CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

MEDICAL REVIEW

NDA 20-941

Medical Officer Review of Clinical Study 92-02: Statistical Addendum

CORRESPONDENCE DATE: March 29, 1999

CDER STAMP DATE: March 30, 1999

REVIEW DATE: October 28, 1999

SPONSOR: AVANIR PHARMACEUTICALS

DRUG: n-docosanol 10% cream

PHARMACOLOGIC CATEGORY: anti-viral

PROPOSED INDICATION: treatment of recurrent episodes of oro-facial herpes labialis

DOSAGE FORM AND ROUTE OF ADMINISTRATION: cream, applied topically to herpes lesions

BACKGROUND:
Clinical Study 92-02, "A Randomized, Double-Blind Study Comparing n-Docosanl 10% Cream and Placebo Cream in Patients with Recurrent Herpes Labialis" was a double blinded, randomized, two center, vehicle controlled, patient initiated trial to study the efficacy of LIDAKOL 10% cream on reducing the duration of recurrent episodes of oro-facial herpes labialis. Sponsor has submitted a statistical addendum, containing additional analyses of the efficacy data from this study.

The medical officer review comprises four parts: (a) an overview of the 92-02 study protocol; (b) summary of the statistical analysis from the original study report; (c) summary of the salient features of the statistical addenda; and (d) reviewer comments.

Study 92-02 Clinical Protocol
The study comprises **two treatment phases: first treatment phase**, in which patients are randomized to LIDAKOL [redacted] and **cross-over phase**, in which patients who are still participating are dispensed the drug they did not receive in the first phase.

First Treatment Phase Overview
1. Screening
Patients with a history of recurrent oro-facial herpes labialis (3 episodes within the past year) were:

- screened to ensure they satisfied inclusion/exclusion criteria (page 34, 35)
- randomized (1:1 active:vehicle in blocks of 10)
- instructed on how to recognize the stages of a herpes episode and when and how to apply study medication ["as early as possible after the patient experiences

(prodromal) symptoms" (pg. 037), for five times a day while awake, for a maximum of 10 days]

- instructed to mark the exact time and date treatment was initiated, and the stage at which treatment was initiated
- given instructions to arrange for a clinic visit as soon as possible after starting treatment

2. First clinic visit

- Patients were queried regarding the onset of the episode
- Relying upon the patients' description of the stage of the herpetic episode at which treatment was first self-administered, patients were classified as starting treatment "early" (prior to the appearance of the papule stage) or "late" (at or after the appearance of the papule stage)
- Patients were staged for baseline clinical determination
- Patients were photographed, had lesions measured, and were assessed for adverse events

3. Telephone contact

- Patients were contacted by telephone 3 or 4 days after the first clinic visit to assess compliance, safety, and tolerability
- Treatment was to continue until healing had occurred for a maximum of 10 days.

4. Follow-up clinic visit [to occur after patient has assessed that lesion has healed, or at 10 days after initiation of therapy, whichever is first]

- Clinical investigators confirmed the patients' self-assessment of healing (defined as re-epithelialization).
- Patients were queried regarding adverse reactions

5. Cross-Over

A total of 22 patients were re-entered in the cross-over extension of the study. Those patients who had for the first treatment been randomized to receive LIDAKOL instead received vehicle to take home and self-apply at the first sign or symptom of a herpes outbreak; those who had first been randomized to receive vehicle were randomized to receive LIDAKOL. As with the first part of the study, patients were instructed to return to clinic as soon as possible for the baseline assessment, which was analogous to the baseline assessment for the first part of the study, and to return after the lesion has healed.

Statistical Analysis: Original Study Results

	Healing Days of First Episodes					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Patients	Mean Days to Heal	Standard Deviation	No. of Patients
Early Treatment	2.5	2.4	10	6.8	4.2	4
Late Treatment	6.8	3.2	21	7.3	2.7	28
All treatment	5.4	3.6	31	7.3	2.8	32
	Source: pg. 13, Vol. 2.45					

Statistical evaluation of healing time was performed using analysis of variance with the factor of treatment (on four levels: LIDAKOL early, LIDAKOL late, vehicle early, and vehicle late) to describe the response model. To locate any differences between the treatment groups, a hierarchical system of contrasts was applied where each comparison was made only in case of a non-significant result in the previous contrast:

a) Vehicle early contrasted versus vehicle late
b) LIDAKOL late contrasted versus vehicle (early + late)
c) LIDAKOL early contrasted versus all others (LIDAKOL late + Vehicle early + Vehicle late)

The contrasts according to the hierarchical system demonstrated no differences between early and late treatment with the vehicle ($p=0.72$), and no differences between late treatment with LIDAKOL and (early plus late) treatments with the vehicle ($p=0.82$), while early treatment with LIDAKOL was found to show highly significant shorter healing times ($p=0.0001$) than the combined data for late treatment with LIDAKOL and all vehicle treatments.

The following table shows that the observed treatment effect is driven almost entirely by the results from the Netherlands center. In comparing outcomes of the LIDAKOL and vehicle treated groups in the Netherlands, an anomalously large difference (4.9 days) in the time to healing in favor of LIDAKOL is noted.

	Comparison of Healing Days by Center: Healing Days of First Episode							
	BELGIUM				NETHERLANDS			
	LIDAKOL		Vehicle		LIDAKOL		Vehicle	
	Mean Days to Heal	No.	Mean Days to Heal	No.	Mean Days to Heal	No.	Mean Days to Heal	No.
Early Treatment	6.7	2	8.2	1	1.4	8	6.3	3
Late Treatment	8.6	8	7.1	4	5.7	13	7.4	24
All treatment	8.2	10	7.3	5	4.1	21	7.3	27
	Source: Appendix 5-1							

The study report notes that "The analyses revealed that the efficacy findings as presented...were solely due to the results obtained in the larger (Dutch) centre. No treatment differences whatsoever could be detected in the smaller (Belgian) centre."

Abortive Episodes

The proportions of early treatments with an abortive course of the episode were LIDAKOL 8/10 (80%), vehicle 1/4 (25%). This difference was not statistically significant (p=0.09, Fisher's test).

Crossover Study Overview

The 22 patients who entered the cross-over phase of the study treated at least 2 different episodes of outbreak (one with LIDAKOL, one with vehicle). The healing times of these 44 episodes, stratified by whether treatment was initiated early or late (as defined previously), are presented in the following table. As the table depicts, only 1 episode was treated early with vehicle.

	Healing Days, Cross-over Study					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Episodes	Mean Days to Heal	Standard Deviation	No. of Episodes
Early Treatment	2.7	2.2	7	7	N/A	1
Late Treatment	5.6	2.1	15	8	2.6	21
All treatment	4.7	2.5	22	8	2.5	22
	Source: pg. 14					

The analysis of variance revealed a significant effect of treatment initiation (shorter durations in early treatment). There was no significant treatment effect when both early

and late treatments were examined. Sponsor reports that if all data following early treatment were excluded, the difference between late treatments were significant (p=0.03, ANOVA).

Intra-patient analysis was possible with these 44 observations, enabling sponsor to employ the non-parametric Wilcoxon's matched-pairs signed-ranks test to test the effect of LIDAKOL treatment on healing time. This test revealed a significant difference between the treatments in favor of LIDAKOL (p=0.0008). Adjusting for covariates such as early or late treatment is not possible with this test. Quoting from the study report: "Due to the unfortunate imbalance [most early patients on LIDAKOL] it is therefore difficult to draw valid conclusions from the analysis of cross-over data."

Overall Analysis Overview

Eight patients in the first phase of the study experienced two herpetic episodes, each treated with the study drug to which they had been assigned during the first phase. Five patients in the cross-over study experienced two herpetic episodes, each treated with the study drug to which they had been assigned during the cross-over phase. Sponsor performed an overall analysis, pooling treatment outcomes from the first phase, the cross-over phase, and from the outcomes in the "extra" episodes in each of the phases.

	Healing Days, Overall Summary					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Episodes	Mean Days to Heal	Standard Deviation	No. of Episodes
Early Treatment	3.4	3.0	13	6.7	3.9	7
Late Treatment	6.5	2.7	35	7.4	2.7	43
All treatment	5.7	3.1	48	7.3	2.9	50
	Source: pg. 77					

Comparing early treatment with LIDAKOL with all other groups (vehicle early/vehicle late/LIDAKOL late), a significant difference was observed (p=0.002).

Reviewer's Comment:

- *This analysis is predicated on the assumption that intra-patient healing times are as much independent events as are inter-patient healing times. Sponsor justifies this assumption by stating there was an absence of "a significant or numerically substantial inter-patient variation as found in the analysis of the cross-over data (pg. 077)". The relevant comparison to support this assumption would have been inter-patient versus intra-patient variation.*

STATISTICAL ADDENDA

Healing Days of First Episode

In sponsor's reappraisal of this part of the study, sponsor notes that rather than using the hierarchical system of contrasts in comparing early LIDAKOL treatment with all other treatment modalities, the "more conventional and appropriate approach using ANOVA would be to compare early-stage treatments with docosanol and placebo with one another. When this was done for early treatment patients only, it was demonstrated that docosanol treated patients had shorter healing times than placebo-treated patients." The sponsor reports a p-value for this analysis of 0.034.

Cross-Over Extension

In the sponsor's reappraisal of the extension, the original statistical analysis plan (Wilcoxon signed rank test) was considered appropriate. Sponsor reports that for the 22 intra-patient comparisons, the time-to-healing while on docosanol was reduced by a median of 3.4 days, with a p-value of .0025 by the Wilcoxon signed rank test.

Overall Analysis Overview

In considering all study subjects, regardless of stage at first application, sponsor reports that episodes treated with docosanol had a median time-to-healing of 5.44 days, compared to 7.25 days for placebo. This difference was assessed as statistically significant as tested by the Gehan-Wilcoxon test, stratified by study center (p-value of 0.0012).

Reviewer Comments

All the efficacy results reported in this study rest upon the assumptions that (a) patients can accurately time the initiation of an herpetic episode, (b) properly determine the stage at which treatment was started, and (c) accurately determine when re-epithelialization has occurred. Assumption (a) seems intuitively reasonable: surely every layperson could tell when their lip is beginning to sting or turn red! But could every layperson tell the difference between a papule and an edematous, erythematous patch? Patient's assessment of the stage at which they first applied the study cream determined whether their episode was stratified as an early or late treatment. Could every layperson tell when their lip has reepithelialized? Patients' assessment marked the time to complete healing, as defined in the protocol.

The instructional information given to patients to help them recognize the stage of their herpetic episode was not included in the study report, and therefore was not available to be reviewed by the medical reviewer. There was no assessment performed in this study to confirm that patients were able to identify properly the stage of their episode.

