo	**18**	**4**	**0.222**
0.1% NTG Ointment	**12**	**2**	**0.167**
0.2% NTG Ointment	**10**	**1**	**0.100**
0.4% NTG Ointment	**15**	**3**	**0.200**
t.i.d.			
Placebo	**17**	**3**	**0.176**
0.1% NTG Ointment	**18**	**2**	**0.111**
0.2% NTG Ointment	**16**	**5**	**0.313**
0.4% NTG Ointment	**19**	**7**	**0.368**

As previously noted, the protocol specified that the statistical analysis of anal fissure healing involved 6 active treatment groups, and some consideration for multiple comparisons was proposed. No plan was presented for handling secondary endpoints for multiple comparisons and multiple endpoints, particularly where the primary endpoint was NS.

PAIN ASSESSMENTS

Three pain assessments were to be made daily by each patient; average pain for the day, worst pain, and pain on defecation. Assessments were to continue to day 56 or anal fissure healing.
Patient assessment of pain on the 0-100mm VAS was made daily and written into a diary which was brought to the clinical visits. At those visits "study site personnel" measured the responses as noted by the patient, and put the result (# of mm between the left end, i.e. no pain, and the patient's mark) on the CRF. The pain data reported was noted to have been "finalized from a database specified and approved by Cellegy."
The sponsor provided a pain analysis pooling the BID and TID dose groups using a mixed effects model. The exact model used was not pre-specified.. This pooling was not pre-specified. The analysis of the primary endpoint, anal fissure healing, was by randomized group.The pooling was justified by the sponsor based on their finding that "No significant main effects or interactions involving dosage frequency were found." It must be noted that increased dose frequency provided higher doses of the active drug, so that pooling frequency of administration also pooled different doses of active.
An analysis using data from 267 of the 304 randomized patients as well as an analysis of those patients with baseline pain >25 mm on the VAS were provided as follows:

Table 11: Percent Pain Decrease From Baseline as a Function of Percent Nitroglycerin Content of Ointment: All Subjects and Subjects With Baseline Average Pain >25 mm (Study NTG 98-02-01)

Type of Pain	All Subjects				Baseline AVG Pain >25 mm			
Day	Placebo	0.1%	0.2%	0.4%	Placebo	0.1%	0.2%	0.4%
Average Pain								
4	22		37[a]	32[b]				
7	26	30	42[c]	40[c]	32	37	52[c]	44[d]
14	42	37	46	49[c]	46	43	55[d]	58[d]
21	39	48[d]	51[d]	58[a]	47	55	60[d]	65[c]
28	52	51	58[d]	60[a]	55	53	65[d]	68[c]
35	50	57	57[d]	66[a]	57	59	66	75[a]
42	54	58	63	65[a]	56	60	70	71[c]
49	54	62	67[c]	69[a]	57	67	74[d]	78[c]
56	51	62	65[c]	72[a]	57	66	76[c]	80[c]
Defecation Pain								
7	42	42	43	51	38	37	49	53
14	56	43	44	59	46	40	44	60
21	53	56	47	64[c]	50	54	46	67
28	57	60	55	68[c]	46	58	58	68[d]
35	58	62	58	72[a]	52	58	62	77[a]
42	61	65	61	72[c]	53	62	66	72[c]
49	61	65	66	77[a]	52	64[d]	74[c]	81[a]
56	61	67	67	80[c]	55	65	78[d]	83[c]
Worst Pain								
7	39	39	46	48[d]	39	38	49	48
14	55	46	52	59[d]	49	47	53	59
21	56	60	56	65[a]	53	63	59	68[d]
28	61	61	61	71[a]	55	58	65	73[c]
35	62	66	61	74[a]	57	63	66	78[c]
42	64	67	67	74[a]	58	65	72[d]	74[c]
49	61	71	70[d]	77[a]	57	71	77[c]	79[c]
56	60	71	69	79[a]	57	70	79[c]	82[c]

[a] p <0.001
[b] p <0.02
[c] p <0.01
[d] p <0.05
NOTE: Significance levels based on mixed model analysis

As can be noted from Dr. Hung's chart of available data (see below), 20 patients had neither baseline nor follow-up data and 8 had only baseline data. There are data from 276 patients who had baseline and some follow-up data. The sponsor's mixed effects analysis used patients only if they had follow-up data including day 7, and used only data at time points baseline, days 7, 14, 21, 28, 35, 42, 49, and 56 as shown above.
While the sponsor stated that secondary analyses were performed to consider the relationship between use of analgesics on pain relief, and that those analyses did not show a different result for those who took more than 6 days of analgesic medication versus those who took less or none, no data were provided.

Dr. Hung, using SAS diskettes from the sponsor, provided independent analyses that clarify the sponsor's summary report.

Distribution of missing pain data followed by baseline average daily pain data per Dr. Hung was:

Table R1-1. Distribution of the patients with incomplete pain data

	No baseline pain data and no post randomization pain data	Have baseline pain data only	Have baseline and post randomization pain data
0.1% NTG BID (N=39)	6 (15%)	2 (5%)	31 (79%)
0.1% NTG TID (N=37)	1 (3%)	1 (3%)	35 (95%)
0.2% NTG BID (N=39)	5 (13%)	2 (5%)	32 (82%)
0.2% NTG TID (N=39)	1 (3%)	1 (3%)	37 (95%)
0.4% NTG BID (N=38)	1 (3%)	0	37 (97%)
0.4% NTG TID (N=42)	3 (7%)	1 (2%)	38 (90%)
Placebo BID (N=34)	1 (3%)	1 (3%)	32 (94%)
Placebo TID (N=36)	2 (6%)	0	34 (94%)

The sponsor did not provide baseline pain data per group. Dr. Hung has provided that data.

Table R1-2. Distribution of baseline measurement on daily average pain

	Mean	SD	Range	1st quartile	Median	3rd quartile
0.1% NTG BID	26.4	20.9	0 - 66	11	18	45
0.1% NTG TID	35.3	23.4	0 - 84	13	36	52
0.2% NTG BID	25.8	20.4	0 - 72	11	22	38
0.2% NTG TID	29.9	27.4	0 - 95	5	18	50
0.4% NTG BID	39.2	25.5	0 - 97	15	42	55
0.4% NTG TID	30.8	24.6	0 - 100	9	27	48
Placebo BID	25.7	24.0	0 - 81	4	21	43
Placebo TID	23.4	22.1	0 - 79	4	19	35

There appeared to be some imbalance in the baseline daily average pain measurement (Table R1-2, $p = 0.081$, ANOVA F-test; $p = 0.10$, Kruskal-Walis test); in particular, among the bid groups ($p = 0.032$, ANOVA F-test; $p = 0.07$, Kruskal-Walis test). This is apparently due to the 0.4% bid group.
Other endpoints were explored to consider the nature of any clinical benefit that NTG ointment might provide in relieving pain.

Percent of patients with zero pain score at last visit

Of the patients who had pain at baseline, 3%-19% had zero pain at the last visit in the bid groups and 16%-38% in the tid groups; see Table R1-3. Only the 0.2% and 0.4% NTG TID groups appeared to have more patients with zero pain at the last visit.

Table R1-3. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

	Zero average pain	Zero worst pain	Zero defecation pain
Placebo BID (N=34)	2/29 (7%)	2/30 (7%)	2/27 (7%)
0.1% NTG BID (N=39)	4/29 (14%)	5/30 (17%)	5/27 (19%)
0.2% NTG BID (N=39)	1/30 (3%)	1/31 (3%)	1/29 (3%)
0.4% NTG BID (N=38)	4/37 (11%)	5/37 (14%)	2/33 (6%)
Placebo TID (N=36)	5/29 (17%)	5/32 (16%)	8/30 (27%)
0.1% NTG TID (N=37)	6/34 (18%)	7/35 (20%)	6/33 (18%)
0.2% NTG TID (N=39)	11/33 (33%)	12/36 (33%)	9/31 (29%)
0.4% NTG TID (N=42)	10/36 (28%)	10/38 (26%)	12/32 (38%)

While only descriptive and exploratory, this analysis suggests that NTG ointment, 2% and 4% TID, may relieve pain due to anal fissures.

Last Available Visit Analysis

Average daily pain

As mentioned above, a total of 28 patients did not have any pain data after randomization. Thus, the last available visit analysis can be performed only on 276 patients.

Numerically, 0.2% and 0.4% NTG seemed to have a greater improvement on pain measurement, but statistical significance is not conclusive. Only 0.4% NTG bid appeared to give a greater improvement, but TID did not, thereby weakening any inference. After adjusting for imbalance in baseline daily average pain, the apparently greater improvement with 0.4%NTG BID disappeared.

Table R1-4. Mean change in last available visit daily average pain from baseline (Reviewer's analysis)

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

* adjusted for baseline daily average pain
$ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change
# NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Worst pain and defecation pain

There was no evidence of a significant difference in last visit change from baseline in daily worst pain or defecation pain between the treatment groups (Tables R1-5 and R1-6).

Table R1-5. Mean change in last available visit daily worst pain from baseline (Reviewer's analysis)

	Baseline Mean	Mean change	Nominal p-value[$]	Adj. mean change*	Nominal p-value[#]
0.1% NTG BID	35.4	-17.9	0.14	-22.3	0.053
0.1% NTG TID	51.4	-41.2	0.041	-37.7	0.15
0.2% NTG BID	43.6	-31.1	0.74	-32.2	0.94
0.2% NTG TID	41.8	-32.0	0.46	-34.6	0.42
0.4% NTG BID	54.4	-43.5	0.034	-37.4	0.24
0.4% NTG TID	51.4	-36.0	0.18	-32.0	0.80
Placebo BID	41.6	-28.7	---	-31.8	---
Placebo TID	40.8	-26.9	---	-30.8	---

* adjusted for baseline daily worst pain
$ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change
# NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Table R1-6. Mean change in last available visit daily defecation pain from baseline (Reviewer's analysis)

	Baseline Mean	Mean change	Nominal p-value[$]	Adj. mean change*	Nominal p-value[#]
0.1% NTG BID	38.0	-16.6	0.60	-19.0	0.39
0.1% NTG TID	46.1	-31.2	0.27	-27.7	0.53
0.2% NTG BID	40.2	-25.0	0.54	-25.5	0.67
0.2% NTG TID	31.9	-23.1	0.97	-29.1	0.35
0.4% NTG BID	49.4	-36.1	0.031	-29.6	0.20
0.4% NTG TID	43.9	-29.0	0.43	-26.6	0.70
Placebo BID	37.8	-20.5	---	-23.4	---
Placebo TID	38.8	-23.4	---	-24.7	---

* adjusted for baseline daily defecation pain
$ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change
# NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Mixed-Effects Analysis for Rate of Change in Pain

According to the study protocol, the pain relief was a secondary endpoint in this study. Generalized mixed-effects regression models were to be used in analyses of the pain data because the repeated evaluation of pain over time induces correlation among the residual model deviations and the unequal number of measurements per subject (due to subject withdrawal and early healing) produces a highly unbalanced design. However, the mixed-effects model was not specified. The computer output in Appendix 2, Statistical Documentation (pages 442-490, Volume 1.30) gave quite different p-values from those reported in the study report.

