Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial

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Background: Recurrent herpes simplex labialis (HSL) occurs in 20% to 40% of the US population. Although the disease is self-limiting in persons with a healthy immune response, patients seek treatment because of the discomfort and visibility of a recurrent lesion.

Objective: Our purpose was to determine whether docosanol 10% cream (docosanol) is efficacious compared with placebo for the topical treatment of episodes of acute HSL.

Methods: Two identical double-blind, placebo-controlled studies were conducted at a total of 21 sites. Otherwise healthy adults, with documented histories of HSL, were randomized to receive either docosanol or polyethylene glycol placebo and initiated therapy in the prodrome or erythema stage of an episode. Treatment was administered 5 times daily until healing occurred (ie, the crust fell off spontaneously or there was no longer evidence of an active lesion) with twice-daily visits.

Results: The median time to healing in the 370 docosanol-treated patients was 4.1 days, 18 hours shorter than observed in the 367 placebo-treated patients ($P = .008$; 95% confidence interval [CI]: 2, 22). The docosanol group also exhibited reduced times from treatment initiation to (1) cessation of pain and all other symptoms (itching, burning, and/or tingling; $P = .002$; 95% CI: 3, 16.5); (2) complete healing of classic lesions ($P = .023$; 95% CI: 1, 24.5); and (3) cessation of the ulcer or soft crust stage of classic lesions ($P < .001$; 95% CI: 8, 25). Aborted episodes were experienced by 40% of the docosanol recipients versus 34% of placebo recipients ($P = .109$; 95% CI for odds ratio: 0.95, 1.73). Adverse experiences with docosanol were mild and similar to those with placebo.

Conclusion: Docosanol applied 5 times daily is safe and effective in the treatment of recurrent HSL. Differences in healing time compared favorably with those reported for the only treatment of HSL that has been approved by the Food and Drug Administration. (J Am Acad Dermatol 2001;45:222-30.)

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Recurrent oral-facial herpes simplex (recurrent herpes simplex labialis [HSL]) is a common disease estimated to occur in 20% to 40% of the US population.[1] A main feature of the disease is the ability of herpes simplex virus (HSV) (generally type 1, HSV-1) to remain latent before erupting in response to stimuli such as stress, sunlight, fever, respiratory tract infections, and menstruation.[2] Episodes that do not progress beyond the papule have been referred to as aborted or nonlesional episodes. Classic lesions are those that progress to the vesiculoulcerative stage before healing.

HSL is self-limiting, with healing normally occurring in 7 to 10 days.[3-5] Lesions evolve rapidly with maximum lesion severity, often occurring within 8 hours of onset.[6] The window of time for treatment is therefore small, and it is essential that antiviral therapies be administered early. Antiviral therapies initiated at the papule or later stages cannot significantly affect lesion severity or the frequency of aborted lesions.

Penciclovir cream 1% is currently the only other treatment approved for HSL in the United States. Docosanol 10% cream was recently (July 2000) approved by the Food and Drug Administration (FDA) as an over-the-counter topical treatment for cold sores (Abreva). Penciclovir was studied in a total of 3057 patients with active HSL in two parallel clinical trials demonstrating reductions in time to healing (0.5 day) and loss of pain (0.5 day).[7,8] Studies with other antiviral agents have not, to date, shown a significant and consistent disease benefit.

Docosanol (also known as *n*-docosanol or behenyl alcohol) is a 22-carbon, saturated, primary alcohol that inhibits in vitro a broad spectrum of lipid-enveloped viruses including HSV-1 and HSV-2, cytomegalovirus, varicella zoster virus, and human herpesvirus 6.[9-13] Its mechanism of action is novel: after cellular incorporation and metabolic conversion,[12] docosanol inhibits one or more steps of viral entry, blocking nuclear localization and subsequent replication of the virus.[9-11,13] More recent experiments indicate that docosanol may exert anti-HSV activity predominantly by interfering with the process of viral fusion with the host cell.[13]

This report describes the results of two identical, double-blind, placebo-controlled, multicenter treatment studies conducted to evaluate the safety, efficacy, and tolerance of topical docosanol 10% cream in patients with episodes of acute, recurrent HSL. Treatment was initiated before papule formation. Efficacy and safety data from the two studies were analyzed as a combined study (as prospectively defined in the protocol) and as individual studies. The results demonstrate the effectiveness of topical docosanol 10% cream in the treatment of this disease.

