LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sitavig
(aciclovir)

SE/H/1123/01/DC

This module reflects the scientific discussion for the approval of Sitavig. The procedure was finalised 2012-12-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

BioAlliance Pharma has applied for a marketing authorisation for Sitavig, muco-adhesive buccal tablet, 50 mg. The active substance is aciclovir. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Sitavig is presented in the form of muco-adhesive buccal tablets providing slow delivery of aciclovir in the oral cavity. Each tablet contains 50 mg of aciclovir. The excipients are microcrystalline cellulose, hypromellose, magnesium stearate, milk protein concentrate, povidone, colloidal anhydrous silica and sodium laurilsulfate. The muco-adhesive buccal tablets are packed in blister packages.

II.2 Drug Substance

Aciclovir is described in a Ph. Eur. monograph.

Aciclovir is a white or almost white, crystalline powder. It is slightly soluble in water, freely soluble in dimethyl sulphoxide and very slightly soluble in ethanol (96 per cent). The structure of aciclovir has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification is in accordance with the Ph. Eur. monograph.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Sitavig muco-adhesive buccal tablets are formulated using excipients described in the current Ph. Eur., except for the milk protein concentrate which is controlled according to an acceptable in house specification. All raw materials used in the product are of vegetable origin/comply with the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the temperature storage restriction "Do not store above 30°C".

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Aciclovir is a widely used antiviral agent with activity against HSV-1, HSV-2 and varicella zoster virus. Selectivity is due to phosphorylation by viral thymidine kinase followed by phosphorylation by cellular enzymes to the active triphosphate form. While resistance to aciclovir is rare it is known to occur in immunocompromised patients. The buccal aciclovir tablet is expected to provide local concentrations that are largely above that for resistant strains.

III.2 Pharmacokinetics

No specific data has been provided. Drug interactions are not expected as systemic absorption is expected to be low and plasma protein binding is low. However, depending on type of diet and liquids, local interactions may be relevant.

III.3 Toxicology

The toxicity of aciclovir is well known. In single dose toxicity studies only very high doses of aciclovir were toxic. At high intravenous doses renal damage can occur and plasma levels measured in toxicology studies were very high and correlated with renal injury. These high levels probably reflected accumulation of the drug secondary to renal tubular obstruction since the main pathway for aciclovir excretion is the kidney. Aciclovir has a relatively low solubility in the urine. In dog, loosening and loss of some toenails as well as footpad ulceration were considered to be related to the acute toxicosis in the initial high dosage groups (45 and 150 mg/kg/day) in the first two weeks of a 12-month repeat-dose toxicity study. After lowering the dose regeneration was apparent.

Aciclovir had no effect on reproductive processes or prenatal, perinatal and postnatal development of offspring in studies conducted in rats, mice and rabbits. Aciclovir was not mutagenic but caused chromosomal damage *in vitro* at very high doses. *In vivo*, aciclovir was found not to be clastogenic in mice. It induced chromosomal damage at extremely high doses in hamsters (dose levels of 500 and 1000 mg/kg corresponding to 602 to 1205 times the human dose level), but did not induce chromosomal damage in bone marrow cells of rats at doses up to 100 mg/kg. Aciclovir was not carcinogenic in any of the species tested (rat, mouse). Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats and mice.

A local tolerance study on the jugal mucosa of hamster did not reveal any toxicity. There were no significant effects after seven days of placing an ABT 50 mg in hamster cheek pouch.

III.4 Ecotoxicity/environmental risk assessment

An environmental risk assessment is available. Following prescribed use the risk to the environment is likely low.

III.5 Discussion on the non-clinical aspects

The potential for systemic toxicity after a single buccal tablet is considered negligible.

IV. CLINICAL ASPECTS

IV.1 Introduction

Labial herpes, also known as cold sores or fever blister, is the most common recurrent infection caused by HSV-1 with considerable incidence (85% of the world population is seropositive for HSV-1). It is aesthetically unpleasant and induces considerable discomfort to patients. It may deteriorate quality of life and results in sick leaves in 6.5% to 12.5% of patients with frequent recurrences. Labial herpes typically resolves spontaneously within 7-14 days. About 25% of all episodes do not progress beyond the papule stage and are considered as "aborted" episodes. Drugs presently recommended as first line treatment of HSV disease belong to the class of nucleoside analogues: aciclovir and its prodrug valaciclovir, penciclovir and its prodrug famciclovir.

Sitavig has been approved for the treatment of episodes of recurrent herpes labialis in immunocompetent adults. The active substance, aciclovir has been approved and widely used for the treatment of cold sores for over 20 years. Millions of patients in numerous countries, including Europe and the United States, have been treated with products containing aciclovir and a favourable safety profile is well established.

IV.2 Pharmacokinetics

The pharmacokinetic data of aciclovir following administration of Sitavig 50 mg buccal tablet was obtained in one study performed in 12 healthy volunteers. In a phase III study, saliva concentration of aciclovir was determined in 56 patients at one time point within 24 hours after Sitavig application.

Sitavig 50 mg buccal tablet is intended for a single-dose administration. In the healthy volunteers, the plasma exposure after Sitavig 50 mg application was much lower compared to administration of an oral 200 mg aciclovir tablet (Zovirax®) (see Table below). The low plasma exposure enables dosing in patients with renal impairment without any dosage adjustment. In addition, the potential for drug-drug interactions is considered low.

The plasma exposure following administration of Sitavig 50 mg buccal tablet and Zovirax 200 mg oral tablet, respectively, in healthy volunteers (n=12)

	Sitavir, 50 mg		**Zovirax®, 200 mg**	
	mean[a]	*sd*	*mean*[a]	*sd*
C_{max} (ng/mL)	28	11	296	168
$AUC_{0\text{-}48\ h}$ (h·ng/mL)	225	132	1603	682

High, sustained salivary concentrations of aciclovir were determined after administration of Sitavig 50 mg buccal tablet to healthy volunteers. These salivary concentrations were reported to be above the IC_{50}-value (here defined as 22.5 ng/mL) of aciclovir against HSV-1 for at least 24 hours. The concentration of aciclovir determined in salivary samples taken from patients in the phase III study are in agreement with results from the healthy volunteers.

