High-Dose, Short-Duration, Early Valacyclovir Therapy for Episodic Treatment of Cold Sores: Results of Two Randomized, Placebo-Controlled, Multicenter Studies

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Oral valacyclovir is better absorbed than oral acyclovir, increasing acyclovir bioavailability three- to fivefold. This provides the opportunity to explore whether high systemic acyclovir concentrations are effective in the treatment of cold sores (herpes labialis). Two randomized, double-blind, placebo-controlled studies were conducted. Subjects were provided with 2 g of valacyclovir twice daily for 1 day (1-day treatment), 2 g of valacyclovir twice daily for 1 day and then 1 g of valacyclovir twice daily for 1 day (2-day treatment), or a matching placebo and instructed to initiate treatment upon the first symptoms of a cold sore. In study 1, the median duration of the episode (primary endpoint) was reduced by 1.0 day ($P = 0.001$) with 1-day treatment and 0.5 days ($P = 0.009$) with 2-day treatment compared to placebo. Similarly, the mean duration of the episode was statistically significantly reduced by 1.1 days with 1-day treatment and 0.7 days with 2-day treatment compared to placebo. The proportion of subjects in whom cold sore lesion development was prevented and/or blocked was increased by 6.4% ($P = 0.096$) with 1-day treatment and 8.5% ($P = 0.061$) with 2-day treatment compared to placebo. The time to lesion healing and time to cessation of pain and/or discomfort were statistically significantly reduced with valacyclovir compared to placebo. In study 2, results similar to those in study 1 were obtained. AEs were similar across treatment groups. These studies provide evidence supporting a simple, 1-day valacyclovir treatment regimen for cold sores that is safe and effective. The 1-day valacyclovir regimen offers patients a unique and convenient dosing alternative compared to available topical therapies.

Herpes labialis, or cold sores, are caused by herpes simplex virus type 1 (HSV-1) and can result in significant irritation, pain, discomfort, and worry (18, 25). The infection is most often acquired in childhood, but the incidence increases with age (2, 5, 12, 18). Up to 90% of persons over the age of 50, depending on race, sex, and country, would test seropositive for HSV-1, and an estimated 20 to 40% of adults experience cold sore outbreaks (5, 12, 18, 25).

Until now, most treatments have consisted of creams that must be applied to affected areas multiple times a day for several days (6, 13, 15, 19, 20, 23). There have been two previous clinical trials of oral antiviral therapy for episodic treatment of herpes labialis. In a double-blind, placebo-controlled trial involving 210 subjects with recurrent cold sores, it appeared that less time was required for the loss of hard crust for subjects taking 200 mg of oral acyclovir 5 times daily for 5 days (14). This difference as well as other measures of clinical healing was not statistically significant. Spruance et al. evaluated a regimen of 400 mg of oral acyclovir 5 times daily for 5 days in comparison with placebo (21). Overall in this study, acyclovir did not affect the duration of the episode, mean maximum lesion size, or the development of lesions, but a subset of early treated patients achieved a 36% mean reduction in pain ($P = 0.02$) and a 27% mean reduction in time to lesion healing ($P = 0.03$). Thus, oral acyclovir may provide some benefit, but it has not proven consistently effective.

The difficulty in treating cold sore outbreaks has been attributed to the rapid development of lesions and a strong secondary immunological response that limits lesion duration in untreated patients (1, 22). However, a window of opportunity for antiviral agents may exist when adequate concentrations are used and treatment is initiated during the time that viral replication dominates temporarily over the host immune response (2, 18). The pathogenesis of the disease suggests that brief and early high-dose antiviral therapy might be a logical approach (18, 22).

Valacyclovir (Valtrex), the L-valine ester of acyclovir, is well

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TABLE 1. Key demographic characteristics[a]

Subject characteristic	Value for treatment group					
	Placebo		Valacyclovir 1 day		Valacyclovir 2 day	
	Study 1 (n = 292)	Study 2 (n = 317)	Study 1 (n = 311)	Study 2 (n = 298)	Study 1 (n = 299)	Study 2 (n = 339)
Race (n) (%)						
White	279 (96)	287 (91)	294 (95)	271 (91)	279 (93)	311 (92)
Other	13 (4)	30 (9)	17 (5)	27 (9)	20 (7)	28 (8)
Sex (n) (%)						
Female	211 (72)	226 (71)	247 (79)	216 (72)	220 (74)	243 (72)
Male	81 (28)	91 (29)	64 (21)	82 (28)	79 (26)	96 (28)
Median age (yr) (range)	36.5 (12–77)	37.0 (12–81)	38.0 (12–72)	36.0 (12–79)	38.0 (12–70)	38.0 (12–82)
Median time with cold sores (yr) (range)	20 (0.5–60)	22 (1–60)	20 (2–55)	20 (2–70)	20 (2–62)	20 (2–70)
Median cold sore episodes in last 12 mo (range)	5 (3–99)	6 (3–45)	5 (3–50)	6 (3–24)	5 (3–30)	6 (3–48)

[a] ITT population.

absorbed and rapidly and almost completely converted to acyclovir after oral administration, increasing the oral acyclovir bioavailability in humans by three- to fivefold relative to traditional oral acyclovir (3, 17, 24). The improved acyclovir bioavailability achieved with valacyclovir has allowed testing of the hypothesis that greater acyclovir exposure early in the recurrence will be effective for treatment of cold sore episodes. Therefore, we conducted two studies that evaluated the efficacy and safety of 1- and 2-day treatment regimens of valacyclovir in the treatment of cold sore outbreaks.