MATERIAL AND METHODS

Patients

Patients were recruited at 21 sites including university clinics, private practices, and public health facilities across the United States. Eight sites were assigned to study 06 and 13 sites were assigned to study 07. All sites were included in the combined study, designated 06/07. No single site enrolled more than 12% of the total study population in the combined study or more than 24% in the individual studies. These sites recruited male and female immunocompetent patients 18 years or older who presented for clinical assessment within 12 hours of noticing the onset of prodrome or erythema. By patient history, signs and symptoms must not have been present for more than 12 hours, and on clinical examination the episode must not have progressed beyond the erythema stage. Patients, determined to be otherwise healthy, must have had a clinical history of HSL with at least two recurrences during the past 12 months. The most recent previous episode must have healed at least 14 days before screening. Institutional Review Board approval for all sites was obtained for the protocol and the informed consent document. All patients were properly informed of the study purpose and risks, and a signed consent form was obtained before their enrollment.

Subjects agreed not to use cosmetics on or around the mouth during the treatment period. Women of childbearing potential were to be practicing an established method of birth control and were not to be pregnant as determined by a negative urine test at enrollment. Subjects with known allergies to topical cosmetics were excluded, as were those with lesions above the nares, below the chin, or inside the mouth. The use of any investigational drug during or within 30 days before the study and the use of an approved antiviral agent, topical corticosteroid, or any other nonspecific therapy for HSL during or within 7 days before the study were not allowed. Concomitant use of systemic corticosteroids or other drugs known to induce immune stimulation or immune suppression was also not allowed.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, clinic-initiated, early-treatment study to compare and evaluate the safety, efficacy, and tolerance of topical docosanol with a placebo in a population of patients with acute recurrences of HSL. Treatment was initiated within 12 hours of episode onset with symptoms in the prodrome or erythema stage and before the papule stage. Subjects were randomized in a double-blind fashion by site in blocks of 4 to receive either docosanol or placebo. At study entry, the first application of study medication was to be made by the subject at the clinic. Subsequent applications were to be made by the subject during normal waking hours. Study medication was to be applied to the lesion area 5 times per day until healing for a maximum of 10 days. Subjects were instructed to reapply study medication after heavy exercise, showering, or bathing. These extra applications were not counted

as scheduled. Subjects kept a daily diary of study medication application times.

Subjects were required to report for twice-daily assessments by the investigator or other trained clinician for the first 7 days. Clinic visits could not be closer together than 6 hours or longer apart than 16 hours. The initial treatment area was marked on a diagram in the case report form at the baseline clinical assessment. Localized signs and symptoms at the treatment area were documented at each visit, including prodrome/erythema, papule, vesicle, ulcer, crust, or healed skin (with or without residual erythema), and subject reports of pain, burning, itching, or tingling. Subjects with HSL episodes that did not abort or heal within 7 days were also followed up once a day for days 8 to 10. Treatment was discontinued for HSL episodes that did not abort or heal within 10 days, and the subjects were again assessed at the point of lesion abortion, healing, or adverse experience. All baseline and safety and efficacy parameters were determined by the clinician.

Study medications

Each gram of docosanol 10% cream contained 100 mg of docosanol formulated into a white, nongreasy, moisturizing cream that was easily applied and readily disappeared into the skin and mucous membranes. A placebo formulation lacking docosanol but containing polyethylene glycol provided a medication similar in appearance to docosanol 10% cream. The polyethylene glycol formulation was identical to that used previously as a vehicle for topical acyclovir and as a placebo for topical HSL trials[6,14,15] and was chosen in consultation with the FDA. In this instance it was not possible to use the vehicle of the cream as placebo because the active drug substance, docosanol at a 10% concentration, is a major contributor to the consistency of the cream. Its removal produces a watery vehicle that is clearly unsuitable as a control for a blinded study.

Efficacy end points

The primary efficacy end point (time to healing) was calculated from the date and time of the initiation of therapy until the date and time of the clinic visit at which complete resolution of all local signs and symptoms was documented, that is, the lesion had aborted or complete healing had occurred (censored at day 10), thereby including patients with both classic and aborted episodes. (The time of the final day 10 visit was used for primary end-point analysis in subjects censored at day 10.) For patients experiencing classic episodes, complete healing was defined as "the absence of crust, with no evidence of active lesion, whether or not there were any residual post-lesion skin changes which might include erythema, flaking, or slight asymmetry."

