

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-941

CORRESPONDENCE



July 24, 2000

James E. Berg
Vice President
Clinical and Regulatory Affairs
Avanir Pharmaceuticals
9393 Towne Centre Drive, Suite 200
San Diego, California 92121

Re: Formal Dispute Resolution Request
NDA 20-941
Abreva (docosanol 10% cream)

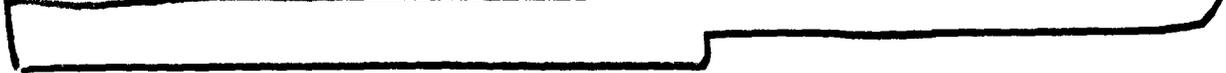
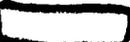
Dear Mr. Berg:

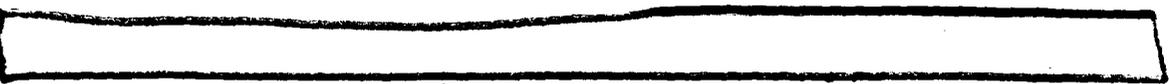
This letter serves as further written documentation of our July 10, 2000 teleconference and subsequent facsimiles dated July 10 and 11, 2000 regarding Avanir Pharmaceuticals' (Avanir) Formal Dispute Resolution Request (FDRR) regarding Abreva (docosanol 10% cream), NDA 20-941.

The July 10, 2000 teleconference participants included:

FDA: Dr. Dianne Murphy, Mr. James Morrison and Ms. M.J. Walling
Avanir: Dr. G. Yakatan, Mr. James Berg and Mr. L. Polk

The teleconference resulted in the following agreements (which were reiterated in a facsimile of the same day):

1. "Dries clear" may be used on the labeling. 

2. Symptoms may be addressed in the following manner: "Shortens healing time" 

3. 
4. 

A subsequent facsimile was sent to you on July 11, 2000, in which the following comments regarding your proposed "Purpose" statement were conveyed:

One of the following two statements, which are consistent with the monograph, and supported by the data submitted, may be used under the "Purpose" (referred to as Identity Statement in the monograph):

- (a) "Treatment of cold sores and fever blisters" or
- (b) "Cold sore/fever blister treatment."

The use of the term "medicine" or "healer" as proposed in your June 2, 2000 correspondence is therefore not acceptable for a "Purpose" (Identity) statement.

This completes my response to your request for a formal dispute resolution request dated June 12, 2000. If you wish to appeal my decision further, the next level of appeal would be to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. If you wish to file such an appeal, please do so just as you did with this one by contacting Ms. Janice Sheehy, CDER's Formal Dispute Resolution Project Manager. Ms. Sheehy can be reached by phone at (301) 594-5413, by fax at (301) 594-6197, or by mail at HFD-2, 5600 Fishers Lane, Rockville, Maryland 20857.

Should you have any further questions, I can be reached through Ms. Sheehy.

Sincerely yours,

/s/

Dianne Murphy, M.D.
Acting Deputy Center Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



June 12, 2000

SENT VIA FEDERAL EXPRESS

Ms. Janice Sheehy
Formal Dispute Resolution Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Mail Code HFD-002
5600 Fishers Lane
Rockville, MD 20857



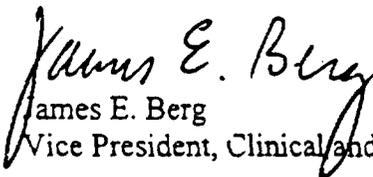
Re: FORMAL DISPUTE RESOLUTION REQUEST
Application Number: NDA 20-941

Dear Ms. Sheehy:

Please accept this request from Avanir Pharmaceuticals for formal dispute resolution by the Center regarding labeling for docosanol 10% cream. Avanir has attempted to resolve its differences with ODE V on this important subject, but to date no consensus has been reached. We are, therefore, requesting the Center's involvement in the labeling for Abreva. Background information about the dispute, specific unresolved issues, and relevant documentation necessary for consideration and resolution of the issues are included in this submission as specified in the Guidelines.

Please contact me with any questions or requests for additional information.

Sincerely yours,


James E. Berg
Vice President, Clinical and Regulatory Affairs

cc: James C. Morrison, Senior Advisor, Ombudsman (HFD-100)



AVANIR
pharmaceuticals

May 25, 2000

SENT VIA FAX

Charles J. Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-941 (Docosanol 10% Cream – Abreva™)

Dear Dr. Ganley:

In responding to FDA's suggested labeling, Avanir Pharmaceuticals recognizes the desire of both parties to reach a consensus as quickly as possible and to avoid a protracted iterative process of label negotiation. To enable this process to be completed in the shortest timeframe, Avanir accepts the majority of the agency's requests. Minimal changes to the suggested FDA label are requested only on items that are of considerable importance to Avanir. In brief, Avanir accepts without condition the comments identified as 1f, 1h, 1i, and 1j in the agency's letter dated May 24, 2000. In addition, Avanir is willing to accept the comments identified as 1d, 1e, and 1g; but we believe that there is a statutory basis supporting our original submission, as detailed below. With regard to 1c and 1k, we believe there is a rational basis for the submitted wording, but are willing to accept the agency's comments. With regard to 1l, the submitted language is supported by physicochemical attributes. Regarding the agency's comments 1a, 1c, and 2a, we believe we understand the spirit of the agency's comments and propose slight modifications that should achieve our mutual objective of clear communication of product attributes and proper usage to the prospective consumer.

1. Carton

Avanir agrees to reflect all of comments 1f, 1h, 1i, and 1j, as requested:

- f. Under Warnings and the subsection "Stop use and ask a doctor if," change the prebulleted statement "condition worsens or does not clear up in 10 days" to "your cold sore gets worse or the cold sore is not healed within 10 days."**
- h. Under Other information, expand the prebulleted phrase "store at or below 20°C (68°F)" to "store at 20°-25°C (68°-77°F)." [The label currently states at or below 25°C (77°F)]**
- i. Under Inactive ingredients, remove "NF" after both benzyl alcohol and light mineral oil, and remove "USP" after propylene glycol and purified water.**

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fax 453 5845

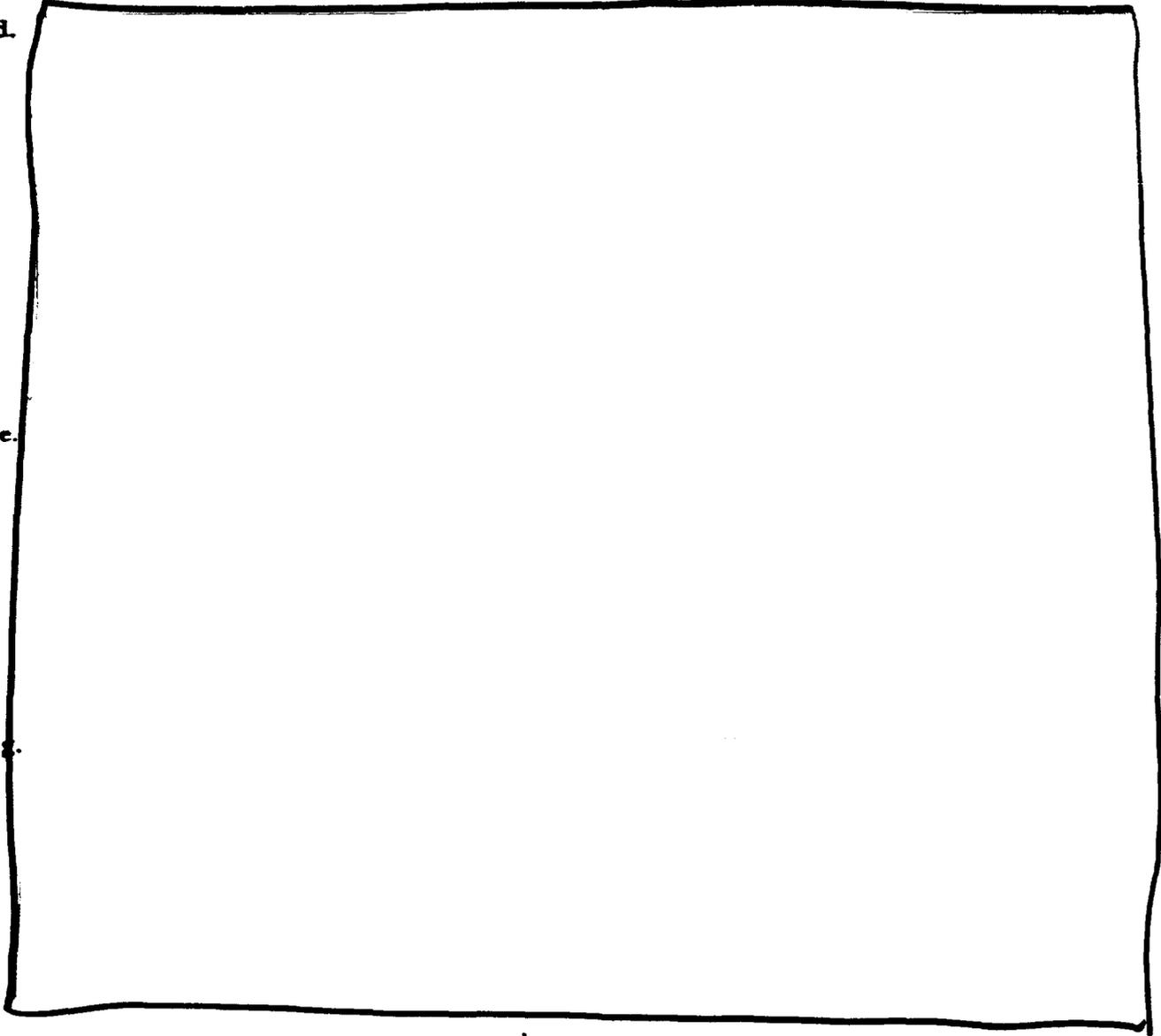
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Suite 200
San Diego, California 92121

- j. The term **NEW** on the outer carton label (top half) can remain for no more than 6 months after initial marketing of the product.

Avanir believes that there is a regulatory basis for the original wording covered by the agency's points 1d, 1e, and 1g, as discussed below. Should our interpretation of the regulations be incorrect, however, we would certainly be willing to make these changes as requested.

d.

e.



2 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

Charles J. Ganley, M.D.

May 25, 2000

Page 5

 2. Immediate tube label

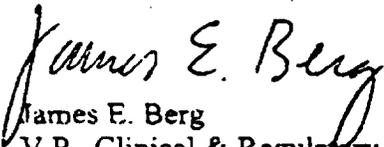
a. Expand "Cold Sore Blocker" to Cold Sore/Fever Blister Treatment

See 1.a. above. 

We appreciate the agency's willingness to consider labeling in advance of final action on NDA 20-941, and we trust the information provided above is responsive to your requests and concerns. We look forward to working cooperatively with you to reach a final decision on this application.

Please contact me with any questions regarding this submission.

Sincerely yours,



James E. Berg

V.P., Clinical & Regulatory Affairs

AVANIR
pharmaceuticals

May 19, 2000

SENT BY FEDERAL EXPRESS

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-941 — Request for waiver of pediatric clinical trials

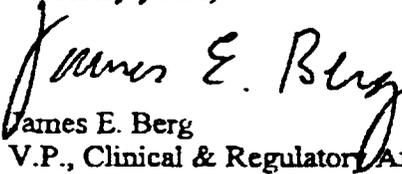
Dear Dr. Wilkin:

As per CFR §314.55(c)(2)(i) Avanir requests a full waiver of pediatric use clinical trials with regard to its NDA for docosanol 10% cream. This request is based on IMS data (NDTI 1998) that indicates there are less than 50,000 pediatric patients (neonates, infants, children, and adolescents) seeking prescriptions for recurrent herpes simplex labialis.

The adolescent population is currently included in the proposed product labeling based on extrapolation from the clinical safety and efficacy data in the adult population.

Please contact me with any questions regarding this submission.

Sincerely yours,


James E. Berg
V.P., Clinical & Regulatory Affairs

Encl.

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fax: 453.5845

8393 Towne Centre Drive
Suite 200
San Diego, California 92121



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May 17, 2000

SENT BY FEDERAL EXPRESS

Robert J. DeLap, M.D., Ph.D.
Director, Office of Drug Evaluation V (HFD-105)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NEW CORRESP

nc

Re: NDA 20-941 (audit of 92-LID-02 -- patient diaries)

Dear Dr. DeLap:

Per your request to James Morrison, Avanir respectfully submits its May 11, 2000 communication to FDA as a formal amendment to the NDA for docosanol 10% cream. This amendment includes:

- The May 11, 2000 letter to Mr. James C. Morrison, CDER Ombudsman and Senior Advisor to Janet Woodcock, M.D., Director, CDER
- A document titled, "Study of Reporting Intervals" by Ronald A. Thisted, Ph.D.
- A data listing for the primary endpoint (time-to-healing) for 92-LID-02, which includes the dates and times of clinic assessments.

We are convinced that the absence of diaries at the clinician site during the audit of 92-LID-02 is not a finding that affects the interpretation of the study results. The presence or absence of the diaries is inconsequential because the CRFs served as a reliable source document for the study. [redacted] the study sponsor of 92-LID-02, has definitively stated that the case report form was the primary source document for determination of the dates and time of treatment initiation, and the dates and times of healing. As was described in the protocol, the information regarding an episode was to be entered into the CRF by the investigator as derived from a direct interview with the patient. The diaries were solely for the use of the patients to help them recall their episode when interviewed by the physician.