Concentrations of aciclovir in the labial mucosa were determined by means of labial stripping in healthy volunteers. The subjects were divided into two groups, which were sampled either at pre-dose, 3, 12, and 24 h after administration, or at predose, 6, 18, and 24 h after administration. The labial concentrations displayed a large inter-individual variability, but were estimated to be much higher than the IC_{50} value of aciclovir. At 24 h after application of Sitavig, *i.e.* the last sample, concentrations were detectable in three out of the 12 healthy volunteers. The data from the labial stripping procedure should be interpreted with caution, due to the uncertainty in the data caused by a risk for sample contamination and high inter-individual variability.

The aciclovir concentration in saliva and labial mucosa and the correlation of these with the IC_{50} value of aciclovir are difficult to interpret. Further clarification of the precise role of saliva and labial mucosa as vehicle for aciclovir to the site of action, however, was not considered a condition for approval.

IV.3 Clinical efficacy

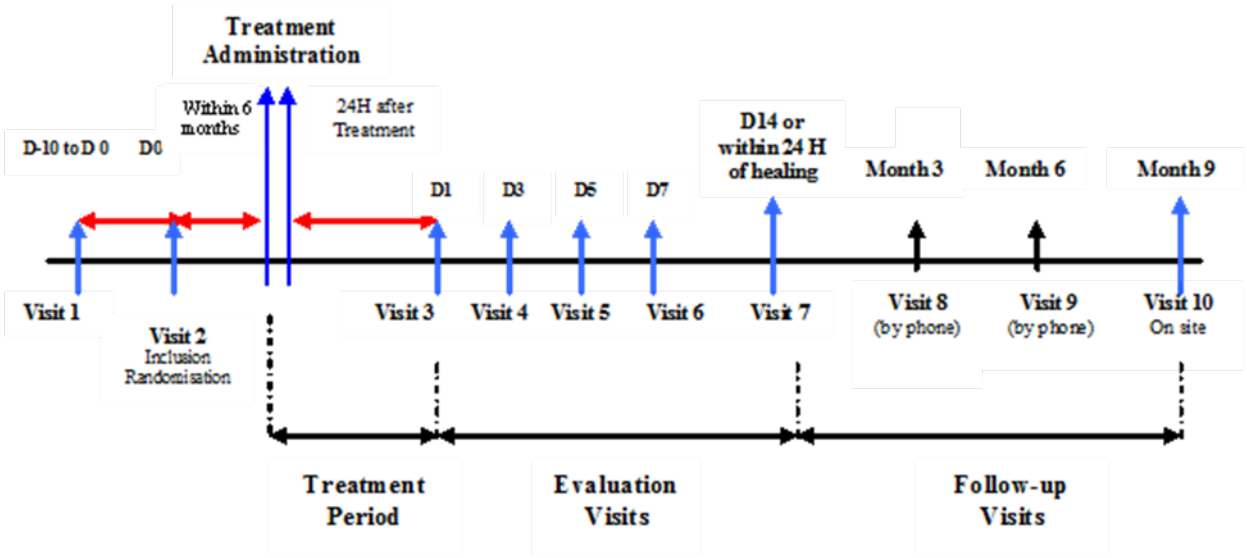
One phase III clinical trial supports the efficacy of Sitavig 50 mg for the treatment of orofacial herpes. This study (BA2005/21/02) forms the basis for this Marketing Authorisation Application. This was a randomised, double-blind, patient-initiated, single dose multicentre study comparing Sitavig 50 mg with matching placebo (randomisation in a 1:1 ratio) in immunocompetent patients suffering from recurrent labial herpes.

Patients were male or female, age > 18 years, and had a history of recurrent herpes labialis lesions. They needed to be deemed immunocompetent, as stated above, and without significant co-morbidities, including no HIV infection or significant abnormalities of s-creatinin.

The study duration for each patient included a screening period of 10 days maximum (Screening; Visit 1) before randomisation (Day 0; Visit 2). The patient then had to wait for a new labial herpes episode to occur. If the patient did not experience an episode of labial herpes within the 6 months after randomisation, he/she was excluded from the study. As soon as the patient experienced prodromal symptoms, he/she self-initiated his/her treatment by positioning the tablet with a finger on the side of the lesion on the upper gum, in the slight depression known as the canine fossa. Treatment was to be applied within one hour after the onset of prodromal symptoms and before the appearance of any signs of labial herpes lesions.

After initiation of treatment, the patients were under evaluation up to Day 14, or up to the healing of primary lesions, whichever came first. Patients were to complete a patient diary composed of a self-questionnaire and visual analogue scale (VAS) daily in the evening to record their symptoms and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, crust).

Figure 1 Study Flow Chart



Objectives

The primary objective was to demonstrate the efficacy of a single dose of Sitavig 50 mg versus a single dose of matching placebo on the primary vesicular lesion of labial herpes.

Endpoints

The primary endpoint of the trial was to compare the time to healing (TTH) of the primary vesicular lesion considered as time-to-event data in the Sitavig 50 mg group versus the placebo group. Healing was defined as the loss of crust. This was to be assessed by the investigator.

Secondary endpoints included:

- The incidence of aborted lesions (herpes lesions that did not progress beyond the papule stage, preceded by recorded prodromal symptoms)
- The TTH of non-primary lesions
- The duration of herpes episode
- The duration of symptoms
- The TTH of aborted primary lesions
- The TTH 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)

Sample size

The primary objective of the trial was to compare (two-sided log-rank test) the TTH of the primary vesicular lesion considered as time-to-event data in the Sitavig 50 mg group versus the placebo group. A hazard ratio of 1.40 with type I Error of 5% and Type II Error of 10% was considered clinically relevant. Under this assumption, 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 who 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), therefore it was expected that the study would be completed after 634 patients were treated. In the literature, the mITT population represents one fifth of the randomised population; therefore, it was expected that approximately 1950 randomised patients would be required.