Secondary end points included the time from treatment initiation to (1) complete healing of classic episodes (episodes that progressed to the vesicular or later stages, censored at day 10); (2) episode abortion; (3) complete cessation of pain; and (4) the proportion of aborted episodes, defined as episodes that did not progress beyond the papule stage.[2] Aborted episodes were considered healed at the time of the clinic visit where cessation of HSL-related signs or symptoms was reported.

Safety end points

Safety and tolerance of topical docosanol 10% cream were determined by adverse experience reports and assessment of clinical laboratory variables.

Statistical analysis

The sample size for the combined study was based on data from previous clinical studies. The combined study was planned to have 700 evaluable patients (350 per group), which would allow the detection of a 13-hour mean difference between treated and placebo groups with 82% power. The two substudies were also analyzed separately.

Statistical methodologies were outlined in the protocol. The intent-to-treat population included all patients who received medication and had at least one treatment evaluation. The efficacy-evaluable population was protocol adherent and applied at least 80% of scheduled doses. Protocol deviations were evaluated before study unblinding. The safety-evaluable population included all those who used at least one application of study medication.

Demographic and medical history data were tabulated by treatment group, and descriptive statistics were used for continuous variables. Frequencies and proportions were used for categorical variables. Baseline variables such as signs and symptoms, location of prodrome, current experience, and lesion stage were compared for homogeneity between randomized treatment groups using either analysis of variance or Cochran-Mantel-Haenszel tests.[16] Descriptive statistics for baseline vital signs were calculated.

For the primary efficacy analyses all patients who had at least one post-baseline efficacy assessment were included. Time-to-event distributions were estimated by Kaplan-Meier product-limit estimates[17] and compared between treatments using the Gehan generalization of the Wilcoxon test,[18] stratified by site. In consultation with the FDA, the generalized Wilcoxon test was chosen because it has good power when the

Table I. Patient characteristics (selected) and historical information: Intent-to-treat population from combined study 06/07

Parameter	Docosanol (n = 370)	Placebo (n = 367)	*P* value*
Sex			.007
Male (No.)	91 (24.6%)	122 (33.2%)	
Female (No.)	279 (75.4%)	245 (66.8%)	
Race			NS†
Caucasian	348 (94.1%)	345 (94.0%)	
Black	10 (2.7%)	13 (3.5%)	
Asian	2 (0.5%)	1 (0.3%)	
Hispanic	8 (2.2%)	4 (1.1%)	
Other	2 (0.5%)	4 (1.1%)	
Age (y)			NS
No.	370	367	
Mean (SD)	37.2 (12.8)	37.4 (13.4)	
Range	18-77	18-80	
Stage of lesion at baseline (No.)			NS
Prodrome	71 (19.2%)	80 (21.8%)	
Erythema	299 (80.8%)	287 (78.2%)	
Average episode duration from patient history (d)			.016
No.	370	367	
Mean (SD)	9.5 (4.2)	8.4 (3.7)	
Range	1-42	1-30	
Duration of most recent previous episode (d)			NS
No.	370	367	
Mean (SD)	9.1 (5.0)	8.2 (4.2)	
Range	1-60	1-30	
Time since last onset of oral-facial herpes simplex (mo)			NS
No.	369	366	
Mean (SD)	3.0 (2.2)	3.0 (2.2)	
Range	0-11	0-12	
Time since first onset of oral-facial herpes simplex (y)			NS
No.	370	366	
Mean (SD)	22.4 (13.8)	21.4 (13.2)	
Range	0-68	0-64	
No. of episodes in past 12 mo			NS
No.	370	367	
Mean (SD)	5.2 (3.7)	5.1 (3.1)	
Range	2-40	2-20	
Does patient experience localized prodrome?			NS
No	3 (0.8%)	1 (0.3%)	
Yes	367 (99.2%)	366 (99.7)	

**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.
†Not statistically significant.

effects of treatment are expected early in the treatment period. Confidence intervals (hours of difference) were obtained by numeric inversion of the stratified Wilcoxon test. Lesion assessments from participants whose lesions were unhealed at 10 days were censored at that point. The percentage of aborted episodes is presented by latest stage at baseline visit.