Average daily pain

In response to Dr. Hung's request for details of the mixed-effect analyses utilized, the sponsor faxed the results of mixed-effects analyses on the daily average pain data (dated October 26, 2001). In their mixed-effects analyses, the model included the main effects of day 0 (baseline), 7, 14, 21, 28, 35, 42, 49, and 55, dose (three dummy coded contrasts where contol = 0 0 0), frequency (0=bid, 1=tid), and all 3 two-way interactions and all 3 three-way interactions. Day was treated as a continuous variable. Intercept and day were specified as random and the residuals were specified as independent. The model provided in the faxed 10/26/01 document was different from the models that were used to generate the computer output of Appendix 2, Statistical Documentation mentioned above.

According to the study report, no significant main effects or interactions involving dosage frequency were found, therefore the data for the two frequencies (bid and tid) were pooled for the subsequent analyses. It must be emphasized that differences in frequency of administration of NTG resulted in different daily doses to the patient. For example a dose of 0.4% NTG BID provided 3 mg of drug versus 4.5 mg when given TID. The sponsor concluded in the study report that in the ITT population, linear time by treatment interactions were significant for the 0.4% NTG group relative to placebo for average pain ($p < 0.0002$). The mixed-effects analysis in the faxed 10/26/01 document gives $p = 0.00018$. With stationary AR(1) residuals, the p-value for this interaction becomes 0.00019. In addition, the sponsor reported that analyses performed on all 56 days of pain yielded similar results. However, the reviewer's analysis of all 56 days of pain gave a $p = 0.0052$, different in an order of magnitude, with independent residuals, but $p = 0.0004$ with AR(1) residuals.

As noted there are concerns about pooling dose frequencies. Not only would the effect, if any, of different doses be ignored, but is inconsistent with the analysis of anal fissure healing, the primary endpoint which was done for each dose group and frequency of administration per protocol. Additionally, the ANOVA method used to detect differences between BID and TID dosing is relatively insensitive, and pairwise comparisons between groups reveals differences than may not be detected by this method. One would be concerned about the analysis of a secondary endpoint by methods selected post-hoc.
To provide an analysis preserving the randomized groups, utilizing all available data, Dr. Hung has provided the following. Table R1-7 presents the results of slope of change in average daily pain without pooling. All daily measurements are incorporated in the analyses. The mixed-effects model is identical to the one used by the sponsor. The results suggest that only 0.4% NTG bid appear to reduce average daily pain in a greater rate over time than placebo. The models with AR(1) residuals appear to be better in terms of likelihood and give better sensitivity in showing statistical significance.

Table R1-7. Slope of change in average daily pain over time (Reviewer's analysis)

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

* for comparison with the corresponding placebo regimen
Indep: model with independent residuals
AR(1): model with AR(1) residuals

Worst pain and defecation pain

The mixed-effects analysis using the same models were also performed on worse pain and defecation pain. The results are summarized in Tables R1-8 and R1-9. The results give the essentially the same suggestion that 0.4% NTG bid appear to reduce pain in a greater rate over time than placebo. Again the models with AR(1) residuals appear to be better in terms of likelihood and give better sensitivity in showing statistical significance. The 0.1% and 0.4% tid doses of NTG give a nominal p-value < 0.05. However, they are difficult to interpret because 1) 0.2% showed no significantly large slope, 2) awkward dose slope relationship, and 3) multiple comparisons and multiple choices of models. In my view, these p-values have not attained statistical significance.

Table R1-8. Slope of change in worst daily pain over time (Reviewer's analysis)

	Mean slope (worst daily pain)		Nominal P-value*	
	indep	AR(1)	indep	AR(1)
Placebo BID (N=34)	-0.39	-0.41	---	---
0.1% NTG BID (N=39)	-0.35	-0.37	0.80	0.79
0.2% NTG BID (N=39)	-0.45	-0.45	0.70	0.72
0.4% NTG BID (N=38)	-0.71	-0.71	0.025	0.007
Placebo TID (N=36)	-0.31	-0.31	---	---
0.1% NTG TID (N=37)	-0.64	-0.59	0.022	0.012
0.2% NTG TID (N=39)	-0.45	-0.46	0.32	0.16
0.4% NTG TID (N=42)	-0.60	-0.59	0.042	0.011

* for comparison with the corresponding placebo regimen
Indep: model with independent residuals
AR(1): model with AR(1) residuals

Table R1-9. Slope of change in defecation pain over time (Reviewer's analysis)

	Mean slope (defecation pain)		Nominal P-value*	
	indep	AR(1)	indep	AR(1)
Placebo BID (N=34)	-0.39	-0.36	---	---
0.1% NTG BID (N=39)	-0.38	-0.38	0.96	0.87
0.2% NTG BID (N=39)	-0.41	-0.41	0.84	0.65
0.4% NTG BID (N=38)	-0.66	-0.66	0.056	0.007
Placebo TID (N=36)	-0.27	-0.27	---	---
0.1% NTG TID (N=37)	-0.53	-0.50	0.064	0.037
0.2% NTG TID (N=39)	-0.36	-0.38	0.50	0.30
0.4% NTG TID (N=42)	-0.52	-0.50	0.075	0.041

* for comparison with the corresponding placebo regimen
Indep: model with independent residuals
AR(1): model with AR(1) residuals

The mixed-effects analyses in this study are purely exploratory. The mixed-effects models chosen for final analyses to generate p-values suggesting potential signals were not pre-specified; thus, there are many possible models that might be used. For instance, the residuals could be modeled to follow an independent covariance structure, AR(1), or some others. From the comparison of residuals, this study seems to suggest that the stationary AR(1) residuals are more likely to show a signal.

Numerically, the bid and tid regimens showed different dose slope relationships, though the differences were not statistically significant (no statistically significant frequency by time interaction). The tid regimen showed an awkward dose slope relationship. These observations have established a ground for doubt of whether pooling the dosage frequencies is sensible. For reasons enumerated above, this study does not

provide convincing support for the efficacy of NTG ointment to relieve anal pain due to fissures, but does establish a hypothesis for study NTG 00-02-01 which tests prospectively the efficacy of NTG ointment for that indication.

SAFETY

304 patients were included in the safety analyses: 70 assigned to placebo; 234 on NTG.

No deaths occurred.

The sponsor reported that 13 patients withdrew for an adverse event as follows:

Treatment Group Subject Number	Age (yrs)	Adverse Event (Primary Term)	Study Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
0.1% NTG b.i.d.						
315121	55	Respiratory disorder	14	Moderate	None	35
		Headache[d]	2	Severe	Possibly	35
		Flu syndrome	14	Moderate	None	35
0.2% NTG b.i.d.						
315104	29	Dizziness[d]	2	Moderate	Possibly	5
		Palpitation[d]	2	Moderate	Possibly	5
322146	24	Rectal disorder[c]	8	Severe	None	10
0.4% NTG b.i.d.						
317115	72	Headache	2	Mild	Possibly	197[e]
		Nausea	2	Mild	Possibly	197
		Pruritus	27	Moderate	Possibly	197
		Accidental injury[c,d]	48	Severe	None	197
Placebo t.i.d.						
323107	41	Headache[d]	1	Moderate	Related	12
0.1% NTG t.i.d.						
317114	41	Headache[d]	1	Severe	Possibly	5
		Vomiting[d]	1	Severe	Possibly	5
		Hypertension[d]	1	Moderate	Possibly	5
323102	71	Vertigo[d]	2	Moderate	Possibly	8
0.4% NTG t.i.d.						
315105	26	Headache[d]	1	Severe	Possibly	3
317127	35	Nausea	1	Mild	Possibly	39
		Headache	1	Severe	Possibly	39
		Headache	4	Severe	Possibly	39
		Headache	21	Severe	Possibly	39
		Headache[d]	24	Severe	Possibly	39
		Hypernatremia	39	Mild	None	39
317138	37	Headache[d]	1	Severe	Related	15
		Vomiting[d]	1	Moderate	Possibly	15
		Sweating[d]	1	Moderate	Possibly	15
319108	21	Headache[d]	1	Severe	Related	6
		Nausea[d]	1	Severe	Related	6
323101	50	Headache[d]	1	Severe	Related	9
		Sweating[d]	1	Moderate	Possibly	9
		Anxiety[d]	2	Moderate	Possibly	9
323111	29	Headache[d]	Unknown[f]	Moderate	Related	11

[a] Relative to start of therapy.
[b] Based on investigator's assessment.
[c] Serious adverse event.
[d] Subjects discontinued therapy due to this adverse event.
[e] Subject 317115 discontinued the study due to a broken hip on 3/06/99. The clinical summary page of the CRF was completed on 9/22/99.
[f] The first day of study drug administration for Subject 323111 was April 20, 1999. The onset of headache was an unknown date in April, 1999.

A review of case report forms for patients without any pain data, only baseline pain data or less than 7 days of pain data revealed in this reviewer's judgment 9 additional patients withdrawn for adverse events:
0.1% NTG TID patient 314105 for anal surgery.
0.1% NTG TID patient 315113 for anal pain necessitating surgery,
0.2% NTG BID patient 322112 for headache,
0.2% NTG TID patient 310101 for headache and vertigo,
0.2% NTG TID patient 317130 for headache,
0.4% NTG TID patient 317117 for headache,
0.4% NTG TID patient 317121 for headache and short arms,
0.4% NTG TID patient 320124 for vomiting,
0.4% NTG TID patient 322123 for headache.
At least 23 patients withdrew for an adverse event; 10 were in the highest dose NTG TID group versus 1 in the placebo TID group.

