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APPLICATION NUMBER:

203791Orig1s000

MEDICAL REVIEW(S)

NDA 203791, SN 0017
BioAlliance Pharma New Drug Application
Acyclovir Lauriad™ 50 mg Buccal Tablet
Addendum to Clinical and Statistical Review
NDA 203,791/S-000 submitted March 13, 2012

Materials Reviewed:

- FDA Discipline Review (DR) letter dated December 7, 2012
- Applicant Response to DR letter dated January 3, 2013 (received 01/04/2013)

Regulatory History: On March 13, 2012 the Applicant, BioAlliance, submitted a 505(b)(2) NDA application for Sitavig a mucoadhesive Buccal Tablet (ABT 50 mg) for the requested indications of “the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, (b) (4)

Concerns regarding the approvability of the application were raised during the initial review process and a discipline review letter outlining the observed deficiencies was communicated to the Applicant via FAX on December 7, 2012. This letter indicated that “while the submitted safety data are adequate to show that ABT-50 presented minimal risks when used in the treatment of herpes labialis (HL), the efficacy data presented in this submission were inadequate to support the Bioalliance Sitavig mucoadhesive Buccal Tablet (ABT 50 mg) for the requested indications of “the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, (b) (4)

In trial BA2005/21/02, the single clinical trial conducted by the Applicant in support of the NDA, ABT-50 was unable to meet the statistical and clinical benchmarks discussed during the April 8, 2010 pre NDA meeting to show that Sitavig was superior to placebo for reducing the time to healing (TTH) of ulcerative herpes labialis lesions. Not only was the Applicant unable to meet the predefined standard for a clinically meaningful benefit, predefined by the Division as a decrease in time to healing of at least one half day, but the difference between Sitavig and placebo for the primary efficacy parameter of TTH did not meet the predefined statistical significance level of < 0.001 for demonstrating efficacy in a single registration trial. The determination of what constitutes clinically meaningful (i.e. at least $\frac{1}{2}$ day) is based on the difference in the TTH achieved in previous applications for topical herpes labialis products. In addition, the evaluation of the totality of evidence regarding efficacy was unable to show clinically meaningful and/or statistical significance in any subpopulation or for any of the secondary efficacy parameters.

In the FDA analysis of TTH in the FDA revised MITT population, using the KM approach, the mean difference of TTH between arms is - 0.47 days, the median difference

is - 0.31 days, and the Log-rank P-value is 0.0645. Using the HL approach the median difference of TTH between the ABT 50 mg and placebo arms is - 0.49 days with 95% CI of (-1.00, 0.00) and P-value of 0.0538 from Kruskal-Wallis test if using all TTH regardless of censoring or not, and is - 0.30 days with 95% CI of (-0.82, 0.15) and P-value of 0.2051 from Kruskal-Wallis test if only using observed events by excluding censored cases (Table 10).

Overall, the median difference of TTH between the two arms ranged between 0.3-0.5 days with a borderline statistically significant p-value, which did not consistently meet the requirement of clinical significance of at least ½ day benefit. This can be seen in the following table copied from the original combined clinical and statistical review dated December 3, 2013.

**Time-To-Healing FDA Analyses
 Study BA2005/21/02**

mITT population	ABT (N=242)	Placebo (N=279)
Total, N	239	271
Event Observed, n (%)	219 (92%)	249 (92%)
Censored, n (%)	20	22
Healing Rate, % (n/N)	92% (219/239)	92% (249/271)
LifeTest (K-M) on TTH		
Mean (days) ± SE	7.09 ± 0.18	7.56 ± 0.18
Median (days) (95% CI)	7.00 (6.72, 7.32)	7.31 (6.95, 7.79)
Log-rank Test P-value	0.0645	
Generalized Wilcoxon test (Gehan)	0.1290	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.88 (239)	7.25 (271)
Median Difference (days) (95% CI)	-0.49 (-1.00, 0.00)	
Kruskal-Wallis Test P-value	0.0538	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.88 (219)	7.00 (249)
Median Difference (days) (95% CI)	-0.30 (-0.82, 0.15)	
Kruskal-Wallis Test P-value	0.2051	

NOTE: Five patients TTH were corrected and eleven patients who took prohibited CM during the trial were excluded from the analysis population (see explanation below).

There were numerous other issues associated with this application that led to a complete response recommendation by the review team.

Issues included flawed collection of efficacy data by the patients primarily because the herpes labialis (HL) lesion assessment was recorded by the patients only once daily at bedtime. This once daily assessment made it very difficult to record the time the lesions healed with accuracy and consequently to calculate time to healing and therefore to attempt to show at least a ½ day improvement over placebo. This infrequent assessment led to concerns on exactly how accurate the investigators were able to calculate the TTH of the primary vesicular lesions.

Other review issues included the inaccurate categorization of the TTH in five patients as well as the use of prohibited antiviral medications by an additional eleven mITT patients.

The latter two issues led to re-categorization of these patients with resultant differences in the efficacy conclusions between the Agency and the Applicant analyses.

In addition to the treatment of HL claim the Applicant also requested the additional claims (b) (4)

It should also be noted that the Applicant agreed not to submit this claim as per the pre NDA meeting minutes but elected to do so anyway despite the Agency's advice.

With regards to the claim that (b) (4)

(b) (4)

and therefore the accuracy of the results were in question

It is recommended that if the Applicant wants to include (b) (4) in the indication (b) (4)

Current Submission:

In their 01/04/2013 response BioAlliance disputed the clinical and statistical deficiencies outlined in the DR letter. Given the extent of the revised analyses submitted as well as the time needed to review them it was decided that this submission constitutes a MAJOR AMENDMENT to the original submission thus extending the review clock by 3 months.

The Applicant's points and the MO's comments follow:

1. Issue 1:

a. Treatment claim for recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients claim

BioAlliance considers that the Phase 3 pivotal study presented in the NDA is adequate to support the treatment claim for recurrent orofacial herpes infection in immunocompetent adult patients.

It is their viewpoint that “ABT-50 delivers high concentrations of acyclovir at the prodromal stage to the site of infection. This is a well established in the HL literature concept of “hit hard, hit early”.

As per the Applicant, “At the pre-NDA meeting held on April 8, 2010, BioAlliance and the Division agreed that given the significant imbalance in the incidence of aborted episodes between treatment groups (significantly higher in the ABT 50 mg than in the placebo group), the ITT population was to be considered as the primary population and, thus, the Duration of Episode (DOE) is the appropriate primary endpoint to analyze efficacy data.”

“The Division asked also to present the Time to Healing (TTH) in the modified Intent to Treat (mITT) population as an additional endpoint and asked that BioAlliance provides these analyses with the following definitions:

- *Duration of Episode (DOE) defined as the time from the treatment initiation to the healing of primary lesions (loss of crust) for patients who experienced a vesicular lesion. For patients whose primary lesions were not vesicular in nature, duration of episode is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms whichever comes last. If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then DOE is missing.*
- *Time to healing (TTH) defined as time to healing is the time from the treatment initiation to the healing of primary lesions (loss of crust) for patients who experienced a vesicular lesion. If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then TTH is missing.*

As planned in the submitted and agreed protocol with the FDA, these analyses were conducted with Kaplan-Meier and Log Rank test methods. They were provided for review at the teleconference held on July 28, 2010, during which FDA indicated that these analyses “appeared to support clinical benefit of at least half a day for the primary endpoint based on the ITT population. Hence, FDA considered the data acceptable to submit a 505(b)(2) NDA application.”

Comments:

- *The MO agrees that the Applicant has shown that ABT 50 achieves high concentrations in the saliva and from there to the lips after licking rapidly after treatment initiation. The Clinical Pharmacology as well as the Virology Agency Reviewers concurred that very high levels of ABT 50 were found in the saliva after the application of the 50 mg tablet. As per the Virology Reviewer, Dr. Mishra, “Virology data analyses showed that for some subjects a high concentration of acyclovir (above EC50 values) was achieved. Virology data analyses suggest that ABT showed anti-HSV activity in subjects who received a*

single dose of 50 mg ABT". Both review disciplines recommended an approval for the application. Further details can be found in the respective reviews.

- *There is agreement that treatment initiation in the prodromal phase, (that is before the appearance of a vesicular lesion), can potentially increase the number of aborted episodes. In the original submission there was a statistically significant difference in the proportion of patients with aborted primary lesions between the treatment arms (ABT 50 mg arm (34.9%) vs placebo (28.1%). The rate difference is 6.85% with exact 95% CI of (0.22%, 13.48%) and P-value 0.043. This was a secondary efficacy endpoint and there was no multiplicity adjustment applied.*
- *Because of the higher percentage of aborted lesions on the ABT 50 arm, there is some merit to the Applicant's position that a TTH of vesicular lesions analysis may not present a complete picture of the effectiveness of a treatment that can achieve this. A key goal of any treatment regimen applied during the prodromal phase is to either shorten the duration of the episode and/or to decrease the severity of the episode. For HL the development of a vesicular lesion would be considered the most severe manifestation of the disease. The increase in the number of aborted lesion leads directly to a decrease in HL-associated morbidity, a clear benefit for the patient population.*
- *A review of the minutes from both the April, 2010 pre NDA meeting and the July, 2010 follow-up Tcon indicate some confusion in the use of the terminologies of DOE and TTH. It is however stated in both sets of minutes that the only relevant clinical endpoint to assess efficacy in the ITT population is the DOE. It should also be noted that this confusion in terminology and definitions extends to many previous applications for the HL indication.*
- *The BioAlliance application under review is a 505(b)(2) application which relies on evidence of established efficacy from another approved drug. In this case the approved drug for the treatment of HL cited is Acyclovir Cream. It is therefore reasonable to use the same primary efficacy endpoint and analysis population that was used in that application in the primary analysis for comparison purposes.*

*Specific to the ACV cream NDA, the **primary efficacy** endpoint was clinician-assessed **time to healing**, which was calculated from the recorded time of clinician-assessed healing minus the recorded time of the first application of study medication on the case report form. The analysis population was the ITT. For the study participants whose lesions began as vesicles, the time until vesicle healing was included as a secondary efficacy endpoint.*

*NOTE: In the ACV cream medical review, the terms TTH and DOE are used interchangeably. Where referring to a primary vesicular lesion the TTH/DOE is also described as duration of healing. When times were assessed **MEAN as opposed to median values** were used. This is important because in the Bioalliance*

application a determination was made by the Agency Reviewers that median values provide a more accurate assessment of the difference in the DOE or the TTH. The reason for this is the greater percentage of patients (35%) on the ABT 50 arm who had aborted lesions as compared to the placebo arm (28%). Because of this difference the data were too skewed to allow for an evaluation of only the mean DOE or TTH. However it was also determined that consistency in the mean and median results were important factors to demonstrate overall efficacy. The results of the DOE in the ITT and the TTH in those with vesicular lesions for the ACV cream application can be seen below:

MEAN DOE ITT (days)

	ACV 5%	VEH
ZOVA 3003	4.4	4.8
ZOVA 3004	4.7	5.2

*NOTE: Difference in DOE ranges from 0.4 – 0.5 days. This difference was determined to be **minimally** clinically significant.*

An approval was recommended because of the consistency of the results across trials despite the fact that the 0.5 day goal of clinical significance was not always achieved.

74% of patients developed a vesicular lesion. The overall difference between the mean healing time in both ZOVA 3003 and ZOVA 3004 was -0.5 days.

MEAN TTH Vesicular lesions ITT (days)

	ACV 5%	VEH
ZOVA 3003	4.2	4.7 (p = 0.028)
ZOVA 3004	4.6	5.1 (p = 0.016)

- There is a lack of consistency across previous applications with regards to the primary endpoint. Copied below is a table supplied by the Applicant which indicates the various endpoints used in previous HL trials. This lack of clear guidance in both the primary endpoint and the populations analyzed has caused confusion across applications as to what expected outcomes should be. In the case of BioAlliance it was determined a priori that the primary endpoint was the TTH applied to the MIIT population defined as those patients with a vesicular lesion. The results of the initial analysis did not attain the required statistical significance in the Agency analysis and were marginally clinically meaningful. However the results were relatively consistent with those obtained for both the DOE endpoint in the ITT population and the TTH endpoint in a MITT population in other applications depending on how they were defined. Although the DOE in the ITT population in the current submission is a post hoc analysis it is reasonable to accept it as further evidence of efficacy consistent with that previously seen with other approved antivirals. In addition this analysis also indicated consistency in the results in both the MITT and ITT populations for either the TTH or the DOE endpoint.*

Table IV. Episode duration and lesion healing results in large important trials. Episode duration is measured from initiation of treatment to loss of hard crust in patients with ulcerative lesions and to normal skin in patients with non-ulcerative lesion. Lesions healing is measured from initiation of treatment to loss of hard crust in patients with ulcerative lesions

Ref.	Treatment	Parameter	Median duration (days)	Median improvement (%)	Hazard ratio	p-value	
(12)	Penciclovir cream	Lesion healing	4.8	12.7	1.33	<0.001	
	Placebo		5.5				
(39)	Penciclovir cream	Lesion healing	4.6	14.8	1.31	0.0001	
	Placebo		5.4				
(26), study 1	Acyclovir cream	Episode duration	4.3 (Mean)	10.4 (Mean)	1.23	0.007	
	Placebo		4.8 (Mean)				
(26), study 2	Acyclovir cream	Episode duration	4.6 (Mean)	11.5 (Mean)	1.24	0.006	
	Placebo		5.2 (Mean)				
(19), study 1	Valaciclovir, 1 day	Episode duration	4.0	20.0		0.001	
			Valaciclovir, 2 days	4.5		10.0	0.009
			Placebo	5.0			
(19), study 2	Valaciclovir, 1 day	Episode duration	5.0	9.1		< 0.001	
			Valaciclovir, 2 days	5.0		9.1	< 0.001
			Placebo	5.5			
(27)	Famciclovir 1500 mg single dose	Lesion healing	4.4	29.0	1.64	< 0.001	
			Famciclovir 750 mg twice per day	4.0	35.5	2.05	< 0.001
			Placebo	6.2			
(5)	Iontophoresis of 5% acyclovir	Lesion healing	5.8	15.7		0.03	
			Placebo	6.9			
(18)	Acyclovir/hydrocortisone	Lesion healing	5.7 (Mean)	12.3		< 0.01	
			Acyclovir	5.9 (Mean)			9.2
			Placebo	6.5 (Mean)			

In Appendix 2 of this review are summaries of the valcyclovir and Xerese reviews. In both applications, the primary endpoint was the DOE applied to the ITT population.

The BioAlliance analysis of the DOE in the ITT population of trial BA2005/21/02 showed a **0.81 day median difference** between ABT and placebo (Table copied from Applicant below, p = 0.003) meaningfully above the 0.5 day difference requested. The **mean difference was 0.77 day**.

The FDA Reviewer was able to confirm this analysis in the Applicant's ITT population. **during 4 to 5 days (Spruance et al, 2002).**

Duration Of Episode (DOE) in ITT population

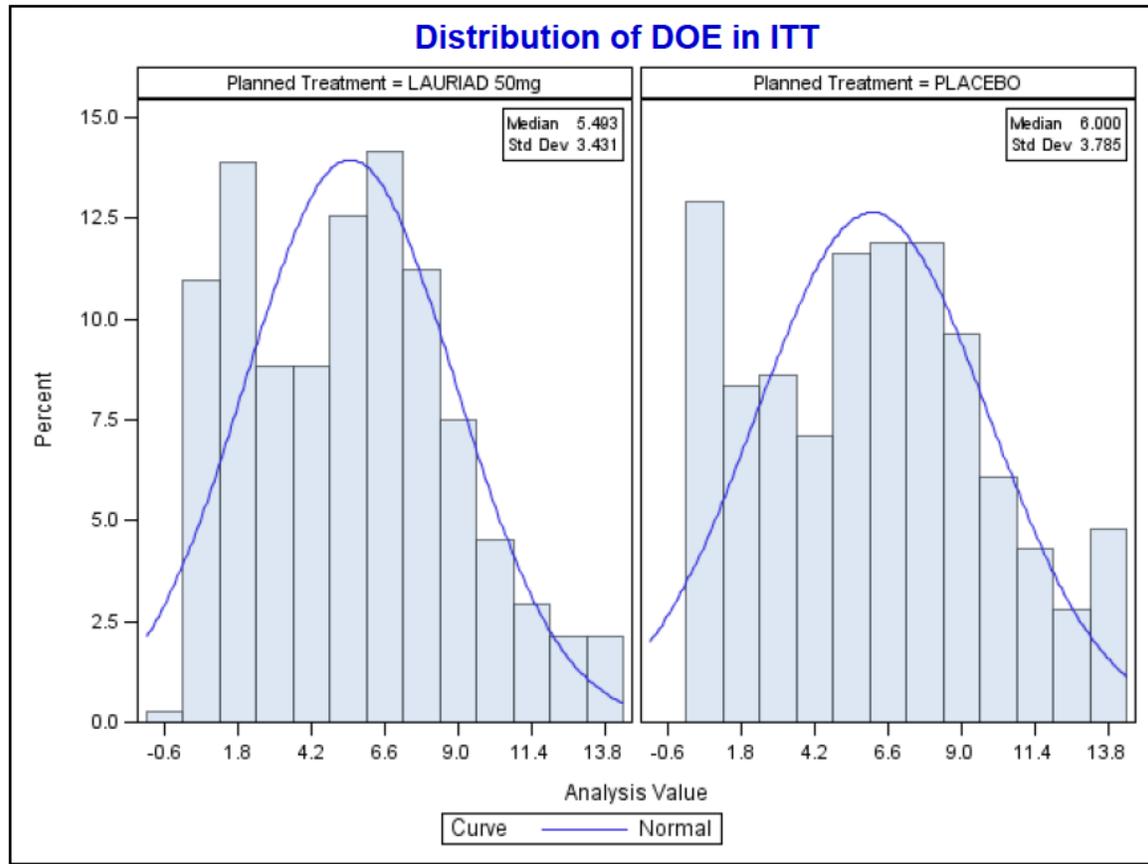
	ABT 50 mg N=376	Placebo N=395	Total N=771
Patients (N [%])	373 (99.2%)	395 (100.0%)	768 (99.6 %)
Events (N)	340	348	688
Censored Observations (N)	33	47	80
Missing Observations (N)	3	0	3
Mean duration in days ± SE	5.67 ± 0.18	6.34 ± 0.20	6.02 ± 0.14
Median in days (95% CI)	5.57 (5.03; 6.01)	6.38 (5.93; 6.97)	6.00 (5.58; 6.40)
Log Rank Test		0.0033	

The FDA analysis of the DOE in the ITT can be seen in the following table:

**FDA results:
 Duration of Episode for Study BA2005/21/02
 (FDA ITT Population)**

ITT population	ABT (N=376)	Placebo (N=395)
Total, N	374	395
Event Observed, n (%)	341	348
Censored, n (%)	33	47
Missing Observations (N)	2	0
Arithmetical Mean (days) ± SE	5.46 ± 0.18	6.08 ± 0.19
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.70 ± 0.18	6.36 ± 0.20
Median (days) (95% CI)	5.58 (5.03, 6.07)	6.38 (5.93, 6.97)
Log-rank Test P-value	0.0049	
Generalized Wilcoxon test (Gehan)	0.0325	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.49 (374)	6.00 (395)
Median Difference (days) (95% CI)	-0.58 (-1.08, -0.03)	
Kruskal-Wallis Test P-value	0.0289	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.25 (341)	5.93 (348)
Median Difference (days) (95% CI)	-0.42 (-0.96, 0.07)	
Kruskal-Wallis Test P-value	0.1100	

Comment: The mean difference in the KM analysis is 0.66 day and the median 0.80 day. These results are consistent with those obtained by the Applicant and confirm the consistency of the DOE in the ITT analysis when applied to the FDA analysis population. As noted in the original review this population includes all patients who received study drug with 5 patients recategorized. When more stringent statistical methods were applied the median difference is smaller (0.58 day) but still greater than 0.5 day. The HL test was applied as it provided more accurate and rigorous statistical results when assessing median outcomes. The following histograms of DOE by treatment arm indicate how the data were skewed towards the right necessitating the application of a more rigorous statistical methodology such as the HL test.



BioAlliance further proposed to overcome the significant treatment-induced imbalance on vesicular lesions and evaluate TTH in the ITT population by considering patients without primary vesicular lesions (patients with aborted episodes) with TTH as 0. This statistical methodology was used in the valacyclovir studies to address the issue of the biased assessment of TTH of primary vesicular lesions “which is by definition a subgroup analysis” (Harmenberg *et al.*, 2010). TTH in the ITT population was thus analyzed by BioAlliance Pharma using a Kaplan Meier analysis and a Log Rank test with patients without primary vesicular lesions considered as having TTH as 0.

Time to Healing in ITT population (TTH of aborted lesions = 0)

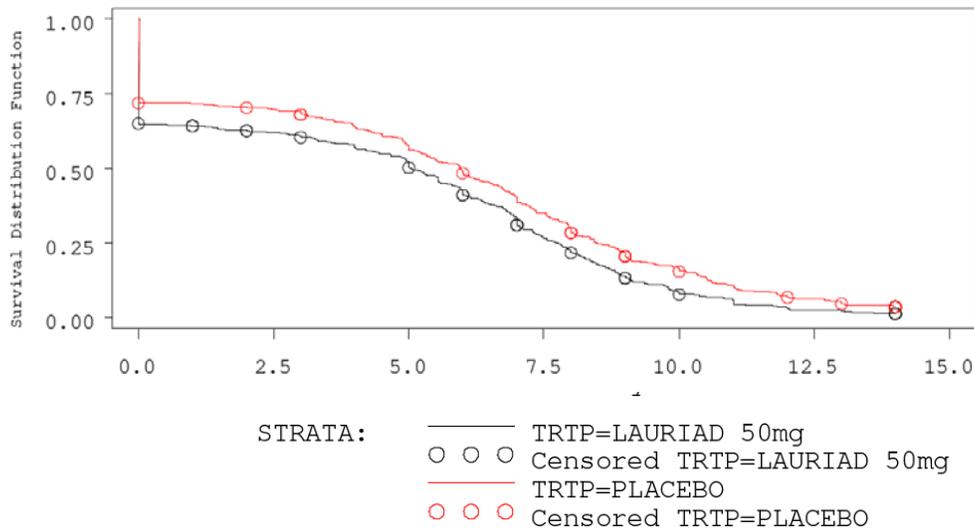
		ABT 50mg	PLACEBO	TOTAL	p-value
Point Estimate (95%CI) (days)	Median (CI)	5.03 [4.40 - 5.58]	5.95 [5.21 - 6.50]	5.50 [5.00 - 5.96]	Log-Rank Test (Wilcoxon Test) 0.0017 (0.0077)
	Mean (SE)	4.58 (0.21)	5.48 (0.22)	5.04 (0.15)	
Total Number of Patients		372	388	760	
Number of Events		352	362	714	
Number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

* Patients with unclassified lesion.

Bioalliance Protocol BA2005/21/02

16FEB2012

Time To Healing of Primary Lesion on ITT Population (time to healing of aborted lesions=0)



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Comment: The significance of such an analysis is unclear given that approximately 31% of the population (35% in the ABT 50 arm and 28% in the placebo arm) did not have vesicular lesions. The Applicant's analysis shows that ABT-50 reduced the TTH in the ITT by a median of 0.92 days or a mean of 0.90 day. This result was associated with a significant p value of 0.0017. However this analysis did not look at a worst case scenario. Rather it included patients who did not complete treatment and who were assigned a TTH of the date they dropped the treatment as well as those without primary lesions.

Note: the Agency Statistical Reviewer performed a number of sensitivity analyses on both the DOE and the TTH in the FDA Revised ITT population with covariates of application and adherence times. These analyses can be found in Appendix 1 of the review. All the FDA analyses support the conclusion as outlined below.

Conclusion: *In conclusion it is reasonable to use the DOE in the ITT population as the primary efficacy parameter for an antiviral agent that not only decreases the TTH of*

vesicular lesions but also increases the number of aborted lesions. Such an agent has an effect on the full spectrum of HL and benefits all patients because it decreases overall morbidity by both shortening the DOE as well as by decreasing the incidence of vesicular lesions. However in order to attain an indication of

(b) (4)
, the Applicant would have to
(b) (4).

When the data were re-analyzed ABT-50 was consistently able to demonstrate a statistically significant and clinically meaningful effect on PHL with a decrease in the DOE of at least 0.81 day ($p=0.003$). The Agency analyses confirmed the Applicant's results.

An issue of concern remains the post hoc nature of the revised primary efficacy analysis from the TTH in the MITT population to the DOE in the ITT population. In this case a determination was made to accept the Applicant's argument because of the lack of clear guidance on the development of Antivirals for the HL application, the fact that DOE in the ITT has been extensively used in previous applications as the primary efficacy parameter, and the fact that in all analyses including stringent sensitivity analyses, ABT 50 was consistently able to achieve a minimum of 0.5 days difference as compared to placebo with regards to the DOE.

b. Data Collection:

As per the DAVP DR letter of 12/7/12:

"The ability to accurately calculate TTH was impeded by the infrequent collection of efficacy data by subjects and the infrequent evaluation of the subjects by the investigators. The primary efficacy endpoint determination was based on investigator assessment. Investigators also relied on subject diary entries to help better define the exact hour of loss of crust. However, subjects were only seen by investigators every other day; whereas in other herpes labialis trials, subjects were seen daily. In addition, subjects only recorded lesion assessments once daily at bedtime. Therefore, the ability to accurately calculate TTH and attempt to demonstrate at least a half day improvement over placebo is severely limited. Of note, in the original protocol submitted in 2006 and up until August 2007 the HL lesions were to be assessed four times daily. The frequency of lesion assessment was changed in a protocol amendment submitted on 8/28/07. However you were repeatedly cautioned as late as 2011 that once daily lesion assessment was not acceptable."

In their response the Applicant states that the data collection was adequate to accurately calculate efficacy endpoints. The patients included in the trial were suffering from recurrent labial herpes and therefore were well able to correctly record date and time of last symptom and loss of crust in their diaries. One of the inclusion criteria was that the patients had to have had at least 4 labial herpes episodes per year and 70% had 5 or more episodes per year.

As per the Applicant, “their accuracy to recognize symptoms and signs of herpes is exemplified by their ability to correctly identify prodromal symptoms. Patients had to visit the investigators within 24 hours after the onset of prodromal symptoms and treatment application to confirm that they were suffering from a recurrence of their herpes episodes. During this visit, the investigators had to record the symptoms and lesions of patients. Among 760 patients, 714 patients had been able to adequately identify and qualify their disease as confirmed by investigators within 24 hours. Reviewing the 239 patients that considered their lesion as abortive, confirmation by investigators was largely given (193 patients had a lesions (erythema or papula) confirmed by the investigators. For only 46 patients, confirmation was not possible by the investigators. Therefore, at least 92.6% of the patients (714/771) were able to adequately recognize prodromal symptoms, as confirmed by investigators, which shows that these recurrent herpetic patients have a very accurate knowledge of their disease and symptoms. It can be inferred that they correctly recorded signs and symptoms on their diary which were used as support for the investigators for their evaluation every other day without impeding the accuracy of their evaluation.”

Comment: The medical literature indicates that 30 – 40% of patients incorrectly identify prodromal symptoms, that is “false prodromes”. Given that the trial was a randomized trial such false prodromes should have been evenly distributed. Further this has not been an issue in previous applications where all patients were included in the ITT analysis. In all the previous applications however patients were assessed at a minimum daily by the investigators.

It is the MO’s opinion that the trial results would have been more accurate with daily investigator assessments. However given that the efficacy data appear consistent with that found in the literature for effective antivirals for HL it is agreed that an ITT analysis will provide real world data and can be accepted in support of this submission despite the infrequent data collection. In order to overcome this factor which led to skewing of the data, median as opposed to mean values were used.

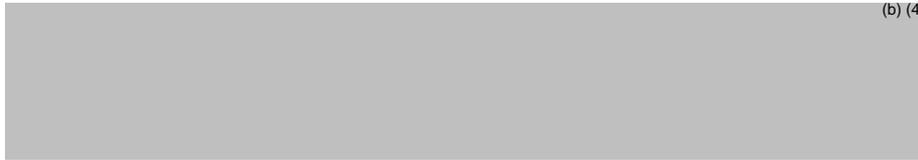
c. Data validation and protocol deviation:

The division “excluded 11 subjects from the efficacy evaluation for protocol violations. These 11 subjects received a prohibited antiviral medication during the trial”. During the meeting held on April 8, 2010 and the teleconference held on July 28, 2010, it was agreed that efficacy should be evaluated on primary endpoint in the ITT population. Usually, no patients are excluded from the ITT population even if they are protocol violators.