Possible adjustment for important baseline covariates was identified in the protocol. Because the generalized Wilcoxon test does not readily allow for adjustments for covariates, proportional hazards regression (Cox regression) was used as a means of gauging whether covariate adjustment would have an effect on the *P* value for treatment. All *P* values reported herein represent the unadjusted analysis.

RESULTS

Characteristics of study patients

In the combined study, 743 subjects were randomized at 21 US sites. Three hundred seventy-three

Table II. Efficacy end points for the intent-to-treat population

Parameter	Combined study 06/07			Study 06		
	Median difference*	Docosanol median time†	*P* value‡ (95% CI)	Median difference*	Docosanol median time†	*P* value‡ (95% CI)
Time to healing (all episodes)	17.5 h	97.8 h	.008 (2, 22)	18.9 h	94.9 h	.023 (1.5, 25.75)
Time to healing (classic episodes)	1.6 h§	142.1 h	.023 (1, 24.5)	.5 h	137.8 h	NS (–4.25, 24.25)
Hours to cessation of pain and all symptoms (burning, itching, tingling)	13.4 h	52.3 h	.002 (3, 16.5)	12.8 h	52.3 h	.02 (1.25, 18.25)

Medians are based on Kaplan-Meier estimates. *NS,* Not statistically significant.
*Difference between docosanol and placebo in median time to event.
†Median time to event for the docosanol-treated group.
‡*P* value from Gehan's generalized Wilcoxon test stratified by site.
§At the 25th and 75th percentiles, the difference was approximately 19 hours.

Table III. Time to cessation of discrete lesion stages from classic episodes

Parameter	Combined study 06/07			Study 06		
	Docosanol	Placebo	*P* value* (95% CI)	Docosanol	Placebo	*P* value* (95% CI)
Median hours to cessation of vesicular stage (from initiation of treatment)	50.5	50.7	NS (–1.75, 9)	49.4	49.9	NS (–3.5, 9.75)
Median hours to cessation of ulcer/soft crust stage (from initiation of treatment)	86.7	94.5	<.001 (8, 25)	76.5	89.0	.014 (2.25, 24.25)
Median hours to cessation of hard crust stage (from initiation of treatment)	142.8	142.3	NS (–2, 21)	138.8	138.3	NS (–5.75, 23.5)

Medians are based on Kaplan-Meier estimates. *NS,* Not statistically significant.
**P* value from Gehan's generalized Wilcoxon test stratified by site.

persons were randomized to receive docosanol, whereas 370 were randomized to receive placebo. Three docosanol-treated and 3 placebo-treated patients (0.8% of the study population) did not return to the clinic after the initial visit. These 6 patients were included in the safety analysis; however, per protocol design, they were excluded from the intent-to-treat efficacy population. The efficacy-evaluable population was nearly identical to the intent-to-treat population; 97.4% of randomized patients were able to be evaluated for efficacy of treatment. As such, only the data from the intent-to-treat population are presented in this report.

In substudy 06, 8 sites randomized 370 patients, 185 to docosanol and 185 to placebo. In substudy 07, 13 sites randomized 373 patients, 188 to docosanol and 185 to placebo.

Patient demographic and baseline characteristics for the intent-to-treat population of the combined study are presented in Table I. The demographics of the individual studies were similar and are not shown. There were no significant differences between treatments in race, age, or frequency of HSL recurrences. The mean age of study patients was 37 years (range, 18-80 years). Minor gender differences were identified. The majority of study participants were female and Caucasian; however, male participants represented a smaller proportion of the docosanol recipients compared with placebo recipients (25% vs 33%, respectively; $P = .01$). At enrollment all recurrent episodes were less than 12 hours in duration. Between 75% and 80% of patients presented for treatment with erythema, with the remainder presenting with prodrome only. This distribution was similar in both treatment groups. Pain reported at baseline also did not differ between treatment groups.