(Results of these studies have been presented as an abstract at the 15th International Conference on Antiviral Research, Prague, Czech Republic, 17 to 21 March 2002 [S. L. Spruance et al., Antivir. Res. **53:**abstr. 60, 2002].)

MATERIALS AND METHODS

Study design. Two studies, identical except for primary endpoints, were conducted. Both studies were multicenter, randomized, double blind, and placebo controlled. Study 1 (HS230027) was conducted at 20 centers in the United States, and study 2 (HS230028) was conducted at 18 centers in the United States and 6 centers in Canada. An institutional review board approved the study protocol for each study site.

TABLE 2. Subject accountability and treatment summary[a]

Parameter	Value for treatment group					
	Placebo		Valacyclovir 1 day		Valacyclovir 2 day	
	Study 1 (n = 292)	Study 2 (n = 317)	Study 1 (n = 311)	Study 2 (n = 298)	Study 1 (n = 299)	Study 2 (n = 339)
Protocol deviations[b] (n) (%)						
None	235 (80)	261 (82)	253 (81)	252 (85)	243 (81)	264 (78)
Noncompliance in study medication	32 (11)	27 (9)	35 (11)	21 (7)	36 (12)	45 (13)
Use of disallowed concurrent medications	20 (7)	14 (4)	17 (5)	13 (4)	12 (4)	20 (6)
At clinic >24 h after treatment start	11 (4)	17 (5)	9 (3)	14 (5)	11 (4)	18 (5)
Other	8 (3)	12 (4)	7 (2)	5 (2)	16 (5)	18 (5)
Treatment initiation (n) (%)						
During prodrome	269 (92)	292 (92)	281 (90)	282 (95)	271 (91)	302 (89)
After prodrome[c]	3 (1)	5 (2)	1 (<1)	4 (1)	0	2 (<1)
Missing	20 (7)	20 (6)	29 (9)	12 (4)	28 (9)	35 (10)
Treatment initiation[d] (range)						
<2 h	219 (75)	257 (81)	249 (80)	243 (82)	217 (73)	262 (77)
2–<6 h	52 (18)	36 (11)	39 (13)	35 (12)	49 (16)	39 (12)
≥6 h	12 (4)	12 (4)	14 (5)	12 (4)	16 (5)	17 (5)
Missing	9 (3)	12 (4)	9 (3)	8 (3)	17 (6)	21 (6)
Median [h (range)]	0.5 (0.0–45.8)	0.3 (−0.4–38.3)	0.5 (0.0–15.8)	0.4 (−0.2–20.4)	0.6 (0.0–14.0)	0.5 (0.0–17.8)

[a] ITT population.
[b] Major protocol deviations. Subjects may have more than one protocol deviation.
[c] Stages of lesion were macule, papule, or vesicle.
[d] Time from first symptom to treatment initiation. Two subjects recorded treatment initiation before any symptoms were experienced.

TABLE 3. Duration of episode[a]

Parameter	Value for treatment group		
	Placebo	Valacyclovir 1 day	Valacyclovir 2 day
Study 1			
No. of subjects	292	311	299
Median no. of days (range)	5.0 (1.0 to 20.0)	4.0 (1.0 to 18.0)	4.5 (1.5 to 18.5)
Difference[b] (95% CI)		−1.0 (−1.5 to 0.0)[c]	−0.5 (−1.0 to 0.0)[e]
Mean no. of days[d]	6.1	5.0	5.3
Difference[b] (95% CI)		−1.1 (−1.6 to −0.6)	−0.7 (−1.3 to −0.2)
Study 2			
No. of subjects	317	298	339
Median no. of days (range)	5.5 (1.5 to 21.5)	5.0 (1.5 to 20.0)	5.0 (1.5 to 15.5)
Difference[b] (95% CI)		−0.5 (−1.0 to −0.5)[f]	−0.5 (−1.5 to −0.5)[f]
Mean no. of days[d]	6.3	5.3	5.5
Difference[b] (95% CI)		−1.0 (−1.5 to −0.5)	−0.8 (−1.3 to −0.3)

[a] ITT population, includes vesicular and nonvesicular lesions. P values were determined by using the Wilcoxon rank sum test stratified by center. Subjects with missing data have been assigned a value of 15 days.
[b] Differences are valacyclovir minus placebo. 95% CI, 95% confidence interval.
[c] P value of 0.001.
[d] Means adjusted for center.
[e] P value of 0.009.
[f] P value of <0.001.

