Cellegesic™ (nitroglycerin ointment) 0.4%
FDA Advisory Committee Meeting

April 25, 2006

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Our Purpose Today

- **Review results of Cellegesic clinical studies**
  - **CP125 03-02-01 (Study 3)**
  - **NTG 98-02-01 (Study 1)**
  - **NTG 00-02-01 (Study 2)**
- **Responses are presented to answer analyses and conclusions of Cardio Renal Division briefing document**
- **Answer any questions or points that the Advisory Committee may have**

Agenda

- **Overview of Phase 1 and Phase 3 Studies**
- **Pathophysiology of Anal Fissure and Clinical Aspects of Diagnosis and Treatment**
- **Overview of Studies and Regulatory History**
- **Safety**
- **Statistical Methods and Analyses**
- **Risk / Benefit**
- **Summary and Conclusions**

Chronic Anal Fissure

- Tear in mucosal lining (anoderm) of the terminal anal canal
-
- Symptoms

  - Severe, often debilitating pain

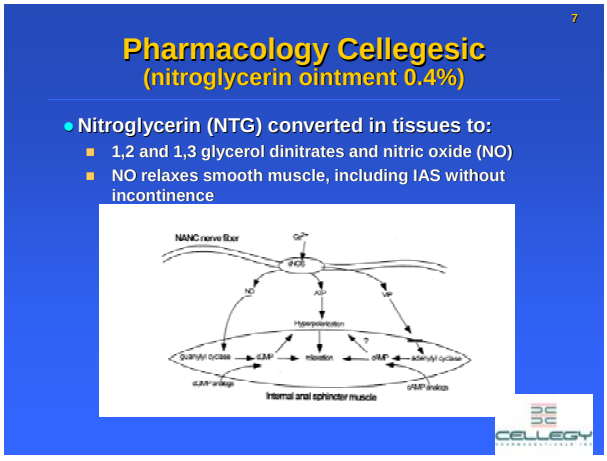
    - Pain secondary to increased tone, spasm internal anal sphincter (IAS)
    -
  - Bleeding

Chronic Anal Fissure

- Cellegy has developed Cellegesic™ nitroglycerin ointment 0.4% for the acceleration of relief of the pain associated with chronic anal fissure
-
- Evidence of efficacy and safety from one phase 1 and three phase 3 studies
-
- No medical treatment specifically approved for chronic anal fissure pain in U.S.
- Current treatment
  - Incidence of incontinence to flatus post-operatively up to 35%, impaired control of feces up to 22% of patients

Pharmacology Cellegesic (nitroglycerin ointment 0.4%)

- Nitroglycerin (NTG) converted in tissues to:
  - 1,2 and 1,3 glycerol dinitrates and nitric oxide (NO)
  - NO relaxes smooth muscle, including IAS without incontinence



Pharmacology Cellegesic (nitroglycerin ointment 0.4%)

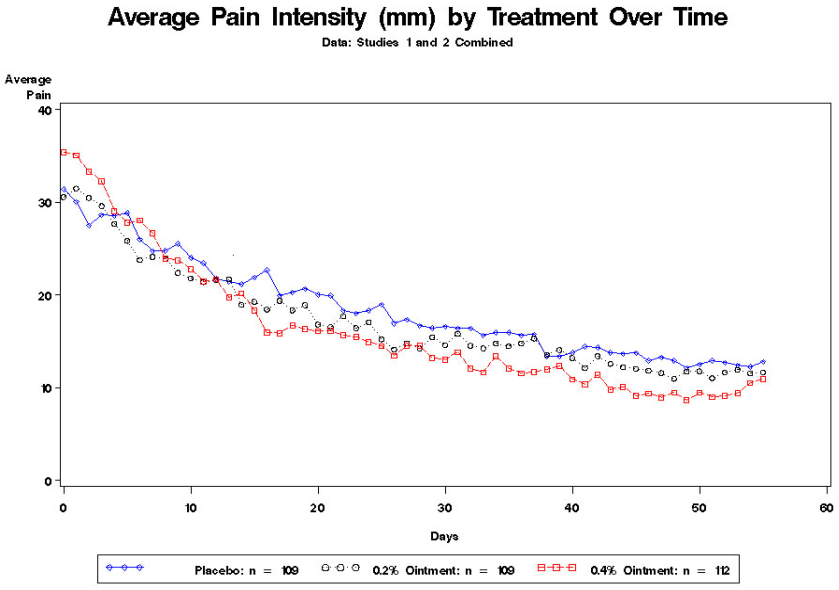
- **IAS does not develop NTG tolerance**
  - **Wang and Fung study in rats** (Wang EQ, Soda DM, Fung HL, Nitroglycerin-induced relaxation of anorectal smooth muscle: evidence for the apparent lack of tolerance development in the anaesthetized rat. Br J Pharmacol, 2001;134:418-424)
  - **Ciccaglione study in patients with fissure** (Ciccaglione AF, Gross L, Cappello G, et al., Short- and long-term effect of glyceryl trinitrate (GTN) ointment 0.2% and 2% on anal canal pressure in patients with chronic anal fissures. Dig Dis Sci, 2000;45:2352-2356)

- **Bioavailability study 98-02-02**
  - **Mean absolute bioavailability 375mg Cellegesic NTG ointment 0.2% (.75 mg NTG) – approximately 50%**

Dose Response
Data from Studies 1 and 2

- **For 21 days, dose by day interaction (p < .0039), smallest effective dose Cellegesic 0.4% (p < .0040)**

- **For 56 days dose by linear time interaction (p < .0001), smallest effective dose Cellegesic 0.4% (p < .0001)**

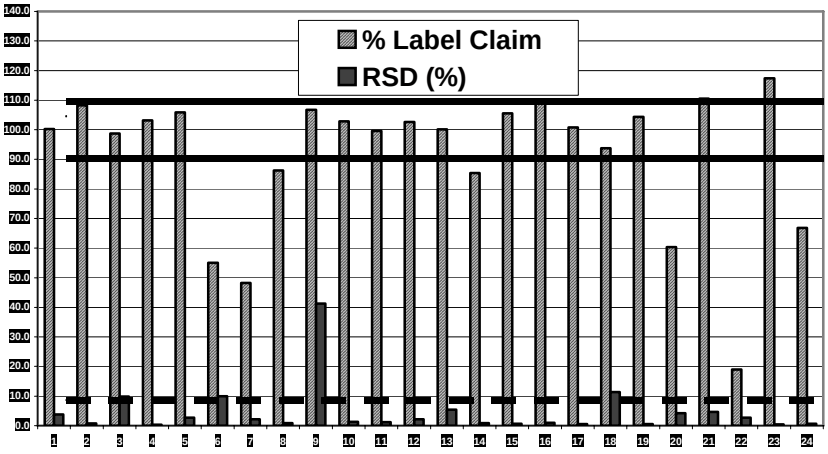


Incidence Anal Fissure

- ***Verispan Physician Drug and Diagnosis Audit*** **(October 2003 – September 2004)**
  - **765,000 patients**
  - **1,130,000 visits**
  - **84,000 uses recorded for NTG ointment**

