Food and Drug Administration
Center for Drug Evaluation and Research

Hilton Washington DC/North Hotel, Gaithersburg, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on April 25, 2006.

The committee discussed new drug application (NDA) 21-359 Cellegesic™ (nitroglycerin [NTG] ointment), 0.4% intra-anal, Cellegy Pharmaceuticals, Inc., for the proposed indication of relief of pain associated with anal fissures

These summary minutes for the April 25, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on May 3, 2006,

I certify that I attended the April 25, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

_____//S//_____
William R. Hiatt, M.D.
(Committee Chair)

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
David L. DeMets, Ph.D.
Steven D. Findlay, M.P.H. (Consumer Representative)
John M. Flack, M.D., M.P.H.
Robert A. Harrington, M.D., F.A.C.C.
William R. Hiatt (Committee Chair)
Frederick J. Kaskel M.D., Ph.D.
Michael A. Lincoff, M.D.
Thomas G. Pickering, M.D, D.Phil.
Ronald J. Portman, M.D.
John R. Teerlink, M.D.
Lynn Warner-Stevenson, M.D.

Special Government Employee Consultants (voting):
Walter A. Koltun, M.D. (participating via teleconference)

(Non-Voting) Participants:
George S. Goldstein, M.D. (Industry Representative)

Cardio-Renal Advisory Committee Members Absent:
John F. Neylan, MD (Industry Representative)

FDA Participants:
Robert Temple, M.D.
Norman Stockbridge, M.D., Ph.D.

Executive Secretary:
Cathy A. Groupe, R.N., B.S.N.

Open Public Hearing Speakers
None

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The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 25, 2006, at the Hilton Washington DC/North Hotel, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the sponsor and the FDA. The meeting was called to order by William R. Hiatt, M.D. (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 50 persons in attendance. There were no speakers for the Open Public Hearing sessions.

Issue: New drug application (NDA) 21-359 Cellegesic™ (nitroglycerin [NTG] ointment), 0.4% intra-anal, Cellegy Pharmaceuticals, Inc., for the proposed indication of relief of pain associated with anal fissures

The agenda was as follows:

Call to Order and Introductions	**William R. Hiatt, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Introduction/Background	**Norman Stockbridge, M.D.** Director - Division of Cardiovascular and Renal Drug Products FDA/CDER

Sponsor Presentation – Cellegy Pharmaceuticals, Inc.

Overview of Phase 1 and	**Daniel L. Azarnoff, M.D., F.A.C.P.**

Phase 3 Studies	President, D.L. Azarnoff Associates Professor of Medicine University of Kansas Medical Center
Pathophysiology of Anal Fissures and Clinical Aspects Of Diagnosis and Treatment	**Michael E. Abel, M.D., F.A.C.S., F.A.S.C.S.** Assistant Clinical Professor of Surgery University of California at San Francisco Medical School
Overview of Studies And Regulatory History	**Daniel L. Azarnoff, M.D., F.A.C.P**
Safety	**Daniel L. Azarnoff, M.D., F.A.C.P.**
Statistical Methods and Analyses	**Robert D. Gibbons, Ph.D.** Professor of Biostatistics and Director Center for Health Statistics University of Illinois at Chicago
Risk Benefit Profile	**Jonathan Lund, B.M.B.S., D.M., F.R.C.S.** Associate Professor School of Medical and Surgical Sciences University of Nottingham
Summary and Conclusions	**Thomas Q. Garvey, III, M.D., F.A.C.P.** President Garvey Associates, Inc
	Questions from the Committee
	Break
	Lunch

FDA PRESENTATION:

Effect Size – Can the Effect Size Be Too Small?	Robert J. Temple Director - Office of Drug Evaluation I (ODEI) FDA/CDER
	Committee Discussion
	Questions to the Committee

Questions to the 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).

   1.1. What is the interpretation of the linear term in an analysis with a quadratic model?

   - *The committee was satisfied that the quadratic model was appropriate and reasonable, citing the non-linear nature of the data. However the use of this model was a post hoc decision.*
   - *Others commented the benefit of the short-term gain in avoiding surgery should be taken into consideration*

(See transcripts of detailed discussion)

1.2. Was the quadratic model the proper analysis for the purpose of decision-making? Please vote.

YES: 7 NO: 5

(See transcripts for detailed discussion)

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?

- *There was general agreement among most of the committee that the analysis based on 'drug-related' headache was not reasonable; most commented that it should have been defined as 'any headache'.*

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?