Subjects. Healthy subjects at least 12 years of age with a clinical history of recurrent cold sores and who experienced at least three episodes in the past year were recruited. They should have experienced prodromal symptoms of cold sores during at least half of the previous cold sore episodes, and they had a history of at least half of the cold sore episodes producing classical lesions (i.e., episodes that progressed through macule, papule, vesicle, crust, and healed). During the study period, subjects agreed to abstain from any mechanical disruption of the prodromal area or lesion, from the use of topical or systemic antiherpetic agents, from anti-inflammatory medications, and from the use of any topical treatments in the lesion area (cosmetics, lip balms, and sun screens, etc.). Subjects were not eligible for inclusion if they had abnormal perioral skin conditions that might have affected the normal course of cold sores (e.g., eczema or psoriasis); had infection with HSV-1 isolates known to be resistant to acyclovir, valacyclovir, famciclovir, or ganciclovir; or had an allergy to any of these medications. Subjects who had a serum creatinine level greater than the upper limit of normal, had received an investigational drug or immunomodulatory treatment in the 30 days prior to randomization, or were immunocompromised, including known human immunodeficiency virus infection, were also excluded from the study. Subjects could not have previously participated in either of these cold sore studies.

Study conduct. Written informed consent was obtained from patients who were then screened for eligibility with a medical history, physical examination, and blood tests for laboratory values. A pregnancy test was performed on all female subjects of childbearing potential. Eligible subjects were randomized in a 1:1:1 ratio to one of the following arms: 2 g of valacyclovir twice daily for 1 day (valacyclovir 1 day), 2 g of valacyclovir twice daily for 1 day followed by 1 g of valacyclovir twice daily for 1 day (valacyclovir 2 day), or matching placebo. The study drug was provided as 500-mg valacyclovir caplets and matching placebo. All subjects, whether receiving active drug or placebo, took 4 caplets twice daily (at approximately 12-h intervals) for 1 day and 2 caplets twice daily (at approximately 12-h intervals) for a second day.

All randomized subjects were given instructions on how to perform lesion self-assessments and were provided a diary in which to record information about their cold sore episode. Subjects were instructed to initiate treatment at the earliest prodromal symptoms and prior to the first clinical sign of a cold sore (i.e., no redness, swelling, blister, or later stage present). Presentation to the clinic had to occur within 24 h after the initiation of study drug treatment. Subjects who could not initiate treatment before the development of visible signs of a cold sore or who could not return to the clinic within 24 h of treatment initiation were advised not to initiate study treatment and to wait until their next cold sore episode.

Subjects reported to the clinic daily until their lesion was assessed as healed or for a minimum of 5 consecutive days. At each clinic visit, the clinician personally observed and recorded his/her evaluation of the lesion stage at the time of the visit (clinician-observed data). In addition, clinicians questioned the subject regarding dosing compliance, the use of concurrent medications, the occurrence of

any adverse experiences, the evolution of lesion stages, and the course and severity of lesion pain and/or discomfort. The clinician verified all information recorded in the subject's diary. At the last patient visit, the clinician made a final assessment of all lesion endpoints based on his/her observations and the diary (clinician-assessed data). Blood samples for clinical chemistry and hematology analyses were also obtained on clinic visit 3 (study day 3) and clinic visit 5 (study day 5) or end-of-study visit.

Efficacy variables. The primary and secondary efficacy measures were the duration of the episode and the proportion of subjects in whom cold sore lesion development was prevented and/or blocked.

Duration of episode. The primary efficacy measure in study 1 and the secondary efficacy measure in study 2 was the clinician-observed duration of all cold sore episodes (vesicular and nonvesicular). This was measured in whole days from the day a subject took the first dose of study drug until the day the clinician determined the lesion was healed, inclusive. However, if the subject was only able to take one dose of study drug on the first day due to a late occurrence of the episode, this was counted as half a day. For subjects who experienced a vesicular lesion, healing was defined as the loss of crust (residual erythema may have been present). For subjects whose lesions were not vesicular in nature, healing was defined as the return to normal skin and/or the cessation of all symptoms.

Prevented and/or blocked lesions. The primary efficacy measure in study 2 and the secondary efficacy measure in study 1 was the proportion of subjects in whom cold sore lesion development was prevented and/or blocked and did not progress beyond the papular stage. Subjects with a blocked lesion could experience prodromal symptoms, erythema, or a papule but not the vesicle, ulcer, or hard-crust lesion stages.

Other efficacy measures. Other efficacy variables were the time to lesion healing and time to cessation of pain and/or discomfort. These endpoints were determined with clinician-assessed data, a synthesis of both the clinician's observations and the diary. The time to lesion healing was defined as the time from treatment initiation to the loss of crust and only included subjects whose lesions progressed to the vesicular stage. The time to cessation of pain and/or discomfort was defined as the time from treatment initiation to the complete cessation of pain and/or discomfort.

Safety variables. Safety was assessed via adverse event (AE) reporting and clinical laboratory analyses.