Comment: The Applicant is correct that all treated patients are generally included in an ITT analysis. Agency analyses originally relied on an analysis of TTH in the MITT population defined as those with a vesicular lesion. However, for the DOE analysis we agree all treated subjects are included in ITT; For the FDA analyses these 11 subjects were assigned a “worst case scenario” outcome of 14 days.

2. Issue of additional claims in labeling:

For the requested claims:



The Applicant agreed with the DAVP conclusions as expressed in the 12/7/2012 DR letter and agreed to remove these claims from the proposed labeling. Therefore the new proposed indication is:

“ABT is indicated in immunocompetent adult patients for the treatment of recurrent orofacial herpes simplex virus infections.”

3. Issue of Dose selection and drug delivery method

As per the Agency DR letter of 12/7/2012:

At the pre-NDA meeting and throughout our review, we questioned the dose selection and delivery method. Specifically, (b) (4) lead to a greater difference in TTH? Although you imply acyclovir is delivered mostly from licking of the lips, we do not have convincing evidence of the delivery mechanism to the site of action. Therefore, we needed to rely on robust clinical data demonstrating efficacy in one or more trials.”

In their response the Applicant reiterated their position that in order to successfully treat HL, the treatment must be designed to hit early and hard, that is to start treatment during the prodromal period when maximum viral replication occurs and to achieve high concentrations. Acyclovir triphosphate has a high affinity for viral DNA polymerase but a short intracellular half-life < 1 hour. In order to circumvent this acyclovir local formulations have to be administered 4-5 times per day. Valacyclovir, an oral acyclovir prodrug, was designed to increase the exposure to acyclovir.

The drug delivery system selected for ABT is well adapted to the pathogenesis of labial herpes infection. Indeed, early and high antiviral concentrations (markedly over the IC50) at the infection site are needed for a rapid and sustained intracellular penetration of the anti viral agent into the cells infected by HSV.

Comment: The Applicant was able to show that ABT 50 achieves the aforementioned goals in a PK/PD trial. A review of this trial can be found in the CP review document. The DAVP CP team did not dispute the Applicant’s position therefore the proposed dose and duration of treatment are deemed acceptable.

4. Issue of limited enrollment of races other than Caucasian

The Phase 3 trial enrolled 95% Caucasians; therefore, the DAVP ability to conduct analyses based on race was limited.

Note: There are concerns about possible diminished effectiveness of acyclovir products in African Americans.

In their response the Applicant stated that “In the LIP pivotal trial, there were no inclusion or exclusion criteria on race and patients from any race could be included. Thus the distribution of race in the trial likely reflects the distribution of labial herpes in the overall population. Lastly, as ABT is a local treatment, no modification in the metabolism of the drug is to be expected among races and consequently concentrations in saliva and mucosa, which supports the efficacy of ABT, are likely unchanged across races.

Comment: The phase 3 trial was conducted primarily at Eastern European centers (Poland, England, and France) and the population enrolled reflects the demographic of those countries. The DAVP requested a PMC to provide efficacy data on African Americans. It should be noted however that literature support of decreased efficacy in African Americans has not been found.

5. Issue of lack of consistency in the subgroup analyses

When using one trial to demonstrate efficacy, we look for consistency among subgroup analyses. However, results for TTH analyses by study drug application (within 1 hour or greater of appearance of prodromal symptoms) and tablet adhesion times (< 6 hours, 6-12 hours and > 12 hours) did not show consistent results compared to the overall population. These findings again question the robustness of the trial results.

BioAlliance Response:

“Overall, 85% of patients applied treatment within 1 hour. Only 0.5% of patients applied the study treatment when vesicular lesions were present, i.e. at a stage where the effects of antiviral treatments are questionable.

The analysis of duration of episodes in the ITT population and in subgroups of patients having applied treatment within 1 hour and after 1 hour following the onset of prodromal symptoms is given in the tables below. There were no clinically meaningful differences between these subgroups of patients. It should be noted that only few patients applied treatment after 1 hour (n=113) (and even lower after 2 hours, n=64), which underlines that patients knew very well their disease and symptoms, that they highly complied with the protocol, requesting an application at prodromal stage and that they were eager to apply treatment as soon as possible.”

Population DOE	Treatment	n patients	Median values	Difference	p values
ITT	ABT	376*	5.57	0.81	0.003
	Placebo	395	6.38		
ITT (within 1h)	ABT	321**	5.57	0.46	0.112
	Placebo	326	6.03		
ITT (>1h)	ABT	51**	5.54	1.46	0.001
	Placebo	62	7.00		

* 3 missing data, **1 missing data

Comment: The original DAVP subgroup analyses focused on the TTH in the MITT population whereas the Applicant has now provided analyses of DOE in the ITT population. Their results however are further indicative of some inconsistencies in the data as the DOE does not appear to be greatly affected by the application of treatment within one hour of the onset of the prodrome. The subset of patients who applied treatment later is relatively small and therefore the ability to draw firm conclusions is limited. These results are similar to the DAVP statistical reviewer's results in Appendix 1.

Population (TTH + aborted = 0)*	Treatment	n patients	Median values	Difference	p values
mITT + aborted	ABT	372	5.03	0.92	0.0017
	Placebo	388	5.95		
mITT + aborted (within 1h)	ABT	317	5.06	0.86	0.026
	Placebo	321	5.92		
mITT + aborted (>1h)	ABT	51	5.00	1.00	0.011
	Placebo	61	6.00		

* 11 patients missing due to unclassified lesions

Tablet Adhesion Time

Similarly the Applicant provided a re-analysis of the data for tablet adhesion times. In the analysis they provided the DOE for the ITT using KM and a log-rank test method.

Population DOE	Treatment	n patients	Median values	Difference	p values
ITT	ABT	376*	5.57	0.81	0.003
	Placebo	395	6.38		
ITT (<6h)	ABT	43	6.00	1.54	0.104
	Placebo	50	7.54		
ITT (6-12h)	ABT	166**	5.58	1.15	0.040
	Placebo	121	6.73		
ITT (>12h)	ABT	165***	5.33	0.68	0.109
	Placebo	222	6.01		

*3 missing data, ** 1 missing data, ***2 missing data

Population DOE	Treatment	n patients	Median values	Difference	p values
ITT	ABT	376*	5.57	0.81	0.003
	Placebo	395	6.38		
ITT (<6h without replacement)	ABT	10	5.07	3.01	0.049
	Placebo	14	8.08		
ITT (> 6h or <6h with replacement)	ABT	364*	5.58	0.65	0.009
	Placebo	378	6.23		

* 3 missing data

Comment: It should be noted again and as stated in the original review that the ability to draw any conclusions from this subgroup analyses is limited because of the very small sample size for those patients with adhesion times less than 6 hours (24/771 (3%)).

The Agency statistical reviewer performed similar analyses and similar conclusions were reached. These analyses can be found in Appendix 1 of this review. It should be noted that these are secondary efficacy analyses and their significance in determining a regulatory action is of lesser importance.

Overall Conclusion: *In conclusion the reanalysis of the data utilizing the DOE in the ITT population indicates that ABT-50 achieves both a consistently clinically and borderline statistically significant difference in the DOE between those treated with ABT 50 and those treated with placebo.*

The use of the DOE in the ITT has traditionally been used in other applications as the primary endpoint for HL trials. There is merit to its use as it provides a more global assessment of the population that presents with HL symptoms. It is possible that ABT 50 increases the percentage of aborted lesions and thus decreases the morbidity associated with this disease.

The risks of ABT 50 are negligible. As noted in the safety analysis there were no SAEs associated with its use and most reported AEs were mild and usually were related to oral cavity discomfort. The benefits of this product include the one time use of a topical product as opposed to the five times a day application of the approved ACV cream or the oral administration of valacyclovir. Overall it seems reasonable to recommend an approval for ABT 50 for the revised requested indication of the treatment of recurrent herpes labialis in immunocompetent patients as the benefits overall outweigh any risks.

Pediatrics:

(Please see original clinical/statistical review section 7.6.3 for discussion on pediatric issues)

There were numerous discussions with the Applicant regarding the submission of a waiver or a deferral depending on the pediatric populations studied. It should again be noted that to date ABT 50 has not been studied in any patients less than 18 years of age.

Bioalliance received a deferral in Europe for patients ages 10 and greater and will perform a PK study there. However the DAVP disagrees with the need for a PK assessment as the only predictor of compliance, efficacy, and safety especially in patients in the youngest age groups.

After review of other applications including XERESE cream it seems reasonable to request that the Applicant follow a similar pediatric plan for ABT 50; that is that it should be studied for both efficacy and safety in children as young as 6 years with a maximum of 17 years. A reasonable number of patients to be studied will be determined at the time of protocol submission with a greater number of younger patients given the potential choking hazards and the need for their assessment from both an efficacy and a safety standpoint. A deferral would then be granted for this age group and a waiver is recommended for patients less than six years of age.

After discussion with the PERC committee a partial waiver will be issued for pediatric patients less than 6 years for the following reasons:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
- Evidence suggests that product would be unsafe in pediatric subpopulations under 6 years of age. Acyclovir Lauriad is a mucoadhesive buccal tablet (ABT) and is to be applied or placed on the gum until the drug completely dissolves. This type of application may be unsafe in young children due to potential choking hazards.
- The nature of the mucoadhesive tablet use requires the need for its accurate application in the oral cavity- i.e. the timing of the application needs to be within the first hour of onset of prodromal symptoms. Young children may not be able to identify prodromal symptoms to know when to apply the medication.

It should be noted that the PERC committee was primarily concerned with safety issues and considered safety the primary rationale for the partial waiver.

A deferral of pediatric studies will be issued for patients ages 6 through 17. The final basis for the deferral is that approval for acyclovir Lauriad™ buccal tablet in adults is anticipated before pediatric studies will be completed [Section 505B(a)(3)(A)(i) of PREA]. There are other antiviral agents such as acyclovir cream approved for the treatment of HL in children. In addition, herpes labialis is a non-serious condition in the majority of patients. The DAVP requests safety and efficacy data prior to an approval for use in children and adolescents ages 6 – 17 because of the nature of the mucoadhesive tablet, the need for its accurate application in the oral cavity, the timing of the application (within the first hour of onset of prodromal symptoms) and the need to replace if it falls out within the first 6 hours of use.

A PREA commitment will be issued for the aforementioned pediatric study.

Labeling

Agreed upon clinical sections of labeling can be seen below. At the time of this review labeling negotiations are still underway and certain sections may sustain changes.

Content modifications were made to section 6, ADVERSE REACTIONS. This section usually includes treatment emergent adverse events that are related to treatment. Due to the relatively infrequent occurrence of adverse events associated with Sitavig, it was determined that a more accurate picture of the adverse event profile could be provide by including a table of adverse events all causality occurring in at least 1% of patients (as opposed to 5%). This ensured that events such as application site pain or discomfort would be conveyed in the USPI.

The CLINICAL STUDIES section (14) was written in order to be consistent with other antivirals approved for the HL indication. The exact differences in the mean and median durations of episodes are not provided. Rather a statement that these were at least half a day shorter in patients treated with SITAVIG compared with patients treated with placebo was made.

The following are agreed upon clinical sections of the USPI:

1 INDICATIONS AND USAGE

SITAVIG is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults.

2 DOSAGE AND ADMINISTRATION

2.1 Basic Dosing Information

One SITAVIG 50 mg buccal tablet should be applied as a single dose to the upper gum region (canine fossa).

2.2 Administration Instructions

SITAVIG should be applied as soon as the first prodromal symptoms or signs occur. The tablet should be applied with a dry finger immediately after taking it out of the blister. The tablet should be placed to the upper gum just above the incisor tooth (canine fossa) and held in place with a slight pressure over the upper lip for 30 seconds to ensure adhesion. For comfort the rounded side should be placed to the upper gum, but either side of the tablet can be applied. The tablet should be applied on the same side of the mouth as the (b)(4).

Once applied, SITAVIG stays in position and gradually dissolves during the day. [See *Clinical Pharmacology (12.3)*]. In addition,

- SITAVIG should not be crushed, chewed or swallowed.
- (b)(4)
- If SITAVIG does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately. If the tablet cannot be repositioned, a new tablet should be placed.
- If SITAVIG is swallowed within the first 6 hours, the patient should drink a glass of water and a new tablet should be applied. [See *Patient Counseling Information (17)*].
- Sitavig does not need to be reapplied if the tablet falls out or is swallowed after the first 6 hours

4 CONTRAINDICATIONS

SITAVIG is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to acyclovir, milk protein concentrate, or any other component of the product.

6. ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The overall safety of SITAVIG was assessed in 378 adult subjects having at least 4 herpes labialis episodes the previous year.

One randomized, double-blind, placebo controlled trial was conducted in patients with recurrent herpes labialis (cold sores). In this trial, 378 HSV infected subjects used SITAVIG as a single dose, and 397 subjects used placebo.

Selected treatment emergent adverse events without regard to causality and reported in at least 1% of patients can be seen in Table 1.

Table 1 Selected Treatment Emergent Adverse Events reported in at least 1% of patients

Event	Sitavig N = 378	Placebo N = 397
Nervous System Disorders		
Headache	3%	3%
Dizziness	1%	1%
Lethargy	1%	0
Gastrointestinal system Disorders		
Gingival Pain	1%	0.3%
Aphthous Stomatitis	1%	0
Administration Site Conditions		
Application Site Pain	1%	1%
Application Site Irritation	1%	0
Skin and Subcutaneous Disorders		
Erythema	1%	0.3%
Rash	1%	0.3%

The treatment emergent adverse events considered related to treatment that occurred in greater than or equal to 1% of patients included headache (1% Sitavig vs. 2% placebo) and application site pain (1% both arms). There was no discontinuation of SITAVIG due to adverse drug reactions. Most treatment related adverse events were mild or moderate in severity. One report of headache from both treatment arms was classified as severe.

8.4 Pediatric Use

Safety and effectiveness of SITAVIG in pediatric patients have not been established. The ability of pediatric patients to comply with the application instructions has not been evaluated.

8.5 Geriatric Use

Clinical studies of SITAVIG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Immunocompromised Patients

The safety of SITAVIG has not been studied in immunocompromised subjects.

14 CLINICAL STUDIES

Study in Patients with Recurrent Herpes Labialis (cold sores)

The efficacy and safety of SITAVIG was evaluated in a randomized, double-blind, placebo-controlled, patient-initiated, multicenter trial comparing SITAVIG 50 mg administered as a single dose (n = 378) to placebo (n = 397) in patients with recurrent herpes labialis (cold sores). A total of 376 Sitavig treated patients and 395 placebo treated patients were included in the Intent to Treat (ITT) efficacy population defined as all patients who took study treatment and who had a start date and time of treatment initiation recorded. The mean age was 41.0 years (range: 18-80 years) and the majority of patients were female (68.6%), and Caucasian (94.9%). All patients had at least 4 herpes episodes in the previous year of whom 68.4% had ≥ 5 episodes. Patients were instructed to initiate treatment at the first symptom of recurrence by applying the tablet to the buccal mucosa in the canine fossa. If the tablet was detached within the first 6 hours, subjects were instructed to reapply a tablet.

The mean and median durations of the recurrent herpes labialis episode (ITT population, n=771) were at least half a day shorter in patients treated with SITAVIG compared with patients treated with placebo.

PPI and Instructions for Use:

Relevant changes were also made to the PPI and Instructions for Use sections of the label by DMPP. These sections are still under negotiation at the time this review was completed.

APPENDIX 1: STATISTICAL COMMENTS and ADDITIONAL ANALYSES:

In order to further bolster confidence in the results the FDA statistical reviewer performed sensitivity analyses with the following revisions to the Applicant's ITT population:

- The TTH of five patients were corrected as noted previously
- Eleven patients who did not have lesion stage information were excluded from the analysis
- The TTH of 29 MITT patients assessed as "Not Healed - min(14, time of event)", were imputed to 14 days
- The eleven MITT patients (3 in the ABT 50 arm and 8 in placebo arm) who took a prohibited CM were handled in one of two ways, they were either excluded from the TTH analysis or included with their TTH imputed to 14 days; there were an additional four ITT but not MITT patients who were handled in the same way.

These revisions served to establish a "worst case scenario" approach and tested the robustness of the ITT analysis. The results can be seen in the tables below. In both analyses the mean and median TTH were above the 0.5 day clinical significance level independent of the analysis method used. In the HL Estimate/Event observed only the median differences were almost ZERO. This was due to the imputation of TTH=0 for all patients who were not in the MITT population, which forced about 31% of patients with TTH=0 as in the histograms of TTHs in ITT by treatment arm below. As a result, the median differences generated with the HL method were nearly ZERO even though the median difference were numerically greater than 0.5 day.

**FDA Analysis results of TTH in ITT
 (Includes 15 patients who took CM)**

ITT population	ABT (N=376)	Placebo (N=395)
Missing	4	7
Total, N	372	388
Event Observed, n (%)	349 (93.8%)	358 (92.3%)
Censored, n (%)	23 (6.2%)	30 (7.7%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.80 ± 0.22	5.67 ± 0.23
Median (days) (95% CI)	5.06 (4.45, 5.79)	6.00 (5.32, 6.65)
Log-rank Test P-value	0.0151	
Generalized Wilcoxon test (Gehan)	0.0114	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.05 (372)	6.00 (388)
Median Difference (days) (95% CI)	-0.07 (-1.03, 0.00)	
Kruskal-Wallis Test P-value	0.0083	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.93 (349)	5.44 (358)
Median Difference (days) (95% CI)	0.0 (-0.75, 0.0)	
Kruskal-Wallis Test P-value	0.0219	

Life Test

Mean difference = 0.87 day

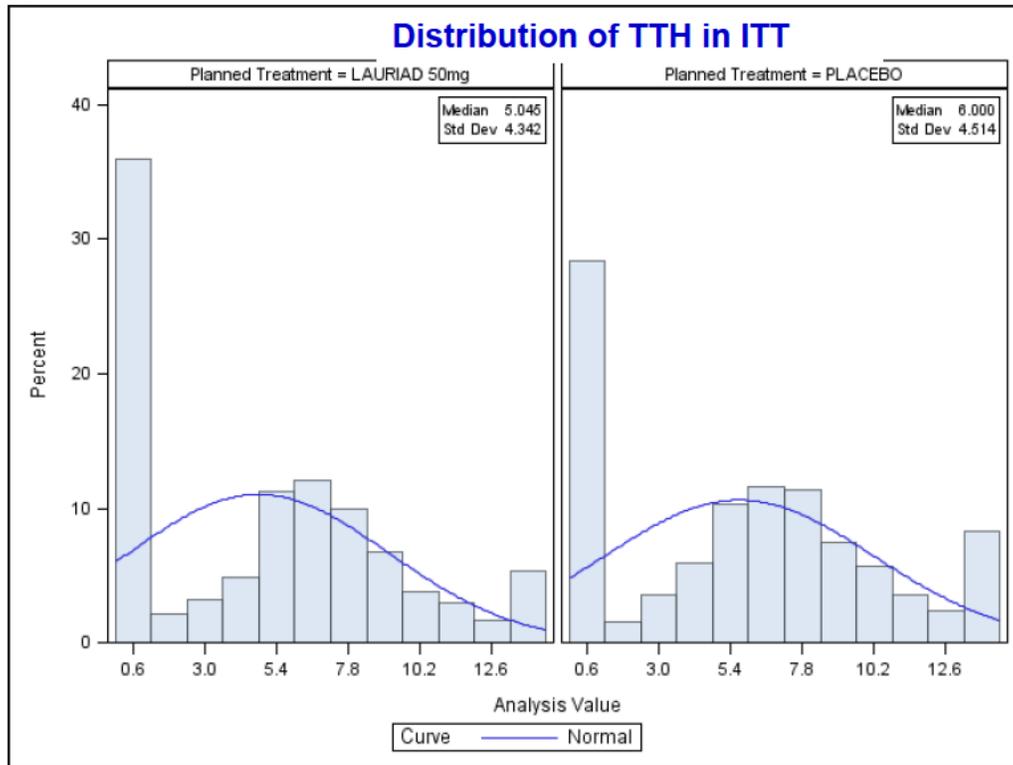
Median difference = 0.94 day

HL Estimates

Median difference = -0.07 day

HL Estimates/Event observed only

Median Difference = 0.00 day



**FDA Analysis results of TTH in ITT
 (Excludes 15 patients who took CM)**

ITT population	ABT (N=370)	Placebo (N=386)
Missing	4	7
Total, N	366	379
Event Observed, n (%)	346 (94.5%)	357 (94.2%)
Censored, n (%)	20 (5.5%)	22 (5.8%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.77 ± 0.22	5.51 ± 0.23
Median (days) (95% CI)	5.06 (4.45, 5.79)	5.94 (5.16, 6.50)
Log-rank Test P-value	0.0457	
Generalized Wilcoxon test (Gehan)	0.0273	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.05 (366)	5.94 (379)
Median Difference (days) (95% CI)	0 (-0.93, 0.00)	
Kruskal-Wallis Test P-value	0.0204	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.97 (346)	5.48 (357)
Median Difference (days) (95% CI)	0.0 (-0.73, 0.0)	
Kruskal-Wallis Test P-value	0.071	

Life Test

Mean difference = 0.74 day

Median difference = 0.88 day

HL Estimates

Median difference = 0.00 day

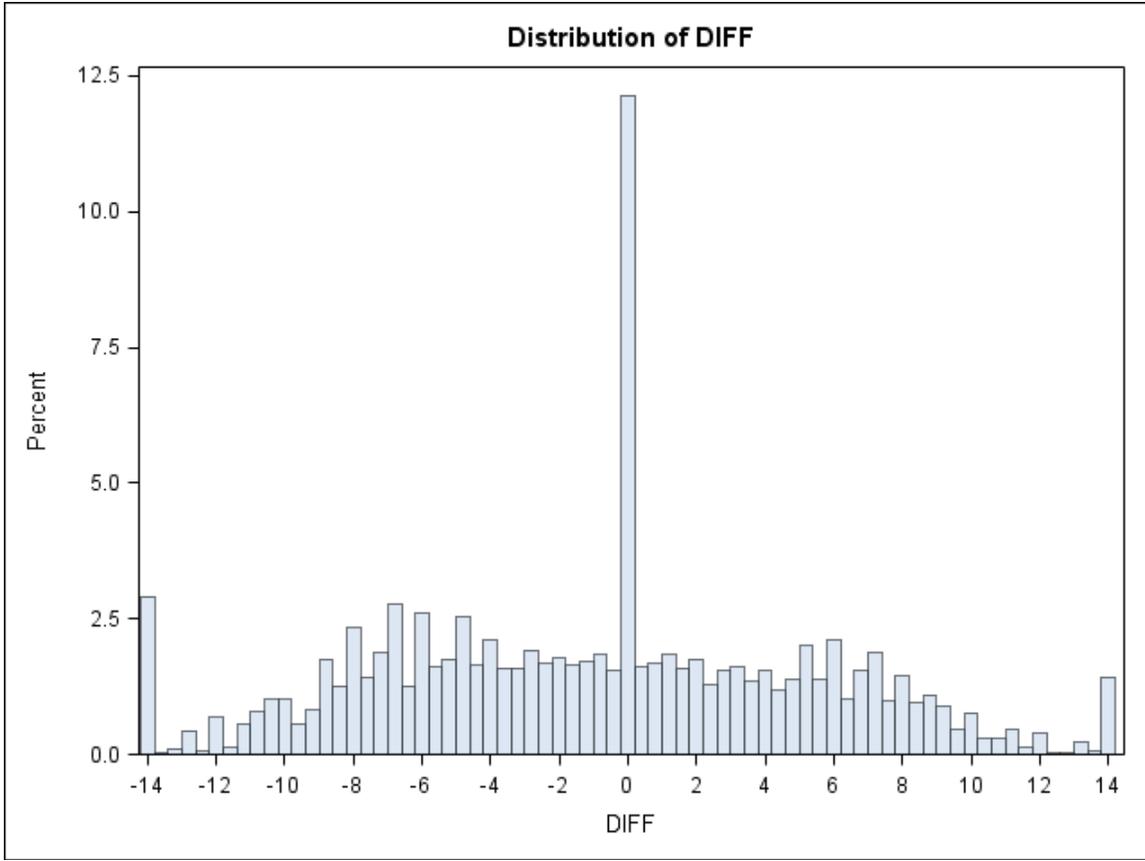
HL Estimates/Event observed only

Median Difference = 0.00 day

Statistical Comment: The TTH in ITT population analysis presented above is a sensitivity analysis because the analysis population is not real ITT population and this is just post-hoc analysis. The purpose of this analysis is to include both aborted group and MITT group in the analysis to show that the drug did shown some benefit, as the test P-value is significant, even use the TTH, the original primary efficacy endpoint. However, the analysis population changed here from the MITT to revised ITT in the analysis.

Because of the imputation of TTH=0 for 31% of subjects, the median differences from the Hodges-Lehmann method were almost ZERO. This is just a point estimator, and only means that about 50% of differences is equal or above ZERO and 50% of difference is equal or below ZERO. In here, there are about 12% of pair-wise differences were ZERO as the histogram of all pair-wise difference of TTH between two arms shown below for the analysis of including 15 subjects. The percentiles of the pair-wise difference of TTH between two arms are listed the table below. As you can see, 25% percentile is -5.6 days, and 75% percentile is 3.6 days, ie 25% of pair-wise differences is equal or less than -5.6 days, and 25% of pair-wise differences is equal or above 3.6 days.

<i>Variable</i>	<i>Mean</i>	<i>25% percentile</i>	<i>Median</i>	<i>75% percentile</i>
<i>TTH in ITT</i>	-0.89	-5.61	-0.07	3.56



Since DOE in ITT analysis is used as the primary efficacy endpoint here. TTH in revised ITT analysis is a sensitivity analysis to check the consistency of results.