Patients did come in for clinical assessment after the patients had concluded their lesions were healed. If there had been concurrence between clinicians' assessment of healing and patients' own assessment, this would have provided supporting evidence that the patients were accurate in assessing whether they had healed. In fact, evidence from the

clinical data (Appendix 10-4) suggests that two of the patients did err in determining the time to healing:

- *Patient no. 11 returned for a second clinic visit 3 days after starting treatment with study cream, presumably under the impression that his/her lesion was healed (the patient should not have returned till 10 days after treatment was started unless he/she thought the lesion was healed). The clinician evaluated the lesion as healing, not healed, at the second study visit; the patient's lesion was not classified as healed until 4 more days had elapsed.*
- *Patient no. 154 returned for a second clinic visit 4 days after starting treatment with study cream. The clinician evaluated the lesion as a scab, not healed, at the second study visit; the patient's lesion was not classified as healed until 6 more days had elapsed.*

Since assessment of efficacy relies entirely on patients' self-assessment, it would have been desirable to confirm this self-assessment by having patients evaluated by the clinician-investigator as soon as possible after the patients conclude they are healed. For several patients (e.g., no. 33, no. 42, no. 43), more than 24 hours elapsed between patients' self-assessment that lesions were healed and clinicians' confirmation that the lesions were healed. The possibility cannot be dismissed that some patients erred in determining the time to healing, but that they healed in the period before clinician assessment occurred. Such an error would be undetectable with the study design.

Other evidence also suggests that some patients may not have completely understood the protocol instructions. Patients had been instructed to start treatment as soon as an herpetic episode began, then to make arrangements for a first clinic visit as soon as possible. Patient 3 reportedly started treatment at the exact moment (Jan 18, 1993, 7:00PM) when the patient was assessed by the clinician investigator. With patient 19, 5 minutes elapsed between treatment initiation and the first baseline visit. It seems unlikely that those patients' episodes really started at the same moment that they were examined by the clinical investigator.

Scattered cases of possible errors in assessing time to healing are less important in a large study than in a study containing as few subjects as does 92-02.

There is precedent within the Agency for a topical treatment for recurrent herpes to be approved based upon patient-initiated trials. A comparison with the clinical trials that led to approval of 1% topical penciclovir (NDA20-629) is instructive. In those pivotal trials, subjects were randomized at the time of enrollment to either active or vehicle control. Subjects were instructed to initiate therapy with study medication within one hour of noticing the first sign or symptom of a recurrence and to continue treatment every 2 hours while awake. Study medication was to be applied for 4 days. The subjects were to report to the clinic for assessments within 24 hours of initiating study medication and to return to clinic daily for at least 4 days or until loss of crust.

Of note, in these studies, assessment of the primary endpoint (duration of critical lesion stages [papule, vesicle, ulcer/soft crust, hard crust]) were to be made by the investigators. Patient assessment was a secondary endpoint.

The study protocol for 92-02 was not reviewed by a medical officer before the study was launched. Because of its design flaws, it would have been found suitable as an exploratory analysis, but not as a study to provide evidence of efficacy. The meaning of statistical analyses performed on unreliable data is unreliable.

Conclusion
Flaws in the study design, and possibly in the method of data collection, call into question the value of clinical study 92-02 in providing proof of efficacy for LIDAKOL cream in the treatment of oro-facial herpes labialis.

/S/ 10/28/99

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA 20-941
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Medical Reviewer/Okun
HFD-540/Project Manager/White

See DD Memorandum, signed 10/29/99

/S/ 10/29/99

APPEARS THIS WAY
ON ORIGINAL

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA# 20-941

Information Reviewed:
NDA Amendment, date of submission 3/29/99
Sponsor's answers to questions pertaining to Amendment, date of submission 4/29/99

Addendum Date: May 07, 1999

Sponsor: AVANIR Pharmaceuticals

Proposed trade name: LIDAKOL®

DRUG: n-docosanol 10% cream

PHARMACOLOGIC CATEGORY: anti-viral

PROPOSED INDICATION: treatment of recurrent episodes of oro-facial herpes labialis

DOSAGE FORM AND ROUTE OF ADMINISTRATION: cream, applied topically to herpes lesions.

BACKGROUND
Sponsor's amendment concerns documentation regarding additional evidence of effectiveness for docosanol 10% cream. Part of this documentation is sponsor's statistical addendum for clinical study 92-LID-02. The medical reviewer's addendum reviews the clinical study results from study 92-LID-02 and the sponsor's addendum for this study.

Study Title: "A Randomized, Double-Blind Study Comparing n-Docosanl 10% Cream and Placebo Cream in Patients with Recurrent Herpes Labialis

Study Design
This was a Phase 2 double blinded, randomized, two center, vehicle controlled, patient initiated trial to study the efficacy of LIDAKOL 10% cream on reducing the duration of recurrent episodes of oro-facial herpes labialis. The study comprises two treatment phases: **first treatment phase**, in which patients are randomized to LIDAKOL or vehicle, and **cross-over phase**, in which patients who are still participating are dispensed the drug they did not receive in the first phase.

Study Aims
- To evaluate and compare the percentage of abortive courses of episodes after application of the test drugs at the prodromal stage (aborted episodes are defined as episodes in which patients "do not develop lesions after prodromes or erythema occur".
- To evaluate and compare the acceleration of healing times in those patients that develop lesions.

- To evaluate safety and tolerability.

Reviewer's Comment:
The statistical report from the original study specified that in all tests the level of statistical significance was set to $\alpha = 0.05$. The study design has multiple endpoints (percentage of aborted episodes, time to healing) and multiple phases (first treatment phase, crossover phase). The statistical section of the study protocol does not prespecify the means by which adjustment for multiple endpoints will occur. Without adjustment, the risk of type I error is inflated.

Chemistry
The chemical compositions of the placebo and active creams is given in the following table:

	Placebo	Active
Ingredient	Percent (w/w)	Percent (w/w)
n-Docosanol		10.0%
[redacted]		
Sucrose stearate and sucrose distearate		
Light mineral oil		
Propylene glycol		
Benzyl alcohol		
Purified water		

Reviewer's Comment:
The compositions of the placebo and active creams are the same as in the three Phase 3 clinical trials 94-LID-04, 95-LID-10, 94-LID-05, and in the Phase 2 trial 92-LID-04. These four trials failed to show statistically significant differences in the time to healing between patients treated with active and placebo creams. Sponsor has attributed the failure of these trials to the presence of anti-herpes activity in [redacted] one of the components of the placebo cream.

First Treatment Phase Overview
1. Screening

Patients with a history of recurrent oro-facial herpes labialis (3 episodes within the past year) were:

- screened to ensure they satisfied inclusion/exclusion criteria
- randomized (1:1 active:vehicle in blocks of 10) and supplied with placebo or active treatment
- instructed on how to recognize the stages of a herpes episode and when and how to apply study medication ["as early as possible after the patient experiences (prodromal) symptoms", for five times a day while awake, for a maximum of 10 days]
- instructed to mark the exact time and date treatment was initiated, and the stage at which treatment was initiated

- given instructions to arrange for a clinic visit as soon as possible after starting treatment

Reviewer's Comment:
The instructional information given to patients to help them recognize the stage of their herpetic episode was not included in the study report, and therefore was not available for review by the medical reviewer. There was no assessment performed in this study to confirm that patients were able to identify properly the stage of their episode.

The primary efficacy variable, time to healing, was measured by subtracting the time and date at which study cream was first applied (as determined by patient) from the time and date at which herpetic lesion re-epithelialized (as assessed by patient). Also, sponsor stratified treatments based on whether treatment was first applied early (i.e., during the erythema or prodrome stages) or late (i.e., papule stage or later). Patients' assessment of the stage at which they first applied the study cream determined whether their episode was stratified as an early or late treatment.

Because it is unclear how well patients were educated to recognize the specific stage of their illness, it is difficult to assess whether the reported results of the primary efficacy variable or the staging at which treatment was started are reliable.

2. First clinic visit

- Patients were queried regarding the onset of the episode
- Relying upon the patients' description of the stage of the herpetic episode at which treatment was first self-administered, patients were classified as starting treatment "early" (prior to the appearance of the papule stage) or "late" (at or after the appearance of the papule stage)
- Patients were staged for baseline clinical determination
- Patients were photographed, had lesions measured, and were assessed for adverse events

Reviewer's Comments:
It is noteworthy that some patients were examined by clinicians during the baseline visit at a time of day that is outside normal working hours. For example, the first clinic visit occurred at 9:45 PM for patient 1, at 10:00 PM for patient 15, at 10:15 PM for patient 119 (Appendix 10-5). It is possible that the times reported for the baseline examination were not accurate.

Patients had been instructed to start treatment as soon as an herpetic episode began, then to make arrangements for a first clinic visit as soon as possible. Patient 3 reportedly started treatment at the exact moment (Jan 18, 1993, 7:00PM) when the patient was assessed by the clinician investigator. With patient 19, 5 minutes elapsed between treatment initiation and the first baseline visit. These observations suggest that (a) the recording of treatment initiation times and/or first clinic visit times was not absolutely accurate, or (b) that some patients may have misunderstood the protocol

instructions and started treatment at the time of the first clinic visit. If either (a) or (b) is true, then the reliability of the primary efficacy variable is called into question, as it is absolutely dependent upon reliable patient self-assessment and data recording.

3. Telephone contact
- Patients were contacted by telephone 3 or 4 days after the first clinic visit to assess compliance, safety, and tolerability

4. Follow-up clinic visit [to occur after patient has assessed that lesion has healed, or at 10 days after initiation of therapy, whichever is first]
- Clinical investigators confirmed the patients' self-assessment of healing (defined as re-epithelialization).
- Patients were queried regarding adverse reactions

Reviewer's Comments:
Since assessment of efficacy relies entirely on patients' self-assessment, it would have been desirable to confirm this self-assessment by having patients evaluated by the clinician-investigator as soon as possible after the patients conclude they are healed. For several patients (e.g., no. 33, no. 42, no. 43), more than 24 hours elapsed between patients' self-assessment that lesions were healed and clinicians' confirmation that the lesions were healed. The possibility cannot be dismissed that some patients erred in determining the time to healing, but that they healed in the period before clinician assessment occurred. Such an error would be undetectable with the study design.

Evidence from the clinical data (Appendix 10-4) suggests that two of the patients did err in determining the time to healing:

- *Patient no. 11 returned for a second clinic visit 3 days after starting treatment with study cream, presumably under the impression that his/her lesion was healed (the patient should not have returned till 10 days after treatment was started unless he/she thought the lesion was healed). The clinician evaluated the lesion as healing, not healed, at the second study visit; the patient's lesion was not classified as healed until 4 more days had elapsed.*
- *Patient no. 154 returned for a second clinic visit 4 days after starting treatment with study cream. The clinician evaluated the lesion as a scab, not healed, at the second study visit; the patient's lesion was not classified as healed until 6 more days had elapsed.*

Two committed errors (that were detectable) in assessing their lesion stage. It is unknown how many patients committed errors that were not detected.