Statistical methodology. A sample size of 310 subjects per treatment group would have at least 90% power to detect a difference in the mean duration of the episode of 0.75 days or larger at the 2.5% level of significance, assuming a standard deviation of 2.6 days in each group (7). For the prevented and/or blocked lesion development endpoint, it was assumed that 45% of placebo-treated subjects would have an episode that was prevented and/or blocked and that a clinically relevant difference was an increase to 60%. With 310 treated subjects in each group, the study would have a power of 90% for a two-tailed test of these proportions at the 2.5% level of significance (7). Seventy percent of
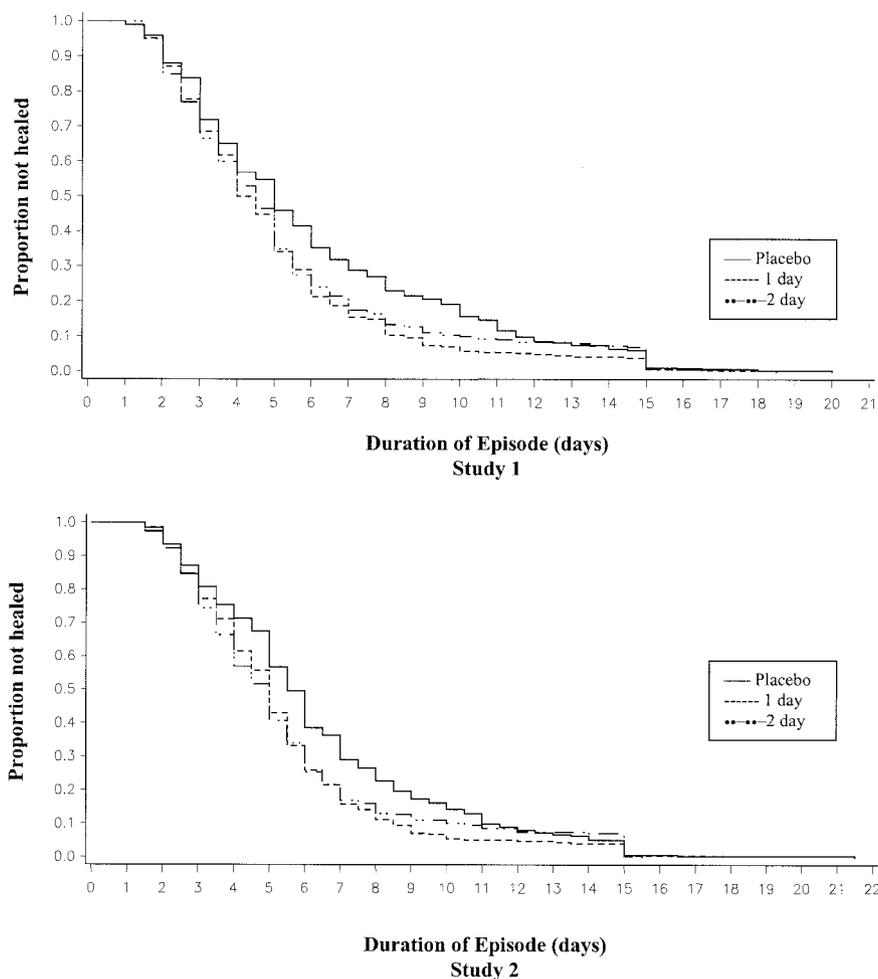
FIG. 1. Kaplan Meier plots of the duration of vesicular and nonvesicular cold sore episodes showing the proportion of subjects not healed versus the duration of the episode (time in days) for each treatment regimen within each study. Study 1: placebo, $n = 292$; 1-day valacyclovir treatment, $n = 311$; 2-day valacyclovir treatment, $n = 299$. Study 2: placebo, $n = 317$; 1-day valacyclovir treatment, $n = 298$; 2-day valacyclovir treatment, $n = 339$.

enrolled patients were predicted to have a cold sore episode and initiate study drug treatment. Thus, for both studies, it was planned to randomize approximately 440 subjects per treatment arm in order to reach the target of 310 evaluable subjects in each treatment arm.

Data were analyzed from the population of subjects that received at least one dose of study medication (intent to treat [ITT]) and the efficacy-evaluable population (patients without any major protocol deviations). If information regarding the timing of treatment initiation was missing, the subject was included in the ITT population and was regarded as a treatment failure. Since the results of the analyses were similar between the ITT and efficacy-evaluable populations, the data presented herein are from the ITT population.

The two regimens of valacyclovir were compared separately against placebo. All efficacy analyses were stratified by center. The Hochberg step-down approach was used to handle multiplicity issues (8). With this approach, the P values were ordered and the larger P value was tested at the 5% significance level. If this reached significance, it implied that the smaller P value was also significant at the 5% level. However, if the larger P value failed to reach significance at the 5% level, then the smaller P value was tested at the 2.5% level.