Statistical methods

The following populations were used in the analysis of the study data:

Intention to Treat (ITT) Population: includes all randomised patients who took at least one dose of the study medication and had complete information recorded for application time. ITT population was also to be the safety population.

Modified Intention to Treat (mITT) Population: includes 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.

Per Protocol (PP) Population: was a sub-group of the mITT population including patients without major protocol deviations, insufficient TTH data and no intake of concomitant medications The 1-hour application delay was not considered as a major protocol deviation considering that application was at prodromal stage. This definition of the PP population was finally decided during the blind review.

Follow up (FU) population: The FU population is a subgroup of the ITT population who continued into the 9 month follow up period and had at least one diary assessment during that period. The FU population is defined as patients whose lesions were all healed at the end of the short term part of the trial with an additional condition of no recurrence within 15 days of healing of all lesions. This population had not been defined in the protocol or statistical analysis plan.

Primary Endpoint: TTH of primary vesicular lesion
Patients were observed up to Day 14; therefore, those patients who did not heal were censored at Day 14. Patients who withdrew before Day 14 and before healing were also censored. If a date was available but no time (for either application or assessment) then the time to event/censoring was taken to be number of days (end date – start date) multiplied by 24.

A log rank test was performed to compare the treatment groups throughout the 14 day period.

Assessment of the study design
On the whole, the study design and population is characteristic of studies conducted for this indication, with drugs such as aciclovir (systemic and topical), valaciclovir, penciclovir and famciclovir. The follow-up of patients to document time to recurrence after treatment of a

herpes labialis episode, however, appears not to have been performed in prior studies in the field.

The use of placebo as a comparator is appropriate, given the benign and self-limiting nature of the disease, and the limited efficacy of available therapies.

The primary objective is the customary in trials of the treatment of herpes labialis episodes.

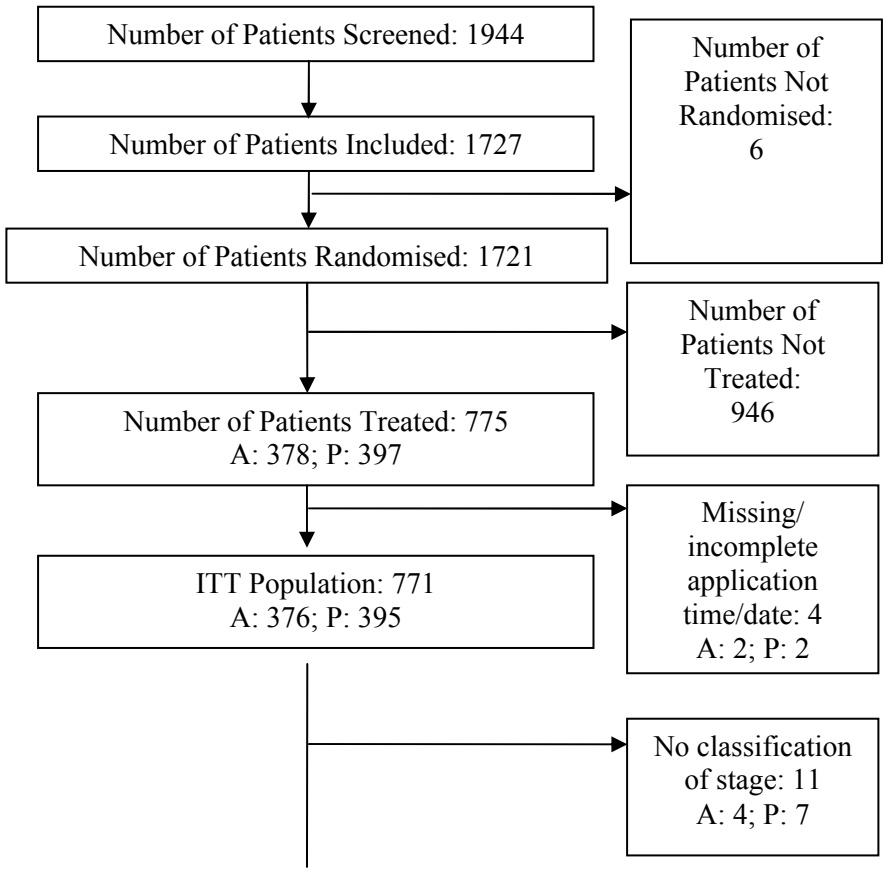
The definition and evaluation of the primary endpoint was in concordance with what is usual in this indication. It is noted that only patients who developed vesicular lesions would be included in the primary efficacy variable. Thus, if the drug impacts the proportion of patients developing vesicular lesion (i.e increases the proportion of patients with "aborted" lesions), a selection bias favouring the control regimen may occur in the primary efficacy population.

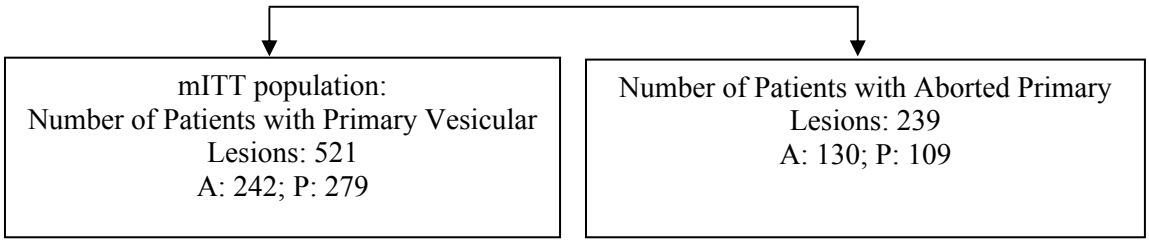
It is notable that, despite five different secondary endpoints, there was no adjustment for multiple testing or any pre-defined hierarchy of statistical tests.