5. Study Results

	Healing Days of First Episodes					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Patients	Mean Days to Heal	Standard Deviation	No. of Patients
Early Treatment	2.5	2.4	10	6.8	4.2	4
Late Treatment	6.8	3.2	21	7.3	2.7	28
All treatment	5.4	3.6	31	7.3	2.8	32
	Source: pg. 13					

Statistical evaluation of healing time was performed using analysis of variance with the factor of treatment (on four levels: LIDAKOL early, LIDAKOL late, vehicle early, and vehicle late) to describe the response model. To locate any differences between the treatment groups, a hierarchical system of contrasts was applied where each comparison was made only in case of a non-significant result in the previous contrast:

a) Vehicle early contrasted versus vehicle late
b) LIDAKOL late contrasted versus vehicle (early + late)
c) LIDAKOL early contrasted versus all others (LIDAKOL late + Vehicle early + Vehicle late)

The contrasts according to the hierarchical system demonstrated no differences between early and late treatment with the vehicle (p=0.72), and no differences between late treatment with LIDAKOL and (early plus late) treatments with the vehicle (p=0.82), while early treatment with LIDAKOL was found to show highly significant shorter healing times (p=0.0001) than the combined data for late treatment with LIDAKOL and all vehicle treatments.

Reviewer's Comment:

- *Pooled treatment outcomes for LIDAKOL late treatment, vehicle early treatment, and vehicle late treatment are not a legitimate comparator for LIDAKOL early treatment. The justification for pooling vehicle early and late treatment results was that sponsor concluded that there were no differences in outcomes between these two groups. This conclusion was based on the results from only four patients who received early treatment with vehicle.*

- *The following table shows that the treatment effect believed by sponsor to be caused by LIDAKOL is driven almost entirely by the results from the Netherlands center.*

	Comparison of Healing Days by Center: Healing Days of First Episode							
	BELGIUM				NETHERLANDS			
	LIDAKOL		Vehicle		LIDAKOL		Vehicle	
	Mean Days to Heal	No.	Mean Days to Heal	No.	Mean Days to Heal	No.	Mean Days to Heal	No.
Early Treatment	6.7	2	8.2	1	1.4	8	6.3	3
Late Treatment	8.6	8	7.1	4	5.7	13	7.4	24
All treatment	8.2	10	7.3	5	4.1	21	7.3	27
	Source: Appendix 5-1							

Late treatment patients in the Belgian center who received LIDAKOL had longer mean times to healing compared to vehicle-treated patients. Quoting from the study report. "The analyses revealed that the efficacy findings as presented...were solely due to the results obtained in the larger (Dutch) centre. No treatment differences whatsoever could be detected in the smaller (Belgian) centre."

Abortive Episodes
The proportions of early treatments with an abortive course of the episode were LIDAKOL 8/10 (80%), vehicle 1/4 (25%). This difference was not statistically significant (p=0.09, Fisher's test).

Reviewer's Comment: Assessment of whether an episode was aborted relied upon patient's own assessment, followed by clinician's confirmation. It is unclear whether patients were sufficiently learned to observe accurately whether their episodes had terminated before a papule stage was reached (the sine qua non of an aborted episode).

Crossover Study Overview

A total of 22 patients were re-entered in the cross-over extension of the study. Sponsor reports that monitor, investigators, and patients remained blinded during both the primary and cross-over phases of the study.

Reviewer's Comment: It is unclear from the study report whether 22 patients volunteered for the cross-over arm, or whether more than 22 volunteered but only 22 returned with another herpetic outbreak, using the cross-over cream.

Those patients who had for the first treatment been randomized to receive LIDAKOL instead received vehicle to take home and self-apply at the first sign or symptom of a

herpes outbreak; those who had first been randomized to receive vehicle were randomized to receive LIDAKOL. As with the first part of the study, patients were instructed to return to clinic as soon as possible for the baseline assessment, which was analogous to the baseline assessment for the first part of the study, and to return after the lesion has healed.

The 22 patients who entered the cross-over phase of the study treated at 2 different episodes of outbreak (one with LIDAKOL, one with vehicle). One-half (11/22) of the patients who participated in the crossover were treated first with Lidakol and one-half (11/22) were treated first with placebo. Among those receiving Lidakol first, 9 healed faster on the occasion they received Lidakol, while two healed faster on the occasion they received placebo. Among those receiving placebo first, 9 healed faster with Lidakol and 2 with placebo. The healing times of these 44 episodes, stratified by whether treatment was initiated early or late (as defined previously), are presented in the following table:

	Healing Days, Cross-over Study					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Patients	Mean Days to Heal	Standard Deviation	No. of Patients
Early Treatment	2.7	2.2	7	7	N/A	1
Late Treatment	5.6	2.1	15	8	2.6	21
All treatment	4.7	2.5	22	8	2.5	22
	Source: pg. 14					

Reviewer's Comment: Analysis of the cross-over study is complicated by the fact that only 1 patient receiving vehicle treatment initiated treatment early. The shorter times observed in the early treatment with LIDAKOL may be due to the effect of LIDAKOL, or to a milder course associated with herpetic episodes that start so gradually that early treatment is possible. Without more patients in the early treatment-vehicle group, these two possibilities cannot be distinguished.

The analysis of variance revealed a significant effect of treatment initiation (shorter durations in early treatment). There was no significant treatment effect when both early and late treatments were examined. Sponsor reports that if all data following early treatment were excluded, the difference between late treatments were significant (p=0.03, ANOVA).

Reviewer's Comment: Sponsor does not provide a rationale for why comparing late treatment outcomes in this analysis is appropriate, while pooling late treatment outcomes for vehicle and LIDAKOL treated patients in the first phase of the study was appropriate.

Intra-patient analysis was possible with these 44 observations, enabling sponsor to employ the non-parametric Wilcoxon's matched-pairs signed-ranks test to test the effect

of LIDAKOL treatment on healing time. This test revealed a significant difference between the treatments in favor of LIDAKOL (p=0.0008). Adjusting for covariates such as early or late treatment is not possible with this test.

Reviewer's Comment: Since many of the short healing times on LIDAKOL were associated with early treatment while there was few data on early treatment with the vehicle, the significant result could be ascribed to the effect of treatment or differences in the time-to healing of lesions depending upon whether they are first detecied in the early or late stage.

Quoting from the study report: "Due to the unfortunate imbalance [most early patients on LIDAKOL] it is therefore difficult to draw valid conclusions from the analysis of cross-over data."

Overall Analysis Overview

Eight patients in the first phase of the study experienced two herpetic episodes, each treated with the study drug to which they had been assigned during the first phase. Five patients in the cross-over study experienced two herpetic episodes, each treated with the study drug to which they had been assigned during the cross-over phase. Sponsor performed an overall analysis, pooling treatment outcomes from the first phase, the cross-over phase, and from the outcomes in the "extra" episodes in each of the phases.

	Healing Days, Overall Summary					
	LIDAKOL			Vehicle		
	Mean Days to Heal	Standard Deviation	No. of Patients	Mean Days to Heal	Standard Deviation	No. of Patients
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Late Treatment	6.5	2.7	35	7.4	2.7	43
All treatment	5.7	3.1	48	7.3	2.9	50
	Source: pg. 77					

Comparing early treatment with LIDAKOL with all other groups (vehicle early/vehicle late/LIDAKOL late), a significant difference was observed (p=0.002).

Reviewer's Comments:
Pooled treatment outcomes for LIDAKOL late treatment, vehicle early treatment, and vehicle late treatment are not a legitimate comparator for LIDAKOL early treatment.

Efficacy Results with Additional Analyses (submitted as Statistical Addenda to clinical study 92-02):

Overall Analysis

Sponsor stated in their statistical addenda to study 92-02 that "a more appropriate approach [for overall analysis] using ANOVA would be to compare only the early-stage treatments with docosanol and placebo to one another. When this was done for early treatment patients only, it was demonstrated that it was demonstrated that docosanol treated patients had shorter healing times than placebo-treated patients (p=0.034)."

Reviewer's Comment:

- *The consequence of performing alternative statistical analyses of the clinical outcomes and examining outcomes in multiple phases of the study (i.e., first phase, crossover phase, overall analysis) is that the risk of type I error is inflated. The statistical protocol did not prespecify an adjustment to α to compensate for multiple comparisons.*
- *The statistical analysis of the Overall Study Results assumes that intra-patient healing times are as much independent events as are inter-patient healing times. While this assumption seems plausible, the burden is on the Sponsor to demonstrate the validity of this assumption. Sponsor justifies this assumption by stating there was an absence of a significant or numerically substantial inter-patient variation as found in the analysis of the cross-over data, but the relevant comparison would be test whether the variation in time-to-healing is as inter-patient versus intra-patient variation.*

Survival Analysis

Sponsor used the Gehan-Wilcoxon test to examine if there are statistical differences in the median time-to-healing for patients treated with docosanol or placebo during the first episode experienced while enrolled in the study. This analysis supplemented the protocol-specified ANOVA test to examine statistical differences in the mean time-to-healing. The results of the Gehan-Wilcoxon analysis are depicted in the following table.

Phase	No. of Patients	Difference in Median Time to Healing	p-value
All episodes (regardless of whether treatment commenced in early or late stage)	63 (31 receiving LIDAKOL, 32 receiving placebo)	1.8 days	.0012
Episodes treated in early stage	14 (10 receiving LIDAKOL, 4 receiving placebo)	1.9 days	.014

Reviewer's Comment:

- *The statistical protocol for this clinical study pre-specified ANOVA, not the Gehan-Wilcoxon test, as the test that would be used to analyze the significance of the study*

results. The consequence of choosing post-hoc alternative statistical analyses of the clinical outcomes is that the risk of type I error is inflated.

Conclusions

1. The statistical report pre-specified that in all tests the level of statistical significance was set to $\alpha = 0.05$. The study design has multiple endpoints (percentage of aborted episodes, time to healing) and multiple phases (first treatment phase, crossover phase, all treated episodes). The statistical section of the study protocol does not prespecify the means by which adjustment for multiple endpoints would occur. The consequence of not adjusting for multiple endpoints is that the risk of type I error is inflated.

2. The primary efficacy variable, time to healing, was measured by subtracting the time and date at which study cream was first applied (as determined by patient) from the time and date at which herpetic lesion re-epithelialized (as assessed by patient). Also, sponsor stratified treatments based on patient's assessment of whether treatment was first applied early (i.e., during the erythema or prodrome stages) or late (i.e., papule stage or later). There was no assessment performed in this study to confirm that patients were able to identify properly when episodes began, the stage of their episode when treatment was started, and when episodes healed. Hence, it is difficult to assess whether the reported results of the primary efficacy variable or the staging at which treatment was started are reliable.

