Table 10. Photoreactivity Testing Results

	LIDAKOL®		Water	
Score	One hour post-irradiation	24 hours post-irradiation	One hour post-irradiation	24 hours post-irradiation
0	23 patients	26 patients	23 patients	27 patients
1	4 patients	1 patients	4 patients	0 patients

All reaction scores measured at 48 and 72 hours were zero. No reaction scores exceeded 1. Based on this study, LIDAKOL® did not induce a significant phototoxic reaction.

According to the protocol, the MED was measured "by titrating each subject during the pre-induction period", but the protocol does not specify the range of doses tested to measure MED, making it impossible to validate the accuracy of the procedure for determination of the MED.

Induction phase: A set of two patches containing 0.2 mL LIDAKOL® and distilled water were applied to sites on the left or right paraspinal back skin for 24 hours, twice weekly for three weeks. A 1 cm^2 site area within the sites were irradiated with 2 X MED UVB light ten minutes after the patches were removed. Following the first, third, and fifth application, sites were evaluated and scored (as above) 24 hours after irradiation; following the second, fourth, and sixth application, sites were evaluated and scored 72 hours after irradiation.

50% of the application sites exposed to LIDAKOL® and more than 60% of the application sites exposed to water developed no evidence of erythema 24 hours after exposure to what was [redacted] of UVB light. This observation suggests that there may have been systematic underestimation of subjects' MED, and calls into question whether subjects were exposed to adequate doses of UVB irradiation during the induction phase.

Rest Phase: No applications were administered for two weeks.

Challenge Phase: Duplicate sets of patches containing 0.2 mL LIDAKOL® and distilled water were applied to naïve sites on the back. After 24 hours, one set of patches were removed, and the sites were exposed to [redacted] UVA irradiation. The other set of patches were then removed, to function as unirradiated controls, and the two sets of sites were evaluated and scored (as above) at 1, 24, 48, and 72 hours.

Table 11. Photoreactivity during the Challenge Phase

	LIDAKOL®				Water			
Score	Hours post-irradiation				Hours post-irradiation			
	1	24	48	72	1	24	48	72
0	9	18	25	25	7	21	25	25

1	16	7	0	0	18	4	0	0

No significant difference was noted between reactivity from UVA exposure to LIDAKOL® and to water.

Conclusion: Based on this study, there is no evidence to suggest that LIDAKOL® is capable of inducing either a phototoxic or photoallergic reaction in human subjects.
Reviewer's Comment: There is no proven effective predictive testing model for photoallergic contact dermatitis. The standard test conducted in humans for this purpose, the photomaximization test, is designed to induce an exaggerated response to both chemical and ultraviolet light (K. Kaidbey, "The evaluation of photoallergic contact sensitizers in humans", Dermatotoxicology, ed. By F. Marzulli and H. Maibach, 4th edition). Customarily, in this test, the induction phase consists of exposure to test material for 24 hours under occlusion, followed by exposure to multiple MEDs (Dr. Kaidbey cites the use of 3 MEDs) from a solar simulator. After a rest period of 48 hours, occlusion and irradiation is repeated. This sequence is repeated for a total of 6 exposures over a period of 3 weeks.
Examination of the individual reaction scores revealed that only 9/25 tested subjects had erythema after each of the 6 induction exposures at sites treated with water and with LIDAKOL. All subjects had at least one erythematous reaction at the LIDAKOL exposure site during the induction phase, but 5/25 had no erythematous reaction at the water site during the induction phase. These results suggested that many of these subjects were not exposed to more than one MED during some or all of the induction phase.
When sponsor was queried about these results, sponsor responded by stating that "there may have been some non-uniformity in the beam of light used to generate the MED and the beam of light used during the initial induction exposure." This reviewer interprets this statement to mean that some of the treated sites may actually have received less than 50% of the designated light dose. The sponsor's expert consultants nevertheless state that the findings of the study are valid. "Dr. Berger and Dr. Sayre base their opinions on the fact that although the protocol specifies two procedures to allow possible photoallergens to penetrate into the skin—1) a sunburn induced by the 2X MED exposure, and 2) occlusion of the test site after each product application—either one alone is sufficient to allow penetration of a topical hapten or photoallergen." No published study is cited buttressing the expert's contention that induction of erythema is not necessary during the induction phase. The question arises: if induction of erythema is not necessary, why is the protocol designed to induce erythema during the induction phase?
While there may have been significant technical flaws in the execution of this study, this reviewer nonetheless deems it unlikely that n-docosanol is a contact photoallergen. Although no UV-visible spectrum information was submitted by sponsor in the DMF, it is highly unlikely that a straight chain aliphatic alcohol like n-docosanol will absorb in the UV-A or UV-B spectrum, which is a typical feature of contact photoallergens. The other components of LIDAKOL have longstanding histories of topical use in humans.

8.2.3 Clinical Trial 95-LID-03c

Study Title: "Repeat Insult Patch Test"
Sponsor: [redacted]
Investigator: Richard S. Berger, M.D.
Duration: from 5/15/95 to 1/26/96
Objective: To evaluate n-docosanol 10% cream for ability to cause allergic contact dermatitis, following sensitization with a modified Draize test.
Subject Numbers: 227 subjects were enrolled, 201 subjects were evaluable at the end of the challenge phase.
Design: The study consisted of 4 phases: induction, rest, challenge, and, if necessary, rechallenge.

Induction phase:
Patches containing 0.2 mL of n-docosanol 10% cream were applied nine times over a three week period (on Mondays, Wednesdays, and Fridays) to sites on the upper left or right arm, or paraspinal region of the back. The patches were left in place for 24 hours, then removed by the subjects, and the patch sites were evaluated for reactivity to the test material at the next induction application (i.e. 24 or 48 hours after patch application). Skin reactivity during induction was evaluated according to the following scale:

0= no visible reaction and/or erythema
1= mild reaction—macular erythema (faint, but definite pink)
2= moderate reaction—macular erythema (definite redness, similar to a sunburn)
3= strong to severe reaction—macular erythema (very intense redness)

The following letter grades were appended, when appropriate, to the numerical grades:

E= Edema—swelling, spongy feeling when palpated
P= Papules—red, solid, pinpoint elevations, with a granular feeling, diameter 5 mm or less
V= Vesicles—small elevation containing serous fluid, diameter 5 mm or less
B= Bulla reaction—fluid-filled lesion greater than 5 mm in diameter
S= Spreading—evidence of the reaction beyond the application site
W= Weeping—result of a vesicular or bulla reaction—clear, serous exudate oozing or covering the patch site
I= Induration—solid, elevated, hardened, thickening skin reaction

The following assessments of superficial observations were appended to the numerical and/or letter grade:

g= Glazing
y= Peeling
c= Scab, dried film of serous exudate of vesicular or bulla reaction
d= Hyperpigmentation (reddish-brown discoloration of test site)
h= Hypopigmentation (loss of visible pigmentation at test site)
f= Fissuring—grooves in the superficial layers of the skin
(C)= Additional comments

If a score of 2 or greater was observed at any site during the induction period, then the next patch was applied to a naïve, adjacent site; if another application also elicited a score of 2 or greater, a second change of site was made. If a third strong reaction to the test sample developed, patch applications were discontinued until after completion of the rest period.

Rest phase:
After the nine applications are completed, subjects were not exposed to *n*-docosanol for a period ranging from 10 to 17 days.

Challenge Phase:
Patches containing 0.2 mL of n-docosanol 10% cream were applied for 24 hours to a pre-exposed site and to a site on the opposite arm with no prior exposure. Twenty four and 72 hours after patch removal, the sites are graded according to the scale used to characterize skin reactivity during induction.

Conclusions:
Of the 227 subjects enrolled in this study, 26 subjects withdrew prematurely because they could not adhere to the study protocol, and 1 subject withdrew due to personal/family reasons. There were five subjects who violated the protocol: challenge reactions were not read at the appropriate times, or a subject removed the patch because of itching at 12 hours, or an evaluation was missed during the induction phase.

Four subjects (#89, #91, #93, and #143) had reactions during the induction phase that were severe enough to necessitate cessation of further induction. Three of these patients (#89, #91, and #143) had positive reactions during the challenge phase.

Two of the 203 evaluable subjects had mild reactions during the challenge phase, and one subject (#89) had a moderate reaction. Subject (#89) underwent rechallenge, which confirmed the prior observed reactivity, and then underwent a second rechallenge phase, which demonstrated that the subject was reactive to the vehicle of the n-docosanol cream.

Based on these results, LIDAKOL® has a low likelihood of inducing allergic sensitization. Of note, drug penetration is likely less efficient through upper arm skin than through vesiculated or ulcerated lip mucosa, suggesting that the likelihood of allergic sensitization is higher when LIDAKOL® use follows the expected route.

8.3 Indication #1

Treatment of recurrent oro-facial herpes simplex labialis.
Sponsor hypothesized that clinical trials 95-10, 94-04, and 94-05 failed to detect a significant difference in healing between patients treated with LIDAKOL® and the (stearic-acid containing) placebo because stearic acid may have some anti-herpes activity. Accordingly, two other clinical trials, 96-LID-06 and 96-LID-07, were performed with a polyethylene–glycol based placebo. Sponsor submitted the results of 96-06 and of 96-06 pooled with 96-07 as the two pivotal clinical trials for this NDA. Agency never concurred with any plan for pooling the results of 96-06 and 96-07; in fact, such an approach is not a legitimate approach to drug development because 96-06 and 96-06 pooled with 96-07 are not independent studies. The results from clinical studies 96-06 and 96-07 are discussed in Sections 8.2.1 and 8.2.2, respectively.

8.3.1 Trial #1: 96-LID-06

8.3.1.1 Objective/Rationale

The objective of this pivotal clinical trial was to assess the safety and efficacy of topical LIDAKOL® in patients with early-stage episodes of acute, recurrent herpes labialis.

8.3.1.2 Design

This was a clinic-initiated, randomized (in blocks of 4), double-blinded, controlled eight-center trial conducted in the United States, having a randomization ratio of 1:1 between active treatment and placebo.

8.3.1.3 Protocol Overview

8.3.1.3.1 Population, procedures

Three hundred seventy patients were randomized: 185 to receive LIDAKOL® and 185 to receive placebo. Five patients in the LIDAKOL® group and five patients in the placebo group withdrew prematurely from the study. Reasons for premature discontinuation were loss to follow-up, personal family reasons, noncompliance with visits, and withdrawal of consent. No patients were discontinued because of adverse experiences.

A. INCLUSION CRITERIA

1. Patient is 18 years of age or older.
2. Patient has a clinical history of recurrent oral-facial HSV and reports at least 2 recurrences per year.

2. Patient has a clinical history of recurrent oral-facial HSV and reports at least 2 recurrences per year.

3. Patient has signs and symptoms of an active oral-facial HSV episode which the patient states to be less than 12 hours old, and which appears to have been present for less than 12 hours and which has not progressed beyond the erythema stage.