- **Participant flow**

This was a multi-centre study conducted in 47 sites in Australia, the Czech Republic, France, Germany, Poland, the UK and the USA. A total of 1950 patients were to be randomised. 780 patients were to be included and treated (390 patients/treatment group) and 1170 patients were to be randomised but not treated. A total of 1727 patients were included and 1721 were randomised to treatment. Patient disposition is summarized in Table 1 below:

Table 1 Patient Disposition (All Patients)





A: ABT 50 mg group; P: Placebo group
Refer to Tables 14.1.1 and 14.2.2.1.1

Mean age of study participants was 41 years, 95% were Caucasian, mean weight 72kg. baseline characteristics were well balanced between groups.

- **Outcomes and estimation**

Primary Endpoint: Time to Healing of Primary Lesion
The primary end-point was Time To Healing (TTH) of primary vesicular lesion. Healing was defined as the loss of crust. Erythema may have been present. This was to be assessed by the investigator. The TTH was the time from the treatment initiation (date and hour recorded) to the healing as defined above. The primary vesicular lesion was the first developed lesion. It should have been located on the lip and should not have extended more than 1 cm outside the lip. Pure intra-oral lesions were not considered to be primary lesions. TTH was assessed by the investigator who used the patient diary to better define the exact hour of lost of crust.

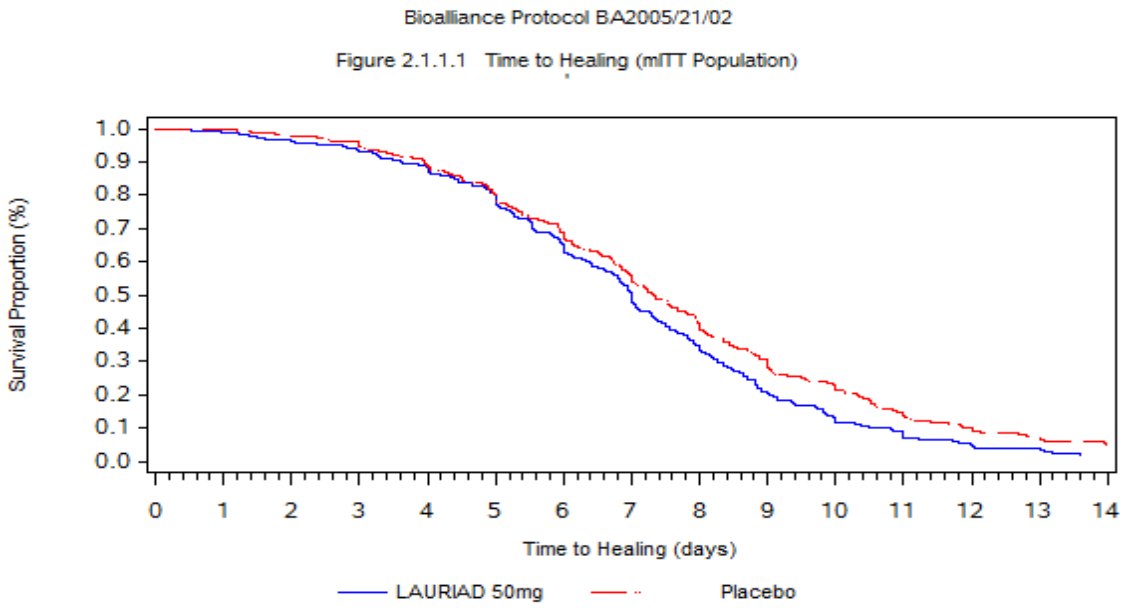
TTH of the primary vesicular lesion was statistically significantly shorter in patients treated with Sitavig 50 mg than in those treated with placebo (Log Rank Test: 0.0150). The median difference was 0.32 days (Refer to Table 2).

Table 2 Time to Healing (mITT Population)

	ABT 50 mg N=242	Placebo N=279	Total N=521
Patients (N [%])	242 (100.0%)	279 (100.0%)	521 (100.0%)
Events (N)	222	253	475
Censored Observations (N)	20	26	46
Missing Observations (N)	0	0	0
Mean (days) ± SE	7.05 ± 0.18	7.62 ± 0.18	7.36 ± 0.13
Median (days) (95% CI)	7.00 (6.75; 7.31)	7.32 (6.97; 7.92)	7.08 (6.95; 7.40
Log rank test	0.0150		

Refer to Table 14.2.1.1.1
CI: confidence interval; N: number; SE: standard error

Figure 2 Time to Healing (mITT population)



Refer to Figure 14.2.1.1.1

The analysis was repeated with the PP population for the primary endpoint as a sensitivity analysis. Only 339 patients were included in the PP population. Most of the excluded patients were excluded due to prohibited concomitant medications. The mean TTH was shorter in the Sitavig 50 mg group than in the placebo groups but there was no statistically significant difference between treatment groups in TTH of the primary vesicular lesion in the PP population.

Assesment of the effect size, primary efficacy variable

Of note, the effect size over placebo in this study was smaller than that seen with systemic famciclovir or valaciclovir (0.8-2 days) (Spruance et al, J Am Acad Dermatol 2006, Spruance et al, Antimicrob Agents Chemother 2003). The sponsor pointed out that the increased proportion of patients with aborted lesions on active therapy may have provided a bias against the active regimen as the primary endpoint was defined, and that the effect size might therefore be underestimated. Still, it was noted that the statistical strength of the statistical inference in favour of the alternative hypothesis is not overwhelming (p=0.0150, log rank test), and that no effect could be seen in the per protocol population. The latter excludes, among other patients, those taking concomitant prohibited medication, including analgesics and topical corticosteroids, which was more common in the placebo group.