- **Quality of extemporaneously compounded NTG ointment is poor**

Quality of Extemporaneously Compounded Nitroglycerin Ointment



Michael Abel, M.D., F.A.C.S, F.A.S.C.R.S

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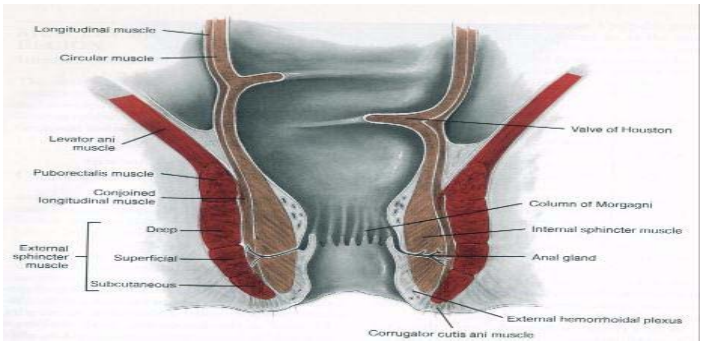
Pathophysiology and Clinical Aspects of Diagnosis and Treatment of Chronic Anal Fissures

Cellegesic™ (nitroglycerin ointment) 0.4%



Pathophysiology Anal Fissure

- **Tear in distal anal canal anoderm**
  - **Benign - approximately same in men and women, and in age groups**
- **Etiology unknown – may be due to decrease in NO synthase activity + inspissated feces**
- **Primarily in posterior midline in distribution of inferior rectal artery**
  - **Decreased blood supply anoderm**
- **Cardinal symptom of severe, debilitating pain is what brings patient to my office**
  - **Due primarily to increased tone and spasm of IAS**
  - **Not correlated with degree of tissue damage**

Pain Relief

- **Pain relief is what patient wants**
- **Pain relief and healing not necessarily concordant**

Physical Findings of Chronic Anal Fissure

- **Sentinel pile**
- **Indurated edges**
- **Visible IAS fibers**
- **Hypertrophied papilla**

Anal Fissure

Photo of Anal Fissure

Current Treatment Options

Traditional treatment

- **Increase fiber in diet, stool softeners, antiinflammatory drugs, local anesthetics**

Surgery

- **Lateral internal sphincterotomy, anal stretch, posterior internal sphincterotomy with advancement flap**
  - **Post-operative incontinence up to 35%**
  - **Significant cost to health care system**

Medical

- **No medical treatment specifically approved for chronic anal fissure pain in U.S.**

- **Extemporaneously compounded nitroglycerin ointment is used**

Medical Treatment

Nitroglycerin metabolized in tissue to nitric oxide (NO)
NO relaxes the IAS (Loder et al) and increases anodermal blood flow (Shouten et al)

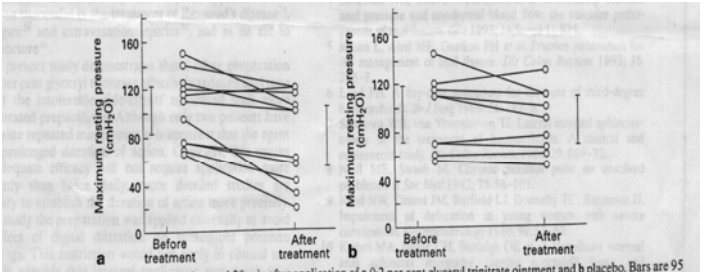


Fig. 3 Maximum resting pressure before and 20 min after application of a 0·2 per cent glyceryl trinitrate ointment and b placebo. Bars are 95 per cent confidence intervals. $P = 0{\cdot}0024$ (pressure before *versus* pressure after application of glyceryl trinitrate), $P = 0{\cdot}033$ (change in pressure after application of glyceryl trinitrate *versus* change in placebo group); Student's *t* test

These two effects are the basis for treatment of anal fissure with nitroglycerin ointment

Conclusions

- **A trial of nitroglycerin ointment before considering surgery has been recommended by:**
  - **American Gastroenterological Association**
  - **American Society of Colon and Rectal Surgeons Standards Practice Force**
- **My colleagues and I successfully use extemporaneously compounded NTG ointment**
- **Need for approved product**

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Overview of Studies and Regulatory History
Cellegesic™ (nitroglycerin ointment) 0.4%

FDA Issues

- **Effect size**
- **Drop-outs**
- **Headache**
- **Acetaminophen effect on anal fissure pain**
- **Dose response**
- **Quadratic term not pre-specified in Study 2**

Primary Outcome Measure

- **Rate of change in the 24-hour average pain intensity (recorded Daily as VAS in diary),**

  NOT DIFFERENCE BETWEEN ACTIVE AND PLACEBO AT ANY ONE TIME POINT

Secondary Outcome Measures

- **Rate of change in defecation pain intensity (recorded daily as VAS in diary)**

Method of Analysis

- **Mixed-effects regression model using all available data**
- **A statistically significant result is evidence of acceleration of pain relief provided by Cellegesic over placebo**

Phase 3 Studies

NTG 98-02-01 (Study 1)

- **Double blind, randomized, parallel groups, placebo controlled**
- **Entry criteria: anal pain and or bleeding for 30 days and fissure on physical examination**
- **Eight arms**
  - **375 mg Cellegesic NTG ointment placebo, 0.1% (0.375 mg NTG), 0.2% (0.75 mg NTG), 0.4% (1.5 mg NTG)**
  - **applied intra-anally b.i.d. and t.i.d. for 56 days or until fissure healed**

Method of Application

Phase 3 Studies

NTG 98-02-01 (Study 1)

- **Primary endpoint: complete healing of fissure (blinded observer)**
- **Secondary endpoints (not post-hoc):**
  - **rate of change in the 24-hour average pain intensity**
  - **rate of change in defecation pain intensity**

Phase 3 Studies

NTG 98-02-01 (Study 1): Study Results

- **289 subjects**
- **Healing approximately 50% but Cellegesic not significantly different from placebo**
- **Rate of change in 24-hour average pain intensity for Cellegesic 0.4% group significantly better than placebo (p <.0001)**

Regulatory History

Post-Study 1 discussion following evaluation of results

Division (Dr. Lipicky) agreed:

- **Pain is an acceptable primary endpoint**
- **Other modifications**
  - **all subjects required to use fiber and could take sitz baths (standard of care)**
  - **subjects to continue clinical trial material for 56 days even if healed, pain reduced/eliminated**
  - **purpose of second trial was to confirm statistically significant pain reduction**
- **Only one additional, confirmatory trial required**

Phase 3 Studies

NTG 00-02-01 (Study 2)

- **Double blind, randomized, parallel groups, placebo controlled**
- **Entry criteria: anal pain at least 3 times/week and or bleeding for 30 days and fissure on physical examination**
- **Three arms**
  - **375 mg Cellegesic NTG ointment placebo, 0.2% (0.75 mg NTG), 0.4% (1.5mg NTG)**
  - **applied intra-anally bid for 56 days irrespective of healing**
  - **subjects provided psyllium (Metamucil®) 3.4 gm bid**

Phase 3 Studies

NTG 00-02-01 (Study 2)

- **Primary endpoint: rate of change in the 24-hour average pain intensity (mixed-effects regression model, not difference between active and placebo on any one day)**
- **Secondary endpoints:**
  - **Rate of change in defecation pain intensity (mixed-effects regression model)**
  - **Complete fissure healing**