Past experience with HSL as obtained by patient report at the baseline visit is also summarized in Table I for the combined study. Between treatment groups there were no statistically significant differences in the time since first onset of HSL or the time since the last HSL episode, the number of episodes in the previous year, the proportion of participants who usually

Study 07		
Median difference*	**Docosanol median time†**	***P* value‡ (95% CI)**
15.9 h	102.3 h	.153 (–2.25, 23.75)
22 h	143.0 h	.021 (1, 37.5)
12.9 h	52.9 h	.03 (0.5, 19.75)

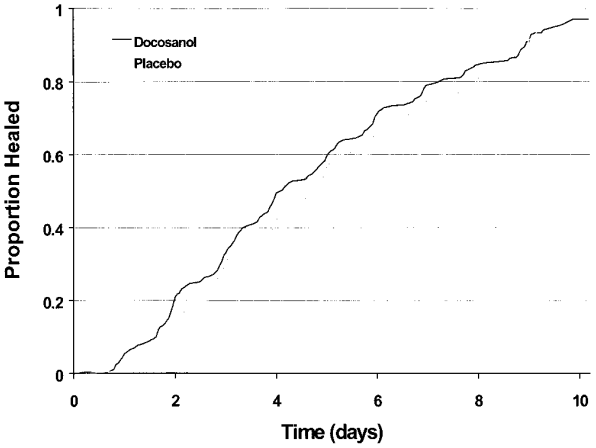

Fig 1. Kaplan-Meier distributions for time to healing. Time to healing was measured from initiation of treatment until the date and time of the clinic visit at which complete resolution of all local signs and symptoms was determined by the clinician.

Study 07		
Docosanol	**Placebo**	***P* value* (95% CI)**
50.9	53.5	NS (–3, 15.75)
92.7	100.8	.007 (4.75, 40.25)
146.0	145.3	NS (–5.25, 26.75)

experience localized prodrome, or the duration of the most recent HSL episode. However, docosanol recipients reported a longer historical mean episode duration compared with placebo recipients (9.5 vs 8.4 days, respectively; $P = .02$). This statistical difference was also observed in study 06 (10.1 days and 8.4 days, respectively; $P = .01$). The mean duration of the most recent previous episode (10.0 vs 8.4 days; $P = .02$, docosanol vs placebo) was also statistically different in study 06. No treatment group differences in HSL history were observed in study 07. When statistical differences were observed in study demographics between treatment groups, Cox regression analysis was utilized to assess the covariate effect.

This population had experience with HSL. Participants reported a median of 5 episodes in the past 12 months, with a mean HSL history of more than 20 years. More than 99% of participants reported that they normally experience prodromal symptoms before their HSL episodes.

The mean number of applications for the docosanol group was 24.1, and the mean number for the placebo group was 25.7. Treatment compliance was assessed by comparing the number of applications actually made to the number that should have been made and averaged 99.2% in the docosanol-treated group and 99.6% in the placebo-treated group. There were no statistically significant differences between treatment groups with respect to the number of applications or compliance.

Treatment effects on HSL episode

Time to healing of the episode (primary end point). Efficacy data are summarized for both the combined study and each substudy in Table II. Only the combined study results are discussed in the text. The vast majority of participants healed during the 10-day treatment period (91% of docosanol recipients and 90% of placebo recipients). Kaplan-Meier curves for times to healing are shown in Fig 1. The median time to complete healing for all lesions was 4.08 days for docosanol recipients versus 4.80 days for placebo recipients, a difference of 15% ($P = .008$; 95% CI: 2, 22 hours). The distribution of healing times also favored docosanol treatment at the 25th and 75th percentiles.

Covariate adjustment utilizing proportional hazards regression for differences in the number of male subjects had no effect on the *P* value for time to healing; however, for historical episode duration, the *P* value decreased (ie, became more significant).

Time to healing of classic episodes. Approximately 60% to 65% of subjects developed classic episodes. The difference in time to healing (Table II) was statistically shorter in the docosanol-

Table IV. Percent of patients with aborted episodes by stage at baseline

Stage at baseline	Combined study 06/07		
	Docosanol	Placebo	*P* value* (95% CI)
All patients (prodrome or erythema at baseline)	39.7% (n = 370)†	34.1% (n = 367)	.109 (0.95, 1.73)
Prodrome at baseline	63.4% (n = 71)	52.5% (n = 80)	NS (0.65, 2.76)
Erythema at baseline	34.1% (n = 299)	28.9% (n = 287)	NS (0.88, 1.78)

NS, Not statistically significant.
**P* value from Cochran-Mantel-Haenszel test adjusted for center. Confidence intervals are given for the odds ratio, adjusted for center. Odds ratios larger than 1.00 indicate that docosanol-treated patients are more likely than placebo recipients to have an aborted episode.
†Total number of patients evaluated.

treated versus the placebo-treated groups ($P = .02$; 95% CI: 1, 24.5 hours). For this end point, larger differences were observed at the 25th and 75th percentiles (~19 hours) than at the median (1 hour).