Secondary endpoints

Aborted lesions were defined as herpetic lesions preceeded by prodromal symptoms that did not progress beyond the papule stage. In the ITT population, the proportion of patients with an aborted herpes episode was higher in the Sitavig 50 mg group than in the placebo group and the difference between treatment groups was statistically significant (Chi-Squared Test; p=0.0419)

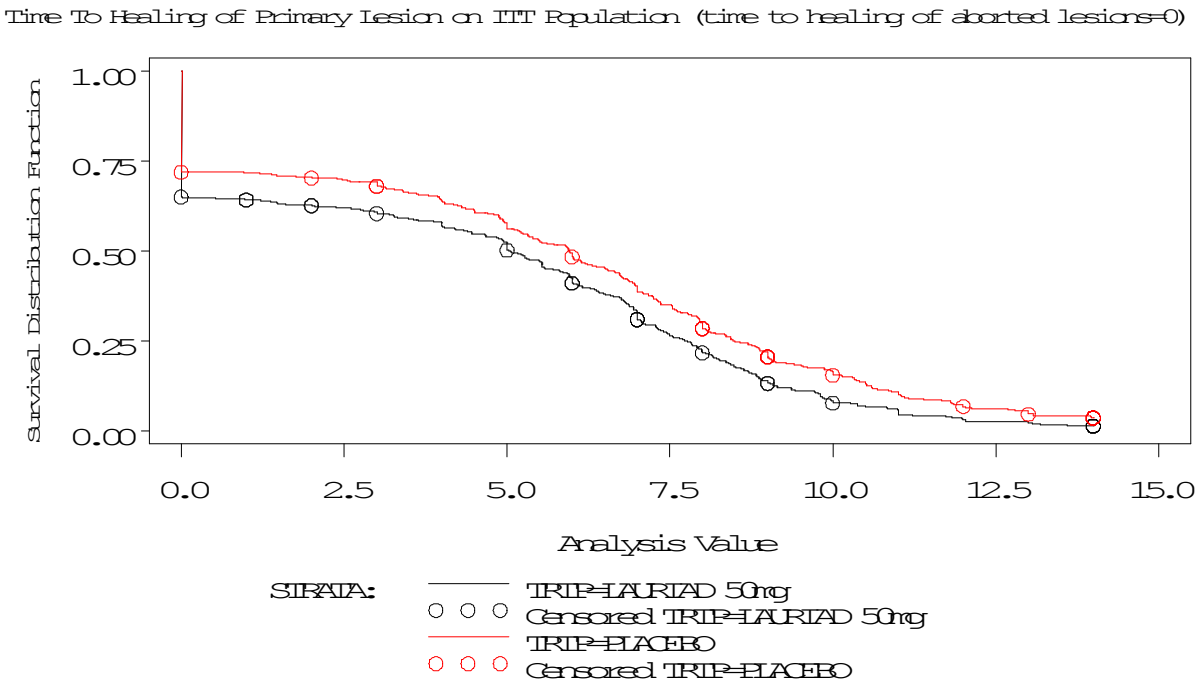
Table 3 Aborted Lesions (ITT Population)

		ABT 50 mg (N=376)	Placebo (N=395)	Total (N= 771)
Patients with aborted lesions	Yes (N [%])	130 (34.9%)	109 (28.1%)	239 (31.4%)
	No (N [%])	242 (65.1%)	279 (71.9%)	521 (68.6%)
	Missing (N)	4	7	11
Treatment Difference (95% CI)			0.0685 (0.0025; 0.1339)	
Chi Squared Test			0.0419	

Refer to Table 14.2.2.1.1
Confidence intervals based on exact method.
N: number of patients; CI: confidence interval

On request, the sponsor performed a supplementary analysis of time to healing in the entire ITT, setting healing time to 0 for patients not progressing to the vesicular stage (aborted lesions). The results were as follows, further indicative that Sitavig 50 mg has some efficacy over placebo:

		ABT 50mg	PLACEBO	TOTAL	p-value
		N=376	N=395	N=771	Log-Rank Test (Wilcoxon Test)
Point Estimate (95%CI) (days)	Median (CI)	5.03 [4.40 - 5.58]	5.95 [5.21 - 6.50]	5.50 [5.00 - 5.96]	0.0017 (0.0077)
	Mean (SE)	4.58 (0.21)	5.48 (0.22)	5.04 (0.15)	
Total Number of Patients		372	388	760	
Number of Events		352	362	714	
Number Censored (%)		20 (5.4%)	26 (6.7%)	46 (6.1%)	
Missing		4	7	11	



TTH of non primary lesions was defined as the time from treatment initiation to healing of all non-primary vesicular lesions. Non-primary lesions were those that developed in addition to and/or in 1 or more days after the primary vesicular lesion and that were located at least 1cm far from the primary lesion. Aborted lesions were not included in this parameter. TTH was to be assessed by the investigator with the support of the patient diary. There were few patients with non-primary lesions in this study, with less patients in the Sitavig 50 mg group than in the placebo group with non-primary lesions: 39 patients (10.4% of 376 patients in the Sitavig 50 mg group assessed in the ITT population) versus 62 patients (15.7% of 395 patients in the placebo group)(p=0.037).

For subjects who experienced a vesicular lesion, duration of episode was the time from treatment initiation to healing of primary and secondary vesicular lesions (loss of crust). For subjects whose primary and secondary lesions were not vesicular in nature, duration of episode was the time from treatment initiation to return to normal skin or to cessation of symptoms whichever came last. The duration of herpes episode was statistically significantly shorter in

the Sitavig 50 mg group than in the placebo group, with median and mean differences of 0.67 and 0.81 days respectively (p=0.0033).
The median and mean durations of symptoms of the herpes episode were 0.67 days and 0.59 days respectively shorter in the Sitavig 50 mg group than in the placebo group and the difference in duration of symptoms between treatment groups was statistically significant (p=0.0098 [Log Rank Test]).

Recurrence of Lesions: incidence and time to recurrence
Recurrence was to be evaluated in a subgroup of patients who agreed to record recurrences during the follow up (optional). The percentage of patients with at least one recurrence during a 9-month follow up was calculated. Time to 1st recurrence was the time from the healing of all lesions of the initial episode to the occurrence of new lesions. It was based on the data recorded in the patient diary.