- *Many committee members commented that a mixed model is the best model when data are missing at random. However since drug-induced headaches accounted for many drop outs, the management of missing data remained an issue.*
- *Some committee members abstained from making a conclusion, commenting lack of knowledge of the difference between the two models.*

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

- *Most of the committee thought that data should have been included in the primary analysis while a few felt it should not be included.*

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

- *Clarification of the question was added, stating 'Should we have used LOCF'?*
- *The majority of the committee did think LOCF was appropriate* [PLEASE CLARIFY THIS, I THOUGHT WE DID APPROVE INCLUSION OF MISSING DATA IN THE ANALYSIS]

(See transcripts for detailed discussion)

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.

- *The committee raised concern about acetaminophen compliance in study patients*
- *Some of the committee members agreed that they were not convinced that analgesics were not confounders while others commented that it is difficult to know. Most agreed, though, that this was not a concern.*

3.2. What magnitude of effect of analgesics can be excluded?

- *Most of the committee agreed that not much of the magnitude of effect can be excluded*

(See transcripts for detailed discussion)

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.

YES: 9 NO: 3

(See transcripts for detailed discussion)

5. Nitroglycerin ointment administered intra-anally is systemically absorbed—mean bioavailability 50% with wide variability even in a small PK study (range 8-99%). At the extreme, the proposed dose thus delivers 1.7 mg of nitroglycerin in the first hour, substantially higher than the usual anti-anginal dose. Dosing was erratic in the trials—apparently as much as 4-fold overdosing based on an FDA site audit. Tachycardia and dizziness were reported in two patients in the small clinical trials, but vital signs were not measured at peak after the first visit. Are there safety issues with the use of nitroglycerin ointment to treat anal fissures?

Comments from the committee included:

- *Dizziness was cited as a potential safety issues, where presyncope or syncope may be a factor.*
- *That there may be safety issues but that these issues may not be a significant factor*
- *We do not know how this drug will interact in patients on other blood pressure medications; this population should be excluded until further data is available*

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

Comments from the committee included:

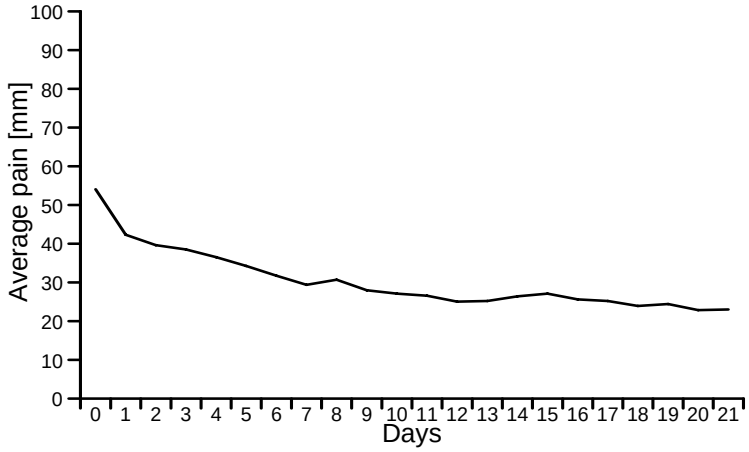
- *Many committee members agreed the magnitude of the effect for all factors is important, while others cite that while these factors matter, effect size is difficult to quantify.*
- *Rapid reduction in pain (symptom) was cited as a significant factor in determining the size of a treatment effect*

(See transcripts for detailed discussion)

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.
   - *While a few of the committee members did not think the effect size matters, a majority of the committee agreed that it does matter*

   (See transcripts for detailed discussion)

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).



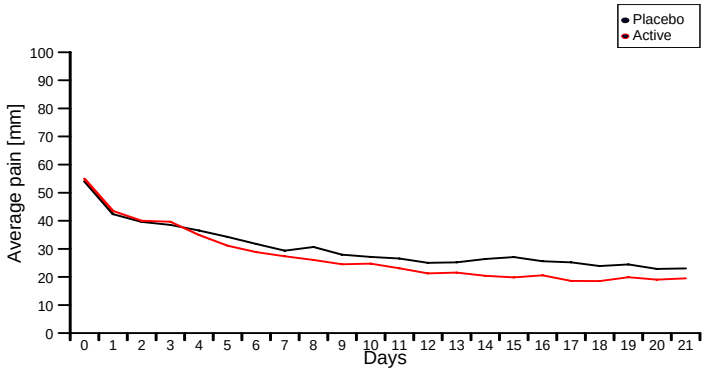
Page 19 of the sponsor's briefing package shows a similar figure for Studies 1 and 2 combined.

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?