Phase 3 Studies

NTG 00-02-01 (Study 2): Study Results

- **219 Subjects**
- **Rate of change in pain intensity in Cellegesic NTG ointment 0.4% group better than placebo ($p < .039$)**
  - **Defecation pain ($p<.04$)**
  - **Percentage healed (54% Cellegesic, 59% Placebo)**

Regulatory History

NTG 00-02-01 (Study 2)

- **Mixed effects regression model included a quadratic term**
- **FDA would not accept inclusion of quadratic term since not pre-specified in protocol or statistical analysis plan**
- **MHRA assessors accepted the quadratic term analysis approving Cellegesic in UK based on Studies 1 and 2**
- **Now also approved in 19 other European countries based on Studies 1, 2 and 3**

Regulatory History

Post-Study 2 discussion following evaluation of results

- **Cellegy met with Division and agreed on basis for Study 3 under a special protocol assessment**
- **Primary endpoint would be rate of change in the 24-hour average pain intensity during the first 21 days of treatment**
- **Drop-outs due to NTG-induced headache would have last observation carried forward (LOCF) rather than standard mixed-effects regression model**

Nitroglycerin Headache Definition in Study 3 Protocol

- **NTG headache defined in protocol so appropriate drop-outs could be determined**
- **FDA agreed 3 subjects dropped out for NTG induced headache (March 31, 2005 Meeting Minutes)**

Phase 3 Studies

CP125 03-02-01 (Study 3)

- **Double blind, randomized, parallel groups, placebo controlled**
- **Entry Criteria: anal pain for 30 days**
  - **¡Ã 35 mm for the two days prior to enrollment**
  - **moderate or severe defecation pain for the two days prior to enrollment**
- **Physical examination: fissure including presence of sentinel pile**
- **Two arms**
  - **375 mg Cellegesic nitroglycerin ointment – placebo, 0.4% (1.5 mg NTG) applied intra-anally every 12 hours for 56 days irrespective of healing**
- **Fiber and sitz baths allowed only if used in week prior to entry**

Phase 3 Studies

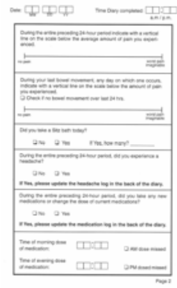
CP125 03-02-01 (Study 3): Study Results

Efficacy Cellegesic nitroglycerin ointment relative to placebo

24-hour average pain 21 days treatment	**p<.0309**
24-hour average pain 56 days treatment	**p<.0167**
defecation pain 21 days treatment	**p<.0504**
defecation pain 56 days treatment	**p<.0211**

Healing

- **Cellegesic NTG ointment** **68.7%**
- **Placebo** **62.9% NS**



PROTOCOL # CP125 03-02-01 **HEADACHE LOG**

Date Started MM/DD/YY	Time Headache Started (circle a.m. or p.m.)	Date Stopped MM/DD/YY	Time Headache Stopped (circle a.m. or p.m.)	Intensity[1] (circle appropriate intensity)	Medications Used (check one)
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No
__/__/__	____ a.m./p.m.	__/__/__	____ a.m./p.m.	1 2 3	❑ Yes ❑ No

[1]**Definitions of Intensity:**
(1) **Mild:** Causing no limitation of usual activities
(2) **Moderate:** Causing some limitation of usual activities
(3) **Severe:** Causing inability to carry out usual activities

Conclusions

- **Study 1 provided evidence that relief of pain, not healing was the appropriate primary endpoint**
  - **Cellegesic nitroglycerin ointment rate of change in the 24-hour average pain relief significantly better than placebo (p<.001)**
- **Analysis Study 2 revealed pain relief was linear for the first 21 days of treatment with Cellegesic nitroglycerin ointment and curvilinear thereafter (p<.0388)**
- **In Study 3 Cellegesic nitroglycerin ointment the rate of change in 24-hour average pain intensity significantly better than placebo over the first 21 days of treatment (p<.0309, p<.05 with LOCF)**

Conclusions

- **Studies 1 and 2 data reanalyzed by the method used in Study 3, through Day 21. In 375 mg 0.4 % Cellegesic ointment every 12 hours treated subjects, the rate of change in the 24-hour average pain intensity was significantly better than placebo in both studies, p<.0063 and p<.0388 respectively**
- **When 0.4% Cellegesic every 12 hour subjects in all studies combined, the rate of change in 24-hour pain intensity was significantly better than placebo p<.0007**

Safety

Cellegesic™ (nitroglycerin ointment) 0.4%

Safety

- **Data from one phase 1 and three phase 3 (double-blind, randomized, placebo-controlled) studies**
  - **375 mg Cellegesic ointment 0.1% (0.375 mg NTG), 0.2% (0.75 mg NTG), 0.4% (1.5 mg NTG) and placebo**
  - **Treatment b.i.d. and t.i.d. for up to 56 consecutive days**

Demographic and Baseline Characteristics

(All Subjects in Completed Phase 3 Studies Evaluable for Safety)

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

Adherence

- **Ointment tubes weighed before dispensing and when returned**
- **Subjects not aware tubes being weighed**
- **Average amount expressed/day/number of days scheduled treatment**

	% scheduled amount
Cellegesic ointment 0.4%	**104.9%**
Placebo	**101.2%**

Subject Disposition

(All Subjects in Completed Phase 3 Studies)

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

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

Frequently Reported Adverse Events

Incidence of Treatment-Emergent Adverse Events ¡Ã 2.0%

	Cellegesic Nitroglycerin Ointment	
	Placebo[a] (N=246)	0.4% b.i.d. (N=206)
Body System Preferred Term	Total Related[d] n (%)	Total Related[d] n (%)
Subjects With Any Adverse Events	73 (29.7)	131 (63.6)
Nervous system disorders	56 (22.8)	126 (61.2)
Headache NOS	55 (22.4)	118 (57.3)
Dizziness	0	9 (4.4)
Gastrointestinal disorders	18 (7.3)	13 (6.3)
Nausea	2 (0.8)	9 (4.4)
Anal discomfort	4 (1.6)	1 (0.5)
Diarrhea NOS	1 (0.4)	0
Hemorrhoids	0	0
Infections and infestations	0	1 (0.5)
Influenza	0	0
Upper respiratory tract infection NOS	0	0
Skin and subcutaneous tissue disorders	6 (2.4)	1 (0.5)
Pruritus NOS	5 (2.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0	0
Pharyngitis	0	0

[a]Includes all subjects receiving placebo (b.i.d. or t.i.d.)
[d]Subjects having Total Related (Possibly Related or Related) adverse events in the treatment group.