Among the 775 patients treated in the pivotal study, 537 entered the optional 9-month follow-up to record the recurrence of herpes episodes: 267/378 (70.6%) patients in the Sitavig 50 mg group and 270/397 (68.0%) patients in the placebo group. About half of patients in the FU population recorded at least one recurrence of primary vesicular lesions during the 9-month follow-up period (330/537, 61.5%). The number of patients with recurrence of primary lesions was significantly lower in the Sitavig 50 mg group (149/267, 64.2%) than in the placebo group (181/270, 73.6%)(p=0.027).

The median time to recurrence of primary vesicular lesion was 40 days longer in the Sitavig 50 mg group than in the placebo group, as shown inTable 4, and the difference between treatment groups was statistically significant (p=0.0412 [Log Rank Test]).

Table 4 Time to Recurrence of Lesions (FU Population)

	ABT 50 mg N=267	**Placebo N=270**	**Total N=537**
Patients (N [%])	232	246	478
Events (N)	114	143	257
Censored observations(N)*	118	103	221
Missing Observations (N)**	35	24	59
Mean (days) ± SE	304 ± 19.4	199 ± 9.3	265 ± 19.5
Median (days) (95% CI)	205.0 (163.0; 287.0)	165.0 (136.0; 203.0)	180.0 (158.0; 217.0)
Log Rank Test		0.0412	

*Censored observations correspond to patients without recurrence.
**The following patients were counted as missing: patients without date for ALL lesions healed (n=2), patients with new herpes episodes before healing (n=14) and patients with new herpes episodes within 14 days of healing (which were thus assumed to be the same infection) (n=43).
Refer to Table 14.2.12.1.1.
CI: confidence interval; N: number; SE: standard error
If there was no recurrence prior to the last recorded visit date, time to recurrence was censored at the last recorded visit date.

In the 469/537 patients (87.3%) who applied the test substance or placebo within 1 hour after the occurrence of prodromal symptoms, the number of patients with recurrence of primary lesions was lower in the Sitavig 50 mg group (n=97/237, 40.9%) than in the placebo group (123/232, 53.0%) (p=0.0495). the median and mean times to recurrence of primary vesicular lesion were respectively 54 and 109 days longer in the Sitavig 50 mg group than in the placebo group, and the difference between treatment groups was statistically significant (p=0.0495 [Log Rank Test]).

Assessment of the analysis of time to recurrence

The finding that treatment of a herpes recurrence with short term antiviral therapy might increase the time to the next recurrence is novel. Though the applicant presents a hypothetical virological rationale for this, the biological plausibility of this finding is not entirely clear. Furthermore, it is noted that this surprising finding emerges in a secondary, though prespecified analysis of a de facto subgroup. Also, the applicant notes that "analyses of time to recurrence should be interpreted with caution as reliability of the data could not be ensured" as recurrent herpes lesions were not confirmed by the investigators.

The biological plausibility and the statistical strength of this finding is not overwhelming, and it has not been seen in more than one trial. Therefore it was considered that the finding that treatment of a herpes labialis episode with one dose of Sitavig 50 mg increases time to herpes labialis recurrence is in need of confirmation in an independent clinical trial, in order to be considered reasonably demonstrated, and that no claims to this effect could be made in the product information.

IV.4 Clinical safety

Data supporting the safety of Sitavig 50 mg were provided by 2 clinical studies, the PK/PD study and the one pivotal Phase III study, both of which have been described above.

A total of 788 subjects were included in the clinical programme; all subjects received at least 1 dose of treatment, as follows:

− 12 healthy volunteers received at least one dose of Sitavig 50 mg, one dose of Sitavig100 mg, and one dose of aciclovir 200 mg oral tablet.

− One healthy volunteer only received one dose of Sitavig 100 mg and then withdrew for personal reason. This subject is not included in the safety overview for Sitavig 50 mg.

− 378 patients with recurrent orofacial herpes received at least one dose of Sitavig 50 mg.

− 397 patients with recurrent orofacial herpes received at least one dose of placebo.

Total exposure to Sitavig 50 mg and placebo MBTs was determined from questionnaires completed by the patients in the pivotal study and by clinical examination by the investigator at predefined time points in the PK/PD clinical trial. Specific information regarding Sitavig 50 mg or placebo dislodgment, adherence and replacement (number of applications replaced and time of replacement) are shown in Table 5. This information was gathered from patient diaries and investigator reports.

Table 5 **Subject Drug Exposure by Treatment Group and Duration of Exposure**

	Total (n = 783)	ABT 50 mg (n = 388)		Placebo MBT (n = 395)
		BA2004/21/01 n=12	BA2005/21/02 n=376	
Adhesion time < 6 hours N (%)	**93 (11.9%)**	**0**	**43 (11.5%)**	**50 (12.7%)**
Adhesion time 6 - 12 hours N (%)	**293 (37.6%)**	**6 (50.0%)**	**166 (44.4%)**	**121 (30.8%)**
Adhesion time > 12 hours N (%)	**393 (50.5%)**	**6 (50.0%)**	**165 (44.1%)**	**222 (56.5%)**
Missing	**4**	**0**	**2**	**2**

Source: BA2005/21/02 – Table 17; BA2004/21/01- Table 11.5

Safety analyses included all subjects who received at least one dose of product. A total of 162 TEAEs were reported by 120 of the 775 patients participating in the phase III clinical trial.

