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Study No.: ZOV30008
Title: A Phase III Multicentre, Double-Blind, Active-Controlled, Parallel Study Comparing the Efficacy and Safety of ZOVIRAX Cold Sore Cream (Aciclovir 5% Cream) and Lidocaine 2% to ZOVIRAX Cold Sore Cream Alone Administered for 5 Days in Subjects with Herpes Labialis Infection.
Rationale: A combination of aciclovir-lidocaine was investigated as a potentially improved treatment for herpes labialis that would provide both pain relief and faster healing of the condition. The study was undertaken because it was anticipated that a combination of aciclovir with lidocaine would benefit subjects with herpes labialis, by rapidly controlling symptoms of pain or discomfort, whilst maintaining antiviral efficacy.
Phase: III
Study Period: 25 May 2000 to 19 December 2000.
Study Design: A multicentre, randomised, double-blind, active-controlled, parallel study.
Centres: 10 centres in the UK.
Indication: Herpes labialis infection.
Treatment: Eligible subjects were equally randomised to study treatment of topical aciclovir 5% cold sore cream or aciclovir 5% cold sore cream with Lidocaine 2%. Subjects applied the cream every 3-4 hours throughout waking hours for a maximum of 5 applications per day for 5 complete (24-hour) days. The total duration for any study subject from time of enrolment to completion was to be 6-15 days.
Objectives: The objectives were 1) to compare the effectiveness of aciclovir-lidocaine compared with aciclovir in the relief of herpes labialis pain or discomfort and the duration of herpes labialis episodes, and 2) to assess safety by comparing the proportions of subjects that experienced adverse events (AEs).
Primary Outcome/Efficacy Variable: The primary efficacy variable was time to onset of meaningful herpes labialis pain relief and was assessed using a herpes labialis pain scoring scale.
Secondary Outcome/Efficacy Variable(s): The secondary efficacy variables were: 1) duration of herpes labialis episode from start of treatment (healing time); 2) weighted mean reduction in herpes labialis pain score after first treatment application; 3) percent of time with meaningful herpes labialis pain relief after first treatment application; 4) meaningful herpes labialis pain relief after second and third treatment applications; 5) adequate relief from herpes labialis pain; 6) duration of herpes labialis pain from start of study; and 7) adverse events.
Statistical Methods: The primary endpoint was analysed using an accelerated failure time model (AFTM) with normal error structure. Effects of treatment, centre/"cluster", initial stage of cold sore, pre-treatment pain score, and interaction terms were investigated. Geometric mean times to onset of meaningful pain relief, adjusted for effects other than treatment within the model, were presented for each treatment. An estimate and 95% confidence interval (CI) for the acceleration factor (defined as the ratio of the geometric means for the 2 treatments on the log scale) was also presented, together with the p-value relating to the treatment effect from the AFTM main effects model. Model checking of the AFTM main effects model was undertaken by examination of residuals. Kaplan-Meier curves for each treatment group were also presented. Secondary endpoints were analysed using techniques based on those used for the primary endpoint, or logistic regression techniques. To have a sufficient subject population to analyse the secondary endpoint of duration of herpes labialis episode from start of treatment, results from the companion study (ZOV30009) were combined with the results from this study. All subjects who were randomised and received at least 1 dose of 1 of the study treatments were included in the full analysis (FAS) population, which was used for all analyses.
Study Population: Male and non-pregnant female subjects using adequate contraception were eligible if they were generally healthy subjects (by history), at least 18 years of age, and experienced recurrent herpes labialis. Subjects were to have: had a clinical history of recurrent herpes labialis with at least 2 episodes of typical lesions in the past year and frequently experienced pain or discomfort during their herpes labialis episodes; had a pre-treatment herpes labialis Pain Score ≥ 3 ; had a history of at least 50% of herpes labialis episodes producing "classical" lesions (i.e. vesicle, ulcer, and/or hard crust); agreed to abstain from the use of ANY topical treatments in the treated area (cosmetics, lip balms, sun screens, etc.) until healing occurred; agreed to abstain from the use of any mechanical disruption of the prodromal area or lesion (i.e. scrubbing, lancing, shaving the area, rubbing with alcohol, cologne, cosmetics, lip balms, sunscreen, etc.) during the treatment period until healing occurred; and had an ability to read, comprehend, and record information. Subjects were excluded from the study if they: had an herpes labialis area of involvement greater than 1 cm in diameter, had multiple simultaneous lesions, lesions involving the nares or oral cavity, or lesions that had already formed a crust; had congenital, acquired, or iatrogenic disorders likely to be

