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Study No.: ZOV30009
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: 24 May 2000 to 27 November 2000.
Study Design: A multicentre, randomised, double-blind, active-controlled, parallel group study.
Centres: 19 centres in Australia (3), France (4), Poland (3), the Netherlands (4), and Germany (5).
Indication: Herpes labialis infection.
Treatment: Eligible subjects were equally randomised (1:1) to study treatment of topical aciclovir 5% cold sore cream with lidocaine 2%, or aciclovir 5% cold sore cream. 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 to compare the effectiveness of aciclovir-lidocaine compared with aciclovir in: the relief of herpes labialis pain or discomfort, the duration of herpes labialis episodes, and 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 (a decrease in pain score of at least 2 units) from first study drug application and was assessed using a herpes labialis pain scoring scale.
Secondary Outcome/Efficacy Variable(s): The secondary efficacy variables were: duration of herpes labialis episode from start of treatment (healing time); weighted mean reduction in herpes labialis pain score after first treatment application; percent of time with meaningful herpes labialis pain relief after first treatment application; meaningful herpes labialis pain relief after second and third treatment applications; adequate relief from herpes labialis pain; and duration of herpes labialis pain from start of treatment.
Statistical Methods: The sample size was calculated using data from 39 subjects who participated in a previously conducted pilot study (ZOV30011). Accelerated failure time modelling (AFTM) was performed on the time to meaningful pain relief and duration of episode from start of treatment. For time to meaningful pain relief, 150 evaluable subjects in each treatment group were considered sufficient to demonstrate that an acceleration factor (acyclovir : acyclovir+lidocaine) of 3.04 was significantly greater than 1, using a two-sided 5% significance level with 90% power and an estimate of the standard deviation on the log-scale of 2.964. For the duration of episode from start of treatment, 300 evaluable subjects in each treatment group in ZOV30008 and ZOV30009 combined have 80% power using a one-sided 2.5% significance level to declare non-inferiority of aciclovir+lidocaine compared with aciclovir if the observed acceleration factor (aciclovir : aciclovir+lidocaine) is at least 0.875. An extra 25 subjects were included in each group to allow for subjects failing to complete the study satisfactorily, thereby failing to be included fully in the statistical analysis. Therefore, the total study sample size, taking into account both pain relief and healing, was estimated as 350 subjects, 175 subjects per group. The primary endpoint was analysed using 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. Secondary endpoints were analysed using techniques based on those used for the primary endpoint, or ordinal 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 (ZOV30008) 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, non-lactating 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; had an ability to read, comprehend, and record information and had completed a signed and dated written informed consent. Subjects were excluded from the study if they: had a 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 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 aciclovir, lidocaine, or other ingredients in the formulation; had 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; had 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	185	182
Completed, n (%)	182 (98)	179 (98)
Total Number Subjects Withdrawn, n (%)	3 (2)	3 (2)
Withdrawn due to Adverse Events, n (%)	1 (<1)	0
Withdrawn due to Lack of Efficacy, n (%)	NA	NA
Withdrawn for Other Reasons, n (%)	2 (1)	3 (2)
Demographics (FAS Population):	Aciclovir + Lidocaine (N=185)	Aciclovir (N=185)
Females: Males	137: 48	130: 52
Mean Age, years (standard deviation [SD])	37.5 (13.1)	37.2 (13.9)
White, n (%)	185 (100)	182 (100)
Primary Efficacy Results: (FAS Population)		
Time to onset of meaningful herpes labialis pain relief, minutes:	Aciclovir + Lidocaine (N=185)	Aciclovir (N=182)
Median, 50 th percentile	25.0	45.0
Adjusted geometric mean time to onset	31.9	53.5
Acceleration factor ^a (95% CI)	1.68 (0.95, 2.96)	
p-value	0.073	
Secondary Outcome Variable(s): (FAS Population)		
	Aciclovir + Lidocaine (N=350)	Aciclovir (N=350)
Duration of herpes labialis episode from start of treatment, days (ZOV30008 + ZOV30009):		
Median, 50 th percentile	4.70	4.72
Adjusted geometric mean duration of episode	4.52	4.44
Acceleration factor ^a (lower 97.5% confidence bound)	0.98 (0.91)	
	Aciclovir + Lidocaine (N=185)	Aciclovir (N=182)
Weighted mean reduction in herpes labialis pain score after first treatment application^b:		
Mean weighted mean reduction in pain score (SD)	-2.00 (1.65)	-1.61 (1.76)
Number (%) of subjects with weighted mean reduction in pain score:		
<-4	20 (11)	18 (10)