A listing of patients reporting severe adverse events was provided as follows:

Table 17: Subjects With Severe Adverse Events Considered to be Severe: Safety Population (Study NTG-98-02-01)

Treatment Group Subject Number	Age	Adverse Event (Primary Term)	Relationship to Study Drug[a]	Action Taken	Outcome
placebo b.i.d.					
316105	55	Headache	Possibly	Rx or OTC drug	Resolved
319109	38	Rectal disorder	None	Procedure	Resolved
0.1% NTG b.i.d.					
312108	45	Rectal disorder	None	Procedure	Resolved
		Rectal Hemorrhage	None	Procedure	Resolved
315121	55	Headache	Possibly	Rx or OTC drug	Resolved
0.2% NTG b.i.d.					
313115	37	Headache	Possibly	None	Resolved
317118	29	Headache	Possibly	Rx or OTC drug	Resolved
322112	36	Headache	Possibly	D/C Study drug	Resolved
322146	24	Rectal disorder	None	Procedure	Resolved
0.4% NTG b.i.d.					
313111	55	Headache	Related	None	Resolved
317115	72	Accidental Injury	None	D/C study drug and hospitalized	Hospitalized
317117	26	Headache	Possibly	Rx or OTC drug	Resolved
317142	23	Headache	Possibly	Rx or OTC drug	Resolved
320105	30	Headache	Related	None	Resolved
		Headache	Related	D/C study drug	Lost to follow-up
322150	32	Gastroenteritis	None	Rx or OTC drug	Resolved
placebo t.i.d.					
312104	31	Headache	Possibly	None	Resolved
317123	41	Menstrual disorder	None	Rx or OTC drug	Resolved
		Menstrual disorder	None	Rx or OTC drug	Resolved
0.1% NTG t.i.d.					
317114	41	Headache	Possibly	D/C Study drug	Resolved
		Vomiting	Possibly	D/C Study drug	Resolved
0.2% NTG t.i.d.					
313109	26	Headache	Related	None	Resolved
317109	59	Headache	Possibly	Rx or OTC drug	Resolved
		Palpitation	Possibly	D/C study drug	Resolved
317119	41	Headache	Possibly	Rx or OTC drug	Resolved
317130	51	Headache	Related	Rx or OTC drug	Resolved
317132	38	Gastrointestinal disorder	None	Rx or OTC drug	Improved
320103	63	Dyspnea[b]	None	Procedure	Resolved
		Chest pain[b]	None	Procedure	Resolved
0.4% NTG t.i.d.					
313105	52	Headache	Related	Rx or OTC drug	Resolved
		Headache	Possibly	None	Resolved
315105	26	Headache	Possibly	Rx or OTC drug	Resolved
316102	34	Headache	Related	Rx or OTC drug	Resolved
317127	35	Headache	Possibly	Rx or OTC drug	Resolved
		Headache	Possibly	Rx or OTC drug	Resolved
		Headache	Possibly	Rx or OTC drug	Resolved
		Headache	Possibly	D/C study drug	Resolved
317138	37	Headache	Related	D/C study drug	Resolved
319108	21	Headache	Related	D/C study drug	Resolved
		Nausea	Related	D/C study drug	Resolved
320124	19	Vomiting	Related	None	Resolved
		Vomiting	Related	D/C study drug	Resolved
323101	50	Headache	Related	Rx or OTC drug	Resolved
325101	41	Headache	Related	Rx or OTC drug	Resolved

[a] Based on investigator's assessment
[b] Serious adverse event
[c] Subjects discontinued therapy due to this adverse event
KEY: Rx = prescription medication; OTC = over-the-counter; D/C = discontinue

Checking the 0.4% NTG TID group against the listing of patients who withdrew for adverse events (see chart above) raises questions of consistency and accuracy in the safety reporting. For example, patient 315105 is listed as headache treated with some RX, but this patient was listed as withdrawn for severe headache. The same situation exists for patients 323101and 323111. Patient 320124 is said to have discontinued the study drug for vomiting, but is not listed on the chart of those withdrawn. This problem is not confined to the 0.4%NTG TID group. For example, patient 320105 from the 0.4%BID group is noted to have withdrawn for headache on the severe adverse events chart above, but not on the withdrawal chart. As noted above when the additional patients withdrawn for adverse events as noted by this reviewer, and inconsistencies resolved at least 23 patients were withdrawn for an adverse event with 10 of these in the highest dose NTG group.

Headache was the most frequent cause of patient withdrawal, as well as the most frequently experienced adverse event, mostly in those treated with NTG and with increasing incidence as the NTG dose increases.

Dosage Frequency/	All Reported (N=97)		Treatment-Related[a] (N=36)		Severe (N=23)	
Dose	n	(%)	n	(%)	n	(%)
b.i.d						
placebo	3	(3.1)	0	(0.0)	1	(4.3)
0.1%	7	(7.2)	1	(2.8)	1	(4.3)
0.2%	13	(13.4)	6	(16.7)	3	(13.0)
0.4%	14	(14.4)	5	(13.9)	4	(17.4)
t.i.d.						
placebo	10	(10.3)	4	(11.1)	1	(4.3)
0.1%	7	(7.2)	0	(0.0)	1	(4.3)
0.2%	18	(18.6)	7	(19.4)	4	(17.4)
0.4%	25	(25.8)	13	(36.1)	8	(34.8)

[a] Includes headaches that were possibly related and related to study drug.

214 patients took medication for pain relief during the study. Of these it was noted that 67 took acetaminophen for headache and 5 took additional pain medication for headache. 36 patients took NSAIDS or salicylates for chronic pain or inflammation.

Other severe adverse events leading to withdrawal were rectal pain, and one case of dizziness, faint felling and heart palpitations (patient 315104, 0.2%NTG BID) where the blood pressure readings were 102/64 predose to 90/58 20 minutes postdose. While the hypotensive effects of nitroglycerin are described in the approved labeling, no severe adverse events other than possibly that noted for patient 315104 might be ascribed to a hypotensive effect of anogesic therapy. The mean, median and extreme blood pressure readings over time do not reveal significant differences between groups. 31 patients had a 20 mm Hg or greater drop in systolic blood pressure predose to 10 or 20 minutes postdose.

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

This multicenter, multinational (USA, UK, Israel and Germany), randomized, placebo controlled, double-blind parallel study of two doses of NTG ointment (0.75mg and 1.5 mg daily for 56 days) to relieve the pain of anal fissures was initiated May 30,2000 and completed August 27, 2001.

229 patients were randomized to placebo (vehicle), NTG 0.2% BID (0.75mg total daily dose), or NTG 0.4% BID (1.5mg total daily dose). To enter a patient had to have an anal fissure with pain. The pain had to have been present after at least 50% of bowel movements for 30 days prior to enrollment and be present at enrollment. Patients could be male or female, 18 years or older, and if female, on an approved method of birth control. Exclusion criteria included fistulo-in-ano, anal surgery within the preceeding 30 days, allergy to any of the medications, require NSAID therapy but for cardiac uses, anal abscess, IBD, anal stenosis, or unwilling to discontinue use of Viagra.

The primary objective was stated in the title of the study. Pain was assessed at baseline and daily on a VAS going from zero (none) to 100 (most severe imaginable). Average daily pain, worst daily pain and pain on defecation were rated. Every two weeks subjects returned with their diaries that were transcribed by the investigators onto the CRFs. Statistically, it was pre-specified in the protocol that a mixed-effects regression model using all values recorded for each subject would be used for the ITT population (defined elsewhere as subjects with baseline and some post-treatment data). In the study report it is stated that the effects of center and a quadratic effect of time were included in the model. The center and quadratic components of the model used for analysis were not pre-specified, and these parameters were not used to analyze study NTG 98-02-01.The study report goes on to note that, if the overall analysis was significant, treatment comparisons at each timepoint would be made. Average daily pain was the primary parameter to be analyzed, but worst pain and defecation pain were also to be analyzed. Secondary endpoints were time to anal fissure healing, safety and Gastrointestinal Quality of Life Index results.
Statistically, the study was sized based on effect size estimates for daily average pain (primary endpoint) from the initial clinical study. For a power of 0.8 and an alpha of .05, adjusting for two active comparisons, it was estimated that 55 patients per group were needed. An attrition rate of 2.5% per week was factored into the proposed sample size.

The schedule of procedures with detailed footnotes was provided in the study report as follows:

Table 1: Schedule of Study Procedures
(Study NTG 00-02-01)

Assessment/Procedure	Screening[a]	Baseline (Day 1)	On-Therapy Evaluation[b]	Exit Visit Evaluation[c]	Open-label[d]	Follow-up
Consent Form Signed	X					
Physical Examination	X			X		
Medical History	X					
Medication History	X					
Clinical Laboratory Tests[e]	X			X		
Anal Examination/Assessment[f]	X		X	X	X[l]	
Vital Signs[g]	X	X[h]	X	X		
CTM Weight Assessment[i]		X	X	X		
Subject Instruction		X				
Pain Intensity Assessment[j]		X	X	X	X[l]	
Gastrointestinal Quality of Life Index	X		X[k]	X		
Daily Sitz Bath Recorded	X----------			----------X	X[l]	
Study Drug Application		X----------			----------X	
Concomitant Medications Recorded		X----------		----------X		
Adverse Events Recorded		X----------			----------X	
Telephone contact						X[m]

[a] Screening was to occur from before Day 1 and was to end just prior to dosing on Day 1; Screening and Baseline could occur on Day 1.

[b] Clinic visits on Days 14, 28, 42, and 56 ±3 days.

[c] Final (exit) clinic visit (whether due to early withdrawal or on Day 56).

[d] For subjects for whom the anal fissure was not completely healed during the 56-day study period.

[e] Including blood chemistry, hematology, and urinalysis; a urine pregnancy test was required to be performed for all women of child-bearing potential (Section 3.8.4.3).

[f] A digital/anoscopic examination could be performed, depending on the investigator's standard of practice, once only during the eighth week.

[g] Baseline and exit visits included measurement of height (baseline visit only), weight, temperature, sitting blood pressure, and pulse. Day 1 and on-therapy visits included measurement of pulse and sitting blood pressure only.

[h] Sitting blood pressure and pulse were to be measured immediately prior to and 15 minutes after administration of first dose of study drug.

[i] The individual CTM (tube with study medication) was to be weighed (to nearest 0.1 g) before being given to the subject and again when returned by the subject at each 2-week visit.