Other Subgroup analyses:

Major covariates:

- subjects with an adherence time less than 6 hours;
- subjects who applied the tablet less than 1 hour after prodromal symptoms occurred;

Application of Treatment within 1 hour after Prodromal Symptoms for Study BA2005/21/02 (ITT Population)

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	4	7
Total Observed (N)	372	388
Within 1 hour, n (%)	321 (86.3%)	326 (84.0%)
After 1 hour, n (%)	51	62

1. Results of TTH on ITT for subjects who applied drug within 1 hour of occurrence of symptoms

1.1 Analysis results of TTH: included 15 subjects who took CM in ITT with their TTH=14 & TTH=0 for aborted subjects (239 subjects)

ITT population	ABT (N=321)	Placebo (N=326)
Missing	4	5
Total, N	317	321
Event Observed, n (%)	300 (94.6%)	300 (93.5%)
Censored, n (%)	17 (5.4%)	21 (6.5%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.83 ± 0.24	5.55 ± 0.25
Median (days) (95% CI)	5.07 (4.45, 5.82)	5.94 (5.10, 6.50)
Log-rank Test P-value	0.0741	
Generalized Wilcoxon test (Gehan)	0.0616	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.06 (317)	5.94 (321)
Median Difference (days) (95% CI)	0.0 (-0.90, 0.00)	
Kruskal-Wallis Test P-value	0.0513	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.99 (300)	5.40 (300)
Median Difference (days) (95% CI)	0.0 (-0.60, 0.0)	
Kruskal-Wallis Test P-value	0.0927	

1.2 Analysis results of TTH: excluded 15 subjects who took CM in ITT & TTH=0 for aborted subjects (239 subjects)

ITT population	ABT (N=316)	Placebo (N=319)
Missing	4	5
Total, N	312	314
Event Observed, n (%)	298 (95.5%)	299 (95.2%)
Censored, n (%)	14 (4.5%)	15 (4.8%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.78 ± 0.24	5.41 ± 0.25
Median (days) (95% CI)	5.06 (4.45, 5.79)	5.91 (5.00, 6.30)
Log-rank Test P-value	0.1320	
Generalized Wilcoxon test (Gehan)	0.0958	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.05 (312)	5.91 (314)
Median Difference (days) (95% CI)	0.0 (-0.78, 0.00)	
Kruskal-Wallis Test P-value	0.0807	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.00 (298)	5.40 (299)
Median Difference (days) (95% CI)	0.0 (-0.60, 0.0)	
Kruskal-Wallis Test P-value	0.1013	

Subgroup analysis: Adhesion time in hours (ExDur="<6h", "6-12h", ">12h") --

Adhesion Time in Hours for Study BA2005/21/02 (ITT Population)

Adhesion Time in hrs	Treatment Arm (ITT)	
	ABT (N=376)	Placebo (N=395)
Missing	2	2
Total N	374	393
<6	43 (11.5%)	50 (12.7%)
6-12	166 (44.4%)	121 (30.8%)
>12	165 (44.1%)	222 (56.5%)

In the group of adhesion time of first tablet <6 hours

1.3 Analysis results of TTH: included 15 subjects who took CM in ITT with their TTH=14 & TTH=0 for aborted subjects

ITT population	ABT (N=43)	Placebo (N=50)
Missing	0	1
Total, N	43	49
Event Observed, n (%)	39 (90.7%)	45 (91.8%)
Censored, n (%)	4 (9.3%)	4 (8.2%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	5.40 ± 0.65	6.23 ± 0.69
Median (days) (95% CI)	6.00 (4.45, 7.69)	7.54 (4.95, 8.87)
Log-rank Test P-value	0.4239	
Generalized Wilcoxon test (Gehan)	0.3686	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.00 (43)	7.54 (49)
Median Difference (days) (95% CI)	-0.06 (-2.72, 0.38)	
Kruskal-Wallis Test P-value	0.3695	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.94 (39)	6.00 (45)
Median Difference (days) (95% CI)	-0.26 (-2.60, 0.0)	
Kruskal-Wallis Test P-value	0.2532	

1.4 Analysis results of TTH: excluded 15 subjects who took CM in ITT & TTH=0 for aborted subjects

ITT population	ABT (N=41)	Placebo (N=47)
Missing	0	1
Total, N	41	46
Event Observed, n (%)	39 (95.1%)	44 (95.6%)
Censored, n (%)	2 (4.9%)	2 (4.4%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	5.08 ± 0.64	6.03 ± 0.68
Median (days) (95% CI)	6.00 (0.00, 7.44)	7.02 (4.80, 8.87)
Log-rank Test P-value	0.2433	
Generalized Wilcoxon test (Gehan)	0.2513	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.00 (41)	7.02 (46)
Median Difference (days) (95% CI)	-0.35 (-2.87, 0.05)	
Kruskal-Wallis Test P-value	0.2526	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.94 (39)	6.24 (44)

Median Difference (days) (95% CI)	-0.46 (-2.81, 0.0)
Kruskal-Wallis Test P-value	0.2017

In the group of adhesion time of first tablet 6-12 hours

1.5 Analysis results of TTH: included 15 subjects who took CM in ITT with their TTH=14 & TTH=0 for aborted subjects

ITT population	ABT (N=166)	Placebo (N=121)
Missing	3	4
Total, N	163	117
Event Observed, n (%)	152 (93.2%)	108 (92.3%)
Censored, n (%)	11 (6.8%)	9 (7.7%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.64 ± 0.34	5.42 ± 0.38
Median (days) (95% CI)	5.03 (2.96, 5.92)	5.92 (4.50, 6.81)
Log-rank Test P-value	0.4112	
Generalized Wilcoxon test (Gehan)	0.1263	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.03 (163)	5.91 (117)
Median Difference (days) (95% CI)	-0.07 (-1.62, 0.38)	
Kruskal-Wallis Test P-value	0.1130	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.23 (152)	5.33 (108)
Median Difference (days) (95% CI)	0.0 (-1.41, 0.0)	
Kruskal-Wallis Test P-value	0.1270	

1.6 Analysis results of TTH: excluded 15 subjects who took CM in ITT & TTH=0 for aborted subjects

ITT population	ABT (N=163)	Placebo (N=120)
Missing	3	4
Total, N	160	116
Event Observed, n (%)	150 (93.7%)	108 (93.1%)
Censored, n (%)	10 (6.3%)	8 (6.9%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.65 ± 0.34	5.35 ± 0.38
Median (days) (95% CI)	5.05 (3.19, 5.92)	5.91 (4.50, 6.81)
Log-rank Test P-value	0.4787	
Generalized Wilcoxon test (Gehan)	0.1636	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.05 (160)	5.91 (116)
Median Difference (days) (95% CI)	0.0 (-1.49, 0.00)	
Kruskal-Wallis Test P-value	0.1477	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.69 (150)	5.33 (108)
Median Difference (days) (95% CI)	0.0 (-1.32, 0.0)	
Kruskal-Wallis Test P-value	0.1597	

In the group of adhesion time of first tablet >12 hours

1.7 Analysis results of TTH: included 15 subjects who took CM in ITT with their TTH=14 & TTH=0 for aborted subjects

ITT population	ABT (N=165)	Placebo (N=222)
Missing	1	2
Total, N	164	220
Event Observed, n (%)	157 (95.7%)	204 (92.7%)
Censored, n (%)	7 (4.3%)	16 (7.3%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.67 ± 0.32	5.61 ± 0.31
Median (days) (95% CI)	4.95 (4.00, 5.70)	5.95 (5.00, 6.74)
Log-rank Test P-value	0.0148	
Generalized Wilcoxon test (Gehan)	0.0675	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	4.94 (164)	5.95 (220)
Median Difference (days) (95% CI)	-0.16 (-1.53, 0.00)	
Kruskal-Wallis Test P-value	0.0526	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.67 (157)	5.48 (204)
Median Difference (days) (95% CI)	0.0 (-1.00, 0.0)	
Kruskal-Wallis Test P-value	0.1898	

1.8 Analysis results of TTH: excluded 15 subjects who took CM in ITT & TTH=0 for aborted subjects (239 subjects)

ITT population	ABT (N=164)	Placebo (N=217)
Missing	1	2
Total, N	163	215
Event Observed, n (%)	156 (95.7%)	204 (94.9%)
Censored, n (%)	7 (4.3%)	11 (5.1%)
LifeTest (K-M) on TTH		
Mean (days) ± SE	4.70 ± 0.32	5.41 ± 0.30
Median (days) (95% CI)	5.00 (4.00, 5.86)	5.91 (4.94, 6.53)
Log-rank Test P-value	0.0708	
Generalized Wilcoxon test (Gehan)	0.1576	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	4.95 (163)	5.91 (215)
Median Difference (days) (95% CI)	0.0 (-1.21, 0.00)	
Kruskal-Wallis Test P-value	0.1268	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.75 (156)	5.48 (204)
Median Difference (days) (95% CI)	0.0 (-0.98, 0.0)	
Kruskal-Wallis Test P-value	0.2133	

2. 2nd endpoints:

DOE Subgroup analyses:

Major covariates:

- subjects with an adhesion time less than 6 hours;
- subjects who applied the tablet less than 1 hour after prodromal symptoms occurred;

Subgroup analysis: Apply treatment within 1 hour (TTAPPLfl="Y") -- 647

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	4	7
Total Observed (N)	372	388
Within 1 hour, n (%)	321 (86.3%)	326 (84.0%)
After 1 hour, n (%)	51	62

2.1 DOE for subjects who applied drug within 1 hour (ITT)

ITT population	ABT (N=321)	Placebo (N=326)
Missing	1	0
Total, N	320	326
Event Observed, n (%)	294 (91.9%)	294 (90.2%)
Censored, n (%)	26 (8.1%)	32 (9.8%)
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.73 ± 0.20	6.12 ± 0.21
Median (days) (95% CI)	5.57 (5.01, 6.11)	6.03 (5.61, 6.84)
Log-rank Test P-value	0.1414	
Generalized Wilcoxon test (Gehan)	0.2347	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.49 (320)	5.94 (326)
Median Difference (days) (95% CI)	-0.27 (-0.89, 0.25)	
Kruskal-Wallis Test P-value	0.3069	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.26 (294)	5.91 (294)
Median Difference (days) (95% CI)	-0.28 (-0.89, 0.25)	
Kruskal-Wallis Test P-value	0.3051	

2.2 DOE for subjects who applied drug after 1 hour

ITT population	ABT (N=51)	Placebo (N=62)
Missing	0	0
Total, N	51	62
Event Observed, n (%)	45 (90.0%)	49 (79.0%)
Censored, n (%)	5 (10.0%)	13 (21.0%)
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.19 ± 0.43	6.98 ± 0.50
Median (days) (95% CI)	5.98 (3.27, 6.75)	7.00 (5.49, 8.69)
Log-rank Test P-value	0.0008	
Generalized Wilcoxon test (Gehan)	0.0195	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.33 (51)	7.00 (62)
Median Difference (days) (95% CI)	-2.06 (-3.67, -0.65)	
Kruskal-Wallis Test P-value	0.0046	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.17 (46)	6.00 (49)
Median Difference (days) (95% CI)	-0.94 (-2.19, 0.43)	
Kruskal-Wallis Test P-value	0.1850	

2.3 Adhesion Time in Hours for Study BA2005/21/02 (ITT Population)

Adhesion Time in hrs	Treatment Arm (ITT)	
	ABT (N=376)	Placebo (N=395)
Missing	2	2
Total N	374	393
<6	43 (11.5%)	50 (12.7%)
6-12	166 (44.4%)	121 (30.8%)
>12	165 (44.1%)	222 (56.5%)

In the response analyses:

2.4 DOE for subjects who had Adhesion time of first tablet <6 hours

ITT population	ABT (N=43)	Placebo (N=50)
Missing	0	0
Total, N	43	50
Event Observed, n (%)	39 (90.7%)	45 (90.0%)
Censored, n (%)	4 (9.3%)	5 (10.0%)
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.77 ± 0.45	6.59 ± 0.56
Median (days) (95% CI)	6.00 (5.00, 7.69)	7.54 (5.00, 8.87)
Log-rank Test P-value		0.1039
Generalized Wilcoxon test (Gehan)		0.3698
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.94 (43)	6.00 (49)
Median Difference (days) (95% CI)		-0.63 (-2.22, 0.88)
Kruskal-Wallis Test P-value		0.3713
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.94 (39)	6.00 (45)
Median Difference (days) (95% CI)		-0.60 (-2.28, 0.90)
Kruskal-Wallis Test P-value		0.3746

2.5 DOE for subjects who had Adhesion time of first tablet 6-12 hours

ITT population	ABT (N=166)	Placebo (N=121)
Missing	1	0
Total, N	165	121
Event Observed, n (%)	150 (90.9%)	101 (83.5%)
Censored, n (%)	15 (9.1%)	20 (16.5%)
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.62 ± 0.29	6.52 ± 0.34
Median (days) (95% CI)	5.58 (4.99, 6.58)	6.73 (5.90, 7.35)
Log-rank Test P-value		0.0356
Generalized Wilcoxon test (Gehan)		0.0443
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.53 (165)	6.30 (121)
Median Difference (days) (95% CI)		-0.90 (-1.74, 0.00)
Kruskal-Wallis Test P-value		0.0496
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.39 (150)	5.96 (101)
Median Difference (days) (95% CI)		-0.48 (-1.36, 0.36)
Kruskal-Wallis Test P-value		0.2595

2.6 DOE for subjects who had Adhesion time of first tablet >12 hours

ITT population	ABT (N=165)	Placebo (N=222)
Missing	1	0
Total, N	164	222
Event Observed, n (%)	151 (92.1%)	201 (90.5%)
Censored, n (%)	13 (7.9%)	21 (9.5%)
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.73 ± 0.27	6.16 ± 0.27
Median (days) (95% CI)	5.33 (4.66, 6.16)	6.01 (5.24, 6.84)
Log-rank Test P-value	0.1471	
Generalized Wilcoxon test (Gehan)	0.4023	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.21 (164)	5.95 (222)
Median Difference (days) (95% CI)	-0.31 (-1.07, 0.43)	
Kruskal-Wallis Test P-value	0.4041	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.00 (151)	5.79 (201)
Median Difference (days) (95% CI)	-0.31 (-1.07, 0.42)	
Kruskal-Wallis Test P-value	0.3984	

APPENDIX 2:

XERESE

Three studies, 2 assessed efficacy. In the primary study, superiority vs. placebo:

- Primary endpoint was the proportion of subjects with non-ulcerative recurrences, defined as the proportion of patients in whom the study recurrences do not progress beyond the papule stage.
- Secondary endpoints were episode duration and duration to normal skin.
- Episode duration was defined as investigator assessment of time from treatment initiation to loss of hard crust for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.
- Episode duration to normal skin was defined as investigator assessment of time from treatment initiation to normal skin for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.
- It appears that 'episode duration' and 'episode duration to normal skin' are deviated from normal distributions and therefore **means would not be appropriate** to use for comparisons. In general, means are 0.6-0.9 days greater than medians. Hence, the FDA statistical reviewer applied Hodges-Lehmann's (H-L) approach to estimate median treatment differences.
- Analyses conducted on the ITT population and the missing 'time-to' parameters were imputed using the Applicant's approach.

Result

Using the H-L method, the median episode duration was **0.38** days shorter for the ME-609 arm (4.77 days) than the vehicle arm (5.09 days), $p=0.062$ by the Kruskal-Wallis test.

The median duration to no signs or symptoms among those with NUR was numerically longer in the ME-609 (4.51 days) than the vehicle (3.77 days) arm, (part 1). However, one might not confer any conclusions because these subgroups were not comparable.

The median H-L episode duration was 0.15 days shorter for the ME609 arm (4.77 days) than the acyclovir arm (4.94 days), $p>0.05$ by Kruskal-Wallis test.

Comment: The efficacy data of 609-04 show that ME-609 cream is numerically superior in treatment of herpes labialis compared with acyclovir and vehicle. However, the significance levels do not meet success criteria pre-defined for a single registration study. Ultimately decision to approve based on totality of evidence.

Comparison to sitavig:

- Different primary endpoint
- Consideration given to using time to return to normal skin in future submissions.
- Secondary endpoints consistent with DOE
- Medians assessed via HL method
- ITT population
- Statistical significance not reached but approval based on totality

VALTREX:

Targeted both healing and prevention.

Two phase 3, randomized, double-blind, placebo-controlled clinical trials demonstrate a modest treatment benefit of one-half to one day as compared to placebo.

Subjects assessed daily.

The primary efficacy measure in HS230027 and the secondary efficacy measure in HS230028 was **clinician-based duration of episode**.

Clinician-based duration of episode was measured in whole days, from the day a subject took the first dose of study drug until the day the clinician assessed the lesion as healed, inclusive.

For subjects who experienced a vesicular lesion, healing was defined as the loss of crust (residual erythema may have been present).

For subjects whose lesions were not vesicular in nature, healing was defined as the return to normal skin, and/or the cessation of all signs and symptoms (including any residual erythema).

Subjects with a blocked lesion could experience a raised red bump (papule) without subsequent blister (vesicle) formation.

Other efficacy measures in HS230027 and HS230028 were time to lesion healing, time to cessation of pain/discomfort and diary-based duration of episode.

FDA analysis considered the efficacy measures of clinician-based duration of episode and prevention/blockage of cold sore lesion development as the two co-primary endpoints for both studies.

Comment: DOE used a primary efficacy parameter. ITT population assessed.

Compared to placebo, the clinician-based duration of episode was significantly reduced by 0.5 to 1.0 days in the valacyclovir 1 and 2 day treatment groups (ss)

Valcyclovir ITT

	Placebo	Val 1 day	Val 2 days
Median DOE (days)			
Study 27	5	4	4.5
Study 28	5.5	5	5
Mean DOE (days)			
Study 27	6.1	5	5.3
Study 28	6.4	5.4	5.5

Valcyclovir PP

	Placebo	Val 1 day	Val 2 days
Median DOE (days)			
Study 27	4.5	4	4
Study 28	5.5	5	4.5
Mean DOE (days)			
Study 27	5.5	4.5	4.6
Study 28	5.5	4.7	4.5

Comparison to sitavig:

- Similar subjects
- Val seen daily, sitavig every other day
- DOE in ITT vs. TTH in MITT
- Decrease in duration ranging from 0.5 – 1 day mean or median

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/s/

M R ALIVISATOS
03/19/2013

KIMBERLY A STRUBLE
03/21/2013

CLINICAL and STATISTICAL REVIEW

Application Type NDA
Submission Number 203,791
Submission Code N-000

Letter Date March 13, 2012
Stamp Date March 13, 2012
PDUFA Goal Date January 11, 2013

Clinical Reviewer Name Regina Alivisatos, MD
Statistical Reviewer Name Wen Zeng, PhD
Review Completion Date December 3, 2012

Established Name Acyclovir
(Proposed) Trade Name Sitavig
Therapeutic Class Antiviral
Applicant Bioalliance

Priority Designation S

Formulation Mucoadhesive Buccal Tablets
(ABT 50 mg)
Dosing Regimen Single tablet to buccal mucosa
Indication Herpes Labialis
Intended Population Adults  (b) (4)


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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A complete response action is recommended for this NDA. Discipline review letters based on substantial statistical and clinical deficiencies identified during the clinical and statistical review process will be issued. While the submitted safety data are adequate to show that ABT-50 presented minimal risks when used in the treatment of herpes labialis (HL), the efficacy data presented in this submission are inadequate to support the Bioalliance Sitavig mucoadhesive Buccal Tablet (ABT 50 mg) for the requested indications of “the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients.” (b) (4)

The application includes one phase 2 PK/PD trial (BA2004/21/01) in 12 normal volunteers and one phase 3 trial (BA2005/21/02) in adults ages 18 and older. The efficacy and safety data from Study BA2005/21/02 are presented in support of Sitavig in adults. Although the Applicant is requesting an approval for adults (b) (4)

In trial BA2005/21/02, the Applicant was unable to meet the statistical and clinical benchmarks discussed during the April 8, 2010 pre NDA meeting to show that Sitavig was superior to placebo for reducing the time to healing (TTH) of ulcerative herpes labialis lesions. Not only was the Applicant unable to meet the predefined standard for a clinically meaningful benefit predefined by the Division as a decrease in time to healing of at least one half day, but the difference between Sitavig and placebo for the primary efficacy parameter of TTH did not meet the predefined statistical significance level of < 0.001 for demonstrating efficacy in a single registration trial. The determination of what constitutes clinically meaningful (i.e. at least $\frac{1}{2}$ day) is based on the difference in the TTH achieved in previous applications for topical herpes labialis products. In addition the evaluation of the totality of evidence regarding efficacy was unable to show clinically meaningful and/or statistical significance in any subpopulation or for any of the secondary efficacy parameters.

There were numerous issues associated with this application that led to a complete response recommendation.)

Issues included flawed collection of efficacy data by the patients primarily because the herpes labialis (HL) lesion assessment was recorded by the patients only once daily at bedtime. This once daily assessment made it very difficult to accurately calculate time to healing and therefore to attempt to show at least a $\frac{1}{2}$ day improvement over placebo. It should be noted that in the original protocol submitted in 2006 and up until August 2007 the HL lesions were to be assessed four times daily. The frequency of lesion assessment was changed in a protocol amendment

submitted on 8/28/07. The rationale behind this change as well as the number of patients who assessed their lesions four times daily during the first year of the trial versus once daily after the protocol was amended is unclear at this time. Further a review of other NDAs for topical HL products showed that the HL lesions were assessed at least twice daily.

The primary efficacy parameter of time to healing (TTH) per protocol was to be performed by the investigators who were to use the patient diary to help to better define the exact hour of lost of crust. However, patients were only seen by the investigators every other day as opposed to daily. This issue also brings into question how accurately the TTH was calculated as by necessity it was a combination of patient and investigator assessments and the investigators ability to accurately determine this parameter based on every other day assessments by definition was severely limited especially when trying to assess for such a short period of only ½ a day..

Other review issues included the inaccurate categorization of the TTH in five patients as well as the use of prohibited antiviral medications by an additional eleven mITT patients. The latter two issues led to re-categorization of these patients with resultant differences in the efficacy conclusions between the Agency and the Applicant analyses.

In order to receive an approval for the requested indication of “the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, (b) (4) the Applicant will need to (b) (4)

In addition to the treatment of HL claim the Applicant also requested the additional claims of the (b) (4). With regards to the (b) (4) claim, (b) (4)

It should also be noted that the Applicant agreed not to submit this claim as per the pre NDA meeting minutes but elected to do so anyway despite the Agency’s advice.

From the statistical point of view, (b) (4) will be needed in order to support the (b) (4) claim. (b) (4)

With regards to the claim that (b) (4)

(b) (4)

Finally all of the secondary efficacy analyses including the assessment of the proportions of subjects with aborted primary lesions did not account for multiple comparisons. As a result, there was no type-I error control for these analyses and therefore the accuracy of the results are in question

(b) (4)

1.2 Risk Benefit Assessment

Overall, ABT 50 mucoadhesive buccal tablet appears tolerable for the proposed treatment dose and duration. No new or unexpected toxicities were observed when compared to available safety data of other approved treatments for HL in immunocompetent patients ages 18 and over. Pediatric and adolescent patients were not assessed in this application.

In the BA2005/21/02 phase 3 trial submitted for review, no deaths were reported and discontinuation rates were low. Most adverse events were mild. The most common adverse reactions (all grades, considered definitely, probably or possibly related to study treatment) were local buccal mucosal reactions that occurred at the site of topical application.

In conclusion, ABT 50 is safe to use for the treatment of primary HL however no benefit was conclusively shown in the BA2005/21/02 phase 3 trial submitted in support of this NDA application.

1.3 Recommendations for Postmarketing Risk Management Activities

No safety concerns were found during the review of this application and therefore postmarketing risk management recommendations are not necessary.

1.4 Recommendations for other Post Marketing Study Commitments

A complete response action is recommended therefore postmarketing study commitments are not necessary at this time.

2 Introduction and Regulatory Background

2.1 Product Information

The Applicant, BioAlliance, has submitted a 505(b)(2) NDA application for Sitavig also known as Acyclovir Lauriad™ or ABT 50 mg, a mucoadhesive buccal tablet that provides extended-release of acyclovir (DCI = aciclovir) in the oral cavity. ABT 50 mg is a white to slightly yellow mucoadhesive buccal tablet with a rounded side and a flat side, debossed with “AL21” on the flat side. Sitavig adheres to the upper gum just above the incisor tooth with the flat surface facing the cheek mucosa.

Each tablet is formulated to contain 50 mg of acyclovir. ABT 50 mg is packaged for marketing in (b) (4) unit dose blisters in cartons of 2 x 1 tablet. Excipients contained in each tablet include microcrystalline cellulose, povidone, sodium lauryl sulfate, hypromellose, milk protein concentrate, magnesium stearate, colloidal silicon dioxide, and (b) (4). All excipients with the exception of the milk protein concentrate (MPC) are standard.

The proposed indication for the ABT 50 mg tablet is for the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients. (b) (4)

The non-proprietary (established) name for the proposed drug product is ABT 50 mg. The proposed proprietary name is Sitavig. This name was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

2.2 Currently Available Treatments for Proposed Indications

There are a number of topical and systemic options approved for the treatment of recurrent herpes labialis:

Note: where applicable the populations and ages for which the approved drugs are indicated have been specified. If absent, they are not clearly stated in the approved USPIs.

- Penciclovir cream (1%) is indicated for the treatment of cold sores (recurrent herpes labialis) that occur on the face and lips.
- Acyclovir cream (5%) is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).
- Famciclovir is indicated for treatment of recurrent herpes labialis (cold sores) in immunocompetent patients.
- Valacyclovir, a prodrug of acyclovir, is indicated for treatment of recurrent herpes labialis (cold sores) in immunocompetent patients.

In addition, Xerese a combination of acyclovir cream 5% and hydrocortisone 1% was approved in 2009 for the treatment of recurrent herpes labialis in adults and adolescents ages 12 and above.

Of note, the acyclovir tablet formulation is not approved for the requested indication.

2.3 Availability of Proposed Active Ingredient in the United States

ABT 50 contains 50 mg of acyclovir per tablet. Acyclovir is widely available in the USA.

2.4 Important Safety Issues with Consideration to Related Drugs

Adverse reactions with 5% acyclovir cream at the site of topical application can include dry lips, cracked lips, dysgeusia, transient burning or tingling following application, erythema, and pigmentation changes or other application site reactions.

Overall, no new or unexpected toxicities were observed with ABT 50 compared to available topical acyclovir safety data.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting was held with the FDA on April 8, 2010 to determine if the clinical data presented at this meeting were adequate to support this NDA submission. A follow-up Type C teleconference occurred on July 28, 2010.

At the pre-NDA meeting several issues were raised by the Agency. These included submission of a re-analysis of data on the duration of episode of the primary lesion as primary analysis, the pediatric plan, safety data on tablet dislodgement, sensitivity analyses (efficacy data based on the location of the lesion to the upper or lower lip, efficacy data stratified by race), and virology data from Trial BA2005/21/02.

Most issues were addressed by the Applicant including the utilization of time to healing of the primary lesion (TTHPL) as the primary efficacy parameter, the submission of a request for a

(b) (4)
[REDACTED]. Relevant virology data were also submitted.

A review of the DAVP meeting minutes indicated that the DAVP was willing to accept a single phase 3 trial in support of the treatment of a recurrent herpes labialis indication if the Applicant was able to provide statistically robust data of a treatment difference between ABT 50 and placebo of $p < 0.001$ for one trial or < 0.05 for two studies. However, DAVP recommended that the Applicant NOT submit an application for the second requested indication of (b) (4) [REDACTED] at the time of the initial NDA submission. To support such an indication a (b) (4) [REDACTED]

Also of note, although the efficacy of ABT 50 appeared significant, DAVP questioned the clinical significance of the initial submitted analysis which revealed a shortening of the duration

of the herpetic episode (TTH) by only a few hours. The Applicant was informed that the benchmark for clinically meaningful results based on other topical treatments for herpes labialis is at least ½ day for the TTH endpoint. The Applicant's reanalysis in accordance with DAVP statistical guidance showed a TTH of ½ day and therefore the DAVP concluded that there was enough data to support an NDA submission.

A pre-NDA CMC meeting was also held on May 26, 2011 to discuss the CMC data to support the NDA submission and the manufacturing site transfer from (b) (4) (clinical manufacturing site) to Farmea (commercial manufacturing site). Please see further details regarding the chemistry issues discussed in the review by Dr.'s Shrikant Pagay and Fuqiang Liu.

2.6 Other Relevant Background Information

ABT-50 has not yet been approved in any country. Of note, EMEA granted the Applicant's request for a waiver from studying all age groups of children below 10 years (September 9, 2011 EMEA website http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500116657.pdf) and a deferral for pediatric patients and adolescents ages 10 through 17.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A routine consult was submitted to the Division of Scientific Investigations (DSI) on April 30, 2012, in response to this NDA submission. Please refer to the DSI review by Dr. Antoine EI-Hage for further details. In Study BA2005/21/02, the following clinical sites with high subject enrollment were inspected (Table 1). At the time this review was completed the outcomes of the DSI inspections were not yet available.

Table 1
Clinical sites Inspected
BA2005/21/02

Site # (Name, Address, Phone number, email, fax#)	Number of Subjects
709 (USA) MATTHEW G.DAVIS, M.D. ROCHESTER CLINICAL RESEARCH, INC. 500 Helendale Road, Suite L20 Rochester, NY 14609 (585) 288-0890 Fax: (585) 288-0893 E-mail: mdavis@rcrclinical.com	Randomized 84, treated 44
706 (USA) Dr Maurice Archuleta, Front Range Clinical Research, 5306 West 38th Ave., Wheat Ridge CO 80033 303-940- 2465 303-940-1936 RESEARCH@WFCLINIC.COM	Randomized 54, treated 22
Center 302 Dr Mireille RUER MULARD Le Bateau Blanc Immeuble A 1er étage 1 Chemin Paradis 13500 Martigues FRANCE +3304 4280 10 13 +3304 4280 05 90 RUERDOC@WANADOO.FR	Randomized 45, treated 19
Center 507 Dr. Maciek Kozina NZOZ PRAKTYKA LEKARSKA IGA GILAS i MIRKIEWICZ, UL.JUGOSLOWIANSKA 65D, WROCLAW 50-354 Poland 00 48 502263093	Randomized 186 Treated 54

3.2 Compliance with Good Clinical Practices

Both the phase 2 and 3 clinical trials were conducted in accordance with the principles of Good Clinical Practices. The trials were written to conform to accepted ethical standards and were reviewed by Institutional Review Boards overseeing each investigative site. The trials were also subjected to internal audits performed by the Applicant's personnel and/or designees.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. No investigators had any conflicts of interest. These financial arrangements do not appear to have any impact on the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the CMC review by Dr. 's Shrikant Pagay and Fuqiang Liu for details. The contents of ABT 50 are summarized in the following table:

Table 2
ABT 50 Ingredients

Name of Ingredient	Quantity per Tablet mg (%)
Acyclovir (active ingredient)	50 (b) (4)
Microcrystalline cellulose	(b) (4)
Povidone	
Sodium Lauryl Sulfate	
Hypromellose (b) (4)	
Milk Protein Concentrate (MPC)*	
Magnesium stearate	
Colloidal Silicon Dioxide	
(b) (4)	
Total	(b) (4) (100%)

*MPC is a non novel, non compendial excipient approved for use by the FDA in Oravig tablets.

