Questions

Nitroglycerin ointment
April 25, 2006

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Committee is asked to opine on Cellegesic (0.4% nitroglycerin ointment) for the symptomatic treatment of pain associated with anal fissures. Study 98-02-01 (or Study 1) was conducted to assess the effect of nitroglycerin ointment on healing of anal fissures. This study was not successful, but the sponsor perceived a favorable trend on pain relief. Study 00-02-01 (Study 2) was undertaken to confirm this finding on pain relief. The second trial was positive ($p<0.05$) by the sponsor's analysis, but this analysis was not fully specified prospectively and it differed from the hypothesis-generating analysis of Study 1. By the Study 1 analysis, Study 2 was not statistically significant, and the Agency deemed the two studies an inadequate basis for approval. Study 03-02-01 (Study 3) was expected by the sponsor and by the Division to provide the necessary assurance of effectiveness.

By the prospective analysis, the sponsor asserts that the p-value in Study 3 was 0.0498, but the sponsor believes a more appropriate analysis gives $p=0.0243$. The review team believes that the prospective analysis gives $p=0.12$. The differences all result from handling of patients with missing data because of early withdrawal for headache.

There are two issues. The Advisory Committee is being asked first whether it finds the data compelling that there is an effect on anal fissure pain. The second issue is whether the apparent effect size warrants approval. At the end, then, the Committee will be asked to choose among 3 outcomes:

- Approval = The evidence is compelling, and the effect size is either large enough to matter or it is irrelevant.
- Approvable = The evidence is not compelling, and the effect size is either potentially large enough to matter or it is irrelevant.
- Not Approvable = Effect size matters and the available data rule out an effect large enough to support approval.

1. The sponsor believes Study 2 should have been considered persuasive, because the post-hoc inclusion of a quadratic term in the regression analysis was justified (backgrounder pages 11 and 28). Does the Committee agree? Please vote.

2. Study 3 called for a Last Observation Carried Forward analysis of pain data from subjects who discontinued "due to headache". The sponsor

interpreted this to mean treatment-related headache, leading to the previously cited p=0.0498. Various alternative analyses are summarized below (from Dr. Hung's review of July 2004):

	Conditions	**P-value**
1	LOCF for withdrawal for drug-related headache	0.0498
2	Add all available data for 1 subject	0.0843
3	LOCF for withdrawal for any headache	0.12
4	LOCF for any withdrawal	0.0943-0.15
5	No imputation	0.0489
6	No imputation and no post-withdrawal data	0.0309

2.1. Is the analysis based on "drug-related" headache a reasonable interpretation of the protocol? Is it reasonable to expect that the determination of drug-relatedness would be unambiguous?

2.2. The sponsor's backgrounder comments extensively on the use of LOCF with a mixed-effects model. Should LOCF have been included in the analysis?

2.3. A few subjects had data following discontinuation. Should their post-discontinuation data have been included in the primary analysis?

2.4. Subjects enrolled with one kind of pain and discontinued with a different pain. Was LOCF conservative enough?

3. The review team questioned whether concomitant analgesic use could have contributed to differences in the groups. The sponsor has argued that the results are not confounded by analgesic use.
   3.1. Do you agree that the results are not confounded? If so, cite the analysis you find compelling.
   3.2. What magnitude of effect of analgesics can be excluded?

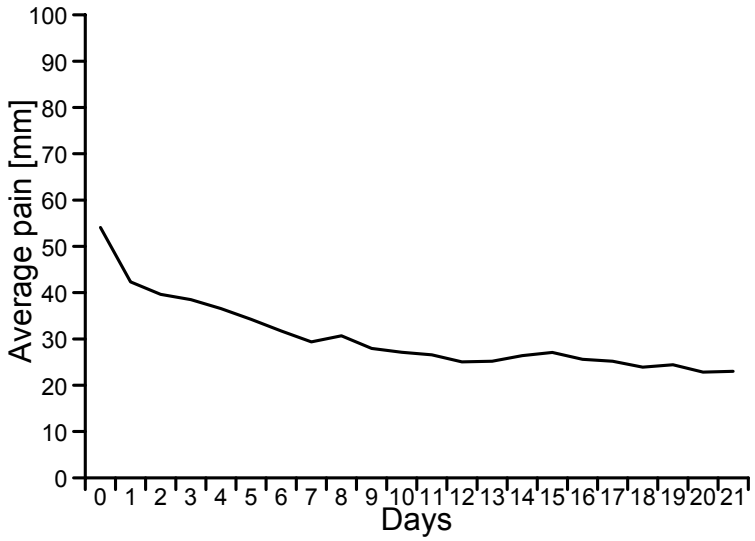
4. Taking all three studies into consideration, do you find the data compelling that there is an effect of nitroglycerin ointment on the pain of anal fissures? Please vote.

