The Combination of Acyclovir 5% and Hydrocortisone 1% Cream (Xerese™) is Safe in Adolescents With Recurrent Herpes Simplex Labialis

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ABSTRACT

Hypothesis: Approximately 62% of adolescents have been infected with the herpes simplex type-1 (HSV-1) virus. Treatment should always be considered as oro-facial herpes can affect quality of life in adolescents in a negative way. Monotherapy with an anti-viral drug alone reduces virus replication; but might not alter the symptoms caused by the immune-mediated response to the virus. It is hypothesized that improved clinical benefit could be achieved with the administration of combination anti-viral and corticosteroid therapy by reducing the skin reaction caused by the immune-mediated response to the infection.

Materials and Methods: A Phase 3, one-arm, open-label, multicenter, subject-initiated study was designed to detect any possible safety concern following administration of combination 5% acyclovir and 1% hydrocortisone cream (ME-609, Xerese) in adolescents with recurrent herpes simplex labialis. Eligible subjects were 12–17 years of age with a history of recurrent labial herpes with ≥2 episodes during the last 12 months. Subjects were instructed to initiate treatment at the first signs or symptoms of a herpes recurrence, at the earliest prodromal phase and preferably before the presence of papule or vesicle. Subjects applied the cream topically 5 times per day for 5 days. Categorization of recurrence (ulcerative or non-ulcerative), maximum lesion area (maximum area of an ulcerative lesion), and adverse events (AE) were assessed.

Results: 134 subjects were analyzed for safety. Of the 131 who had data for categorization of recurrence at the post-treatment visit 3 weeks ±1 week after the last dose, 78 (59.5%) had non-ulcerative recurrences and 53 (40.5%) had ulcerative recurrences. All 131 subjects reached the stage of normal skin/no signs or symptoms at the follow-up visit. The mean±SD maximum lesion areas in the 53 subjects with ulcerative herpes lesion was 39±40.8 (range: 6–260) mm^2. There were 5 AEs reported by 5 subjects (secondary herpes labialis recurrences, n=2; infectious rhinitis, n=1; application site inflammation, n=1; bronchial asthma, n=1). There were no serious AEs; all AEs were of mild-to-moderate intensity.

Conclusions: The combination of 5% acyclovir and 1% hydrocortisone cream was safe and well tolerated in the treatment of recurrent herpes simplex labialis in adolescents.

INTRODUCTION

- Herpes simplex labialis (HSL), also known as cold sores or fever blisters, is a common recurring orofacial viral infection caused by herpes simplex virus (HSV); primarily HSV type 1 (HSV-1)[1,2]
- HSL is associated with significant morbidity, has a negative impact on health-related quality of life in adults[3] and adolescents, and is easily transmitted.
- Acyclovir 5% and hydrocortisone 1% (AHC) cream is approved as Xerese™ for the treatment of recurrent herpes labialis (cold sores) in the United States and as Xerclear™ in the European Union.
- Early treatment with topical AHC cream has been shown to reduce the likelihood of ulcerative cold sores and shorten the lesion healing time in adults[4]

OBJECTIVE

- Evaluate the safety of AHC cream for the treatment of herpes labialis recurrences in immunocompetent adolescents aged 12–17 years, following a 5-day treatment with 5-times daily topical administration of AHC cream

METHODS

Study Design

- Single-arm, open-label, multicenter, Phase 3 study conducted at 6 sites in Sweden and 20 sites in Russia between December 2006 and September 2007

Study Treatment

- Treatment was subject-initiated and consisted of application of AHC cream 5 times daily for 5 days at the first signs or symptoms of a herpes labialis recurrence (during the earliest prodromal period, preferably prior to the first clinical sign of a cold sore, and before swelling, blister, or later stages were present)
- An overview of the study design is presented in Figure 1. Definitions of stages and categories of HSL recurrences used in the study are presented in Figure 2.

Figure 1. Overview of Study Design

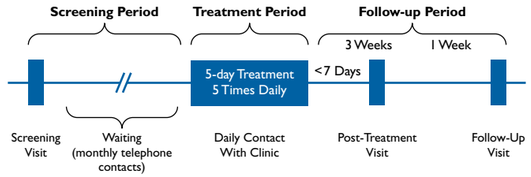
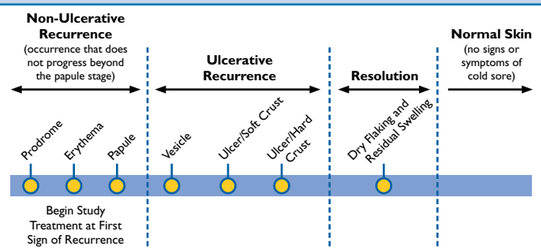


Figure 2. Definitions of Stages and Categories of HSL Recurrences Used in the Study



Patients

Inclusion Criteria

- Healthy male or female subjects 12–17 years of age with a history of recurrent HSL with at least 2 recurrences during the past year