4.2 Clinical Microbiology

Please refer to Dr. Lalji Mishra's Microbiology review for details.

Acyclovir resistance was assessed in a BioAlliance sponsored study entitled "In vitro evaluation of the antiviral activity towards herpes simplex viruses of a mucoadhesive gingival tablet delivering acyclovir."

This report presented the results concerning ACV susceptibility of 81 HSV clinical isolates from both immunocompetent and immunocompromised individuals obtained in the Virology Department of the Pitié-Salpêtrière University Hospital in Paris between 2007 and 2010. The results indicated the possible emergence of HSV resistance to ACV in particular in immunocompromised patients. However, this resistance remained extremely rare in immunocompetent individuals. These results were obtained using a newly designed *in vitro* assay performed with two HSV ATCC reference strains and eight clinical isolates and were in accordance with the results previously obtained by both phenotypic and genotypic assays in the Virology Department. These results strengthen the validation of the EC50 value at 10 µM concerning HSV susceptibility to ACV. These data were consistent with the ACV concentrations measured during *in vitro* dissolution kinetic of the mucoadhesive tablet (i.e., twice as high as the EC50 value after only one hour).

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were provided for this 505(b)(2) application. The Applicant relied on previous P/T findings from the referenced drugs Acyclovir (cream and tablet).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2), and varicella zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared with VZV is due to its more efficient phosphorylation by the viral thymidine kinase.

4.4.2 Pharmacodynamics

Pharmacodynamic data were included in trial BA2004/21/01 which is described in section 4.4.3.

4.4.3 Pharmacokinetics

BA2004/21/01 was a single-center, randomized, cross-over, pharmacokinetic/pharmacodynamics (PK/PD) trial conducted in 12 healthy men and women (nine males/three females), 21 to 37 years of age, to compare the pharmacokinetic parameters and tolerability of a single dose of ABT 50 mg and ABT 100 mg in plasma, saliva and labial mucosa to those of a single dose of acyclovir oral tablet (Zovirax® 200 mg tablet).

Acyclovir plasma and salivary concentrations were measured over a 48-hour period. Acyclovir concentrations were measured in the labial mucosa using labial stripping over a 24-hour period. Acyclovir concentrations in plasma, saliva and labial mucosa were then compared to the IC₅₀ of acyclovir for a PK/PD evaluation.

This PK/PD trial showed that:

- a single local application of ABT 50 mg or 100 mg provided rapid (<30 min), high (\geq IC₅₀) and prolonged (\geq 24 hours) acyclovir concentrations in saliva and in labial mucosa, markedly over the IC₅₀ (22.5 ng/mL) and those obtained after a single administration of

acyclovir 200 mg tablet (Zovirax®) (11,700-fold and 25,500-fold higher for saliva and at least 4- and 70-fold higher for labial mucosa for ABT 50 mg and 100 mg respectively). In contrast, plasma concentrations were lower than those observed with acyclovir 200 mg oral tablet with a relative bioavailability corrected by the dose of 49% and 70% for ABT 50 mg and 100 mg, respectively.

- ABT 100 mg induced much higher (over the IC₅₀) plasma concentrations than ABT 50 mg and its pharmacokinetic profile is intermediate between those of a topical and a systemic agent. In contrast, the 50 mg dose of ABT provided low (below the IC₅₀) plasma concentrations and high (over the IC₅₀) concentrations in saliva and labial mucosa, and therefore fulfills the prerequisites for a sustained release local treatment.
- The detection of very high acyclovir concentrations in saliva and labial mucosa persisting several hours after ABT dislodgment or complete erosion, and the higher acyclovir concentrations in labial mucosa than in saliva support the assumption of acyclovir storage in mucosa.

Based on these results (low plasma concentrations, high saliva and labial concentrations), the Applicant elected to use the 50 mg dose for clinical development.

Comment: The Agency had significant concerns with the Applicant's premise regarding the delivery mechanism of acyclovir to the active HL lesions. As per the Applicant, the efficacy of the mucoadhesive tablet is dependent on the concentrations achieved in the saliva (> IC₅₀) and then topically at the site of the HL lesions via the licking of the lips. It should be noted during the April, 2010 pre-NDA meeting the Agency review team advised the Applicant to consider using the ABT 100 mg dose which appeared to achieve more consistent and higher acyclovir concentrations in the saliva and labial mucosa or alternatively to explore two consecutive days of dosing. The Applicant disagreed with the Agency and determined that the ABT 50 tablet had the advantage of lower systemic exposures and therefore fewer safety issues while at the same time achieving what they determined were adequate concentrations in the saliva and labial mucosa. It may be prudent for the Applicant to reassess the 100 mg tablet or consecutive doses for use in future trials.

5 Sources of Clinical Data

This review is primarily based on data from study BA2005/21/02, a pivotal phase 3 trial in adults ages 18 and older.

5.1 Tables of Clinical Studies

Table 3
Clinical Studies in support of application

Table 5.2-1 Clinical Studies Conducted with Acyclovir Lauriad™ 50mg Mucoadhesive Buccal Tablet								
Type of Study	Study No. Identifier Report Location	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects Included/ Safety Population	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status/ Type of Report
PK/PD	BA2004/21/01 Module 5.3.3.1	- PK (saliva and plasma) - PD - Dose ranging - Tolerability - Acceptability	Open, single-centre, randomized, cross-over, with 1-week wash out, 3 periods,	ABT 50 mg, SD, application to the gum ABT 100 mg, SD, application to the gum Acyclovir tablet 200 mg, SD, oral route	13/13	Healthy volunteers	1 day	Completed/ Full report
Efficacy /Safety	BA2005/21/02 (LIP)/ Module 5.3.5.1	- Efficacy - Safety - PK (saliva)	multicentre, multinational, Randomized, DB, SD with early administration, 2 parallel groups, comparative versus placebo	ABT 50 mg or matching placebo SD Applied to the gum (as single dose)	775/378	Patients with recurrent Herpes labialis	1 day	Completed/ Full report

DB: Double blind; ABT: Acyclovir Lauriad™ Mucoadhesive buccal tablet; PK/PD: Pharmacokinetic/Pharmacodynamic; and SD: Single dose. LIP: Lauriad™ Immunocompetent Patients

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5.2 Review Strategy

Efficacy and safety data were reviewed for Study BA2005/21/02. Safety data were also reviewed for Study BA2004/21/01. Safety data review included case report tabulations and case report forms when applicable. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. This MO reviewed study design, patient demographics, and adverse events. FDA clinical and statistical reviewers collaborated extensively throughout the review process, and the efficacy analyses in this review were performed by the FDA statistical reviewer, Dr. Wen Zeng. Additionally, there was significant interaction with the FDA CMC, clinical pharmacology, and microbiology reviewers. Their assessments are summarized in this document, but complete details of their findings are available in the respective discipline reviews.

5.3 Discussion of Individual Studies

The clinical section of the NDA focuses on efficacy and safety data from Study BA2005/21/02 (pivotal phase 3 trial- adults) and safety data from Study BA2004/21/01.

BA2005/21/02: A Randomized, Double-Blind, Single dose, One-Day Early Administration, Multicenter Study comparing the Efficacy and Safety of ABT 50 mg muco-adhesive buccal tablet to matching Placebo, in the Treatment of Herpes Labialis in Immunocompetent Patients

Synopsis:

- First patient screened: 23 March 2007
- Last patient completed follow-up: 04 September 2009

- The study was conducted in 47 sites in Australia, the Czech Republic, France, Germany, Poland, the UK and the USA.

Objectives: The primary objective of the trial was to demonstrate the efficacy of a single dose of ABT 50 mg versus a single dose of matching placebo on the primary vesicular lesion of labial herpes in immunocompetent patients.

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
- To compare the local tolerability and general safety of ABT 50 mg to those of placebo;
- To evaluate the concentration of acyclovir in saliva 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.

Key Inclusion/exclusion criteria: Adult patients with a history of recurrent characteristic lesions of labial herpes defined by at least 4 episodes in the preceding 12 months and accompanied by prodromal symptoms in at least 50% of the recurrent episodes were enrolled. At least 50% of previous episodes were to have produced classical lesions to the vesicular stage.

Patients were excluded if more than 50% of previous recurrences spontaneously aborted or primary herpes lesions were outside the lips, if they received concomitant treatment likely to interfere with acyclovir or topical steroids in the oral area (< 4 weeks) and finally presented with any immunocompromised clinical condition.

Population: 1944 patients were screened and 1721 were randomized in 1:1 ratio to receive either single dose of ABT 50 mg or matched placebo. 775 patients were treated; 378 patients in the ABT 50 mg group and 397 patients in the Placebo group. 521 patients had a primary vesicular lesion and formed the mITT population.

Methodology: The trial was carried out by the Applicant according to a randomized, double-blind, single dose, patient-initiated, comparative with two parallel groups design. The primary efficacy endpoint of the trial was to compare (two-sided log-rank test) the time to healing of the primary vesicular lesion considered as time-to-event data in the ABT 50 mg group versus the

placebo group (mITT population). Efficacy analyses were also performed by the Applicant using the ITT populations. Endpoints were assessed up to Day 14 or up to the healing of lesions or cessation of symptoms. Note: Both the Applicant's and the Agency's analysis methodologies are extensively discussed in section 6.

Study design: The study duration for each patient included a screening period of 10 days maximum (Screening; Visit 1) before randomization (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 six months after randomization, 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. The subject had to return to the clinic within 24 hours of treatment initiation.

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 requested to return to the clinic within 24 hours following treatment application. According to the CSR page 23, 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). However, on page 33 of the original protocol, it is stated that patients will record symptoms 4 times daily at fixed times: on waking, at lunch, at dinner, and at bedtime, tablet adhesion, local tolerability pain, tenderness, tingling, itching, discomfort using a VAS.

Comment: It should be noted that in the original protocol submitted in 2006 and up until August 2007 the HL lesions were to be assessed four times daily. The frequency of lesion assessment was changed in a protocol amendment submitted on 8/28/07. The rationale behind this change as well as the number of patients who assessed their lesions four times daily during the first year of the trial versus once daily after the protocol was amended is unclear at this time. Further a review of other NDAs for topical HL products showed that the HL lesions were assessed at least twice daily.

The once daily assessment of their lesions by the patients and the calculation of the TTH by the investigators based on patient diaries and every other day face to face assessments brings into question how accurately the TTH was calculated.

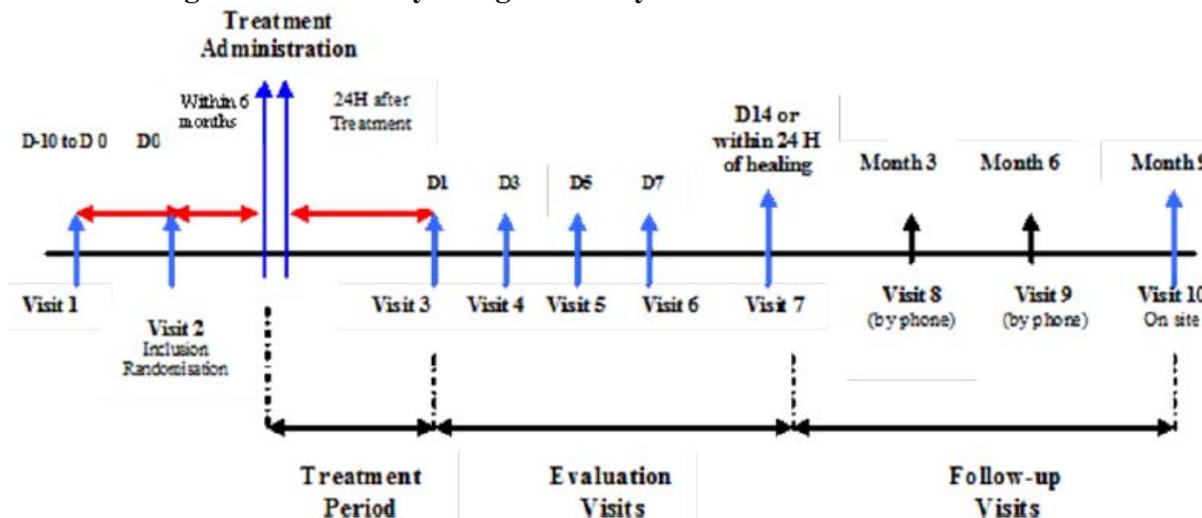
At selected sites, saliva samples were taken within 24 hours following treatment application to measure viral HSV-1 load and acyclovir concentration. Evaluation visits took place on Days 1, 3, 5, 7 and 14 or when healing was reached (Visits 3, 4, 5, 6 and 7). A one day tolerance interval was permitted for each visit. Blood samples were taken before inclusion and at Visit 7 (Day 14).

Optional follow-up visits were conducted to record the number of new herpes episodes and the

time to their recurrence for a period of 9 months; patients were to be contacted by telephone three months and six months after Visit 7 (Visits 8 and 9) and to return to the clinic for a final visit 9 months after visit 7 (Visit 10). Please see the diagram in Figure 1 below.

For patients who were not treated because of the absence of recurrence of labial herpes in the 6 months following randomization, the patient participation was 190 days. For those in whom the treatment was initiated and who did not enter the follow up evaluation, it was a maximum of 204 days. Patients who were treated and entered the optional follow up period were followed for an additional 9 months (total participation: 470 days).

Figure 1: The Study Design of Study BA2005/21/02



Definitions the primary efficacy endpoint and secondary endpoints:

The primary endpoint was **Time-To-Healing (TTH) of primary vesicular lesion**, defined as a lesion that has passed through the vesicular stage to crust (as opposed to erythema or papular alone).

1. Healing was defined as the loss of crust. Erythema may have been present. This was to be assessed by the investigator.
2. The TTH was the time from the treatment initiation (date and hour recorded) to the healing as defined above.
3. 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 determine the exact hour of lost of crust.

The investigator-assessed TTH of the primary lesion was compared between the ABT 50 mg and matching placebo.

Secondary Efficacy Endpoints:

Aborted lesions: Aborted lesions were defined as herpetic lesions preceded by prodromal symptoms that did not progress beyond the papule stage.

TTH of all non-primary lesions (aborted lesions excluded): 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.

Duration of episode: 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.

Time to cessation of symptoms: Time to cessation of symptoms was defined as the time from treatment initiation to cessation of all symptoms: pain, burning, itching, tingling, tenderness and discomfort. It was to be assessed by the investigator with the support of the patient diary.

TTH of aborted primary lesions: TTH of aborted primary lesions was defined (in the relevant subgroup of patients) as the time from treatment initiation to healing of the primary lesion (erythema or papular) or cessation of symptoms, whichever came last. It was to be assessed by the investigator with the support of the patient diary.

TTH of intra-oral/mucosal non primary lesions: TTH of intra-oral/mucosal non-primary lesions was defined (in the relevant subgroup of patients) as the time from treatment initiation to healing of intra-oral/mucosal non primary lesions. It was also evaluated by the investigator.

Relationship between saliva viral titer, acyclovir saliva concentration and efficacy parameters: The relationship between saliva viral titer and acyclovir saliva concentration and efficacy parameters was to be investigated as an exploratory analysis. Saliva samples were taken on Day 1 (Visit 3: within 24 hours of study drug application). The saliva viral titers and acyclovir saliva concentrations (in patients from selected centers) were summarized after logarithmic transformation of the data if appropriate.

Incidence of and time to recurrence of non aborted lesions during 9-month follow-up
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.

Also assessed was the adhesion time of acyclovir and placebo tablets, incidence of detachment and/or swallow within 6 hours post-dosing, and the incidence of tablet replacement.

Sample Size Calculation and Hypothesis

As per the Applicant, the intention of the trial was to perform a comparison (two-sided log-rank test) on the time to healing of the primary vesicular lesion considered as time-to-event data. The null hypothesis (H_0) corresponded to the absence of difference between treatment groups (hazard ratio = 1.00) and the alternative hypothesis (H_1) 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 pre-defined in the protocol:

- The Intent-To-Treat (ITT) population (also the safety population) included all randomized patients who took at least one dose of the study medication. This is used for demographic and safety analyses.
- The modified ITT (mITT) population included all randomized 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 analyses.
- The Per Protocol (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. This is mainly used for the efficacy sensitivity analyses.
- 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 pre-defined in the protocol or SAP.

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.

In the Applicant's analysis, 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 difference of TTH. 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.

6 Review of Efficacy

Efficacy Summary

The Applicant submitted a phase 3 trial, BA2005/21/02, for review. The primary objective of the phase 3 trial was to demonstrate the efficacy of a single dose of ABT 50 mg versus a single dose of matching placebo on the primary vesicular lesion of labial herpes in immunocompetent patients using Time-To-Healing (TTH) of primary vesicular lesion as the primary efficacy endpoint.

During the process of data validation, the statistical reviewer identified errors in terms of TTH calculation in five patients. In addition, eleven patients received prohibited concomitant antiviral medications during the trial. Prohibited antivirals included acyclovir, valcyclovir, famciclovir as well as topical acyclovir products such as Xerese or penciclovir. Over the counter products such as Abreva were also used. As a result, in the Agency analyses, the TTH values of the five patients were corrected regardless of which analysis population was being assessed. The eleven patients who took prohibited concomitant medications were excluded from the mITT population for all analyses using the mITT population. This revised dataset constitutes the Agency statistical reviewer's analysis dataset.

Overall, the median difference of TTH between ABT 50 mg arm and placebo arm ranged between - 0.3 to - 0.5 day depending on the method used with a borderline statistically significant p-value. This outcome did not consistently meet the Agency's definition of clinically meaningful of at least a half day difference in the TTH parameter as well as statistical significance at the < 0.001 level.

The median difference of TTH between two arms is approximately - 0.3 day for patients who applied drug within 1 hour of the occurrence of prodromal symptom (~84% of total patients in the mITT population).

In the exploratory analyses without any type-I error control the effect of adhesion time of ABT-50 relative to TTH was further assessed. In 37% of patients in the mITT population the adhesion time of the first tablet was between 6-12 hours. For these patients, the median difference of TTH between the two arms was about 0.01 day, ie, there was no difference between the two arms. For those patients where the adhesion times of the first tablet was > 12 hours (51% of mITT patients), the median difference of TTH between the two arms was about - 0.7 day. In 12% of patients of the mITT population with adhesion times of first tablet < 6 hours, the median difference of TTH between the two arms was greater than - 0.79 day, ie, the TTH in the ABT 50 mg arm was shorter by at least 0.79 day than that in the placebo arm. This difference was reduced to - 0.1 day in those patients who replaced the first tablet.

The secondary endpoint “proportion of subjects with aborted primary lesions” in ABT 50 mg arm (34.9%) was significantly higher than that in the placebo arm (28.1%). The rate difference is 6.85% with exact 95% CI of (0.22%, 13.48%) with exact p-value of 0.043. However, this analysis could not be used to support the Applicant’s claim that ABT-50 prevented the

(b) (4) for two reasons. First, (b) (4)

The median difference of duration of episode between the two arms is about - 0.58 day, and the median differences of time to cessation of symptoms between the two arms is about - 0.45 day.

The Applicant’s claim (b) (4) could not be supported by the efficacy data submitted. (b) (4)

6.1 Indication

The sponsor proposed the following indication: SITAVIG is indicated in adults (b) (4) for the treatment of recurrent orofacial herpes simplex virus infections in immunocompetent patients, (b) (4)

6.1.1 Methods

As mentioned in Section 5, this submission contains the efficacy results of a single Phase 3 trial, BA2005/21/02, for adult patients 18 years and older with a history of at least four episodes of recurrent labial herpes during the prior 12 months.

The statistical reviewer's efficacy analyses to verify the Applicant's results of the phase 3 trial included the following three parts:

1. Reviewing protocols, statistical analysis plans (SAP), efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
 - Module 2. 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
 - Module 5- Clinical Study Reports (CSRs) of the Phase 3 Study BA2005/21/02.
2. Converting SAS transportable files '*.xpt' in \analysis\legacy\datasets subfolder as analysis datasets, some of the raw datasets in \tabulations\sdtm subfolder into SAS data files for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and Statistical Analysis Plan (SAP) in the CSR. These files are under CDER Electronic Document Room (EDR) directory of

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3. Conducting efficacy analyses from the raw data for Study BA2005/21/02 to verify the Applicant's results.

In this section, all tables and figures are generated by the reviewer. If not, the citation will be added.

6.1.2 Demographics

In study BA2005/21/02 the ITT population consisted of 771 patients, 376 treated with ABT 50 and 395 with placebo.

The majority of patients were Caucasian (95%) and female (69%), with a mean age of 41 years. The majority of patients on both treatment arms had experienced greater than 4 episodes of recurrent herpes labialis within the last year (69% both arms). All patients in both treatment groups had experienced prodromal symptoms and vesicular lesions in at least 50% of the episodes within the past year. As shown in Table 4, baseline demographics characteristics and baseline disease severity were balanced across treatment groups.

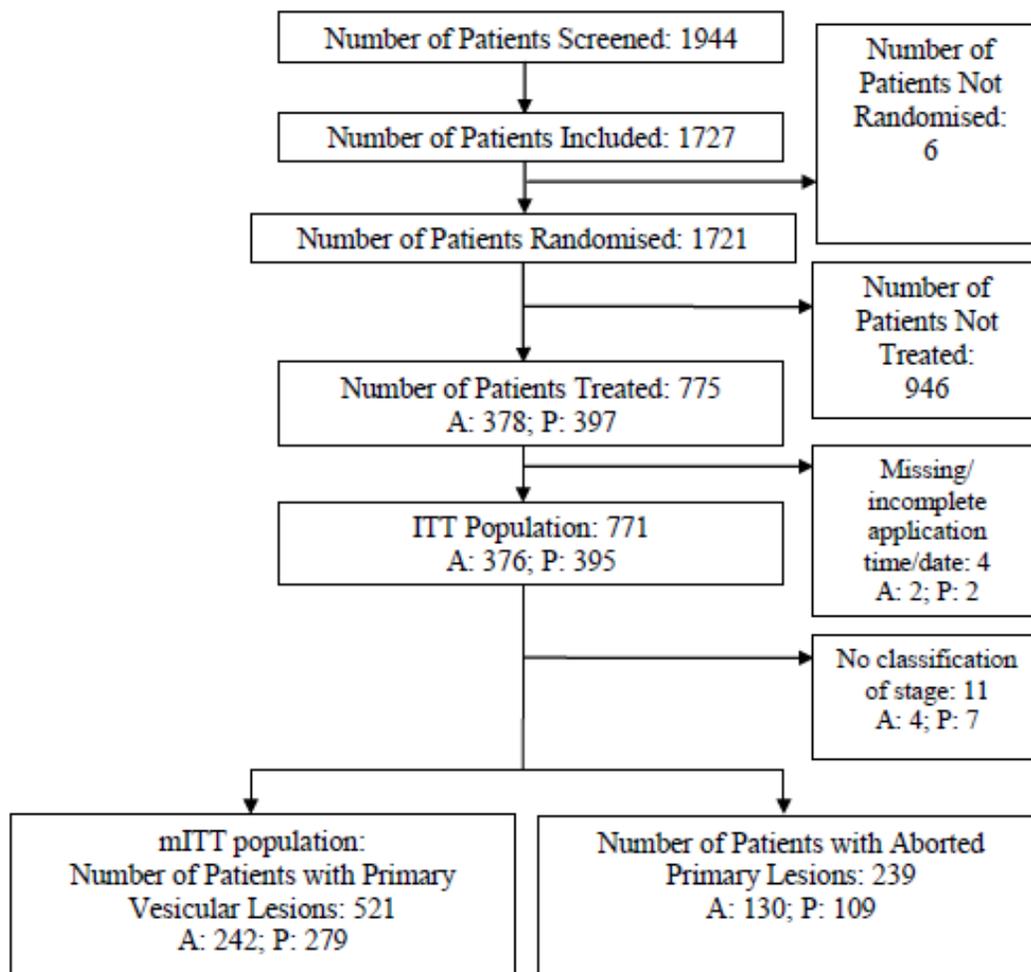
Table 4
Demographics ITT Population

	ABT 50 N = 376	Placebo N = 395	Total N = 771
Age (years)			
Mean	40	41.9	41
Range	18, 80	18, 73	18, 80
Gender			
Female	258 (69%)	271 (69%)	529 (69%)
Male	118 (31%)	124 (31%)	242 (31%)
Ethnicity			
Caucasian	359 (96%)	373 (94%)	732 (95%)
Black	7 (2%)	4 (1%)	11 (1%)
Asian	4 (1%)	2 (0.5%)	6 (0.8%)
Hispanic	3 (0.8%)	9 (2.3%)	12 (2%)
Others	3 (0.8%)	7 (1.7%)	10 (1%)
HL History			
> 4 episodes in last 12 months			
Yes	257 (68%)	273 (69%)	530 (69%)
No	119 (32%)	122 (31%)	241 (31%)
Vesicular lesion on lip			
Yes	364 (97%)	382 (97%)	746 (97%)
No	10 (3%)	11 (3%)	21 (3%)
Missing	2	2	4
Prodromal symptoms			
Yes	370 (99%)	389 (99%)	759 (99%)
No	4 (1%)	4 (1%)	8 (1%)
Missing	2	2	4

6.1.3 Patient Disposition

In Study BA2005/21/02, 1944 patients were screened and 1721 patients were randomized to treatment. Seven hundred seventy five patients were treated (378 ABT 50 and 397 placebo); however, data were missing on four patients, two from each arm. Therefore the ITT population consisted of 376 ABT 50 treated patients and 395 placebo treated patients. Eleven patients were excluded from the analysis (4 ABT 50 and 7 placebo) because they did not have their diseases accurately staged. A total of 521 patients, 242 ABT 50 and 279 placebo developed vesicular primary lesions and were included in the mITT population. Two hundred thirty nine patients (130 ABT 50 and 109 placebo) had aborted primary lesions and were not included in the mITT population. Please see Figure 2 below.

Figure 2
The Disposition of all Screened Subjects in Study BA2005/21/02 (Copied from CRS)



A summary of the number of patients in each arm of the FDA statistical reviewer’s analysis populations can be seen in table 5 below.

Table 5
Analysis Populations by Arm

	ABT 50	Placebo	Total
Randomized	867	854	1721
Safety / Treated	378	397	775
ITT ¹	376	395	771
mITT ²	239	271	510
Patients with Aborted Primary Lesions	130	109	239

¹: Four patients had missing date/time and were excluded from the ITT population, even though the definitions of ITT and Safety population are the same.

²: Eleven patients who took prohibited concomitant antiviral medication during the trial were excluded from the mITT population here. Please see section 6.1.4.3 for details.

Of note, there were three patients with vesicular lesions during the trial who were excluded from the mITT population. Two were not treated and one has missing starting date/time.

Table 6 displays the safety population (all treated population) and includes 775 patients.

Generally ABT 50 was well tolerated. The primary reason for treatment withdrawal was not adverse events but non-compliance or protocol deviations. Other reasons included travel, fear of side effects, possibility of malignancy, and use of steroids, both topical and systemically.