- *Committee members commented on the difficulty in determining this, while most agreed that the first part of the curve (day 1), is clearly regression to the mean. Estimates included 10-20 days as the natural history of the disease.*

(See transcripts for detailed discussion)

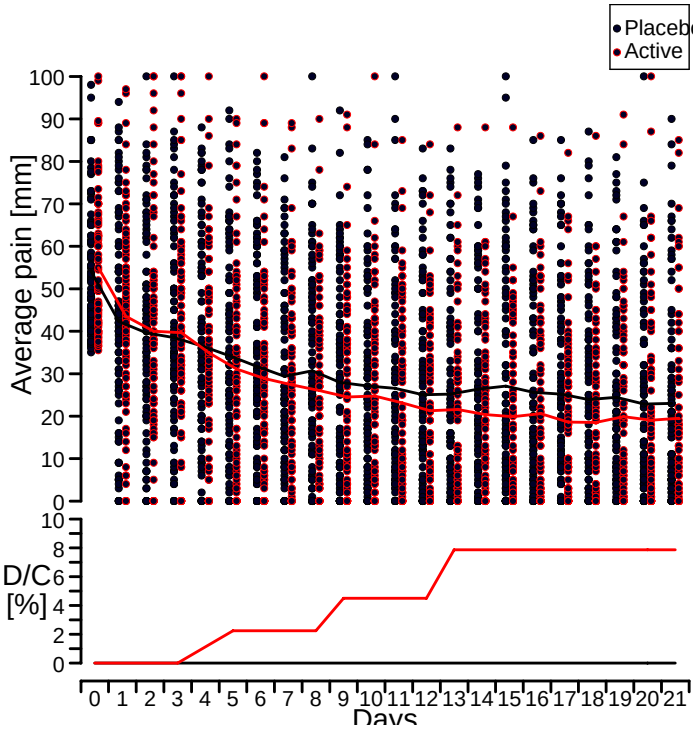
The figure below shows the mean effect in the placebo and active treatment groups in Study 3 (again with no imputation).



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 effect size varies over time*
- *Many committee members estimate a 1/3 nominal treatment effect compared with placebo*
- *Others comment that there is clearly an effect but it is unclear if they improved a lot versus a little*

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.

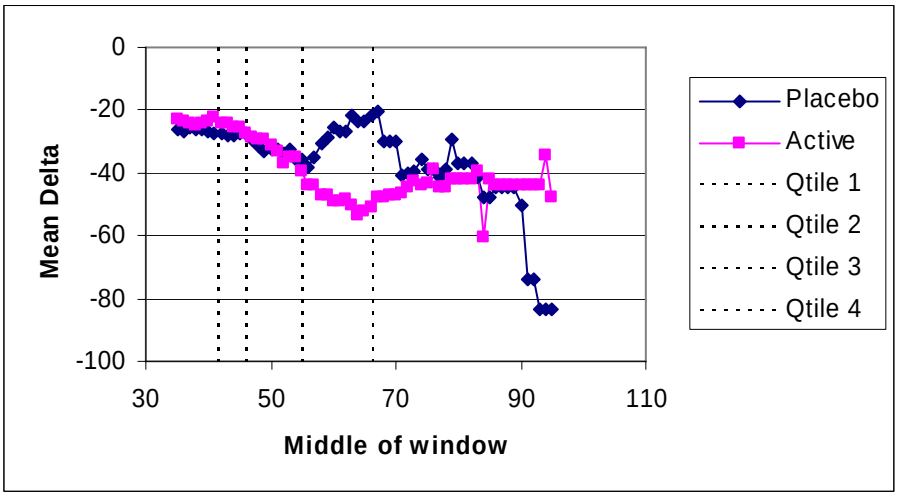


8.3. A patient, regardless of Cellegesic, is, generally, going to feel better over time. Is a patient apt to perceive the contribution Cellegesic makes?

- *Some committee members agreed that, yes, the patient is apt to perceive the contribution Cellegesic, adding that while it is a small effect, it is a real one. Still others commented that what individual patients perceive is unclear.*
- *Other committee members commented that it is difficult, from the figure above, to make a determination.*

(See transcripts for detailed discussion)

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?

- *The committee cited that this is a hypothesis generating plot for a follow-up study*
- *A majority of the committee agree that, yes, the data are compelling that patients with worse pain at baseline response better to Cellegesic; others commented that this was suggestive but not compelling*

(See transcript for detailed discussion)

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**

APPROVAL: 6
APPROVABLE PENDING ANOTHER STUDY OF EFFECTIVENESS: 6
NOT APPROVABLE: 0

- *Those committee members who voted for 'Approval' cited that additional studies may not provide beneficial data as well as adding that the drug is currently being used extensively off-label, which would challenge adequate enrollment in a new trial*

The committee adjourned at approximately 5:50 P.M.

(See transcript for detailed discussion