3. Evidence from the data listings suggest that the recording of treatment initiation times and/or first clinic visit times may not have been always accurate, and that some patients may have misunderstood the protocol instructions and started treatment at the time of the first clinic visit rather than at the first appearance of signs or symptoms of an episode.

4. Treatment effect was driven almost entirely by the results from one of the two centers participating in the study.

5. Analysis of the cross-over study was complicated by the fact that only 1 patient randomized to the vehicle treatment arm initiated treatment early. Since many of the short healing times on LIDAKOL were associated with early treatment while there was little data on early treatment with the vehicle, the significant result could be ascribed to the effect of treatment, or to differences in the course of an herpetic episode depending upon whether it was first detected by patients in an early or late stage. Without more patients in the early treatment-vehicle group, these two possibilities cannot be distinguished.

6. The consequence of performing post-hoc an alternative statistical analysis (i.e., Gehan-Wilcoxon test) is that the risk of type I error is inflated. The statistical protocol only pre-specified the ANOVA test for analysis.

7. The statistical analysis of the Overall Study Results assumes that intra-patient healing times are as much independent events as are inter-patient healing times. While this assumption seems plausible, the burden is on the Sponsor to demonstrate the validity of this assumption.

8. Based upon these shortcomings, it is concluded that the the results reported and analyzed in Clinical Study 92-02 and its Statistical Addenda do not provide substantial evidence of the effectiveness of LIDAKOL® for the studied indication.

/S/

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin /S/ 5/26/99
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun
HFD-725/Biostatistics Team Leader/Srinivasan
HFD-725/Biostatistician/Gao /S/ 7/30/99
HFD-540/Project Manager/White

Medical Officer's Review of NDA 20-941

Correspondence date: 8/03/99
HFD540 #: 993889
Document ID: BZ

CDER Stamp date: 8/03/99
Review date: 8/19/99
Revised date: 8/26/99

SPONSOR: AVANIR PHARMACEUTICALS

DRUG: n-docosanol 10% cream

PHARMACOLOGIC CATEGORY: anti-viral

PROPOSED INDICATION: treatment of recurrent episodes of oro-facial herpes labialis

DOSAGE FORM AND ROUTE OF ADMINISTRATION: cream, applied topically to herpes lesions

BACKGROUND:
For analysis of efficacy in the two pivotal trials of the NDA, the pre-specified statistical test methodology was time-to-event analysis employing the Gehan generalization of the Wilcoxon test, stratified by study site. The pre-specified analysis plan did not include adjustment for any baseline covariate other than that of study site. Clinical trial 96-LID-06 demonstrated an 18 hour median shortening in disease course associated with LIDAKOL use, with a p value of 0.02 using the Gehan-Wilcoxon test. Clinical trial 96-LID-07 demonstrated a 16 hour median shortening in disease course, with a p value of 0.15 using the Gehan-Wilcoxon test. All other clinical trials have failed to demonstrate that LIDAKOL has any efficacy for this indication.

Sponsor has reanalyzed the efficacy results using the Proportional Odds Ratio method for covariate adjustment, with adjustment for multiple baseline covariates (study site, erythema vs. prodrome at baseline, historical episode duration). Sponsor justified reanalysis with multiple covariates on the grounds that in early drafts of the Phase 3 protocols (but not the final draft) the statistical analysis plan stated that adjustment for baseline covariates may be used. After adjusting for all these baseline covariates, treatment with LIDAKOL in both clinical studies was associated with higher odds of regression that had p values less than 0.05 for both studies. Based on this reanalysis, sponsor argues that they have met the evidentiary standard of adequate and well controlled studies supporting efficacy.

Agency responded to this claim by noting that the Proportional Odds Ratio method was not the pre-specified statistical analysis plan, that the external validity of this method in this context has not been abundantly established, and that the only identified covariate for adjustment in the Phase 3 protocol was study site. The consequences of using alternate analysis plans and including covariates that were not pre-specified in the analysis would be to inflate the type I error.

In response to Agency request that sponsor use Wilcoxon test methodology to reanalyze efficacy data to include not only center as a stratification factor but also other covariates of interest, sponsor has submitted an exploratory analysis.

The shortcomings of this analysis, as the sponsor acknowledges, is that "subset analyses and post-randomization selection of grouping factors have the potential for bias, for identification of spurious effects, and for selective interpretation." Sponsor also states that the results of these requested analyses are uninformative about consistency and about individual covariate effects, "due to the large variability introduced by examining small subsets."

Sponsor's criticisms of post-hoc analysis performed in this manner are valid. Any conclusions generated from such analysis properly should be regarded as hypothesis-generating rather than conclusively proving efficacy. The rationale for why such exploratory analyses were requested was that if LIDAKOL were found to be consistently superior to vehicle for patients within a subset for both pivotal studies, then differences in the baseline distribution of patients in this subset across the two studies might suggest an explanation for why the difference in median time-to-healing was statistically significant for 96-06 but not 96-07. Such evidence would increase the likelihood that LIDAKOL does have efficacy, at least within that patient subset.

There is evidence from the scientific literature that episodes that begin with a prodrome stage are more amenable to anti-viral treatment. Spotswood ("Clinical management of herpes viruses" in Herpes Simplex Labialis, IOS Press, 1995) notes that in two large clinical trials in which oral acyclovir and topical idoxuridine, respectively, were tested for their efficacy in herpes simplex labialis, "drug efficacy in both studies was segregated exclusively within the subgroup of patients who experienced a prodrome. Accordingly, the type of classical lesions may be an important new variable that determines the outcome of chemotherapy, a "prodrome-classical" lesions heralding a positive result and the "no prodrome-classical" lesions being unresponsive to treatment." To the reviewer's knowledge, there are no previously published studies that explore the predictive value of mean historical episode duration upon the duration of a nascent episode.

If it were found for both studies that LIDAKOL shortened the median time-to-healing for patients who enter the study in the prodrome stage but not those who enter in the erythema stage, such a result could be rationalized on the basis that for LIDAKOL to exert therapeutic activity, application must begin early in the herpes episode. Conversely, if it were found for both studies that LIDAKOL shortened the median time-to-healing for patients who enter the study in the erythema stage but not those who enter in the prodrome stage, such a result could be rationalized on the basis that LIDAKOL has a more pronounced effect on time to healing in those patients with more fulminant onsets of herpetic episodes. The desideratum is consistency across studies.

RESULTS:

Sponsor uses the difference in median healing times as an estimate of effect as a basis for assessing the impact of a covariate. To calculate the Gehan Wilconxon test statistic, tests were stratified by center, which is appropriate given that this analysis is the closest to that pre-specified in the statistical analysis plan. The (unavoidable) shortcoming of this approach is that it produces tests with low power due to the small within-stratum sample size.

Table 5 compares the median time-to-healing for LIDAKOL- and placebo-treated patients who enter 96-06 and 96-07 study in the prodrome stage:

	Number of LIDAKOL patients	Number of placebo patients	LIDAKOL, median time-to-healing (hours)	Placebo, median time-to-healing (hours)	Gehan-Wilcoxon P value
96-06	40	50	76.5	74.0	0.788
96-07	31	30	49.4	87.6	0.072

This table shows that for 96-06, median time-to-healing for LIDAKOL patients entering in the prodrome stage is **longer** than is the median time-to-healing for placebo patients entering in the prodrome stage. *In contrast*, for 96-07, median time-to-healing for LIDAKOL patients entering in the prodrome stage is **shorter** (and substantially shorter: 38.2 hours) than is the median time-to-healing for placebo patients entering in the prodrome stage. Sponsor performed several simulations with similar sample sizes seen in 96-06 that demonstrated that the observed outcome in 96-06 is not inconsistent with a 25% beneficial treatment effect with LIDAKOL. Sponsor simulated 19 studies with sample sizes similar to that observed in 96-06 in which LIDAKOL enjoyed a 25% advantage in the odds of healing at any specific point in time. The estimates produced ranged from –22 hours to 38 hours in favor of LIDAKOL, suggesting the observed value of –2.5 hours is not inconsistent with LIDAKOL having a beneficial effect.

Table 6 compares the median time-to-healing for LIDAKOL- and placebo-treated patients who enter 96-06 and 96-07 study in the erythema stage:

	Number of LIDAKOL patients	Number of placebo patients	LIDAKOL, median time-to-healing (hours)	Placebo, median time-to-healing (hours)	Gehan-Wilcoxon P value
96-06	143	133	96.3	118.5	.002
96-07	156	154	116.7	122.0	.717

For both studies, patients with erythema at baseline who are treated with LIDAKOL have shorter median times-to-healing than do patients treated with placebo. In study 96-06, this difference is substantial (22 hours), while in study 96-07 it is minimal (5 hours).

Looking at the effect of this baseline covariate in isolation, the reduced median time-to-healing observed in study 96-06 is driven entirely by the patients who entered in the

erythema stage. The reduced median time to healing in study 96-07 is largely driven by the patients who entered in the prodrome stage, though the outcomes of patients who entered in the erythema stage did contribute substantially to the overall difference in median time-to-healing. The results are not consistent across different studies. It is acknowledged that these results are not incompatible with a biologically consistent treatment effect across two studies among patients with the same baseline stage—just that such a consistent treatment effect for patients who enter with either prodrome or erythema has not been convincingly demonstrated.

Table 7 compares the median time-to-healing for LIDAKOL- and placebo-treated patients who enter 96-06 and 96-07 study with historical episodes lasting less than or equal to 5 days:

	Number of LIDAKOL patients	Number of placebo patients	LIDAKOL, median time-to-healing (hours)	Placebo, median time-to-healing (hours)	Gehan-Wilcoxon P value
96-06	16	38	91.8	72.7	0.136
96-07	31	36	70.0	101.4	0.043

In clinical study 96-06, the median time-to-healing is **longer** for LIDAKOL treated patients than for placebo treated patients, while in clinical study 96-07, the median time-to-healing is **shorter** for LIDAKOL treated patients than for placebo treated patients. The results from these two studies are inconsistent. The sample sizes within these subsets are relatively small, suggesting that it would not be implausible for the outcomes in 96-06 to be observed even with LIDAKOL hastening time-to-healing.

Table 8 compares the median time-to-healing for LIDAKOL- and placebo-treated patients who enter 96-06 and 96-07 study with historical episodes lasting longer than 5 days (most enrolled patients fall within this subset):

	Number of LIDAKOL patients	Number of placebo patients	LIDAKOL, median time-to-healing (hours)	Placebo, median time-to-healing (hours)	Gehan-Wilcoxon P value
96-06	167	145	95.5	118.2	.002
96-07	156	148	114.8	119.0	.586

In both clinical studies, median time-to-healing is shorter for those patients in this subset treated with LIDAKOL compared to those patients treated with placebo. The difference in time-to-healing is larger for those patients in the 96-06 study.