The duration of the episode was compared between each valacyclovir treatment group and the placebo group by using a Wilcoxon rank sum test stratified by center (10). The duration was summarized by the median and mean for each treatment group and also graphically with Kaplan-Meier survival curves for each treatment group. For subjects whose duration of episode was unknown, a duration of 15.0 days was assigned. This imputation was based on the results from a previous acyclovir study (19). An estimate and confidence interval of the differ-

ence between medians was calculated by using the percentile bootstrap method (4). The proportion of subjects in whom cold sore lesion development was prevented and/or blocked was compared between each valacyclovir treatment group and the placebo group by using a Mantel-Haenszel chi-square test stratified by center (7). Estimates and 95% confidence intervals for the differences in proportion between treatment groups were calculated by using the normal approximation to the binomial distribution (7). Subjects for whom the prevention and/or blocking of lesions was unknown were assumed to be treatment failures, i.e., assumed to have had a vesicular lesion. Time to lesion healing and time to cessation of pain and/or discomfort were compared between treatments by using a Wilcoxon rank sum test stratified by center.

Safety measures reported were AEs, drug-related AEs, AEs leading to permanent discontinuation of study drug, and laboratory data. The proportion of subjects reporting AEs were tabulated for each treatment group. The numbers of subjects with laboratory abnormalities were also summarized.

RESULTS

A total of 1,524 and 1,627 subjects were randomized in studies 1 and 2, respectively. The ITT population included 902 subjects in study 1 and 954 subjects in study 2. In both studies, demographics were similar (Table 1). Subjects were primarily white (91 to 96%) and female (71 to 79%), with a median age

TABLE 4. Cold sore lesion development[a]

Parameter	Value for treatment group		
	Placebo	Valacyclovir 1 day	Valacyclovir 2 day
Study 1			
No. of subjects	292	311	299
Lesion development prevented/blocked (n) (%)	111 (38)	138 (44)	139 (46)
Difference[b] (95% CI)		6.4 (−1.8 to 14.5)	8.5 (0.2 to 16.7)
Odds ratio[c] (95% CI)		1.32 (0.95 to 1.84)[d]	1.38 (0.98 to 1.94)[e]
Study 2			
No. of subjects	317	298	339
Lesion development prevented/blocked (n) (%)	112 (35)	129 (43)	147 (43)
Difference[b] (95% CI)		8.0 (−0.1 to 16.0)	8.0 (0.3 to 15.8)
Odds ratio[c] (95% CI)		1.39 (0.99 to 1.95)[f]	1.41 (1.02 to 1.94)[g]

[a] ITT population. P values were determined by using the Mantel Haenszel test stratified by center. Subjects whose prevention and/or blockage of lesions is unknown have been assumed to be treatment failures.
[b] Differences in proportions are valacyclovir minus placebo. 95% CI, 95% confidence interval.
[c] Odds ratios compare valacyclovir to placebo.
[d] P value of 0.096.
[e] P value of 0.061.
[f] P value of 0.054.
[g] P value of 0.036.

of 36 to 38 years, a history of cold sores for a median of 20 to 22 years, and a median of 5 to 6 recurrences per year.

Subject completion and protocol violations were similar across treatment arms in both studies. In both studies, 95% of subjects completed the study, regardless of protocol violations. In each treatment arm, ≥78% of subjects had no protocol violations (Table 2). The most common protocol violations were noncompliance with study medication, subject presenting to the clinic >24 h after initiation of treatment, and use of disallowed concurrent medications. In both studies, compliance and time to treatment initiation in relation to the onset of the cold sore lesion were similar between the treatment arms (Table 2). In study 1, 89% of subjects were considered compliant throughout the study. In study 2, 90% of subjects were

considered compliant. In both studies, 89 to 95% of patients within a treatment group initiated treatment during prodrome and a similar percentage started therapy within 6 h of first symptoms of a cold sore.

Efficacy. (i) Duration of episode. Both studies showed a significant reduction in the median and mean duration of the episode with either the 1- or 2-day valacyclovir treatment regimen compared to that of the placebo (Table 3). Two days of therapy provided no additional efficacy over 1 day of treatment. In study 1, the treatment differences from placebo for the median duration of the episode were −1.0 days (P = 0.001) and −0.5 days (P = 0.009) for the 1- and 2-day treatment groups, respectively. Similarly, treatment differences versus placebo for the mean duration of episode were −1.1 days (P <
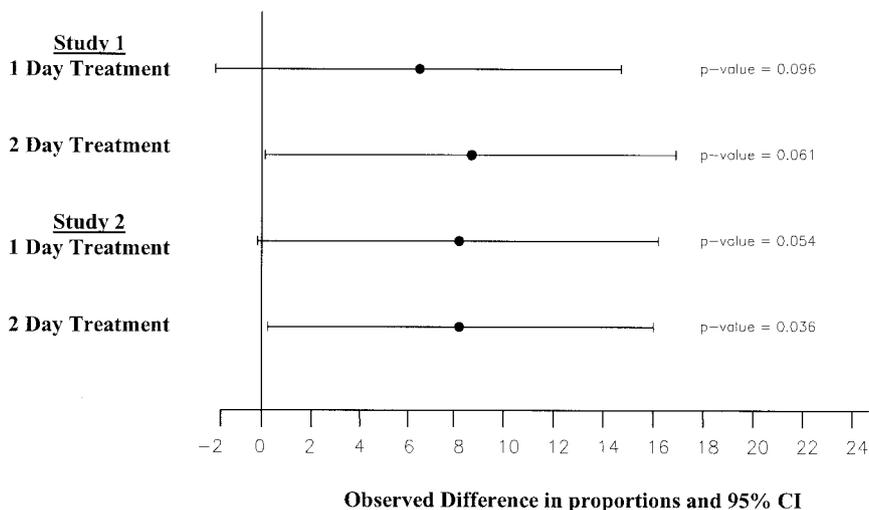