5. Are there safety issues with the use of nitroglycerin ointment to treat anal fissures?

6. Independent of the need to show net benefit exceeding risk, which of the following factors, if any, influence whether or not the size of a treatment effect matters for regulatory decision-making?
   - Benefit is a reduction in major clinical outcomes
   - Benefit is an improvement in functional status
   - Benefit is an improvement in global patient assessment
   - Benefit is an isolated symptom

7. Does treatment of anal fissure pain belong to a class of indication for which the effect size matters? If not, proceed directly to question 10.

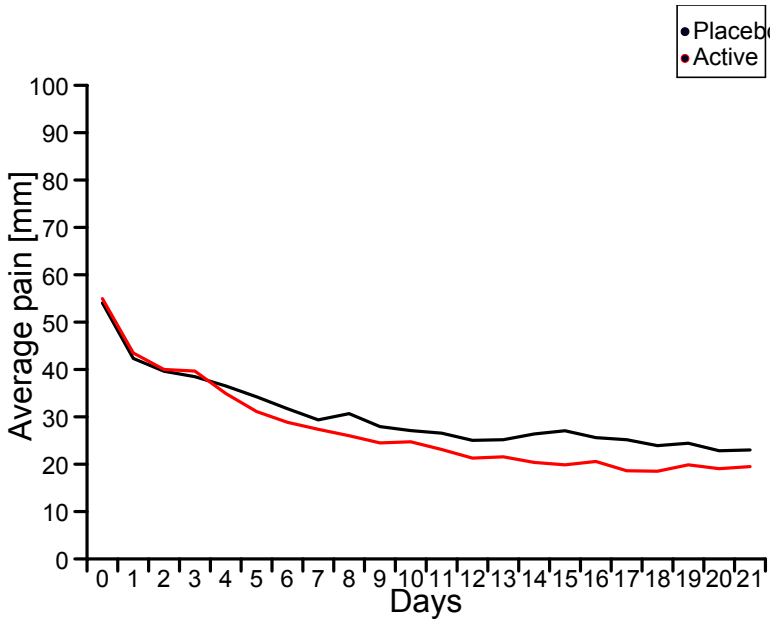
8. The instrument used to assess effectiveness in these trials was a 100-mm visual analog scale. In study 3, mean response in the placebo group is shown in the figure below (no imputation).



Page 19 of the sponsor's briefing package shows a similar figure for Studies 1 and 2 combined.