4. If female, patient has been practicing an established method of birth control (oral contraceptive tablets, hormonal implant device, intrauterine device, diaphragm and contraceptive cream or foam, or condom with spermicide, or abstinence), or is surgically sterile or post-menopausal.

5. If female and of child-bearing potential, patient is not pregnant, breast-feeding or planning a pregnancy during the course of the study, and has had a negative urine pregnancy test immediately prior to the first study drug application.

B. EXCLUSION CRITERIA

1. Patient has clinical history or evidence, either physical or laboratory, of significant systemic disease, including any hepatic, renal, hematological or immunological disorder which is likely to interfere with participation in this study.

2. Patient is suspected of having secondary bacterial or yeast infection or other mouth or facial skin disease which may confuse the assessment of the clinically-treated area.

3. Patient has a known allergy to topical cosmetics.

4. Patient has used any oral or systemic drug which may induce immune stimulation (*e.g.*, BCG, Corynebacterium parvum, levamisole) or immune suppression (*e.g.*, corticosteroids [except topical/inhaled], azathioprine, cyclosporine) within the past 30 days.

5. Patient is known to be HIV positive.

6. Patient's symptoms have been present for more than 12 hours.

7. Patient presents with lesions which have progressed beyond the prodrome/erythema stage.

8. Patient presents with lesions above the nares, below the chin, or inside the mouth.

9. Patient has used any investigational drug within the past 30 days.

10. Patient has used an approved antiviral agent (*e.g.*, systemic acyclovir) within the past seven days.Oih

11. Patient has used topical corticosteroids or any non-specific therapy for oral-facial herpes infection (*e.g.*, phototherapy) within the past seven days.Ouh

12. Patient suffers from chronic alcoholism or drug abuse.

13. Patient's last episode of recurrent herpes labialis healed less than 14 days ago.

Patients were randomized to receive either LIDAKOL® or placebo. The first dose of study medication was applied by the patient in private, at the study site. Patients were instructed to keep a daily diary of study medication application times. Study medication was to be applied topically to the affected area five times per day until (i) the episode aborted, or (ii), for episodes which progressed to the vesicular or later stage, complete healing occurred. Study medication was to be applied for a maximum of 10 days. Patients were instructed to re-apply study medication after heavy exercise, showering, or bathing. These unscheduled, additional applications were not to be counted as one of the five scheduled applications per day.

Patients presented to the clinic for assessment twice daily for the first seven days. These visits were to be no less than six hours or greater than 16 hours apart. All visits were to be at least one hour after the previous application of study medication. Patients whose herpes episodes did not abort or heal by Visit 14 (within seven days) were instructed to return once per day for days eight to 10. Patients whose herpes episodes did not abort or heal within the 10 day treatment period were instructed to return to the clinic when the episode aborted or healed, or earlier if they had an adverse experience before they healed.

At each study visit the patient was evaluated as to whether the herpes episode had aborted or progressed to a vesicular or later stage. Clinical assessment of the specific HSV episode signs included the presence or absence of prodrome/erythema, papule, vesicle, ulcer, crust, or what the sponsor termed "healed skin" (i.e. skin with or without residual erythema). Note that by the definition of complete healing given by Spruance et al. that was cited in the introduction, sponsor's definition of complete healing actually corresponds to the seventh of eight stages in the healing process. If episode abortion or complete healing was documented prior to 10 days on-study, the patient's participation in the study was considered complete. If the patient's episode did not abort or heal prior to or on Day 10, termination procedures were done on Day 10. The patient was asked to return to the clinic when the episode aborted or healed.

Reviewer's Comments:

Because of the obvious color differences between placebo and LIDAKOL®, the protocol specified that the first application of study medication in these studies (the only application made at the study site) was to be done by the patient in private, and study personnel were not to see the patient apply the first dose of drug, or to see an open tube of the study medication. After the subject applies the first dose, he or she returns to the examination room for accurate recording of the time of first drug application. All follow-up visits were to be at least one hour after the previous application of medicine. According to protocol, by one hour after application, it should not have been possible for investigator to distinguish between patients receiving active and receiving placebo:

> an amount of study medication sufficient to cover the entire area of outbreak was to be squeezed onto a cotton-tipped swab. Enough study medication was to be used to cover an area at least the size of a dime, plus an area of about one-half inch all the way around the edge of the involved area (localized symptoms, redness, or vesicle/ulcer/crust). The study medication was to be applied with a finger, and **rubbed in until the study medication was no longer visible.** [emphasis added by reviewer]

- *Sponsor provides no data to demonstrate that cream applied in this manner by subjects would be rubbed in until no longer visible when the patient leaves clinic after the first application, or at one hour after application. If any visible cream is present on the lips, the investigator blind is broken.*
- *It is reasonable to presume that subjects would be reluctant to "rub in" cream onto a painful, burning vesicular or ulcerative lesion; despite instructions to the contrary, it is more likely that they apply a thick coat and leave it unperturbed.*
- *Studies on the placebo effect have demonstrated that "perceptual characteristics of drug preparations play a role in individuals' responses. Larger capsules tend to be viewed as stronger, yellow capsules tend to be perceived as stimulants or antidepressants, and white capsules tend to be perceived as analgesics or narcotics." [from Turner et al. "The Importance of Placebo Effects in Pain Treatment and Research", JAMA 1994;271:1609-1614]. In these pivotal trials, it is possible that color differences between active and placebo may affect subjects' assessment of their degree of improvement.*
- *Because patients were instructed to return the epoxy-lined aluminum tubes containing study medications to the clinic at the end of study participation, this provides another means by which the color differences between active and comparator could lead to breaking the study blind: if any residual cream was located on the **outside** of the tube after study completion, the investigator blind could be broken when subjects return unused medication. This would not create investigator bias toward the subject who has just completed the study, but with subjects randomized in blocks of 4 per site, investigators may be biased in their evaluation of the fourth subject of each block, if they have inadvertently ascertained the assignment of the other three subjects in the block.*

In summary, given the concerns expressed above, it is possible that investigator and/or subject bias is introduced in these pivotal trials. To some degree, these biases are unavoidable because the drug substance (docosanol) constitutes a high percentage (10%) of the drug product, so that using vehicle (a runny off-white gel) as the comparator would also create investigator or subject bias. Sponsor rejected Agency's suggestion that titanium dioxide be added to placebo to help minimize the color difference, arguing that this would introduce another ingredient in the comparator that could potentially create adverse events in patients using the comparator; this argument does not seem weighty, given the inert nature of titanium dioxide and its common use in OTC products.

Safety Reporting

According to the protocol, all patients are expected to inform promptly the Principal Investigator of any adverse experience (AE). These were recorded by the Investigator in the Case Report Form, along with the Investigator's assessment of its relationship to study medication. The following information was collected for each AE:

- whether the AE was serious (defined as fatal, life-threatening, permanently disabling, resulting in inpatient hospitalization, a congenital anomaly, cancer, or overdose)
- start and stop dates
- intensity (mild, moderate, severe, or life-threatening)
- frequency (single episode, intermittent, or continuous)
- relationship to study medication (unlikely, possible, or probable)
- action taken with study medication (none, reduced, interrupted, or discontinued)
- treatment required (none, concomitant medication, hospitalization, other)
- outcome (recovered, not recovered, recovered with sequelae, fatal, or unknown)

All AEs were summarized using the COSTART dictionary by body system, and by severity.

The following laboratory assessments were drawn on Day 1 and Day 10 (or sooner if the patient discontinued the study or was healed by Day 10):

Hemoglobin	Red Blood Cell Count	Platelet estimate
Hematocrit	WBC count and differential	

calcium	chloride	total protein	LDH
phosphorus	bicarbonate	albumin	AST/SGOT
glucose	BUN	total bilirubin	ALT/SGPT
sodium	creatinine	direct bilirubin	CPK
potassium	uric acid	alkaline phosphatase	

8.3.1.3.2 Evaluability criteria

The ITT population, as defined by the sponsor, includes all patients who received double-blind medication and had at least one efficacy evaluation by the clinician.Two subjects in the LIDAKOL arm and two subjects in the placebo arm who were dispensed their repective study cream but did not return for any post-baseline clinical assessment were excluded from the ITT analysis. The ITT analysis should included all subjects who were dispensed study drug, regardless of whether they had an efficacy evaluation, but exclusion of these four subjects from the ITT analysis did not likely result in a significant change in the efficacy variable outcomes. The safety analyses included all patients who had at least one application of double-blind medication.

8.3.1.3.3 Endpoints defined

The primary efficacy assessment is defined by the sponsor (pg. 2, protocol) as "the time from therapy initiation to complete resolution of all local signs/symptoms (censored at day 10) in all subjects, thereby including those with classical episodes and those with aborted episodes." **Classical episode** is defined in the Glossary of Terms as "a typical localized recurrence which progresses to the vesicular (or later) stage and through complete healing." **Complete healing** is defined in the Glossary of Terms as "absence of crust with no evidence of active lesion, whether or not there are any residual post-lesion skin changes which may include erythema, flaking, or slight asymmetry, in those patients in whom vesicles/ulcer/crust developed." **Aborted episode** is defined in the Glossary of Terms as "a typical, recurrence-associated localized, site-specific prodrome and/or redness and/or papule, which completely resolves without ever progressing to the vesicular stage. Patients who experience prodrome only prior to episode abortion ...[are]...included in efficacy analyses." All episodes began at treatment initiation and ended with an aborted episode for those episodes that did not progress beyond the papule stage, or the loss of crust for those episodes that did progress beyond the papule stage. The episode baseline and endpoint were determined by the clinician.

Reviewer's Comment:

Sponsor's concept of complete healing, as defined above, differs from a layperson's concept of complete healing, which would be return of lesional skin to normal both in signs and symptoms. Sponsor's criteria for healing is appropriate in measuring drug efficacy because it is unlikely that an effective drug for this indication would accelerate the resolution of erythema, flaking, or slight asymmetry that remains after the hard crust of an herpetic lesion is lost. Consequently, measuring classical episode termination at the time only when both signs and symptoms are normal would inappropriately dilute the power of a clinical trial. It is necessary that the FPL reflect the disparity between sponsor's definition and a layperson's understanding of the term "complete healing".

In contrast, it would be impossible to determine the time of conclusion of an aborted episode unless criteria for conclusion included the resolution of both signs and symptoms.