[j] Record of VAS scores for average pain intensity for the day, maximum pain intensity that day, and pain intensity at most recent defecation reported prior to first dose of study medication and on each evening during the study were to be transcribed onto the CRF by study site personnel.

[k] Gastrointestinal Quality of Life Index was to be completed at the Week 2 and Week 4 on-therapy assessments only.

[l] Only for subjects who participated in the open-label phase.

[m] Applicable only for those subjects who healed during either the double-blind or open-label phase of the study. These subjects were contacted every 12 weeks to determine if sphincterotomy had been performed.

Key: CTM = clinical trial material; VAS = visual analog scale

The disposition of patients randomized and included in various analyses were:

Figure 1: Subject Disposition

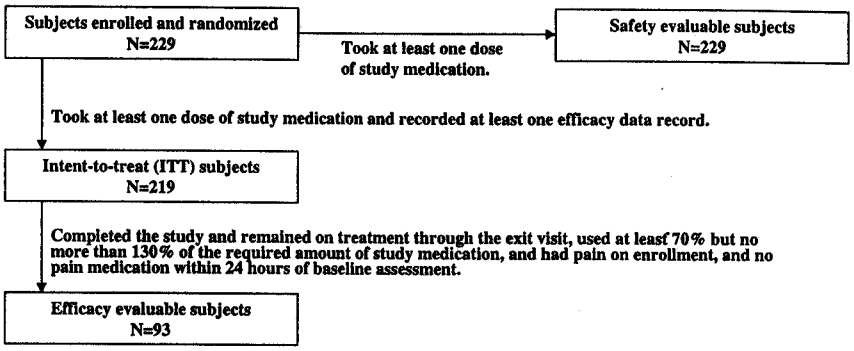


Table 2 presents the number of subjects in each treatment group for each analysis population.

Table 2: Number of Subjects in Each Population
(Study NTG 00-02-01)

	ITT (N=219)		Efficacy Evaluable (N=93)		Safety (N=229)	
Treatment Group	n	(%)[a]	n	(%)[a]	n	(%)[a]
Placebo	75	(34.25)	34	(36.56)	78	(34.06)
0.2% NTG Ointment	70	(32.00)	29	(31.18)	73	(31.88)
0.4% NTG Ointment	74	(33.79)	30	(32.26)	78	(34.06)

[a] Percentages represent the portion (n) of subjects from the total population (N).

Table 3: Study Completion/Withdrawal Information: Intent-to-Treat Population
(Study NTG 00-02-01)

	Placebo		0.2% NTG Ointment		0.4% NTG Ointment	
Subject Disposition	n	(%)	n	(%)	n	(%)
Number of Subjects Randomized	75		70		74	
Number of Subjects Completing 56-day Treatment Phase	67	(89.33)	57	(81.43)	56	(75.68)
Number of Subjects Who Prematurely Withdrew From Treatment Phase	8	(10.67)	13	(18.57)	18	(24.32)
Reason for Premature Withdrawal						
Adverse Event	2	(2.67)	3	(4.29)	10	(13.51)
Protocol Violation/Deviation	0		0		2	(2.70)
Subject Non-Compliance	0		3	(4.28)	0	
Subject Choice	3	(4.00)	4	(5.71)	4	(5.41)
Lost to Follow-up	3	(4.00)	3	(4.29)	1	(1.35)
Other[a]	0		0		1	(1.35)

[a] The subject who withdrew for "Other" reasons was taking an unexpected holiday.

According to the sponsor, the ITT population for efficacy analysis contained 219 out of 229 randomized patients. In the sponsor's statistical report the following patients were excluded from the ITT population. According to the report, all exclusions were for no baseline data.

PLACEBO
007-111
022-107
048-105

NTG 0.2%
007-110
009-110
028-110

NTG 0.4%
009-105
028-109
030-101
048-107

Review of the case report tabulations for pain response revealed 6 types of problems raising questions of who should be included in the analyses. These were: dropouts(pain data not recorded to endpoint), no pain data, no baseline data, only baseline data, zero pain at entrance, and missing days of pain data in the middle of the treatment period.

The dropouts identified were:

PLACEBO
007-114
007-123
008-102
009-101
019-101
028-107

NTG 0.2%
001-103
001-114
002-101
005-114
008-103
009-103
010-102
014-102
019-108
022-102
048-108

NTG 0.4%
002-103
002-104
007-102
007-107
007-115
008-101
008-104
008-114
010-106
012-104
015-105
021-101
028-105
028-106
048-102
The case report forms were reviewed for these patients. All but two were reported as having not completed the study. Various choices for the primary reason for early termination were provided, i.e. adverse event, protocol violation, patient non-compliance, patient choice, lost to follow-up, and other. While a choice such as protocol violation may have been made, no detail was provided to support the choice, and often other factors such as treatment failure or adverse events seemed probable influences. Adverse events such as headache were frequently present in the NTG ointment groups, and will be discussed in the safety section. Some data recording problems were found. Patient 002-101 had zero recorded for defecation pain when no defecation occurred. Patient 048-108 was called a completer by the investigator, but no pain data was recorded after day. Pain data of patient 028-106 was correct by date but not by days in the study. Such errors were not frequent or systematic, though it must be noted that we do not have the original diaries to correlate with the case report form data.

Adding these withdrawals to those listed by the sponsor, there were 11 in the placebo group, 17 in the 0.2%NTG group and 21 in the 0.4% NTG group.

Some patients had no pain data recorded at all.
PLACEBO
007-111
022-107
048-105

NTG 0.2%
007-110
009-110
028-110

NTG 0.4%
009-105
028-109
030-101
048-107
This list accord with the sponsor's list of exclusions.

Those with no baseline data were:
PLACEBO
022-108
029-110

NTG 0.2%
008-116
048-104 (average pain data not recorded)

NTG 0.4%
009-106
013-102

There were patients with only baseline data.
PLACEBO
None

NTG 0.2%
008-108
010-111
010-112
010-117

NTG 0.4%
007-108
010-109
010-115
011-101

There were patients with no pain at entrance.
PLACEBO
009-109
010-118

NTG 0.2%
None

NTG 0.4%
None

Some patients had missing pain data for considerable lengths of time in the middle of the study with pain data resuming after the hiatus. Centers 007 and 010 had the same PI (Dr. Ziv, Israel).
PLACEBO
007-121
009-102
010-116
010-120
015-106
NTG 0.2%
007-101

007-122
010-113
028-102
NTG 0.4%
007-115
007-120
010-123

According to the sponsor the efficacy ITT analysis should include patients with baseline and some post treatment data. To accord with this definition, patients with no baseline data and only baseline data should also be excluded. This would lead to an additional 2 patients on placebo, 6 on NTG 0.2%, and 6 on NTG 0.4% being excluded. Additionally, the two patients on placebo who had no pain at entrance should be excluded, since they did not have the condition of primary interest.
This would lead to 71 patients on placebo, 64 on NTG 0.2%, and 68 on NTG 0.4% being included in the analysis of the ITT. Since those who withdrew and those with missing data in the middle of the study had anal pain at entrance, baseline and follow-up pain data they should be included in the analyses.

Using their ITT population, the sponsor provided the following demographic information:

Table 4: Demographic and Baseline Characteristics: Intent-to-Treat Population (Study NTG 00-02-01)

	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)
	n (%)	n (%)	n (%)
Sex			
Female	34 (45.33)	27 (38.57)	31 (41.89)
Male	41 (54.67)	43 (61.43)	43 (58.11)
Race			
Asian	2 (2.67)	1 (1.43)	0
Black	5 (6.67)	3 (4.29)	5 (6.76)
Caucasian	64 (85.33)	62 (88.57)	67 (90.54)
Hispanic/American or Latino	4 (5.33)	3 (4.29)	2 (2.70)
Other	0	1 (1.43)	0
Age (years)			
≤45	44 (58.67)	41 (58.57)	39 (52.70)
46-64	25 (33.33)	25 (35.71)	33 (44.59)
≥65	6 (8.00)	4 (5.71)	2 (2.70)
Age (years)			
N	75	70	74
Mean (SD)	43.1 (13.93)	43.4 (13.74)	43.6 (12.72)
Min. - Max.	19.0-78.0	20.0-83.0	19.0-71.0
Median	42.0	44.5	45.0
Missing	0	0	0
Weight (kg)			
N	75	68	74
Mean (SD)	82.8 (21.55)	79.7 (20.05)	81.7 (17.23)
Min. - Max.	47.0-157.3	45.5-172.7	50.0-131.8
Median	79.5	78.0	81.3
Missing	0	2	0
Height (cm)			
N	75	69	73
Mean (SD)	170.4 (9.46)	171.8 (10.75)	172.5 (9.97)
Min. - Max.	142.0-190.0	147.0-198.1	146.0-193.0
Median	170.0	174.0	174.0
Missing	0	1	1
Body Mass Index (kg/m^2)			
N	75	68	73
Mean (SD)	28.4 (6.84)	26.8 (5.53)	27.3 (4.70)
Min. - Max.	17.9-48.5	15.5-53.1	18.8-41.6
Median	26.7	25.9	26.2
Missing	0	2	1
Alcohol Use			
No	54 (72.00)	43 (61.43)	44 (59.46)
Yes	21 (28.00)	27 (38.57)	30 (40.54)
Tobacco Use			
No	65 (86.67)	56 (80.00)	60 (81.08)
Yes	10 (13.33)	14 (20.00)	14 (18.92)

Cross-reference: Appendix 3.1.3

To enter patients had to have an anal fissure with pain at entrance and a history of at least 50% of days in the preceeding 30 days of pain on defecation.
According to the sponsor, anal fissure baseline data was:

Table 5: Baseline Anal Exam/Assessment:
Intent-to-Treat Population
(Study NTG 00-02-01)

	Placebo (N=75)		0.2% NTG Ointment (N=70)		0.4% NTG Ointment (N=74)	
	n	(%)	n	(%)	n	(%)
Anal Fissure[a]						
Present	75	(100.00)	70	(100.00)	74	(100.00)
Fissure Features[b]						
Visible Fibers	49	(65.33)	43	(61.43)	52	(70.27)
Indurated edges	47	(62.67)	41	(58.57)	56	(75.68)
Sentinel pile	39	(52.00)	31	(44.29)	29	(39.19)
Hypertrophied Papilla present	20	(26.67)	15	(21.43)	14	(18.92)
No. of Fissure Features						
<3 features	49	(65.33)	53	(75.71)	52	(70.27)
≥3 features	26	(34.67)	17	(24.29)	22	(29.73)
Fissure Length (cm)						
Mean (SD)	1.0	(0.73)	1.0	(0.38)	1.1	(0.73)
Min. – Max.	0.2-6.0		0.4-2.0		0.1-4.5	
Median	1.0		1.0		1.0	
Missing	0		0		0	

[a] To be eligible for enrollment, subjects were to have a single anal fissure.
[b] Subjects are included in all applicable categories.