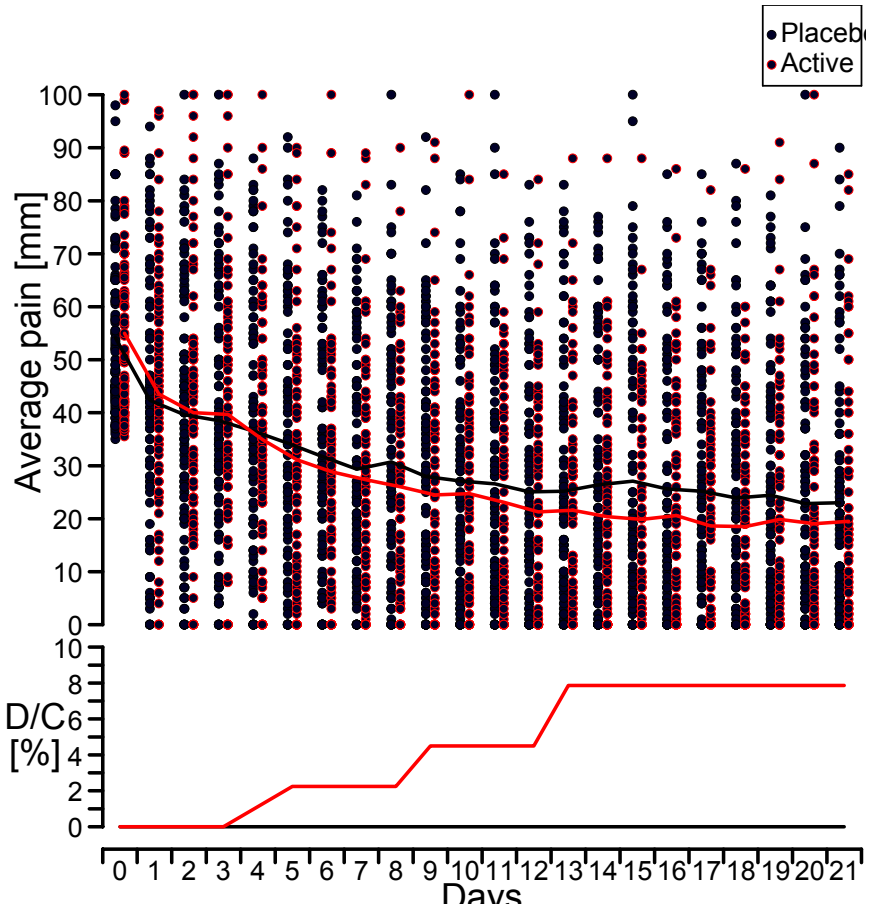
8.1. Since subjects had to have some minimum pain score to get into the study, some of this effect is regression to the mean. Can you estimate how much is regression to the mean and how much is the natural history of the disease?

The figure below shows the mean effect in the placebo and active treatment groups in Study 3 (again with no imputation).



8.2. How large is the nominal treatment effect (active minus placebo)? How does it compare with the effect seen in the placebo group?

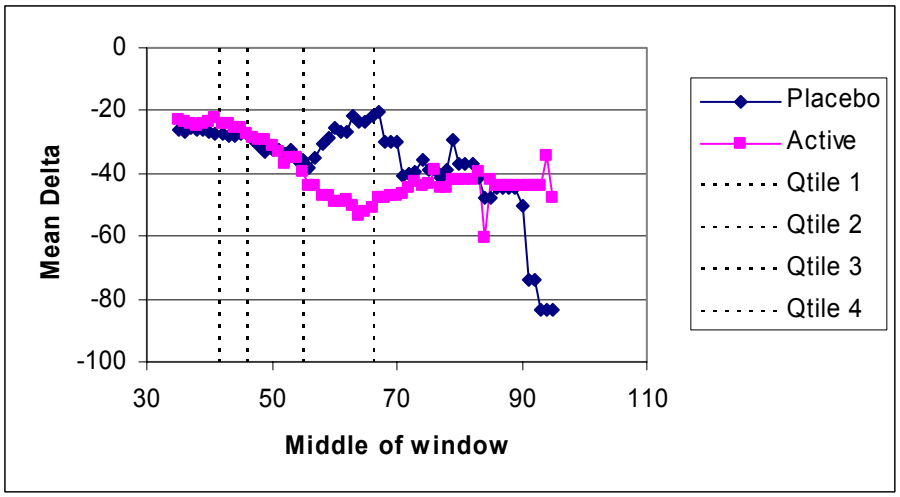
The figure below shifts the placebo and active group curves slightly and adds all of the observed data. Along the bottom now runs the discontinuation rate in the two groups.



8.3. A patient, regardless of Cellegesic, is, generally, going to feel better over time. Is a patient apt to perceive the contribution Cellegesic makes?

8.4. The primary end point was rate of change in pain, so the LOCF process carries forward the last observed rate. For early discontinuation, this rate is (at least) dominated by regression to the mean and the natural history of the disease, benefiting the group with the earlier withdrawals. Was this reasonable?

9. The sponsor presents an analysis (backgrounder pages 39-42) to show that the effect of Cellegesic is larger in upper quintiles of baseline pain score. Compare this with an analysis performed using a 10-mm-wide moving bin, shown in the figure below.



Overall, are the data compelling that patients with worse pain at baseline respond better to Cellegesic?

10. What is the appropriate regulatory action for Cellegesic? Please vote for one of the following options:
    - Approval
    - Approvable pending another study of effectiveness
    - Not approvable