Secondary efficacy assessments included:

- the time from treatment initiation to complete cessation (duration) of pain and/or burning, itching or tingling
- the time from treatment initiation to complete cessation (duration) of burning, itching or tingling
- the time from treatment initiation to complete cessation (duration) of pain
- the time from first experience of pain to first reduction of pain
- the time from treatment initiation to complete healing of lesions which progressed to the vesicular or later stages (i.e., classical episodes)
- the time from treatment initiation to cessation of vesicular stage, of ulcer/soft crust stage, and of hard crust stage
- the percentage of cases that were aborted episodes (i.e., did not progress to the vesicle stage)

8.3.1.3.4 Statistical considerations

All analyses were performed using SAS version 6.08 or later except where explicitly noted in this report. Treatment group comparisons were declared statistically significant at or below the 5% alpha level using two-tailed tests, unless otherwise noted.

Categorical data are descriptively presented in terms of the number and percentage of patients falling into each category. Tabulations are broken down by treatment groups. The Cochran-Mantel-Haenszel test was used to inferentially analyze categorical data. Sites were used as a stratification factor.

For continuous data, descriptive statistics (N, mean, median, standard deviation, range) are presented by treatment groups. Analysis of variance was performed to inferentially analyze continuous data. Sites were used as a main effect and site-by-treatment interaction was included in the model.

Treatment comparisons for time-to-event analyses employed the Gehan generalization of the Wilcoxon test, stratified by study site. This test was selected for its favorable power characteristics when effects of treatment are expected early in the treatment period. The Gehan generalized Wilcoxon test was calculated with a SAS macro using center specific results from [redacted]

The sample size for this protocol was calculated based on data from a prior LIDAK clinical study of LIDAKOL, protocol 94-LID-04. The following assumptions were used to generate power curves based upon a two-sided, two sample t-test.

- Significance level (alpha) = 0.05
- Standard deviation (sigma) = 60.0 hours
- Mean differences (delta) = 13, 14, 15, 16, 17, 18, 19, 20, 21 hours

Based on power curves presented in the protocol, it was recommended that a sample size of 350 evaluable patients (175 per treatment group) would have a power of 80% to detect

an 18-hour mean difference between the two treatment groups. Assuming 5% of the enrolled patients would be non-evaluable, 369 enrolled patients were necessary to ensure 350 evaluable patients.

8.3.1.4 Study Results

The results of this clinical trial were presented in the clinical summary, integrated clinical and statistical report section, report tables and figures, and subject data listings of the NDA. The medical officer has reviewed this information, and has crosschecked the clinical report tables against the data listings and/or statistical report tabulations (in Appendix D, Vol. 2.16).

8.3.1.4.1 Demographics, Evaluability

Demographic and baseline characteristics are summarized for the ITT population in Table 12.

Table 12. Demographic and Baseline Characteristics - ITT Population, for Clinical Study 96-LID-06

Parameter	LIDAKOL (N=183)	Placebo (N=183)	P-Value[a]
Gender			0.061
Male	47 (25.7%)	63 (34.4%)	
Female	136 (74.3%)	120 (65.6%)	
Race			0.456
Caucasian	174 (95.1%)	176 (96.2%)	
Black	1 (0.5%)	2 (1.1%)	
Asian	0 (0.0%)	0 (0.0%)	
Hispanic	6 (3.3%)	2 (1.1%)	
Other	2 (1.1%)	3 (1.6%)	
Age (years)			0.804
N	183	183	
Mean (SD)	36.9 (13.5)	36.2 (13.7)	
Range	18 - 74	18 - 80	
Height (in)			0.501
N	183	182	
Mean (SD)	66.2 (3.6)	66.6 (4.1)	
Range	58 - 77	59 - 80	
Weight (lb)			0.987
N	183	181	
Mean (SD)	160.0 (34.7)	164.6 (38.7)	
Range	95 - 310	95 - 320	

[a] P-value for categorical parameters from Cochran-Mantel-Haenszel test adjusted for center. P-value for continuous parameters from analysis of variance model with effects for treatment, center, and center-by-treatment interaction.

Source: Vol 2.15, Appendix C.1, Table 4A.

There was a statistically significant difference between the LIDAKOL and placebo groups with respect to mean historical average episode duration (10.1 days versus 8.4 days, respectively; p=0.007) and mean duration of most recent previous episode (10.0 days versus 8.4 days, respectively; p=0.017). There were no statistically significant differences between treatment groups with respect to other demographic and baseline characteristics. Twenty-two percent (21.9%; 40/183) of the LIDAKOL® group and 27.3% (50/183) of the placebo group were staged at prodrome; the remainder of patients in each treatment group were staged at erythema.

Table 13 depicts the evaluability of patients by center/investigator.

Table 13. Evaluability by Center/Investigator

		LIDAKOL®			PLACEBO		
		(No. of patients)			(No. of patients)		
Investigator ID	Center ID	Enrolled	Eval.	% Eval.	Enrolled	Eval.	% Eval.
C. FORSZPANIAK Naples, FL, USA	12	18	18	100	18	18	100
S. ZELLNER Ft. Myers, FL, USA	14	21	20	95	22	22	100
T. JONES Bryan, TX, USA	15	46	46	100	46	46	100
J. DADDABBO Miamiville, OH, USA	16	14	14	100	14	14	100
R. BARBARASH St. Louis, MO, USA	17	40	39	97.5	40	39	97.5
D. MIKOLICH Providence, RI, USA	18	23	23	100	22	22	100
J. JORIZZO Winston-Salem, NC, USA	19	16	16	100	16	16	100
R. ETTINGER Bend, OR, USA	20	7	7	100	7	6	86

Source: Vol. 2.15, Appendix C1, Table 1.2, Appendix A.5

8.3.1.4.2 Efficacy

8.3.1.4.2.1 Clinical

8.3.1.4.2.1.1 Primary Efficacy Results

Table 14 depicts the outcomes of subjects enrolled in clinical study 96-LID-06. Eleven patients classified by the sponsor as undergoing aborted episodes (5 in the LIDAKOL® arm, 6 in the placebo arm) missed at least one clinic visit during their course of treatment. Because of the possibility that these patients did experience a brief classical episode that was not detected because of the missing office visit, they were reclassified by the medical reviewer as patients with aborted episodes, with incomplete data sets. This revision did not have a significant impact upon the classification of patient outcomes, and reviewer's classification very closely agreed with that performed by the sponsor. Compared to the sponsor's tabulation, the medical reviewer counted one more patient treated with LIDAKOL® who was unhealed by Day 10, and two more patients treated with placebo who were lost to follow-up.

Table 14. Disposition of Patients in Clinical Study 96-LID-06

	LIDAKOL	Placebo
Patients with baseline clinical assessments (from Data Listing #8)	185	185
Patients with at least one post-baseline clinical assessment (from Data Listing #8-Data Listing #11)[ITT population]	183 (missing patients 1411, 1748)	183 (missing patients 1733, 2004)
Patients with aborted episodes, with complete data sets	65	47
Patients with aborted episodes, with incomplete data sets	5 (patients 1760, 1780, 1835, 1917, 1925)	6 (patients 1416, 1443, 1621, 1624, 1777, 1840)
Patients with classical lesions, resolved within 10 days	102	115
Patients with classical lesions, unresolved within 10 days	8 (patients 1901, 1907, 1915, 2009, 2012, 1214, 1712, 1722)	8 (patients 1801, 1904, 1921, 2010, 1228, 1404, 1706, 1709)
Patients lost to follow-up[(a) withdrew consent, (b) non-	3 (patients	7 (patients

compliant with F/U visits, (c)withdrew due to personal/family reasons, (d) possessing erythema at EOT]	1602[c], 1627[b], 1911[d])	1235[b], 1427[a], 1776[b], 1902[d], 1701[d], 1839[b], 1841[b])
Patients withdrawn 2° Adverse Event	0	0
TOTAL	183	183

from Data Listing 9, Volume 2.16

The primary efficacy parameter was the time from therapy initiation to complete resolution of all local signs/symptoms (censored at Day 10) for all patients, including those with classical episodes and those with aborted episodes. Primary efficacy results are presented for the ITT population in Table 15. Ninety-four percent (172/183) of the LIDAKOL® arm and 92% (168/183) of the placebo group healed within 10 days. The sponsor calculated that the median time to complete healing was 94.9 hours (4.0 days) in the LIDAKOL® arm and 113.8 hours (4.7 days) in the placebo group, and that the difference between time-to-event curves was statistically significant (p=0.0235). Although there are slight discrepancies between the sponsor's and the medical reviewer's count of the number of subjects healed within ten days, these discrepancies would not substantially change the calculations of the median time to complete healing for the two treatment arms, or the p-value of the difference in median times.

Table 15. Sponsor's Calculation of the Primary Efficacy Results - ITT Population

	LIDAKOL (N=183)	Placebo (N=183)	P-Value[a]
Number (%) Healed within 10 days	173 (95%)	170 (93%)	--
Number (%) Censored[b]	10 (5%)	13 (7%)	--
Number (%) Discontinued Early (lost to follow-up, etc.)	3 (2%)	5 (3%)	
Number (%) Not Healed by Day 10	7 (4%)	8 (4%)	
Hours to Complete Healing[c]			0.0235
25th Percentile	55.3	65.5	
50th Percentile (Median)	94.9	113.8	
75th Percentile	150.9	161.5	

Percentiles are based on Kaplan-Meier estimates.

[a] P-value from Gehan's generalized Wilcoxon test stratified by center.

[b] Includes patients who were not healed by the time of their last clinical visit.

[c] Includes patients with aborted episodes and patients with classical episodes.

Source: Appendix C.1, Table 13A, Vol 2.15.

Twenty six subjects (11 in the LIDAKOL® arm and 15 in the placebo arm) were censored at Day 10, and therefore not followed until their lesions healed completely. Without following all patients to complete healing, it is not possible to calculate precisely the difference in the median times to healing between the two study arms, but it is unlikely that the value of the primary efficacy outcome variable would be substantially

changed even had all censored subjects been followed until their lesions healed completely,.

8.3.1.4.2.1.2 Secondary Efficacy Results

Reductions in Signs/Symptoms

Sponsor's calculations of the times to reduction/cessation of signs and symptoms for the ITT population are summarized in Table 16. The following parameters were statistically significantly shorter in the LIDAKOL® group than in the placebo group:

- the time from first experience of pain to first reduction of pain
- the time from treatment initiation to complete cessation of pain
- the time from treatment initiation to cessation of burning, itching or tingling
- the time from treatment initiation to complete cessation of pain and/or burning, itching or tingling

Table 16. Sponsor's Calculation of the Time to Reduction/Cessation of Signs and Symptoms - ITT Population

	LIDAKOL	Placebo	P-Value[a]
Hrs to first reduction of pain score[b]			0.0062
Number reduced/Total N	102/103	106/106	
Median	20.0	23.5	
Mean (SEM)	28.4 (2.6)	32.3 (2.7)	
Hrs to cessation of pain[c]			0.0125
Number reduced/Total N	102/103	106/106	
Median	48.3	53.0	
Mean (SEM)	56.7 (4.1)	69.3 (4.7)	
Hrs to cessation of burning/itching/tingling			0.0403
Number reduced/Total N	176/179	175/178	
Median	48.7	54.2	
Mean (SEM)	64.7 (3.5)	66.7 (3.1)	
Hrs to cessation of pain and/or burning/itching/tingling			0.0182
Number reduced/Total N	179/183	176/179	
Median	52.3	65.1	
Mean (SEM)	69.6 (3.6)	74.8 (3.6)	

Median, mean, and standard error of the mean are based on Kaplan-Meier estimates.
Total N = number of patients who experienced the indicated sign or symptom during the study.