As reported by [redacted] in their response to FDA Form 483, diaries were used appropriately to help the patient report the beginning and end of an episode to the physician. Because, eight years later, the diaries cannot now be located for review, the entries they contain cannot be compared to the physician-entered data in the CRF. This may have led to a concern by FDA about the accuracy of patient recall during the clinic visit interviews. Avanir has addressed this concern in the attached report by Dr. Thisted that evaluates the time intervals between the initiation of treatment and the first clinic visit and the time interval between healing and the final clinic visit ("reporting intervals"). The

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Suite 200

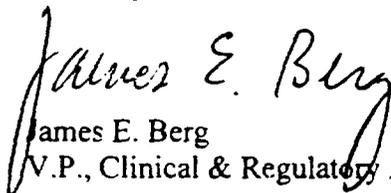
San Diego, California 92121

report addresses the two significant issues: (1) Are the reporting intervals short enough so that, even in the absence of any diaries, the physician-entered data is credible? and (2) Is there any evidence that patients receiving docosanol reported event times differently from patients receiving the control? Due to the blinded, randomized nature of the study, only the second concern could render the statistical analysis of the primary endpoint invalid.

Dr. Thisted's report reveals that the average interval between the clinic visit and the start of treatment (or healing time and clinic visit) was short, just over a day, and is a time interval over which otherwise healthy individuals would ordinarily have accurate recall. This reporting interval is short enough that even without any use of diaries to assist patient memory, accuracy to within an hour or two could reasonably be expected. Moreover, even when individuals who had extremely long reporting intervals (at either the treatment initiation or healing end of the study) are omitted from the analysis, the data strongly favor docosanol. Thus, there is no reason to believe that the study findings are driven by inaccurate event reporting. With respect to the second issue, there was no appreciable (or statistical) difference between treatment groups in the time interval of reporting to the clinic after treatment initiation (or between healing and clinic visit), which suggests that any systematic reporting effects apply equally to the two treatment groups. Consequently, there is no evidence that differential reporting is responsible for the strong findings in favor of docosanol.

The trial was randomized and the study blind was maintained. The physician assumed the responsibility to correctly enter the data into the CRF based on patient interview during which the patient could be assisted in his recall by the patient diary. Given the totality of the information, the most careful reading of the situation and the most valid conclusion to be drawn from it is that the information recorded by the physician during patient interviews, hours after the event, is accurate and robust. The CRFs are a verifiable and valid source of data even in the absence of patient diaries.

Sincerely,


James E. Berg
V.P., Clinical & Regulatory Affairs

cc: Mr. James C. Morrison (HFD-100)

Encl.



AVANIR
CORPORATION

May 17, 2000

SENT BY FEDERAL EXPRESS

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

NDA ORIG AMENDMENT

BM

Re: NDA 20-941 — copies of CRFs for clinical study 92-LID-02

Dear Dr. Wilkin:

As requested by Mr. Kevin Darryl White in a telephone conversation on April 28, 2000, Avanir is amending the NDA with copies of the case report forms from [REDACTED] clinical study 92-LID-02. The case report forms are presented in order by (tabbed) patient number in a total of 12 volumes.

Please contact me with any questions regarding this submission.

Sincerely yours,

James E. Berg
V.P., Clinical & Regulatory Affairs

Encl.

ORIGINAL



May 11, 2000

SENT VIA FEDERAL EXPRESS

James C. Morrison
Senior Advisor, CDER Ombudsman, HFD-100
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, Room 6022
Rockville, MD 20852

Re: NDA 20-941 (audit 92-LID-02)

Dear Jim:

For study 92-LID-02, several analyses were carried out to assess the possible effects of the reporting interval between treatment initiation and the first clinic visit and the reporting interval between healing and the final assessment visit. Dr. Ronald Thisted summarized these results in a brief report that may be useful to FDA in the completion of its review of the NDA for docosanol 10% cream. Please find the following two documents enclosed:

- Report entitled, "Study of Reporting Intervals" by Professor Ronald A. Thisted, Ph.D.
- Data listing for the primary endpoint (time-to-healing) for 92-LID-02 which includes the dates and times of clinic assessments.

The protocol for 92-LID-02 required patients to report to the clinic after initiation of treatment on "the first *clinic day* (i.e., the first day the clinic is open)" and to report to the clinic "on the first *clinic day* after healing" thus allowing for more than 24 hours to elapse between the event and the clinic visit. During our review of the data from 92-LID-02, Avanir sought to determine the actual time interval between initiation of treatment and the first clinic visit and the actual time interval between healing and the final clinic visit in order to assess the potential impact that the time intervals might have if they were inordinately long or were disproportionate between active and placebo groups.

In this analysis, Dr. Thisted found that patients, on average, reported to the clinic in just over one day after initiating treatment and in just over one day after being healed. There was no statistically significant difference between active-treated patients and placebo-treated patients in the clinic reporting time intervals. It is our conclusion, as well as the conclusion of others who have looked at this data, that a patient's recall should be very

good over the time period described in this analysis. (In actual practice it is not uncommon for similar time intervals to occur between an event and its entry by a patient into a diary.) Dr. Thisted's report demonstrates that the primary endpoint for the study remains statistically significant in favor of docosanol ($p=0.026$) when patients with longer than average reporting intervals (>48 hours for either interval) are excluded from the analysis.

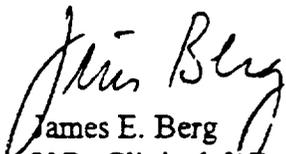
The information needed for the analyses Dr. Thisted performed was actually included in the original NDA (vol. 2.45, pp. 113-120). Appendix 10 of the statistical report for 92-LID-02, authored by [redacted] provides a listing of the primary endpoint data for that study and includes the assessment date and time for initial and final clinic visits. The data listing I am sending was prepared based on the information in [redacted] statistical report but includes only episodes relevant to the primary endpoint. The information in this data listing should facilitate additional analysis by the FDA. All of the information in the data listing, including the assessment times, has been checked for accuracy directly against the CRFs.

Avanir has a complete set of CRFs needed for the assessment of the primary endpoint of the study (at our request, [redacted] shipped them to us in 1993), however, ancillary CRFs were not necessarily included. What the FDA requested on April 28, 2000 was a copy of *all* the CRFs for 92-LID-02, and so that is what we requested from [redacted] has confirmed to us today that they will be sending copies to us tomorrow (5/12/00) by DHL Express. After they are received (which may not be until the middle of next week) copies will immediately be sent to FDA.

We understand that the FDA needs to be very careful in its final decision regarding the robustness of 92-LID-02. The information in Dr. Thisted's report provides the FDA with the assurance that the temporal relationship of the patients' reporting to the physician is reasonable and the data is accurate as recorded on the CRFs.

Please contact me if I can provide further information about the report or data listing included.

Sincerely,



James E. Berg
V.P., Clinical & Regulatory Affairs



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AMENDMENT

BL

May 5, 2000

SENT VIA FEDERAL EXPRESS

Charles J. Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



Re: NDA 20-941 — Revised Final Draft Labeling

Dear Dr. Ganley:

We are amending the NDA with revised proposed (revised) final draft labeling for docosanol 10% cream. Additionally, we respectfully request confirmation that the FDA has reviewed and approved the trade name **Abreva™**.

Please find the following enclosed:

- Proposed carton (box) labeling
- Proposed container (tube) labeling
- Annotated carton labeling
- Annotation document

If you have any questions regarding this submission please contact me.

Sincerely,

James E. Berg
James E. Berg
V.P., Clinical & Regulatory Affairs

Attachment

ORIGINAL

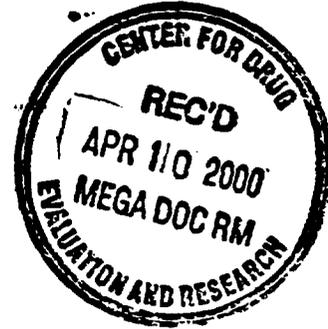
NDA ORIG AMENDMENT

April 7, 2000

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

XR



Re: NDA 20-941 — Revised Patent Information

Dear Dr. Wilkin:

We are amending the NDA with revised patent information (NDA Index Item 13) and revised patent certification (NDA Index Item 14).

If you have any questions regarding this submission please contact me.

Sincerely,

James E. Berg
James E. Berg
V.P., Clinical & Regulatory Affairs

Attachment

ORIGINAL

February 25, 2000

SENT VIA FEDERAL EXPRESS

Charles J. Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

BL
NEW COMMENT
HC



Re: NDA 20-941 — Final Draft Labeling

Dear Dr. Ganley:

We are amending the NDA with proposed final draft labeling. The trade name **Abreva** is the trade name of choice for docosanol 10% cream. Earlier (6/99) FDA communicated to Avanir that the LNC (CMCC) had approved this trade name. Additionally, after discussion with the HFD-540 this month (2/00) regarding the trade name **Abreva**, it is our understanding that the Office of Postmarketing Drug Risk Assessment (OPS/ONDC) has reviewed and approved this trade name.

Given that there are pressing lead-time considerations concerning the procurement of printed tubes we would greatly appreciate prompt confirmation that the trade name from both the Division's perspective and OPDRA's perspective is in fact acceptable as we have previously been informed and that the label copy, at least as it relates to the container (tube), is acceptable.

Please find the following enclosed:

- Carton (box) labeling
- Container (tube) labeling
- Annotated carton labeling
- Annotation document

If you have any questions regarding this submission please contact me.

Sincerely,

James E. Berg
James E. Berg
V.P., Clinical & Regulatory Affairs

Attachment

ORIGINAL



January 21, 2000

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pharmaceuticals

SENT BY FEDERAL EXPRESS

Robert J. DeLap, M.D., Ph.D.
Director, Office of Drug Evaluation V (HFD-105)

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products (HFD-540)

BM



Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

NDA 20-941 AMENDMENT

Re: NDA 20-941 (docosanol 10% cream) Study 92-LID-02 investigational site audit; Form FDA 483 response and supporting documentation

Dear Drs. DeLap and Wilkin:

The audit of clinical study 92-LID-02 in The Netherlands was conducted from December 6-9, 1999 by Jose A. Carreras, M.D., Medical Officer, HFD-45 and Gerald N. McGirl, D.D.S., HFR-PA150. The audit was mainly conducted at the facility of the study sponsor, [redacted]

[redacted] Because both clinical investigators (Loek Habbema, M.D. and Koenraad de Boule, M.D.) had relocated after 92-LID-02 was completed, no meeting with the investigators at their new sites had initially been planned. However, following a request by one of the auditors, [redacted] arranged on short notice a meeting with Dr. Habbema at his new facility.

According to reports from [redacted] the inspectors found [redacted] records in order and were satisfied with the quality of the study file available there. There were no issues related to the study blind, drug randomization, or the accuracy of the database. Following the audit of [redacted] and Dr. Habbema, a Form FDA 483 was issued by FDA and copied to Avanir by [redacted] has prepared and faxed to Drs. McGirl and Carreras a formal response to the Form FDA 483, a copy of which follows this letter.

As the sponsor of NDA 20-941, Avanir is augmenting the response of [redacted] to the Form FDA 483 with additional documentation as described in this letter. A summary table follows.

The first of two observations in the Form FDA 483 describes minor deviations from the protocol — that photographs were not taken and that the patients were not contacted by telephone during the study. After the study was initiated, the investigator and the sponsor agreed that performing these tasks was impractical and would not provide useful information. This reasoning regarding the telephone calls is documented in a letter dated October 8, 1993 from Geertjan Roders, M.D. (the medical monitor for the study) and Hans Verschoor (the statistician who wrote the statistical report for 92-LID-02) to Jim Berg of Avanir Pharmaceuticals (Attachment 1). The protocol was

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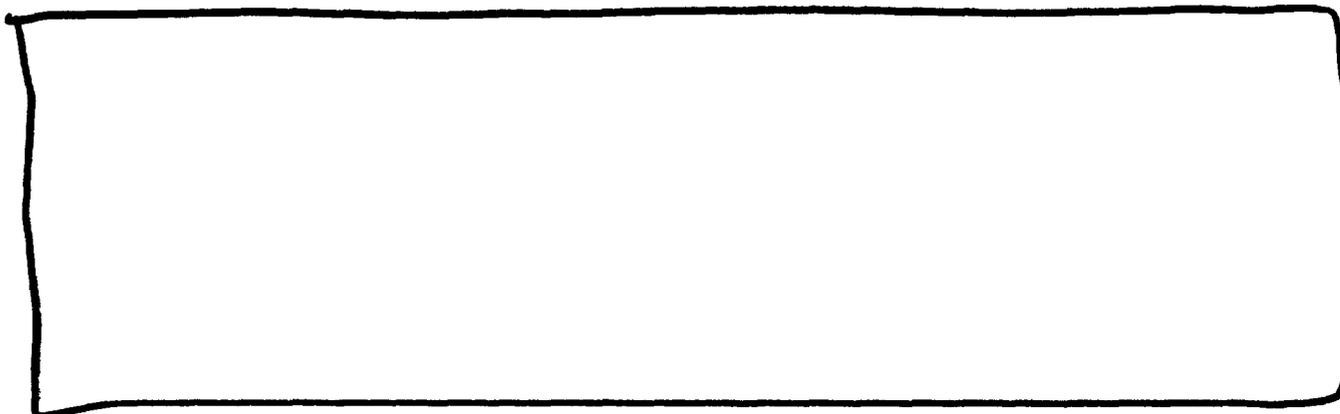
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San Diego, California 92121

not formally amended by (then) [redacted] to reflect these procedural changes. The changes are, however, apparent in the statistical report of the study.