Table 6
Patient disposition (All Treated)

	ABT 50 N = 378	Placebo N = 397	Total N = 775
Completed the study			
Yes	361 (96%)	384 (97%)	745 (96%)
No	17 (5%)	13 (3%)	30 (4%)
Reason for Withdrawal			
Adverse Event	0	1 (0.3%)	1 (0.1%)
Withdrew consent	1 (0.3%)	3 (1%)	4 (0.5%)
Investigator decision	1 (0.3%)	0	1 (0.1%)
Lack of efficacy	0	3 (1%)	3 (0.4%)
Lost to F/u	1 (0.3%)	2 (0.5%)	3 (0.4%)
No episode within 6 mos but used treatment afterwards	1 (0.3%)	0	1 (0.1%)
Non compliance or protocol deviation	13 (3%)	7 (2%)	20 (3%)
Other	5 (1%)	2 (0.5%)	7 (1%)

Source: ADDS and ADDV datasets in esub

6.1.4 Analysis of Primary Endpoint(s)

The FDA statistical reviewer conducted primary and sensitivity analyses on the primary efficacy endpoint and on selected secondary efficacy endpoints for Study BA2005/21/02. As shown in the following sections, FDA's efficacy analyses differed with the Applicant's efficacy analyses with regards to conclusions regarding statistical significance independent of the methods used.

6.1.4.1 Analysis Method:

For the primary efficacy endpoint, TTH, the Applicant proposed to use the K-M method for their mean, median, and their 95% CI calculation and the stratified Log-rank test (by center) for the P-value calculation for testing the quality of the survival function. These were implemented in PROC LifeTest in SAS 9.2.

The Agency statistical reviewer used the generalized Wilcoxon test (Gehan test) to perform a sensitivity analysis on P-value calculations in addition to the Log-rank test.

Because of the likelihood that this type of data would be skewed, the Hodges-Lehmann (HL) method for median difference with its 95% CI, and Kruskal-Wallis Test (non-parametric one

way ANOVA) for the P-value calculation were also conducted by the statistical reviewer. The HL method is the preferred method for use in these types of data by the Agency statisticians because the HL analysis does not distinguish whether the data are censored or not; therefore, the analyses were conducted using both the “all TTH data regardless of censoring” and the “only observed TTH data by excluding censored data.” This method was used in the reviews of other applications for herpes labialis including most recently the Xerese NDA (NDA 22,436) submission where it was used for the analysis of secondary endpoints analysis as the primary efficacy endpoint was not TTH. It should be noted however that the primary endpoint for the reference drug, acyclovir cream was TTH.

For rate difference, exact 95% CI, and related P-value were calculated using StatXact procedures for some secondary efficacy endpoint analyses.

Two days were of importance in the statistical analyses:

- **Day 0:** The randomization day for treatment allocation at visit 2.
- **Day 1:** The first doctor visit within 24 hours after the occurrence of prodromal symptoms and gingival application of treatment at visit 3.

6.1.4.2 Applicant’s Results:

The Applicant’s primary efficacy endpoint results are listed below (Table 8 from CSR). The mean difference of TTH between arms is - 0.57 days, the median difference is - 0.32 days, and the Log-rank P-value is 0.015.

Table 8 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

6.1.4.3 Data Validation:

Before conducting any analyses, the Agency statistical reviewer validated the Applicant’s TTH calculation. During this validation process, some issues were identified which led to changes in the assessment of the TTH data.

Out of 771 patients in the ITT population, there were 727 patients who had a primary lesion (PL) event recorded in the trial. The rest of 44 patients had either no value for PL event description or no classification of lesion stage. The event descriptions of these 727 patients are listed in Table 7 below. The primary lesions of 521 patients (out of 727) reached the vesicular stage, and thus were included in the mITT population. Patients whose primary lesions did not reach the vesicular stage were excluded from the mITT population per protocol.

Table 7
The Primary Lesion Event Description of Study BA2005/21/02

Event Description ¹	# of patients overall	# of patient in mITT population
HEALED	3	0
HEALED - min(14, TIME OF EVENT) ²	12	11
HEALED BEFORE 14 DAYS	670	475
HEALED WITHOUT DATE - min(14, TIME OF EVENT)	6	6
NOT HEALED	1	0
NOT HEALED - min(14, TIME OF EVENT)	35	29
Total number of patients having PL event	727	521

¹: ADPL.EvntDesc is the variable name used in the analysis dataset named ADPL.

²: Min(14, TIME OF EVENT) indicates that the smaller value between 14 and the difference in days between last observation date/time of primary lesion and the starting date/time of primary lesion was used to impute TTH.

When assessing how the Applicant calculated TTH for the patients in the mITT population the following issues were identified by the Agency statistical reviewer:

1. TTH for five patients who were classified as “healed without date - min (14, time to event)” were calculated incorrectly.

As shown in Table 7, six patients in mITT population were classified as “healed without date - min (14, time to event)”. One patient, 3070002, healed but had a missing primary lesion ending date and only had one record on DAY 1. Therefore the TTH for this patient was imputed as 1 day using hard-coding by the Applicant during the analysis data creation process.

Another five patients had missing lesion ending dates. In these five the Applicant used the next to the last visit date for their TTH calculation instead of the final disposition date as shown in T 3 in the appendix. In T 3 all visit records for these five patients are listed separately. The term CRITIFL='Y' indicated that the record was used for the TTH calculation by the Applicant. The final TTH and original Applicants’ TTH values are

listed in Table 8. The new TTHs assigned by the Agency statistical reviewer are longer in duration as compared to the Applicant’s assigned values for all five patients.

Table 8
TTH Values of the Six Patients from Both the Statistical Reviewer and the Applicant Study BA2005/21/02

USUBJID	EVNTDESC	SVSTDT	ADT	TRTSDTM	SVDISPDT	New TTH	Sponsor's TTH
BA2005/21/02-2010005	HEALED WITHOUT DATE	8/13/2007		8/5/2007		14	8
BA2005/21/02-4060024	HEALED WITHOUT DATE -min(14,TIME OF EVENT)	3/10/2008	6/10/2008	3/8/2008	6/10/2008	14	2
BA2005/21/02-4060019	HEALED WITHOUT DATE -min(14,TIME OF EVENT)	9/26/2007	10/1/2007	9/19/2007	10/1/2007	12	7
BA2005/21/02-4060015	HEALED WITHOUT DATE -min(14,TIME OF EVENT)	11/8/2007	11/12/2007	11/6/2007	11/12/2007	6	2
BA2005/21/02-7020010	HEALED WITHOUT DATE -min(14,TIME OF EVENT)	12/28/2007	12/29/2007	12/23/2007	12/29/2007	6	5
BA2005/21/02-3070002	HEALED WITHOUT DATE -min(14,TIME OF EVENT)	4/9/2008	4/9/2008	4/8/2008		1	1

Of note, patient 2010005 did not have visit date or disposition date for the healing record and was reclassified as “Healed without date.” If the healing ending date was missing the TTH was imputed to 14. In Table 8 the SVSTDT was the visit date used by the Applicant for TTH calculation. The SVDISPDT was used by the statistical reviewer for the TTH calculation. TRTSDTM is the treatment starting date and time.

In the Agency primary efficacy endpoint analysis the new TTH values were used for the efficacy evaluation.

2. In the mITT population eleven patients received prohibited per protocol concomitant medications (CM) and should be excluded from the primary efficacy endpoint analyses.

As per the protocol a number of antiviral concomitant medications were prohibited during the trial. Prohibited CM list included the following: “ABREVA”, “ACICLOVIR”, “ACYCLOVIR”, “DENA VIR”, “DOCOSANOL”, “FAMVIR”, “GEN ACICLOVIR”, “OTHER AVIRALS”, “PENCICLOVIR”, “VALACICLOVIR”, “VALTREX”, “ZELITREX”, and “ZOVIRAX”.

A review of the datasets revealed fifteen patients who received at least one of these prohibited CM. Of the fifteen, eleven were included in the mITT population, three on the ABT 50 mg arm and eight on the placebo arm as listed in table T4 in the appendix.

In the Agency primary efficacy endpoint analyses these eleven subjects were excluded from the efficacy evaluation.

3. In the mITT population, 29 patients who were classified as “NOT healed - min (14, time to event)” had TTH values ranging from 0-14 days in both arms even though these patients were censored according to the dataset variable. One sensitivity analysis was to use the maximum day 14 for the TTH calculation.

6.1.4.4 Analysis Results:

❖ Using the Applicant's TTH data analyzed by the Agency preferred HL method:

Using the Applicant's data, the histograms of TTH for both arms and the KM plot are listed in Figures 3 and 4 respectively. As expected, the TTH for both arms were skewed to the right and there was almost no separation between two healing times in the KM plot.

The Agency was able to reproduce the Applicant's TTH analysis by using their data and their analysis method (mean difference of TTH between arms is - 0.57 days, the median difference is - 0.32 days, and the Log-rank P-value is 0.015).

Using the HL approach, which is the preferred method with this type of data, the median difference of TTH between ABT 50 mg and placebo arm is - 0.53 days with 95% CI of (-1.02, -0.02) if using all TTH regardless censoring or not, and is - 0.30 days with 95% CI of (-0.81, 0.15) if only using observed event by excluding censored cases (Table 9).

Figure 3: Histogram of TTH by arm in mITT population (Applicant's Data)

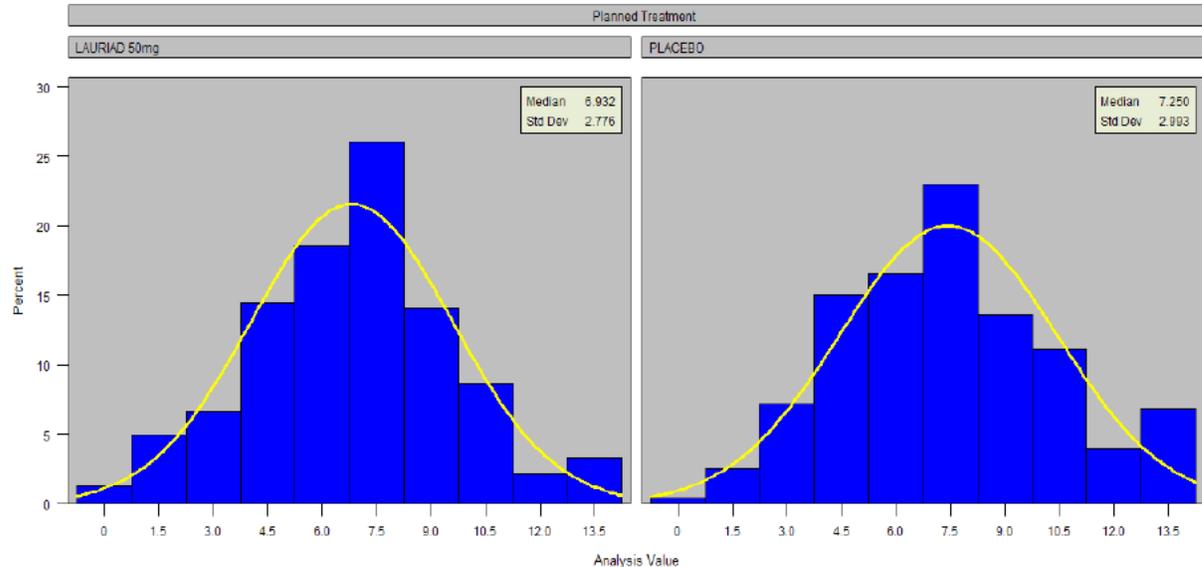


Figure 4: K-M plot of TTH Using the Applicant's Data

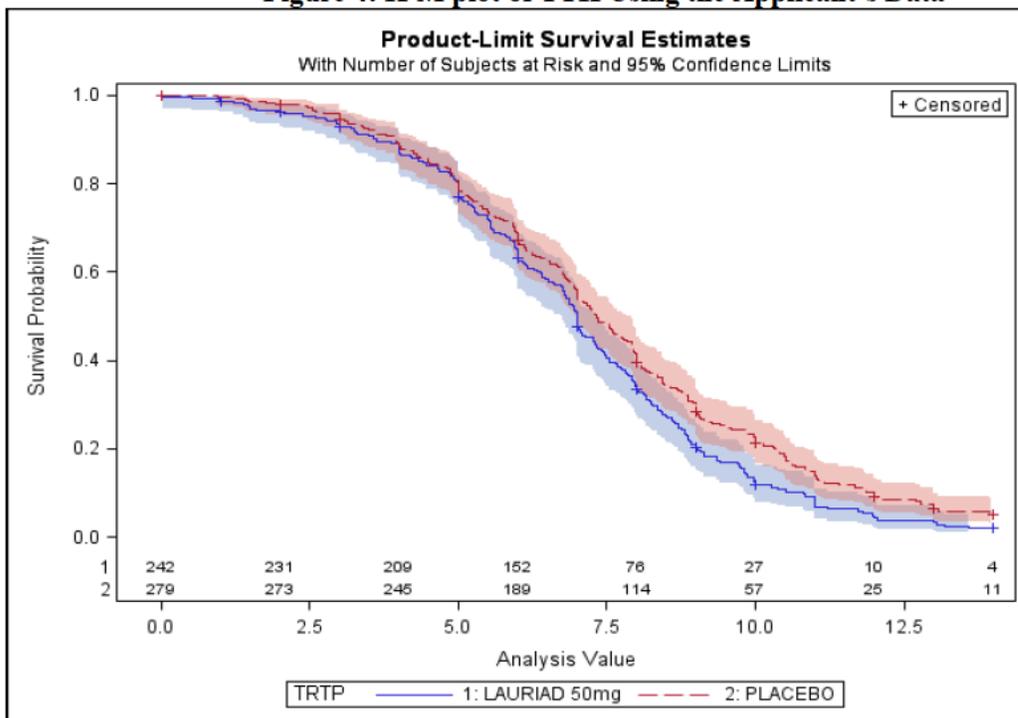


Table 9
Time-To-Healing Using the Applicant's Data
Study BA2005/21/02
mITT Population

mITT population	ABT (N=242)	Placebo (N=279)
Total, N	242	279
Event Observed, n (%)	222 (92%)	253 (91%)
Censored, n (%)	20	26
Healing Rate, % (n/N)	93% (225/242)	94% (262/279)
LifeTest (K-M) on TTH		
Mean (days) ± SE	7.05 ± 0.18	7.62 ± 0.18
Median (days) (95% CI)	7.00 (6.75, 7.31)	7.32 (6.97, 7.92)
Log-rank Test P-value	0.015	
Generalized Wilcoxon test (Gehan)	0.0805	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.93 (242)	7.25 (279)
Median Difference (days) (95% CI)	-0.53 (-1.02, -0.02)	
Kruskal-Wallis Test P-value	0.034	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.90 (222)	7.00 (253)
Median Difference (days) (95% CI)	-0.30 (-0.81, 0.15)	
Kruskal-Wallis Test P-value	0.207	

❖ Analyses using the Agency statistical reviewer's data by both KM and HL methods:

NOTE: Five patients TTH were corrected and eleven patients who took prohibited CM during the trial were excluded from the analysis population.

Using the reviewer's data, the histograms of TTH for both arms and the KM plot can be seen in Figures 5 and 6 respectively. Of note, the TTH for both arms is still skewed to the right hand side and there was almost no separation between two healing times in the KM plot.

Using the KM approach, the mean difference of TTH between arms is - 0.47 days, the median difference is - 0.31 days, and the Log-rank P-value is 0.0645. Using the HL approach the median difference of TTH between the ABT 50 mg and placebo arms is - 0.49 days with 95% CI of (-1.00, 0.00) and P-value of 0.0538 from Kruskal-Wallis test if using all TTH regardless censoring or not, and is - 0.30 days with 95% CI of (-0.82, 0.15) and P-value of 0.2051 from Kruskal-Wallis test if only using observed event by excluding censored cases (Table 10).

Overall, the median difference of TTH between the two arms ranged between 0.3-0.5 days with a borderline statistically significant p-value, which did not consistently meet the requirement of clinical significance of at least ½ day benefit.

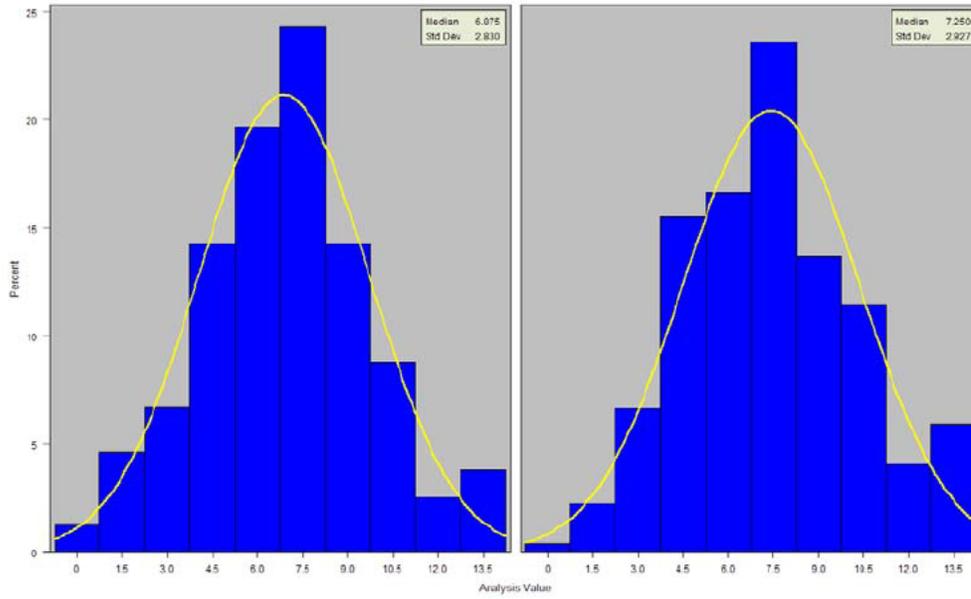
Comment: As described by the statistical reviewer there are numerous statistical methods that can be used in the assessment of a "time to healing" analysis. The goal of applying numerous methods is to assess the robustness of the results and therefore to have some confidence that clinical efficacy is consistent. There were many drawbacks in this application. Most significant was the lack of confidence in the ability to assess time to healing. Patients generally assessed the status of their lesions once a day and were seen by the investigators every other day. Therefore the ability of the investigator to accurately specify a TTH is called into question.

In addition the make-up of the primary analysis population, the MITT population, was called into question because of the inaccurate calculation of the TTH of five patients and the use of antiviral agents in an additional 11 patients.

As noted in figures 3 – 6, the various analyses performed by the Agency served to show the lack of robustness of the efficacy data generated by the Applicant. Not only did the primary efficacy analysis of TTH fail to stand up to various statistical methods using both the Applicant's and the Agency's MITT populations but they also failed to meet the standard of clinical significance of consistently showing at least one half day difference in TTH. The standards for both statistical and clinical significance which needed to be attained in order to support an approval of the application were conveyed to the Applicant in the preNDA meeting as previously described.

Figure 5: Histogram of TTH by arm in mITT population (Reviewer's)

Simple summary of TTH using the Wen's result and excluded CM 11 subjects, mITT



data)

Figure 6: K-M plot of TTH Reviewer's Data

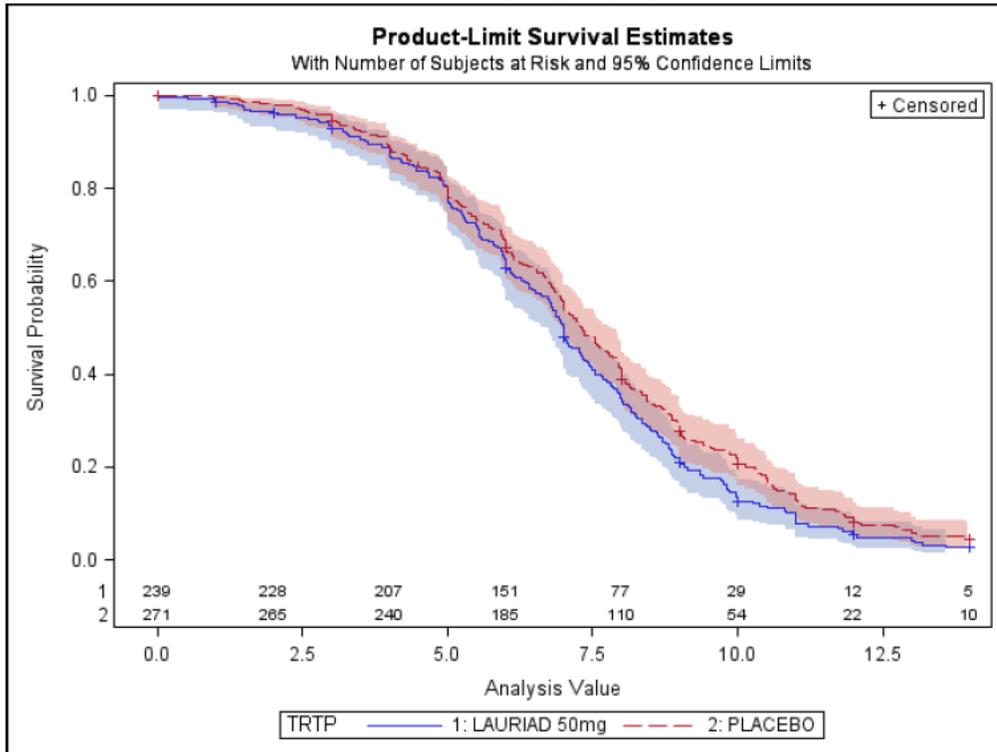


Table 10
Time-To-Healing
Reviewer's Data
Study BA2005/21/02

mITT population	ABT (N=242)	Placebo (N=279)
Total, N	239	271
Event Observed, n (%)	219 (92%)	249 (92%)
Censored, n (%)	20	22
Healing Rate, % (n/N)	92% (219/239)	92% (249/271)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.09 ± 0.18	7.56 ± 0.18
Median (days) (95% CI)	7.00 (6.72, 7.32)	7.31 (6.95, 7.79)
Log-rank Test P-value	0.0645	
Generalized Wilcoxon test (Gehan)	0.1290	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.88 (239)	7.25 (271)
Median Difference (days) (95% CI)	-0.49 (-1.00, 0.00)	
Kruskal-Wallis Test P-value	0.0538	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.88 (219)	7.00 (249)
Median Difference (days) (95% CI)	-0.30 (-0.82, 0.15)	
Kruskal-Wallis Test P-value	0.2051	

- ❖ Sensitivity analysis using corrected TTH data for five patients and 29 additional patients by both KM and HL methods. Note this analysis includes the eleven patients who took prohibited CMs.

As described in section 6.1.4.3, the TTH for these 29 patients in this analysis were imputed to 14 because they were not healed at their last visit, which occurred before study day 14. The TTHs generated by the Applicant for these 29 patients were less than 14 days.

Results are listed in Table 11 and are similar to those shown in Table 10. The median difference between two arms ranged between 0.29 - 0.43 days, which is less than ½ day even if the 11 patients who took prohibited antiviral concomitant medications were included in the analysis.

Table 11
Time-To-Healing
Reviewer's Data Without Deletion of Any Patients
Study BA2005/21/02 (mITT Population)

mITT population	ABT (N=242)	Placebo (N=279)
Total, N	242	279
Event Observed, n (%)	222 (92%)	253 (91%)
Censored, n (%)	20	26
Healing Rate, % (n/N)	93% (225/242)	94% (262/279)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.30 ± 0.20	7.80 ± 0.19
Median (days) (95% CI)	7.00 (6.78, 7.40)	7.35 (7.00, 7.94)
Log-rank Test P-value	0.0931	
Generalized Wilcoxon test (Gehan)	0.1359	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.00 (242)	7.35 (279)
Median Difference (days) (95% CI)	-0.43 (-0.99, 0.03)	
Kruskal-Wallis Test P-value	0.0407	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.90 (222)	7.00 (253)
Median Difference (days) (95% CI)	-0.29 (-0.81, 0.15)	
Kruskal-Wallis Test P-value	0.0921	

In this study, there were a variety of factors that may have impacted the outcome of the primary efficacy analysis including:

- **Delaying the treatment:** Whether the patient applied the drug within 1 hour of the occurrence of the prodromal symptoms or not.
- **Adhesion time of the first tablet:** How many hours did the first tablet stay on, <6, 6-12, or >12 hours?
- **Tablet replacement:** Was the first tablet replaced or not?
- **Herpes history:** Did the patients have at least 4 episodes of lesions in past 12 months?

The impact of these factors on the primary efficacy endpoint was assessed further and these analyses are presented below.

6.1.4.5 Delaying the Treatment:

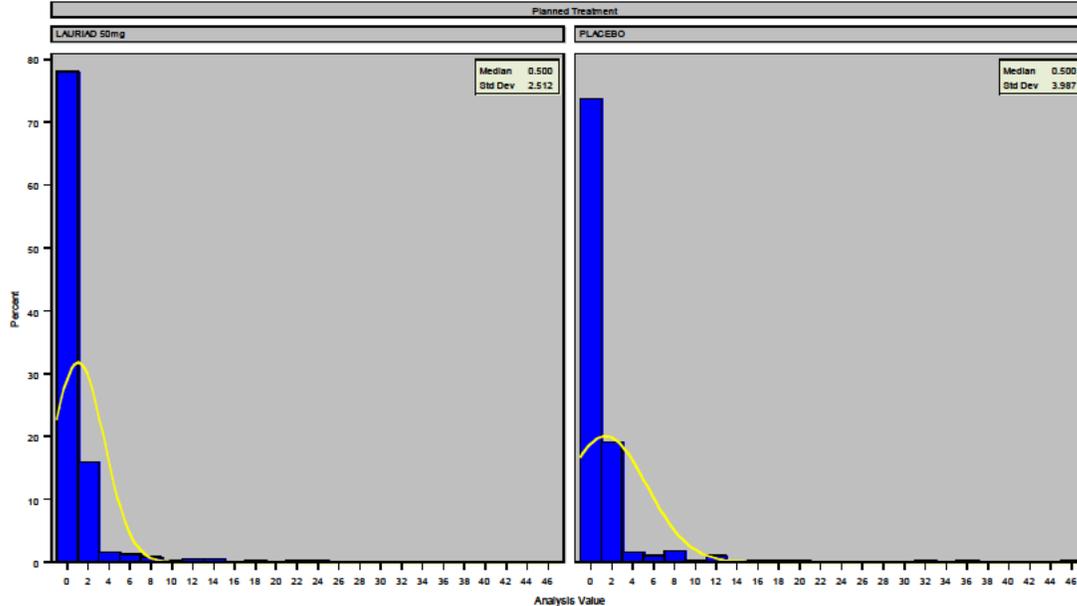
The protocol specified that the patient should apply the ABT-50 tablet within 1 hour of the occurrence of the prodromal symptoms. However, not all patients on both treatment arms did this. As shown in Table 12 over 84% of patients applied the study drug within 1 hour of the occurrence of the prodromal symptoms, and the two arms were similar for both the ITT and

mITT populations. The distribution of hours between the occurrences of the prodromal symptoms and the application of treatment on both arms are similar as shown in Figure 7.

Table 12
Application of Treatment within 1 hour after Prodromal Symptoms
Study BA2005/21/02
ITT and mITT Populations

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	4	7
Total Observed (N)	372	388
Within 1 hour, n (%)	321 (86.3%)	326 (84.0%)
After 1 hour, n (%)	51 (13.7%)	62 (15.9%)
mITT population	ABT (N=242)	Placebo (N=279)
Missing (n)	2	6
Total Observed (N)	240	273
Within 1 hour, n (%)	206 (85.8%)	228 (83.5%)
After 1 hour, n (%)	34 (14.1%)	45 (16.4%)

Figure 7
Histogram of Number of Hours between Occurrence of Symptom and Applying Drug
Treatment delay Wen's result, ITT



The primary efficacy endpoint analysis was repeated for only those patients who applied treatment within 1 hour of the occurrence of prodromal symptoms. As shown in Table 13 for patients who applied study drug within 1 hour of the occurrence of prodromal symptoms the median difference of TTH between the two arms ranged between - 0.17 and - 0.31 day which is less than that result seen for the total mITT population.

Table 13
The Time-To-Healing Using the Reviewer’s Data for Subjects who Applied Drug within 1 Hour of the Occurrence of Prodromal Symptoms
Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	203	222
Event Observed, n (%)	189	207
Censored, n (%)	14	15
Healing Rate, % (n/N)	94.1% (191/203)	95.1% (211/222)
LifeTest (K-M) on TTH		
Mean (days) ± SE	7.16 ± 0.20	7.50 ± 0.20
Median (days) (95% CI)	7.04 (6.76, 7.49)	7.22 (6.86, 7.68)
Log-rank Test P-value	0.2174	
Generalized Wilcoxon test (Gehan)	0.3708	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.00 (203)	7.20 (222)
Median Difference (days) (95% CI)	-0.31 (-0.90, 0.20)	
Kruskal-Wallis Test P-value	0.2469	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.97 (189)	7.00 (207)
Median Difference (days) (95% CI)	-0.17 (-0.74, 0.33)	
Kruskal-Wallis Test P-value	0.4825	

Comment: One would expect that patients who applied the study drug within one hour of the appearance of prodromal symptoms, in other words, before the development of the primary lesion, would have a better outcome, that is a greater decrease in the TTH. This did not occur rather the difference in TTH was less than that seen in the total mITT population and less than the minimum required ½ day. This analysis serves to show the lack of robustness in the data.

