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A Single Application of Acyclovir Mucoadhesive Buccal Tablet Reduces Recurrence of Herpes Labialis in a Randomized Double-blind Phase 3 Study: Exploratory Results

Authors: S. K. Tyring[1], T. O. Bieber[2], O. Chosidow[3], M. Bloch[4], M. Lewis[5], M. Davis[6], P. Attali[7]

1. Dermatology, University of Texas Health Science Center, Houston, TX, United States. 2. Dermatology and Allergy, University of Bonn, Bonn, Germany. 3. Dermatology, Hopital Henri Mondor, Creteil, France.
4. Holdsworth House Medical Practice, Darlinghurst, NSW, Australia. 5. School of Dentistry, Cardiff University, Cardiff, United Kingdom. 6. Rochester Clinical Research, Rochester, NY, United States. 7. BioAlliance Pharma, Paris, France.

ABSTRACT

Objectives: Acyclovir mucoadhesive buccal tablet (ABT), is an innovative drug delivery system that provides high sustained-release local exposure to acyclovir in oral mucosa. ABT 50mg was reported in the LIP study to significantly reduce the time to healing (TTH) of vesicular lesions and increase the incidence of aborted episodes of herpes labialis (HL). A secondary endpoint was to examine incidence and time to next recurrence of HL.

Methods: In a randomized, multicenter, phase 3, double-blind, placebo-controlled study, 775 patients, (378 in the ABT group and 397 in the placebo group), with at least 4 recurrent HL lesions per year were treated. Participants self-applied a single ABT 50mg or placebo tablet as soon as prodromal symptoms occurred. 537 patients, 267 patients ABT and 270 placebo, agreed to participate in a 9-month follow-up evaluation for assessing whether one single dose administration of ABT could have an impact on incidence and time to the next recurrence of HL (TTR).

Results: Following a single application of ABT 50mg or placebo during the HL episode, a HL episode recurred during the 9-month follow up period in 64.2% of patients treated with ABT50mg vs 73.6% in the placebo group (p=0.027). The mean TTR in the ABT 50mg group (304±19.4 days) was significantly longer than that of the placebo group (199±9.3 days, Δ=105 days, Logrank test p=0.042). Good safety and tolerability were found in both ABT 50mg and placebo groups.

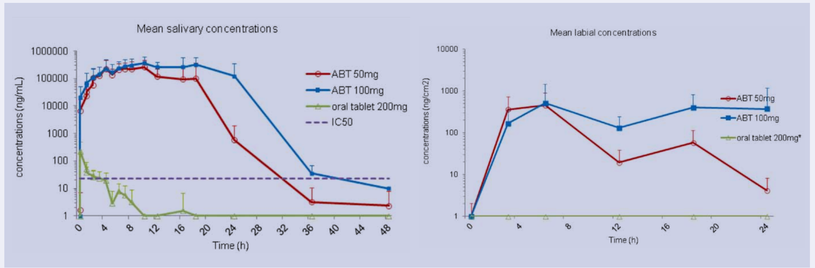
Conclusions: A single application of ABT 50 mg during the prodromal symptoms of HL reduces the incidence of the next recurrence and delays the recurrence of next herpes episodes. Thus ABT 50mg may modify the clinical course of labial herpes.

INTRODUCTION

Labial herpes is caused by herpes simplex virus (HSV). HSV replicates in the trigeminal ganglion and in the oral mucosa (basal layers). It is detected in herpes lesions and in saliva before and during herpes episodes. In patients with recurrent infections, oral acyclovir is the reference treatment and is administered 4-5 times/day because of its short half-life inside the infected cell (~1h).

ABT is a mucoadhesive buccal tablet of acyclovir 50mg to be placed on the gum.

It has been previously demonstrated [1,2] that a single application of ABT 50mg rapidly results in higher and more sustained acyclovir concentrations in saliva than those obtained with a single administration of oral acyclovir tablet 200mg (see figures below). High and sustained concentrations were also observed in the labial mucosa, whereas they were undetectable after administration of 200mg tablet.