FIG. 2. Plot of the difference in proportion (%) of subjects in whom cold sore lesion development was prevented and/or blocked with 1-day treatment (2 g of valacyclovir twice daily for 1 day) and 2-day treatment (2 g of valacyclovir twice daily for 1 day and then 1 g of valacyclovir twice daily for 1 day) from placebo within each study. 95% CI, 95% confidence interval.

TABLE 5. Time to lesion healing[a]

Parameter	Value for treatment group		
	Placebo	Valacyclovir 1 day	Valacyclovir 2 day
Study 1			
No. of subjects	292	311	299
No. progressing to crust (%)	171 (59)	164 (53)	142 (47)
Median no. of days (range)	5.1 (1.0 to 19.1)	4.3 (0.2 to 16.7)	4.3 (0.7 to 17.4)
Difference[b]		−0.8[c]	−0.8[e]
Mean no. of days[d]	6.1	4.8	5.0
Difference (95% CI)		−1.3 (−1.9 to −0.7)	−1.1 (−1.7 to −0.5)
Study 2			
No. of subjects	317	298	339
No. progressing to crust (%)	192 (61)	161 (54)	170 (50)
Median no. of days (range)	5.4 (1.6 to 20.6)	4.8 (1.0 to 15.0)	4.6 (1.4 to 15.0)
Difference[b]		−0.6[c]	−0.8[c]
Mean no. of days[d]	6.4	5.1	5.2
Difference (95% CI)		−1.2 (−1.8 to −0.7)	−1.2 (−1.7 to −0.7)

[a] ITT population (includes only vesicular lesions). P values were determined by using the Wilcoxon rank sum test stratified by center. Subjects with missing data have been assigned a value of 15 days.
[b] Differences are valacyclovir minus placebo. 95% CI, 95% confidence interval.
[c] P value of <0.001.
[d] Means adjusted for center.
[e] P value of 0.001.

0.001) and −0.7 days ($P = 0.008$) for the 1- and 2-day treatment groups, respectively. Similar treatment differences were observed in study 2 (Table 3). Figure 1 shows the Kaplan-Meier plot of the duration of the episode for each study.

(ii) Prevention and/or blocking of cold sores. Increases in the proportion of subjects in whom cold sore lesion development was prevented and/or blocked were observed with both treatment regimens when compared to placebo (Table 4). In study 1, a greater proportion of subjects (6.4% [$P = 0.096$] of the 1-day treatment group and 8.5% [$P = 0.061$] of the 2-day treatment group) experienced prevention and/or blockage of cold sore lesions than those in the placebo group, but the treatment differences were not statistically significant at the two-sided 5% level. In study 2, a greater proportion of subjects (8%) in both treatment groups experienced prevention and/or blockage of cold sore lesions than those in the placebo group ($P = 0.054$ for 1-day treatment and $P = 0.036$ for 2-day treatment). However, after adjustment for multiple comparisons, neither treatment difference was statistically significant at the 5% level. Figure 2 shows the difference in proportion of subjects in whom cold sore lesion development was prevented and/or blocked for the 1- and 2-day valacyclovir treatment regimens in each study.

(iii) Time to lesion healing and cessation of pain and/or discomfort. In agreement with the duration of episode data (all lesions), time to lesion healing (for only vesicular lesions) showed that both the 1- and 2-day valacyclovir regimens significantly shortened healing in comparison to placebo (Table 5). Median or mean treatment differences from placebo were approximately 1 day for both valacyclovir treatment groups, and similar results were observed between studies. Figure 3 shows the Kaplan-Meier plot of time to lesion healing for each study, and the results are similar to those shown in Fig. 1.

Valacyclovir treatment provided a significantly shorter time (approximately half a day) to cessation of pain and/or discomfort in comparison to placebo (Table 6). Similar results were observed in the 1- and 2-day treatment groups and between studies.

Safety. AEs (all events) and drug-related AEs (considered by the investigator to be attributable to therapy) were similar across treatment groups in both studies. The most commonly reported AEs were headache, nausea, and diarrhea. Of the drug-related AEs (Table 7), only headache appeared higher in the two valacyclovir treatment groups upon comparison to placebo (an increase of 4 to 5%). All other AEs were similar across treatment groups. No serious AEs were reported in either trial. Clinical laboratory abnormalities (data not shown) were infrequent and similar across treatments.