associated with immunodeficiency or who were being treated with any systemically administered immuno-modifying agents; had a medical or surgical condition that might alter their susceptibility to herpes simplex virus (HSV) infections; had abnormal skin conditions that might affect the normal course of herpes labialis (e.g. eczema, psoriasis, albinism, or chronic vesiculobullous disorders); had an allergy or sensitivity to acyclovir, lidocaine, or other ingredients in the formulation; used the following items in the timeframe indicated prior to Day 1 and until healing occurred: oral or topical antivirals within 14 days, oral steroids within 28 days (steroids administered by inhalation or nasal spray were permitted), anti-inflammatory medications (including aspirin, ibuprofen, and naproxen) within 2 days, analgesics (including paracetamol) within 1 day; concurrently or previously participated in a clinical study in which the subject was exposed to an investigational or a non-investigational drug or device within the previous 3 months; or had previously participated in this study or the pilot study (ZOV30011).		
	Aciclovir + Lidocaine	Aciclovir
Number of Subjects:		
Planned, N	175	175
Randomised, N	165	168
Completed, n (%)	159 (96)	163 (97)
Total Number Subjects Withdrawn, n (%)	6 (4)	5 (3)
Withdrawn due to Adverse Events, n (%)	1 (<1)	0
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for Other Reasons, n (%)	5 (3)	5 (3)
Demographics		
	Aciclovir + Lidocaine	Aciclovir
N (FAS)	165	168
Females: Males	115: 50	117: 51
Mean Age, years (SD)	34.4 (9.8)	37.0 (12.5)
White, n (%)	164 (>99)	163 (97)
Primary Efficacy Results: (FAS population)		
Time to onset of meaningful herpes labialis pain relief^a, minutes:	Aciclovir + Lidocaine (N=165)	Aciclovir (N=168)
Median, 50 th percentile	9.0	35.0
Adjusted geometric mean time to onset	18.7	54.9
Acceleration factor ^b (95% CI)	2.93 (1.58, 5.44)	
p-value	<0.001	
Secondary Outcome Variable(s): (FAS Population)		
	Aciclovir + Lidocaine (N=165)	Aciclovir (N=168)
Duration of herpes labialis episode from start of treatment, days:		
Median, 50 th percentile	4.70	4.72
Adjusted geometric mean duration of episode	4.52	4.44
Acceleration factor ^b (lower 97.5% confidence bound)	0.98 (0.91)	
Weighted mean reduction in herpes labialis pain score after first treatment application:		
Number (%) of subjects with weighted mean reduction in pain score:		
<-4	20 (12)	13 (8)
[-4 and <-2	44 (27)	39 (23)
[-2 and <0	74 (46)	81 (49)
≥0	23 (14)	33 (20)
Weighted mean reduction in pain score (SD)	-1.80 (1.68)	-1.47 (1.59)
Odds ratio for treatment (95% CI)	0.54 (0.36, 0.82)	
Percent of time with meaningful herpes labialis pain relief after first treatment application:		
Number (%) of subjects with meaningful pain relief at percentage of time		
>50%	78 (48)	65 (39)
≥50%	83 (52)	102 (61)
Mean percentage of time with meaningful herpes labialis pain relief (SD)	49.18 (42.29)	38.07 (40.94)
Odds ratio for treatment (95% CI)	0.61 (0.38, 0.96)	
Meaningful herpes labialis pain relief^c after second treatment application:		
Number (%) subjects meeting the meaningful relief criteria before or at 2 hours post treatment	120 (75)	105 (63)

Odds ratio for treatment (95% CI)	0.49 (0.30, 0.82)	
Meaningful herpes labialis pain relief^c after third treatment application:		
Number (%) subjects meeting the meaningful relief criteria before or at 2 hours post treatment	121 (76)	114 (69)
Odds ratio for treatment (95% CI)	0.60 (0.35, 1.03)	
Adequate relief from herpes labialis pain^d:		
Number (%) of subjects achieving adequate relief from cold sore pain or discomfort from:		
100% of applications	80 (50)	68 (41)
70% to 100% of applications	58 (36)	60 (36)
<70% of applications	23 (14)	39 (23)
Mean percentage of treatment applications yielding adequate relief from cold sore pain and discomfort (SD)	85.9 (24.4)	78.4 (30.3)
Odds ratio for treatment (95% CI)	0.66 (0.43, 0.99)	
Duration of herpes labialis pain from start of treatment, days:		
Median, 50 th percentile	3.04	3.81
Adjusted geometric mean time to onset	2.76	2.90
Acceleration factor ^b (lower 97.5% confidence bound)	1.05 (0.88, 1.26)	
<p>a Defined as time from the first study drug application (but before the second application) until meaningful pain relief (a decrease in pain score of at least 2 units) was achieved.</p> <p>b Ratio of geometric means (aciclovir/aciclovir+lidocaine).</p> <p>c Defined as frequency counts of pain score reduction of 2 units or more at 2 hours after the second and third applications, respectively, compared to the first application pre-treatment pain score.</p> <p>d Defined as percentage of applications for which the subject recorded adequate relief from herpes labialis pain.</p>		
Safety Results: (FAS Population) –AEs and serious adverse events (SAEs) were recorded on Day 1 (just prior to study drug application and just prior to subject dismissal for the day), on Days 2 and 7 and once the episode ended, and for 24-hours following the last application of study drug. Only those AEs and SAEs that started during treatment are displayed below.		
	Aciclovir + Lidocaine (N=165)	Aciclovir (N=168)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	16 (10)	8 (5)
Viral skin infections	6 (4)	4 (2)
Hypoesthesia	4 (2)	0
Application site complications	2 (1)	0
Oral lesions	1 (<1)	1 (<1)
Pain	1 (<1)	1 (<1)
Contusions and haematomas	1 (<1)	0
Desquamation and desquamative rashes	1 (<1)	0
Discomfort	1 (<1)	0
Non-specific conditions	1 (<1)	0
Oral discolourations	1 (<1)	0
Paresthesia	1 (<1)	0
Ear, nose and throat infections	0	1 (<1)
Gastrointestinal infections	0	1 (<1)
Gum signs and symptoms	0	1 (<1)
Inflammation of oral mucosa	0	1 (<1)
Oral discomfort and pain	0	1 (<1)
Pruritus	0	1 (<1)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Aciclovir + Lidocaine (N=165)	Aciclovir (N=168)
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Aciclovir+lidocaine subjects experienced a shorter Time to Onset of Meaningful Herpes Labialis Pain Relief (≥ 2 units reduction) than subjects who received aciclovir.

Adverse events were reported in 16 (10%) subjects in the acyclovir + lidocaine group, and 8 (5%) subjects in the acyclovir group. Viral skin infections were the most frequently reported event in both groups. No fatal or non-fatal serious adverse events were reported.

Publications: No Publication

Date Updated: 17-Jan-2006