6.1.4.6 Adhesion Time of the First Tablet:

The adhesion time in hours of the first tablet was grouped into three categories, < 6 hours, 6-12 hours, or >12 hours. This was recorded by the patients. As shown in Table 14 more patients on the ABT 50 mg arm (44.4%) had adhesion times in the 6-12 hours group than those on the placebo arm (30.8%). The reverse was true for the >12 hours group.

Table 14
Adhesion Time in Hours
Study BA2005/21/02
ITT & mITT Populations

Adhesion Time in hrs	Treatment Arm (ITT)	
	ABT (N=376)	Placebo (N=395)
Missing	2	2
Total N	374	393
<6	43 (11.5%)	50 (12.7%)
6-12	166 (44.4%)	121 (30.8%)
>12	165 (44.1%)	222 (56.5%)
Adhesion Time in hrs	Treatment Arm (mITT)	
	ABT	Placebo
Missing		
Total N	237	269
<6	27 (11.4%)	33 (12.3%)
6-12	100 (42.2%)	86 (32.0%)
>12	110 (46.4%)	150 (55.8%)

The primary efficacy endpoint analyses were repeated in these three (adhesion time in hours) groups separately. The histograms of TTHs of these three groups can be seen in Figures 8, 9, and 10 respectively and the analysis results are shown in Tables 15, 16, and 17 respectively.

The median difference of TTH between the two arms in the < 6 hours group ranged between - 0.79 and - 1.06 day. Therefore, the treatment difference for this subgroup with a shorter time of drug exposure is greater than that of the mITT population (range 0.3 - 05).

The median difference of TTH between the two arms in the 6-12 hours group ranged between 0.01 and 0.20 days indicating that in this subgroup the placebo treated patients had a faster TTH than the study drug treated patients.

The median difference of TTH between the two arms in the > 12 hours group ranged between - 0.59 and - 0.70 day, which again is greater than the median difference of TTH of the mITT population.

The distributions of TTHs in three groups are similar to those of the mITT population.

Table 15
Time-To-Healing Using the Reviewer's Data for Patients With First Tablet Adhesion Time
of < 6 Hours
Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	27	33
Event Observed, n (%)	25 (92.6%)	31 (93.9%)
Censored, n (%)	2 (7.4%)	2 (6.1%)
Healing Rate, % (n/N)	92.6% (25/27)	93.9% (31/33)
LifeTest (K-M) on TTH		
Mean (days) ± SE	7.37 ± 0.38	8.18 ± 0.49
Median (days) (95% CI)	7.44 (6.00, 8.35)	8.87 (7.54, 9.02)
Log-rank Test P-value	0.0480	
Generalized Wilcoxon test (Gehan)	0.1225	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.06 (27)	8.75 (33)
Median Difference (days) (95% CI)	-1.06 (-2.51, 0.18)	
Kruskal-Wallis Test P-value	0.0847	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	7.44 (25)	8.75 (31)
Median Difference (days) (95% CI)	-0.79 (-2.10, 0.47)	
Kruskal-Wallis Test P-value	0.1713	

Table 16
Time-To-Healing Using the Reviewer's Data for Patients With First Tablet Adhesion Time of 6-12 Hours
Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	100	86
Event Observed, n (%)	90 (90.0%)	78 (90.7%)
Censored, n (%)	10 (10.0%)	8 (9.3%)
Healing Rate, % (n/N)	91.0% (91/100)	93.0% (80/86)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.23 ± 0.29	7.09 ± 0.30
Median (days) (95% CI)	7.04 (6.58, 7.55)	7.03 (6.30, 7.54)
Log-rank Test P-value	0.8587	
Generalized Wilcoxon test (Gehan)	0.7316	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.00 (100)	7.03 (86)
Median Difference (days) (95% CI)	0.01 (-0.75, 0.82)	
Kruskal-Wallis Test P-value	0.9477	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.93 (90)	6.84 (78)
Median Difference (days) (95% CI)	0.20 (-0.54, 0.99)	
Kruskal-Wallis Test P-value	0.5746	

Table 17
Time-To-Healing Using the Reviewer's Data for Patients With First Tablet Adhesion Time of >12 Hours
Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	110	150
Event Observed, n (%)	103 (93.6%)	139 (92.7%)
Censored, n (%)	7 (6.4%)	11 (7.3%)
Healing Rate, % (n/N)	95.5% (105/110)	96.0% (144/150)
Life Test (K-M) on TTH		
Mean (days) ± SE	6.89 ± 0.28	7.65 ± 0.25
Median (days) (95% CI)	6.87 (6.01, 7.35)	7.25 (6.77, 7.92)
Log-rank Test P-value	0.0648	
Generalized Wilcoxon test (Gehan)	0.0845	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.77 (110)	7.22 (150)
Median Difference (days) (95% CI)	-0.70 (-1.47, 0.04)	
Kruskal-Wallis Test P-value	0.0723	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.76 (103)	7.00 (139)
Median Difference (days) (95% CI)	-0.59 (-1.30, 0.12)	
Kruskal-Wallis Test P-value	0.1102	

Figure 8
Histogram of TTH by arm for Patients with <6 hours of Adhesion Time in mITT Population (Reviewer's data)

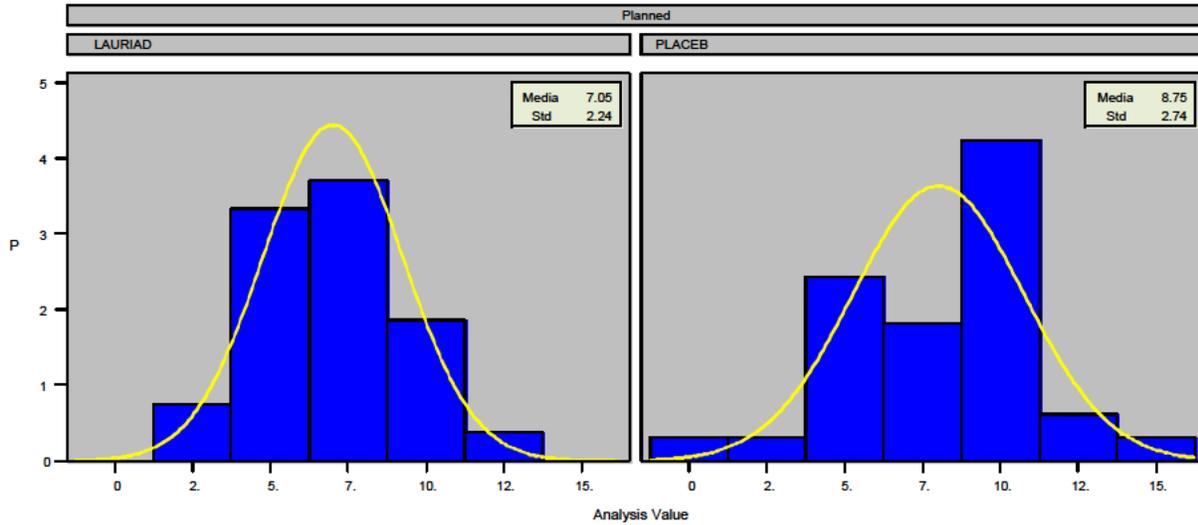


Figure 9
Histogram of TTH by arm for Patients with 6-12 hours of Adhesion Time in mITT Population (Reviewer's data)

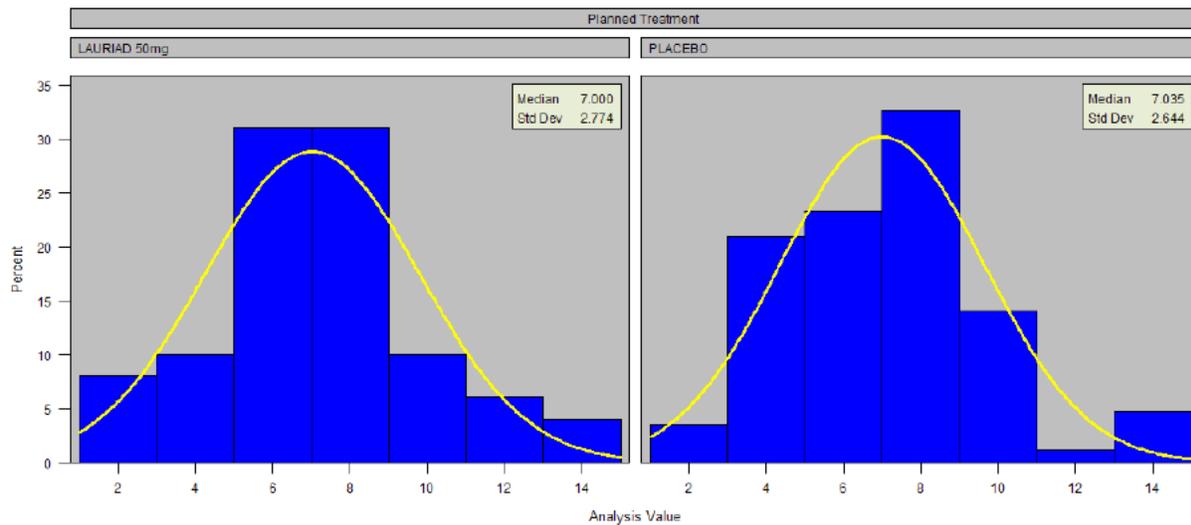
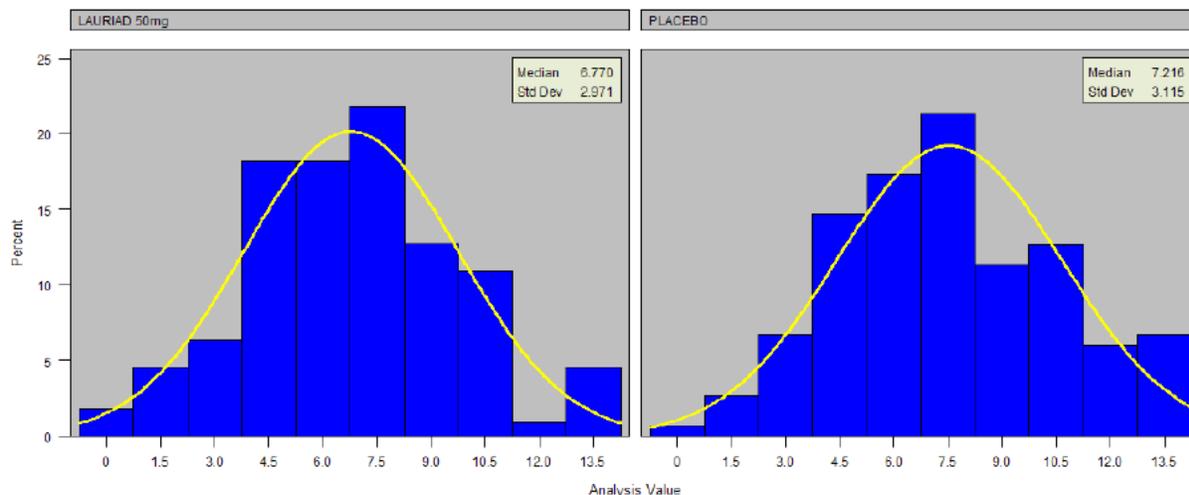


Figure 10
Histogram of TTH by arm for Patients with >12 hours of Adhesion Time in mITT Population (Reviewer's data)



Comment: This analysis of TTH by adhesion time again points to the lack of robustness in the data collected. One would expect that the greater the adhesion time, the greater the exposure and therefore more rapid TTH. This did not occur. There is no clear explanation from a PK or clinical standpoint for these conflicting results beyond that as already stated the data collection was not consistent and therefore the results cannot be fully relied upon or the results are simply random.

6.1.4.7 Replacement of the First Tablet:

In this trial the protocol required that if the adhesion time of the first tablet was < 6 hours, the tablet needed to be replaced. As shown in the Table 18 not all patients in this category applied a second tablet in ITT population. In addition there were three patients with adhesion times of at least 6 hours who applied a second tablet.

The median difference of TTH between the two arms in the < 6 hours group with tablet replacement ranged between - 0.10 and 0.03 day (Table 19) which is much shorter than that of the mITT population.

If there was no tablet replacement the median difference ranged between -3.55 and - 4.15 day (Table 20). However given the very small sample size, these results are not reliable.

Comment: These post hoc analyses appear to show that when the ABT 50 tablet was replaced, TTH was greater on the ABT 50 arm as compared to the ABT 50 arm when the tablet was not replaced (7.44 days (HL estimates) vs 5.54 days (HL estimates) respectively. These results cannot be easily explained and put into question the reliability of this type of post hoc analysis as

a whole as one would expect the opposite to be true. Also contributing to the unreliability of these results are the very small sample sizes.

Table 18
Summary of Adhesion Time of First Tablet and Tablet Replacement of Study BA2005/21/02 (ITT Population)

Adhesion Time in hrs	Treatment Arm			
	ABT 50 mg (n=45)		Placebo (n=50)	
	Was the tablet replaced?		Was the tablet replaced?	
	Yes	No	Yes	No
<6	33	10	35	14
6-12	1			
>12	1		1	

Table 19
The Time-To-Healing Using the Reviewer's Data for Patients with First Tablet Adhesion Time < 6 Hours and Tablet Replacement
Study BA2005/21/02, mITT Population

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	21	26
Event Observed, n (%)	20 (95.2%)	24 (92.3%)
Censored, n (%)	1 (4.8%)	2 (7.7%)
Healing Rate, % (n/N)	95.2% (20/21)	92.3% (24/26)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.66 ± 0.43	7.72 ± 0.57
Median (days) (95% CI)	7.58 (6.00, 8.82)	8.08 (5.40, 9.00)
Log-rank Test P-value	0.5091	
Generalized Wilcoxon test (Gehan)	0.8666	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.44 (21)	8.04 (26)
Median Difference (days) (95% CI)	-0.10 (-1.60, 1.23)	
Kruskal-Wallis Test P-value	0.8389	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	7.58 (20)	8.04 (24)
Median Difference (days) (95% CI)	0.03 (-1.49, 1.52)	
Kruskal-Wallis Test P-value	0.9624	

Table 20
The Time-To-Healing Using the Reviewer's Data for Patients with First Tablet Adhesion Time < 6 Hours and without Tablet Replacement
Study BA2005/21/02, mITT Population

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	6	7
Event Observed, n (%)	5 (83.3%)	7 (100.0%)
Censored, n (%)	1 (16.7%)	0 (0%)
Healing Rate, % (n/N)	83.3% (5/6)	100.0% (7/7)
Life Test (K-M) on TTH		
Mean (days) ± SE	6.21 ± 0.68	9.86 ± 0.65
Median (days) (95% CI)	6.00 (4.45, 7.82)	10.00 (8.00, 11.00)
Log-rank Test P-value	0.0003	
Generalized Wilcoxon test (Gehan)	0.0006	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.54 (6)	10.00 (7)
Median Difference (days) (95% CI)	-4.15 (-6.79, -2.00)	
Kruskal-Wallis Test P-value	0.0027	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.00 (5)	10.00 (7)
Median Difference (days) (95% CI)	-3.55 (-5.93, -0.93)	
Kruskal-Wallis Test P-value	0.0045	

6.1.4.8 Herpes History:

In this trial one inclusion criterion was that patients should have had at least 4 episodes of herpes labialis in the preceding 12 months in order to be qualified as recurrent herpes labialis patients. Sixty-eight percent of patients fell into this category (Table 21).

The median difference of TTH between the two arms of patients who had at least 4 episodes of HL within past the 12 months ranged between - 0.29 and - 0.52 days (Table 22), which is similar to the results of the mITT population. The median difference of TTH between the two arms in patients who had less than 4 episodes of HL within past the 12 months is approximately- 0.35 day (Table 23).

Comment: The factor of either having or not having at least 4 episodes of HL within past the 12 months did not have a significant impact on the primary efficacy endpoint, TTH. However, this is an exploratory analysis and results should be interpreted with caution.

Table 21
Herpes History -- at least 4 episodes of HL within past 12 months
Study BA2005/21/02 (ITT and mITT Population)

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)		
Total Observed (N)	376	395
≥4 episodes, n (%)	257 (68.4%)	273 (69.1%)
<4 episodes, n (%)	119 (31.7%)	122 (30.9%)
mITT population	ABT (N=242)	Placebo (N=279)
Missing (n)		
Total Observed (N)	242	279
≥4 episodes, n (%)	166 (68.6%)	192 (68.8%)
<4 episodes, n (%)	76 (31.4%)	87 (31.2%)

Table 22
The Time-To-Healing Using the Reviewer's Data for Patients who Had at Least 4 Episodes of HL within Past 12 Months for the Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	163	190
Event Observed, n (%)	149 (91.4%)	177 (93.2%)
Censored, n (%)	14 (8.6%)	13 (6.8%)
Healing Rate, % (n/N)	92.6% (151/163)	95.3% (181/190)
LifeTest (K-M) on TTH		
Mean (days) ± SE	6.95 ± 0.22	7.41 ± 0.22
Median (days) (95% CI)	6.93 (6.41, 7.13)	7.00 (6.75, 7.57)
Log-rank Test P-value	0.1411	
Generalized Wilcoxon test (Gehan)	0.2435	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.82 (163)	7.00 (190)
Median Difference (days) (95% CI)	-0.52 (-1.08, 0.05)	
Kruskal-Wallis Test P-value	0.0925	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.82 (149)	6.97 (177)
Median Difference (days) (95% CI)	-0.29 (-0.90, 0.25)	
Kruskal-Wallis Test P-value	0.3072	

Table 23
The Time-To-Healing Using the Reviewer's Data for Patients who had less than 4 Episodes of HL within the Past 12 Months Study BA2005/21/02

mITT population	ABT (N=206)	Placebo (N=228)
Total, N	76	81
Event Observed, n (%)	70 (92.1%)	72 (88.9%)
Censored, n (%)	6 (7.9%)	9 (11.1%)
Healing Rate, % (n/N)	93.4% (71/76)	92.6% (75/81)
LifeTest (K-M) on TTH		
Mean (days) ± SE	7.32 ± 0.31	7.87 ± 0.32
Median (days) (95% CI)	7.44 (6.16, 8.17)	8.00 (7.10, 8.44)
Log-rank Test P-value	0.1986	
Generalized Wilcoxon test (Gehan)	0.3012	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.30 (76)	7.94 (81)
Median Difference (days) (95% CI)	-0.39 (-1.34, 0.50)	
Kruskal-Wallis Test P-value	0.3279	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	7.11 (70)	7.59 (72)
Median Difference (days) (95% CI)	-0.34 (-1.24, 0.59)	
Kruskal-Wallis Test P-value	0.4227	

6.1.5 Analysis of Selected Secondary Endpoints(s)

The following selected secondary efficacy endpoints were analyzed by the Agency statistical reviewer:

- ❖ Proportion of subjects with aborted primary lesions
- ❖ Duration of herpes episode
- ❖ Time to cessation of symptoms

These analyses were performed in the ITT population. Of note, the Applicant did not specify any multiplicity adjustments in the protocol for these secondary endpoint analyses.

6.1.5.1 Aborted primary lesions (PL): Defined as herpetic lesions preceded by prodromal symptoms that do not progress beyond the papule stage (ie, Erythema and papule, no vesicle/blister).

The Applicant's results were reproduced by the Agency for the proportion of subjects with aborted primary lesions in the ITT population (Table 24). Eleven ITT patients, four on the ABT 50 mg arm and seven on the placebo arm had missing information regarding their primary lesion (PL) reaching the vesicular stage. As a result only 760 subjects were included in the analysis as opposed to the 771 in the ITT population. The proportion of subjects with aborted PL on the ABT 50 mg arm (34.9%) was significantly higher than the placebo arm (28.1%). The rate difference is 6.85% with exact 95% CI of (0.22%, 13.48%) and P-value 0.043.

Comment: Although this analysis was statistically significant in favor of ABT 50, there was no multiplicity adjustment because this endpoint is one of 10 secondary efficacy endpoints analyzed. As a result, there is no type-I error control for this analysis. The application under review is a 505(b)(2) application which depends on previous findings of efficacy in order to grant an indication. Acyclovir in either the oral or topical form is not approved for the claim that the product increases the number of aborted lesions. However these results would be considered supportive if reproduced in a second prospective trial at the 0.05 significance level from the clinical standpoint. A determination that such an outcome would be considered clinically beneficial could be made if the results are reproducible.

(b) (4)



Table 24
Proportion of Subjects with Aborted Primary Lesion
Study BA2005/21/02
ITT Population

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	4	7
Total Observed (N)	372	388
Aborted, n (%)	130 (34.9%)	109 (28.1%)
Vesicular, n (%)	242	279
Abortion Rate Difference (ABT - Placebo)	6.85%	
Exact 95% CI of two one-sided tests	(0.18%, 13.45%)	
Exact 95% CI of one two-sided test	(0.22%, 13.48%)	
Exact P-value of the two-sided test	0.0430	

❖ The impact of adhesion time on the proportion of subjects with aborted PLs:

The impact of the adhesion time of the first tablet on the rate of aborted lesions was assessed here. Please see section 6.1.4.6 for the detailed summary of adhesion time of the first tablet.

As mentioned above, the total number of patients in the analysis is 756 instead of the 771 in the ITT population because eleven patients, four on the ABT 50 mg arm and seven on the placebo arm, had missing information regarding aborted PLs.

The difference between the ABT 50 mg arm and the placebo arm for the proportion of subjects with aborted PLs is 4.0%, 12.4%, and 3.4% for adhesion times of < 6 hours, 6-12 hours, and > 12 hours groups, respectively (Table 25). Of note, the overall difference between the two arms is 6.85% with exact 95% CI of (0.22%, 13.48%). The difference between the two arms mainly comes from the group of subjects who had adhesion times of 6-12 hours.

Comment: The results of this analysis are encouraging. Generally it appears as if ABT 50 did increase the number of aborted PLs across the groups with the greatest difference in those patients with adhesion times ranging from 6 – 12 hours. This analysis (b) (4) can be used as supportive data for a resubmission in response to the CR action.

Table 25
Proportion of Subjects with Aborted PL by Patients Adhesion Time
Study BA2005/21/02 (ITT Population)

Adhesion time < 6 hours		
ITT population	ABT (N=376)	Placebo (N=395)
Total Observed (N)	43	49
Aborted, n (%)	14 (32.6%)	14 (28.6%)
Vesicular, n	29	35
Aborted PL Rate Difference (ABT - Placebo)	4.0%	
Exact 95% CI of two one-sided tests	(-15.4%, 23.3%)	
Exact 95% CI of one two-sided test	(-15.7%, 23.2%)	
Exact P-value of the two-sided test	0.7111	
Adhesion time 6-12 hours		
ITT population	ABT (N=376)	Placebo (N=395)
Total Observed (N)	163	117
Aborted, n (%)	62 (38.0%)	30 (25.6%)
Vesicular, n	101	87
Aborted PL Rate Difference (ABT - Placebo)	12.4%	
Exact 95% CI of two one-sided tests	(1.3%, 23.1%)	
Exact 95% CI of one two-sided test	(1.24%, 23.1%)	
Exact P-value of the two-sided test	0.0299	
Adhesion time >12 hours		
ITT population	ABT (N=376)	Placebo (N=395)
Total Observed (N)	164	220
Aborted, n (%)	54 (32.9%)	65 (29.6%)
Vesicular, n	110	155
Aborted PL Rate Difference (ABT - Placebo)	3.4%	
Exact 95% CI of two one-sided tests	(-6.0%, 12.9%)	
Exact 95% CI of one two-sided test	(-5.9%, 12.9%)	
Exact P-value of the two-sided test	0.4822	

6.1.5.2 Duration of episode (DOE): For patients who experienced a vesicular lesion, duration of episode is the time from treatment initiation to the healing of the primary and secondary lesions. For patients whose primary and secondary lesions were not vesicular in nature, duration of episode is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms whichever comes last.

If one of primary and secondary lesions was not healed, DOE was classified as not healed and censored. If both the primary and secondary lesions were healed DOE was classified as healed and the healing date was the later one.

In the data validation in addition to the previously mentioned five patients whose TTHs were calculated incorrectly, the statistical reviewer also found a calculation error in one additional patient. This did not have any impact on the final results. The Applicant's results of the DOE analysis can be seen in Applicant's Table 11 copied from the CSR.

The statistical reviewer's results can be seen in Table 26. Using the KM approach the median difference of DOE between arms is - 0.80 days with Log-rank test P-value of 0.0049. The median differences of DOE using the HL method are - 0.58 using all DOE data regardless of censoring and -0.42 days observed DOE only.

Comment: At this time there is no treatment standard in effect for the duration of episode (DOE) parameter. These data show the variability if the treatment effect of ABT 50 depending on which analysis was used. The difference in the DOE in these analyses ranged from 0.4 – 0.8 days again indicating the lack of robustness in the data.

The DOE distributions for both arms are skewed as shown in Figure 11.

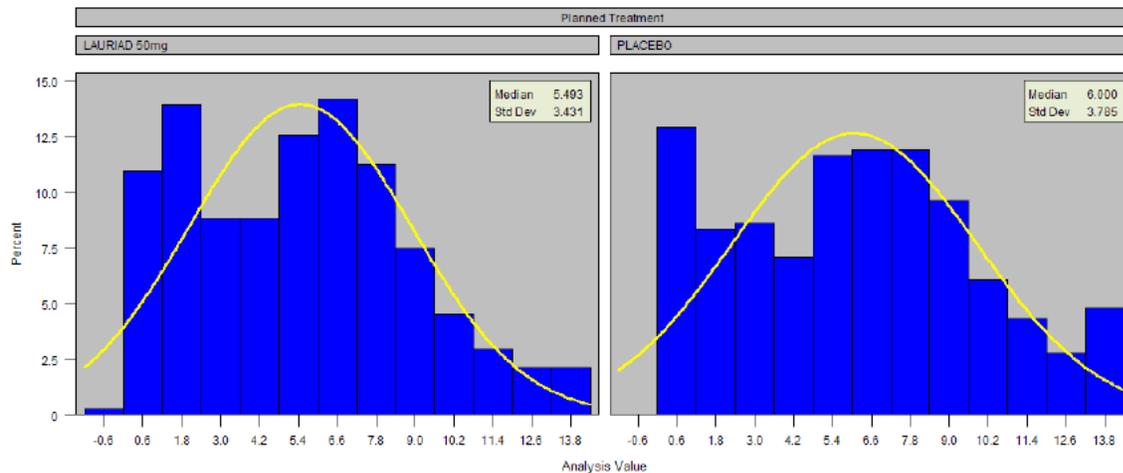
Table 11 Duration of Episode (ITT Population)

	ABT 50 mg N=376	Placebo N=395	Total N=771
Patients (N [%])	373 (99.2%)	395 (100.0%)	768 (99.6 %)
Events (N)	340	348	688
Censored Observations (N)	33	47	80
Missing Observations (N)	3	0	3
Mean duration in days ± SE	5.67 ± 0.18	6.34 ± 0.20	6.02 ± 0.14
Median in days (95% CI)	5.57 (5.03; 6.01)	6.38 (5.93; 6.97)	6.00 (5.58; 6.40)
Log Rank Test		0.0033	

Table 26
Duration of Episode for Study BA2005/21/02 (ITT Population)

ITT population	ABT (N=376)	Placebo (N=395)
Total, N	374	395
Event Observed, n (%)	341	348
Censored, n (%)	33	47
Missing Observations (N)	2	0
Arithmetical Mean (days) ± SE	5.46 ± 0.18	6.08 ± 0.19
LifeTest (K-M) on DOE		
Mean (days) ± SE	5.70 ± 0.18	6.36 ± 0.20
Median (days) (95% CI)	5.58 (5.03, 6.07)	6.38 (5.93, 6.97)
Log-rank Test P-value	0.0049	
Generalized Wilcoxon test (Gehan)	0.0325	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.49 (374)	6.00 (395)
Median Difference (days) (95% CI)	-0.58 (-1.08, -0.03)	
Kruskal-Wallis Test P-value	0.0289	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	5.25 (341)	5.93 (348)
Median Difference (days) (95% CI)	-0.42 (-0.96, 0.07)	
Kruskal-Wallis Test P-value	0.1100	

Figure 11
Duration of Episode (DOE)
Study BA2005/21/02 (ITT)



6.1.5.3 Time to cessation of symptoms (TTC): Defined as the time from treatment initiation to the cessation of all symptoms: pain, burning, itching, tingling, tenderness and discomfort. It will be assessed by the investigator with the support of the patient diary.