[a] P-value from Gehan's generalized Wilcoxon test stratified by center.

[b] Time since first experience of pain.

[c] Time since treatment initiation.

Source: Appendix C.1, Table 20A.

Patients with Classical Oral-Facial Herpes Simplex Episodes

Classical episodes are defined as typical localized recurrences which progress to the vesicular (or later) stage and through complete healing. The medical reviewer compared sponsor's reported count of classical episodes with a count determined from examination of subject data listings (Listing No. 9, Vol. 2.16); the two counts closely agree. Within each arm of the study, the medical reviewer subcategorized subjects who developed classical lesions by the presence of erythema or symptoms during prodrome (pain, burning, itching, or tingling). Most subjects in both arms developed both erythema and prodrome during the study. Fifty one of 110 subjects (46%) assigned to the LIDAKOL® arm and 48 of 125 subjects (38%) assigned to the placebo arm presented with erythema and prodrome at baseline; 57 of 110 subjects (52%) assigned to the LIDAKOL® arm and 74 of 125 subjects (59%) assigned to the placebo arm presented with prodrome without erythema. These differences were not determined to be statistically significant by Chisquare testing.

Table 17. Classical Episodes in Clinical Trial 96-06

			LIDAKOL®	Placebo
Sponsor's Count of Classical Episodes [ITT Population]			109	125
Sponsor's Count of Classical Episodes Healed by Day 10			102	115
Sponsor's Count of Censored Classical Episodes (unhealed by Day 10 or lost to follow-up)			7	10
MO's Count of Classical Episodes [ITT Population]			110	125
MO's Count of Classical Episodes Healed by Day 10			102	115
MO's Count of Censored Classical Episodes (unhealed by Day 10 or lost to follow-up)			8(unhealed by Day 10)	10 (8 unhealed by Day 10, 2 (patients 1839, 1841) lost to F/U)
	Erythema	Prodrome		
Classical episodes, signs/symptoms at baseline:	+	+	51	48
Classical episodes, signs/symptoms at baseline:	-	+	57	74
Classical episodes,	+	-	2	3

signs/symptoms at baseline:				
		Total	110	125
Classical episodes, signs/symptoms during treatment:	+	+	102	113
Classical episodes, signs/symptoms during treatment:	-	+	3	4
Classical episodes, signs/symptoms during treatment:	+	-	5	8
		Total	110	125
Classical episodes, signs/symptoms at baseline or during treatment	+	+	106	119
Classical episodes, signs/symptoms at baseline or during treatment	-	+	3	4
Classical episodes, signs/symptoms at baseline or during treatment	+	-	1	2
		Total	110	125

The time to healing of classical episodes in this study is the time from treatment initiation until complete healing (as defined by the sponsor) has occurred. Sponsor's calculation of the number and percentage of patients with classical episodes and the time to complete healing are presented for the ITT population in Table 18. Of the patients who developed classical lesions, 94% (102/109) of the LIDAKOL group and 92% (115/125) of the placebo group healed completely within 10 days. The median time to complete healing of classical oral-facial herpes simplex episodes was 137.8 hours (5.7 days) in the LIDAKOL group and 138.3 hours (5.8 days) in the placebo group, not a statistically significant difference (p=0.2658). Despite this absence of a significant difference between the two treatment arms in the observed median time to complete healing of classical episodes, there is a significant difference between the two treatment arms in the median time to complete healing of aborted and classical episodes, combined, (as depicted in Table 15) because (1) a higher percentage of subjects receiving LIDAKOL experienced episode abortion than did the subjects who received placebo (by sponsor's count, 71/183 for LIDAKOL vs. 55/183 for placebo, p=.078) and (2) aborted episodes were substantially shorter than classical episodes [e.g. for subjects in the LIDAKOL arm,

median time to episode abortion was 54.6 hours (sponsor's calculations), while median time to complete healing of classical episodes was 137.8 hours(sponsor's calculations)]. There is not a significant difference in the median time to healing of aborted episodes when comparing subjects treated with LIDAKOL and placebo.

Table 18. Sponsor's Calculation of the Time-to-Healing for Classical Oro-Facial Herpes Simplex Episodes - ITT Population

	LIDAKOL® (N=109)	Placebo (N=125)	P-Value[a]
N (%) Classical Episodes Healed	102 (94%)	115 (92%)	--
N (%) Censored	7 (6%)	10 (8%)	--
Hours to Complete Healing[b]			0.2658
25th Percentile	91.0	103.6	
50th Percentile (Median)	137.8	138.3	
75th Percentile	176.3	190.0	

Percentiles are based on Kaplan-Meier estimates.

[a] P-value from Gehan's generalized Wilcoxon test stratified by center.

[b] Includes patients whose lesions progressed beyond the papule stage.

Source: Appendix C.1, Table 15A.

The time to cessation of the individual lesion stages vesicle, ulcer/soft crust and hard crust within classical episodes are presented in Table 19.

Table 19. Sponsor's Calculation of the Time to Cessation of Discrete Classical Lesion Stages - ITT Population

	LIDAKOL®	Placebo	P-value[a]
Hrs to cessation of vesicular stage[b]			0.4671
Number Evaluated/Total N	70/70	91/91	
Median	49.4	49.9	
Mean (SEM)	57.3 (3.3)	56.1 (2.5)	
Hrs to cessation of ulcer/soft crust stage[b]			0.0141
Number Evaluated/Total N	90/90	110/110	
Median	76.5	89.0	
Mean (SEM)	86.7 (4.7)	95.8 (3.8)	
Hrs to cessation of hard crust stage[b]			0.3562
Number Evaluated/Total N	93/100	110/120	
Median	138.8	138.3	
Mean (SEM)	138.1 (5.5)	143.0 (4.5)	

Median, mean, and standard error of the mean are based on Kaplan-Meier estimates.

[a] P-value from Gehan's generalized Wilcoxon test stratified by site.

[b] Time since treatment initiation.

Source: Appendix C.1, Table 20A.

Patients with Aborted Episodes

The medical reviewer compared sponsor's reported count of aborted episodes with a count determined from examination of subject data listings (Listing No. 9, Vol. 2.16); the two counts largely agree. Several subjects classified by the sponsor as having undergone aborted episodes missed one or more of their clinic visits. The medical reviewer removed these patients from the count of patients who underwent aborted episodes. This adjustment in the classification was felt to be necessary because of the possibility that these subjects may have had brief classical episodes that would have been noted had these subjects not missed any clinic visits. This adjustment had a modest and approximately equal impact on both arms of the study.

Within each arm of the study, the medical reviewer subcategorized subjects who developed aborted lesions by the presence of erythema or prodromal symptoms. Most subjects in both arms developed both erythema and prodrome during the study. 51 of 110 subjects (46%) assigned to the LIDAKOL® arm and 48 of 125 subjects (38%) assigned to the placebo arm presented with erythema and prodrome at baseline; 57 of 110 subjects (52%) assigned to the LIDAKOL® arm and 74 of 125 subjects (59%) assigned to the placebo arm presented with prodrome without erythema. These differences were determined to be not statistically significant by Chisquare testing.

Table 20. Episode Abortions in Clinical Trial 96-LID-06

			LIDAKOL®	PLACEBO
Sponsor's count			71	55
MO's count of "abortions", including those with complete and incomplete data sets			70*	53**
MO's count of abortions with complete data sets (ABORTIONS)			65***	47****
	Erythema	Prodrome		
Abortions, signs/symptoms at baseline:	+	+	26	14
Abortions, signs/symptoms at baseline:	-	+	39	32
Abortions, signs/symptoms at baseline:	+	-	0	1
		Total	65	47
Abortions, signs/symptoms during treatment:	+	+	50	31

Abortions, signs/symptoms during treatment:	-	+	9	14
Abortions, signs/symptoms during treatment:	+	-	5	2
Abortions, signs/symptoms during treatment:	-	-	1	0
		Total	65	47
Abortions, signs/symptoms at baseline or during treatment	+	+	56	35
Abortions, signs/symptoms at baseline or during treatment	-	+	9	12
		Total	65	47

*Minus one patient outcome (1911) misclassified as abortion: patient had erythema at EOT, and has been reclassified as lost-to-followup.
**Minus two patient outcomes (1902, 1701) misclassified as abortions: patients had erythema at EOT, and have been reclassified as lost-to-followup.
***Minus five patient outcomes (1760, 1780, 1835, 1917, 1935) with incomplete data sets: patients have been reclassified as possible abortions.
****Minus six patient outcomes (1416, 1443, 1621, 1624, 1777, 1840) with incomplete data sets: patients have been reclassified as possible abortions.

Sponsor subcategorized patients on the basis of their presentation at baseline [prodrome without erythema (**prodrome**) versus patients with erythema, with or without prodrome (**erythema**)], and calculated the proportion of patients within each subcategory whose episodes aborted (Table 21). Patients presenting without erythema had a higher proportion of aborted episodes than those presenting with erythema. Patients with erythema at baseline enrolled in the LIDAKOL® arm had a higher proportion of abortions than patients enrolled in the placebo arm. Though the P-value for this comparison was marginally significant, this analysis was not adjusted for multiple endpoints, and it is unclear what the impact on this analysis would be resulting from reclassifying patients with incomplete data sets out of the aborted epsodes count, which was not performed for this analysis.

Table 21. Sponsor's Calculation of the Number (%) of Patients with Aborted Episodes by Stage at Baseline Visit - ITT Population

	LIDAKOL®	Placebo	P-Value[a]
Patients with Prodrome at Baseline	40	50	0.559
Patients with aborted episodes(%)	22 (55.0%)	24 (48.0%)	
Patients with Erythema at Baseline	143	133	0.048
Patients with aborted episodes(%)	49 (34.3%)	31 (23.3%)	
Patients with Prodrome or Erythema	183	183	0.078
Patients with aborted episodes(%)	71 (38.8%)	55 (30.1%)	

[a] P-value from Cochran-Mantel-Haenszel test adjusted for center.
Source: Appendix C.1, Table 19A.

The time to episode abortion in this study is the time from treatment initiation until there has been resolution of the signs and/or symptoms of an episode that has not progressed beyond the papule stage. Sponsor's calculation of the time to episode abortion are presented for the ITT population in Table 22.