Duration of lesion stages. Values for the time to cessation of individual lesion stages for classic episodes are shown in Table III. The median for time to cessation of vesicles was approximately 2.1 days, and the median for time to cessation of hard crusts was approximately 5.8 days. Neither was statistically different between treatment groups. However, the median time to cessation of the ulcer/soft crust stage was shorter in the docosanol-treated group (3.61 vs 3.94 days; $P < .001$; 95% CI: 8, 25 hours).

Lesion-associated symptoms. A total of 705 (96%) of the 737 patients in the intent-to-treat group, equally distributed between placebo- and docosanol-treated populations, experienced lesion pain and/or burning, itching, or tingling during the study. Median times to complete cessation of pain and/or burning, itching, or tingling for all participants (Table II) was 2.18 days for docosanol recipients versus 2.74 days for placebo recipients (~20% reduction; $P = .002$; 95% CI: 3, 16.5 hours).

Aborted episodes. Results for patients with aborted episodes by stage at baseline are summarized in Table IV. For all subjects, a trend (not statistically different) toward more aborted episodes was identified with 39.7% of docosanol recipients experiencing aborted episodes versus 34.1% of placebo recipients ($P = .109$; CI for odds ratio: 0.95, 1.73). For substudy 06, in subjects who had erythema when they began treatment, 34.3% of docosanol recipients versus 23.3% of placebo recipients ($P = .048$; CI: 1.00, 2.75) experienced aborted episodes. The times to episode abortion were rapid and not different between treatment groups.

Safety assessments

Adverse experiences were quantitatively and qualitatively similar between docosanol- and placebo-treated patients. At least one adverse experience was reported by 19.6% (73/373) of docosanol recipients and 18.9% (70/370) of placebo recipients for the combined study population. Headache, which was reported by 5.9% of patients in each treatment group, was the most common adverse experience. With the exception of application site reaction (2.1% of the docosanol-treated group and 1.9% of the placebo-treated group) and herpes simplex outside of the treatment area (2.4% of the docosanol-treated group and 1.4% of the placebo-treated group), all adverse experiences were reported by fewer than 2% of the patients in either treatment group. Two patients (one patient in each group) were withdrawn from the study because of adverse experiences of rash (docosanol) and herpes simplex outside the treatment area (placebo). There were no statistically significant differences between treatment groups with respect to change from baseline in either hematologic or clinical chemistry parameters.

DISCUSSION

This trial with docosanol 10% cream demonstrates clinical efficacy of early clinic-initiated therapy for recurrent HSL. The combined study analysis showed statistically significant reductions in time to complete healing, time to complete healing of classic episodes, cessation of the most active infectious lesion stage (ulcer/soft crust), and cessation of all HSV symptoms. Median time to healing was the primary efficacy parameter and was reduced by 0.72 day compared with placebo. The times to healing of classic lesions and the times to cessation of ulcer/soft crust were also significantly reduced. The ulcer/soft crust stage represents the peak period of viral replication and inflammation,[4] which may explain its sensitivity of response.

The statistical differences identified in the individual substudies (06 and 07) were slightly less robust than in the combined study, which is reflective of

Study 06			Study 07		
Docosanol	Placebo	*P* value* (95% CI)	Docosanol	Placebo	*P* value* (95% CI)
38.8% (n = 183)	30.1% (n = 183)	.078 (0.96, 2.24)	40.6% (n = 187)	38.0% (n = 184)	NS (0.73, 1.73)
55.0% (n = 40)	48.0% (n = 50)	NS (0.55, 3.02)	74.2% (n = 31)	60.0% (n = 30)	NS (0.37, 5.71)
34.3% (n = 143)	23.3% (n = 133)	.048 (1.00, 2.75)	34.0% (n = 156)	33.8% (n = 154)	NS (0.59, 1.59)

fewer participants. The substudies were similar in treatment effects to the combined study and to each other. Consistency of the results across the substudies was analyzed by using various methods of analysis and measures of effect, including proportional odds regression, proportional hazards regression, and log-logistic regression models (results not shown) in addition to the generalized Wilcoxon test reported herein. The estimated treatment effects are very similar regardless of the measure of effect used. Furthermore, confidence intervals for treatment effects computed are almost completely overlapping.