A placebo-controlled, randomized, double-blind, self initiated treatment, multicenter phase 3 study assessed the efficacy of ABT 50mg vs placebo for the treatment of labial herpes in 771 patients. The time to healing (TTH) of primary vesicular lesions and mean duration of herpes episodes were significantly reduced in the ABT group. The incidence of blocked (aborted) episodes was significantly increased and the percentage of secondary vesicular lesions was reduced in ABT group. In the study, the effect of ABT on next recurrence was also assessed. Safety was good. [3,4]

	ABT 50 mg (n = 242)	Placebo (n = 279)	p
TTH of primary vesicular lesion (mITT population)			
Mean (days) ± SE	7.05±0.18	7.62±0.18	0.0150
Aborted episodes: n (%)	130 (34.9%)	109 (28.1%)	0.0419**
Duration of episode (Mean ± SE, **days)**	5.7±0.2	6.3±0.2	0.0033*
Non-primary lesions	10.4%	15.7%	0.037*

CI: confidence interval; n: number; SE: standard error;
*Log Rank test; **Chi Square test

OBJECTIVE

Given the low dose of acyclovir in ABT 50mg, but the rapid and high local exposure, it was considered mandatory to explore whether this treatment strategy would modify the natural history of labial herpes and in particular modify the incidence and delay of the next recurrence.

PATIENTS and METHODS

Inclusion/Exclusion Criteria - patients enrolled in LIP trial[3]: immunocompetent patients with at least 4 recurrent labial herpes episodes in the preceding 12 months.

- Having accepted to enter a 9-month follow-up evaluation

Method

- All patients contacted by phone every 3 months and an on site visit 9 months after inclusion in the follow-up
- Record of all episodes of labial herpes in a diary
- Treatment of episode according to current practice

Exploratory Endpoints

- Incidence and time to recurrence during the 9-month follow-up (FU- defined as the time from the healing of all lesions of the initial episode to the occurrence of new lesions)
- Incidence and time to recurrence during the 9-month follow-up in patients having applied ABT within the first hour after symptoms of the initial herpes episode

Statistical Analysis

- Kaplan Meier and log rank test (median, CI90) and Chi Square test

RESULTS

Study Population

- 537 / 775 of the LIP trial

Patients Characteristics

- No differences between the FU population and the LIP trial population showing that the subpopulation included in the follow up period was not biased.
- No differences between the ABT and placebo FU population at baseline (table below).

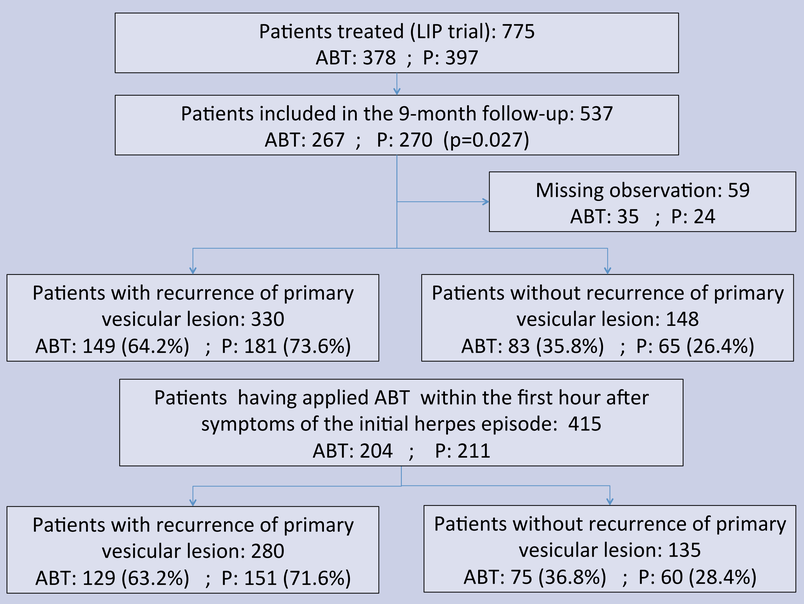
Baseline demographic characteristics of patients in the LIP study (FU population)