Exclusion Criteria

- Use of other topical medical, over-the-counter, or cosmetic products in or around the oral area during the herpes recurrence
- Use of other topical or systemic antiviral agents or corticosteroids within the 2 weeks prior to inclusion
- Any evidence of an immunosuppressed state
- Significant skin conditions (such as atopic dermatitis, acne, eczema, psoriasis, or chronic vesiculobullous disorders) in the area of herpes recurrences
- History of hypersensitivity or serum sickness to any nucleoside analog antiviral agent, any topical steroid, or to the cream vehicle

Study Endpoints

- ***Adverse events*** from the start of treatment until the follow-up visit at 3±1 weeks after the last dose of the study medication
- ***Categorization of recurrence*** as either ulcerative or non-ulcerative
- ***Maximum lesion area***, measured as the maximum area of an ulcerative lesion, during the papular, vesicular, ulcerative, or hard crust stages

Statistical Methods

- All subjects who had applied at least one dose of study medication were included in the safety analysis set, which was the sole analysis set used. However, as treatment was dependent on a herpes labialis recurrence, not all included subjects were treated. Therefore, some data were recorded for the "included subjects set"
- Continuous data were presented with the number of observations, mean value, standard deviation (SD), minimum, median and maximum value; categorical data were summarized in frequency tables, by absolute and relative frequencies

RESULTS

Study Disposition

- Of the 254 subjects screened for and included in the study, 120 did not experience a study recurrence and were not treated
- In total, 134 subjects were treated with AHC cream and 132 subjects completed the study. Two subjects discontinued treatment (adverse event, n=1; diabetes, n=1)
- Baseline subject demographic and disease characteristics are shown in Table 1

Table 1. Demographic and Disease Characteristics in Subjects Treated With AHC Cream

	AHC Cream (n=134)
Demographic Characteristic	
Age at screening, years	
Mean (SD)	14.5 (1.7)
Range	12–17
Gender, n (%)	
Female	67 (50.0)
Male	67 (50.0)
Race, n (%)	
White/Caucasian	134 (100)
Herpes Simplex Labialis History	
Time since first episode, years[a]	
Mean (SD)	5.5 (2.8)
Minimum/Maximum	1.0/16.0
Number of recurrences in previous 12 months, n	
Mean (SD)	4.0 (2.2)
Minimum/Maximum	2.0/15.0

[a] n=131

Safety

- Treatment-emergent adverse events are summarized in Table 2. A total of 5 adverse events were recorded in 5 subjects during the study; 3 adverse events were of mild intensity and 2 were of moderate intensity
- Only 1 adverse event was considered to be related to the study medication (application site inflammation of moderate severity), leading this subject to withdraw from the study

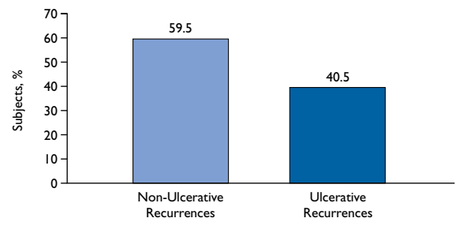
Table 2. Treatment-Emergent Adverse Events (TEAEs) in Subjects Treated With AHC Cream

	AHC Cream (n=134)		
TEAE, n (%)	**Overall**	**Mild**	**Moderate**
Any	5 (3.7)	3 (2.2)	2 (1.5)
Not related to treatment	4 (3.0)	3 (2.2)	1 (0.7)
Secondary oral herpes infection	2 (1.5)	2 (1.5)	0 (0)
Infectious rhinitis	1 (0.7)	1 (0.7)	0 (0)
Asthma	1 (0.7)	0 (0)	1 (0.7)
Related to treatment	1 (0.7)		
Application site inflammation	1 (0.7)	0 (0)	1 (0.7)

Categorization of Recurrences

- Of the 132 subjects with available recurrence data, herpes recurrence consisted of a single lesion in 126 subjects (95.5%), and 2 lesions in 6 subjects (4.5%), giving a total of 138 lesions (ulcerative or non-ulcerative)
- Of the 131 subjects who had data for categorization of recurrence at the follow-up visit 3±1 weeks after the last dose of AHC cream was applied, 78 (59.5%) had non-ulcerative recurrences and 53 (40.5%) had ulcerative recurrences (Figure 3)

Figure 3. Proportion of Ulcerative and Non-Ulcerative Herpes Labialis Recurrences in Immunocompetent Adolescents Treated With AHC Cream



Maximum Lesion Area

- The mean maximum lesion area in the 53 subjects with ulcerative herpes lesions was 38.8±40.8 (range: 6–260) mm^2. The maximum lesion area was recorded at the papule stage in 10 subjects
- Lesions healed completely in all evaluable subjects, with normal skin and no signs or symptoms at the follow-up visit

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CONCLUSIONS

- **Results of this study demonstrate that AHC cream was safe and well tolerated in the treatment of recurrent HSL in adolescents and no safety concerns were identified during the study**
- **The benefit of safe and effective treatment of this condition in adolescents and young adults should not be underestimated due to the potential social and psychological consequences**
- **Despite the self-resolving characteristic of HSL and subsequent latency, medical treatment for HSL should always be considered**

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