CLINICAL STUDY REPORT

1 TITLE PAGE

Study Title:	A Randomised, Double-Blind, Single dose, One-Day Early Administration, Multicentre Study comparing the Efficacy and Safety of Acyclovir Lauriad™ 50 mg muco-adhesive buccal tablet to matching Placebo, in the Treatment of Herpes Labialis in Immunocompetent Patients
Investigational Product:	Acyclovir Lauriad™ 50 mg Muco-adhesive Buccal Tablets
Indication Studied:	Labial Herpes
Description of Study:	Randomised, double-blind, single dose, one-day early administration, multicentre study comparing acyclovir Lauriad™ 50 mg muco-adhesive buccal tablet to matching placebo (randomisation in a 1:1 ratio)
Name of Sponsor:	BioAlliance Pharma
Protocol Number:	BA2005/21/02
Development Phase:	Phase III
First Patient Screened:	23 March 2007
First Patient Enrolled:	04 April 2007 (first randomisation)
Last Patient Completed:	Last patient treated: 13 October 2008 Last patient completed follow-up period: 04 September 2009
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GCP Compliance:	This study and the archiving of essential documents were performed in compliance with Good Clinical Practice (GCP).
Date of the Report:	Final; 04 August 2011

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2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
BioAlliance Pharma</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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Page</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Acyclovir Lauriad™ 50 mg Muco-adhesive Buccal Tablets</td></tr>
<tr><td>Name of Active Ingredient:
Acyclovir</td></tr>
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A Randomised, Double-Blind, Single dose, One-Day Early Administration, Multicentre Study comparing the Efficacy and Safety of Acyclovir Lauriad™ 50 mg muco-adhesive buccal tablet to matching Placebo, in the Treatment of Herpes Labialis in Immunocompetent Patients</td></tr>
<tr><td colspan="3">Investigators:
Australia: Site 101: Dr Fiona Bisshop; Site 102: Dr Mark Bloch; Site 103: Dr Neil Bodsworth.
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<tr><td colspan="3">Study Centres:
The study was conducted in 47 sites in Australia, the Czech Republic, France, Germany, Poland, the UK and the USA.</td></tr>
<tr><td colspan="3">Publication (Reference):
Not yet published</td></tr>
<tr><td colspan="2">Study Period:
First patient screened: 23 March 2007
First patient randomised: 04 April 2007
Last patient completed study treatment: 13 October 2008
Last patient completed follow-up: 04 September 2009</td><td>Phase of Development:
Phase III</td></tr>
</table>

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Objectives:

Primary Objective: To demonstrate the efficacy of a single dose of acyclovir Lauriad™ 50 mg muco-adhesive buccal tablet (ABT) versus a single dose of matching placebo on the primary vesicular lesion of labial herpes

Secondary Objectives:

- To compare the efficacy of ABT 50 mg versus placebo on:
  - The evolution of prodromal symptoms to aborted lesions;
  - The healing of non primary lesions;
  - The duration of herpes episode;
  - The duration of symptoms;
  - The healing of aborted primary lesions;
  - The healing of intra-oral and mucosal non primary lesions;
  - The incidence of and time to recurrence during 9 months following treatment (ancillary study in selected centres);
- To compare the local tolerability and general safety of ABT 50 mg to those of placebo;
- To evaluate the concentration of acyclovir in saliva (ancillary study in selected centres) and to assess its relationship with viral load in saliva and efficacy criteria;
- To evaluate the adhesion time of ABT (50 mg), the incidence of detachment and/or swallow within 6 hours post-dosing and the number of tablets replaced.

Methodology:

Randomised, double-blind, single dose, one-day early administration, multicentre study comparing ABT 50 mg to matching placebo (randomisation in a 1:1 ratio)

Number of Patients (Planned and Analyzed):

Planned: 1950 patients were to be randomised. 780 patients were planned to be included and treated in order to get 380 patients with vesicular lesions (190 patients /treatment group: mITT population) and 1170 patients were planned to be randomised but not treated.

Actual: 1944 patients were screened and 1721 were randomised. 775 patients were treated; 378 patients in the Lauriad™ 50 mg group and 397 patients in the Placebo group. 521 patients had a primary vesicular lesion and formed the mITT population.