Frequently Reported Adverse Events

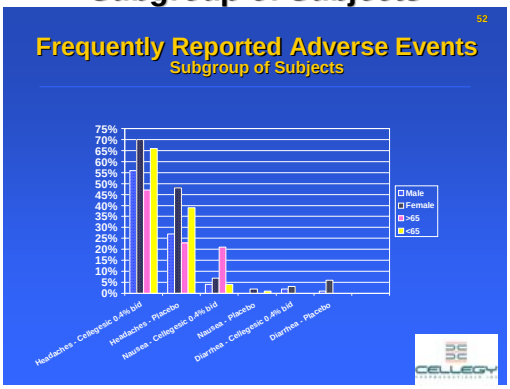
Incidence of Treatment-Emergent Adverse Events ¡Ã 2.0% Considered Treatment

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

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

Frequently Reported Adverse Events

Subgroup of Subjects



Headache

- **Study 3 (at least one NTG-related headache)**
  - **Cellegesic 0.4% bid** **64/90 (71%)**
  - **Placebo** **29/98 (30%)**

- **Used concomitant headache medication**
  - **Cellegesic 0.4% bid** **48%**
  - **Placebo** **38%**

- **Development of tolerance**

		Subjects reporting headache
First week	Cellegesic 0.4% bid	71/71
Fourth week	Cellegesic 0.4% bid	32/65

  - **Also decrease in severity of headaches during this period**

Deaths, Serious AEs and Discontinuations due to AEs

- **Deaths - None**

- **Serious AEs - (10) 6 Cellegesic, 4 placebo**
  Subj 009-110 history migraine headaches, severe migraine headache first day Rx Cellegesic 0.2%

- **Discontinuations (Studies 1, 2, & 3) Due to Adverse Events of 0.4% Cellegesic**
  - **Cellegesic ointment** **20 subjects (9.7%)**
  - **Placebo** **7 subjects (2.8%)**

	Headache
Cellegesic 0.4%	16/206 (7.8%)

  - **9/16 pain improvement, 9/16 VAS < 30 mm**
  - **10/16 either pain improvement and or VAS < 30 mm**

Clinical Laboratory

No consistent clinically significant differences between Cellegesic 0.4% and placebo in hematology or clinical chemistry value changes during treatment

Vital Signs

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

[a] Baseline is the last measurement taken prior to the first CTM application. Post-baseline vital signs were to be collected at the Day 1 (10-20 minutes post-dose), 14, 28, 42, and exit visits in Studies NTG 98-02-01 and NTG 00-02-01, and at the Day 7, 21, 35, and exit visits in study CP125 03-02-01.
[b] Includes all subjects receiving the indicated treatment (b.i.d. or t.i.d.).
[c] Includes all subjects receiving any Cellegesic 0.4% (b.i.d. or t.i.d.).
[d] Includes all subjects receiving any concentration of Cellegesic (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.
NOTE: n = number of subjects with a decrease from baseline at the indicated visit
N = number of subjects with a diastolic blood pressure at baseline and the indicated visit.

Conclusions

- The safety of nitroglycerin has been established by over a century of clinical use
- The dose of Cellegesic nitroglycerin ointment 0.4% (1.5mg NTG) applied intra-anally every 12 hours is less than many of the approved NTG products currently on the market
- The adverse events observed in three phase 3 trials are consistent with the known adverse events of nitroglycerin
  - headache may be managed with mild analgesics
  - others by appropriate labeling

Robert D. Gibbons, Ph.D.
Professor of Biostatistics
Director, Center for Health Statistics
University of Illinois at Chicago

Statistical Methodology and Analyses
Cellegesic™ (nitroglycerin ointment) 0.4%

Method for Analysis of Pain in Studies 1, 2 and 3 Comparison to Traditional "Repeated Measures" ANOVA

Mixed-effects regression model

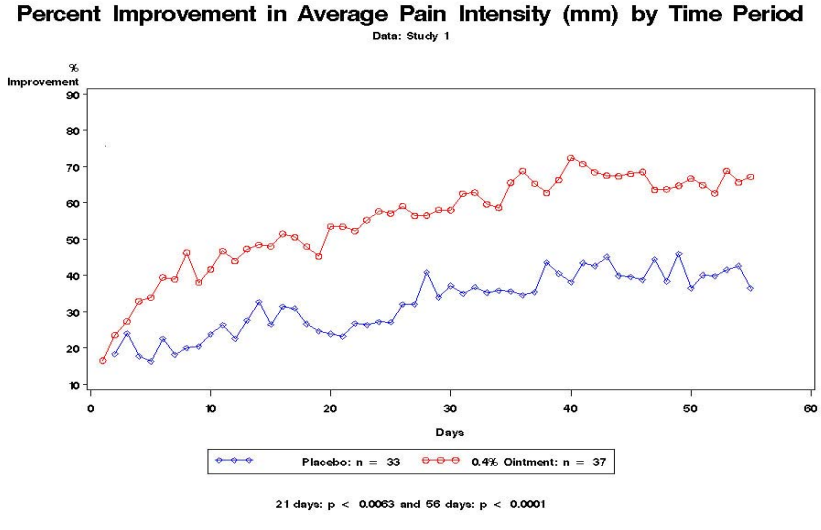
- **Does not assume an overly restrictive correlational structure in which variances and covariances are assumed constant over time**

- **It can accommodate missing data and drop outs**

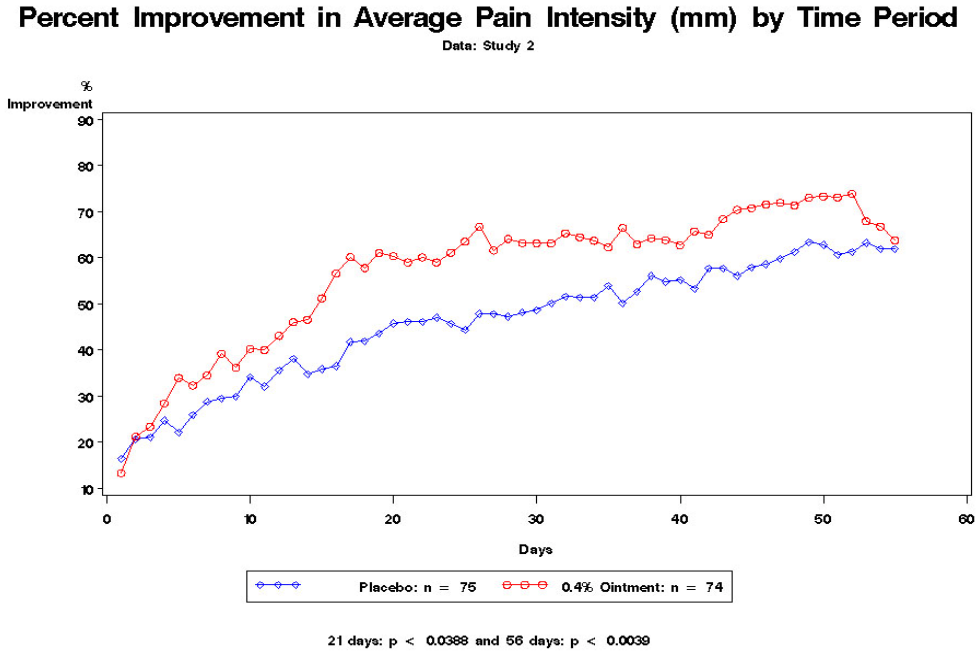
How Missing Data Are Handled

- **No restriction on number of observations per individual**
- **Subjects do not have to be measured at the same times**
- **Subjects are not excluded if missing data from a prescribed observation**
- **No need to impute value for missing observations**
- **Assumption of model**
  - **data available for a given subject (outcomes and covariates) are representative of that subject's responses following drop-out**
- **Random-effects models for longitudinal data using maximum likelihood estimation provide valid inferences under Missing at Random (MAR) and Missing Completely at Random (MCAR)**

NTG 98-02-01 (Study 1)



NTG 00-02-01 (Study 2)



Validation Non-Ignorable Non-Response (Study 3)