Average pain was the primary parameter for the efficacy analysis. Per the sponsor the baseline data for average pain was:

Table A-1.1
Mean Average Pain Intensity (mm) Due to Anal Fissure by Time Period:
Intent to treat population

Time Period	Statistics	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)
Baseline	N	73	68	72
	Mean (SD)	34.0(22.5)	32.9(20.7)	33.4(22.2)
	Median	31.0	30.0	30.5
	Min. - Max.	0.0 - 93.0	2.0 - 87.0	1.0 - 84.0

As previously noted, two placebo patients had recorded zero average pain at entrance.

Worst pain at entrance was:

Table A-1.2
Mean Worst Pain Intensity (mm) Due to Anal Fissure by Time Period:
Intent to treat population

Time Period	Statistics	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)
Baseline	N	73	69	72
	Mean (SD)	51.4(27.3)	51.8(23.7)	53.0(25.8)
	Median	52.0	55.0	53.0
	Min. - Max.	0.0 - 100	8.0 - 100	7.0 - 100

Defecation pain was:

Table A-1.3
Mean Defecation Pain Intensity (mm) Due to Anal Fissure by Time Period:
Intent to treat population

Time Period	Statistics	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)
Baseline	N	68	65	63
	Mean (SD)	48.1(28.2)	46.6(26.1)	47.5(26.0)
	Median	50.0	44.0	46.0
	Min. - Max.	0.0 - 100	0.0 - 100	0.0 - 100

Some patients on NTG ointment and placebo had no baseline defecation pain recorded. It should also be noted that mean and median worst and defecation pain were more severe than average pain. That would be an expected finding, not only because the intensity would vary throughout the day, but because one of the pain requirements for entrance was pain on defecation in the previous 30 days before randomization.

Dr. Hung provided the following analyses of missing pain data and baseline demographics:
A total of 10 patients had no pain data at all. In addition, six patients had no baseline pain data but had pain data after baseline; 8 patients had baseline pain data but no pain data recorded after this.

Distribution of the patients with incomplete pain data

	0.2% NTG BID (N=73)	0.4% NTG BID (N=78)	Placebo BID (N=78)
No pain data recorded at all	3	3	4
No baseline pain data	2	2	2
No post randomization pain data	4	4	0

Baseline Pain Data

The three treatment groups appeared to be comparable with respect to baseline pain.

Distribution of baseline measurement on daily average pain

	Mean	SD	Range	1st quartile	Median	3rd quartile
Average Pain						
0.2% NTG BID (N=68)	32.9	20.7	2 - 87	16	30	46.5
0.4% NTG BID (N= 72)	33.4	22.2	1 – 84	14	30.5	48
Placebo BID (N= 73)	34.0	22.5	0 – 93	15	31	50
Worst Pain						
0.2% NTG BID (N=69)	51.8	23.7	8 - 100	33	55	69
0.4% NTG BID (N= 72)	53.0	25.8	7 – 100	31	53	75
Placebo BID (N= 73)	51.4	27.3	0 – 100	31	52	76
Defecation Pain						
0.2% NTG BID (N=65)	46.6	26.1	0 - 100	25	44	64
0.4% NTG BID (N= 63)	47.5	26.0	0 – 100	26	46	68
Placebo BID (N= 68)	48.1	28.2	0 – 100	20.5	50	72

RESULTS
EFFICACY
I. PAIN

The protocol specified that a mixed-effects regression model would be used to analyze pain response throughout the trial. Dr. Hung provided the following analysis of these data:

Mixed effects analysis

In the protocol, mixed-effects analysis was proposed as the primary analysis to test whether there is a difference in rate of change of average pain during the course of the trial. A general mixed-effects regression model would be used but the form of the model, i.e., a linear model or a quadratic model, was not specified, nor were the covariance structure of the random-effects components and the covariance structure of the residual pre-specified.

According to the protocol, the primary hypothesis would be tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects). Thus the rate of change in the average pain score is the primary efficacy parameter.There is no specific definition of rate of change in the protocol.
Depending on the model, the rate of change is defined differently. In a linear model (straight line model that the sponsor used in the first study), the rate of change is the slope of the linear trend. In a quadratic model (linear trend plus quadratic trend over time), the rate of change is no longer the slope of the linear trend. Mathematically, it is the first-order derivative of the quadratic function in the model, i.e. the slope of the response curve. Consequently, the rate of change varies over time. According to the sample size plan in the protocol, intercept and slope and their variability were used to project the treatment difference at the end of treatment (day 56) and calculate the sample size. This indicates that the linear model was the model the sponsor had in mind for design and analysis of the study. The linear model was the model used in the sponsor's exploratory analysis to suggest that 0.4% NTG may have a greater rate of change in pain over time in the previous study, NTG 98-02-01.

In Study NTG 00-02-01, the sponsor's analyses and statistical inference were based on the quadratic model with an unstructured covariance matrix for the random-effects component (intercept and slope) and a simple covariance matrix for the residual. This differs from the model used in Study NTG 98-02-01, which is a linear model with a simple covariance matrix for the random-effects component and a simple covariance matrix for the residual. In addition, the model in NTG 00-02-01 contains sites for adjustment and the model in NTG 98-02-01 does not. Adjustment for sites in statistical analysis was not pre-specified in the protocol of either study.

Sponsor's Results

Average Pain

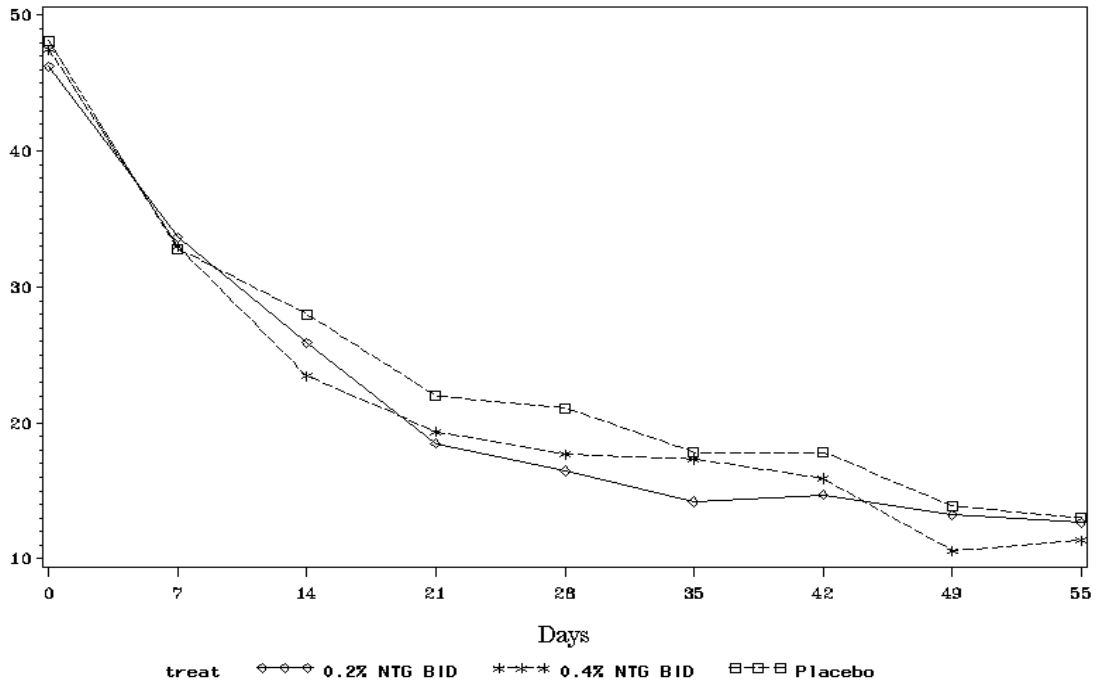
In response to the reviewer's request, the sponsor provided the results of the mixed-effects analyses for average pain, worst pain and defecation pain (dated 1/22/02). Average pain intensity was the primary efficacy parameter. In their analyses, week was the unit of analysis in the primary analysis. The sponsor concluded that in the ITT population, for comparisons with the placebo group, a significant treatment by linear time interaction for average pain intensity was observed for the 0.4% NTG group (p=0.005), but not for the 0.2% NTG group; see Table S2-1 which summarizes the sponsor's results from the computer output. In addition, a significant treatment by quadratic time interaction was observed for the 0.4% NTG group. Mean average pain for 0.2% NTG group was also numerically lower than the placebo group throughout the eight weeks of treatment (Sponsor's Table 9, Table A-1.1). To aid in interpretation, the sponsor presented percent improvement from baseline in Figure A-1 to show the quadratic trend. The mean average daily pain score versus days 0, 7, 14, 21, 28, 35, 42, 49, 55 is illustrated in Figure R2-1.

Table S2-1. Testing the differences in linear trend and quadratic trend parameters between treatments on average pain score (Sponsor's results summarized by Reviewer)

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

* nominal p-value

Figure R2-1. Mean average daily pain score versus Days 0, 7, 14, 21, 28, 35, 42, 49, 55 (Reviewer's analysis)



Worst Pain and Defecation Pain

Worst pain and defecation pain intensities were secondary efficacy parameters. The sponsor reported that similar patterns seen for these variables when compared to the patterns seen for mean average pain (Sponsor's Tables A-1.2, A-1.3). Individual dosage group versus the placebo group by linear time interactions were observed for both 0.2% and 0.4% groups for worst pain (0.2% $p < 0.04$; 0.4% $p < 0.005$), and defecation pain (0.2% $p < 0.01$; 0.4% $p < 0.04$); see Table S2-2 in the following. In all these comparisons, significant treatment by quadratic time interactions were observed (see also Sponsor's Figures A-2 and A-3, for percent improvement from baseline over weeks).