Looking at the effect of this baseline covariate in isolation, the results observed in 96-06 are driven entirely by the patient subset with historical episode duration of longer than 5 days. The results observed in 96-07 are driven principally by the patient subset with historical episode duration less than 5 days, though the other subset does contribute

substantially to the observed treatment effect. These results are also not consistent across different studies.

Sponsor also performed exploratory subset analysis (Table 9) according to both stage at treatment initiation and historical episode duration. Sponsor notes that the consequences of multiple stratifications as performed here are that each strata has comparatively small sample size, making estimates of treatment effects less reliable due to sampling variation.

Study	Stage/ Historical Duration	Difference in Median Times to Healing	Gehan Wilcoxon P value
96-06	Prodrome ≤ 5 days	3.3 hours	0.356
96-06	Prodrome > 5 days	0.9 hours	0.631
96-06	Erythema ≤ 5 days	-0.8 hours	0.349
96-06	Erythema > 5 days	21.8 hours	0.007
96-07	Prodrome ≤ 5 days	-4.2 hours	0.606
96-07	Prodrome > 5 days	44 hours	0.014
96-07	Erythema ≤ 5 days	45.1 hours	0.019
96-07	Erythema > 5 days	2.4 hours	0.854

The stratum responsible for the treatment effect observed in study 96-06 (Erythema > 5 days) has minimal effect in study 96-07; the strata responsible for the treatment effect observed in study 96-07 (Prodrome > 5 days, Erythema ≤ 5 days) have minimal effect in study 96-06.

CONCLUSIONS:

The search among possible subsets across the two pivotal studies submitted has not revealed convincing evidence for a consistent effect. It is unclear whether LIDAKOL works better than placebo for those patients who start application in the prodrome stage or in the erythema stage; it is unclear whether LIDAKOL works better than placebo for those patients who have a history of prolonged healing or for those in whom healing is typically shorter. This uncertainty arises either because the subset size is too small to accurately estimate treatment effect for the subsets, or because no such treatment effect exists.

The evidence submitted is not sufficient to alter the initial recommendation regarding the approvability of this application. To alter this recommendation, sponsor should submit a second adequate and well controlled clinical trial which demonstrates the efficacy of LIDAKOL in the treatment of recurrent oro-facial herpes simplex labialis.

/S/ _ 8/26/99

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA# 20-941

General Information:

Sponsor: AVANIR Pharmaceuticals

DEC 30 1998

Addendum Date: December 21, 1998

Proposed trade name: LIDAKOL®

Proposed Indication: treatment of recurrent oro-facial herpes labialis

BACKGROUND

On December 18, 1998, at an FDA-sponsor meeting to discuss Agency tentative decision regarding the approvability of NDA 20-941(LIDAKOL® for the treatment of oro-facial herpes labialis), sponsor challenged Agency to reconsider their decision not to approve the NDA. The thrust of sponsor's argument is that:

(1) it was inappropriate to consider trials 96-06 and 96-07 separately, because each was underpowered to detect a difference between active and placebo;
(2) Though 96-07 does not demonstrate that LIDAKOL® causes a statistically significant enhancement in time-to-healing compared to placebo, the trend in 96-07 is that LIDAKOL® is superior to placebo and the difference in median time (15.9 hours for 96-07) is close to the difference in median time for 96-06 (18.9 hours)
(3) the pooled study 96-06/07 does demonstrate a statistically significant enhancement of median time to healing (P value=.0076, time difference 17.5 hours);
(4) based upon the recent Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May, 1998), there is sufficient evidence for efficacy based upon the "pooled" single trial 96-06/07 to justify approvability.

REVIEWER'S ANALYSIS

The central issue upon which the sponsor's argument rests is (4) above: whether a single trial demonstrating efficacy is sufficient for approval. Whether that single trial is 96-06/07 (as sponsor prefers), or 96-06 is a secondary consideration. The purpose of this addendum is to provide the rationale for why a single clinical trial (either 96-06 or 96-06/07) demonstrating efficacy in the primary efficacy variable would be insufficient for approvability.

Quoting from the above-cited Guidance:

> "FDA has relied on only a single adequate and well-controlled efficacy study to support approval—generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survial, and a confirmatory study would have been difficult to conduct on ethical grounds.(pg. 3)"

Reviewer's Comment: In the study population of immunocompetent adults with recurrent oro-facial herpes labialis, the clinical lesions receiving ***placebo*** *treatment healed at a*

*median of 4.7 days for study 96-06. 92% of the patients receiving **placebo** healed within 10 days in this study. While the medical reviewer recognizes that having a topical treatment available that accelerates healing of oro-facial herpes labialis lesions would be a significant health benefit, the reviewer does not feel that it is as important a clinical benefit as effect on survival. Similarly, the reviewer does not feel that it would be difficult to condut another confirmatory study on ethical grounds.*

The Guidance identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim:
(1) large multicenter study
(2) consistency across study subsets
(3) multiple studies in a single study
(4) multiple endpoints involving different events
(5) statistically very persuasive finding

Reviewer's Comments:

*(1) large multicenter study: If Agency were to accede to sponsor's request and consider 96-06/07 to be the pivotal multicenter study in this NDA, this "pooled" study would have 737 ITT subjects, of whom 370 received active and 367 received placebo. In comparison, NDA 20-629, also for treatment of oro-facial herpes labialis, had **two** pivotal clinical studies, each convincing on its own (with p-values less than .05). In those studies, 1573 subjects (782 on active, 791 on vehicle) and 1484 subjects (734 on active, 750 on vehicle) initiated treatment, respectively.*

[redacted]

(2) consistency across study subsets: Neither 96-06 nor 96-07 randomized patients separately within different strata, so this consideration is not germane for this NDA.

(3) multiple studies in a single study: This consideration is not germane for this NDA.

(4) multiple endpoints involving different events: Only one primary endpoint, time-to-healing of all lesions (aborted and classical) was prospectively identified for 96-06 and 96-07. Sponsor has argued that for three of the secondary efficacy variables (time to cessation of ulcer/ soft crust, hours to cessation of pain/burn/itch/tingle, and hours to cessation of burn/itch/tingle), both pivotal clinical trials demonstrated significant improvement in LIDAKOL® compared to placebo. However, there is no adjustment made for multiple endpoints, and there is no generally accepted method for treatment of significant secondary endpoints if the primary endpoints are not significant.

(5) statistically very persuasive finding: The p-value for 96-06/07, .0076, is low, but is not lower than the product of two p-values that each on its own is below .05: $(.05)^2 = .0025$.

*In summary, evaluation of the five characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim reveals that **none** of the characteristics are present in the studies of NDA 20-941.*

In addition to the absence of convincing confirmatory evidence that lends support for approval of this NDA based on a single study, this reviewer cites below evidence that provides additional grounds for Agency to be suspicious concerning the clinical efficacy of this product. While the information cited below does not in and of itself argue against approval in the face of other, overwhelming, evidence of efficacy, it does buttress Agency arguments that another pivotal clinical efficacy study is warranted.

(1) Clinical Studies 96-06 and 96-07 do not have the same effect on time-to-healing of classical and of aborted episodes:

Parameter	96-06, Difference vs. Placebo	96-07, Difference vs. Placebo
Primary Efficacy Variable: Time-to-healing (abortion and classical, combined)	+19 hours, p=.02 (Table 15, pg. 35)	+16 hours, p=.15 (Table 28, pg. 49)
Time-to-healing (classical)	+1 hours, p=.27 (Table 18, pg. 39)	+22 hours, p=.02 (Table 31, pg. 53)
Percentage with aborted episodes	39% vs. 30%, p=.08 (Table 21, pg. 42)	41% vs. 38%, p=.60 (Table 34, pg. 56)
Time-to-healing (aborted)	-3, p=.56 (Table 22, pg. 42)	+7, p=.88 (Table 35, pg. 56)

In 96-06, LIDAKOL shows a statistically significant difference in the primary efficacy variable because (1) the percentage of aborted episodes trends higher for LIDAKOL, and (2) time-to-healing of aborted episodes is much shorter than is time-to-healing of classical episodes (~50 hours vs.~100 hours), so a trend towards higher proportion of aborted episodes has a proportionately large effect on the primary efficacy variable.

In 96-07, LIDAKOL does not show a statistically significant difference in the primary efficacy variable, despite the statistically significant difference in time-to-healing of classical episodes, because the percentage of aborted episodes for LIDAKOL and placebo are almost equal.

(2) 96-06 nor 96-07 are placebo-controlled, not vehicle-controlled trials.

The "gold standard" is vehicle-controlled trials. For most dermatologic drug products, the drug substances are such a small component of the drug product that it is possible to use the vehicle without drug substance as a negative control in clinical efficacy studies. For LIDAKOL®, where n-docosanol is 10% of the drug product, this approach is impossible. The consequences of this on the validity of the pivotal trials are discussed in detail on pg. 27 of the medical officer's review. Of note, sponsor did not agree to all Agency suggestions to minimize the differences between active and placebo.

(3) Three prior Phase 3 clinical efficacy studies (94-04, 95-10, and 94-05) failed to detect statistically significant differences in median time-to-healing between LIDAKOL® and stearic-acid placebo-treated patients.

Sponsor argues that the reason these trials failed is that stearic acid present in the placebo of these trials inadvertently contained anti-herpes activity. If Agency accepts sponsor's arguments at face value, one would therefore predict that 96-06 and 96-07 should demonstrate efficacy because the time-to-healing is **prolonged** in the placebo arms of these trials compared to the earlier trials, while the time-to-healing should be approximately the same in the active arms of 96-06, 96-07, and the earlier trials. However, examination of those trial results reveals that **exactly the opposite** has occurred: 96-06 demonstrates efficacy and 96-07 trends to efficacy because time-to-healing is **reduced** in the active arms of these trials compared to the earlier trials, while the time-to-healing is approximately the same in the placebo arms of 96-06, 96-07, and the earlier trials:

Trial	Median time to abortion and/or healing, active	Median time to abortion and/or healing, placebo
94-04	4.9 days	4.7 days
95-10	5.7 days	5.9 days
94-05	7.0 days	6.9 days
96-06	4.0 days	4.7 days
96-07	4.3 days	4.9 days

There are uncertainties inherent in comparing results in this manner across trials with different clinical designs, but it is certainly disconcerting that the results directly contradict sponsor's proffered explanation for the failure of trials 94-04, 95-10, and 94-05. In the face of the failure of 3 earlier Phase 3 trials, it would seem especially problematic to grant approvability on the basis of one successful Phase 3 trial.