- **Mixed-effects regression models used in analysis of these data assumes that missing data (i.e. following drop-out) are ignorable conditional on the covariates in the model and available outcomes (VAS scores) for each subject**
  - **Models based on MAR ("missing at random") are generally robust to MNAR and**
  - **MNAR models can be used as sensitivity analyses to verify the robustness of the findings under MAR** Molenberghs, G, Thijs, H., Jansen, I., and Beunckens, C. Analyzing incomplete longitudinal clinical trial data, 2004, Biostatistics, 5, 445-464

MNAR Sensitivity Analysis (Study 3)

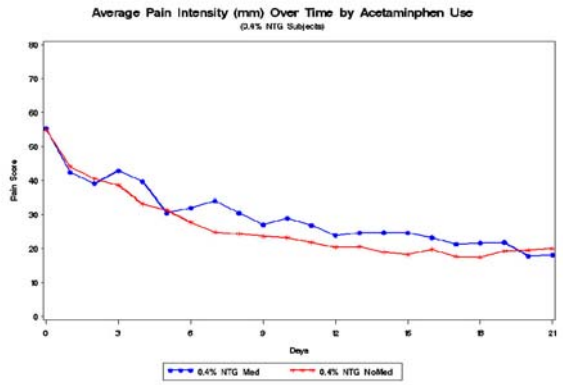
Following method of Hedeker and Gibbons (Hedeker D and Gibbons RD, Longitudinal Data Analysis, Wiley, New York, 2006. Chapter 14. In press.)

- **a MNAR model (shared parameter model) based on jointly fitting a model for drop-out (complementary log-log person-time survival model) and mixed-effects regression model for response (AVG VAS score) to treatment (SAS NLMIXED)**
- **Jointly modeled data for 24-hour average VAS scores per week and drop-out rates per week**
- **Drop out model included headache, and random intercept and slope (shared parameters from the outcome model), and headache by intercept and headache by slope interactions**

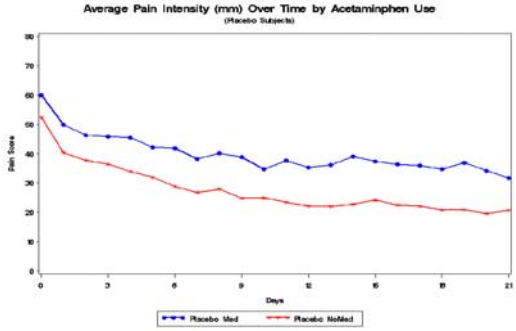
Validation Non-Ignorable Non-Response (Study 3)

- None of the terms related to headache were significantly associated with drop-out
- Treatment by time interaction was significant (p<.0131)
  - This probability value is even smaller that probability value obtained under the MAR assumption (p<.0243)
- These findings clearly establish that:
  - MAR is not biasing the significance of the treatment by time interaction (since it remains significant under MNAR)
  - Headache is not related to drop-out or treatment efficacy

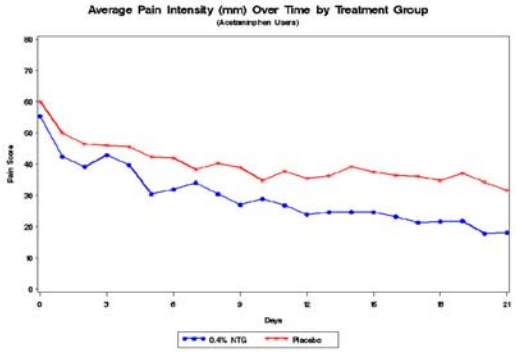
Evidence That The Effects of Cellegesic Nitroglycerin Ointment Are Not Confounded by Analgesic Use (Study 3)



Evidence That The Effects of Cellegesic Nitroglycerin Ointment Are Not Confounded by Analgesic Use (Study 3)



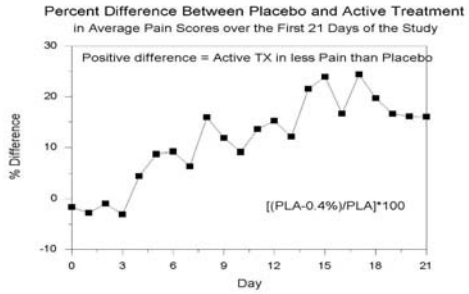
Evidence That The Effects of Cellegesic Nitroglycerin Ointment Are Not Confounded by Analgesic Use (Study 3)



FDA Analytical Requirements for Study 3

- **FDA required Cellegy to combine sites with fewer than 6 subjects**
- **Despite our objections, FDA also required**
  - **for the primary endpoint, 24-hour average pain over the first 21 days, post–drop out data for subjects who discontinued from the study due to a NTG-induced headache be imputed as the last available measurement prior to dropout plus or minus normally distributed random error with mean zero and variance equal to the residual variance from a model fitted using all available data**
- **The primary endpoint utilizing the above model requirements found Cellegesic nitroglycerin ointment to be statistically significantly better than placebo (p<.05)**
- **The more appropriate analysis using the mixed-effects regression model using all available data also found Cellegesic nitroglycerin ointment significantly better than placebo (p<.0309)**

Percent Improvement in 24 Hour Pain Intensity (Study 3)



- **Although primary endpoint is rate of change, individual point in time contrasts were significantly different for:**
  - **Days 13-15 (p<.003)** **Days 7-9 (p<.089)**
  - **Days 16-18 (p<.004)** **Days 10-12 (p<.061)**
  - **Days 19-21 (p<.028)**
- **Important to note:**
  - **Analysis that uses all available data from each subject is unbiased under MAR**
  - **Analysis that imputes LOCF for the missing data is biased both under MCAR and MAR**

Additional Efficacy Results (Study 3)

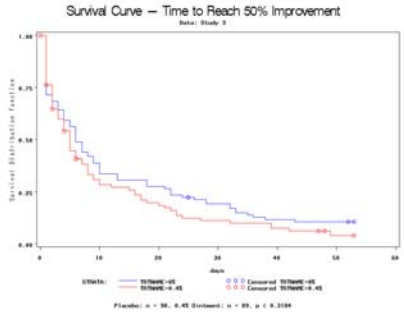
Efficacy Cellegesic nitroglycerin ointment relative to placebo

24-hour average pain 21 days treatment	**p<.0309**
24-hour average pain 56 days treatment	**p<.0167**
defecation pain 21 days treatment	**p<.0504**
defecation pain 56 days treatment	**p<.0211**

Healing

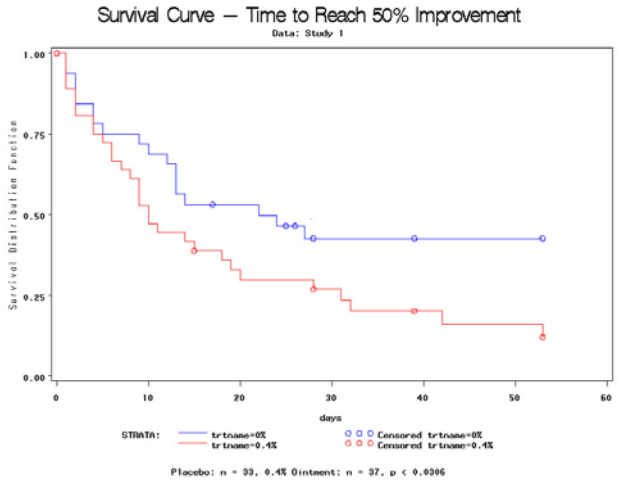
- **Cellegesic NTG ointment** **68.7%**
- **Placebo** **62.9% NS**