Diagnosis and Main Criteria for Inclusion:

- Male or female
- Age > 18 years
- History of recurrent herpes labialis lesions where:
  - Recurrence was defined as at least 4 episodes in the preceding 12 months
  - Herpes labialis lesions were characterised by their localisation on the cutaneous and/or mucosal surfaces of the lips.
- At least 50% of previous episodes were to have produced classical lesions to the vesicular stage (i.e. episodes that progressed through macula, papule, vesicle, crust and healed);
- Prodromal symptoms (itching, tingling, pain etc.) should have preceded herpes labialis lesions in at least 50% of the recurrent episodes

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- Good general health (Eastern Cooperative Oncology Group < 2), immunocompetent
- Women of childbearing potential were to use an effective contraception method
- Subjects were to agree to abstain from any mechanical disruption of the prodromal area or lesion (i.e. scrubbing, lancing, shaving the area, rubbing with alcohol...)
- Signed and dated written informed consent

Patients who did not develop herpes episodes within 6 months after their randomisation in the study were to be excluded. They were required to return their study medication to the investigating site.

Test Product, Dose and Mode of Administration, Batch Number:
ABT 50 mg: one tablet for one day of treatment. The tablet was to be applied and stuck to the upper gum in the slight depression known as the canine fossa after correct positioning.
Batch number: CPM6639

Duration of Treatment:
1 day

Reference Therapy, Dose and Mode of Administration, Batch Number:
Matching placebo muco-adhesive buccal tablet: one tablet for one day of treatment.
Batch number: CPM6640

Criteria for Evaluation:
Primary criterion: Time To Healing (TTH) of primary vesicular lesion
Secondary criteria:
1. Abortion of primary lesion
2. TTH of all non-primary lesions (aborted lesions excluded)
3. Duration of episode
4. Time to cessation of symptoms
5. TTH of aborted primary lesion
6. TTH of intra-oral/mucosal non primary lesions
7. Relationship between saliva viral titre, acyclovir saliva concentration and efficacy parameters.
8. Adhesion time of acyclovir and placebo tablets, incidence of detachment and/or swallow within 6 hours post-dosing, and the incidence of tablet replacement
9. Incidence of and time to recurrence of non aborted lesions during 9-month follow-up (evaluated in selected centers)
10. The nature, incidence and severity of adverse events (AEs) through the spontaneous reporting, biological safety evaluated by lab tests, and local tolerability using self-questionnaire and gingival index.

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Statistical Methods:

Sample Size Calculation and Hypothesis

The explicit intention of the trial was to perform a comparison (two-sided log-rank test) on the time to healing of primary vesicular lesion considered as time-to-event data. The null hypothesis (H0) corresponded to the absence of difference between treatment groups (hazard ratio = 1.00) and the alternative hypothesis (H1) retained was a hazard ratio of 1.40, with type I error of 5% and type II error of 10%. Under these assumptions, the required total sample size was 380 patients in the modified intention to treat (mITT) population (190 per treatment group). The study was to be completed once a total of 380 patients having reached the vesicular stage were treated. Based on literature data, it was calculated that the mITT population represented 60% of the intention to treat (ITT) population (treated patients). However, an ongoing review of recruitment showed that this proportion was closer to 35% - i.e. the mITT population represented one third of the randomized population, therefore it was expected that the study would be completed after 634 patients were treated and approximately 1900 patients were randomized.

Statistical Methods

Three populations were defined in the protocol:

- The ITT population (also the safety population) included all randomised patients who took at least one dose of the study medication.
- The mITT population included all randomised patients who took at least one dose of the study medication and who reached the vesicular stage. This was the primary population for the primary efficacy endpoint.
- The PP population involved patients of the mITT population who applied MBT within one hour of prodromal symptoms, had no major protocol deviations including violation of inclusion/exclusion criteria, had information on time to healing (TTH) and had no intake of forbidden medications.

In general, categorical data were presented using counts and percentages, whilst continuous variables were presented using the mean, standard deviation (SD), median, minimum, maximum, number of observations and number of missing observations.