In the study, there were two places in the case report form (CRF) where this information was collected:

- **AP:** Prodromal symptoms, and
- **AR:** Any symptoms related to the Lesion(s).

The latest time in days of disappearance of all possible symptoms was used for the TTC calculation. If any one of symptoms was still present the TTC was classified as censored and the latest available visit date of all symptoms was used for the TTC calculation.

In the data validation the statistical reviewer found a miscalculation in one patient. This had no impact on the final results. The Applicant's results for TTC are listed below in Table 12 copied from the CSR. The statistical reviewer's results can be seen in Table 27. Using the KM approach the median difference of TTC between arms is was - 0.59 days with Log-rank test P-value of 0.0098. The median differences of TTC using the HL method were - 0.45 (TTC regardless of censoring) and - 0.38 day (observed TTC only).

The TTC distributions for both arms are skewed to the left hand side as shown in Figure 12.

The statistical reviewer's TTC analysis results in mITT population are listed in Table 28. Of note, the median difference of TTC using the HL method is about - 0.8 days, which is longer than that in the ITT population (about -0.4 days).

Comment: This analysis again points out the variability in the results depending on the analysis method used. Generally ABT 50 appears to have had a treatment effect however the variability in the results leads to concerns regarding the ultimate clinical significance of these findings.

Table 12 Time to Cessation of Symptoms (ITT Population)

	ABT 50 mg N=376	Placebo N=395	Total N=771
Patients (N [%])	373 (99.2%)	393 (99.5%)	766 (99.4%)
Events (N)	341	353	694
Censored observations (N)	32	40	72
Missing Observations (N)	3	2	5
Mean duration in days ± SE	4.27 ± 0.16	4.94 ± 0.19	4.63 ± 0.13
Median in days (95% CI)	3.57 (3.04; 4.01)	4.16 (3.75; 4.89)	3.98 (3.58; 4.18)
Log Rank Test		0.0098	

Table 27
Time to Cessation of Symptoms
Study BA2005/21/02
ITT Population

ITT population	ABT (N=376)	Placebo (N=395)
Total, N	374	393
Event Observed, n (%)	342 (91%)	353 (89%)
Censored, n (%)	32	40
Missing Observations (N)	2	2
Arithmetical Mean (days) ± SE	4.08 ± 0.16	4.66 ± 0.17
LifeTest (K-M) on TTC		
Mean (days) ± SE	4.27 ± 0.16	4.94 ± 0.179
Median (days) (95% CI)	3.57 (3.04, 4.01)	4.16 (3.74, 4.89)
Log-rank Test P-value	0.0098	
Generalized Wilcoxon test (Gehan)	0.0501	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	3.39 (374)	4.00 (393)
Median Difference (days) (95% CI)	-0.45 (-0.90, 0)	
Kruskal-Wallis Test P-value	0.0423	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	3.33 (342)	3.92 (353)
Median Difference (days) (95% CI)	-0.38 (-0.83, 0.03)	
Kruskal-Wallis Test P-value	0.0834	

Figure 12
Time to cessation of symptoms (TTC)
Study BA2005/21/02 (ITT)

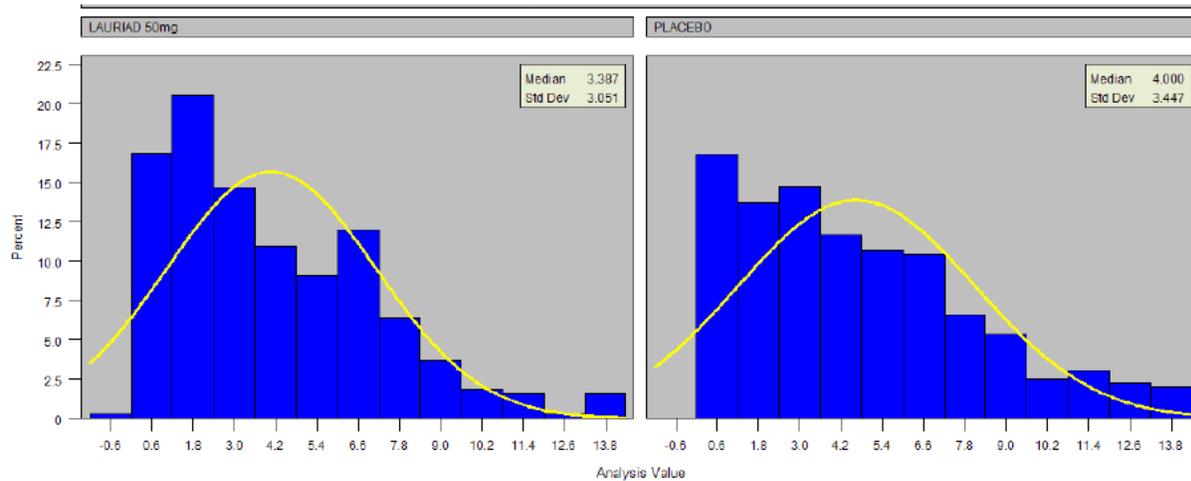


Table 28
Time to Cessation of Symptoms
Study BA2005/21/02
mITT Population

mITT population	ABT (N=242)	Placebo (N=279)
Total, N	242	277
Event Observed, n (%)	216 (89%)	247 (89%)
Censored, n (%)	26	30
Missing Observations (N)	0	2
Arithmetical Mean (days) ± SE	4.89 ± 0.20	5.71 ± 0.20
LifeTest (K-M) on TTC		
Mean (days) ± SE	5.10 ± 0.20	5.99 ± 0.21
Median (days) (95% CI)	4.95 (4.18, 5.29)	5.71 (5.13, 6.03)
Log-rank Test P-value	0.0126	
Generalized Wilcoxon test (Gehan)	0.0082	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	4.63 (242)	5.40 (277)
Median Difference (days) (95% CI)	-0.82 (-1.34, -0.21)	
Kruskal-Wallis Test P-value	0.0057	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	4.38 (216)	5.27 (247)
Median Difference (days) (95% CI)	-0.79 (-1.34, -0.20)	
Kruskal-Wallis Test P-value	0.0071	

6.1.6 Other Endpoints

The Applicant noted the treatment difference between ABT 50 mg and placebo was narrower than expected. Further the Applicant claims that the differences in efficacy between the arms were due to the fact that there were more patients with severe PLs on the ABT arm as compared to the placebo arm. They reached this conclusion because the proportion of subjects with aborted PL on the ABT arm was 35% and was greater than that observed on the placebo arm (28%). In order to assess the validity of this claim, three types of comparative analyses were conducted by the statistical reviewer looking at the:

- ❖ The severity of previous episodes of lesions
- ❖ The greatest severity of all symptoms at DAY 1 (visit 3)
- ❖ The greatest severity of all symptoms at all visits

Symptoms assessed included itching, tingling, pain/burning, discomfort, and tenderness. This information was collected in two places in the CRF:

- **AP:** Prodromal symptoms, and
- **AR:** Any symptoms related to the Lesion(s).

Severity levels were classified as mild, moderate, or severe. Some patient/symptoms were classified as absent.

The information regarding previous severity of herpes labialis was collected by the investigators on visit 1 (Day -10 to Day 0) according to the patients' information.

The information regarding the severity of the current lesions was collected by the investigators on visits 3 (Day 1), 4 (Day 3), 5 (Day 5), 6 (Day 7), and 7 (Day 14).

❖ **The severity of previous episodes of lesions:**

The percentages of mild, moderate, and severe previous episodes between the two arms are balanced in both the ITT and mITT populations (Table 29).

Table 29
Severity of Previous Herpes Episodes
Study BA2005/21/02
ITT & mITT Populations

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	0	1
Total Observed (N)	376	394
Mild, n (%)	42 (11.2%)	40 (11.2%)
Moderate, n (%)	173 (46.0%)	181 (45.9%)
Severe, n (%)	161 (42.8%)	173 (43.9%)
mITT population	ABT (N=242)	Placebo (N=279)
Missing (n)		
Total Observed (N)	242	279
Mild, n (%)	30 (12.4%)	29 (10.4%)
Moderate, n (%)	112 (46.3%)	130 (46.6%)
Severe, n (%)	100 (41.3%)	120 (43.0%)

❖ **Greatest severity of all symptoms at DAY 1 (visit 3):**

As shown in Table 30, the percentages of mild, moderate, and severe categories of all symptoms between the two arms at DAY 1 (Visit 3) were balanced in both the ITT and mITT populations.

Table 30
Severity of Herpes Symptoms at DAY 1
Study BA2005/21/02
ITT & mITT Populations

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	1	2
Total Observed (N)	375	393
Absent, n (%)	0	2 (0.5%)
Mild, n (%)	122 (32.5%)	119 (30.5%)
Moderate, n (%)	194 (51.7%)	207 (53.1%)
Severe, n (%)	59 (15.7%)	62 (15.9%)
mITT population	ABT (N=242)	Placebo (N=279)
Missing (n)		
Total Observed (N)	242	276
Absent, n(%)		
Mild, n (%)	63 (26.0%)	75 (27.2%)
Moderate, n (%)	140 (57.9%)	153 (55.4%)
Severe, n (%)	39 (16.1%)	48 (17.4%)

❖ **Greatest severity of all symptoms at all visits:**

As shown in Table 31 the percentages of mild, moderate, and severe categories of all symptoms between the two arms at all visits were balanced in both the ITT and mITT populations.

Table 31
Severity of Herpes Symptoms at All Visits
Study BA2005/21/02
ITT & mITT Populations

ITT population	ABT (N=376)	Placebo (N=395)
Missing (n)	1	2
Total Observed (N)	375	393
Absent, n(%)	0	2 (0.5%)
Mild, n (%)	100 (26.7%)	97 (24.9%)
Moderate, n (%)	207 (55.2%)	212 (54.4%)
Severe, n (%)	68 (18.1%)	79 (20.3%)
mITT population	ABT (N=242)	Placebo (N=279)
Missing (n)		
Total Observed (N)	242	276
Absent, n(%)		
Mild, n (%)	46 (19.0%)	55 (19.9%)
Moderate, n (%)	148 (61.2%)	158 (57.3%)
Severe, n (%)	48 (19.8%)	63 (22.8%)

Conclusion: Overall, the severity of symptoms between two arms was similar and therefore the narrower than expected differences in efficacy outcomes between the treatment arms cannot be explained by this factor.

6.1.7 Subpopulations

Subgroup analyses by sex and race were also conducted by the Agency statistical reviewer. The race category has been regrouped into Caucasian or Other because 95% of patients in the mITT population were Caucasian. The simple summary of mITT population by sex and race group is listed in Table 32 below.

Table 32
Simple Summary of Patient by Sex and Race Group
Reviewer’s Data (mITT Population)
Study BA2005/21/02

	Treatment			Total (N=510)
		ABT (N=239)	Placebo (N=271)	
Sex	Female	161	184	345 (67.6%)
	Male	78	87	165 (32.4%)
Race Group	Caucasian	232	260	492 (96.5%)
	Other ¹	7	11	18 (3.5%)

¹: Other includes Asian, Black, Hispanic, and Others.

6.1.7.1 Primary Efficacy Endpoint Analysis by Sex

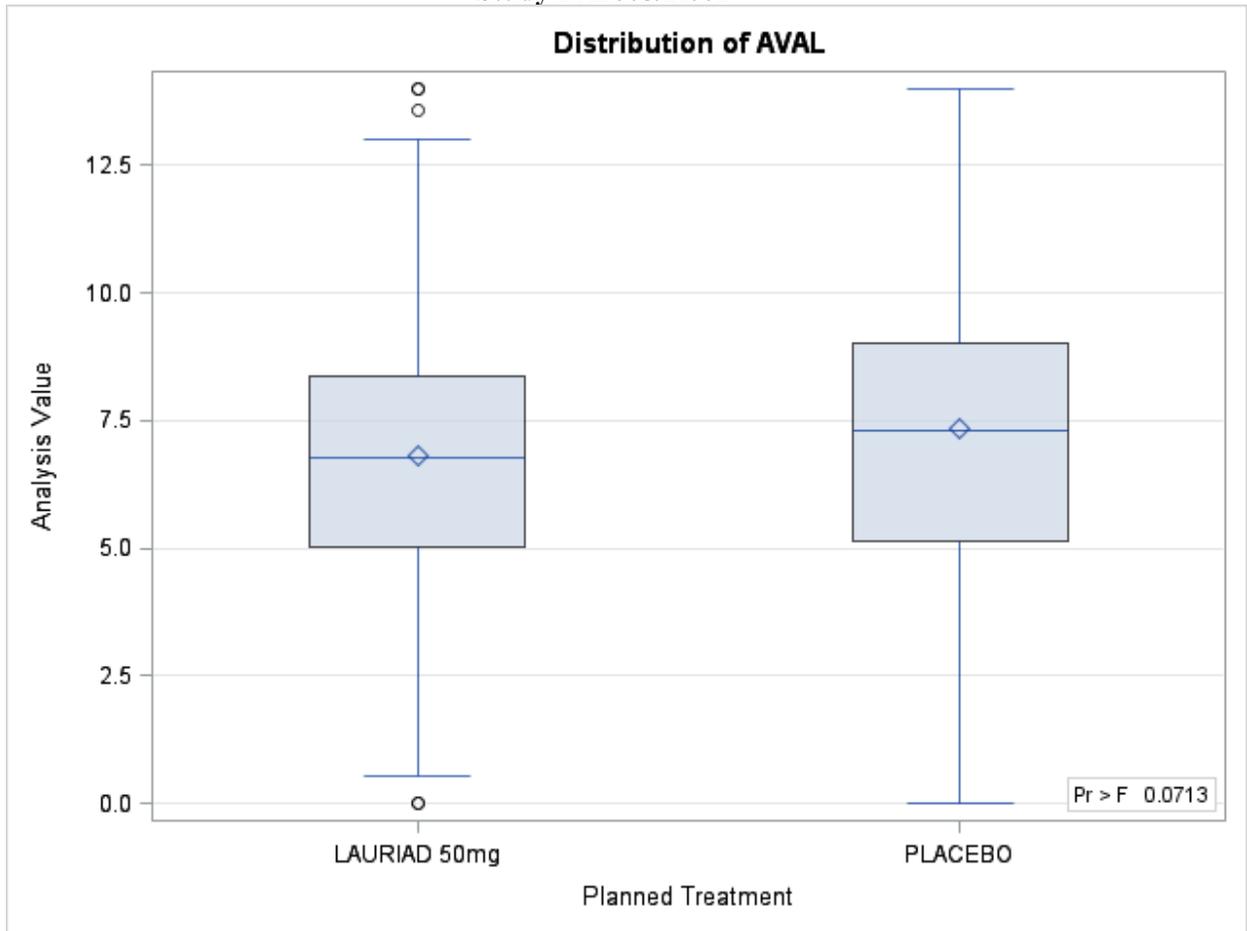
The TTH analysis by sex results are listed in Tables 33 and 34 for Female and Male patients respectively. The results of female patients are very close to the mITT overall results. Of note, there is smaller TTH median difference between two arms than that in the overall mITT population. The variability of TTH in the male group are larger than that in female group as well as the overall mITT population due to the much smaller sample sizes.

The box-plots of female and male patients’ TTHs are shown in Figure 13 and 14 respectively.

Table 33
Time-To-Healing of Female Patients Only
Reviewer's Data
Study BA2005/21/02

mITT population	ABT (N=161)	Placebo (N=184)
Total, N	161	184
Event Observed, n (%)	150 (93%)	169 (92%)
Censored, n (%)	11 (7%)	15 (8%)
Healing Rate, % (n/N)	93% (150/161)	95% (174/184)
LifeTest (K-M) on TTH		
Mean (days) ± SE	6.96 ± 0.22	7.50 ± 0.22
Median (days) (95% CI)	6.88 (6.38, 7.31)	7.32 (6.97, 7.96)
Log-rank Test P-value	0.0630	
Generalized Wilcoxon test (Gehan)	0.1177	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.79 (161)	7.30 (184)
Median Difference (days) (95% CI)	-0.56 (-1.13, 0.03)	
Kruskal-Wallis Test P-value	0.0770	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.79 (150)	7.17 (168)
Median Difference (days) (95% CI)	-0.38 (-0.78, 0.19)	
Kruskal-Wallis Test P-value	0.2170	

Figure 13
Box-Plot of Female's TTH (mITT)*
Reviewer's Data
Study BA2005/21/02

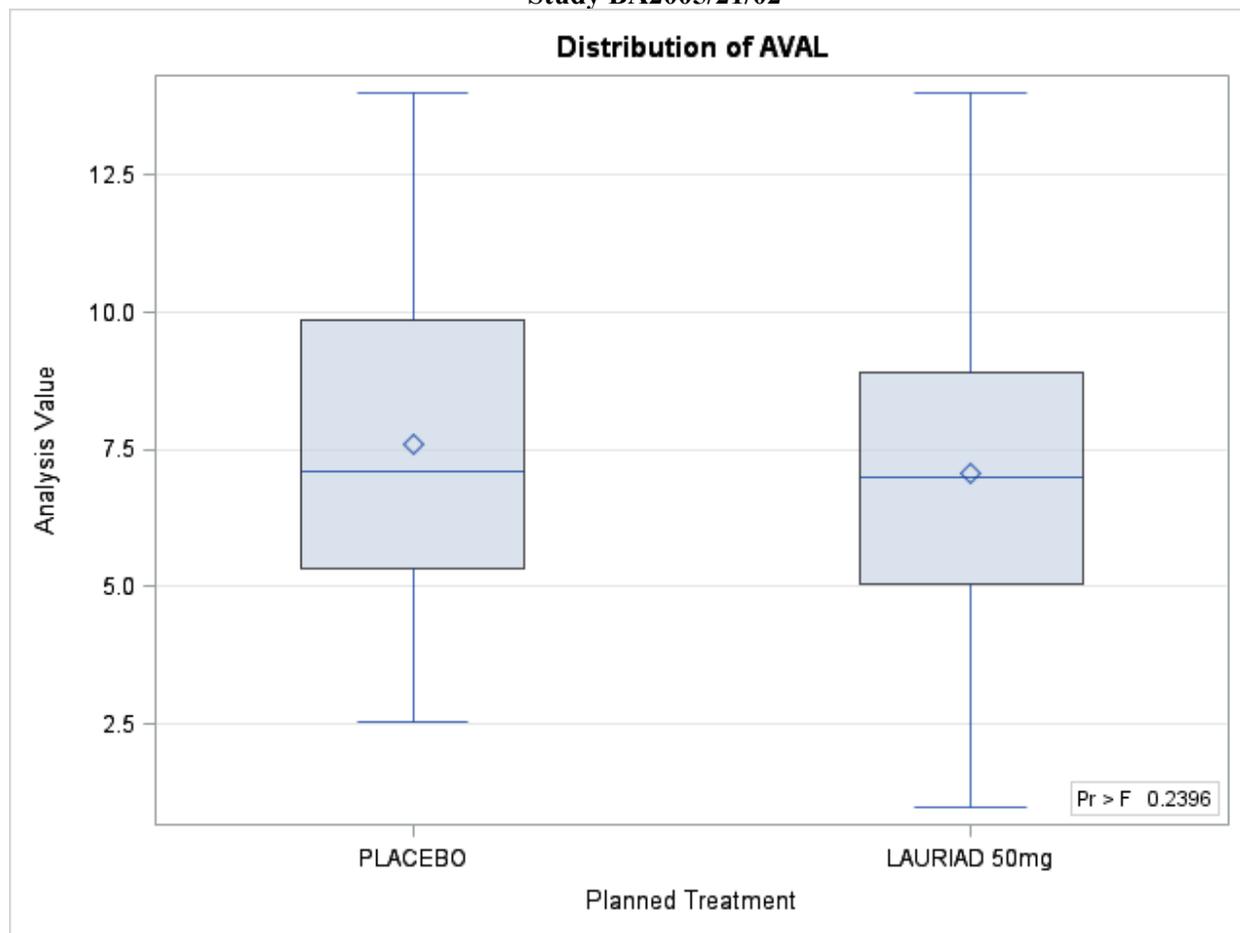


*: including both observed and censored Female's TTH data in mITT Population

Table 34
Time-To-Healing of Male Patients Only
Reviewer's Data
Study BA2005/21/02

mITT population	ABT (N=78)	Placebo (N=87)
Total, N	78	87
Event Observed, n (%)	69 (88%)	80 (92%)
Censored, n (%)	9 (12%)	7 (8%)
Healing Rate, % (n/N)	92% (72/78)	94% (82/87)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.34 ± 0.33	7.69 ± 0.32
Median (days) (95% CI)	7.28 (6.51, 7.99)	7.17 (6.30, 7.96)
Log-rank Test P-value	0.5150	
Generalized Wilcoxon test (Gehan)	0.6656	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	7.00 (78)	7.10 (87)
Median Difference (days) (95% CI)	-0.39 (-1.36, 0.52)	
Kruskal-Wallis Test P-value	0.3790	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	7.00 (69)	6.90 (80)
Median Difference (days) (95% CI)	-0.18 (-1.10, 0.70)	
Kruskal-Wallis Test P-value	0.6533	

Figure 14
Box-Plot of Male's TTH (mITT)
Reviewer's Data
Study BA2005/21/02



*: including both observed and censored Male's TTH data in mITT Population

6.1.7.2 Primary Efficacy Endpoint Analysis by Race Group

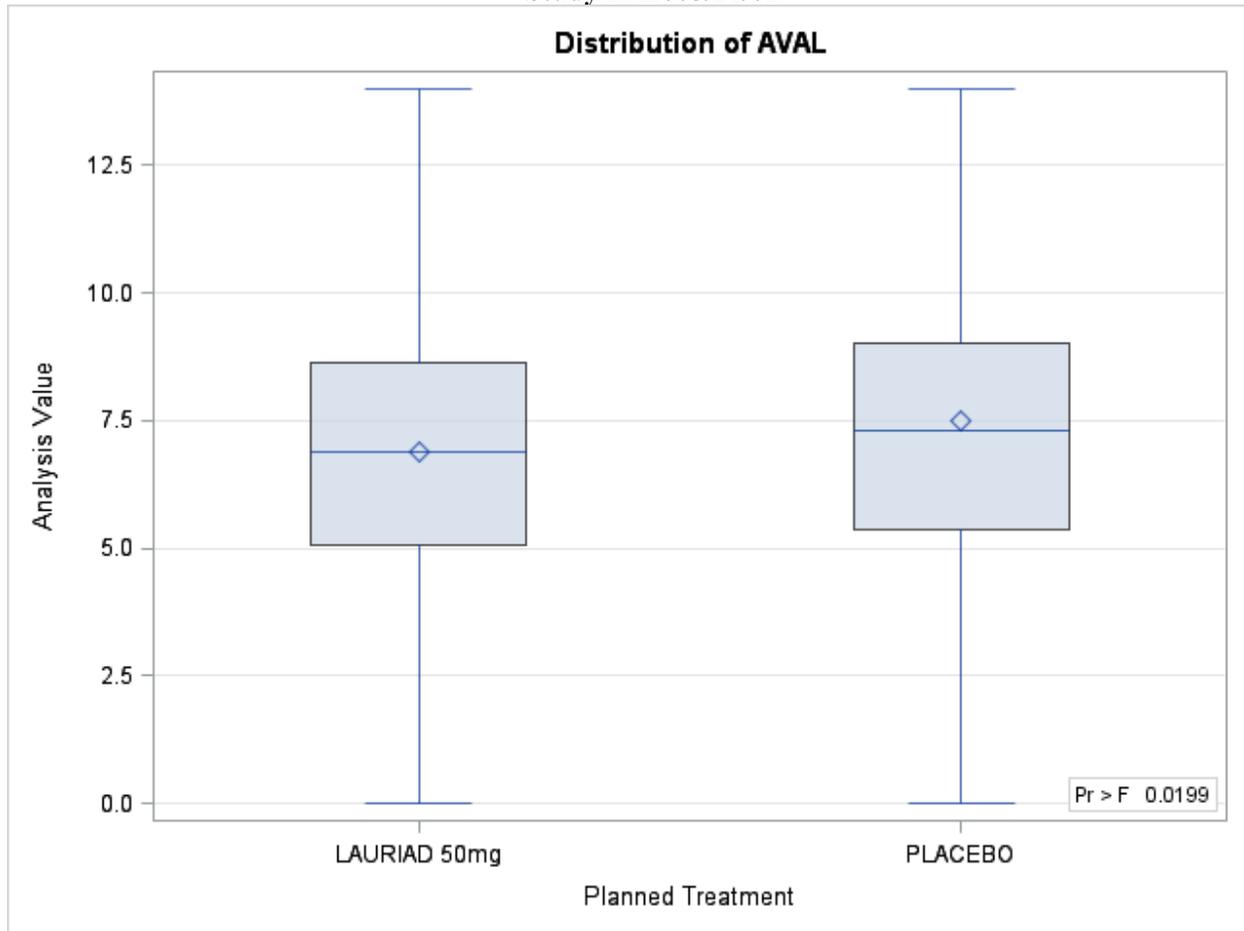
The TTH analysis results by race are listed in Tables 35 and 36 for Caucasian and Other patients respectively. As expected, the results of Caucasian patients, which accounted for over 96% of the total mITT patient population, are very close to those of the mITT overall. The results from the "Other" subgroup are not reliable due to the extremely small sample size.

The box-plots of Caucasian and Other patients' TTHs are shown in Figure 15 and 16 respectively.