Table 6 **Number and Percentage of Patients Experiencing TEAEs (Incidence ≥ 0.5%) During Treatment by Preferred Term and Treatment Group**

Preferred Term	50 mg ABT Single dose (n = 378)	Placebo Single dose (n = 397)	Total (n = 775)
TEAEs	78	84	162
Patients ≥ 1 TEAE	60 (15.9 %)	60 (15.1%)	120 (15.5 %)
Headache	12 (3.2%)	12 (3.0%)	24 (3.1%)
Application site pain	4 (1.1%)	4 (1.0%)	8 (1.0%)
Nasopharyngitis	4 (1.1%)	3 (0.8%)	7 (0.9%)
Application site irritation	2 (0.5%)	0 (0.0%)	2 (0.3%)
Viral infection	3 (0.8%)	0 (0.0%)	3 (0.4%)
Dizziness	2 (0.5%)	2 (0.5%)	4 (0.5%)
Pharyngolaryngeal pain	2 (0.5%)	2 (0.5%)	4 (0.5%)
Aphtous stomatitis	2 (0.5%)	0 (0.0%)	2 (0.3%)
Gingival pain	2 (0.5%)	1 (0.3%)	3 (0.4%)
Fatigue	2 (0.5%)	0 (0.0%)	2 (0.3%)
Erythema	2 (0.5%)	1 (0.3%)	3 (0.4%)
Rash	2 (0.5%)	1 (0.3%)	3 (0.4%)
Lethargy	2 (0.5%)	0 (0.0%)	2 (0.3%)
Stomach discomfort	2 (0.5%)	0 (0.0%)	2 (0.3%)
Pharyngitis	2 (0.5%)	0 (0.0%)	2 (0.3%)
Nausea	1 (0.3%)	6 (1.5%)	7 (0.9%)
Lip dry	1 (0.3%)	3 (0.8%)	4 (0.5%)
Influenza	1 (0.3%)	3 (0.8%)	4 (0.5%)
Oral herpes	0 (0.0%)	3 (0.8%)	3 (0.4%)
Cough	1 (0.3%)	2 (0.5%)	3 (0.4%)

Table 6 Number and Percentage of Patients Experiencing TEAEs (Incidence ≥ 0.5%) During Treatment by Preferred Term and Treatment Group

Preferred Term	50 mg ABT Single dose (n = 378)	Placebo Single dose (n = 397)	Total (n = 775)

n= number of patients; safety population includes phase III safety population

source: Study Report BA2005/21/02 Table 14.3.1

Table 7 Percentage and Number of Patients with Treatment Emergent Adverse Events During Treatment by Intensity and Treatment Group

Intensity	50 mg ABT Single dose (n = 378)	Placebo MBT Single dose (n = 397)	Total (N = 775)
Total TEAEs	78	84	162
Patients with ≥1 TEAE	60 (15.9%)	60 (15.1%)	120 (15.5%)
Mild	54 (69.2%)	43 (51.2%)	97 (59.9%)
Moderate	21 (27.3%)	32 (38.1%)	53 (32.9%)
Severe	3 (3.9%)	6 (7.1%)	9 (5.65%)
Life-threatening	0	1 (1.2%)	1 (0.6%)
Fatal	0	0	0
Missing Data	0	2 (2.4%)	2 (1.2%)

Source: Study report BA2005/21/02 Table 3.1

Overall, the administration of Sitavig 50 mg was not associated with an increase in adverse event compared to placebo.

Local Tolerance

To investigate local tolerance in the pivotal study, investigators examined study drug application sites at baseline and at the end of study period. Local inflammation (gingival index) was evaluated using a 0-3 scale. The gingival index was not significantly different between treatment groups at baseline or at the end of treatment. There was an absence of inflammation in the majority of patients in both treatment groups: (92.5-99.1% in the Sitavig 50 mg group and 94.0-99.4% in the placebo group).

Local TEAEs spontaneously reported by patients are listed in Table 8.

Table 8 Number and Percentage of Patients Experiencing local TEAEs During Treatment by Preferred Term and Treatment Group

Preferred Term	ABT 50 mg Single dose (n = 378)	Placebo MBT Single dose (n = 397)	Total (n = 775)
TEAEs	26	25	51
Patients ≥ 1 TEAE	23 (6.1%)	24 (6.0%)	47 (6.1%)
Application site pain	4 (1.1%)	4 (1.0%)	8 (1.0%)
Nasopharyngitis	4 (1.1%)	3 (0.8%)	7 (0.9%)
Lip dry	1 (0.3%)	3 (0.8%)	4 (0.5%)
Pharyngolaryngeal pain	2 (0.5%)	2 (0.5%)	4 (0.5%)
Oral herpes	0 (0.0%)	3 (0.8%)	3 (0.4%)
Gingival pain	2 (0.5%)	1 (0.3%)	3 (0.4%)
Application site irritation	2 (0.5%)	0 (0.0%)	2 (0.3%)
Dry mouth	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pharyngitis	2 (0.5%)	0 (0.0%)	2 (0.3%)
Aphtous Stomatitis	2 (0.5%)	0 (0.0%)	2 (0.3%)
Application site discomfort	1 (0.3%)	1 (0.3%)	2 (0.3%)
Application site erythema	1 (0.3%)	0 (0.0%)	1 (0.1%)
Application site paraesthesia	1 (0.3%)	0 (0.0%)	1 (0.1%)
Lip haemorrhage	0 (0.0%)	1 (0.3%)	1 (0.1%)
Lip swelling	1 (0.3%)	0 (0.0%)	1 (0.1%)
Mouth ulceration	0 (0.0%)	1 (0.3%)	1 (0.1%)
Mucosal erosion	0 (0.0%)	1 (0.3%)	1 (0.1%)
Oral bacterial infection	1 (0.3%)	0 (0.0%)	1 (0.1%)
Oral pain	0 (0.0%)	1 (0.3%)	1 (0.1%)
Stomatitis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Throat irritation	0 (0.0%)	1 (0.3%)	1 (0.1%)
Tooth abcess	0 (0.0%)	1 (0.3%)	1 (0.1%)
Toothache	0 (0.0%)	1 (0.3%)	1 (0.1%)

n= number of patients; safety population includes phase III safety population; TEAE: Treatment emergent adverse event

Source: Pooled Safety Analysis, Table 14.3.2.1-local

The frequency of reported application site pain/discomfort is low and not appreciably different between placebo and Sitavig

Incidence of Tablet Dislodgement
Of the 376 Sitavig 50 mg tablets and 395 placebo MBT tablets applied in the Phase III study, 43 (11.5%) Sitavig 50 mg and 50 (12.7%) placebo dislodged from the application site within 6 hours after the tablet was initially applied, when more than 60% of aciclovir had been released from the tablet (Table 9).