The second observation is that the investigator did not maintain complete study records, since study subjects' diaries were not present in the study file. The protocol (Attachment 2) described the use of diaries to help the patients recall the episode (start time, stage at initiation, symptoms, and healing time) for report to the physician at the clinic visit (Section 1, Summary, p. 7). The protocol also described the requirement that the patient be queried by the physician regarding the onset and end of the episode (Section 6.2, Methods of Assessment, p. 16). The investigator was to question the patients, confirm their responses, and enter the data directly on the CRF (Section 9.1, Data Collection, p. 19). [redacted] staff considered this clinician-generated data as the primary source data with the diary card to be used only as an aid to the patient as stated in the October 8, 1993 letter to Jim Berg (Attachment 1). As such they did not collect or copy the diaries for retention in their files. That the CRFs and not the diaries were the primary source document in this study was prospectively described by the protocol for study 92-LID-02 (Section 9.1, Data Collection, p. 19). The protocol does not specify that diaries should be archived (Section 11.8, Data Archiving, p. 22). Because the CRFs were the primary source documents, that the diaries were not archived does not affect the credibility and reliability of the study data.

The investigators cannot locate the diary cards and now, seven years after the study and after moving to new facilities, do not remember their disposition. (Dr. Habbema conducted two other clinical studies with docosanol since completion of 92-LID-02 in mid-1993, 94-LID-01 and 95-LID-02; Dr. de Boule conducted one other study with docosanol, 94-LID-03 [see NDA 20-941]). After the audit visit was completed, [redacted] was able to verify — by further discussions with the investigators and with [redacted] staff, as well as through contact with subjects formerly enrolled in 92-LID-02 — that diaries were indeed used as described above. Due to the take-over [redacted] change of location of investigators, and changes of staff [redacted] and [redacted] (investigators), however, they have been unable, to date, to locate the diaries.

Documentation available to Avanir Pharmaceuticals and provided to Dr. Carreras (Attachment 3) that confirm the use of patient diaries includes the following:



Robert J. DeLap, M.D., Ph.D.

Jonathan K. Wilkin, M.D.

January 21, 2000

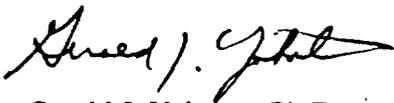
Page 3



In summary, both of the observations on the Form 483 are procedural or clerical in nature and are not discrepancies affecting the reliability of the study results. The investigator-generated data is complete and was used as the source data for the information reported in the NDA. There were no issues related to the study blind, drug randomization, or the accuracy of the study database, and there were no serious discrepancies in the conduct of the study. The observations listed in the Form FDA 483 were equally relevant to both study groups — docosanol and placebo. As such, study 92-LID-02 meets the criteria defined by Dr. Woodcock for a confirmatory study in her letter of November 3, 1999 to Avanir Pharmaceuticals.

It is our hope that this information, together with our December 2, 1999 response to Dr. Wilkin's request for information, and our January 14, 2000 fax to Mr. Tom Parmelee, HFD-560 will allow FDA to issue an approval letter for docosanol cream soon.

Sincerely yours,



Gerald J. Yakatan, Ph.D.
President and CEO

cc: James C. Morrison, HFD-001



TELECOMMUNICATION TRANSMITTAL

CONFIDENTIALITY NOTE:

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ATTN: Kevin Darryl White	DATE: 1/18/00
COMPANY: Food and Drug Administration Regulatory Health Manager DDDDP - HFD-540	FAX #: (301) 827-2075
	TIME: 6:15 PM PST
FROM: James E. Berg	FAX #: (858) 453-5845
TITLE: VP Clinical & Regulatory Affairs	TEL #: (858) 410-2598

NUMBER OF PAGES, INCLUDING COVER SHEET: 4

RE: NDA 20-941 FDA Team Meeting

Dear Kevin Darryl:

Today we received a copy of [redacted] response to the Form FDA 483 regarding the site audit for clinical study 92-LID-02. It is my understanding that the two auditors, Drs. McGill and Carreras, were also faxed this document today; however, I wanted to be sure that you were copied prior to the FDA team meeting scheduled for tomorrow.

Obviously we are anxious to find out what the next steps are pertaining to the approval of our NDA and would appreciate your communicating them to us at the earliest moment.

Best regards,

Jim

If there are any problems with the transmission of this fax, please call 858.558.0364; ext. 201.

Direct line (071) 545 5 824

Direct fax (071) 545 5 209

Our ref. PMB/ask/00.034

Your ref.

Date 17 January 2000

BY COURIER AND TELEFAX

United States Food and Drug Administration
Attn. Gerald N. McGirl, D.D.S.
San Francisco District Office
1431 Harbor Bay Parkway
Alameda, California 94502-7070
USA

Subject: Investigational site audit (December 6-9, 1999) for clinical study 92-LID-02 (NDA 20-941) of Louis Habbema, M.D., formerly located in Rotterdam, the Netherlands

Dear Dr. McGirl,

Study 92-LID-02, a Phase II double-blind study conducted from December 1992 to June 1993, was sponsored by [redacted] and hereinafter referred to as "Sponsor") to evaluate the efficacy of docosanol 10% cream in the treatment of recurrent herpes labialis. As indicated during the FDA's audit, this study was conducted as a proof-of-concept study to evaluate the potential of the drug product. The study was conducted according to the principles of Good Clinical Practice (GCP) as understood and practiced by [redacted]. Following the FDA investigational site audit of this study, Dr. Jose A. Carreras, Medical Officer, HFD-45 and Dr. Gerald N. McGirl, HRF-PA150 issued a Form FDA 483 listing two observations. The observations regarding protocol 92-LID-02 and Sponsor's response, addressing them, follow:

OBSERVATION

1. The clinical study was not conducted according to the relevant protocol. For example, photographs were not taken and telephone calls were not performed.

RESPONSE

All major aspects of the study were, in fact, conducted according to protocol. For example, ethics committee approval, patient consent, compliance with inclusion and exclusion criteria, blinding, randomization of drug, the number of drug applications, the frequency of clinic visits, reporting of adverse events, laboratory evaluations including HSV serology, completion of the CRFs, safety reporting, and statistical analysis were all performed as described in the protocol. Only minor deviations that were not directly relevant to the primary study endpoint, i.e., the two cited above, occurred.

With the study design described in protocol 92-LID-02, photographic evaluation of lesions at clinic visits would have provided little information about the primary endpoint, time-to-healing. Most patients had only two clinic visits. The initial clinic visit would have provided a single point during an episode at which a lesion may or may not have been present, and, since the study was patient-initiated, would not even have provided a baseline value.

The final clinic visit was to be scheduled after healing had occurred and would have resulted in photos of healed skin for all patients. The inclusion in the protocol of photographs derived from earlier [redacted] clinical studies of other dermatological disorders and should not have been included in protocol 92-LID-02. For these reasons, the sponsor determined that photographs would not be taken. Although this message was conveyed to the two investigators, Dr. Habbema and Dr. de Boule, no formal protocol amendment was generated.

Shortly after the study was begun, it was realized that the telephone check, scheduled in the protocol for Day 4, was not practical to complete (e.g., patients would not be home or could not be reached because of work or privacy reasons). The investigator and the sponsor, therefore determined that Day 4 telephone contact would not be necessary. This reasoning is documented in writing by the Clinical Research Manager. No formal protocol amendment was generated.

Currently, in 1999, it is Sponsor's standard operating procedure to formally amend a clinical study protocol regardless of the perceived significance or nature of the proposed change, to advise the investigators and obtain their signatures indicating their understanding and acceptance of the change, and to provide ethics committees with the proposed changes and seek their approval. Protocol amendments, being essential according to ICH guidelines, are filed in central study archives at Sponsor's headquarters in accordance with Sponsor SOP MED-2.01, dated 1 March 1997, revised from the 1 February 1995 version and SOP MED-8.01, dated 1 June 1997, revised from the 15 February 1995 version.

OBSERVATION

2. Adequate case histories pertinent to the clinical study were not maintained. For example, there were not subjects' diaries present in the study records.

RESPONSE

With the exception of the study subject diaries, patient histories appear to be complete at the study site where copies of CRFs and informed consent forms are on file. Copies of the lab reports and the original CRF's are present at the Sponsor's study archive. The CRFs required the Investigator to provide for each patient information regarding demographic data, medical history, herpes labialis history, normal location of outbreaks, first clinical assessment, second or final clinic assessment, concomitant medications, adverse events, and study termination. The CRF was the primary source document for 92-LID-02; the Investigators were to record information about the patients directly on those forms. The diaries were to be used only as an aid by the patients to help them respond to the physicians' questions about their episode. During the audit, Dr. Habbema could not locate the diary cards and, seven years after the study and after moving to a new facility, could not remember their disposition.

(Dr. Habbema conducted two other clinical studies with docosanol since completion of 92-LID-02 in mid-1993 - 94-LID-01 and 95-LID-02.) After the audit visit concluded on December 9, 1999, Dr. Habbema and Sponsor have continued an attempt to determine the disposition of the study subject diaries. Sponsor has been able to verify that indeed diaries have been used in the way as described above, but due to the take-over, change of location and changes of staff, has not been able to determine their final disposition.

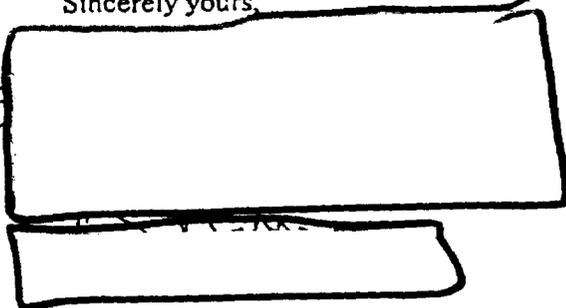
The 92-LID-02 protocol described the use of diaries to help the patients recall the episode (start time, stage at initiation, symptoms, and healing time) for report to the physician at the clinic visit. The protocol also described the requirement that the patient be queried by the physician regarding the onset and end of the episode. The Investigator was to question the patients, confirm their responses, and enter the data directly to the CRF. To be clear, as is customary when patient diaries are used, the physician carefully questioned the patient and entered the clinically correct information into the CRF. Sponsor's staff saw this clinician-generated data as the primary source data with the diary card to be used only as an aid to the patient. Involved individuals who remain on staff at this time do not recall collecting or copying the diaries for retention in Sponsor's files. The clinical monitor does remember, however, checking diaries against the CRFs at the Investigator's site during a monitoring visit.

Currently Sponsor advises its Investigators that they must maintain all study records for at least 15 years following study completion as required by EEC guidelines for GCP. Established SOPs at Sponsor require them to maintain study records for the lifetime of the product (SOP MED-8.02, dated 1 June 1997, revised from the 15 February 1995 version and SOP MED-3.03, dated 1 April 1997, revised from the 6 October 1992 version).

It is our intent to be fully compliant with all ICH guidelines pertaining to GCP. Sponsor has made significant improvements in clinical practice since 1992. This was our first interaction with auditors from the U.S. Food and Drug Administration, and it was an excellent learning experience for us even though the study audited was conducted seven years ago. We very much appreciate the information provided to us by you and Dr. Carreras during the audit, further assisting us in our goal of complete global regulatory compliance.

Please contact us with any questions about this letter.

Sincerely yours,

A large rectangular area of the document is redacted with a thick black border. Below it, a smaller, narrower rectangular area is also redacted with a thick black border. The redaction covers the signature and any text that might have been present.

cc: Dr J.A. Carreras, MD

This letter is the response by Sponsor as referred to by letter of the Investigator, Mr. L. Habbema M.D. as sent to Dr. Carreras and Dr. McGirl on 20 December 1999, in the above-captioned matter (copy enclosed). Please include this letter in your response.

December 2, 1999

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



Re: NDA 20-941

Dear Dr. Wilkin:

Thank you for your letter of November 22, 1999 concerning the remaining items needed for FDA to complete its review of NDA 20-941 for docosanol cream 10%. As you know, the site audit of study 92-02 has been scheduled by CIB/HFD-47. Avanir responses to the remaining items follow:

A. Chemistry

We were surprised that chemistry (and microbiology) items appeared as FDA issues since Avanir was informed during the March 15, 1999 meeting that our responses (provided in the meeting read-ahead document) to the relevant issues listed in the December 22, 1998 not-approvable letter were acceptable. As directed by the FDA, these were formally submitted to the NDA on March 18, 1999. Nonetheless, our response to items A1 and A2 follows this letter (APPENDIX A). If, after reviewing these responses, you still find it advisable for us to schedule a meeting with your CMC staff to discuss chemistry issues, please let us know so that we can schedule a teleconference as soon as possible.