DISCUSSION

These studies show that 1-day, high-dose valacyclovir therapy at the first symptom of a cold sore is a safe and effective treatment. Both 1- and 2-day valacyclovir regimens provide clinically and statistically significant benefits over placebo in duration of the episode and time to lesion healing. Time to cessation of pain and/or discomfort was also significantly decreased by 1- or 2-day treatment with valacyclovir. The proportion of subjects with prevented and/or blocked cold sore lesions was higher in the valacyclovir-treated groups, although statistical significance was not reached. These two large, well-controlled trials provide evidence that early, high-dose, short-duration antiviral intervention can shorten the clinical course of cold sores and that 2 days of therapy provide no additional benefit over 1 day.

These results support the premise that achieving and maintaining high concentrations of acyclovir in plasma above the HSV-1 99% inhibitory concentration level, during the period of early viral replication, can interrupt the 2 to 3 cycles of viral replication thought to be necessary to produce clinically apparent lesions (18, 22). The valacyclovir 1-day treatment regimen of 2 g twice daily was expected to provide a peak acyclovir concentration of approximately 8 μg/ml and a concentration-time profile in excess of the 99% inhibitory concentration of 4.21 μg/ml for approximately 5.5 h (~23%) during the first 24-h period (3, 17, 24). A single-day valacyclovir regimen of 2 g
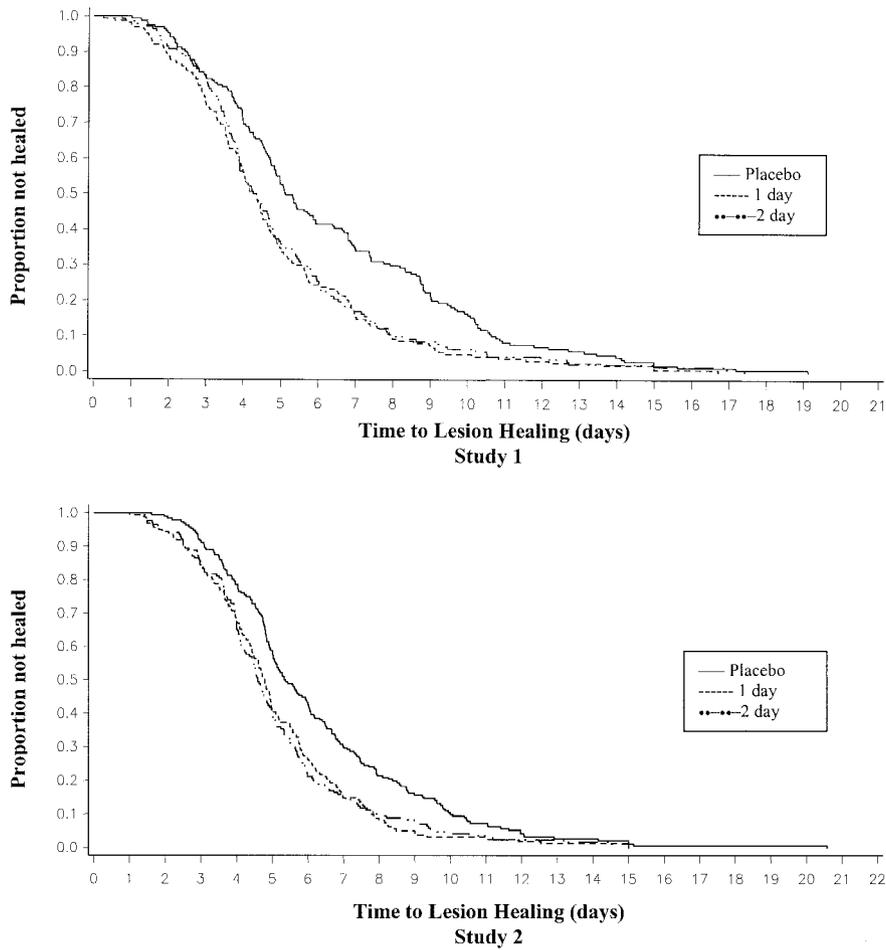
FIG. 3. Kaplan Meier plots of time to vesicular lesion healing showing proportion of subjects not healed versus duration of lesion healing (time in days) for each treatment regimen within each study. Study 1: placebo, $n = 171$; 1-day valacyclovir treatment, $n = 164$; 2-day valacyclovir treatment, $n = 142$. Study 2: placebo, $n = 192$; 1-day valacyclovir treatment, $n = 161$; 2-day valacyclovir treatment, $n = 170$.

TABLE 6. Time to cessation of pain and/or discomfort[a]

Parameter	Value for treatment group		
	Placebo	Valacyclovir 1 day	Valacyclovir 2 day
Study 1			
No. of subjects	292	311	299
Median no. of days (range)	1.8 (0.0 to 15.0)	1.2 (0.0 to 15.0)	1.3 (0.0 to 15.0)
Difference[b]		−0.6[c]	−0.5[e]
Mean no. of days[d]	2.9	2.1	2.5
Difference (95% CI)		−0.7 (−1.3 to −0.2)	−0.4 (−0.9 to 0.1)
Study 2			
No. of subjects	317	298	339
Median no. of days (range)	2.2 (0.0 to 14.8)	1.5 (0.0 to 14.8)	1.5 (0.0 to 14.8)
Difference[b]		−0.7[f]	−0.7[g]
Mean no. of days[d]	3.1	2.3	2.8
Difference (95% CI)		−0.8 (−1.4 to −0.3)	−0.3 (−0.8 to 0.2)

[a] ITT population. P values were determined by using the Wilcoxon rank sum test stratified by center. Subjects with missing data in study 1 have been assigned a value of 15 days. Subjects with missing data in study 2 have been assigned a value of 14.8 days. This was the maximum observed duration plus 1 day.
[b] Differences are valacyclovir minus placebo. 95% CI, 95% confidence interval.
[c] P value of 0.009.
[d] Means adjusted for center.
[e] P value of 0.008.
[f] P value of <0.001.
[g] P value of 0.003.