Table 9 Number of ABT 50 mg and MBT swallowed and second tablet application by group

	Total (n = 93)	ABT 50 mg (n = 43)	Placebo MBT (n = 50)
Tablet swallowed	27 (29.0%)*	12 (27.9%)	15 (30.6%)*
Tablet replaced	68 (73.1%)*	33 (76.7%)	35 (71.4%)*

* 1 missing data

Source: BA2005/21/02, Table 17

The applicant found no evidence that tablet swallowing or replacement were associated with an increase in adverse effects.

There were no deaths, serious adverse events or emerging laboratory abnormalities associated with Sitavig 50 mg.

IV.5 Discussion on the clinical aspects

Drugs approved for the indication of herpes labialis recurrences in immunocompetent adults include topical and systemic aciclovir, systemic valaciclovir and topical penciclovir. These drugs have shown efficacy, primarily when initiated during the prodromal stage of a herpes labialis recurrence, shortening the time from administration to healing of the primary vesicular lesion by 0.5-2 days. Sitavig 50 mg contains aciclovir, a substance previously shown to be efficacious in this sense. Sitavig, however, is not a systemic but rather a topical therapy, to be administered once, preferably within 1h of the onset of prodromal symptoms. The relative systemic exposure compared to a 200 mg dose of aciclovir is low, with a relative bioavailability of 49% and a lower dose. Drug concentrations in saliva are considerably higher than with a single oral dose of aciclovir; however, the quantitative relation between saliva concentration and efficacy has not been explored. The applicant has performed a single pivotal clinical trial on which all efficacy claims for this novel formulation are based. The study appears to have been designed and performed according to the paradigm provided by earlier studies for drugs and applications in the class.

In the mITT population, including patients taking the drug and developing vesicular lesions, TTH of the primary vesicular lesion was statistically significantly shorter in patients treated with ABT 50 mg than in those treated with placebo (Log Rank Test: 0.0150). The mean and median differences were 0.57 days and 0.32 days respectively. The clinical efficacy of Sitavig 50 mg is supported by a higher proportion of patients with aborted lesions, with fewer patients developing secondary lesions and with a shorter duration of symptoms, compared to placebo. Previous efficacy demonstrations with other applications of aciclovir or its prodrug valaciclovir could be considered indirect supportive evidence for the findings in this single pivotal clinical trial. Therefore, it seems likely that Sitavig 50 mg has a clinical efficacy that is superior to placebo,

The claim that a single dose of Sitavig 50 mg during one episode would increase the time to recurrence is not clearly biologically plausible, and is not supported by any other trials than the present. Based on new data on a reservoir of HSV in the oral mucosa, the applicant suggests that this is a specific effect related to the formulation and the high aciclovir concentrations in saliva and labial mucosa. The applicant states in its discussion that “given that HSV replication

is the highest before and within the first 8 hours of lesion development and diminishes as the lesions mature, and given that HSV is located in mucosa, it was expected that rapid, high and sustained aciclovir concentrations in saliva and labial mucosa, at the site of the viral reactivation and replication, may reduce the mucosal viral reservoir and thus delay the recurrence of the next herpes episodes".

While this possibility is indeed highly intriguing, the theoretical relevance of this observation is not self-evident. In terms of empirical evidence, the claim of the applicant is based on a subgroup analysis of one single study, unsupported by any other solid clinical observations. Furthermore, the applicant itself warns about the integrity of these data, based on the absence of direct confirmation by the investigators. The median time to recurrence of primary vesicular lesion was 40 days longer in the Sitavig 50 mg group than in the placebo group: However, the statistical strength of the finding is low - (p=0.0412, Log Rank Test) It is not possible to accept the entirely novel and clinically important claim of an increased time to recurrence on the basis of a finding of borderline significance in a subgroup analysis of a single clinical trial.

In summary, available data indicate that Sitavig 50 mg has efficacy over placebo in patients with herpes labialis recurrences, as evidenced by the primary outcome measure, time to healing of vesicular lesions.

Aciclovir is a very well known and generally well-tolerated substance that has been used for decades. The present application is a buccal, slow release tablet taken as a 50 mg single dose. Dose adjusted systemic bioavailability, compared with a 200 mg oral dose of aciclovir, is 49%. Thus, systemic exposure is low compared with systemic treatment with approved doses, and systemic side effects of a single dose are expected to be very low. The safety database presented by the applicant contains nearly 400 patients exposed to the therapeutic regimen, or a higher dose. The side effect profile, including local tolerability at the site of application, is similar to placebo. Local tolerability data in general appear reassuring. Regarding the formulation, the applicant cites an approved micoazole-containing product, Loramyc®/Sitamic®/Oravig®, an antifungal drug using the same vehicle, providing further experience.

Aciclovir is excreted renally, and its main putatively serious adverse effects, including renal impairment and neurological side effects, are mainly seen in patients with higher systemic exposure due to decreased renal clearance. Apart from the low systemic exposure with sitavig 50 mg, this is a single dose application; thus, the risk of accumulation with unacceptably high systemic exposure in patients with renal impairment seems very low. Despite the fact that the study only recruited patients without "clinically relevant" increases in creatinine, the applicant has not proposed any warnings or precautions in the SmPc for patients with renal impairment. Given that it is clarified that no more than one dose be taken per herpetic episode (including the possibility of a substitution dose in case of early dislodgement or swallowing, this is acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

All in all, the safety profile is such that the risk-benefit is considered positive, despite the relatively small clinical benefit that has been demonstrated. It is deemed that previous experience of aciclovir applications may be considered a basis for a single pivotal trial, demonstrating some efficacy also with the present administration form and posology, and it is concluded that the presently proposed indication “the treatment of recurrent herpes labialis in immunocompetent adults with frequent herpes episodes”, is acceptable, supported by data indicating a positive benefit-risk.

The risk/benefit ratio is considered positive and Sitavig, muco-adhesive buccal tablet, 50 mg, is recommended for approval.

VI. APPROVAL

The decentralised procedure for Sitavig, muco-adhesive buccal tablet, 50 mg was successfully finalised 2012-12-18.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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