B. Pharmacology and Toxicology

Avanir Pharmaceuticals commits to conduct as Phase 4 studies 1) a study to examine the dermal carcinogenicity potential of docosanol cream 10% and 2) a study to address the long-term potential of the product to enhance UV-associated skin carcinogenesis. Please accept this letter as written confirmation of such. Further FDA guidance regarding the rationale behind these studies and methodology to be employed will be requested at a later date.

C. Microbiology

A revised stability protocol for microbial limits and preservative effectiveness stability testing follows this letter (APPENDIX B).

D. Clinical

Labeling has been drafted and is included for your review (APPENDIX C). The March 17, 1999 Federal Register document "Over-the-Counter Human Drugs; Labeling Requirements; Final Rule" (64 FR 13254) was used as guidance in its preparation. A mock-up draft carton will be provided when available.

The possible requirement for a labeling comprehension study will be discussed with the Division of Over-the-Counter Drug Products.

We look forward to your evaluation of the information provided in this submission.

Sincerely,



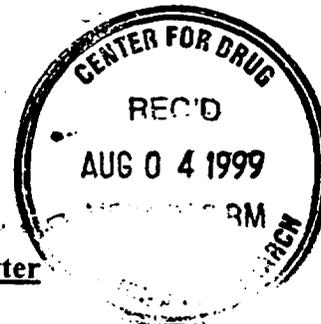
Gerald J. Yakatan, Ph.D.
President and CEO



August 3, 1999

SENT VIA FAX AND FEDERAL EXPRESS

Robert J. DeLap, M.D., Ph.D.
Director, Office of Drug Evaluation V (HFD-105)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Re: NDA 20-941 — Information requested in FDA's 7/21/99 letter

Dear Dr. DeLap:

NDA ORIG AMENDM

BC BZ
DEF CSO

Thank you for your letter of July 21, 1999 and your commitment to continue to work with us to further examine the data from our prior clinical trials on docosanol (Lidakol). We are pleased that you have completed reviewing our additional analyses and interpretations with respect to our studies 96-LID-06 and 96-LID-07 and that you recognize that we have used sound statistical principles to address your fundamental issue of approvability. We have noted your interest in the Proportional Odds Ratio method for covariate adjustment and believe that information we have presented in various submissions beginning in March, 1999 provides evidence for the statistically significant effectiveness of docosanol in studies 96-LID-06, 96-LID-07, and 92-LID-02. We continue to feel that the consistent demonstration of effectiveness seen in these studies, and the need to have a product with a different mechanism of antiviral action available for prescribing physicians, should lead you to approve docosanol.

Your July 21 letter requests certain information still outstanding as a result of our June 8, 1999 meeting with you:

“At our June 8, 1999, meeting with you, we requested that you also consider exploratory analyses using Wilcoxon test methodology including not only center as a stratification factor but also the other covariates of interest; this could help to assess the effects of the individual covariates and could provide a complementary way to examine these findings and assess the consistency of the data. We remain interested in seeing such analyses.

Also, since the Proportional Odds Ratio analyses previously submitted considered only two of the three covariates that had been specified in the original study protocols, we requested that you submit analyses including all three covariates. We note that your June 25, 1999, submission included this analysis for study 96-06, but the analysis for 96-07 was reported as still in progress.

Attached are detailed suggestions from our statistical specialists regarding the application of the stratified Generalized Gehan-Wilcoxon test in exploratory analyses to look at effects of the individual covariates....”

We are pleased to be able to provide you with this information. The results of the Proportional Odds Ratio analyses using all three covariates in the 96-07 study are shown below. The exploratory analyses using Wilcoxon test methodology are quite extensive and are included in a separate statistical report that we have attached for your use. Some of the issues associated with this methodology are summarized in this letter as well.

Results from analyses previously reported as in progress. Our original proportional odds analysis used only two of the three originally specified covariates. In the June 8 discussion we stated that this was appropriate since fewer than 1% of individuals did not experience prodrome (the defining characteristic of the third covariate), and hence, that covariate could not account for more than a small amount of variation in healing times once the other covariates were taken into account. We predicted that adding the third covariate would likely change the p-values by a negligible amount and that the estimated size of the Lidakol effect would also change only slightly. In our June 25, 1999 submission we described this reasoning at greater length — adding that the covariate increased variance while decreasing bias by a smaller amount suggesting slightly larger p-values. This was borne out in the analysis of the 96-06 study that we were able to report at that time. As expected, the same findings hold for the 96-07 study. These results, and their relationship to the two-covariate results, are given in the now completed Table 1B below. The effect estimate is listed first and the p-value is listed in parenthesis under each study.

Center effect in analysis	Covariates	96-LID-06	96-LID-07
Indicators for center	2	1.177 (0.010)	1.231 (0.006)
Indicators for center	3	1.192 (0.013)	1.217 (0.007)

Table 1B Efficacy results using proportional odds regression with the covariates historical episode duration and stage at entry with and without the covariate presence of prodrome.

These results further demonstrate the consistency of the findings from the two studies. Individually, each study consistently shows an approximately 20% advantage for Lidakol (regardless of covariate adjustments or method of analysis). Moreover, when the full set of covariates is taken into account the consistency *between studies* is evident, and strong statistical significance is demonstrated.

It is worth noting that, even using the less powerful statistical method of Cox regression (proportional hazards) with all of the prespecified covariates, the estimated effects are consistent with the findings above. This Cox regression analysis was proposed in the original protocol submission and shows advantages of 24% and 27% for Lidakol with p-values of 0.058 and 0.045 in studies 96-06 and 96-07, respectively [June 25, 1999 submission, Table 1A].



Exploratory analyses using Wilcoxon test methodology. At the June 8 meeting, FDA statisticians asked whether additional analyses could be done using the Wilcoxon test to include covariates as well to get another indication of the covariate effect. We indicated at the meeting that we could see no valid way to do so that would not split the existing data into very small subsets. The suggestion was then made that perhaps combining small centers would be a way to avoid the small sample size problem.

In preparing our June 25, 1999 response, we considered in detail whether such an approach would be feasible, valid, and useful. We concluded that, while feasible, any such approach:

1. would not adequately address the issue of small sample size due to over-stratification;
2. would require a number of *ad hoc* choices [such as the cutoff size for combining centers or the criteria for selecting which centers to combine];
3. would have the potential for introducing substantial bias through combining small centers; and
4. would not provide sufficiently stable estimates of effectiveness to be useful in assessing consistency.

For these reasons we elected in our submission of June 25, 1999 to demonstrate both consistency and the effect of covariates with statistical methods not limited by these features.

We noted that your letter requesting this information describes the requested analyses as "exploratory." We agree that the 24 sets of post-hoc subset analyses suggested in the third section of your letter cited above can *only* be considered as exploratory. Subset analyses and post-randomization selection of grouping factors have the potential for bias, for identification of spurious effects, and for selective interpretation. Throughout our submissions we have adhered as closely as possible to the prospectively defined plans for statistical analysis. We believe that the requested analyses can provide little evidence, positive or negative, about either the covariate effects or the consistency of the data.

We are concerned that the requested analyses can neither establish consistency nor reliably detect inconsistency. We are, however, supplying the requested information in the report that accompanies this letter. In that report, written by Professors Thisted and Pearl, we also articulate in some detail the difficulties alluded to in the preceding two paragraphs, and we provide as much context as possible for interpreting these results. *We believe that the results of these requested analyses are uninformative about consistency and about individual covariate effect. These are due, respectively, to the large variability introduced by examining small subsets and to the fact that the stratified Wilcoxon test procedure produces no direct estimate of the size of effects.* To understand the extent to which variability must be taken into account in assessing the requested analyses, we have undertaken extensive simulation studies. The results of these studies are incorporated into the report.

In summary, we have provided in this letter the results of the covariate analysis for study 96-07 that was completed shortly after the June 25, 1999 submission. The consistency of the studies in demonstrating the efficacy of Lidakol has been shown. Results of explor-



atory Gehan-Wilcoxon analyses suggested by FDA statisticians are included in the attached report. The SAS data set requested (containing the variable "history" and other efficacy variables in the dataset "totality") by FDA is also being provided at this time.

The additional information regarding the effectiveness of Lidakol provided since receipt of the December 22, 1998 action letter and including the current submission is summarized in the attached table. These documents address the issues of consistency of the studies and effects of covariates in great detail. We are confident they provide thorough and compelling scientific evidence of effectiveness supporting approval of the drug.

Sincerely,



Gerald J. Yakatan, Ph.D.
President and CEO

ORIGINAL

ORIG AMEND

BS



June 25, 1999

ORIG AMENDMENT SENT VIA FAX AND FEDERAL EXPRESS

Robert J. DeLap, M.D., Ph.D.
 Director, Office of Drug Evaluation V (HFD-105)
 Jonathan K. Wilkin, M.D.
 Director, Division of Dermatologic and Dental Drug Products (HFD-540)
 Food and Drug Administration
 9201 Corporate Blvd.
 Rockville, MD 20850

*No action indicated
 content reviewed
 previously
 Mike Metzger
 6/28/99*

Re: NDA 20-941—Documentation Regarding Statistical Issues

Dear Drs. DeLap and Wilkin:

We appreciate the on-going discussions between Avanir and the Agency regarding our NDA submission. To increase your familiarity with the new statistical analysis, Drs. Ronald Thisted and Dennis Pearl have prepared the attached document, "Clarification of Remaining Statistical Issues for the Approval of Lidakol" that addresses specific statistical issues raised at the 3/15/99 and 6/8/99 meetings with the FDA. We're confident that you will find the document addresses your concerns and that it is concise and readable.

As we now approach the decision point on the additional evidence of efficacy we have provided, I feel it is important to summarize the situation to date including new statistical information relative to the remaining questions before us. That is the purpose of this cover letter. The letter is followed, for your use, by a "bullet point" summary of the major issues.

The NDA submission

On December 22, 1997, Avanir Pharmaceuticals submitted the NDA for docosanol 10% cream. Avanir pointed to the data from a large, multi-center clinical trial as its primary proof of efficacy for the product. This study (96-06/07) convincingly demonstrated statistically significant differences in the primary efficacy parameter (time-to-healing) between docosanol and the placebo. The study was a pre-specified combination of two identical studies, 96-06 and 96-07, which were combined to assure there was enough power to assess differences in treatment effect. HFD-530 asked that in addition to analyzing the data from 96-06/07, we analyze 96-06 and 96-07 separately. We thought that performing the individual study analyses would show whether the data in each study demonstrated the same trend of effect and whether the two studies were "telling the same story." After analysis, one of the studies (96-06) showed statistical significance on its own. The other showed approximately the same magnitude of effect but was not significant to $p \leq 0.05$. In our view, the effectiveness of the product was clear. Not only did the combined study demonstrate effectiveness, but each of the sub-studies, in every way we

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Statistical validity and computational correctness of the proportional odds method

The proportional odds regression model is the logical extension of the Wilcoxon test in the same way as the well-known Cox regression method extends the [redacted]. In fact, the proportional odds regression model reduces to the Wilcoxon test when no covariates are used, and the model has power for detecting early events in the same manner as the Wilcoxon. All that we have done is to utilize statistical methodology that both the sponsor and the FDA would have used was appropriate had the technology been available at the time.

While the proportional odds model has been in use for some time, the Shen algorithm that allows use for censored data is relatively new. However, this algorithm is stable, and without covariates the results from the Wilcoxon are reproduced (See Table 2 of the Statistical Report). The algorithm provides the appropriate response on simulated data sets and duplicates the results obtained from another algorithm on a standard data set. Appropriate statistical diagnostics corroborate the appropriateness and goodness of fit of the model. All in all, *Avanir has utilized respectively identified statistical methodology that demonstrates the effectiveness of docosanol studies 96-06 and 96-07. While that methodology was not computationally feasible at the time of the original NDA submission, it is now possible and its use in our March 1, 1999 submission was both statistically valid and computationally correct.*

Summary

The FDA should approve our NDA because docosanol 10% cream has been shown to be safe and effective for its intended use based on the results from multiple clinical trials. The combined 96-06/96-07 trial shows statistically significant efficacy with and without covariate adjustment. Studies 96-06 and 96-07 show statistically significant efficacy individually after covariate adjustment. A smaller trial (Study 92-02) also shows statistically significant efficacy (See 1999 submission, Appendix H). Studies 96-06 and 96-07 both demonstrate significant treatment efficacy for multiple secondary endpoints recognized as being important by clinicians in the field.

Dr. Sacks said at the March 15, 1999 meeting, because its mechanism of action differs from that of currently available anti-herpes agents, physicians need a drug such as Lidakol available to prescribe to their patients.

In this submission Avanir believes it has addressed all the statistical concerns of the FDA, and, as such, has fulfilled the FDA's request for additional evidence of effectiveness for docosanol. We look forward to a prompt review of this submission.

Thank you for your continued interest in working with us to satisfy the Agency requirements for approval.

Sincerely,



Eld J. Yakatan, Ph.D.