Table 22. Sponsor's Calculation of the Time-to-Episode Abortion- ITT Population

	LIDAKOL® (N=74)	Placebo (N=58)	P-Value[a]
N (%) Patients with Aborted Episodes	71 (96%)	55 (95%)	--
N (%) Censored	3 (6%)	3 (5%)	--
Hours to Complete Healing[b]			0.5660
25th Percentile	39.8	42.3	
50th Percentile (Median)	54.6	51.6	
75th Percentile	86.9	70.5	

Percentiles are based on Kaplan-Meier estimates.
[a] P-value from Gehan's generalized Wilcoxon test stratified by center.
[b] Includes patients whose lesions did not progress beyond the papule stage.
Source: Appendix C.1, Table 14A.

8.3.1.4.3 Safety

Extent of Exposure

183 subjects were treated at least once with LIDAKOL®, with a maximal exposure of 10 days. For the ITT population, the mean number of applications of study medication was 23.3 in the LIDAKOL® group; assuming 5 applications per day, the mean number of days of treatment is 5 days. The 180 patients for whom follow-up exists used a mean of 5.48 grams of LIDAKOL® during the study period; the mean amount of LIDAKOL® used per application is 0.24 grams. Assuming one gram of cream covers 100 cm^2 of skin, then the average patient is applying enough cream to cover a 25 cm^2 skin lesion (which is considerably larger than the typical oro-facial herpes recurrence). This lends credence to

the possibility that patients are not rubbing in cream until it is no longer visible, making it less likely that investigator blinding is maintained when patients return for follow-up.

Discontinuations

No subjects were permanently or temporarily discontinued from the study due to adverse events or to laboratory abnormalities. No patients reduced the frequency or amount of medicine applied due to adverse events or to laboratory abnormalities.

Adverse Events

There were 50 adverse events reported in 37 patients receiving LIDAKOL®, and 53 adverse events reported in 36 patients receiving placebo (from Appendix D, Data Listing 10). Sponsor provided a table of adverse experiences reported by at least 1% of patients in either active treatment or placebo:

Table 23. Adverse Events, by COSTART Term, in Clinical Trial 96-LID-06

COSTART Term	LIDAKOL (N=185)	Placebo (N=185)
Headache	12	11
Herpes Simplex	5	1
Dysmenorrhea	3	2
Lab Test Abnormal	2	3
Liver Function Test Abnormal	2	1
Rhinitis	2	1
Infection	2	0
Application Site Reaction	1	4
Back Pain	1	3
Pain	1	3
Myalgia	0	2

Source: Appendix C.1, Table 32

For patients in both the LIDAKOL® and placebo arms, the majority of AEs were mild or moderate in intensity:

Table 24. Nature of Adverse Events in LIDAKOL® and Placebo Arms of 96-LID-06

Degree of Severity	MILD	MODERATE	SEVERE
LIDAKOL®	27	20	3
Placebo	37	13	3

The three patients with severe AEs in the LIDAKOL® arm (patient numbers 1502, 1528, and 2005) experienced headache, herpes simplex pain, and exacerbation of low back pain. Investigators considered these episodes unlikely to be related to exposure to LIDAKOL®. All severe episodes resolved.

In relating adverse events to the use of study medication, investigators assessed vasodilation in one patient treated with placebo, and application site reaction in three patients treated with placebo and one patient treated with LIDAKOL® as probably related to use of study medication.

8.3.1.5 Reviewer's Comments/Conclusions of study results

Efficacy

This trial has demonstrated the efficacy of LIDAKOL in reducing the time to healing in patients with oro-facial herpes lesions. Subjects' use of LIDAKOL® in Clinical Study 96-LID-06 was associated with a statistically significant shortening ($p=0.0235$) in the time from treatment initiation to "complete healing" (as defined by sponsor) of recurrent oro-facial herpes labialis lesions, compared to subjects who used a placebo with a substantially different chemical composition, and a different appearance, than LIDAKOL®. Shortening of lesion duration was the *a priori* primary efficacy variable agreed upon by Agency and Sponsor. Median lesion duration was shortened approximately 19 hours. One shortcoming of this study is that 11 subjects (6%) in the LIDAKOL® arm and 15 subjects (8%) in the placebo arm were censored at Day 10 of the study, before complete healing had occurred. Consequently, the impact that this subset of late-healing subjects would have had on calculations of the median lesion durations in the two arms of this study, had these subjects been followed to complete healing, is unknown.

Sponsor argues that for several secondary efficacy variables [(1) the time from treatment initiation to complete cessation (duration) of pain and/or burning, itching or tingling; (2) the time from treatment initiation to complete cessation (duration) of burning, itching or tingling; (3) the time from treatment initiation to complete cessation (duration) of pain; (4) the time from first experience of pain to first reduction of pain; and (5) the time from treatment initiation to cessation of ulcer/soft crust stage], subjects in the LIDAKOL® arm have statistically significant better outcomes than do subjects in the placebo arm. However, there is no adjustment made for the effect of multiple endpoints in this analysis.

Safety

LIDAKOL® has not demonstrated any contraindications to approval due to concerns about safety when used five times daily for up to 10 days.

8.3.2 Trial #2--96-LID-07

8.3.2.1 Objective/Rationale/Design

Identical to 96-LID-06

8.3.2.2 Protocol Overview

All aspects of this protocol, including population, procedures, evaluability criteria, defined endpoints, and statistical considerations, were identical to 96-LID-06.

8.3.2.3 Study Results

The results of this clinical trial were presented in the clinical summary, integrated clinical and statistical report section, report tables and figures, and subject data listings of the NDA. The medical officer has reviewed this information, and has crosschecked the clinical report tables against the data listings and/or statistical report tabulations (in Appendix D, Vol. 2.20).

8.3.2.3.1 Demographics, Evaluability

Demographic and baseline characteristics for the ITT population are summarized in Table 25. There were no statistically significant differences between treatment groups with respect to demographic and baseline characteristics. Seventeen percent (16.6%; 31/187) of the LIDAKOL group and 16.3% (30/184) of the placebo group were staged at prodrome; the remainder of patients in each treatment group were staged at erythema. Results for the efficacy population were similar.

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Table25. Demographic and Baseline Characteristics – ITT Population, for Clinical Study 96-LID-07

Parameter	LIDAKOL (N=187)	Placebo (N=184)	P-Value[a]
Gender			0.054
Male	44 (23.5%)	59 (32.1%)	
Female	143 (76.5%)	125 (67.9%)	
Race			0.803
Caucasian	174 (93.0%)	169 (91.8%)	
Black	9 (4.8%)	11 (6.0%)	
Asian	2 (1.1%)	1 (0.5%)	
Hispanic	2 (1.1%)	2 (1.1%)	
Other	0 (0.0%)	1 (0.5%)	
Age (years)			0.933
N	187	184	
Mean (SD)	37.5 (12.1)	38.7 (12.9)	
Range	18 – 77	18 – 77	
Height (in)			0.554
N	187	183	
Mean (SD)	65.8 (3.5)	66.4 (3.5)	
Range	56 – 75	59 – 77	
Weight (lb)			0.476
N	187	182	
Mean (SD)	168.6 (43.9)	169.4 (39.7)	
Range	103 – 322	87 – 300	

[a] P-value for categorical parameters from Cochran-Mantel-Haenszel test adjusted for site. P-value for continuous parameters from analysis of variance model with effects for treatment, site, and site-by-treatment interaction.
Source: Appendix C.1, Table 4A.

Evaluability by center is summarized in Table 26.

Table 26. Evaluability by Center/Investigator, Clinical Study 96-LID-07

		LIDAKOL®			PLACEBO		
		(No. of patients)			(No. of patients)		
Investigator ID	Center ID	Enrolled	Eval.	% Eval.	Enrolled	Eval.	% Eval.
C. ZUSCHKE Mobile, AL, USA	51	13	12	92	12	12	100
M. HANNIGAN Louisville, KY, USA	52	4	4	100	4	4	100
BOWMAN Clearwater, FL, USA	53	11	11	100	10	10	100
C. MILLER St. Louis, MO, USA	54	30	30	100	30	30	100
J. PAPPAS Lexington, KY, USA	55	29	29	100	28	28	100
MARBURY Orlando, FL, USA	57	30	30	100	30	30	100
G. RUOFF Kalamazoo, MI, USA	58	27	27	100	26	26	100
N. KASSMAN Statesville, NC, USA	60	4	4	100	5	5	100
J. POWERS Scottsdale, AZ, USA	61	13	13	100	14	14	100
J. BAGGISH Baltimore, MD, USA	62	8	8	100	9	9	100
MARR Portland, OR, USA	63	7	7	100	6	6	100
R. TUCKER Wenatchee, WA, USA	64	9	9	100	8	8	100
W. LANG San Francisco, CA,	65	3	3	100	3	2	67

USA							

Source: Vol. 2.18, Appendix C1, Table 1.2, and Vol. 2.19, Appendix A.5

8.3.2.3.2 Efficacy

8.3.2.3.2.1 Clinical

8.3.2.3.2.1.1 Primary Efficacy Results

Table 27 depicts the outcomes of subjects enrolled in clinical study 96-LID-07: Three subjects in the placebo arm classified by the sponsor as undergoing aborted episodes missed at least one clinic visit during their treatment. Because of the possibility that these patients did experience a (brief) classical episode that was undetected because of the missing office visit, these subjects were reclassified by the medical reviewer as patients with aborted episodes, with incomplete data sets. This revision did not have a significant impact upon the classification of subject outcomes, and the reviewer's classification very closely agreed with that performed by the sponsor.

Table 27. Disposition of Patients in Clinical Study 96-LID-07

	LIDAKOL®	Placebo
Patients with baseline clinical assessments (from Data Listing #8)	188	185
Patients with at least one post-baseline clinical assessment (from Data Listing #8-Data Listing #11)[ITT population]	187	184
Patients with abortions, with complete data sets	76	67
Patients with abortions, with incomplete data sets	0	3
Patients with classical lesions, healed within 10 days	90	93
Patients with classical lesions, unhealed within 10 days	19	14
Patients lost to follow-up[(a) withdrew consent, (b) non-compliant with F/U visits, (c)withdrew due to personal/family reasons]	1 (patient no. 6105[b])	6 (patient nos. 5715[b], 5805, 5837[b], 6210[b], 6215[b], 6506[b])
Patients withdrawn 2° Adverse Event	1(patient no. 5317)	1(patient no. 6409)
TOTAL	187	184

from Data Listing 9, Vol 2.20

Compared to the sponsor's tabulation, the medical reviewer's tabulation of patients from the line listings yielded one more patient treated with LIDAKOL® who was unhealed by Day 10, one less patient treated with placebo who was unhealed by Day 10, and one less patient treated with placebo who was lost to follow-up.