/S/ 12/21/98

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin /S/ 12/23/98
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun /S/ 12/30/98
HFD-725/Biostatistics Team Leader/Srinivasan
HFD-725/Biostatistician/Gao
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Reid
HFD-540/Chemistry/Hathaway
HFD-540/Project Manager/White

Medical Officer's Review of NDA# 20-941 NOV 9 1998

1 General Information

1.1 NDA submission number 000

1.2 Applicant identification

1.2.1 Name: LIDAK Pharmaceuticals

1.2.2 Address and telephone number

11077 North Torrey Pines Road, La Jolla, CA 92037, (619)558-0364

1.2.3 Name of company official or contact person

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

1.3 Submission/review dates

1.3.1 Date of submission: December 19, 1997

1.3.2 CDER stamp date: December 22, 1997

1.3.3 Date submission received by reviewer: January 6, 1998

1.3.4 Date review begun: February 26, 1998

1.3.5 Date review completed: October 1, 1998

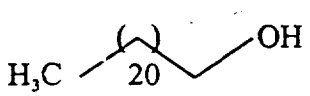
1.4 Drug identification

1.4.1 Generic name: *n*-Docosanol, Behenyl Alcohol

1.4.2 Proposed trade name: LIDAKOL®

1.4.3 Chemical name: *n*-Docosanol

1.4.4 Chemical structure



1.4.5 Molecular formula: $C_{22}H_{46}O$

1.4.6 Molecular weight: 326.61

1.5 Pharmacologic Category: Anti-viral, straight-chain aliphatic alcohol.

1.6 Dosage Form: Cream

1.7 Route of Administration: Topical

1.8 Proposed Indication & Usage section

Treatment of recurrent oro-facial herpes labialis. From the proposed label: "LIDAKOL is indicated for the treatment of recurrent oral-facial herpes simplex (fever blisters or cold sores) in adults."

1.9 Proposed Dosage & Administration section

Five times daily. From the proposed label: "LIDAKOL should be applied topically 5 times/day until lesion is healed, up to a maximum of 10 days. It should be rubbed in gently, but completely. Treatment should begin as early as possible in the course of the episode."

1.10 Related Drugs

None

1.11 Material Reviewed

1.11.1 NDA volumes reviewed

Table 1. NDA Volumes Reviewed and their Contents

Volume	Contents
Vol 2.1 Vol 2.12	Index Volume Clinical Pharmacology
Vol2.14-17	Clinical Study 96-LID-06
Vol 2.18-21	Clinical Study 96-LID-07
Vol 2.59	Integrated Efficacy Summary
Vol 2.60-61	Integrated Safety Summary
Vol 2.63	Dermal Toxicity Studies
Vol 2.114-119	CRFs

1.11.2 Other documents reviewed

<u>Regulatory Documents Reviewed</u>

Minutes of the End-of -Phase II Meeting, held August 8, 1994

Memoranda of Telephone Conversations between LIDAK Pharmaceuticals and FDA, held October 19, 1994, January 13, 1995, July 25, 1996,
Letters between LIDAK Pharmaceuticals and FDA, dated December 8, 1994, March 15, 1996, April 10, 1996, June 17, 1996, July 1, 1996, July 17, 1996, July 23, 1996, February 1, 1996
Minutes of pre-NDA Meeting, held October 27, 1997
Medical Officer Consultations, dated July 22, 1994, August 16, 1995, May 31, 1996
Related FDA Reviews

Non-Regulatory Documents Reviewed

Literature search: natural history of herpes simplex oro-facial labialis, referenced in the body of the review
Amendments reviewed--None

Regulatory Background

July 11, 1991 [redacted] submitted to HFD-530
August 8, 1994 End of Phase 2 Meeting. Key issue: Primary endpoint for Phase 3 studies 94-LID-01, 94-LID-04, 94-LID-05
February 1, 1996 FDA Advice Letter. Recommended that the sponsor define primary endpoint as "episode abortion as complete resolution of herpes lesions which never reached the vesicular stage."
April 10, 1996 FDA received letter from sponsor indicating failure of 94-LID-04, believed to be due to inadvertent use of a placebo with anti-viral activity. FDA advise was requested on designing a new placebo to be used in two new trials.
June 17-July 1, 1996 (1) FDA Advice Letter. Recommended the use of a polyethylene glycol based formulation as a placebo control. A sample of the proposed placebo formulation was requested. (2) A remarkable color difference was noted between the placebo and n-Docosanol. A telecon was held with sponsor on the color difference and it was recommended that titanium dioxide be added to placebo to make it identical in color. The consequence of lack of identity in color is that investigators know which patients are getting the different test formulations (i.e. the blind is compromised). (3) Sponsor rejected this recommendation.
July 2, 1996 FDA was informed that controlled clinical trials performed to that date (including 95-10, 94-04, and 94-05) had failed to detect a significant difference in healing between patients treated with LIDAKOL® and placebo.
July 17, 1996 FDA Advice Letter. The feasibility of continuing investigation of this indication is questioned. FDA to LIDAK: "We are puzzled that in the face of negative results from at least three controlled studies, you believe data from an additional two studies would be sufficiently compelling to support a New Drug Application for this indication."
July 23, 1996 FDA Advice Letter. Recommended primary endpoint be defined as the time from therapy initiation to complete resolution of all local signs/symptoms in all subjects, thereby including those with classical episodes and those with aborted episodes. Concern over the color differences between placebo and active was restated. Recommended that "all [reviewer's emphasis] subjects should be followed twice daily

until complete healing takes place. Otherwise, the ascertainment of the time until healing will be delayed for those lesions that heal after medication is discontinued."

July 25, 1996 In a teleconference between LIDAK and FDA, Dr. Katz, President of LIDAK, stated that he believes the failure of the clinical trials to date were due to the effectiveness of the stearic acid placebo, and expressed confidence that with a different placebo, the proposed Phase 3 clinical trials will show significant healing times.

October 27, 1997 Pre-NDA meeting

December 19, 1997 NDA#20-941 is submitted, with two new clinical trials (96-06, 96-07), using as a placebo the polyethylene glycol-based cream.

APPEARS THIS WAY
ON ORIGINAL

2 Table of Contents

3 Chemistry/Manufacturing Controls

Docosanol is a saturated 22-carbon, straight-chain aliphatic alcohol. Physically, it is a white, waxy solid. The n-Octanol-water partition coefficient is 12.1 (log P), as determined by high performance liquid chromatography. It is freely soluble in chloroform and 1-octanol, partially soluble in n-hexane, methanol, and 95% ethanol, and practically insoluble in water. Stability according to the sponsor is at least 24 months when stored at or below 25°C (77°F). In the volumes reviewed by the medical officer, there is no information provided concerning the visible or UV absorbance of drug product.

Manufacturer Bulk Drug Substance:

Manufacturer Drug Product:

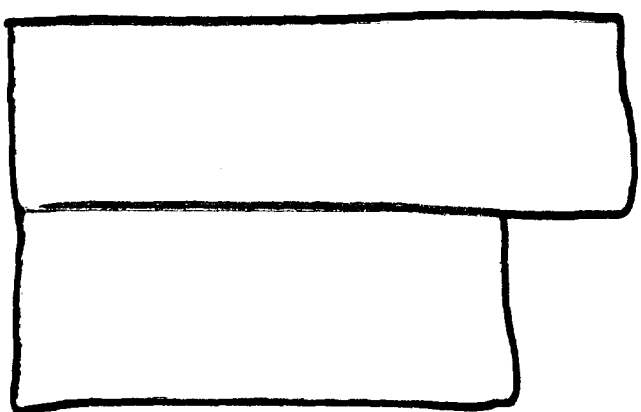


Table 2 describes the composition of the formulations used in clinical trials:

Table 2. Formulations Used in Clinical Trials

Formulation 1 (% by weight)	Formulation 3 (% by weight)	Ingredient	Function/Rationale
10	10	n-Docosanol	Active Drug Substance
		Sucrose Stearate/ Sucrose Distearate	
		Light Mineral Oil,	
		Propylene Glycol,	
		Benzyl Alcohol,	
		Purified Water,	

Source: Vol. 2.1, Table 9

Formulation 1 was used in three clinical studies of topical safety (IRAD 040-001, 040-002, 040-003), and in one non-clinical study (LP-17339) in which Formulations 1 and 3 were compared for the in vitro penetration of human cadaver skin in Franz static diffusion chambers (see Section 4, Human Pharmacokinetics/Pharmacodynamics). The motive for the change to Formulation 3 was concern regarding the safety of [redacted] Pivotal clinical trials, and other topical safety studies, were performed using Formulation 3. The trials performed with Formulation #1 have no regulatory utility. Placebo formulations for the pivotal clinical trials were [redacted]

4 Animal Pharmacology/Toxicology

Oral ADME studies in rats revealed that post-oral gavage, around 80% of *n*-docosanol is not absorbed and is excreted in feces. Following oral administration, systemic exposures to *n*-docosanol appeared similar across several species and were characterized by non-linear (dose-dependent) kinetics. The absorbed *n*-docosanol was metabolized to *n*-docosanoic acid, then to polar phosphatides, which were distributed in a wide variety of tissues. This pattern is similar to that observed for other orally administered fatty alcohols. After intravenous doses, 50% of the radioactivity was excreted in the expired air, presumably as CO_2. Topical ADME studies revealed that systemic absorption of n-docosanol is <0.0003% of the applied dose in mice. Following four weeks of daily docosanol exposure to abraded and non-abraded rabbit skin, there was no difference in docosanol serum levels between animals treated with docosanol and those treated with placebo. Four weeks of dermal applications of LIDAKOL® 10% cream in rabbits at dose levels of up to 1000mg/kg (approximately 1000 times expected human dose levels) for 6 hours/day (occluded) on intact and abraded skin did not produce any histologic evidence of local or systemic toxicity. Reproductive and developmental toxicology studies in rats revealed that there were no dose-related effects on reproduction or on induction of teratogenicity at doses up to 1000 mg/kg/day.

5 Microbiology

This protocol did not include any viral culture assays for the detection of herpes virus from lesions, either at baseline or during the clinical trial. Accordingly, positive HSV-1 culture was not required as an inclusion criteria for study entry. Requiring positive HSV-1 cultures on a suspect lesion prior to study entry would have been inappropriate, as it would have delayed patient enrollment for at least 24 hours and would have reduced the ability of active drug to exert a beneficial effect on lesion healing. Clinical diagnosis of herpetic recurrence is both sensitive and specific. Since clinicians usually treat empirically lesions suspicious for being herpetic recurrences, a study design in which treatment is initiated based upon a clinical diagnosis of recurrence, rather than a virologic diagnosis, closely emulates clinical practice. 98% of the study patients' sera tested positive at baseline for the presence of anti-HSV antibodies, an expected result if patients with frequent oro-facial recurrences are recruited into the trial.