President & CEO

ORIGINAL

BL

AVANIR
pharmaceuticals

May 24, 1999

DRUG AMENDMENT

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: NDA 20-941

- Request for expedited review by the LNC of the tradename *abree*.™
- Revised product labeling (annotated product insert)

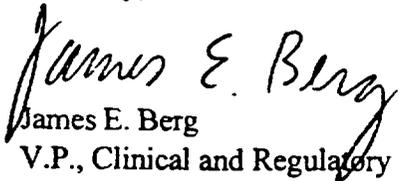
Dear Dr. Wilkin:

During the 3/15/99 meeting in Rockville Dr. Steve Hathaway stated that the three trade-names Avanir had submitted to the FDA for docosanol 10% cream (Lidakol, Abreva, and Abreve) were approved. Due to trademark concerns Avanir requests that the Labeling and Nomenclature Committee review one additional name that Avanir owns for docosanol 10% cream, *abree*. It is our understanding that the LNC meets monthly but that at special request will consider reviewing a proposed tradename outside of the standard time frame. We would be most appreciative if *abree*. could be considered in this way as it would allow Avanir to quickly move forward with draft container labeling to submit to the Agency as was requested during the 3/15/99 meeting.

In addition, based on Dr. Hathaway's 3/15/99 comment that approvability will depend on the labeling, please find enclosed revision 1 to the annotated package insert submitted with NDA 20-941.

Please address any questions regarding this submission to my attention.

Sincerely,


James E. Berg
V.P., Clinical and Regulatory Affairs

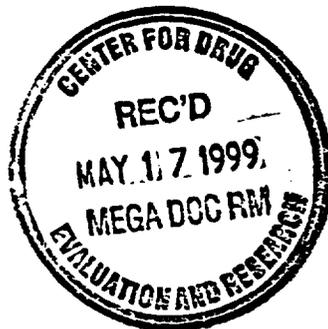
www.avanir.com

619.558.0364
fax: 453.5845

9393 Towne Centre Drive
Suite 200
San Diego, California 92121

ORIGINAL

NC
AVANIR
pharmaceuticals



May 14, 1999

NEW CORRESP

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

**SUBJECT: NDA 20-941 — Completed Table A of the Briefing Document; and
Request for Meeting on Biostatistical Issues**

Dear Dr. Wilkin:

We refer to our meeting with Division 540 on March 15, 1999 and the minutes of that meeting sent to the FDA on March 24, 1999. We also refer to the following table, which provides a reference to the interactions between FDA and Avanir occurring since March 1, 1999.

Material requested by or provided to the FDA	Date sent to the FDA
Pre-meeting Briefing Document (15 copies)	3/1/99
Formal submission to the NDA of the CMC and Pharm/Tox responses contained in the Briefing Document	3/18/99
3/15/99 meeting minutes composed by Avanir and Avanir overhead presentations	3/24/99
Formal submission to the NDA of the Additional Evidence of Effectiveness contained in the Briefing Document and presented at the 3/15/99 meeting	3/29/99
References (two) listed in Dr. Thisted's 3/19/99 letter to Dr. Wilkin regarding the scientific basis for using the proportional odds model	3/25/99
Three additional desk copies of the Briefing Document with Table A updated through 3/30/99	4/2/99
Clinical information from study 92-02	4/29/99 (faxed) 4/30/99 (submitted to the NDA)
The statistical code for the Shen algorithm	5/3/99 (by hard copy and e-mail) 5/5/99 (submitted to the NDA)
Update completing Table A of the Briefing Document	5/14/99

This table includes reference to information we are submitting today. We are submitting an updated and complete version of Table A, which was originally included in the Briefing Document for the March 15 meeting. This table is now complete and includes results of the proportional odds regression analysis of Study 96-06/07 just finished by Drs. Pearl and Shen.

At the March 15 meeting, there were statistical issues identified as needing internal discussion. The FDA suggested that, following sufficient time for such internal discussion, a meeting of FDA and Avanir statisticians be held to address any remaining statistical concerns or questions. So that 540 can complete its review of the additional evidence of effectiveness submitted by Avanir, we would like to schedule this previously proposed meeting of statisticians as soon as possible. (One day available to both our statisticians is May 28, 1999.)

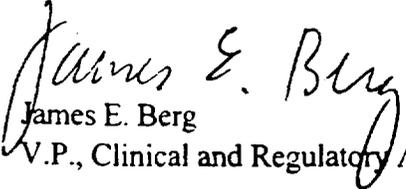
Based on the minutes of the March 15 meeting with the FDA, it appears that it would be useful at our meeting to address and to resolve issues involving the following areas:

1. Statistical aspects of the proportional odds regression model
 - A. To what extent is the proportional odds regression model accepted in regular statistical practice?
 - B. What is the relationship of the proportional odds model to standard frailty models?
2. Appropriateness of the proportional odds regression model for analysis of 96-06 and 96-07
 - A. To what extent are there unique features of the 96-06 and 96-07 data that make the proportional odds model particularly suitable for analyzing these studies?
 - B. To what extent is the proportional odds regression model a logical covariate adjustment method based on the design criteria set forth in the 96-06 and 96-07 sub-studies? In particular, is proportional odds regression the logical extension of the Wilcoxon test?

Avanir understands that 540 has already met and sought consultation on some or all of these issues, so perhaps a meeting to discuss these items is no longer necessary. If, however, because of those meetings and consults, you have additional or different questions and/or points to consider, we ask that you send those to us in sufficient time for us to adequately address the issues.

Please address any questions regarding this submission to my attention.

Sincerely,


James E. Berg
V.P., Clinical and Regulatory Affairs

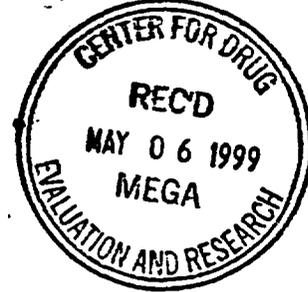
ORIGINAL

AVANIR
pharmaceuticals

May 5, 1999

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



~~ORIG AMENDMENTS~~

BS

SUBJECT: NDA 20-941
Statistical information requested by reviewing statistician

Dear Dr. Wilkin:

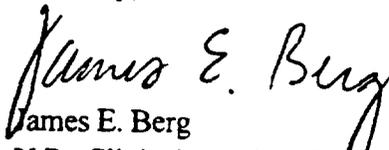
We are amending our NDA with information that was requested regarding the technique used to analyze the efficacy data from studies 96-06 and 96-07 under the Proportional Odds Regression model. This information was previously sent by courier to the FDA to the attention of Mr. Kevin Darryl White and Dr. Ping Gao on 5/3/99.

The materials sent today include the following:

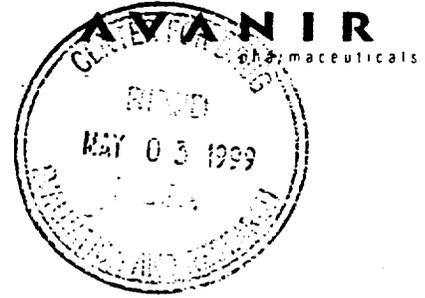
- Cover letter from Professors Pearl and Shen
- A note explaining the function to be maximized
- A note on the structure of the Shen algorithm and why it works
- Instruction on how to run the program
- The FORTRAN code (also sent by e-mail/D. Pearl, Ph.D. to Dr. Gao)
- A sample data set that can be run quickly (also sent by e-mail/D. Pearl, Ph.D. to Dr. Gao)
- *The Annals of Statistics* reprint proving properties of the estimation technique

Please address any questions regarding this submission to my attention.

Sincerely,


James E. Berg
V.P., Clinical and Regulatory Affairs

ORIGINAL



April 30, 1999

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

~~CONFIDENTIAL~~
BM

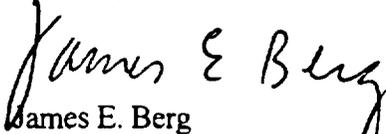
SUBJECT: NDA 20-941
Questions from medical officer regarding clinical study 92-02

Dear Dr. Wilkin:

We are amending our NDA with answers to questions communicated to us on 4/22/99 by Dr. Okun regarding clinical study 92-02. This information was previously faxed to the attention of Mr. Kevin Darryl White on 4/29/99.

Please address any questions regarding this submission to my attention.

Sincerely,


James E. Berg
V.P., Clinical and Regulatory Affairs

BS
ORIGINAL

AVANIR
pharmaceuticals

March 29, 1999

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: NDA 20-941
Additional evidence of effectiveness for docosanol 10% cream

Dear Dr. Wilkin:

We are amending our NDA with documentation regarding the additional evidence of effectiveness for docosanol 10% cream. The majority of this data was stated in the Briefing Document submitted to the NDA on March 1, 1999 and was presented during a meeting with the FDA, held in Rockville, Maryland on March 15, 1999.

This amendment also contains the following new information not included in the Briefing Document (i) a letter from Dr. Thisted to Dr. Wilkin (faxed on March 24, 1999) regarding the relationship between the Wilcoxon test and the proportional odds model; and (ii) a statistical addendum for clinical study 92-LID-02.

Please address any questions regarding this submission to my attention.

Sincerely,


James E. Berg
V.P., Clinical and Regulatory Affairs



AVANIR
pharmaceuticals

March 24, 1999

SENT VIA FEDERAL EXPRESS

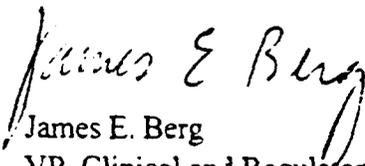
Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: NDA 20-941
Minutes and overheads from 3/15/99 meeting

Dear Dr. Wilkin:

We are amending our NDA with the minutes and overheads presented during the 3/15/99 meeting. Please advise us if the FDA finds the minutes acceptable. If the FDA would like to propose changes we would welcome its input.

Sincerely,


James E. Berg
VP, Clinical and Regulatory Affairs

www.avanir.com

619.558.0364
fax: 453.5845

9393 Towne Centre Drive
Suite 200
San Diego, California 92121

BL
ORIGINAL

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pharmaceuticals

March 18, 1999

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: NDA 20-941
Responses to Chemistry, Microbiology and Pharmacology/
Toxicology comments from the FDA's 12/22/98 N/A letter

Dear Dr. Wilkin:

During Avanir's 3/15/99 post-NDA review meeting, the FDA requested that Avanir amend the NDA with its responses to the Chemistry, Microbiology and Pharmacology/Toxicology comments from the FDA's 12/22/98 N/A letter. Avanir's responses to these issues had been submitted to the FDA (3/1/99) as part of a "Briefing Document" put together in preparation for the 3/15/99 meeting.

Drs. Hathaway (Chemistry) and Reid (Pharmacology/Toxicology) relayed that all of Avanir's responses to the Chemistry and Pharmacology/Toxicology comments as communicated to the FDA in the Briefing Document were satisfactory to the FDA. The FDA reiterated its position that Avanir should commit to conduct phase 4 studies of dermal carcinogenicity and (studies) to address the long-term potential of the product to enhance UV-associated skin carcinogenesis.

Thank you for your direction regarding this submission.

Sincerely,

James E. Berg
VP, Clinical and Regulatory Affairs



AVANIR
pharmaceuticals

February 26, 1999

SENT VIA FEDERAL EXPRESS

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Products, HFD-540
Food and Drug Administration
Center of Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

NDA 20-941
LIDAKOL® (Docosanol 10% Cream) for Oral-facial Herpes

Briefing Document

For Meeting on March 15, 1999 to Discuss N/A Letter of December 22, 1998

Dear Dr. Wilkin:

The attached Briefing Document (BD) is submitted as an Amendment to our above-captioned NDA and is intended for review before our meeting to discuss the not-approvable letter (N/A) of December 22, 1998. In the BD we present new analyses and discussions demonstrating efficacy of LIDAKOL (docosanol 10% cream) for the treatment of recurrent herpes simplex labialis (HSL). These analyses and discussions are aimed to address the Agency's concerns regarding the NDA for LIDAKOL.

The N/A appears to be based on the conclusion that efficacy had been shown in only one clinical study (not multiple studies). The N/A and the meeting of December 18, 1998 also indicated that the Division considered the results of earlier Phase III clinical studies comparing LIDAKOL with stearic acid as weighing against approval. Both of these and all other topics from the N/A are covered in the BD.

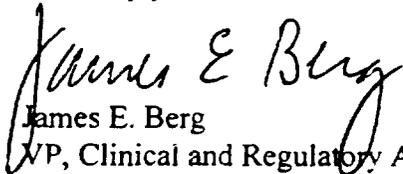
Also included in the BD for your review is a capsule overview of the history of our interaction with the Agency and the response we are making to the N/A letter.

As you will see, we have focused the meeting agenda on the lone efficacy related deficiency that the FDA cited as the basis for the FDA's determination that the NDA was not-approvable. While there were other issues detailed in the N/A letter (Chemistry/Microbiology and Pharmacology/Toxicology) these issues were described in the N/A as not being the basis for the not-approvable finding. As such, the Chemistry and Pharm/Tox issues are addressed in the BD but are not listed on the meeting agenda as discussion items. Avanir would be happy to discuss the Chemistry/Microbiology and Pharmacology/Toxicology issues in more detail if the FDA thinks this is necessary at a later time.

As you know, we have had communications with Dr. DeLap and have already requested that he be invited to attend the meeting. We also would like to have key reviewers from HFD-540 present, including Dr. Okun and Ping Gao, Ph.D., and Rajagopalan Srinivasan, Ph.D., the biostatistical reviewers/team from HFD-725.

Please inform me if I can be of any assistance.