Study 3

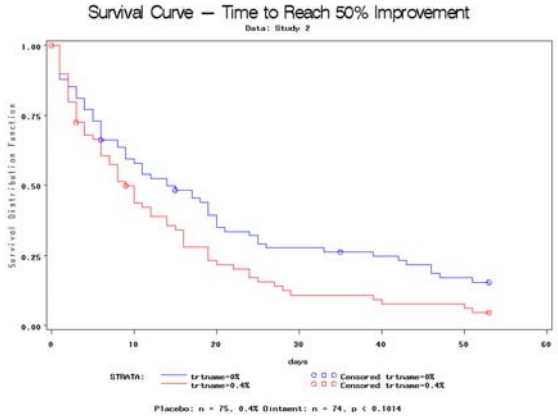


- **Time to 50% improvement in 24-hour average pain p<.3184**
- **Differences however as much as 7 days earlier through day 21 (i.e. 75% of NTG treated subjects achieved 50% improvement 7 days earlier (day 10) than 75% of the control subjects achieved 50% improvement (day 17)**

Time to 50% Improvement (Study 1)



Time to 50% Improvement (Study 2)

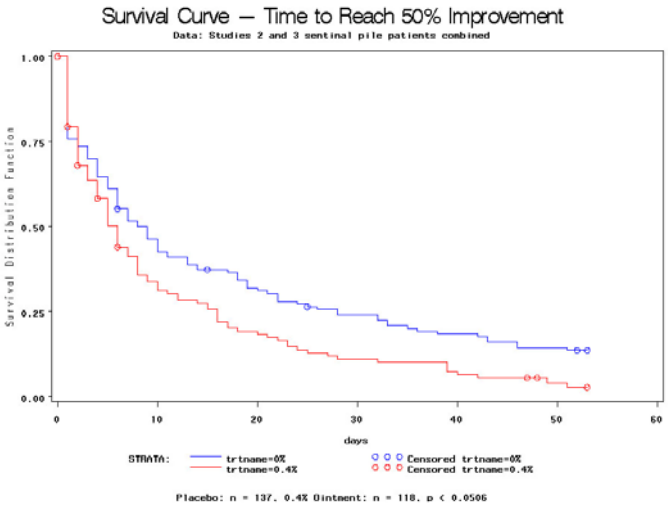


Reanalysis (Studies 1 and 2)

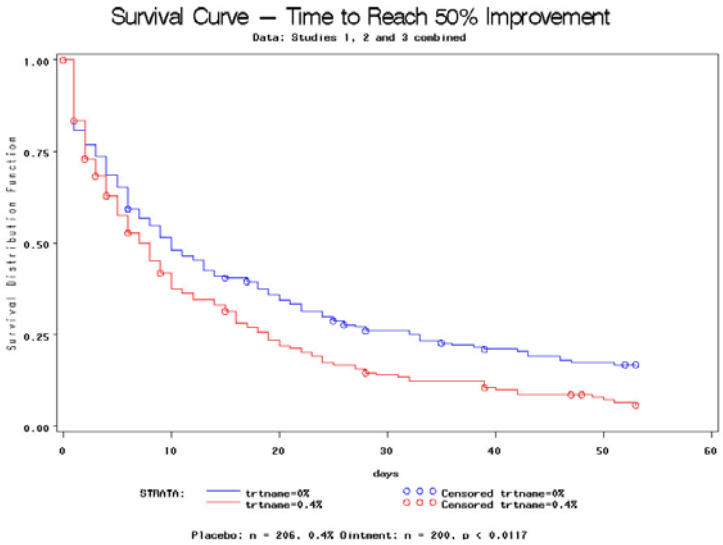
Rate of Change in 24-Hour Pain Intensity over 21 and 56 Days

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

Subjects with Sentinel Pile



Time to 50% Improvement



Analysis of Patients in Moderate and Severe Pain

(24-hour average pain VAS >50mm)

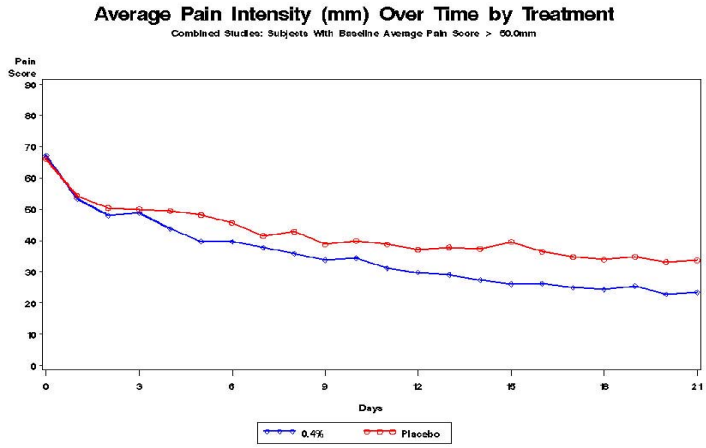
144 subjects met criterion baseline >50 mm

- **17 subjects from Study 1, 35 subjects from Study 2, and 92 subjects from Study 3**

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

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

Subjects with Moderate to Severe Baseline Pain



Efficacy Data by Quintiles
(Studies 1, 2, and 3 Combined)

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

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

Quintiles 1-3 little drug effect

	24-hr. avg. pain		defecation pain	
% Difference	Day 15	Day 21	Day 15	Day 21
Quintile 4	46%	45%	33%	39%
Quintile 5	23%	21%	10%	15%

Efficacy Data by Quintiles (Study 3)

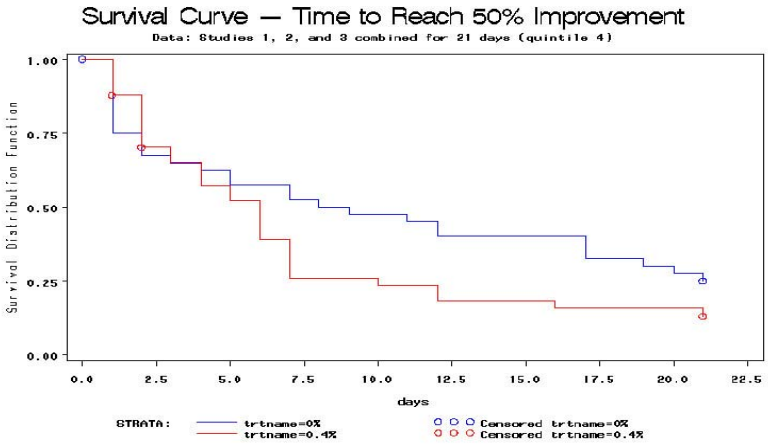
Average Pain Score at Days 15 and 21 by Quintiles of Baseline Score (Study 3)

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

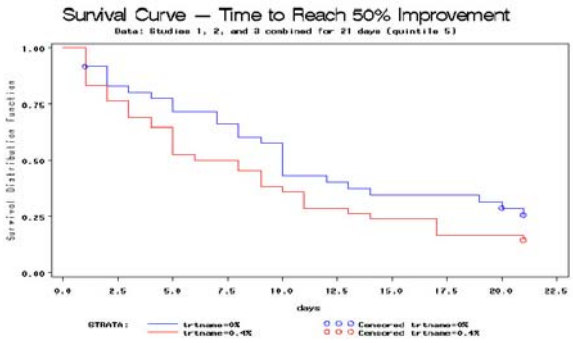
Quintiles 1-3
little drug effect

	24-hr. avg. pain		defecation pain	
% Difference	Day 15	Day 21	Day 15	Day 21
Quintile 4	67%	65%	42%	31%
Quintile 5	25%	9%	20%	22%