The combined analysis approach for the substudies was planned by the protocol. The two studies combined represented a cohort size approximately half that recently reported for each of two topical penciclovir cream studies in HSL[7,8]; nevertheless, the studies demonstrated clinical and statistical significance for docosanol against both the healing and symptom components of HSL. With the use of this early, clinic-initiated model with twice-daily observations, a cohort of 700 to 800 patients appears sufficient to demonstrate these key efficacy components of HSL treatment. In contrast, demonstration of lesion prevention may require a larger patient population. Despite the interesting trends in favor of docosanol treatment, this study was not sufficiently powered to demonstrate lesion prevention at the rates observed, and, unfortunately, to date lesion prevention has never been unequivocally demonstrated. Nevertheless, clinic-initiated treatment before lesion onset clearly offers the potential for demonstration of this treatment benefit (given the proper cohort size) where it exists. No other reported study design truly provides the opportunity to demonstrate such effects because a high proportion of patients who self-initiate therapy in the prodromal phase may actually have early, established lesions before the commencement of therapy.[3,4]

Penciclovir cream 1% is currently available by prescription for the topical treatment of recurrent HSL. Based on information from the product insert for penciclovir cream, in the US multicenter study more than twice the size of the current study, Spruance et al[7] demonstrated that penciclovir-treated patients experienced a significantly shorter mean time to healing, with a 0.5-day difference (4.5 vs 5.0 days; $P < .001$). Lesion pain was reduced, as demonstrated by an approximate half-day reduction in the mean duration of lesion pain (3.9 vs 4.4 days; $P < .001$). Spruance et al reported that viral shedding was reduced by penciclovir as demonstrated by changes over the shedding period followed (vesicle and ulcer/soft crust), although no differences in median times to loss of viral shedding were observed (3.0 vs 3.0 days). The difficulty in demonstrating an antiviral effect with penciclovir cream, given the large numbers of subjects tested, suggests that viral cultures must be aggressively obtained to make this the sensitive efficacy marker it has been in studies of herpes genitalis.[19-21] Aggressive viral culturing has often not been pursued in HSL because of a possible effect on delaying healing, which may, in turn, contribute to the lack of sensitivity of this parameter in HSL studies. Accordingly, viral cultures were not performed in the current studies.

As observed in the penciclovir studies, the placebo-treated time of about 5 days in these studies is shorter than the reported natural history of HSL lesion healing of 7 to 10 days.[3-5] This raises suspicions of a placebo effect, which has been well recognized in HSL.[2,22] Placebo effects often occur with dermatologic products, resulting not only from the psychologic effects typically associated with placebo treatment,[23] but also from simply covering the lesion, which itself alters the physiology of untreated skin.

Although the effect of docosanol 10% cream in HSL may appear modest, the self-limiting nature of

the disease makes decreased duration of almost a day (18 hours) significant to patients. Reduced healing time is accompanied by relief of pain and/or burning, itching, or tingling, which is also important to patients. The time of the most severe stage (ulcer/soft crust) of the lesion is significantly reduced, a medically important effect that has not been previously reported. Furthermore, the apparent magnitude of the clinical effect may be lessened by what appears to be a substantial placebo effect in the treatment of HSL, as discussed earlier.

Docosanol appears to inhibit viral entry into host cells by inhibiting the normal process of viral fusion with the cell's plasma membrane, thereby blocking entry and subsequently limiting viral replication.[9-13] Docosanol and its metabolites do not interact directly with viral proteins or nucleic acids. Accordingly, the emergence of drug-resistant HSV is unlikely. Because of the different mode of action from antiviral nucleosides, resistance to docosanol would not diminish the effectiveness of other topical or systemic antivirals, even if it were shown to exist. In addition, the unique mechanism of action suggests that combination therapy with antiviral nucleosides is worthy of consideration.

In conclusion, docosanol 10% cream was shown to be effective in the clinic-initiated, placebo-controlled, clinical trial in early HSL. This treatment reduced episode duration overall, duration of those episodes that developed into classic lesions, and the duration of all lesion symptoms. On the basis of these studies, treatment with docosanol 10% cream should be initiated as early as possible in the course of HSL.

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