Because this study did not include any measurements of lesion titers at baseline or from healing lesions, the final package label should not contain any claims relating to LIDAKOL®'s effect on the duration or titer of viral shedding from lesions.

Sponsor provides no data indicating that there exist any specific interactions between docosanol or its metabolites with any viral protein or other viral macromolecule. The implications of a lack of specific interactions are two-fold: (1) it is unlikely that treatment of patients with docosanol will result in the generation of mutant docosanol-resistant HSV-1; and (2) it is unlikely that treatment of patients with docosanol will result in mutant viruses arising that are resistant to systemic anti-viral medications.

6 Human Pharmacokinetics/Pharmacodynamics

Mechanism of Action—Docosanol is metabolized to n-docosanoic acid, and n-docosanoic acid is incorporated into ether lipids and into phospholipids containing [redacted] head groups. Docosanol and its metabolites do not interfere with the binding of virions to the cell surface, but rather interfere with the process of fusion between the virus and cell surface lipid membranes, and with subsequent productive entry of virus capsid into the cytoplasm. In vitro, docosanol has the ability to inhibit a broad spectrum of lipid-enveloped viruses, including CMV, VZV, HHV-6, HSV-1, HSV-2, RSV, influenza A, and HIV-1.

Absorption and Distribution—The in vitro penetration of n-[1-^{14}C] labelled docosanol in into human cadaver skin was evaluated using Franz static diffusion chambers filled with a [redacted] The study measured cumulative penetration of n-[1-^{14}C] docosanol over 24 hours and skin tissue distribution

at 24 hours. The results depicted below are for penetration with Formulation 3, the formulation used in pivotal clinical trials.

Table 3. 24-Hour Cumulative In Vitro Penetration of 30 mg n-[1-^{14}C] docosanol

	Mean ± SD 24-Hour Cumulative Penetration, µg	% Dose ± SD
Stratum Corneum	34.47 ± 32.98	1.15 ± 1.10
Epidermis	21.92 ± 18.63	0.73 ± 0.62
Dermis	1.28 ± 0.56	0.04 ± 0.02
Reservoir	0.083 ± 0.028	0.003 ± 0.001

Study Report, Tables VII and X

These results show that there is virtually no penetration of docosanol into the reservoir solution, most likely due to the low water solubility of the drug. There is also very low penetration of the drug into the stratum corneum, epidermis, and dermis. It is unclear if the results from this study are relevant for the penetration of docosanol into lingual mucosal epithelium, which does not have a fully keratinized stratum corneum such as would be present in human cadaveric skin.

Plasma levels of n-docosanol after topical dosing of LIDAKOL® to patients with oral-facial herpes simplex were below the limit of quantitation in virtually all samples tested, thus precluding further pharmacokinetic analysis. Because LIDAKOL® is indicated for perioral use, oral exposure may occur in clinical practice. Pharmacokinetic analysis of excretion characteristics of a single oral dose of n-[1-^{14}C] labelled docosanol was performed:

Table 4. Excretion Characteristics Following a Single Oral Dose of ^{14}C-Labelled n-Docosanol

Elimination via:	% of Oral Dose (Mean +/- SD)
Feces	103.73 +/- 3.96
Urine	0.028 +/- 0.049
Air	0.907 +/- 0.400
Total	104.68 +/- 3.99

Source: 95-LID-01 Study report, Table 3

Negligible amounts of n-[1-^{14}C] labelled docosanol were absorbed from the gastrointestinal tract. In the feces, n-docosanol accounted for 80% and n-docosanoic acid for 7% of the radioactivity.

7 Human Clinical Experience

7.1 Foreign Experience

LIDAKOL® has not been approved for marketing in any country.

7.2 Post-Marketing Experience

Since no other formulation has been approved, there is no pertinent post-marketing experience for this drug substance.

8 Clinical Studies

8.1 Introduction[1]

Recurrent oro-facial herpes simplex is a virally-mediated disease characterized by episodic vesicular eruptions on the lips and perioral skin. It is caused by the intermittent activation of herpes simplex virus type-1 (HSV-1) that customarily lies latent in the sensory nerve ganglia of persistently infected patients, and by subsequent acute viral infection of labial and/or peri-oral keratinocytes. Herpes simplex virus type-2 (HSV-2) may rarely cause primary oro-facial herpes simplex infections, but recurrent disease caused by this virus is rare. In the United States, serological studies have indicated that 30% to 60% of children under the age of 10, and 80% to 90% of those aged 50 and older, have been exposed to and have developed antibodies against HSV-1. Roughly 25-40% of the United States population experience recurrent episodes of oro-facial herpes simplex; thus, only one-third of persistently infected patients experience recurrent episodes. The outbreak frequency is extremely variable, ranging from once every five to ten years, to monthly or more frequent outbreaks among a small proportion of individuals. The morbidity of episodes is also quite variable, ranging from prodromal symptoms without the development of any signs to extensive disease of both lips and cheeks following severe sunburn.

The eight stages of a "classical" herpes recurrence are: (1) prodrome (i.e. pain, burning, itching, or tingling in the area in which a lesion will subsequently develop); (2) erythema; (3) papule; (4) vesicle; (5) ulcer/ soft (moist) crust; (6) hard (dry) crust; (7) dry flaking/ residual swelling; and (8) complete healing. Roughly 40-54% of episodes of herpes labialis begin without prodromes. Patients with prodromes have more severe lesions than patients without prodromes. Roughly 25% of incipient lesions abort. Of the aborted lesions, one-half abort at the prodrome stage ("false prodrome"), and the other half at the

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[1] Spruance, S.L., "Herpes Simplex Labialis", in Clinical Management of Herpes Viruses, IOS Press, Washington, D.C., 1995.
Spruance, S.L., Overall, J.C. Jr., Kern, E.R., Krueger, G.G., Pliam, V., Miller, W., "The natural history of recurrent herpes simplex labialis: implications for antiviral therapy" in N Engl J Med, Vol. 297, No. 2, pg. 69-75, 1977.

erythema or papule stage. The so called "false prodromes" are probably caused by reactivation of HSV-1, because patients who experience false prodromes have a 60% rate of HSV excretion in the oral cavity. In addition, histologic studies of patients with prodromal symptoms have found cytopathologic changes in the epidermis characteristic of HSV infection.

The most frequent "trigger factors", believed to cause an outbreak, are: emotional stress, illness, UV light exposure, trauma, fatigue, menses, chapped lips, and season of the year. UV-induced lesions tend to be more severe and to last longer than lesions not caused by UV exposure. For sun-induced lesions in immunocompetent patients, mean time to complete healing is 9.7 days, with a standard deviation of 3.9 days; for non-sun-induced lesions, mean time to complete healing is 8.1 days, with a standard deviation of 3.5 days. Patients are in greatest pain during the vesicle and ulcer/soft crust stages of classical lesions.

Primary infection of the oral cavity is either asymptomatic or causes gingivostomatitis. After primary infection, HSV-1 is thought to migrate through sensory nerve axons, to establish chronic, latent infection in sensory ganglia, including those of the trigeminal, facial, and vagus nerves. During its latency in neuronal cells, HSV DNA is thought to persist in a circular form without integration into host cell DNA. It has been hypothesized that recurrences develop in a subset of infected patients who mount an immune response to the primary HSV infection that is predominantly TH2 (i.e. characterized by T cells that produce interleukin-4 and -5) rather than TH1 (i.e. characterized by gamma-interferon and interleukin-2 production). Reinfection of the epidermis occurs via a process of multifocal inoculation from the multiple branches of a single infected neuron. Each infected keratinocyte produces approximately 50,000 to 200,000 infectious virions before lysing. It is hypothesized that only 2 or 3 such cycles of viral replication are required at each microfocus before a clinically apparent lesion develops. In patients with normal immune function, enlargement of the lesion is stalled by the appearance within the lesion of high levels of gamma-interferon and of HSV-specific cytotoxic T-cell activity. The factors favoring lesion spread (i.e. viral replication, infection of contiguous cells, and virally-mediated keratinocyte lysis) eventually are overwhelmed by immune effects acting to limit infection. Pharmacologic intervention tips this balance toward more rapid lesion resolution.

The regulatory history of the one currently approved drug in the United States for the topical treatment of recurrent oro-facial herpes labialis in immuno-competent patients is summarized below:

Table 5. Regulatory Information about DENAVIR® Cream

DRUG NAME	DENAVIR
CHEMICAL NAME	Penciclovir
SPONSOR	SmithKline Beecham

	Pharmaceuticals
INDICATION	Treatment of recurrent herpes labialis (cold sores) in adults
NDA	20-629
PREGNANCY CATEGORY	B
APPROVAL DATE	9/24/96
CLASSIFICATION	1S
DIVISION	HFD-530
DOSAGE	5% cream
FREQUENCY	Every 2 hours while awake
LENGTH OF TREATMENT	Starting as early as possible (i.e., during the prodrome or when lesions appear), for a period of 4 days.
HOW SUPPLIED	2 gram tubes

from: DENAVIR® NDA approval package

Penciclovir's mechanism of action is that it is phosphorylated by the HSV-encoded thymidine kinase to a monophosphate form which, in turn, is converted to penciclovir triphosphate by cellular kinases. In vitro studies demonstrate that penciclovir triphosphate inhibits HSV DNA polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and replication are selectively inhibited. Two patient-initiated phase III clinical trials demonstrated that DENAVIR® use was associated with a statistically significant decrease in the duration of critical stage lesions (defined as papules, vesicles/pustules, ulcers/soft crusts, and hard crusts) and a decrease in the duration of lesion pain. In both studies, the mean duration of lesions and lesion pain was approximately one-half day shorter in patients treated with DENAVIR® than in patients treated with placebo. Because these trials had as their primary efficacy variable the duration of critical stage lesions, these trials were not designed to test if DENAVIR® increased the likelihood that episodes abort prior to reaching the critical lesion stage.

The following table lists all studies submitted in NDA 20-941, with enrollment numbers for study drug and active control.