Sincerely yours,



James E. Berg

VP, Clinical and Regulatory Affairs

Enclosure

ORIG NEW CORRES

AVANIR
pharmaceuticals



January 15, 1998

SENT VIA FAX AND U.S. MAIL

Robert J. DeLap, M.D., Ph.D., Director
Office of Drug Evaluation V, HFD-105
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. DeLap:

Further to our phone conversation on Monday (1/11/99), we have requested a meeting with the Division to discuss the single issue ("additional evidence of effectiveness") the FDA cited in its 12/22/98 action letter as the basis for not approving the NDA (20-941) for docosanol cream. The purpose of the meeting as I understood you and as I envision it will be to elucidate specifically why the application was not approved and, based on that knowledge, to determine if we can provide the FDA with the evidence it needs for the NDA's approval. So that there is no confusion as to the agenda for that meeting, I wanted to write to you and verify your concurrence.

On January 8, 1999 we sent a letter by fax to Dr. Wilkin requesting the FDA's medical and statistical reviews for our NDA. While the 12/22/98-action letter states the need for additional evidence of effectiveness, AVANIR remains at a loss to understand why the efficacy data that was submitted fails to achieve that end. During the 12/18/98 meeting at the FDA we heard several issues discussed regarding the Division's negative position, but we truly do not understand the basis for those general statements. We left the meeting with the take-home message, it was the "reviewer's judgement. . ." This leaves us without a specific clinical or statistical item which we can address. We cannot respond to the important overall issue of clinical effectiveness until we understand exactly what led the reviewer to his conclusion.

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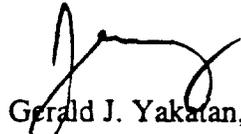
619.558.0364
fax: 453 5845

9393 Towne Centre Drive
Suite 200
San Diego, California 92121

On Monday (1/11) we followed up with an e-mail to Kevin Darryl White asking when we might expect to receive the documents requested. Yesterday, (1/14) Kevin called Jim Berg to say he was working on our request, but that he couldn't provide a date by which he could send the reviews. If we had more complete information as to what led to the Division's position, we could prepare a more detailed agenda that might make our meeting more productive. However, since the meeting has been tentatively scheduled for 2/11 our time is very short, and we may need to utilize the meeting to learn the details of the reviewer's analysis.

Please let me know if have other thoughts regarding this meeting.

Sincerely,



Gerald J. Yakatan, Ph.D.
President and CEO

Cc: Jonathan Wilkin, M.D.

NC
ORIGINAL

AVANIR
pharmaceuticals

January 13, 1999

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: Request for meeting [NDA 20-941]

Dear Dr. Wilkin:

We would like an opportunity to meet with you to understand completely what is required for the NDA for docosanol cream to be approved. Specifically, we need to know what will suffice as additional evidence of effectiveness. The development program for docosanol cream is currently at a standstill and cannot move forward until we are completely sure of the approach(es) to be taken. We ask that you grant our request for a face-to-face meeting within 30 days of this letter.

Further to the phone call from Ms. Childs today (1/13/99), the only issue that remains open for discussion related to the FDA's 12/22/98 not approvable letter is the question of "additional evidence of effectiveness." The following individuals will attend the meeting in addition to me: James Berg, VP Clinical Affairs & Product Development, Laura Pope, Ph.D., Director, Preclinical Development, Ronald Thisted, Ph.D., statistical consultant to AVANIR, and Frank Sasinowski, regulatory consultant to AVANIR.

It also seems appropriate to request that Dr. DeLap be invited to attend the meeting.

Sincerely,

A handwritten signature in cursive script that reads 'Gerald J. Yakatan'.

Gerald J. Yakatan, Ph.D.
President and CEO

NAE
MSZ
M. E. ...
6/29/99

ORIGINAL

ORIG NEW CORRES
NC

AVANIR
pharmaceuticals

January 11, 1999

SENT VIA FAX AND U.S. MAIL

Johnathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

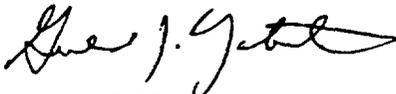
Re: Request for meeting [NDA 20-941]

Dear Dr. Wilkin:

We would like an opportunity to meet with you to understand completely what is required for the NDA for docosanol cream to be approved. Specifically, we need to know what will suffice as additional evidence of effectiveness. The development program for docosanol cream is currently at a standstill and cannot move forward until we are completely sure of the approach(es) to be taken. We ask that you grant our request for a face-to-face meeting within 30 days of this letter.

It also seems appropriate to request that Dr. DeLap be invited to attend the meeting.

Sincerely,



Gerald J. Yakatan, Ph.D.
President and CEO



ORIGINAL

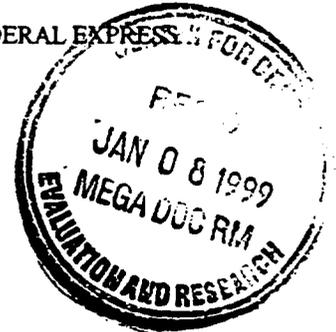
AVANIR
pharmaceuticals

January 8, 1999

NEW CORRESP
NE

SENT VIA FAX AND FEDERAL EXPRESS

Jonathan Wilkin, M.D., Director, HFD-540
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



Re: Request for Medical and Statistical Reviews of NDA 20-941 and Internal Meeting Minutes From [REDACTED] NDA 20-941.

Dear Dr. Wilkin:

In order to fully respond to the non-approvable action letter of the Center dated December 22, 1998, AVANIR is requesting copies of all reviews for NDA 20-941. Please verify that the information sent includes all summaries or reviews which may have been done, whether by a line reviewer, a group leader, the Office Director, or other. Please also include any summaries or reviews written by staff from DAVDP. We understand that it may take some time to gather the information from all disciplines, however, we need immediately copies of all clinical and statistical reviews. The others can be sent as they become available.

In order to better understand the issues leading to the non-approvable status of our drug product, we are also requesting copies of all minutes from internal FDA meetings concerning [REDACTED] NDA 20-941. Most of these may be with the DAVDP. Thank you for your assistance with this request. Please call if I can provide further clarification.

Sincerely,


James E. Berg
VP, Clinical Affairs & Product Development

Cc: Robert DeLap, M.D., Ph.D., Director Office Drug Evaluation V
Kevin Darryl White, CSO, HFD-540

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fax: 453 5845

9393 Towne Centre Drive

Suite 200

San Diego, California 92121

ORIGINAL

NEW CORRESP

NC



AVANIR
pharmaceuticals

December 22, 1998

SENT VIA FAX AND FEDERAL EXPRESS

Robert DeLap, M.D., Ph.D., Director
Office of Drug Evaluation V
Food and Drug Administration
Center of Drug Evaluation and Research
9201 Corporate Blvd., HFD-105, South 218
Rockville, MD 20850

Re: Response to action letter on NDA 20-941

Dear Dr. DeLap:

This responds to your action letter dated December 22, 1998 by notifying you that AVANIR, the sponsor of this new drug application, intends to file an amendment to this NDA. The amendment will address the single efficacy-related deficiency you cited in that letter as the basis for your determination that the NDA was not approvable at this time [see 21 CFR 314.120(a)(1)]. In that amendment, AVANIR also intends to address many, if not all, of the other issues raised in your letter that are not part of the basis for your conclusion on the current approvability of this NDA.

We look forward to working interactively with the Division and you in the future to resolve the single issue that was the basis for your current conclusion on approvability as well as the other issues raised in your December 22nd letter. We thank you for giving us the opportunity to meet with you late last Friday afternoon (December 18, 1998). That initial opportunity to discuss with the Division their views and our views of the critical clinical data was constructive. We anticipate that future interactions will similarly be mutually helpful for everyone to understand all aspects of and perspectives on the available data.

Sincerely,

James E. Berg
VP, Clinical Affairs & Product Development

Cc: Jonathan Wilkin, M.D., Director, HFD-540

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619.558.0364

fax: 453 5845

9393 Towne Centre Drive

Suite 200

San Diego, California 92121

LIDAK

PHARMACEUTICALS
ORIGINAL

October 20, 1998

NEW CORRESP

NC

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



**SUBJECT: NDA 20-941; *n*-docosanol 10% cream
10/15/98 telephone call from FDA (CMC)**

Dear Dr. Wilkin:

On October 15, 1998, LIDAK received a phone call from Dr. Steve Hathaway and Mr. Kevin Darryl White of the FDA asking us to confirm that LIDAK does not intend to use [REDACTED]

[REDACTED] in the manufacturing of the approved drug product. LIDAK wishes to confirm to the FDA that it does not intend to use either analytical laboratory in the manufacturing or quality control testing of the approved drug product.

Also, LIDAK has applied for a United States Adopted Name (USAN) for *n*-docosanol. Please find enclosed a copy of the USAN application. Please note that LIDAK's first choice for a USAN is *Docosanol* and the second choice is *Docovirol*.

Thank you for your assistance in quickly resolving these CMC issues related to the review of our NDA.

Sincerely,


James E. Berg

VP, Clinical Affairs & Product Development

Encl.: Copy of USANC Submission Form 1004 (7/98)

October 6, 1998

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



**SUBJECT: NDA 20-941; (n-docosanol 10% cream); Serial Number 006
FDA request for information regarding CMC**

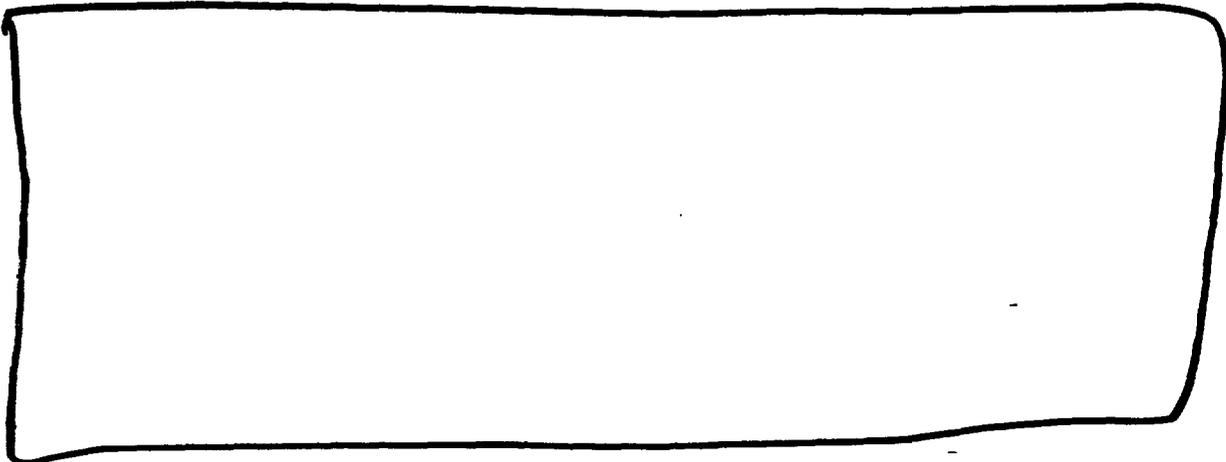
Dear Dr. Wilkin:

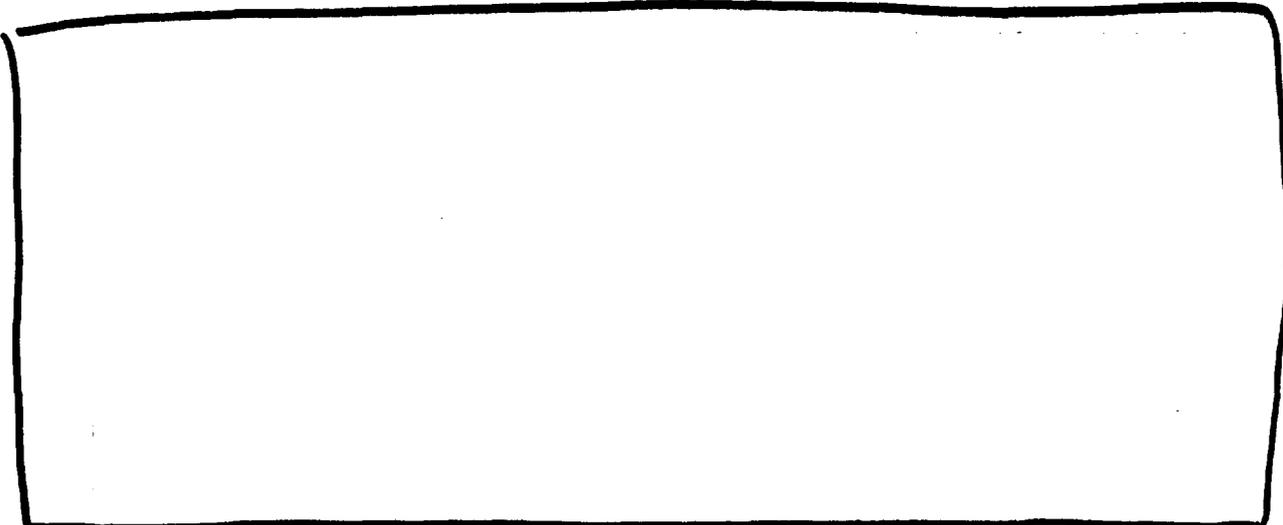
Noted
JSH
11/2/98

On Friday October 2, 1998, LIDAK received a phone call from Dr. Steve Hathaway and Mr. Kevin Darryl White of the FDA advising us 1) that DMFs completed by the drug substance manufacturer, [redacted] had deficiencies that had not yet been addressed; and 2) that our NDA did not contain the addresses of two analytical laboratories employed during the development program [redacted] and therefore the inspection program for the CMC review was not yet complete. I would like to respond to these issues as follows:

- 1) A FDA-initiated teleconference, chaired by Dr. Tony DeCamp, was held on December 3, 1997. The purpose was to supply the DDDDP with background CMC and pharm/tox information. During this teleconference, Dr. DeCamp asked if a DMF would be referenced. LIDAK responded that the manufacturing process for the drug substance was fully described in Section 3—submitted to the FDA on November 25, 1997—and therefore there would not be reference to a DMF in the NDA. Dr. Decamp replied that the reviewer, Dr. Hathaway, would be happy to hear this fact. I assumed that this was because it would streamline the review process to some degree.