Time to 50% Improvement
in Quintile 4



Time to 50% Improvement
in Quintile 5



Summary and Conclusions

- **Acceleration in rate of change in 24-hour pain intensity over first 21 days of treatment is significantly better than placebo with and without LOCF**
- **Reanalysis of Studies 1 and 2 for 21-day endpoint were similarly significant**
- **Major effect of Cellegesic nitroglycerin ointment is in those subjects with moderate to severe anal fissure pain (baseline pain > 50 mm VAS)**
- **Analysis of data from Study 3 provides evidence that headache, dropouts and acetaminophen usage does not affect the efficacy results, providing further validation of the MAR assumption for the mixed-effects regression model**

Jonathan Lund B.M.B.S., D.M., F.R.C.S.

Associate Professor
School of Medical and Surgical Sciences University of Nottingham

Risk / Benefit

Cellegesic™ (nitroglycerin ointment) 0.4%

Risk / Benefit Profile

●One phase 1 and three phase 3 studies provide the evidence that Cellegesic nitroglycerin ointment 0.4% applied intra-anally safely accelerates the pain relief associated with a chronic anal fissure

●

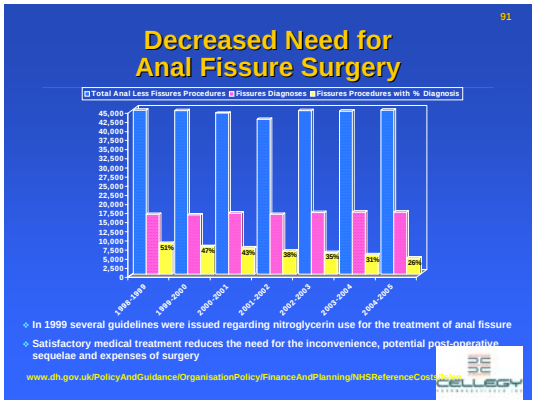
●Healing occurred in 65% of subjects, same as most other studies reported in literature, although not significantly different than placebo

Risk / Benefit Profile

Patient headache complaints:

- **Rectogesic® 0.2% (brand of Cellegesic outside U.S.) approved in Australia, New Zealand, Singapore and South Korea**
  - **Approximately 200,000 tubes of Rectogesic have been sold in Australia with only 10 complaints of headache reported to Cellegy**
- **Rectogesic® rectal ointment 0.4% approved in United Kingdom and 19 additional European countries**
  - **Since May 2005, more than 34,000 tubes sold in UK**
  - **Product has "black triangle"**
  - **Only one report each of nausea and dizziness; no reports of headache**
- **Headache can be managed with mild analgesics**

Decreased Need for Anal Fissure Surgery



Quality of Life

Study 2 Gastrointestinal QOL Questionnaire

- **Few questions related to fissure symptoms**
- **Wide range results in placebo, 0.2% and 0.4% groups**
- **Results favored subjects having an improved QOL**
- **Did not suggest frequency or severity of headache had a detrimental effect on QOL**

Quality of Life

Griffin study (Griffin N, et al, Quality of Life in Patients with Chronic Anal Fissure. Colorectal Dis, 2004;6:39-440)

- **Most significant determinant poor quality life – pain associated with anal fissure**
  - **Worse the pain, poorer the health of patient**
- **Pain assessed by VAS correlated well with scores on SF36 --**
  - **higher levels pain associated with bodily pain (p<.001)**
  - **poorer general (p<.03) and mental (p<.001) health**
  - **less vitality (p<.006)**
  - **decreased physical (p<.02) and social (p<.001) functioning**
  - **greater role limitations due to physical (p<.02) and emotional (p<.04) problems**
- **Any acceleration in pain relief is very important to the progress of treatment**

Other Factors

Poor quality of extemporaneously compounded nitroglycerin ointment:

■46% of 24 retail pharmacies did not meet USP criteria and dispensed ointment in jars, making dosing difficult

Vast majority of studies in literature demonstrate efficacy of nitroglycerin ointment – headache primary adverse event

Personal Usage

- **Cellegesic 0.4% works well in primary and secondary care**
- **Headaches occur but extremely unusual to stop treatment (different order of magnitude to anal fissure pain)**
- **Referrals from primary care and operations for fissure fewer**

Conclusions

- **Nitroglycerin ointment 0.4% provided as a GMP product will assure accurate dosing**
- **Benefit of accelerating the rate of pain relief and potentially decreasing the need for surgery, by use of Cellegesic, clearly outweighs any risk of adverse outcomes**

Thomas Q. Garvey III, M.D.

Gastroenterologist
President, Garvey Associates

Summary and Conclusions

Cellegesic™ (nitroglycerin ointment) 0.4%

Indication

Cellegesic administered intra-anally BID accelerates improvement in pain associated with chronic anal fissure

Cellegy's Three Randomized, Double-Blind, Placebo-Controlled, 56 Day Trials of
NTG 0.4 % BID for Anal Fissure

Study	Venue	ITT Subjects (Cellegesic/ Placebo)	1° Effectiveness Measure	1° Analysis
1 (NTG 98-02-01)	US Multicenter	38/33	Healing Rate	Life-Table (Kaplan-Meier)
2 (NTG 00-02-01)	International Multicenter including US	74/75	Rate of Pain Relief	MERM[1] at 56 d
3 (CP125 03-02-01)	International Multicenter including US	89/98	Rate of Pain Relief	MERM at 21 d

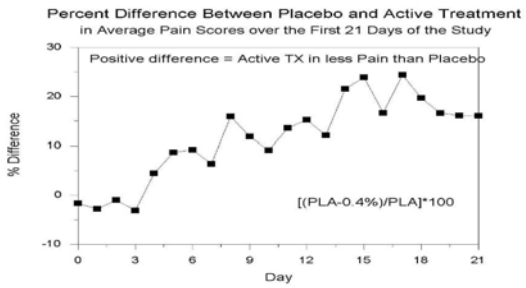
1 MERMA = mixed effects regression model analysis
TT50 = time to 50% pain relief Kaplan-Meier analysis
2 + = NTG 0.4mg > placebo, $p < 0.05$
3 = 1° effectiveness analysis timepoint

Anal Fissure Pain Results for 0.4 % NTG BID in the Three Cellegy Studies

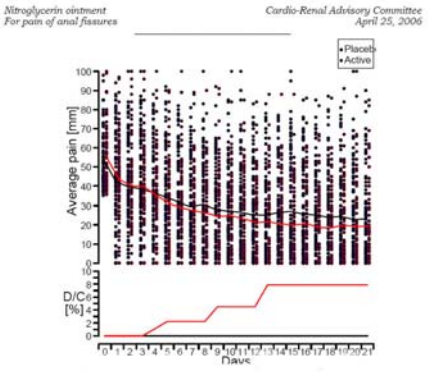
Study	NDA Support Status of Study	Objective(s)	MERMA 21d	MERMA 56d	TT50 21d	TT50 56d	FDA Advice Pre-Study	FDA Criticism
1	Exploratory 2° Support	Identify dose and dosing frequency	+[2]	+	-	+	-	Pain 2° not 1° outcome measure prospectively
2	2° Support	Assess safety and efficacy	+	+	-	-	One more study may be sufficient	Quadratic term in 1° MERMA not prospectively stipulated
3	2° Support	Assess safety and efficacy	+[3]	+	-	-	SPA Impute results for dropouts 2° to NTG headache using Agency ad hoc method	NTG v Placebo difference not significant (p = 0.12) when imputed results for "headache" dropouts are included (Cellegy p< 0.0498: no imputation p< 0.0309)