As with clinical study 96-LID-06, the primary efficacy parameter was the time from therapy initiation to complete resolution of all local signs/symptoms (censored at Day 10) for all patients. For subjects experiencing a classical episode (i.e. an episode that does progress beyond the papule stage), the time to complete resolution equals the time to complete healing, as defined in the protocol's Glossary of Terms as "absence of crust with no evidence of active lesion, whether or not there are any residual post-lesion skin changes which may include erythema, flaking, or slight asymmetry, in those patients in whom vesicles/ulcer/crust developed." For subjects experiencing an aborted episode (i.e. an episode that does not progress beyond the papule stage), the time to complete resolution equals the time to disappearance of the prodrome and/or erythema.

Eighty eight percent (165/187) of the LIDAKOL® group and 88% (162/184) of the placebo group healed within 10 days. As depicted in Table 28, the median time to complete healing was 102.3 hours (4.3 days) in the LIDAKOL® group and 118.2 hours (4.9 days) in the placebo group. While the difference between the time-to-event curves was not statistically significant (p=0.1529), the trend favored LIDAKOL-treated patients.

Table 28. Primary Efficacy Results - ITT Population, for Clinical Study 96-LID-07

Primary Efficacy Parameter	LIDAKOL® (N=187)	Placebo (N=184)	P-Value[a]
Number (%) Healed within 10 days	165 (88%)	162 (88%)	
Number (%) Censored[b]	22 (12%)	22 (12%)	
Number (%) Discontinued Early (Lost to follow-up, etc.)	2 (1%)	8 (4%)	
Number (%) Not Healed by Day 10	20 (11%)	14 (8%)	
Hours to Complete Healing[c]			0.1529
25th Percentile	60.5	68.5	
50th Percentile (Median)	102.3	118.2	
75th Percentile	166.8	189.0	

Percentiles are based on Kaplan-Meier estimates.

[a] P-value from generalized Wilcoxon test stratified by site.

[b] Includes patients who were not healed by the time of their last clinical visit.

[c] Includes patients with aborted episodes and patients with classical episodes.

Source: Appendix C.1, Table 13A., Vol 2.19

Thirty four subjects (20 in the LIDAKOL® arm and 14 in the placebo arm) were censored at Day 10, and therefore not followed until their lesions healed completely. Without following all patients to complete healing, it was not possible to calculate precisely the difference in the median times to healing between the two study arms.

8.3.2.3.2.1.2 Secondary Efficacy Results

Time to Reduction/Cessation of Signs and Symptoms

Times to reduction/cessation of signs and symptoms for the ITT population are summarized in Table 29. The following parameters were statistically significantly shorter in the LIDAKOL® group than in the placebo group:

- the time from treatment initiation to cessation of burning, itching or tingling.
- the time from treatment initiation to complete cessation of pain and/or burning, itching or tingling.

Table 29. Sponsor's Calculation of the Time to Reduction/Cessation of Signs and Symptoms - ITT Population, Clinical Study 96-07

	LIDAKOL®	Placebo	P-Value[a]
Hrs to first reduction of pain score[b]			0.4461
Number reduced/Total N	125/125	125/128	
Median	22.3	24.0	
Mean (SEM)	27.6 (1.9)	29.9 (2.4)	
Hrs to cessation of pain[c]			0.6746
Number reduced/Total N	123/125	123/128	
Median	46.2	45.5	
Mean (SEM)	57.8 (3.9)	62.4 (4.8)	
Hrs to cessation of burning/itching/tingling			0.0054
Number reduced/Total N	178/187	174/181	
Median	46.8	64.3	
Mean (SEM)	60.6 (3.8)	75.6 (4.1)	
Hrs to cessation of pain and/or burning/itching/tingling			0.0312
Number reduced/Total N	177/187	173/183	
Median	52.9	65.8	
Mean (SEM)	67.6 (3.9)	79.9 (4.3)	

Median, mean, and standard error of the mean are based on Kaplan-Meier estimates.
Total N = number of patients who experienced the indicated sign or symptom during the study.

[a] P-value from generalized Wilcoxon test stratified by site.

[b] Time since first experience of pain.

[c] Time since treatment initiation.

Source: Appendix C.1, Table 20A., Vol. 2.19

Patients with Classical Oral-Facial Herpes Simplex Episodes

The medical reviewer compared sponsor's reported count of classical episodes with a count determined from direct examination of subject data listings (Listing No. 9, Vol. 2.20). The two tabulations closely agree. Within each arm of the study, the medical reviewer subcategorized subjects who developed classical lesions by the presence of

erythema or prodromal symptoms. Most subjects in both arms developed both erythema and prodromal symptoms at baseline; 41 of 111 subjects (37%) assigned to the LIDAKOL® arm and 48 of 114 (42%) assigned to the placebo arm presented with prodrome without erythema. This difference between the two arms was determined to be not statistically significant by Chisquare testing.

Table 30. Classical Episodes in Clinical Trial 96-07

			LIDAKOL	Placebo
Sponsor's Count of Classical Episodes [ITT Population]			109	112
Sponsor's Count of Classical Episodes Healed by Day 10			89	92
Sponsor's Count of Censored Classical Episodes (unhealed by Day 10, lost to follow-up, or D/C'd due to adverse event)			20	20
MO's Count of Classical Episodes [ITT Population]			111	114
MO's Count of Classical Episodes Healed by Day 10			90	94
MO's Count of Censored Classical Episodes (unhealed by Day 10, lost to follow-up, or D/C'd due to adverse event)			21 (19 unhealed by Day 10, 1 lost to F/U, 1 D/C'd due to adverse event)	20 (13 unhealed by Day 10, 6 lost to F/U, 1 D/C'd due to adverse event)
	Erythema	Prodrome		
Classical episodes, signs/symptoms at baseline:	+	+	69	63
Classical episodes, signs/symptoms at baseline:	-	+	41	48
Classical episodes, signs/symptoms at baseline:	+	-	1	3
		Total	111	114
Classical episodes, signs/symptoms	+	+	103	110

during treatment:				
Classical episodes, signs/symptoms during treatment:	-	+	2	2
Classical episodes, signs/symptoms during treatment:	-	-	1	1
Classical episodes, signs/symptoms during treatment:	+	-	5	1
		Total	111	114
Classical episodes, signs/symptoms at baseline or during treatment	+	+	108	111
Classical episodes, signs/symptoms at baseline or during treatment	-	+	3	3
		Total	111	114

Sponsor calculated the number and percentage of patients with classical episodes and the time to complete healing of the classical episodes; the results are presented in Table 31. One hundred nine (109) patients in the LIDAKOL® group and 112 patients in the placebo group progressed past the papule stage. Of these, 82% (89/109) of the LIDAKOL group and 82% (92/112) of the placebo group healed completely within 10 days. The median time to complete healing of classical oral-facial herpes simplex episodes was 143.0 hours (6.0 days) in the LIDAKOL group and 165.0 hours (6.9 days) in the placebo group.

Table 31. Classical Oral-Facial Herpes Simplex Episodes - ITT Population

Signs/Symptoms	LIDAKOL (N=109)	Placebo (N=112)	P-Value[a]
N (%) Classical Episodes Healed	89 (82%)	92 (82%)	--
N (%) Censored	20 (18%)	20 (18%)	--
Hours to Complete Healing[b]			0.0206
25th Percentile	100.2	116.3	
50th Percentile (Median)	143.0	165.0	
75th Percentile	211.5	214.9	

Percentiles are based on Kaplan-Meier estimates.
[a] P-value from generalized Wilcoxon test stratified by site.
[b] Includes patients whose lesions progressed beyond the papule stage.
Source: Appendix C.1, Table 15A, Vol. 2.19

The time to cessation of the individual lesion stages of vesicle, ulcer/soft crust and hard crust within classical episodes are presented in Table 32. The time to cessation of the ulcer/soft crust stage was substantially shorter in the LIDAKOL® group compared to the placebo group.

Table 32. Time to Cessation of Discrete Classical Lesion Stages - ITT Population

	LIDAKOL®	Placebo	P-value[a]
Hrs to cessation of vesicular stage[b]			0.3318
Number Evaluated/Total N	79/79	75/78	
Median	50.9	53.5	
Mean (SEM)	60.6 (3.6)	69.8 (5.1)	
Hrs to cessation of ulcer/soft crust stage[b]			0.0066
Number Evaluated/Total N	89/92	83/89	
Median	92.7	100.8	
Mean (SEM)	103.6 (5.4)	120.0 (5.6)	
Hrs to cessation of hard crust stage[b]			0.2226
Number Evaluated/Total N	72/87	82/96	
Median	146.0	145.3	
Mean (SEM)	152.4 (5.9)	158.5 (5.7)	

Median, mean, and standard error of the mean are based on Kaplan-Meier estimates.
[a] P-value from Gehan's generalized Wilcoxon test stratified by site.
[b] Time since treatment initiation.
Source: Appendix C.1, Table 20A, Vol 2.19.

Patients with Aborted Episodes

The medical reviewer compared sponsor's reported count of aborted episodes with a count determined from examination of subject data listings (Listing No. 9, Vol 2.20); the two counts largely agree. Three subjects in the placebo arm of the trial who were

classified by the sponsor as having undergone aborted episodes missed one or more of their clinic visits. The medical reviewer removed these patients from the count of patients who underwent aborted episodes. This adjustment in the classification was felt to be necessary because of the possibility that these subjects may have had brief classical episodes that would have been noted had these subjects not missed any clinic visits. This adjustment had a modest impact (4% reduction) in the number of subjects in the placebo arm classified as having undergone aborted episodes.

Within each arm of the study, the medical reviewer categorized subjects who developed aborted lesions by the presence of erythema or prodromal symptoms. Most subjects in both arms developed both erythema and prodrome during the study. 36 of 76 subjects (47%) assigned to the LIDAKOL® arm and 34 of 67 subjects (51%) assigned to the placebo arm presented with erythema and prodrome at baseline; 39 of 76 subjects (51%) assigned to the LIDAKOL® arm and 30 of 67 subjects (45%) assigned to the placebo arm presented with prodrome without erythema. These differences between the two treatment arms were determined to be not statistically significant by Chisquare testing.