Table S2-2. Testing the differences in linear trend and quadratic trend parameters between treatments on worst pain and defecation pain (Sponsor's results summarized by Reviewer)

	Linear trend	p-value for linear*	Quadratic trend	p-value for quadratic*
Worst pain				
0.2% NTG minus placebo	-0.22	0.040	0.0035	0.005
0.4% NTG minus placebo	-0.30	0.005	0.0044	0.0004
Defecation pain				
0.2% NTG minus placebo	-0.26	0.013	0.0030	0.012
0.4% NTG minus placebo	-0.22	0.039	0.0031	0.009

* nominal p-value

Reviewer's Analysis and Evaluation

Average Pain

The mixed-effects analysis results depend on the regression model used. As mentioned above, based on the plan of estimating sample size, the model the sponsor intended to use at the time of planning the study was a linear model in which the trend of average pain intensity is linear over time. The previous study NTG98-02-01 also suggested that the linear model was the model to use. In the linear model, the rate of change in pain is the slope of the linear trend that does not change over time. Using the linear model (excluding sites, using a simple covariance matrix for random-effects components and for residual as the sponsor used in Study NTG 98-02-01), the reviewer performed the mixed-effects analysis and the results are summarized in Table R2-1. Adding sites or using an unstructured covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference. Based on the linear model, there was no significant difference in slope (rate of change of average pain intensity over time) among the treatment groups, though the 0.4% NTG group had a numerically greater rate of decrease of average pain intensity compared to the placebo group.

Table R2-1. Slope of change in average daily pain over time
(Reviewer's analysis, using linear model[#])

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

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

The results of the sponsor's mixed-effects analysis, using a quadratic model with the unstructured covariance matrix for the random-effects components and the simple covariance matrix for the residual, were confirmed by the reviewer. The results suggest that the mean average pain intensity over time behaved differently in the 0.4% NTG group as compared to the placebo group. The treatment differences quantified by the differences in the linear and quadratic trends were suggested by the data ($p = 0.005$ for linear trend; $p < 0.0001$ for quadratic trend; Table S2-1 and Figure R2-1). Adding sites or using a simple covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference.

The primary parameter to be tested, however, was the rate of change according to the protocol. As explained above, with the quadratic model, the rate of change (or decrease) in average pain score over time should be the first-order derivative of the quadratic model, i.e. the slope of the mean average pain curve. Consequently the rate of decrease changes over time. This reviewer performed mixed-effects analysis to estimate the differences between 0.4% NTG and placebo in the rate of change of average pain at Days 7, 14, 21, 28, 35, 42, 49 and 55 using the quadratic model the sponsor used. The results of the reviewer's analyses are summarized under Model 1 in Table R2-2 and suggest that the 0.4% NTG group seemed to have a significantly larger rate of decrease in average pain intensity than the placebo group in the first week or possibly two. Thereafter, no statistical significant difference in rate of change favoring 0.4% NTG was found. The numerical differences in the rate of change decreased in days and showed a reversed trend favoring placebo in last few weeks. That is, numerically, the 0.4% NTG group had a smaller rate of decrease in average pain intensity than the placebo group in the last few weeks. Using simple covariance for random effects or excluding the 16 patients who had zero pain at baseline, no baseline pain score

recorded, or no post-randomization pain score recorded (Model 2 or 3), the mixed-effects analyses gave similar results (Table R2-2). Including sites in the model made little change on the results.

Table R2-2. Differences (0.4% NTG minus placebo) in the rate of change of average pain score over weeks (Reviewer's Analysis, using quadratic model)

	NTG (N=74)	Placebo (N=75)	Model 1		Model 2		Model 3	
	N	n	Diff	p-value	Diff	p-value	Diff	p-value
Day 7	65	72	-0.22	0.014	-0.23	0.008	-0.24	0.009
Day 14	62	72	-0.16	0.053	-0.19	0.031	-0.18	0.031
Day 21	59	69	-0.10	0.20	-0.12	0.12	-0.13	0.11
Day 28	57	69	-0.045	0.56	-0.067	0.40	-0.076	0.35
Day 35	57	67	0.011	0.89	-0.011	0.89	-0.021	0.80
Day 42	56	63	0.068	0.42	0.045	0.60	0.033	0.71
Day 49	53	67	0.12	0.17	0.10	0.27	0.088	0.35
Day 55	46	63	0.18	0.068	0.16	0.11	0.14	0.17

n= number of patients having average pain score
Diff = difference in the rate of change of average pain score
Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual
Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual
Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain
Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Worst Pain and Defecation Pain

Analyses of worst pain and defecation pain showed a similar pattern as the average pain intensity did; see Tables R2-3, R2-4 and R2-5.

Table R2-3. Slope of change in worst pain and defecation pain over time
(Reviewer's analysis, using linear model[#])

	Mean slope	Nominal p-value*
Worst Pain		
Placebo (N=75)	-0.51	---
0.2% NTG (N=70)	-0.59	0.44
0.4% NTG (N=74)	-0.63	0.21
Defecation Pain		
Placebo (N=75)	-0.45	---
0.2% NTG (N=70)	-0.60	0.12
0.4% NTG (N=74)	-0.57	0.19

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

Table R2-4. Differences (0.4% NTG minus placebo) in the rate of change of worst pain score over weeks (Reviewer's Analysis, using quadratic model)

	NTG (N=74)	Placebo (N=75)	Model 1		Model 2		Model 3	
	n	n	Diff	p-value	Diff	p-value	Diff	p-value
Day 7	65	72	-0.25	0.010	-0.25	0.012	-0.26	0.009
Day 14	62	72	-0.19	0.035	-0.19	0.042	-0.20	0.030
Day 21	59	69	-0.13	0.13	-0.12	0.16	-0.14	0.11
Day 28	57	69	-0.068	0.42	-0.062	0.47	-0.081	0.36
Day 35	57	67	-0.007	0.94	-0.000	1.00	-0.020	0.83
Day 42	56	63	0.055	0.56	0.062	0.51	0.041	0.67
Day 49	53	67	0.12	0.25	0.12	0.23	0.10	0.33
Day 56	46	63	0.18	0.11	0.19	0.10	0.16	0.16

n= number of patients having worst pain score
Diff = difference in the rate of change of worst pain score
Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual
Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual
Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain
Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Table R2-5. Differences (0.4% NTG minus placebo) in the rate of change of defecation pain score over weeks (Reviewer's Analysis, using quadratic model)

	NTG (N=74)	Placebo (N=75)	Model 1		Model 2		Model 3	
	n	n	Diff	p-value	Diff	p-value	Diff	p-value
Day 7	65	72	-0.21	0.028	-0.18	0.062	-0.22	0.027
Day 14	62	72	-0.17	0.060	-0.14	0.13	-0.18	0.054
Day 21	59	69	-0.13	0.14	-0.096	0.27	-0.14	0.12
Day 28	57	69	-0.086	0.32	-0.053	0.54	-0.098	0.28
Day 35	57	67	-0.043	0.63	-0.010	0.91	-0.056	0.54
Day 42	56	63	0.0005	1.00	0.034	0.72	-0.014	0.89
Day 49	53	67	0.044	0.67	0.077	0.45	0.028	0.79
Day 56	46	63	0.087	0.44	0.12	0.28	0.070	0.54

n= number of patients having worst pain score
Diff = difference in the rate of change of worst pain score
Model 1: quadratic model with unstructured covariance for random effects and simple covariance for the residual
Model 2: quadratic model with simple covariance for random effects and simple covariance for the residual
Model 3: Model 2 plus excluding the 16 patients with zero pain at baseline, no baseline pain, or no post-randomization pain
Quadratic model contains intercept, days, days*days, treatment*days, treatment*days*days with intercept and days being random effects

Effect of Dropouts

The 0.4% NTG group had a greater percent of the patients who did not complete the pain study compared to placebo (11% for placebo and 24% for 0.4% NTG). Most of the 0.4% NTG group dropped out because of headache compared to placebo. This difference might have an impact on the interpretation of the statistical results from both LOCF analysis and mixed-effects analysis. If anal pain perception is independent of headache perception, then both LOCF analysis and mixed-effects analysis may be valid in

the sense that statistical significance based on p-values can be correctly interpreted. If that is not the case, the p-values of both LOCF analysis and mixed-effects analysis may be biased in either direction for assessing statistical significance. If the patients dropping out of the study because of headache had worsening pain, then the degree of the quadratic trend for the 0.4% NTG group might be greater than that the current data showed. Consequently, this NTG group might show a much worse trend than the placebo group in the later weeks.

Last Available Visit Analysis

Average pain

The last available visit analysis of average pain can be performed only on 205 patients due to exclusion of 14 patients with no baseline average pain or with no post randomization pain data. As in Table R2-6, there was virtually no difference between treatment groups in mean change from baseline of last available visit average pain. Excluding the two placebo patients with zero baseline average pain had little change of the result.

Table R2-6. Mean change in last available visit daily average pain from baseline (Reviewer's analysis)

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

* adjusted for baseline daily average pain
$ NTG bid vs. placebo bid, based on mean change
# NTG bid vs. placebo bid, based on adjusted mean change

Worst pain and defecation pain

There was no significant difference between the treatment groups with respect to change from baseline to last available visit worst pain or defecation pain (Table R2-7).

Table R2-7. Mean change baseline to last available visit: worst pain and defecation pain (Reviewer's analysis)

	Baseline Mean	Mean change	Nominal p-value[$]	Adj. mean change*	Nominal p-value[#]
Worst Pain					
0.2% NTG BID	52.1	-35.3	0.70	-35.4	0.70
0.4% NTG BID	53.0	-35.4	0.69	-34.8	0.82
Placebo BID	51.4	-33.3	---	-33.9	---
Defecation Pain					
0.2% NTG BID	46.0	-33.6	0.60	-34.8	0.17
0.4% NTG BID	47.4	-34.2	0.53	-34.2	0.23
Placebo BID	48.6	-30.8	---	-29.8	---

* adjusted for baseline daily average pain
$ NTG bid vs. placebo bid, based on mean change
# NTG bid vs. placebo bid, based on adjusted mean change

Percent of patients with zero pain at last visit

NTG 0.4% BID group appeared to have fewest patients that had zero average or worst pain at last visit; see Table R2-8.