		ABT (n = 265)	Placebo (n = 270)
Women	N (%)	185 (69.8%)	183 (67.8%)
Age (years)	Mean ± SD	39.7± 13.4	41.3± 13.1
	Range	18 – 80	18 – 72
Ethnicity N (%)	Caucasian	253 (95.5%)	258 (95.6%)
	Black/African American	5 (1.9%)	2 (0.7%)
	Asian	2 (0.8%)	2 (0.7%)
	Hispanic or Latino	3 (1.1%)	3 (1.1%)
	Other	2 (0.8%)	4 (1.5%)
Previous episodes of herpes in last 12 months	At least	265 (100%)	270 (100%)
	> 4 Episodes	178 (67.2%)	196 (72.6%)
Duration of previous herpes episodes	Mean± SD	8.71 ± 2.91	8.43 ± 2.89
	Range	3 - 21	2.5 - 21

n, number; SD, standard deviation

Efficacy

- Recurrence of herpes episodes in the 9-month follow-up was reduced by 22.7%



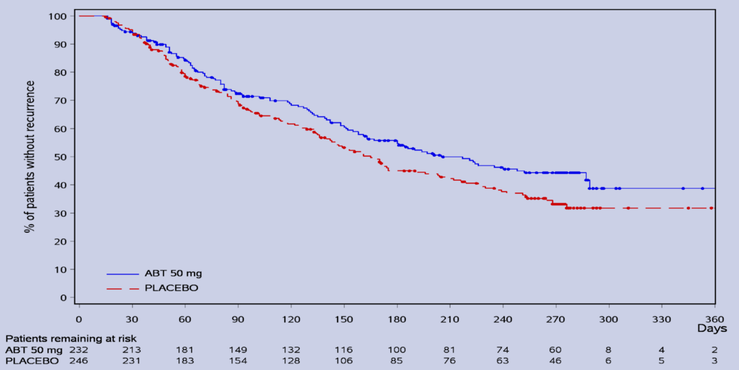
RESULTS

Efficacy (cont.)

- Median time to first recurrence of herpes episodes was significantly longer (p=0.041) in the ABT group (205 days) than in the placebo group (165 days)
- There was no statistical differences between patients having applied the tablet within one hour and those having applied it later during the initial herpes episode

Time to first recurrence of lesions	ABT (n = 242)	Placebo (n = 279)	p
Mean (days) ± SE	304 ± 19.4	199 ± 9.3	
Median (days) (95% CI)*	205 (163; 287)	165 (136; 203)	0.041
In patient applying the tablet within 1 hour (ABT: n= 204, Placebo n=211)			
Mean (days) ± SE	312 ± 20.6	203 ± 10.0	
Median (days) (95% CI)*	224 (180; 585)	170 (142; 212)	0.049

*Log Rank test



DISCUSSION

A one day administration of systemic antiviral drugs (valacyclovir 4g/d) was demonstrated to be effective in the treatment of labial herpes. The rationale was to deliver high concentrations of the antiviral agent at the replication site of the virus during its maximal replication[5,6].

No effect on long term recurrence has been reported for antiviral treatments. These exploratory data of the LIP trial demonstrated that ABT 50mg reduces the risk of recurrence by 22.7% in a 9-month follow up and delays the recurrence by a mean of 105 days in patients whose herpes lesions recurred. Rapid, high and sustained acyclovir concentrations in saliva and labial mucosa, at the site of viral reactivation and during the maximal replication phase, may reduce the mucosal viral load and thus delay the recurrence of the next herpes episodes. However, these data on incidence and delay of the next recurrence deserves further confirmation as they were obtained on a subset of patients. If confirmed, this "delayed" effect may also reduce the interindividual transmission of HSV-1 through a decrease in the oral shedding of patients with frequent HL episodes.

CONCLUSION

A single unique application of ABT 50 mg in immunocompetent patients is efficacious for the episodic treatment of recurrent HL infection and delays the time of onset to next recurrence of HL.

It may modify the paradigm of labial herpes treatment and deserves further investigations.

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DISCLOSURES

This study was sponsored by BioAlliance Pharma and conducted by Orion Clinical.
Pierre Attali is employee and shareholder of BioAlliance Pharma.
Olivier Chosidow has served as consultant or has received research grants from BioAlliance Pharma.

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