TABLE 7. Incidence of drug-related AEs $\geq 1.5\%^a$

AE	Value for treatment group					
	Placebo		Valacyclovir 1 day		Valacyclovir 2 day	
	Study 1 ($n = 292$)	Study 2 ($n = 317$)	Study 1 ($n = 311$)	Study 2 ($n = 298$)	Study 1 ($n = 299$)	Study 2 ($n = 339$)
Any event (n) (%)	51 (17)	50 (16)	55 (18)	55 (18)	61 (20)	52 (15)
Specific events (n) (%)						
Headache	12 (4)	16 (5)	27 (9)	29 (10)	28 (9)	29 (9)
Nausea	12 (4)	17 (5)	12 (4)	13 (4)	16 (5)	13 (4)
Diarrhea	9 (3)	10 (3)	11 (4)	6 (2)	8 (3)	5 (1)
Dyspepsia	5 (2)	3 (<1)	5 (2)	3 (1)	3 (1)	1 (<1)
Dry mouth	5 (2)	2 (<1)	2 (<1)	2 (<1)	5 (2)	2 (<1)
Flatulence	1 (<1)	2 (<1)	2 (<1)	1 (<1)	5 (2)	0

^{a} ITT population.

twice daily for 2 doses produces systemic concentrations not clinically achievable with oral acyclovir dosing or topical therapy. Hence, this may explain the inconsistent efficacy results observed in previous clinical trials with oral acyclovir therapy for cold sores (14, 16, 21). It is presumed, but not proven, that a strong antiviral effect hastens wound resolution by decreasing the extent of keratinocyte destruction, the viral antigen load, and the attendant inflammatory response, which impair reepithelization at the site of infection (1, 9, 11, 22).

One-day, two-dose oral valacyclovir constitutes a convenient treatment for herpes labialis in comparison to topical therapies, which typically require frequent applications for multiple days (13, 15, 19, 20, 23). While direct comparisons between oral and topical therapy have not been conducted, the available data suggest that oral therapy is more effective. Penciclovir 1% cream (Denavir) is indicated for the treatment of cold sores. The clinical studies leading to approval demonstrated that the cream was efficacious in shortening the median healing time of classical cold sore episodes by 0.7 to 1.0 days (13 to 17%) compared to the vehicle controls (13, 20). Acyclovir 5% cream (Zovirax cream) is also indicated for cold sores and has been shown in two large, well-controlled clinical trials to shorten the duration of classical cold sore episodes by a similar magnitude to that of penciclovir 1% cream (19). The clinical results reported in the two valacyclovir studies indicate a difference between valacyclovir and placebo-treated patients in mean classical lesion healing time of 1.1 to 1.3 days (18 to 21%) (Table 5).

Although the proportion of subjects with prevented and/or blocked cold sore lesions was higher in the valacyclovir-treated groups, statistical significance was not reached. Two studies, one using topical acyclovir cream and one using oral acyclovir, have shown some apparent effect on the prevention of cold sore lesion progression (6, 16). However, these results have not been reproduced in subsequent studies (14, 19, 21). The present valacyclovir studies are the two largest, placebo-controlled trials of herpes labialis treatment designed to test the hypothesis that the progression of cold sore lesions could be prevented with oral medication if taken early (i.e., at the first symptoms). Both studies showed similar trends in favor of valacyclovir, and in a combined analysis of these two trials, a statistically significant effect on preventing and/or blocking cold sore lesion development was demonstrated (S. K. Tyring,

S. L. Spruance, M. Vargas-Cortes, and M. Schultz, Proc. Summer Session Am. Acad. Dermatol., abstr. 31, 2002).

The magnitude of benefit to the patient that can be achieved by the episodic treatment of herpes labialis is less than the efficacy of prophylactic drug administration. Nevertheless, many patients prefer intermittent to continuous medication. For these individuals, the 1.1- to 1.3-day effect on mean lesion healing time shown in this trial, an 18 to 21% reduction, would be clinically significant to many of them. While considered a minor illness, herpes labialis lesions can be disfiguring and painful during eating or talking and can adversely affect self-image, particularly among teenagers.

These two large trials indicate that valacyclovir therapy, taken at the first symptom of a cold sore, reduces the duration of an episode, the time to lesion healing, and the duration of pain and/or discomfort. The 1-day valacyclovir regimen is a safe and effective treatment of cold sores while also offering the potential advantage of simple and convenient dosing over currently available treatments.

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