Table R2-8. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

	Zero average pain	Zero worst pain	Zero defecation pain
0.2% NTG BID	14/68 (21%)	14/68 (21%)	13/63 (21%)
0.4% NTG BID	8/72 (11%)	10/68 (14%)	13/62 (21%)
Placebo BID	14/71 (20%)	14/71 (20%)	12/67 (18%)

Complete Pain Relief

The number of patients in each group who had pain (average) at baseline and were completely relieved (zero average pain) at last visit. NTG 0.4% BID group appeared to have fewest patients that had zero average or worst pain at last visit; see Table R2-9.

Table R2-9. Number (%) of patients who had pain at baseline but zero pain at last visit (Reviewer's analysis)

	Zero average pain	Zero worst pain	Zero defecation pain
0.2% NTG BID	14/68 (21%)	14/68 (21%)	13/63 (21%)
0.4% NTG BID	8/72 (11%)	10/68 (14%)	13/62 (21%)
Placebo BID	14/71 (20%)	14/71 (20%)	12/67 (18%)

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

II. ANAL FISSURE HEALING

For the secondary efficacy endpoint of anal fissure healing there was no benefit versus placebo noted in either the percentage of patients healed:

Comparison of Proportion of Subjects With Healed Anal Fissure in Each Treatment Group
Intent-to-Treat Population

	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)	P-value
Number (%) of Subjects with Healed Fissure	44(59%)	41(59%)	40(54%)	0.571 [p = 0.587 (W/ controlling center)]

or the time to healing:

Time to Healing of Anal Fissures-Results of Cox Regression: Intent-to-Treat Population

Prognostic Variables	Regression Coefficients (S.E.)	P-value
0.2% NTG Ointment vs. Placebo	0.0004604 (0.22357)	0.9984
0.4% NTG Ointment vs. Placebo	-0.07905 (0.22275)-	0.7227

III. QUALITY OF LIFE

No benefit of drug to placebo in quality of life assessments were found:

Table 17: Gastrointestinal Quality of Life Index-Total Score by Study Day: Intent-to-Treat Population (Study NTG 00-02-01)

Study Day	Statistics	Placebo (N=75)	0.2% NTG Ointment (N=70)	0.4% NTG Ointment (N=74)
Day 1	N	75	70	73
	Mean (SD)	109.0 (24.47)	114.9 (18.06)	112.9 (20.08)
	Min. - Max.	24-140	62-141	57-142
	Median	116.0	119.5	122.0
	Missing	0	0	1
Day 14	N	73	66	65
	Mean (SD)	116.4 (20.77)	119.7 (17.15)	117.7 (14.72)
	Min. - Max.	60-144	72-141	82-139
	Median	124.0	124.0	121.0
	Missing	2	4	9
Day 28	N	69	59	62
	Mean (SD)	118.2 (19.47)	125.1 (14.08)	121.3 (16.22)
	Min. - Max.	65-144	80-144	68-140
	Median	126.0	128.0	126.0
	Missing	6	11	12
Day 56	N	66	57	55
	Mean (SD)	121.3 (22.66)	126.8 (14.04)	125.8 (15.43)
	Min. - Max.	63-144	86-144	86-144
	Median	131.5	131.0	132.0
	Missing	9	13	19

Total score could range for 0 (least desirable score) to 144 (most desirable score).

SAFETY

No deaths occurred. The sponsor stated that 23 patients withdrew for adverse events and provided the following table.

Table 27: Subjects Who Discontinued Due to Adverse Events: Safety Population (Study NTG 00-02-01)

Subject No.	Age (Yr)	Sex	Preferred Term	Day of Onset[a]	Severity	Relationship to Study Drug	Duration (Days)	Day of Discontinuation
Treatment: Placebo								
007-111	33	Female	Headache[b]	1	Severe	Related	5	5
007-123	19	Female	Pain[b,c]	22	Moderate	None	22	23
015-106	46	Male	Hepatitis C[b,c]	3	Moderate	None	Ongoing	61
			Hemorrhage Rectal	42	Mild	None	3	61
			Pain Abdominal	43	Moderate	None	5	61
022-107	44	Male	Asthenia[b]	13	Moderate	Possibly	1	13
			Libido Decreased[b]	13	Severe	Possibly	1	13
			Pruritus[b]	13	Moderate	Possibly	1	13
028-104	48	Female	Allergic Reaction[b]	7	Moderate	None	9	15
Treatment: 0.2% NTG Ointment								
007-110	34	Female	Headache[b]	1	Severe	Related	8	8
008-108	35	Female	Headache[b]	1	Severe	Related	3	44
009-110	41	Male	Vasodilator	1	Mild	Related	1	2
			Headache[b,c]	1	Severe	Related	1	2
			Headache	1	Mild	Related	1	2
010-112	36	Male	Headache[b]	1	Severe	Related	6	6
010-117	36	Male	Headache[b]	1	Severe	Related	8	8
028-110	53	Female	Constipation[b]	6	Mild	None	7	12
			Pain[b]	6	Mild	Related	7	12
Treatment: 0.4% NTG Ointment								
001-101	60	Female	Headache	1	Moderate	Related	1	57
			Headache	14	Moderate	Possibly	1	57
			Pain[b]	52	Mild	Possibly	1	57
			Hemorrhage Rectal	56	Mild	None	1	57
			Pain	56	Mild	Possibly	1	57
002-104	53	Female	Headache	1	Moderate	Related	6	57
			Headache[b]	7	Mild	Related	41	57
			Cough Increased	24	Mild	None	3	57
			Sinusitis	24	Mild	None	3	57
			Dizziness	28	Mild	Possibly	20	57
			Twitching	28	Mild	Possibly	20	57
			Thinking Abnormal[b]	32	Moderate	Possibly	16	57
007-107	19	Female	Headache[b]	1	Severe	Related	11	15
			Vaginitis	1	Mild	None	5	15
007-108	38	Male	Headache[b]	1	Moderate	Related	8	8
008-101	55	Male	Headache[b]	1	Severe	Possibly	6	8
009-105	25	Female	Vertigo[b]	2	Mild	Related	12	15
			Nausea[b]	3	Mild	Related	11	15
			Vomit[b]	3	Mild	Related	11	15
			Tachycardia[b]	7	Moderate	Related	7	15
010-106	25	Male	Headache[b]	1	Moderate	Related	40	40
010-115	29	Male	Headache[b]	1	Severe	Related	3	3
015-105	28	Female	Headache	1	Severe	Related	12	15
			Rectal Disorder[b]	9	Moderate	None	Ongoing	15
016-103	71	Female	Headache[b]	1	Severe	Related	2	2
			Nausea[b]	1	Moderate	Possibly	2	2
			Pain[b]	1	Moderate	Possibly	2	2
021-101	52	Male	Headache[b]	1	Mild	Related	25	29
028-109	40	Male	Dizziness[b]	2	Mild	Related	3	4

[a] Relative to first dose of study drug (Day 1).
[b] Subject discontinued therapy due to this adverse event.
[c] Serious adverse event.

The sponsor noted that only 1 of 6 placebo withdrew for headache compared to 5 of 6 intermediate NTG dose and 8 of 12 high dose NTG ointment patients. As previously noted there were 11 placebo, 17 0.2% NTG ointment patients and 21 0.4% NTG ointment patients who terminated early. Review of the case reports shows that many not noted by the sponsor terminated early for headache. For example patient 005-114 (0.2% NTG) terminated for severe headaches as did patients 007-102 and 008-104 (0.4% NTG). Headache was present as an adverse event in 3 other 0.2% NTG patients and 4 other 0.4% NTG patients. This analysis leads to the finding that in this study of those who terminated early 1 out of 11 (9%) placebo patients, 9 out of 17 (53%) 0.2% NTG, and 16 out of 21(76%) 0.4% NTG patients had headache associated with that early withdrawal. Of those randomized 11 of 73 (15%) placebo patients, 17 of 78 (22%) of 0.2% NTG patents, and 21 of 78 (27%) of 0.4% NTG patients did not complete the study. It should also be noted that while patient 019-108 (0.2%NTG) and patient 008-114 (0.4% NTG) withdrew for "patient choice", both had elevated liver enzymes at termination. Therefore it appears that treatment with NTG ointment to relieve anal pain associated with anal fissures is not well tolerated and is associated with a high incidence of headache severe enough to lead to discontinuation of that treatment. While no orthostatic hypotension or interaction with drugs such as sildenafil (use was an exclusion criterion) was found in this study, these would be concerns with any nitroglycerin product.

According to the sponsor, the incidence of headache in each randomized group was:

Table 25: Incidence of Adverse Event of Headache: Safety Population (Study NTG 00-02-01)

	Placebo (N=78)	0.2% NTG Ointment (N=73)	0.4% NTG Ointment (N=78)
Subjects Reporting Headache	14 (17.95%)	31 (42.47%)	40 (51.28%)
Subjects Reporting Treatment-Related Headache	14 (17.95%)	30 (41.10%)	40 (51.28%)
Subjects Reporting Severe Headache	1 (1.28%)	7 (9.59%)	9 (11.54%)
Subjects Treated with Concomitant Medication for Headache	8 (10.26%)	11 (15.07%)	16 (20.51%)
Subjects Withdrawn Due to Headache	1 (1.28%)	5 (6.85%)	8 (10.26%)

Cross-reference: Appendix 3.7.1

Headache is clearly more prevalent in the NTG ointment treated patients versus those on placebo with some suggestion that an increased incidence of headache occurs with increasing NTG dose.
A listing of frequently reported adverse events were provided by the sponsor as follows:

Table 22: Incidence of Frequently Reported (≥1%) Adverse Events[a] by Body System and Preferred Term – Possibly-Related or Related to Study Drug: Safety Population (Study NTG 00-02-01)