Anal Fissure Pain Results for Study 3

Cellegy

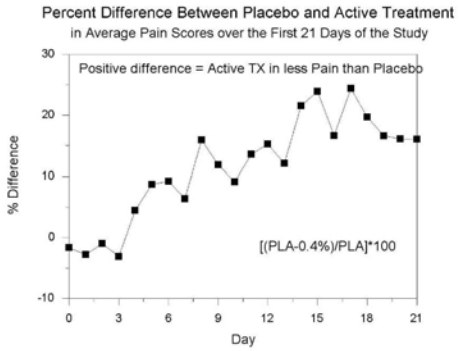


FDA



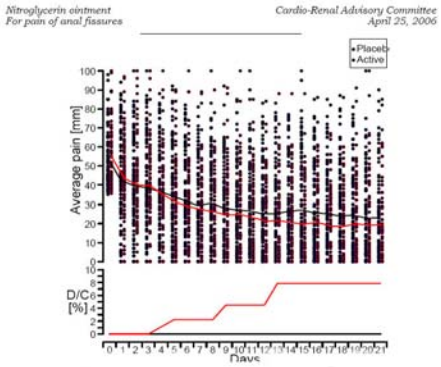
Anal Fissure Pain Results
for Study 3

Celleqy



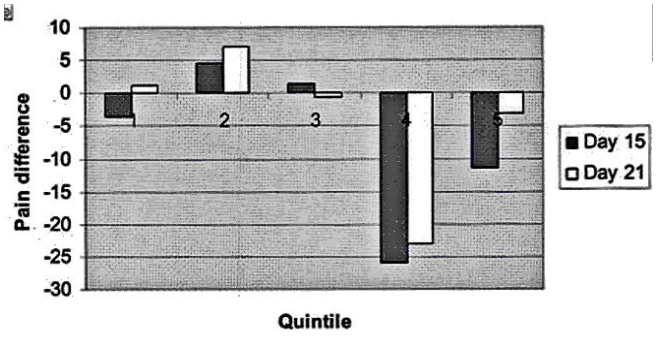
Anal Fissure Pain Results
for Study 3

FDA



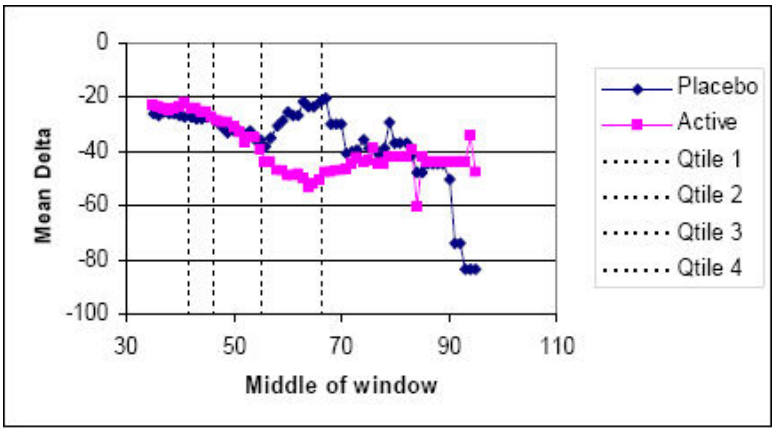
Anal Fissure Pain Results
for Study 3

FDA

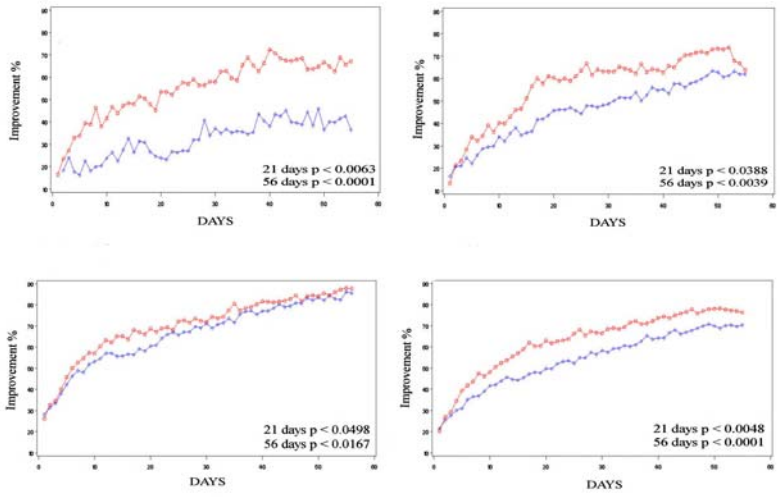


Anal Fissure Pain Results
for Study 3

FDA



Percent Improvement in Daily Average Pain Intensity (mm) by Study Day for
Celleqy Studies 1, 2 and 3



Key Points

●The American Gastroenterological Association (AGA) and the American Society of Colon and Rectal Surgeons both recommend a trial of NTG ointment before surgery for anal fissure

●NTG ointment is regularly compounded by pharmacists for treating anal fissures in the U.S., but 46% of these compounded formulations do not meet USP standards

●A 50% decrease in surgical procedures for anal fissure has been seen in the U.K. following recommendation of NTG ointment for treatment of anal fissures by professional organizations and the NHS

●Cellegy's 0.4% NTG ointment product has been approved for treatment of anal fissure in 20 countries, including France, Finland, Germany, Italy, Spain, Sweden and the U.K.

Key Points

- **All three randomized, double-blind, placebo-controlled, parallel-groups Cellegesic studies show 0.4% NTG ointment BID effective for accelerating improvement in anal fissure pain after 21 days of use**
- **Analyses of studies employing the last-observation-carried-forward (LOCF) convention are incurably biased for all missing data mechanisms [i.e., missing at random (MAR), missing completely at random (MCAR) and missing not at random (MNAR)]**
  - **Mixed effects regression model analysis of such data is, however, invulnerable to bias under both MAR and MCAR and is often robust to MNAR, as in this case**
  - **Use of LOCF in a mixed effects regression model for Study 3 in fact makes results of the analysis vulnerable to bias under both MAR and MCAR. Nevertheless the superiority of NTG over placebo remains statistically significant**

Key Points

●NTG headaches do not confound interpretation of pain results for the Cellegesic studies

●Use of acetaminophen for headache does not confound interpretation of fissure pain results for the Cellegesic studies

●Cellegesic is adequately safe. The safety profile of NTG is very well established by many decades of use in patients with advanced and often life-threatening coronary artery disease – such patients are, in general, far more vulnerable to serious sequelae of the unwanted effects of NTG such as hypotension

●Study 3 met prospective criteria for demonstration of the effectiveness of Cellegesic according to FDA's SPA