[redacted] for the manufacturing process and facility were completed in late 1991 and submitted to the FDA in January 1992 by [redacted] n-docosanol. After LIDAK was allowed to thoroughly review both DMFs, it was concluded that the documents needed to be updated. For this reason, [redacted] were not cited in our new drug application. It was our decision, together with [redacted] that LIDAK would describe the manufacturing process in the NDA and not rely on a DMF. Therefore, there is no reference to a DMF for the drug substance in the NDA.





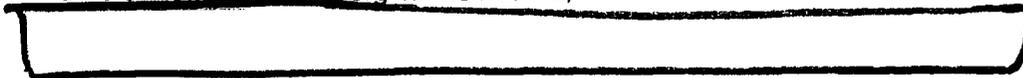
We have not seen the FDA's (DMF) deficiency letter that Dr. Hathaway mentioned during the 10/2/98-phone conversation. It appears the letter was sent to [redacted] and not directly to [redacted]. We have requested that [redacted] provide us with a copy of the letter. Because the manufacturing process was described in the NDA, the DMF does not appear to be an issue that should impact the review of NDA 20-941. We are happy to provide the addresses of the two analytical laboratories and hope that providing these addresses now will prevent delay of review completion.

On September 25, 1998, in response to my inquiries, Mr. White advised me that the CMC and Clinical reviews for our NDA remained outstanding. With regard to the CMC review, the reason articulated to me by Mr. White for the lack of its completion was a surprise. The FDA's phone call shortly following my review status inquiry causes me to wonder if there are other outstanding issues. I would appreciate your assurance that neither the DMF issue or the request for the addresses of [redacted] or any other issues will cause a delay in the timely completion of the review of our NDA. Please don't hesitate to contact me if there are any questions about today's submission. Thank you.

Sincerely,

James E. Berg
James E. Berg
VP, Clinical Affairs & Product Development

Encl.: Possible meeting participants (issued by the FDA) for 12/3/97 teleconference;
12/10/97 letter from J. Berg to K.D. White;



LIDAK

PHARMACEUTICALS

ORIGINAL

NEW CORRESPONDENCE
NO

September 10, 1998

*Correspondence filed
No action required
MOK
9/23/98*

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



SUBJECT: NDA 20-941
LIDAKOL® (*n*-docosanol) 10% Cream
Serial Number 005
FDA request for information regarding [redacted]
Study 95-4740-74 [LIDAK study designation 95-LID-03b]

Dear Dr. Wilkin:

With reference to the pending application for LIDAKOL in the treatment of recurrent oral-facial herpes, please find enclosed a communication from [redacted] dated August 27, 1998. The letter specifically addresses points 4 and 5 from an e-mail addressed to me, dated August 11, 1998, sent by Mr. Kevin Darryl White. Point 4 raised a question about the adequacy of the MED (minimum erythema dose) exposure of subjects undergoing photoallergy testing in the above referenced study, and point 5 asked for a rationale justifying the validity of the study.

As you will see from [redacted] response, that although the subjects received the prescribed UVB exposure there may have been some non-uniformity in the beam of light used to generate the MED and the beam of light used during the initial induction exposure. You will also see that [redacted] has carefully reviewed all of the data generated during the study and after having done so definitively states that the study finding of no evidence of phototoxicity or photoallergy is appropriate.

I hope this information satisfactorily addresses the issues raised in Mr. White's 8/11/98 e-mail regarding photoallergy testing of *n*-docosanol 10% cream. Please don't hesitate to contact me if there are any questions about today's submission. Thank you.

Sincerely,

James E Berg
James E. Berg
VP, Clinical Affairs & Product Development

[redacted]



September 11, 1998

NEW CORRESPONDENCE

NC

SENT VIA FEDERAL EXPRESS

Mr. Kevin Darryl White, Regulatory Health Manager
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: NDA 20-941
Trade names for *n*-docosanol 10% cream

Dear Kevin:

It is our understanding that the FDA's Labeling and Nomenclature Committee meets on the 4th Tuesday of each month and that for September they will be meeting on the 23rd. It is also our understanding that product names for consideration by the committee at this month's meeting need to be to them by September 16th.

We would greatly appreciate it if LIDAK could get on this month's Labeling and Nomenclature Committee agenda with the following potential product names for *n*-docosanol 10% cream:

1. Abreva (a•breev•a)
2. Abreve (a•breev)

Knowing that one or both of the proposed product names for *n*-docosanol 10% cream are acceptable to the FDA will be a big help to us. Our management is very interested for marketing reasons in an alternate to the trademark LIDAKOL. Can you please advise me if our proposal is acceptable to you? Thank you
Kevin.

Sincerely,

James E. Berg
VP, Clinical Affairs & Product Development

NC
ORIGINAL

July 2, 1998

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850



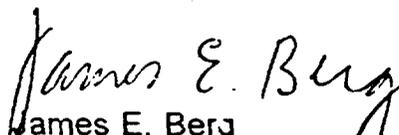
SUBJECT: NDA 20-941
LIDAKOL® (n-docosanol) 10% Cream
Serial Number 004
FDA request for additional information dated 6/19/98

Dear Dr. Wilkin:

With reference to the pending application for LIDAKOL in the treatment of recurrent oral-facial herpes, please find enclosed a communication from [redacted] that answers the two questions (both regarding topical safety study 95-LID-03b, Evaluation of Human Phototoxicity and Photoallergy) faxed to LIDAK by Mr. Kevin Darryl White, Regulatory Health Project Manager on June 19, 1998. (The [redacted] internal designation for topical safety study 95-LID-03b is 95-4740-74.)

I hope this information adequately addresses the two questions posed in Mr. White's 6/19 fax. Please don't hesitate to contact me if there are any questions regarding today's submission.

Sincerely,


James E. Berg
VP, Clinical Affairs & Product Development

[Redacted signature line]

June 11, 1998

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



SUBJECT: NDA 20-941
Serial No. 003
LIDAKOL® (n-docosanol) 10% Cream
FDA request for additional information dated 6/4/98

Dear Dr. Wilkin:

With reference to the pending application for LIDAKOL Cream in the treatment of recurrent oral-facial herpes, please find enclosed the following items requested via telefax by Mr. Kevin Darryl White, Regulatory Health Project Manager on June 4, 1998:

- Desk copies of final (topical) safety study reports for, 95-LID-03a, 95-LID-03b, and 95-LID-03c
- The algorithm and comprehensive information regarding the Gehan-Wilcoxon (stratified) test used in the SAS-macro 'wilcomon.sas'
- SAS labels
- PROC CONTENTS with labels applied
- A diskette containing the following four files:
 - labels.sas
 - 980605.sas
 - 980605.log
 - 980605.out

Regarding the diskette described above, label.sas contains label statements for all of the previously unlabeled variables in the totality dataset. The file 980605.sas illustrates how to add these labels to the totality dataset, and the other two files show the SAS output and the SAS log for running these commands. The output file contains within it the results of PROC CONTENTS after the labels have been applied.

All of the above information except desk copies of safety study reports for 95-LID-03a, 95-LID-03b, and 95-LID-03c have been previously faxed directly to Ping Gao, PhD at (301) 827-2577. Dr. Gao has appropriately communicated directly with Ronald A. Thisted, PhD, [redacted] regarding these biostatistics issues. Dr. Thisted is a consultant to LIDAK on all biostatistics issues related to NDA 20-941. Dr. Gao and Dr. Thisted established their working relationship at the pre-NDA meeting for LIDAKOL Cream held on October 27, 1998.

I hope this adequately addresses all of the issues mentioned in Mr. White's 6/4/98 fax. Please don't hesitate to contact me if there are any questions regarding today's submission.

Sincerely,


James E. Berg
VP, Clinical Affairs & Product Development



SU
ORIG AMENDMENT

ORIGINAL

SENT VIA FEDERAL EXPRESS

April 23, 1998

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



SUBJECT: NDA 20-941
LIDAKOL®, (*n*-Docosanol, Behenyl Alcohol) 10% Cream
120 Day Safety Update

Dear Dr. Wilkin:

LIDAK is amending its pending NDA for LIDAKOL 10% Cream with the 120 day safety update. There is no additional safety data for the proposed indication, recurrent oral-facial herpes simplex.

The additional safety data being presented are for other indications, [redacted] both in HIV-positive patients. Since there is minimal additional safety data (13 non-serious, non-application site adverse events) to be reported at this time, LIDAK is submitting a brief report along with complete AE data listings from clinical studies 95-LID-KS2 [redacted] and 95-LID-MC2 [redacted] rather than modifying the Integrated Summary of Safety.

Final study reports for clinical studies 95-LID-KS2, 95-LID-MC, and 95-LID-MC2 will be submitted to the IND when available. There are no ongoing or planned studies at present for LIDAKOL 10% Cream.

The information contained in the safety update does not require any modification to the proposed draft labeling submitted in the original new drug application.

Sincerely,

James E. Berg
VP, Clinical Affairs & Product Development

Enclosures

March 18, 1998

SENT VIA FEDERAL EXPRESS

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



SUBJECT: NDA 20-941
Serial No. 001
LIDAKOL[®], (*n*-Docosanol, Behenyl Alcohol) 10% Cream
Change in Responsible Official

Dear Dr. Wilkin:

With reference to the pending application for LIDAKOL[®] in the treatment of oral-facial herpes (NDA 20-941), please be advised that David H. Katz, M.D. is no longer employed by LIDAK Pharmaceuticals. Therefore, please note that the following individual has now been designated as the responsible official on behalf of the company:

Gerald J. Yakatan, Ph.D.
President & CEO

All communications pertaining to this application should continue to be addressed to James E. Berg, Vice President of Clinical Affairs and Product Development.

Sincerely,

A handwritten signature in cursive script, appearing to read "Gerald J. Yakatan".

Gerald J. Yakatan, Ph.D.
President & CEO

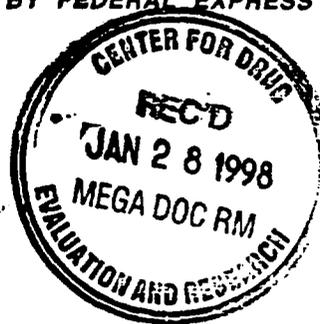
LIDAK
PHARMACEUTICALS

FYI. K.O.
me
ORIGINAL

January 27, 1998

SENT BY FEDERAL EXPRESS

Debra Bowen, M.D., Division Director
Division of Over-the-Counter Drug Products/HFD-560
ODE-5/CDER
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



Dear Dr. Bowen:

LIDAK Pharmaceuticals (LIDAK) has developed topical *n*-docosanol 10% cream (LIDAKOL[®]) as a treatment for recurrent oral-facial herpes simplex infections. The Investigational New Drug Application [redacted] was submitted in July 1991 to the Division of Antiviral Drug Products (DAVDP). In November of 1996 our CSO, David Staten, was kind enough to investigate several questions LIDAK had regarding the best way to have LIDAKOL 10% Cream considered for OTC clearance by the FDA. Dave indicated to me that he had initially spoken with Dr. Weintraub who, in turn, said Dave should speak directly with you. Perhaps you recall his inquiries on our behalf. In any case, LIDAK is seeking regulatory guidance from the FDA with our letter today. Specific questions are posed at the close of this letter.

Please allow me to briefly summarize the product's development to-date. On December 22, 1997 LIDAK submitted an (Rx) Original New Drug Application for LIDAKOL for the indication of recurrent oral-facial herpes simplex infections (NDA 20-941). For reasons best articulated by the FDA at the pre-NDA meeting (held on 10/27/97 at CRP2), it was decided that the NDA for LIDAKOL would be reviewed by the Division of Dermatologic and Dental Drug Products (DDDDP) rather than DAVDP.

While LIDAK submitted the NDA as an Rx application, we believe that LIDAKOL is best suited for the OTC marketplace. There are a number of reasons we think this is true. These include several properties unique to the drug substance as well as the nature of the disease itself. These are further discussed below.

The active ingredient in LIDAKOL is *n*-docosanol which is present at a 10% concentration. *n*-Docosanol (CAS Registry Number 661-19-8), also known as 1-docosanol and as behenyl alcohol, is a 22-carbon saturated straight chain alcohol. The safety of the compound for human use is well established: (i) the compound has a long, documented, history of safe use in human foods and

cosmetics; (ii) it and its major metabolite, *n*-docosanoic acid, occur endogenously in man, other animals, fish, and plants; (iii) *n*-docosanoic acid is on the FDA GRAS List; and (iv) following topical application of the compound, very little, if any, *n*-docosanol or metabolites thereof are absorbed into the bloodstream. A review of information on the use and safety of the compound led the FDA to conclude that carcinogenicity studies for *n*-docosanol were not necessary.