Table 6. Studies submitted for NDA 20-941

Study No.	Dates	Location	Design	No. of Patients	Outcome
Clinical Pharmacology Studies					
94-LID-02	01/05/94-03/17/95	The Netherlands	Pharmacokinetic study in healthy male subjects	6 subjects	

95-LID-01	02/08/95-03/02/95	The Netherlands	Excretion balance, pharmacokinetic and metabolism study after a single oral dose of ^{14}C-labeled n-docosanol in healthy male subjects	6 subjects	
95-LID-02	06/29/95-11/11/95	The Netherlands	Pharmacokinetic study in patients undergoing a recurrence of oral-facial herpes simplex	10 subjects	
Dermal Toxicity Studies in Humans					
IRAD 040-001	08/26/91-08/30/91	U.S.A.	Safety study (phototoxicity) of LIDAKOL® Formulation 1	10 subjects	Formulation 1 did not appear to cause phototoxicity
IRAD 040-002	09/09/91-10/18/91	U.S.A.	Safety study (repeat insult patch test) in healthy subjects	55 subjects	Formulation 1 had the potential to cause allergic sensitization; one exposed subject experienced contact dermatitis
IRAD 040-003	10/11/91-10/18/91	U.S.A.	Safety study (cumulative irritation) in healthy subjects	13 subjects	Formulation 1 was a mild primary irritant
95-LID-03a	05/01/95-05/22/95	U.S.A.	Masked, single center, negatively and positively controlled 21-day cumulative irritancy trial of LIDAKOL® Formulation 3	30 subjects were enrolled, 27 were evaluable	LIDAKOL® as formulated is probably a mild irritant in normal use
95-LID-03b	05/02/95-06/16/95	U.S.A.	Single center evaluation of the potential for LIDAKOL® to induce human phototoxicity and photoallergenicity of LIDAKOL® Formulation 3	30 subjects were enrolled, 25 were evaluable	No evidence that LIDAKOL® is capable of inducing either a phototoxic or photoallergic reaction in human subjects
95-LID-03c	05/15/95-01/26/96	U.S.A.	Single center evaluation of the potential for LIDAKOL® Formulation 3 to induce phototoxicity and photoallergenicity	227 were enrolled, 201 were evaluable	One subject developed allergic sensitization to the LIDAKOL® vehicle
Clinical Efficacy Studies					

96-LID-06	07/29/96-04/21/97	U.S.A.	Randomized, clinic-initiated, multicenter, double-blind, PEG placebo-controlled study	LIDAKOL®=183 Placebo=183	Median time to abortion and/or healing: LIDAKOL® 94.9 hours, placebo 113.8 hours; P-value 0.02
96-LID-07	10/04/96-05/12/97	U.S.A.	Randomized, clinic-initiated, multicenter, double-blind, PEG placebo-controlled study	LIDAKOL®=187 Placebo=184	Median time to abortion and/or healing: LIDAKOL® 102.3 hours, placebo 118.2 hours; P-value 0.15
94-LID-04	12/12/94-08/17/95	U.S.A. & Canada	Randomized, clinic-initiated, multicenter, double-blind, stearic acid placebo-controlled study	LIDAKOL®=159 Placebo=154	Median time to abortion and/or healing: LIDAKOL® 4.9 days, placebo 4.7 days
95-LID-10	05/04/95-10/20/95	U.S.A.	Randomized, clinic-initiated, multicenter, double-blind, stearic acid placebo-controlled study	LIDAKOL®=168 Placebo=164	Median time to abortion and/or healing: LIDAKOL® 5.7 days, placebo 5.9 days
94-LID-05	12/15/94-10/27/95	U.S.A. & Canada	Randomized, clinic-initiated, multicenter, double-blind, stearic acid placebo-controlled study	LIDAKOL®=270 Placebo=272	Median time to abortion and/or healing: LIDAKOL® 7.0 days, placebo 6.9 days
92-LID-04	03/14/93-03/06/95	U.S.A.	Randomized, Phase 2, patient-initiated, single center, double-blind, stearic acid placebo-controlled study	LIDAKOL®=35 Placebo=27	Median time to abortion and/or healing: LIDAKOL® 7-8 days, placebo 6-7 days
92-LID-02	12/00/92-06/00/93	Europe	Randomized, patient-initiated, multicenter, double-blind, stearic acid placebo-controlled study treatment of recurrent oral-facial herpes simplex	LIDAKOL®=32 Placebo=33	Mean time to healing: LIDAKOL® 5.4 days, stan.dev. 3.6 days; placebo 7.3 days, stan.dev. 2.8 days.
94-LID-01	03/00/94-	Europe	Randomized, patient-	LIDAKOL®=	Median time to

	03/00/95		initiated, multicenter, double-blind, parallel group study of LIDAKOL versus acyclovir 5% cream	235 Acyclovir 5% cream=239	healing: LIDAKOL® 131 hours, acyclovir 5% cream 122 hours
94-LID-03	08/00/94-03/00/96	Europe	Open-label, patient-initiated multicenter, safety and tolerability study	LIDAKOL®= 150	
from: Table 1. Summary Table of Clinical Studies, Vol 2.60					

8.2 Dermal Toxicity Studies

The results from the dermal toxicity studies of LIDAKOL® Formulation 1 will not be reviewed because Formulation 1 was not used in any clinical efficacy studies. The dermal toxicity of Formulation 3 was studied in 95-LID-03a, 95-LID-03b, and 95-LID-03c.

8.2.1 Clinical Trial 95-LID-03a

Study Title: "Evaluation of Cumulative Irritation Potential in Humans, 21-Day Trial"
Sponsor: [redacted]
Investigator: Robert A. Harper, Ph.D., D. Mark Oelrich, M.D.
Duration: from 5/1/95 to 5/22/95
Objective: To test n-docosanol 10% cream for human skin irritation elicited by repetitive topical application over a 21-day period.
Subject Numbers: 30 subjects entered study. 1 was discontinued due to adverse reaction to adhesive tape; 2 failed to return to the test site, 27 subjects were evaluable.
Design: 21 consecutive daily applications of test article to paraspinal regions of the back (0.2 mL of n-docosanol 10% cream (Formulation 3), and of 2 control articles (0.2 mL of negative control of 0.89% NaCl in distilled water, and 0.2 mL of positive control of 0.1% sodium lauryl sulfate in distilled water). All three articles were applied concurrently, in a randomized pattern to separate regions of the left and right paraspinal regions. The skin sites were graded daily for reactions by an observer blinded to treatment assignments. The protocol specifies that scorer will also be blinded to previous scores, yet "all reasonable attempts will be made to ensure that the same individual will do all the scoring of reactions to the test article"; these seem like mutually contradictory specifications. The articles were left in place for 23 +/- 1 hour, then removed 1 hour prior to returning to lab daily for evaluation.

Daily reapplication of the articles was continued for the 21 day duration of the study, unless reactions were so strong as to make reapplication inadvisable. The following numeric and alphabetic scales to assess irritancy were used:

0= no evidence of irritation
1= minimal erythema
2= definite erythema
3= erythema and papules
4= definite edema
5= erythema, edema, and papules
6= vesicular erythema
7= strong reaction spread beyond site

A=0= slight glazed appearance
B=1= marked glazing
C=2= glazed with peeling and crackling
F=3= glazing with fissures
G=3= film of dried serous exudate
H=3= small petechial erosions and/or scabs

The individual reaction score was the sum of the numeric score plus the numeric value of the alphabetic score. Any individual reaction score at the maximum allowable limits of the study (3) was not repatched for the remainder of the study, and was scored at 3 to the conclusion of the study.

The following classification system, suitable for differentiating the irritation potential of relatively mild test articles, was used to standardize the interpretation of the 10 subject mean total group score:

Table 7. Classification system for assessment of irritation potential

Class	Total Group Score (Base 10)*	Indications from Test	Description of Observed Responses
1	0-49	Mild material—no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e. continuous reapplication and occlusion at concentration specified)
2	50-199	Probably mild in normal use	Evidence of a slight potential for very mild cumulative irritation under conditions of test
3	200-449	Possibly mild in normal use	Evidence of a moderate potential use for mild cumulative irritation under conditions of test
4	450-580	Experimental cumulative	Evidence of a strong potential for mild to

			irritant moderate cumulative irritation under conditions of test
5	581-630	Experimental primary irritant	Evidence of potential for primary irritant irritation under conditions of test

* Total Score= $\sum_{i=1}^{21} \sum_{j=1}^{N} S_{ij}$,

S_{ij} is the irritation score for the ith application for the jth subject, N is the total number of subjects for the ith day or any one treatment.

Total Group Base 10 Score ($T.S._{10}$) adjusts for differences in number of subjects enrolled in different studies , to enable comparison across different potential irritants.

$(T.S._{10}) = (10)(1/N)(\text{Total Score})$

The evaluated parameters included the cumulative scores for the total panel, the total score per 10 subjects exposed to treatment (10 subject mean total group score), and the number of subjects with each reaction score at each of the evaluations.

Adverse Events: One subject was discontinued because of adverse reaction to the tape. This adverse reaction resolved three days after discontinuation.

Results:

Table 8. Irritation Potential of LIDAKOL®

Test Article	10 subject mean total group score	Irritation Classification
n-docosanol 10% cream	187.2	Probably mild in normal use
negative control of 0.89% NaCl in distilled water	13.1	Mild—no experimental irritation
positive control of 0.1% sodium lauryl sulfate in distilled water	574.3	Experimental cumulative irritant

Conclusions:

The study was appropriately designed and controlled, and of appropriate duration, and demonstrated that LIDAKOL® as formulated is probably a mild irritant in normal use.

8.2.2 Clinical Trial 95-LID-03b

Study Title: "Evaluation of Human Phototoxicity and Photoallergenicity."
Sponsor: [redacted]
Investigator: Richard S. Berger, M.D.
Duration: 5/2/95 to 6/16/95
Objective: To evaluate the potential of LIDAKOL® for inducing phototoxicity and photoallergy in humans.
Subject Numbers: 30 subjects enrolled; 5 dropped out due to difficulty adhering to the study protocol.
Design:
The study was comprised of four phases: pre-induction, induction, rest, and challenge.

Pre-induction phase: Duplicate sets of patches containing 0.2 mL LIDAKOL® and distilled water were applied to sites on the left and right volar forearms. After 24 hours application, one set of each pair of patches were removed, and the sites were irradiated with [redacted] UVA radiation. The irradiance source was a [redacted] to emit UVA radiation. Energy levels were measured at the skin surface with an [redacted] radiometer equipped with a calibrated photodetector. The duplicate patch was subsequently removed to serve as an unirradiated control. Both sites were scored at 1, 24, 48, and 72 hours. Reactions to test materials were scored according to the following scale:

Table 9. Photoreactivity Scale

0	No evidence of any reaction
1	Reaction readily visible but mild unless letter grade appended (see grades E and F below). Mild reactions include weak but definite erythema, and weak superficial skin responses such as glazing, cracking, or peeling.
2	Definite papular response (E, F, or S appended if
3	Definite edema (E, F, or S appended if appropriate)
4	Definite edema and papules (E, F, or S appended if
5	Vesicular/bullous eruption
E	Strong erythema at the patch site
F	Fissures, film of dried serous exudate, small petechial erosions and/or scabs
S	Reaction spreading beyond test site