≥-4 and <-2	61 (33)	46 (25)
≥-2 and <0	83 (45)	78 (43)
≥0	19 (10)	39 (22)
Odds ratio for treatment (95% CI) ^c	0.63 (0.42, 0.93)	
Percent of time with meaningful herpes labialis pain relief after first treatment application^d:		
Mean percentage of time with meaningful herpes labialis pain relief (SD)	49.95 (41.01)	42.01 (43.23)
Number (%) of subjects with meaningful pain relief at percentage of time		
>50%	90 (49)	82 (45)
≤50%	93 (51)	100 (55)
Odds ratio for treatment (95% CI) ^c	0.94 (0.59, 1.49)	
Meaningful herpes labialis pain relief^e after second treatment application:		
Number (%) subjects meeting the meaningful relief criteria before or at 2 hours post treatment	130 (71)	106 (59)
Odds ratio for treatment (95% CI) ^c	0.60 (0.37, 0.98)	
Meaningful herpes labialis pain relief^e after third treatment application:		
Number (%) subjects meeting the meaningful relief criteria before or at 2 hours post treatment	147 (81)	121 (68)
Odds ratio for treatment (95% CI) ^c	0.49 (0.28, 0.85)	
Adequate relief from herpes labialis pain:		
Mean percentage of treatment applications yielding adequate relief from cold sore pain and discomfort (SD)	65.6 (36.2)	66.3 (34.0)
Number (%) of subjects achieving adequate relief from cold sore pain or discomfort from:		
100% of applications	58 (32)	56 (31)
70% to 100% of applications	47 (26)	47 (26)
<70% of applications	78 (43)	79 (43)
Odds ratio for treatment (95% CI) ^c	0.96 (0.64, 1.45)	
Duration of herpes labialis pain from start of treatment, days:		
Median, 50 th percentile	3.45	3.30
Adjusted geometric mean duration of herpes labialis pain	2.88	2.67
Acceleration factor ^a	0.93 (0.76, 1.13))	
<p>a Ratio of geometric means (aciclovir / aciclovir+lidocaine), based on accelerated failure time model containing main effects (centre/"cluster", initial stage of cold sore and pre-treatment pain score).</p> <p>b Weighted mean pain score after the first application (up to and including the second application pre-treatment pain score) minus the first application pre-treatment pain score.</p> <p>c Derived as common odds in favour of 'success' and ratio aciclovir / aciclovir+lidocaine from ordinal logistic regression model including effects for centre/"cluster", initial stage of cold sore and pre-treatment pain score.</p> <p>d Percentage of time between first and second applications during which the subject's pain score was at least 2 units below the pre-treatment value.</p> <p>e Defined as a 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>		
Safety Results: (FAS Population) - AEs were monitored throughout the subject's participation in the study. An on-therapy AE was defined as one that occurred during treatment.		
	Aciclovir + Lidocaine (N=185)	Aciclovir (N=182)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	32 (17)	10 (5)
Hypoesthesia	20 (11)	4 (2)
Cold sensations	4 (2)	0
Oral burning	2 (1)	0
Pruritus	2 (1)	3 (2)

Viral skin infections	2 (1)	1 (<1)
Application site complications	1 (<1)	0
Bacterial skin infections	1 (<1)	0
Burning sensations	1 (<1)	0
Hyposalivation	1 (<1)	0
Oral lesions	1 (<1)	0
Discomfort	0	1 (<1)
Eye edema and swelling	0	1 (<1)
Skin and subcutaneous operations	0	1 (<1)
Skin erythema	0	1 (<1)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Aciclovir + Lidocaine (N=185)	Aciclovir (N=182)
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

This study showed that there was no statistically significant difference between the aciclovir + lidocaine group and the aciclovir group in terms of time to onset of meaningful herpes labialis pain relief. In the aciclovir + lidocaine group, 32 (17%) subjects reported , with the most frequently reported being hypoesthesia and cold sensations. In the aciclovir group, 10 (5%) subjects reported AEs with the most frequently reported being hypoesthesia and pruritus. There were no SAEs, fatal or otherwise, reported during the study.

Publications:

No Publications

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