	Placebo (N=78)		0.2% NTG Ointment (N=73)		0.4% NTG Ointment (N=78)	
	n	(%)	n	(%)	n	(%)
Subjects With Adverse Events						
Any Event	18	(23.08)	33	(45.21)	48	(61.54)
Body as a Whole						
Any Event	16	(20.51)	32	(43.84)	41	(52.56)
Abscess					1	(1.28)
Asthenia	1	(1.28)				
Headache	14	(17.95)	30	(41.10)	40	(51.28)
Pain	1	(1.28)	1	(1.37)	4	(5.13)
Pain Abdominal			1	(1.37)		
Cardiovascular System						
Any Event			2	(2.74)	5	(6.41)
Migraine					1	(1.28)
Tachycardia			1	(1.37)	2	(2.56)
Vasodilator			1	(1.37)	2	(2.56)
Digestive System						
Any Event	3	(3.85)	5	(6.85)	6	(7.69)
Diarrhea	1	(1.28)	2	(2.74)		
Flatulence	1	(1.28)	1	(1.37)		
Hemorrhage Rectal	2	(2.56)			2	(2.56)
Nausea			1	(1.37)	5	(6.41)
Rectal Disorder	1	(1.28)	1	(1.37)		
Vomit					2	(2.56)
Metabolic and Nutritional Disorders						
Any Event			1	(1.37)		
Phosphatase Alkaline Increase			1	(1.37)		
SGOT Increased			1	(1.37)		
SGPT Increased			1	(1.37)		
Musculoskeletal System						
Any Event					1	(1.28)
Twitching					1	(1.28)
Nervous System						
Any Event	1	(1.28)	1	(1.37)	12	(15.38)
Amnesia					1	(1.28)
Dizziness			1	(1.37)	8	(10.26)
Intracranial Hypertension					1	(1.28)
Libido Decreased	1	(1.28)				
Nervousness					1	(1.28)
Thinking Abnormal					1	(1.28)
Vertigo					2	(2.56)
Skin and Appendages						
Any Event	3	(3.85)				
Pruritis	1	(1.28)				
Pruritus	1	(1.28)				
Rash	1	(1.28)				
Special Senses						
Any Event			1	(1.37)		
Pain Ear			1	(1.37)		
Urogenital System						
Any Event					1	(1.28)
Urination Frequency					1	(1.28)

[a] Number and percent of subjects reporting one or more adverse events.

PUBLISHED CLINICAL STUDIES

Five placebo controlled published studies, which evaluated NTG ointment for the relief of anal pain were submitted. These are:

1. Altomare et al, Dis. Colon Rectum 2000; 43: 174-181.
2. Carapeti et al, GUT, 1999; 44; 727-730.
3. Kennedy et al, Dis. Colon Rectum, 1999, 42; 1000-1006.
4. Lund and Scholefield, Lancet, 1997, 349, 11-14.
5. Tander et al, J. Pediatric Surgery, 1999, 34; 1810-1812.

1. Altomare et al.

This study was a multicenter, randomized, placebo-controlled study to compare chronic anal fissure healing with NTG or placebo. Pain relief and safety were also evaluated. Pain on defecation was recorded on a 0-10 scale, zero being no pain. 132 patients were randomized to 0.2% glycerol trinitrate or placebo BID for 4 weeks. Of the 132 randomized patients, 13 dropped out (9 on active, 4 on placebo), leaving 119 to be analyzed.

Anal fissure healing occurred in 29 (49%) NTG treated patients and 31 (52%) of the placebo treated patients. Pain scores decreased from 7.56 ± 1.8 to 4.13 ± 2.7 in the NTG group and from 6.9 ± 2.3 to 3.97 ± 2.8 in the placebo group. While change from baseline was significant in both groups, no statistical difference was found between groups. Pain relief was significantly greater in patients who healed versus those who did not.

Concerning safety, headache was noted in 34% of the NTG patients versus 8% of the placebo patients. Orthostatic hypotension was documented in 4 of the NTG treated patients.

2. Carapeti et al.

This was a randomized, double-blind study of two doses of glyceral trinitrate ointment and placebo to assess healing and pain relief in patients with chronic anal fissure. 70 patients were randomized to placebo, 0.2% NTG TID, and 0.2% TID increasing by 0.1% to a maximum concentration of 0.6% GTN. Treatment was to be continued for 8 weeks followed by a 2 week off treatment observation period. Pain was recorded on daily diary cards using a 0-10 scale. 24 patients were randomized to each of the active groups, while 22 were assigned to placebo.

After 10 weeks the anal fissures had healed I 32% of the placebo patients, compared to 65% and 70% of those on 2% and escalating dose NTG. The comparison of placebo versus both active groups gave a $p=0.008$ by Fisher's Exact test. Pain reduction occurred in all groups, but there were no significant differences in pain relief comparing placebo to the actives ($p=0.4$).

Headache occurred in 72% of patients on NTG and in 27% of those on placebo ($p<0.001$), but no significant difference comparing the rate of headache in the actives. No data on orthostatic hypotension or BP effect are provided.

3. Kennedy et al.

This was a randomized, double-blind study of 0.2% NTG ointment versus placebo for 4 weeks in 43 patients with anal fissures severe enough to warrant sphincterotomy. The primary endpoints were fissure healing and pain relief. 24 patients received NTG and 19 placebo, and 39 patients completed treatment (4 patients discontinued NTG because of headache). At the end of treatment 46% of the fissures had healed in the NTG group compared to 16% in the placebo group (p=0.001). Pain was significantly reduced from baseline in both NTG and placebo treated patients, but no between group significant differences are mentioned for this parameter. Headache was noted in 7 NTG treated patients, and, as mentioned, was severe enough to cause discontinuation of treatment by 4 NTG patients.

4. Lund and Scholefield.

This was a randomized double-blind study of 80 patients with anal fissures to compare 0.2% NTG ointment versus placebo BID for 8 weeks in healing the fissures and relieving pain. 38 patients received NTG as allocated, and 40 received placebo. Healing occurred in 68% of those who received NTG versus 8% of those on placebo ($p<0.001$). At 2 weeks pain was significantly relieved in both treatment groups, but it was noted that the pain relief was sustained in those receiving NTG, not those on placebo. At 8 weeks pain relief from baseline was reported to be significantly greater in the NTG group compared to placebo. Headache occurred in 22 NTG treated patients versus 7 in the placebo group ($p<0.05$), and 1 patient on NTG withdrew due to headache.

5. Tander et al.

This was a randomized, double-blind single center study of 0.2% NTG ointment, 10% lidocain ointment or placebo BID for 8 weeks in 62 children with anal fissure to assess healing and pain relief. 31 patients received NTG, 14 lidocain, and 17 placebo. Results were provided in the following chart:

Table 2. Summary of Results

		Total Healing of the Fissure, (%)		Relief of Symptoms, (%)	
	No.	(+) Responders	(−) Nonresponders	(+)	(−)
Group I (GTN)	31	26 (83.87)*	5 (16.13)*	29 (93.55)*	2 (6.45)*
Group II (lidocaine)	14	3 (21.43)†	11 (78.57)†	7 (50)†	7 (50)†
Group III (placebo)	17	6 (35.29)	11 (64.71)	6 (35.29)	11 (64.71)
Total	62	35 (56.45)	27 (45.55)	43 (69.35)	19 (30.65)

*$P < .001$ GTN treatment compared with lidocaine and placebo treatments.
†$P > .05$ Lidocaine treatment compared with placebo treatment.

No patient experienced headache during the trial. One NTG treated patient had transient fecal incontinence.

The publications do not consistently demonstrate a benefit of NTG ointment compared to placebo in the healing or relief of pain of anal fissures. The finding of a benefit of NTG ointment to heal anal fissures is not confirmed by the sponsor's studies.

VI: DISCUSSION AND RECOMMENDATIONS

The sponsor provided two clinical studies to demonstrate efficacy. The first study (NTG 98-02-01) examined a dose range from 0.75 mg to 4.5 mg daily for 56 days. The primary endpoint was anal fissure healing, and presumably the duration of treatment was thought to be sufficient to heal. However, no significant benefit on healing was found. A secondary endpoint was relief of anal fissure pain (average pain, worst pain, and defecation pain), but pain was not required at entrance. Noting that it was likely that there would be missing pain data, the sponsor selected a mixed effects model to analyze the pain data available. No specific model was pre-specified, and, rather than analyze per randomized group, the sponsor post-hoc pooled the active dose groups in their analysis. Given the surprising null result on anal fissure healing and a possible statistical active drug effect on anal fissure pain, the sponsor performed a second study (NTG-00-02-01) using relief of anal fissure pain as the primary endpoint. The doses of active were limited to 0.75 mg and 1.5 mg given daily in divided doses for 56 days. Healing and quality of life were secondary endpoints. No difference of active drug versus placebo in the last available observation analysis or in those with no pain at the end of 56 days of therapy was found. No benefit of anal fissure healing or quality of life was found.

A mixed effects analysis to evaluate the rate of change over time was pre-specified in the second study, but without details of the model terms to be used. The sponsor using a quadratic term in the model and evaluating the shapes of the curves, found statistically significant difference in linear trend and quadratic trend for the 1.5 mg dose compared to placebo. Dr. Hung, using the linear mixed effects model that was used by the sponsor in the first study to evaluate the rate of change as specified in the protocol, found no significant difference between active drug and placebo.

Since the quadratic model gave somewhat different results, Dr. Hung found that the quadratic model results suggested an early difference in the rate of change, but no sustained difference. If one considered this early difference real and due to active therapy, tachyphylaxis to nitroglycerin might provide a rationale. It is not clear that any early difference in the shape of the curves could be perceived clinically. Even if an early clinical benefit could be established, the lack of a sustained benefit and no difference in total relief of pain at the end of therapy would raise questions of clinical efficacy. Directions for use would be hard to write, since the 56 days of therapy were not needed for any purported benefit. Also undercutting the significance of any difference found was the fact that many patients withdrew from active therapy because of headache. It is unclear what effect headache had on anal pain perception in these patients. It is unclear how a treatment to relieve anal pain can be considered effective if it produces pain such as headache.

What was clear from the sponsor's studies was that NTG ointment was not well tolerated. Of those who withdrew from the active treatment, most did so for headache. A larger number of patients remained in the study, but had headache, often requiring analgesics. More serious adverse reactions, such as postural hypotension and interactions with drugs like sildenafil, were not noted, but remain concerns with any NTG product.

In conclusion, we find that no benefit of NTG ointment to relieve anal pain associated with anal fissures was established by the studies provided. The studies did confirm that the drug was not well tolerated, producing an amount of frequent and severe headache, not acceptable in a drug purported to relieve pain. Consequently we recommend that a not approvable action be taken.

CC: Dr. Throckmorton
Dr. Stockbridge
Dr. Nhi Nguyen
Dr. Anello
Dr. Chi
Mr. Fromm

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/s/

Stephan Fredd
2/26/02 09:50:58 AM
MEDICAL OFFICER

James Hung
2/27/02 10:40:18 AM
BIOMETRICS

George Chi
2/27/02 04:11:11 PM
BIOMETRICS