The primary endpoint (TTH in the mITT population) was compared between treatment groups by using a log-rank test and including 95% confidence intervals (CIs) for hazard ratios and median times. The same approach was followed on the other time-to-event secondary criteria (e.g. duration of episodes in the ITT population). Proportions of patients were compared between treatment groups using a chi-square test and estimates and 95% CI for the difference in proportions between treatments were provided. Additional explanatory analyses investigated the influence of treatment delay (taken as a covariate) and herpes location (subgroup analyses).

Safety analysis was descriptive.

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Summary – Conclusions:

Patient Disposition

A total of 1727 patients were included and 1721 were randomised to treatment. A total of 775 patients self initiated treatment (acyclovir (ABT): 378, placebo (P): 397). Thirty patients dropped out (ABT: 17, P: 13), 20 for non compliance or deviations to the protocol (ABT: 13, P: 7), 1 patient (ABT) for the absence of herpes lesions and 3 (P) for inefficacy

Treatment groups in the ITT population were balanced at baseline with respect to gender, age, race, physical examination and laboratory tests. The duration of previous herpes episodes was slightly higher in the ABT than in the placebo group

Efficacy Conclusions

There was an uneven distribution of patients between ABT and placebo groups within vesicular and aborted lesions. More placebo-treated patients had vesicular lesions and more ABT-treated patients had aborted lesions (p=0.042). This imbalance, observed after randomization and start of treatment, introduced a bias in the analysis of the primary endpoint (TTH of primary vesicular lesion: mITT population) and mITT patients in the ABT group likely had initially more severe herpes episodes than those in the mITT placebo group.

Primary endpoint:
ABT significantly reduced the TTH of primary vesicular lesion as compared to placebo (median: 7.00 (6.75; 7.31) days vs 7.32 (6.97; 7.92), log rank test p=0.015) in the 521 patients of mITT population. The magnitude of clinical effect was certainly underestimated in this trial due to the abovementioned bias.

Secondary endpoints:
The proportion of patients in the ITT population (n=771) with lesions not progressing beyond the papule stage (aborted herpes episodes in patients with prodromal symptoms) was significantly greater (p=0.042) in the acyclovir group (130/372 patients: 34.9%) than in the placebo group (109/388 patients: 28.1%). This was a 24.2% increase in the incidence of aborted episodes in the ABT group as compared to the placebo group. The TTH of aborted episodes was not different (log rank test p=0.80) in the ABT (median: 2.57 (2.00; 2.96) days) and placebo MBT groups (median: 2.67 (2.10; 3.04) days).

Only 101 patients (13.1%) in the ITT population had non-primary lesions. The number of patients with non primary lesions was slightly lower in the ABT group (39/376: 10.4%) than in the placebo (62/395: 15.7%) group, a reduction in incidence of 33.8%. The TTH of non-primary vesicular lesions was markedly but not significantly reduced (p=0.068) in the ABT group (median: 7.70 (5.53; 8.70) days) as compared to the placebo group (median: 9.08 (7.46; 11.00) days).

The duration of herpes episode in the ITT population (n=771) was significantly shorter (p=0.003) in the ABT group (median 5.57 (5.03; 6.01) days) than in the placebo group

(median: 6.38 (5.93; 6.97) days).

The time to cessation of symptoms in the ITT population was reduced in the ABT group (median: 3.57 (3.04; 4.01) days) as compared to the placebo group (median: 4.16 [3.75; 4.89] days). The difference was statistically significant (p=0.010).

The TTH of intra-oral/mucosal non-primary lesions was not evaluable due to the very small number of patients (N=18, ABT: 8, P: 10).

The number of patients with recurrence of lesions among the 537 who accepted to record herpes episodes for 9 months after the single dose treatment was lower in the ABT group (n=149/267, 64.2%) than in the placebo group (181/270, 73.6%). The median time to recurrence of non-aborted lesions during a 9-month follow-up was 40 days longer (p=0.041) in the ABT group (205 days) than in the placebo MBT group (165 days).

Symptoms intensity recorded by patients using a visual analogue scale rapidly decreased from treatment application up to day 14 in both groups. The decrease was more rapid and more marked in the ABT group than in the placebo group and statistically significant (p=0.008) at Day 5: 12.7±17.6 mm versus 17.3±20.7 mm respectively.