Furthermore, no important toxicological findings were noted following completion of 35 GLP compliant toxicology studies conducted under [redacted] to meet U.S. and international regulatory guidelines. The studies included single dose topical, single dose oral, repeat dose (chronic) topical, repeat dose (chronic) oral, oral reproductive toxicology, and special toxicology (local tolerance) studies of *n*-docosanol in several animal species.

n-Docosanol has a novel mechanism of action that renders the emergence of drug resistance improbable. The predominant mechanism for the anti-HSV activity of *n*-docosanol appears to be inhibition of fusion between the host cell plasma membrane and the HSV envelope and, as a result, the blocking of entry and subsequent viral replication. This mechanism of action explains the effectiveness of *n*-docosanol against all tested lipid-enveloped viruses that employ fusion as the sole or major means of entry into cells. This is in marked contrast to the mode of action of conventional antiviral agents that target a single viral protein. Most drug resistant viral strains arise from a mutation in a single gene. For example, acyclovir-resistant mutants commonly arise from mutations in the viral thymidine kinase gene resulting in a viral strain phenotypically negative for thymidine kinase and unable to process acyclovir to the inhibitory species. In contrast, *n*-docosanol may not target a single viral protein, and the emergence of drug-resistant mutants is therefore unlikely.

In clinical studies encompassing over 1,400 patients, LIDAKOL demonstrated an excellent safety profile. Overall adverse experience rates were comparable between LIDAKOL and placebo with respect to both frequency and type of adverse experiences.

In pivotal placebo controlled studies, LIDAKOL was demonstrated to be effective for the treatment of acute recurrent oral-facial herpes simplex when treatment was initiated in the prodrome/erythema stage, resulting in a statistically significantly shorter healing time with LIDAKOL as compared to placebo ($p=0.0076$). In addition, LIDAKOL-treated patients experienced relief from the herpes associated symptoms of pain, burning, itching, or tingling faster than placebo-treated patients. This difference was statistically significant ($p=0.0015$).

Debra Bowen, M.D.
January 27, 1998
Page 3

The combination of safety profile, clinical benefit, indication, and route of administration make LIDAKOL an ideal candidate for OTC use. Extensive toxicology studies of *n*-docosanol, in doses far exceeding potential exposure by chronic human use, have not revealed any negative findings. Individuals with recurrent oral-facial herpes simplex have excellent historical awareness of their disease, and early intervention – preferably in the prodrome or erythema stage – is necessary if an impact is to be made on the clinical course of a recurrence. Scheduling an appointment with a health provider to obtain a prescription to treat an episode is unrealistic given the relatively rapid evolution to the most painful and disfiguring stages of the disease. As such, access to a drug (preferably topical) to effectively treat a recurrence should be simple and quick. This, we believe, typifies the OTC marketplace.

LIDAK would like to bring LIDAKOL to the OTC marketplace as quickly as possible and your input/guidance on the following issues is critical:

- Can the same NDA (identical in format and content) that has been submitted for Rx approval be submitted for OTC approval?
- Are there specific clinical and/or regulatory requirements unique to an OTC filing that would be germane to LIDAKOL?
- Is there a regulatory requirement that a drug like LIDAKOL be an approved "prescription only" drug before an OTC NDA can be submitted?
- What are the primary considerations beyond the demonstration of safety and efficacy that enter into a decision related to a request like ours?

A letter seemed to be the best way to introduce LIDAK to you and present the background of this important issue. LIDAK would be happy to supply HFD-560 with the Application Summary from NDA 20-941, if it would be helpful in consideration of our questions. We are prepared to discuss these questions in a meeting or telephone conference call. You may contact me at (619) 558-0364 (voice) or (619) 453-5845 (fax). Your assistance is much appreciated.

Sincerely,


James E. Berg

VP, Clinical Affairs & Product Development

LIDAK
PHARMACEUTICALS

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SENT VIA FEDERAL EXPRESS

January 21, 1998

NC
NEW CORRESP
ORIGINAL

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

SUBJECT: NDA 20-941
LIDAKOL[®], (*n*-Docosanol, Behenyl Alcohol) 10% Cream
**Request for additional desk copy and electronic versions of
selected NDA sections**

Dear Dr. Wilkin:

As per Kevin Darryl White and the Medical Officer's telephone request(s) of January 20, 1998, LIDAK is providing the FDA with the following:

- A desk copy of Volume 1.2 (NDA 20-941)
- Electronic copies of the following:
 - ⇒ Final Protocol 96-LID-06 (Protocol 96-LID-07 is identical to 96-LID-06 in every respect except for the protocol number)
 - ⇒ Final Integrated Clinical and Statistical Reports for 96-LID-06/07, 96-LID-06, and 96-LID-07
 - ⇒ Integrated Summary of Efficacy (ISE)
 - ⇒ Integrated Summary of Safety (ISS)
 - ⇒ Human Pharmacokinetics and Bioavailability (Section 6)
 - ⇒ Background and Overview of Clinical Investigations (Section 8B)

All of the files listed above are in Word for Windows 6.0 (2 labeled diskettes with read-me text are included).

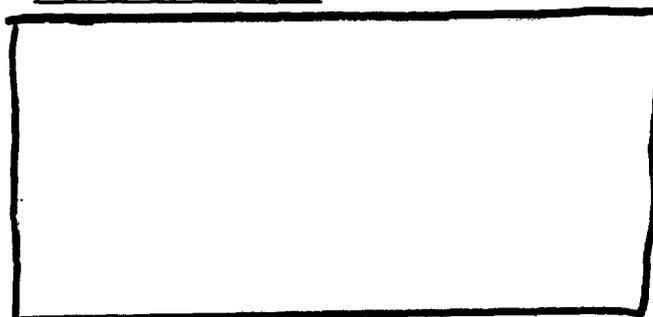
Jonathan Wilkin, M.D.
January 21, 1998
Page 2

- Regarding manufacture of the drug substance for LIDAKOL, the headquarters and the manufacturing plant of [redacted] are located in [redacted] respectively. The addresses and phone numbers of the two facilities are as follows:

Headquarters



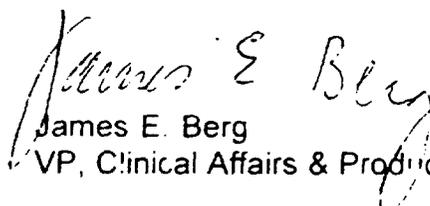
Manufacturing Plant



Unfortunately, case report forms from LIDAK's clinical studies are not in electronic format. A total of 17 complete CRFs were submitted (Section 12, Volumes 2.132 and 2.133) with NDA 20-941. These CRFs represent a grand total of 16 unique patients, across all of the clinical studies (Safety, U.S., and European) for LIDAKOL, that were discontinued due to an adverse event.

Please don't hesitate to let us know if we can be of any further assistance.

Sincerely,


James E. Berg
VP, Clinical Affairs & Product Development

Enclosures

David H. Katz, M.D.
President/Chief Executive Officer



December 19, 1997

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

**SUBJECT: NDA 20-941
LIDAKOL[®], (*n*-Docosanol, Behenyl Alcohol) 10% Cream
ORIGINAL NEW DRUG APPLICATION**

Dear Dr. Wilkin:

In accordance with regulation of 21 CFR 314.50, we are submitting an original New Drug Application for LIDAKOL[®], for the treatment of recurrent oral-facial herpes simplex. Reference is made to User Fee ID# 3365.

This application comprises 133 volumes. Efficacy data in 737 patients with recurrent oral-facial herpes simplex from adequate and well controlled trials provide the basis for approval. Safety information is provided for 3074 subjects worldwide treated with LIDAKOL[®], an active control, or placebo. This data was derived from 10 trials in patients with recurrent oral facial herpes simplex and 8 trials in healthy volunteers.

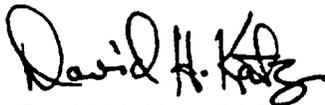
A presubmission to this NDA was made on (November 25, 1997, Amendment Serial Number 075). This presubmission contained 17 volumes. Two of the volumes (1.1 and 1.2) contained drug substance, drug product and environmental assessment information for Section 3. The remaining 15 volumes (1.3-1.17) contained nonclinical studies evaluating the pharmacology, toxicology and pharmacokinetics of LIDAKOL[®].

Jonathar Wilkin, M.D.
December 19, 1997
Page 2

A Compact Diskette (CD) containing the data and SAS programs for LIDAK's pivotal clinical studies is included with this submission. The CD is located in the Section 10, Statistical Review Copy, Volume 2.62.

We look forward to working with you during the review of this NDA. If you require any additional information, please do not hesitate to contact James E. Berg, Vice President of Clinical Affairs at (619) 558-0364.

Sincerely,



David H. Katz, M.D.

Enclosures: Copy of Check # (User Fee ID# 3365, submitted 12/19/97)
Copy of FDA Form 3397 (User Fee Cover Sheet)
Original NDA 20-941

LIDAK
PHARMACEUTICALS

INTELLECTUAL PROPERTY LAW
KNOBBE, MARTENS, OLSON & BEAR

A LIMITED LIABILITY PARTNERSHIP INCLUDING
PROFESSIONAL CORPORATIONS

PATENT, TRADEMARK AND COPYRIGHT CAUSES

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DANIEL E. JOHNSON**
JIAPU HUANG
JEFFERY KOEPEKE

December 11, 1997

Secretary
U.S. Food and Drug Administration
Washington, D.C.

Re: New Drug Application No. 20-941
Sponsor: LIDAK PHARMACEUTICALS

Dear Mr. Secretary:

The following information summarizes U.S. Patents which claim the drug, or the method of using the drug in topical applications, for which marketing approval is being sought in New Drug Application No. 20-941. These U.S. Patents and their expiration dates are listed in the Patent and Exclusivity Information submitted with New Drug Application No. 20-941.

U.S. Pat. No. 4,874,794 (expiration date: October 17, 2006) claims the use of a composition containing 0.1 to 25% docosanol for topical treatment of virus-induced or inflammatory diseases.

U.S. Pat. No. 5,071,879 (expiration date: October 17, 2006) claims methods of treating or preventing human disease or virus infection by transmucous membranar or transdermal penetration of a composition consisting essentially of a C-22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Pat. No. 5,194,451 (expiration date: December 10, 2008) claims methods of treating or preventing human inflammatory disease by transmucous membranar or transdermal penetration of a composition consisting essentially of a C-22 aliphatic alcohol in a physiologically compatible carrier.

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Secretary,
U.S. Food and Drug Administration
December 11, 1997
Page -2-

U.S. Pat. No. 5,166,219 (expiration date: December 3, 2008) claims methods of treating human inflammatory disease or arthritis by transmucous membranal or transdermal penetration of a composition consisting essentially of a C-22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Pat. No. 5,534,554 (expiration date: December 13, 2013) claims therapeutic creams containing *n*-docosanol at greater than 5% by weight, or 5-15% by weight, to topical application. This patent also claims methods of treating viral infections and inflammation of skin and mucous membranes, or reducing pain of surface inflammation of skin or a membrane by topical application of a cream containing 5-25% *n*-docosanol.

U.S. Pat. No. 5,098,896 (expiration date: March 24, 2009) claims methods of corneal treatment by topically applying docosanol to an eye to promote epithelial healing.

U.S. Pat. No. 5,214,071 (expiration date: May 25, 2010) claims methods of corneal treatment by topically applying to a cornea an effective amount of docosanol to promote corneal healing.

U.S. Pat. No. 5,296,514 (expiration date: March 22, 2011) claims methods of corneal promoting corneal healing by applying topically to an injured cornea an effective amount of docosanol to promote corneal healing.

Based on information available to us, I believe that all of the above patents are owned by LIDAK PHARMACEUTICALS.

Yours very truly,


Ned A. Israelsen

CAG-3643
121197

006

LIDAK

PHARMACEUTICALS

re submission
ORIGINAL

December 10, 1997

Mr. Kevin Darryl White, Regulatory Health Manager
Division of Dermatologic and Dental Drug Products/HFD-540
Office of Drug Evaluation IV
Room N460
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850



Dear Kevin:

It was a pleasure talking with you and the other members of our review team last week. Per Dr. DeCamp's inquiry during the telephone conference on December 3, 1997, LIDAK has obtained five FDA Form(s) 2656E from companies it is using for manufacturing and analytical testing and is forwarding them to the DDDDP with my letter. The function of each of these companies is described in Section 3. We hope this will facilitate the Chemistry review process for Dr. Hathaway.

Thank you for your instructions concerning the use of form 356h, instead of form 1571, for LIDAK's pre-submission of Sections 3 and 5 of the NDA for LIDAKOL® 10% Cream. LIDAK is following your advice and sending a completed 356h to the FDA for inclusion with our November 25, 1997 pre-submission filing.

We look forward to working with the Division of Dermatologic and Dental Drug Products. LIDAK is confident the Division will find our NDA complete, fully indexed, and well-written. We are ready and willing to assist in your review of our NDA and in the change-over from the DAVDP to the DDDDP.

Sincerely,

James E. Berg
James E. Berg,
Vice President, Clinical Affairs & Product Development

Encl.: FDA Form 356h:



JEB/cam