Table 33. Number of Aborted Episodes in Clinical Trial 96-LID-07

			LIDAKOL	PLACEBO
Sponsor's count			76	70
MO's count of "abortions", including those with complete and incomplete data sets			76	70
MO's count of abortions with complete data sets (ABORTIONS)			76*	67**
	Erythema	Prodrome		
Abortions, signs/symptoms at baseline:	+	+	36	34
Abortions, signs/symptoms at baseline:	-	+	39	30
Abortions, signs/symptoms at baseline:	+	-	1	3
		Total	76	67
Abortions, signs/symptoms during treatment:	+	+	56	52
Abortions, signs/symptoms during treatment:	-	+	8	5

Abortions, signs/symptoms during treatment:	+	-	10	9
Abortions, signs/symptoms during treatment:	-	-	2	1
		Total	76	67
Abortions, signs/symptoms at baseline or during treatment	+	+	66	60
Abortions, signs/symptoms at baseline or during treatment	-	+	10	5
Abortions, signs/symptoms at baseline or during treatment	+	-	0	2
		Total	76	67

*Patient outcome 6202 should be shortened from 3 visits to 2 visits

**(a) Patient outcome 6201 should be shortened from 11 visits to 6 visits: it represents 2 different episodes. (b) Minus 3 patient outcomes (5403, 6206, 6217) with incomplete data sets; patients have been reclassified as possible abortions

Sponsor subcategorized patients on the basis of their presentation at baseline [prodrome without erythema (**prodrome**) versus patients with erythema, with or without prodrome (**erythema**)], and calculated the proportion of patients within each subcategory whose episodes aborted (Table 34). As with clinical study 96-LID-06, patients presenting without erythema had a higher proportion of aborted episodes than those presenting with erythema. The proportion of episode abortions for patients receiving LIDAKOL® and placebo were essentially identical.

Table 34. Number (%) of Patients with Aborted Episodes by Stage at Baseline Visit - ITT Population, Clinical Study 96-LID-07

	LIDAKOL®	Placebo	P-Value[a]
Patients with Prodrome at Baseline			0.595
N	31	30	
Patients with aborted episodes	23 (74.2%)	18 (60.0%)	
Patients with Erythema at Baseline			0.895
N	156	154	
Patients with aborted episodes	53 (34.0%)	52 (33.8%)	
Patients with Prodrome or Erythema			0.602
N	187	184	
Patients with aborted episodes	76 (40.6%)	70 (38.0%)	

[a] P-value from Cochran-Mantel-Haenszel test adjusted for site.
Source: Appendix C.1, Table 19A, Vol. 2.19

The time to episode abortion in this study is the time from treatment initiation until there has been resolution of the signs and/or symptoms of an episode that has not progressed beyond the papule stage. Sponsor's calculation of the time to episode abortion are presented for the ITT population in Table 35.

Table 35. Sponsor's Calculation of the Time-to-Episode Abortion- ITT Population, Clinical Study 96-07

	LIDAKOL® (N=78)	Placebo (N=72)	P-Value[a]
N (%) Patients with Aborted Episodes	76 (97%)	70 (97%)	--
N (%) Censored	2 (3%)	2 (3%)	--
Hours to Complete Healing[b]			0.8810
25th Percentile	41.7	44.3	
50th Percentile (Median)	59.5	66.5	
75th Percentile	93.5	91.5	

Percentiles are based on Kaplan-Meier estimates.
[a] P-value from Gehan's generalized Wilcoxon test stratified by center.
[b] Includes patients whose lesions did not progress beyond the papule stage.
Source: Appendix C.1, Table 14A.

8.3.2.3.2 Safety

Extent of Exposure

187 subjects were treated at least once with LIDAKOL®, with a maximal exposure of five times daily, for ten days. For the ITT population, the mean number of LIDAKOL®

applications was 24.8, and the mean number of placebo applications was 26.4 in the placebo group.

Discontinuations

The only discontinuation in the active treatment group was patient no. 5317, a 34 year old female who presented with prodrome and erythema on her upper lip, left side. She discontinued due to the development by Day 4 of "small bumps and redness on her upper and lower lips". This adverse event was characterized as moderate in intensity and probably related to medication use. LIDAKOL® was discontinued but no other treatment was required, and the subject recovered three days after the episode began. Of note, this subject also reported suffering from an upper respiratory infection. The differential diagnosis for this adverse event includes xerosis resulting from her URI, or an irritant or allergic contact dermatitis resulting from test medication use. One subject in the placebo group withdrew because of development of a new herpetic lesion during treatment.

Adverse Events

There were 52 adverse events reported in 38 patients receiving LIDAKOL®, and 54 adverse events reported in 34 patients receiving placebo (from Appendix D, Data Listing 10). Sponsor provided a table of adverse experiences reported by at least 1% of patients in either active treatment or placebo:

Table 36. Adverse Events, by COSTART Term, in Clinical Trial 96-LID-07

COSTART Term	LIDAKOL ®(N=187)	Placebo (N=184)
Headache	10	11
Application Site Reaction	7	3
Herpes Simplex	4	4
Pharyngitis	3	2
Lab Test Abnormal (Hemic/Lymphatic System or Metabolic/Nutritional System)	2	2
Myalgia	2	2
Rhinitis	0	3
Dyspepsia	0	3
Infection	1	3
Lymphadenopathy	2	1
Pain	1	2
Asthenia	2	0
Nausea	0	2
Skin Disorder	2	0

Source: Appendix C.1, Table 32, Vol 2.19

For patients in both the LIDAKOL® and placebo arms, the majority of AEs were mild or moderate in intensity:

Table 37. Severity of Adverse Events in LIDAKOL® and Placebo Arms of Clinical Study 96-LID-07

Degree of Severity	MILD	MODERATE	SEVERE
LIDAKOL®	32	19	1
Placebo	27	26	1

Source: Appendix D, Data Listing 10, Vol. 2.20

The patient in the LIDAKOL® arm who experienced a severe AE (patient number 6408) had a reaction to blood draw. This is unlikely to be related to exposure to LIDAKOL®.

Six adverse experiences in the LIDAKOL® arm (classified as application site reaction, rash, or vasodilatation) and one in the placebo arm (classified as circumoral paresthesia), were assessed by the investigators as probably related to study medication. Three adverse experiences in the LIDAKOL® arm (classified as application site reaction or circumoral paresthesias) and five in the placebo arm (classified as headache, application site reaction, and herpes simplex) were assessed by the investigators as possibly related to study medication. All other adverse experiences were assessed as unlikely to be related to medication use.

8.3.2.4 Reviewer's Comments/Conclusions of study results

Efficacy

Subjects' use of LIDAKOL® in Clinical Study 96-LID-07 was associated with a reduction in the time from treatment initiation to "complete healing" (as defined by sponsor) of recurrent oro-facial herpes labialis lesions, compared to subjects who used a placebo with a substantially different chemical composition and appearance than LIDAKOL®. Median lesion duration was shortened approximately 16 hours. This reduction in healing time was not statistically significant (p=0.1529). Shortening of lesion duration was the *a priori* primary efficacy variable agreed upon by Agency and Sponsor. One shortcoming of this study is that 20 subjects (11%) in the LIDAKOL® arm and 14 subjects (8%) in the placebo arm were censored at Day 10 of the study, before complete healing had occurred. Consequently, the impact that this subset of late-healing subjects would have had on calculations of the median lesion durations in the two arms of this study, had these subjects been followed to complete healing, is unknown.

Sponsor argues that for several secondary efficacy variables [(1) the time from treatment initiation to complete cessation (duration) of pain and/or burning, itching or tingling; (2) the time from treatment initiation to complete cessation (duration) of burning, itching or tingling; (3) the time from treatment initiation to complete healing of lesions which progressed to the vesicular or later stages (i.e., classical episodes) and (4) the time from treatment initiation to cessation of ulcer/soft crust stage], subjects in the LIDAKOL® arm have statistically significant better outcomes than do subjects in the placebo arm.

However, there is no adjustment made for the use of multiple endpoints in this analysis. Also, the clinical utility of a shorter ulcer/soft crust stage, if the other stages of the classical lesion are not shortened as a result of treatment, is not substantial.

Safety

LIDAKOL® has not demonstrated any contraindications to approval due to concerns about safety when used five times daily for up to 10 days.

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ON ORIGINAL

9 Overview of Efficacy

Table 38 compares the sponsor's assessment of outcomes in primary and secondary efficacy parameters for the two pivotal clinical trials, 96-LID-06 and 96-LID-07. Sponsor also assessed these outcomes on data pooled from these two studies.

Table 38. Sponsor's Assessment of Outcomes in Pivotal Trials, Primary and Secondary Efficacy Variables

	96-06 and 96-07, pooled	96-06	96-07
PRIMARY EFFICACY VARIABLE: median time to complete healing	**SIGN. (P value =0.0076)**	**SIGN. (P value =0.0235)**	**NOT SIGN. (P value =0.1529)**
Difference in median time to complete healing between LIDAKOL® and placebo:	17.5 hours[2]	18.9 hours[3]	15.9 hours[4]
SECONDARY EFFICACY VARIABLES			
Of patients who experienced the following symptom during the study:			
Hours to first reduction of pain score	SIGN.[5]	SIGN.	NOT SIGN.[6]
Hours to cessation of pain	SIGN.	SIGN.	NOT SIGN.
Hours to cessation of burn/itch/tingle	SIGN.	SIGN.	SIGN.
Hours to cessation of pain/burn/itch/tingle	SIGN.	SIGN.	SIGN.

[2] Based on power curves presented in the substudy protocols, a sample size of 700 evaluable patients (350 per treatment group) would have a power of 82% to detect a 13-hour mean difference between the two treatment groups. With more than 360 patients per treatment group, the observed difference exceeds the predicted difference.

[3] Based on power curves presented in the protocol, a sample size of 350 evaluable patients (175 per treatment group) would have a power of 80% to detect an 18-hour mean difference between the two treatment groups. With 183 patients per treatment group in the ITT population, the observed difference exceeds the predicted difference.

[4] Based on power curves presented in the protocol, a sample size of 350 evaluable patients (175 per treatment group) would have a power of 80% to detect an 18-hour mean difference between the two treatment groups. With 187 and 184 patients per treatment group in the ITT population, the observed difference is less than the predicted difference. The study is powered to greater than 70% to detect a 16 hour treatment difference between the study arms.

[5] SIGN.: p-value less than 0.05. No adjustment is made for multiple comparisons.

[6] NOT SIGN.: p-value greater than 0.05

	96-06 and 96-07, pooled	96-06	96-07
Of patients who progress to vesicle or later stages:			
Median time to complete healing	SIGN.	NOT SIGN.	SIGN.
Time to cessation of vesicle stage	NOT SIGN.	NOT SIGN.	NOT SIGN.
Time to cessation of ulcer/ soft crust	SIGN.	SIGN.	SIGN.
Time to cessation of hard crust	NOT SIGN.	NOT SIGN.	NOT SIGN.
Of patients whose episodes aborted:			
Proportion of patients aborting presenting with prodrome at baseline	NOT SIGN.	NOT SIGN.	NOT SIGN.
Proportion of patients aborting presenting with erythema at baseline	NOT SIGN.	SIGN.	NOT SIGN.
Proportion of patients aborting presenting with prodrome or erythema at baseline	NOT SIGN.	NOT SIGN.	NOT SIGN.

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.