Most patients were satisfied with the treatment. Satisfaction was reported more frequently (p=0.002) by patients treated with ABT (297/363 patients: 81.8%) than by those treated with placebo MBT (275/380 patients, 72.4%). Likewise, treatment was considered efficacious more frequently in the ABT group (very active: 154/353 patients, 43.6%) than in the placebo MBT group (146/373 patients, 39.1%) and the difference was statistically significant (p=0.0477 [Cochran-Mantel-Haenszel test]).

Acyclovir concentrations in saliva are given in an addendum to the report.

Safety Conclusions

ABT and placebo MBT adhered to the gum for more than 6 hours in 331/376 (88.0%) and 343/395 (86.8%) patients respectively. The MBT was replaced according to protocol instructions by 33/43 (76.7%) and 35/50 (71.4%) patients with MBT adhesion < 6 hours respectively. MBTs were swallowed by 12 and 15 patients respectively and no AEs related to swallowing were reported.

There was no major safety issue during the LIP trial. In the ABT group, 60/378 (15.9%) patients reported 78 Treatment Emergent Adverse Events (TEAE) versus 60/397 (15.1%) patients reporting 84 TEAEs in the placebo group. There was no treatment discontinuation due to TEAE. One SAE was reported in the placebo group. Thirty-one related TEAEs were reported by 27 patients (7.1%) in the ABT group versus 47 related TEAEs in 31 patients (7.8%) in the placebo group. There were no differences in the nature and severity of TEAEs between treatment groups. The most frequent TEAEs were headache (ABT: 3.2% versus placebo: 3.0%) and application site pain (ABT: 1.1% versus placebo: 1.0%). There were no other TEAEs reported with an incidence >1%. There were 414 patients taking at least one concomitant medications, 193/378 (51.1%) in the ABT group and 221/397 (55.7%) in the

placebo group. The nature and the incidence of TEAE in patients receiving concomitant treatments were not different from those without concomitant treatments.

Local tolerability was good: application site TEAEs (discomfort, pain, irritation, erythema, paresthesia) were reported in 9 patients in the acyclovir group versus 6 in the placebo group. A mild inflammation of the gum (gingival index) was recorded slightly more frequently (p=0.079) the day following the application of MBT in the ABT group (n: 15/226, 6.6%) than in the placebo MBT group (n: 6/240, 2.5%). The gingival index returned to pre-treatment values within 2 days. There were no differences between treatment groups. There were no clinically relevant changes in vital signs and no clinically relevant abnormalities in laboratory tests in either group.

Overall Conclusions

The application of a single dose of ABT after the occurrence of prodromal symptoms was shown to be efficacious in the treatment of labial herpes in this randomised, double blind, placebo-controlled patient-initiated trial in 775 patients. ABT significantly reduced the TTH of the primary vesicular lesion (p=0.015), significantly increased by 24.2% (p=0.042) the number of aborted herpes episodes (episodes not progressing beyond the papule stage). In addition, ABT significantly reduced the overall duration of the herpes episode (p=0.003) and symptom intensity (p=0.008 at day 5) as compared to placebo. The duration of symptoms (pain, tingling…) was also markedly reduced but the difference was statistically significant (p=0.010). A single application of ABT significantly reduced the number of patients with at least one recurrence of herpes episode [ABT: n=149/267, 64.2%) versus placebo: n=181/270, 73.6%)] in the 9-month follow up and the median time to recurrence was delayed by 40 days (p=0.041) in the ABT group as compared to the placebo group. ABT was well tolerated the incidence of TEAE (15.9%) was identical to that of placebo (15.1%); there were no differences in the nature (headaches 3.2% vs 3.0%, application site pain: 1.2% vs 1.0%) and the severity of TEAEs. There were no SAE and no unexpected TEAE. Local tolerability was good.

This large multicentre, randomised, placebo-controlled, patient-initiated study showed a single application of ABT to be an efficacious and well tolerated treatment of labial herpes that may delay the recurrence of the next episodes.

Date of the Report:
Final; 04 August 2011