Since the protocols for 96-LID-06 and 96-LID-07 are identical, the difference in outcomes between these trials cannot be explained by differences in protocol. Based upon power curves presented in the protocols, both studies were adequately powered to detect statistically significant outcome differences between the two study arms. A comparison of the demographic characteristics of subjects (Tables 12 and 25) reveals no substantial differences to explain the outcome differences.

Subjects in 96-LID-06 and 96-LID-07 were subcategorized by the reviewer based upon whether they presented at baseline with (i) **prodrome** (defined by the medical reviewer as presenting with pain or burn/itch/tingle) **without erythema**, or (ii) **prodrome with erythema**, as depicted in Table 39 below.

Table 39. Subcategorization of subjects based on presence of erythema at baseline

	96-LID-06			96-LID-07		
At baseline:	Aborted Episodes	Classical Episodes	Total (%)	Aborted Episodes	Classical Episodes	Total
Prodrome +/ Erythema -	71	131	**202 (59%)**	69	89	**158 (44%)**
Prodrome +/ Erythema +	40	99	**139 (41%)**	70	132	**202 (56%)**

59% of the subjects in 96-LID-06 presented without erythema, while only 44% of the subjects in 96-LID-07 presented without erythema; this difference was statistically significant (Chisquare test, $p<0.001$). Subjects without erythema are likely to be at an earlier stage of an herpetic episode than are subjects with erythema, and therapeutic intervention may be less efficacious at the later stages of an episode. This difference could possibly account for the difference in outcomes observed between the two trials.

10 Overview of Safety

Some of the safety issues relevant to clinical studies 96-LID-06 and 96-LID-07 have been discussed in sections 8.2.1.4.3 and 8.2.2.4.3, respectively. In addition to these two pivotal clinical studies, other clinical studies with LIDAKOL®, both for this and for other indications, have been performed. All clinical efficacy studies of LIDAKOL® for the treatment of recurrent oro-facial herpes simplex are tabulated in Table 6. Including study 95-LID-02 (the clinical pharmacology study conducted in patients with oro-facial herpes simplex), 1435 patients with oro-facial herpes simplex have been exposed to LIDAKOL®. Including the other clinical pharmacology studies conducted on LIDAKOL® and other efficacy studies performed for other indications (herpes genitalis, Kaposi's sarcoma, molluscum contagiosum), a total of 1779 subjects have been exposed to LIDAKOL® in the present formulation (Formulation 3).

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

No patient receiving active treatment died during the clinical trials.

10.1.2 Other Significant/Potentially Significant Events

Across all studies, the serious adverse events that arose in patients receiving LIDAKOL® [ileitis, motor vehicle accident, lung carcinoma, vein varicosity] were deemed unlikely to be related to use of LIDAKOL®.

Across all clinical studies examining LIDAKOL® for treatment of recurrent oro-facial herpes labialis, 0.6% of the subjects treated with LIDAKOL® and 0.3% of the subjects treated with placebo were withdrawn due to adverse events. Adverse events causing withdrawal that could be considered possibly or probably related to exposure to LIDAKOL® included application site reaction (one patient), rash (one patient), skin disorder (one patient), and herpes simplex outside the treatment area (three patients). All patients forced to discontinue medication recovered from their adverse events.

10.1.3 Overdosage exposure

No information is presented.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

For safety analysis, results were pooled from all North American placebo-controlled Phase 2/3 studies, referred to as the Integrated Studies (pivotal studies 96-LID-06 and 96-LID-07, and studies 94-LID-04, 95-LID-10, 94-LID-05, and 92-LID-04). The median duration of exposure to LIDAKOL® and to placebos in these studies is between 5 and 10 days.

Table 40. Incidence of Treatment-Emergent Adverse Events Reported in ≥1% of Patients Treated with LIDAKOL® During Double-Blind Treatment

Body System/ Preferred Term	LIDAKOL® (N=1008) N (%)	Stearic Acid-containing Placebo (N=619) N(%)	Polyethylene Glycol-containing Placebo (N=370) N(%)
Body as a Whole			
Headache	105 (10.4)	84 (13.6)	22 (5.9)
Infection	22 (2.2)	10 (1.6)	3 (0.6)
Pain	19 (1.9)	11 (1.8)	6 (1.6)
Flu Syndrome	13 (1.3)	5 (0.8)	2 (0.5)
Metabolic/Nutritional			
Creatinine Phosphokinase Increase	22 (2.2)	17 (2.7)	0 (0.0)
Respiratory System			
Pharyngitis	13 (1.3)	8 (1.3)	2 (0.5)
Skin and Appendages			
Herpes Simplex	53 (5.3)	48 (7.8)	6 (1.6)
Application Site Reaction/ Rash/	35 (3.5)	19 (3.1)	9 (2.4)

Rash (maculopapular)			
Urogenital System			
Dysmenorrhea	20 (2.0)	11 (1.8)	3 (0.8)

from: Table 6, Vol 2.60

The reporting of herpes simplex as an adverse event refers to the occurrence of a new episode outside the treatment area. Upon integrating these six clinical studies, which together encompass more than one thousand subject exposures to LIDAKOL®, there is no adverse event that occurs at a substantially greater frequency in the LIDAKOL®-treated group than in the placebo groups.

10.2.2 Laboratory Findings, Vital Signs; ECGs

Withdrawals

One patient receiving LIDAKOL® in clinical study 94-LID-04 and one patient receiving the stearic-acid containing placebo were forced to withdraw from their respective studies due to laboratory abnormalities. Patient 2124 in 94-LID-04, who was also taking trimethoprim/sulfamethoxazole for prostatitis while enrolled in this clinical trial, experienced an erythema multiforme-like rash and liver function test abnormalities. Once his sulfa medications and LIDAKOL® were discontinued, his rash abated, his AST values returned to normal, and his other laboratory abnormalities improved. Rash and laboratory abnormalities were considered likely to be related to exposure to the sulfa medication.

Clinically Significant Laboratory Abnormalities

In the Integrated Studies, 64 (6.3%) patients treated with LIDAKOL®, 53 (8.6%) of patients treated with Placebo 1, and 13 (3.5%) of patients treated with Placebo 2 had clinical laboratory values that the investigator deemed clinically significant at baseline and/or the final visit. The criteria by which investigators decided whether an abnormality was clinically significant was not specified. As depicted in the following table, there were no clinically relevant differences in any of the laboratory findings among the LIDAKOL® or the two placebo groups.

Table 41. Patients with Clinically Significant Laboratory Abnormalities

	LIDAKOL® (n=1002)	Stearic Acid-Containing Placebo (n=617)	Polyethylene Glycol-Containing Placebo (n=367)
Serum Lab Parameter Abnormalities			
Serum CPK	5	2	1
Serum Triglycerides	1	0	0
Serum Alkaline	1	0	0

Phosphatase			
SGPT/SGOT	4	4	0
LDH	1	1	0
Direct/Total Bili.	2	0	0
Serum GGT	2	0	0
Hematology Lab Parameter Abnormalities			
WBC Count	0	3	1
Platelet Count	0	0	1
HCT/HGB	0	2	0
Urine Lab Parameter Abnormalities	LIDAKOL® (n=1002)	Stearic Acid-Containing Placebo (n=617)	Polyethylene Glycol-Containing Placebo (n=367)
Urine WBC Count	1	0	0
Urine Glucose	1	1	0
Urine RBC Count	1	0	0
from Appendix B, Listing 4, Vol. 2.61			

In examining **all** abnormal laboratory parameters (i.e. not just those deemed clinically significant by the investigators), the active treatment and the two placebo groups had comparable percentages of patients who shifted from having normal laboratory parameters at baseline to abnormal parameters at end-of-treatment.

Table 42. Shifts From Normal Laboratory Parameters at Baseline to Abnormal Parameters at End of Study

Abnormal Laboratory Parameters Detected in at least 1% of Patients	LIDAKOL® (n=1002)	Stearic-Acid Containing Placebo (n=617)	Polyethylene Glycol-Containing Placebo (n=357)
Serum Uric Acid, Elevated	21 (2%)	8 (1%)	7 (2%)
Serum Glucose, Elevated	65 (6%)	54 (9%)	41 (11%)
Serum Glucose, Depressed	1 (<1%)	1 (<1%)	0
Serum Cholesterol, Elevated	9 (<1%)	5 (<1%)	N.D.
Serum Triglycerides, Elevated	41 (4%)	46 (7%)	N.D.
SGPT, Elevated	19 (2%)	13 (2%)	9 (2%)
SGOT,Elevated	15 (1%)	12 (2%)	11 (3%)
Serum CPK, Elevated	41 (4%)	28 (5%)	14 (4%)
White Blood Cell Count, Elevated	19 (2%)	13 (2%)	8 (2%)

from Table 16, Vol. 2.60

10.2.3 Drug-Demographic Interactions

None were demonstrated.

10.2.4 Drug-Disease Interactions-

None were demonstrated.

10.2.5 Drug-Drug Interactions

No information is presented.

10.2.6 Withdrawal Phenomena/Abuse Potential

No information is presented.

10.2.7 Human Reproduction Data

No information is presented.

10.3 Safety Conclusions

LIDAKOL® has not demonstrated any contraindications to approval due to concerns about safety when used five times daily for up to 10 days.

11 Resistance

No information is presented.

12 Recommendations

Not Approvable— Those who aspire to develop effective pharmacologic intervention to treat recurrences of oro-facial herpes labialis face the challenge of hastening the resolution of a disease that, in the majority of non-immunocompromised patients, will resolve spontaneously within a week without any treatment. Against this setting, any treatment that is associated with a significant shortening of illness, even by only a matter of hours, is an acceptable intervention in the course of the illness, and potentially of great value to affected patients (so long as the treatment is safe). Sponsor has adequately demonstrated the safety of LIDAKOL® for use in the treatment of recurrent oro-facial herpes labialis. Though there are some shortcomings in the design of trials 96-06 and 96-07 (the obvious color difference between active and placebo that makes blind breaking possible and, to some degree, the censoring of patients who are unhealed after ten days), clinical trial 96-LID-06 demonstrated a statistically significant 18 hour median shortening in disease course associated with LIDAKOL® use. Clinical trial 96-LID-07 demonstrated a 16 hour median shortening in disease course, but the results were not statistically significant. All other clinical trials have failed to demonstrate that LIDAKOL® has any efficacy for this indication. In summary, sponsor has not demonstrated LIDAKOL is efficacious for this indication.

For the clinical section of the action letter:

- In one adequate, well controlled clinical trial (96-LID-06), the sponsor has demonstrated the safety and efficacy of Lidakol® compared to placebo in the treatment of recurrent oral-facial herpes simplex. The sponsor should submit a second adequate and well controlled clinical trial which demonstrates the safety and efficacy of Lidakol® in the treatment of this condition.
- It is recommended that the sponsor request an end-of-phase 2 meeting prior to initiation of any pivotal trials.

/S/

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

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun
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

/S/ 11/4/98