Table 35
Time-To-Healing of Caucasian Patients Only
Reviewer's Data
Study BA2005/21/02

mITT population	ABT (N=232)	Placebo (N=260)
Total, N	232	260
Event Observed, n (%)	212 (91%)	238 (92%)
Censored, n (%)	20 (9%)	22 (8%)
Healing Rate, % (n/N)	93% (215/232)	94% (245/260)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.09 ± 0.19	7.62 ± 0.18
Median (days) (95% CI)	7.00 (6.72, 7.35)	7.32 (7.00, 7.92)
Log-rank Test P-value	0.0471	
Generalized Wilcoxon test (Gehan)	0.0948	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	6.90 (232)	7.30 (260)
Median Difference (days) (95% CI)	-0.53 (-1.02, -0.01)	
Kruskal-Wallis Test P-value	0.0374	
Hodges-Lehmann (HL) Estimates (Event observed only)		
Median (days) (N)	6.88 (212)	7.08 (238)
Median Difference (days) (95% CI)	-0.34 (-0.87, 0.12)	
Kruskal-Wallis Test P-value	0.1578	

Figure 15
Box-Plot of Caucasian's TTH (mITT)
Reviewer's Data
Study BA2005/21/02



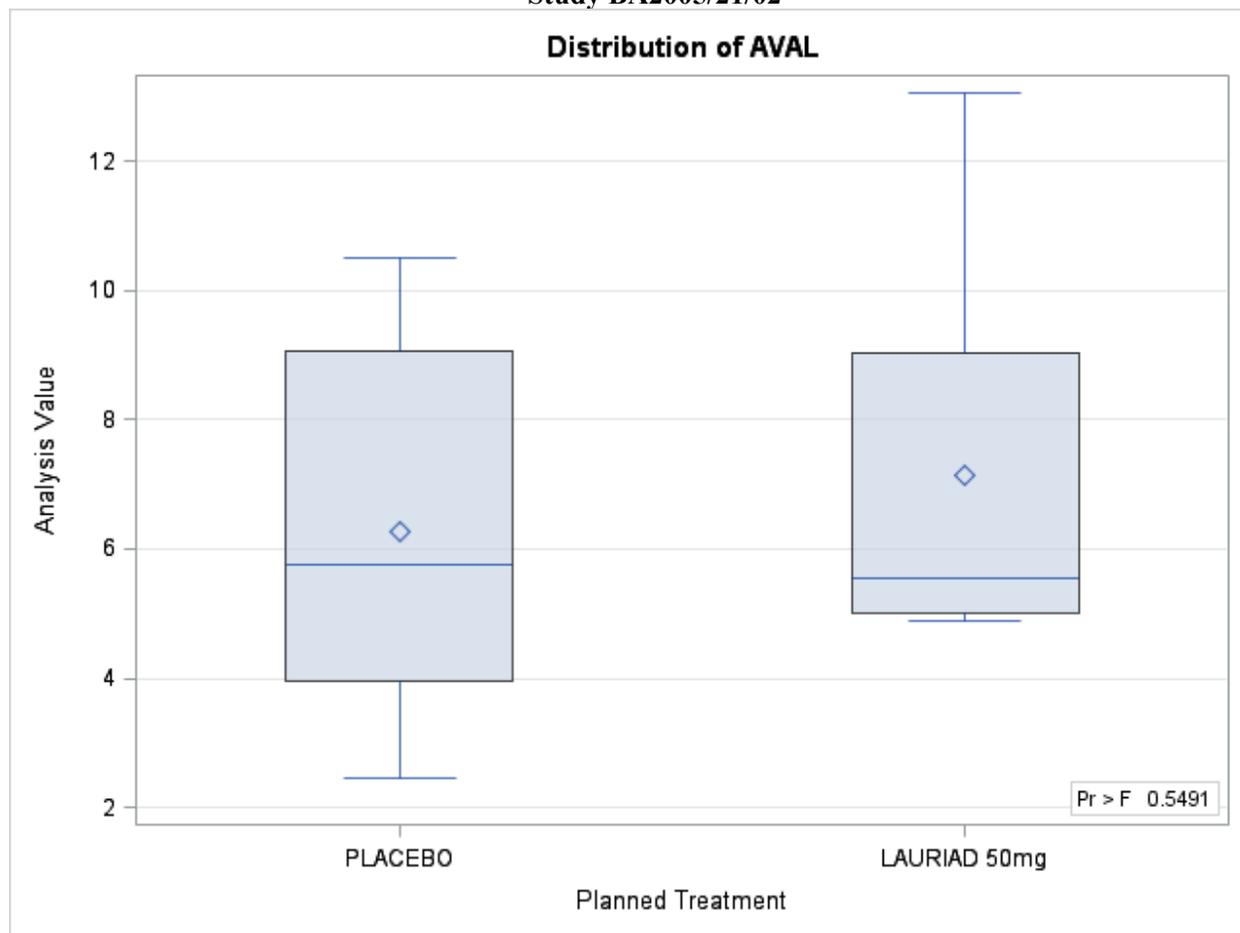
*: including both observed and censored Caucasian's TTH data in mITT Population

Table 36
Time-To-Healing of Other Patients Only*
Reviewer's Data
Study BA2005/21/02

mITT population	ABT (N=7)	Placebo (N=11)
Total, N	7	11
Event Observed, n (%)	7 (100%)	11 (100%)
Censored, n (%)	0	0
Healing Rate, % (n/N)	100% (7/7)	100% (11/11)
Life Test (K-M) on TTH		
Mean (days) ± SE	7.13 ± 1.13	6.27 ± 0.86
Median (days) (95% CI)	5.54 (4.88, 9.03)	5.76 (3.08, 9.08)
Log-rank Test P-value	0.6276	
Generalized Wilcoxon test (Gehan)	0.5656	
Hodges-Lehmann (HL) Estimates		
Median (days) (N)	5.54 (7)	5.76 (11)
Median Difference (days) (95% CI)	0.92 (-2.93, 3.27)	
Kruskal-Wallis Test P-value	0.5561	
Hodges-Lehmann (HL) Estimates (Event observed only) -- The same as above		
Median (days) (N)		
Median Difference (days) (95% CI)		
Kruskal-Wallis Test P-value		

* Other includes Asian, Black, Hispanic, and Others.

Figure 16
Box-Plot of Other Race's TTH (mITT)
Reviewer's Data
Study BA2005/21/02



*: including both observed and censored Other race's TTH data in mITT Population

Comment: In the preNDA meeting the Agency requested that the Applicant provide efficacy analyses by race because there may be a lower response rate in blacks/ African Americans as was seen in the Famvir NDA application. Any future trials should include a larger patient population and a greater diversity in races (including blacks/ African Americans).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing recommendations cannot be made during this review cycle because of the lack of robustness of the primary efficacy parameter results. In addition to issues of data collection, the Agency continues to have concerns regarding the 50 mg dose as opposed to the 100 mg dose which appeared to achieve greater salivary and labial mucosal concentrations and therefore may be more efficacious. As the Applicant performed minimal dose selection work during phase 2 of

drug development this is an issue that cannot easily be addressed at this time. One suggestion would be to add a third arm to a new clinical trial and to compare both the 50 and the 100 mg tablets to placebo.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this review.

6.1.10 Additional Efficacy Issues/Analyses

Statistical Issues:

1. Frequency of recording of diary data:

According to the CSR page 23, 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). However, on page of 33 of the original protocol submitted in 2006 and up until August 2007 it was stated that patients will record symptoms 4 times daily at fixed times: on waking, at lunch, at dinner, and at bedtime, tablet adhesion, local tolerability pain, tenderness, tingling, itching, discomfort using a VAS.

Because the primary efficacy endpoint is time to healing (TTH) of the primary vesicular lesion, hours and minutes will be used in the TTH calculation.

Based on this discrepancy, the accuracy of the recording of symptoms was called into question as once daily assessments are very different from four times a day assessments. This discrepancy as well as the fact that the investigator saw the patients only every other day greatly affected their ability to accurately identify the time to healing for each patient and therefore calls into question the robustness of the analysis of the primary efficacy parameter.

2. Who performed the TTH assessment?

Even though the protocol stated that healing had to be assessed by the investigator, patients were not seen in the clinic every day during the study. They visited the investigator on Days 1, 3, 5, 7, and 14 if needed. Therefore in large part the TTH calculation relied on the patient daily self-assessment data which as noted above occurred only once daily.

3. The TTH calculation for five patients classified as “healed without date - min (14, time to event)” was calculated incorrectly. Please see section 6.1.4.3 for details.

4. In the mITT population, eleven patients were found to have received prohibited antiviral concomitant medications (CM) during the trial and should have been excluded from the primary efficacy endpoint analyses. Please see section 6.1.4.3 for details.

5. There were two issues for the claim that more subjects receiving ABT 50 mg had aborted PL compared to placebo. First, acyclovir and valacyclovir are not approved to prevent the occurrence of vesicular lesions. Current regulatory guidance recommends two independent, controlled clinical trials to support a new indication, or one well-designed trial with P-value of <0.001 . Secondly, there was no multiplicity adjustment in the protocol. As a result, there is no type-I error control for this analysis. Therefore [REDACTED] (b) (4)
[REDACTED]
6. The median difference of TTH between the two arms in male patients is numerically smaller than that in female patients whose TTH is closer to that of the mITT population overall. The trial was not powered to evaluate gender differences. For future trials more males are needed to assess if gender differences exist for TTH.
7. The majority of patients ($>96\%$) enrolled in the study were White or Caucasian. It is impossible to assess the impact of race on the primary efficacy endpoint, TTH. There are concerns regarding the possibility of decreased efficacy in the Black African American population as has previously been seen with famciclovir in the treatment of herpes genitalis. For future trials a more racially diverse population is needed.

7 Review of Safety

Safety Summary

FDA analyses of key safety signals were performed using safety data from study BA2005/21/02 the sole clinical study submitted in support of the requested treatment of recurrent herpes labialis indication. In addition, safety data from the PK study BA2004/21/01 performed in 13 healthy volunteer subjects were also reviewed. The safety review included review of the datasets, clinical study reports, case report tabulations, and selected case report forms.

The safety analysis in Study BA2005/21/02 provides safety data for immunocompetent adults ages 18 years and older who received ABT 50 mucoadhesive buccal tablet for the treatment of recurrent herpes labialis. The safety data from the PK study BA2004/21/01 performed in 13 healthy volunteer subjects were primarily reviewed for deaths, discontinuations, or SAEs. Overall, the safety data provided in this submission are adequate for evaluation of exposure with regard to the size of the safety database and the duration of administration.

As discussed in Section 5.3, the results of the studies could not be pooled because of major differences in the study design (randomized controlled versus open label pharmacokinetic trial) and the nature of the populations studied. Therefore, the safety analyses were performed separately on each study.

Overall, no new or unexpected toxicities were observed with the ABT 50 tablet compared to available safety data for the 5% acyclovir cream (ZOVIRAX) and XERESE cream (5% acyclovir cream and 1% hydrocortisone cream) in an adult population. Safety data from adolescent or immunocompromised patients were not available.

No deaths were reported in either trial. There was no evidence of an increase in discontinuations due to toxicity for ABT 50 as compared to historical acyclovir or vehicle discontinuation rates. (Please refer to Section 7.3).

In study BA2005/21/02 there was one serious adverse event (SAE), non-fatal and unrelated that occurred during treatment. The event was a peanut allergy in a placebo-treated patient and was categorized as life-threatening. There were no treatment related SAEs reported in ABT 50 recipients in either trial (section 7.3.2).

Treatment emergent adverse events independent of relatedness were reported in 60 patients in the ABT 50 group (16%) as compared to 60 patients in the placebo group (15%). The ABT 50 patients reported 78 treatment-emergent adverse events as compared to 84 reported events from the placebo patients. Approximately 50% of the reported events on each arm were considered related to treatment. Specifically, 27 patients (7%) on the ABT 50 treatment arm reported 31 TRAEs as compared to 31 patients (8%) of the placebo patients reporting 47 TRAEs.

The most commonly reported adverse events in the ITT population from study BA2005/21/02 included headache in 3% of the patients on both the ABT 50 and the placebo treatment arms, application site pain, and nasopharyngitis in 1% on each arm. The TEAEs considered related to treatment (N = 78) that occurred in $\geq 1\%$ of patients included headache (1% ABT 50 vs. 2% placebo) and application site pain (1% both arms). Most TRAEs were classified as mild or moderate. Only 1 event of headache on both treatment arms was classified as severe.

Most reported treatment emergent adverse events were classified as mild to moderate in intensity. Ten events on the ABT 50 arm and 13 on the placebo arm were considered severe AEs. Only the events of bronchitis and headache were reported in two patients each (placebo). All other severe events occurred in one patient each. Reported severe AEs included acne, blepharitis, cough, foot fracture, hand fracture, headache, hypercholesteremia, influenza, oral herpes, and pneumonia in the ABT 50 patients. The severe AEs in the placebo patients included abdominal pain, acne, astigmatism, erythema multiforme, erythrodermic psoriasis, nephrolithiasis, ARF, and tooth abscess.

The primary safety concerns for ABT 50 included local buccal mucosa reactions in the area of the application site and possible choking or dyspepsia events due to swallowing of the tablet when it falls off. Of these, gingival pain and application site irritation occurred in two patients (0.5%) each on the ABT 50 arm as compared to 1 (0.3%) and none respectively of the placebo patients. There were fewer reported local events from the placebo patients (12, 3%) as compared to the ABT 50 recipients (14, 4%). However the differences were too small to be clinically significant. There were no reported events of choking or dyspepsia.

Laboratory assessments were performed infrequently (pretreatment and at Day 14) because the ABT 50 product under study is a topical product with negligible systemic absorption and therefore unlikely to cause systemic toxicities. There was little change in any hematology or serum chemistry parameters between these visits on either treatment arm. The number and percentages of patients with normal values at baseline and abnormal values after treatment were comparable between treatment groups and were comparable to those with abnormal values at baseline and normal values at the end of treatment.

Neither trends nor relevant changes from baseline were observed in vital signs, ECG parameters or physical examination.

Study BA2004/21/01 assessed PK and tolerability study of single administration of acyclovir Lauriad® (50 and 100 mg), mucoadhesive buccal tablet 2, compared with single administration of oral tablet of acyclovir (200 mg) in thirteen healthy volunteers. One subject withdrew after one dose for personal reasons and was replaced. Five of the thirteen subjects (39%) reported a TEAE during the study. There were no deaths, SAEs or premature discontinuations due to TEAEs.

There were no serious TEAEs during the study. Six TEAEs (headache and inflammation at the application site with acyclovir Lauriad® 50 mg and 100 mg MBT, nausea with acyclovir Lauriad® 100 mg MBT and oral soft tissue disorder with acyclovir 200 mg oral tablet) were

reported by five subjects. The only TEAE classified as possibly related to the treatment was a headache of moderate intensity. The two cases of mild inflammation at the application site were classified as probably related to the treatment. The three other TEAEs were not related to the treatment, one of them was moderate in intensity and the two others were mild. All TEAEs resolved spontaneously without any corrective action.

For both studies, the Applicant's common AE frequencies were overall similar to the MO's analyses. This reviewer also agrees with the Applicant's assessments of causality of adverse events. Overall, ABT 50 appears safe for the proposed treatment indication in the proposed patient population.

Of note, in study BA2005/21/02 there were 23 patients aged 65 and older. There were too few patients studied in this age group to draw any substantive conclusions regarding safety specific to the elderly.

To date, no clinical trials have been conducted with ABT 50 in patients less than 18 years old. Due to the pathophysiology and epidemiology of herpes labialis it is unlikely that ABT 50 would be used in pediatric patients younger than 6 years old, but it might be used in pediatric patients ages 6-11 with recurrent herpes labialis. Therefore ABT 50 should be adequately evaluated in pediatric patients ages 6 – 17 via a prospective study. This should be the subject of a deferral request from the Applicant. Finally, a partial waiver (for ages less than 6 years old) should be granted.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The Applicant proposed to use the safety results from Study BA2005/21/02 in the label for approval. Therefore, FDA analyses of key safety signals were performed using safety data from this study. In addition, data from the PK study BA2004/21/01 performed in 13 healthy volunteer subjects were reviewed for deaths, discontinuations, or SAEs. The safety review included review of the datasets, clinical study reports, case report tabulations, and selected case report forms.

7.1.2 Adequacy of Data

The data sources used in the safety assessment were adequate, and the Applicant's methods of safety assessment were appropriate. In Study BA2005/21/02 the safety population was comprised of all randomized patients who took at least one dose of the study medication, including 378 patients in the ABT 50 mg group and 397 patients in the placebo group. Four patients were excluded from the safety analysis because of missing data. In study BA2004/21/01, all 13 healthy volunteer subjects were included in the safety analysis.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Safety data from the two studies were not pooled because of the differences in the populations studied as well as in the study design.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In study BA2005/21/02, 1721 patients were randomized. Of these, 775 were treated (ITT) with either ABT 50 (N = 378) or placebo (N = 397). There were inadequate data on the extent of exposure in four patients, two on each arm and these patients were excluded from this analysis.

Table 37
Extent of Exposure for ITT population

Adhesion time (hrs.)	ABT 50 mg N = 376	Placebo N = 395
N (%)		
< 6 hrs.	43 (12%)	50 (13%)
6 – 12 hrs.	166 (44%)	121 (31%)
> 12 hrs.	165 (44%)	222 (57%)
Missing	2	2

Comment: The extent of exposure and need for replacement of the tablet (12% ABT 50 and 13% placebo) were similar across treatment groups suggesting that ABT 50 was generally tolerable in this adult population. Of note more placebo-treated patients had exposures greater than 12 hours as compared to ABT 50 treated patients. The reason for this is not clear.

Of the ABT 50 treated patients who had an adhesion time of less than six hours (N = 43), 12 or 28% swallowed the tablet. On the placebo arm 15 (31%) of the 49 patients who had adhesion times of less than six hours swallowed the tablet. The tablet was replaced in greater than 70% of patients on both arms (33 (77%) ABT 50 and 35 (71%) placebo).

The ITT population was primarily female and white on both treatment arms. Age distribution was similar between arms and patients were primarily between 20 and 60 years of age. Twenty-three patients were 65 years of age or greater. Fifteen of these received placebo and 8 received ABT 50.

Similar numbers of patients had mild, moderate, or severe disease between the treatment arms.

Table 38
Demographics of ITT Population
MO table using ADDM dataset

	All N = 775	ABT 50 N = 387	Placebo N = 397
Age			
20 - < 40	362 (47%)	183 (47%)	179 (45%)
40 < 60	330 (43%)	158 (41%)	172 (43%)
< 20	16 (2%)	9 (2%)	7 (2%)
60 and above	67 (9%)	28 (7%)	39 (10%)
Sex			
Female	531 (69%)	259 (67%)	272 (69%)
Male	244 (31%)	119 (33%)	125 (31%)
Race			
White/Caucasian	736 (95%)	361 (93%)	375 (94%)
Hispanic	12 (2%)	3 (1.5%)	9 (2%)
Asian	6 (.7%)	4 (1%)	2 (.5%)
Native American	2 (.5%)	0	2 (.5%)
Black	11 (1%)	7 (2%)	4 (1%)
Hawaiian	1 (.2%)	1 (.25%)	0
Other	7 (.8%)	2 (.5%)	5 (1%)
Severity of PL			
Mild	82 (11%)	42 (11%)	40 (10%)
Moderate	355 (46%)	174 (45%)	181 (46%)
Severe	337 (43%)	162 (44%)	175 (44%)
Missing	1 (< 1%)	0	1 (<1%)

7.2.2 Explorations for Dose Response

Not applicable since the same dose was used for all subjects.

7.2.3 Special Animal and/or In Vitro Testing

Preclinical animal testing was not performed for this 505(b)(2) application.

7.2.4 Routine Clinical Testing

The extent and frequency of routine clinical testing of this topical product was appropriate. After self-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 comprised of a self-questionnaire and visual analogue scale (VAS) daily (in the evening) and to record their symptoms and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, crust).

Patients were requested to return to the clinic within 24 hours following treatment application. In selected centers, saliva samples were taken within 24 hours following treatment application to measure viral HSV-1 load and acyclovir concentration. Evaluation visits took place on Days 1, 3, 5, 7 and 14 (or when healing was reached) (Visits 3, 4, 5, 6 and 7). Visits 3 to 7 were to be

conducted by the same investigator. Blood samples were taken before inclusion and at Visit 7 (Day 14). Optional follow-up visits were conducted to record the number of new herpes episodes and the time to their recurrence for a period of 9 months; patients were to be contacted by telephone 3 months and 6 months after Visit 7 (Visits 8 and 9) and to return to the clinic for a final visit 9 months after visit 7 (Visit 10).

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate for a topical product. Please refer to Section 4.4 for details. There are no major potential safety consequences of drug/drug interactions with this topical product due to the demonstration of limited systemic absorption.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This is a new formulation comprised of an approved active drug, acyclovir, in a novel delivery system. Anticipated adverse reactions at the site of topical buccal application could include dry lips, cracked lips, transient burning or tingling or stinging following application, dysgeusia, erythema, pigmentation changes, or other application site reaction including signs and symptoms of inflammation

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in either study.

7.3.2 Nonfatal Serious Adverse Events

There was one SAE, non-fatal and unrelated that occurred during treatment. The event was a peanut allergy in a placebo-treated patient. This event was categorized as life-threatening.

44-year old white female, signed consent on 12 February 2008. The patient had 6 episodes of Herpes Labialis in the 12 months preceding her enrollment into the study. On 06 April 2008, the patient received a single dose of blinded study drug (ABT 50 mg /placebo). The patient had known sesame and nut allergy and depression and was taking iron (45 mg as needed) and duloxetine (40 mg once a day) at the time of the event. On (b) (6) the patient was admitted to the emergency department with difficulties breathing secondary to an allergic reaction to sesame. The patient complained of severe throat swelling with difficulties breathing, swallowing and speaking 20 minutes after eating a meal which she suspected to have contained sesame seeds or sesame oil. The patient had difficulty speaking in full sentences secondary to her difficulty in breathing and noted voice changes. The patient also had an intermittent mild cough. The patient denied itching to her skin or throat, nausea, vomiting, lightheadedness, dizziness, cough or any other acute medical concerns. CXR showed no acute pulmonary disease. The patient was treated with intravenous (iv) heparin, iv methylprednisolone (solu-medrol), iv ranitidine (zantac), epinephrine and diphenhydramine hydrochloride (Benadryl). The patient was feeling better later and was discharged with diphenhydramine hydrochloride 50 mg twice a day on the same day of admission (discontinued on (b) (6)). She was also prescribed ranitidine (zantac; 150 mg every 12 hours) and a methylprednisone taper (24 mg once-a-day, decreasing by 4 mg per day), both of which were also discontinued on (b) (6). The AE was assessed as

CTCAE Grade 4, and was considered serious as it was an important medical condition. The patient was discharged from hospital on [REDACTED] and the event was considered resolved on [REDACTED] ^{(b) (6)}. The study drug remained blinded throughout the study. The study drug was unblinded on 21 July 2009 and the patient received placebo. The Investigator and the Medical Monitor considered the AE to be without relationship to the study drug.

In addition, there was one pregnancy diagnosed after treatment in a placebo recipient. The baby was born without defects.

There were no treatment-related SAEs. There were no SAEs in the ABT 50 treated patients.

7.3.3 Dropouts and/or Discontinuations

There were no treatment emergent adverse events leading to treatment discontinuation.

7.3.4 Significant Adverse Events

The Applicant provided narratives for the following unrelated SAEs reported in patients randomized to treatment who were either not treated or in patients who were treated in whom the event occurred prior to treatment: slipped lumbar disc (ABT 50) broken ankle (placebo), broken finger (ABT 50), exacerbation of erythrodermic pustulosis psoriasis (no treatment), acute closed right angle glaucoma (ABT 50), worsening of depression (no treatment), kidney stones and acute renal failure (no treatment).

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concerns are local buccal mucosa reactions in the area of the application site and possible choking or dyspepsia events due to swallowing of the tablet when it falls off.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse reactions commonly reported with ZOVIRAX (5% acyclovir) cream include local application site reactions (5% of patients). The most common adverse reactions with ZOVIRAX at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each occurring in less than 1% of patients receiving ZOVIRAX Cream.

Adverse reactions reported with Xerese cream (acyclovir and hydrocortisone) were similar to those reported with ZOVIRAX cream. The most commonly reported AEs (all grades, regardless of causality, $\geq 1\%$ incidence in any treatment group) were herpes simplex recurrences, nasopharyngitis, dry lips, application site dryness, and headache. Most AEs were mild and most were considered unrelated to study treatment.

Treatment emergent adverse events independent of relatedness were reported in 60 patients in the ABT 50 group (16%) as compared to 60 patients in the placebo group (15%). The ABT 50 patients reported 78 treatment-emergent adverse events as compared to 84 reported events from the placebo patients. Approximately 50% of the reported events on each arm were considered related to treatment. Specifically, 27 patients (7%) on the ABT 50 treatment arm reported 31 TRAEs as compared to 31 patients (8%) of the placebo patients reporting 47 TRAEs.

The most commonly reported adverse events in the ITT population from study BA2005/21/02 included headache in 3% in both treatment arms, application site pain, and nasopharyngitis in 1% on each arm. All other events occurred in less than 1% of the patients. The most frequently reported TEAEs by treatment arm that occurred in $\geq 1\%$ of the patients can be seen in the following table generated by the MO using the ADAE-jmp dataset.

Table 39
Treatment Emergent Adverse Events occurring in $\geq 1\%$
Safety Population
Independent of Causality Assessment

Event	ABT 50 N = 378	Placebo N = 397
Nervous System Disorders	15 (4%)	13 (3%)
Headache	12 (3%)	12 (3%)
GI Disorders	14 (4%)	16 (4%)
Nausea	1 (0.3%)	6 (2%)
Infections and Infestations	14 (4%)	14 (4%)
Nasopharyngitis	4 (1%)	3 (0.9%)
General Disorders and Administration Site Conditions	11 (3%)	7 (2%)
Application Site Pain	4 (1%)	4 (1%)
Skin and Subcutaneous Tissue Disorders	6 (2%)	7 (2%)
Respiratory, Thoracic, Mediastinal Disorders	3 (0.9%)	4 (1%)

*generated by MO using ADAE dataset

Most reported treatment emergent adverse events were classified as mild or moderate in intensity. Ten events (10/74 events (13.5%) on the ABT 50 arm and thirteen (13/84 (15.5%) on the placebo arm were considered severe.

Of the severe events, only the events of bronchitis and headache were reported in two patients each (placebo). All other severe events occurred in one patient each. Reported severe AEs included acne, blepharitis, cough, foot fracture, hand fracture, headache, hypercholesteremia, influenza, oral herpes, and pneumonia in the ABT 50 patients. The severe AEs in the placebo patients included abdominal pain, acne, astigmatism, erythema multiforme, erythrodermic psoriasis, nephrolithiasis, ARF, and tooth abscess. One report of headache on the ABT 50 arm was considered related to treatment by the investigator.

Events of interest including gingival pain and application site irritation occurred in 2 patients (0.5%) each on the ABT 50 arm as compared to 1 (0.3%) and none respectively of the placebo patients. There were fewer reported local events from the placebo patients (12, 3%) as compared

to 14 or 4% from the ABT 50 recipients. However the differences were too small to be clinically significant. Events classified as application site events or events related to the lips or oral cavity can be seen in the following table:

Table 40
Treatment Emergent Adverse Events from the Application site, lips and oral cavity
Safety Population

Event	ABT 50 N = 378	Placebo N = 397
Application site discomfort	1 (0.3%)	1 (0.3%)
Application site erythema	1 (0.3%)	0
Application site irritation	2 (0.6%)	0
Application site pain	4 (1%)	4 (1%)
Application site paresthesia	1 (0.3%)	0
Dry Mouth	1 (0.3%)	1 (0.3%)
Gingival Pain	2 (0.6%)	1 (0.3%)
Dry Lip	1 (0.3%)	3 (1%)
Lip hemorrhage	0	1 (0.3%)
Lip swelling	1 (0.3%)	0
Oral pain	0	1 (0.3%)
Total	14 (4%)	12 (3%)

*generated by NO using ADAE dataset

All of the above events were classified as mild with the exception of one event each of application site discomfort and lip swelling on the ABT 50 arm and one event each of application site pain and dry lips on the placebo arm. None of these events were classified as severe.

The TEAEs considered related to treatment (N = 78) that occurred in $\geq 1\%$ of patients included headache (1% ABT 50 vs. 2% placebo) and application site pain (1% both arms).

In the following table are the treatment related events reported in $\geq 0.5\%$ from both treatment arms:

Table 41
Treatment Related Adverse Events reported in $\geq 0.5\%$ of patients

Event	ABT 50 N = 378	Placebo N = 397
Headache	4 (1%)	9 (2%)
Application Site Pain	4 (1%)	4 (1%)
Erythema	2 (0.5%)	1 (0.3%)
Gingival Pain	2 (0.5%)	1 (0.3%)
Aphthous Stomatitis	2 (0.5%)	0
Application Site Irritation	2 (0.5%)	0
Nausea	1 (0.3%)	5 (1%)
Dizziness	1 (0.3%)	2 (0.5%)
Dry lip	0	2 (0.5%)

*generated by NO using ADAE dataset

All TEAEs assessed as related to treatment were primarily mild or moderate in severity. One report of headache from both treatment arms was classified as severe. Treatment related events classified as moderate or severe can be seen in the following table:

Table 42
Treatment Related Adverse Events by Severity

Event	Severity	ABT 50	placebo
ABDOMINAL PAIN UPPER	Moderate	0	1
ALT INCREASED	Moderate	0	1
APPLICATION SITE DISCOMFORT	Moderate	1	0
APPLICATION SITE PAIN	Moderate	0	1
AST INCREASED	Moderate	0	1
BLOOD CREATINE INCREASED	Moderate	0	1
EPISTAXIS	Moderate	0	1
gGT INCREASED	Moderate	0	1
GASTROESOPHAGEAL REFLUX DISEASE	Moderate	1	0
GINGIVAL PAIN	Moderate	0	1
HEADACHE	Moderate	2	2
HEADACHE	Severe	1	1
HEAT RASH	Moderate	0	1
INFLUENZA LIKE ILLNESS	Moderate	0	1
LETHARGY	Moderate	1	0
LIP DRY	Moderate	0	1
LIP SWELLING	Moderate	1	0
MEAN CELL HAEMOGLOBIN INCREASED	Moderate	0	1
NAUSEA	Moderate	0	2
PRURITUS	Moderate	0	1
RASH ERYTHEMATOUS	Moderate	1	0
STOMATITIS	Moderate	1	0
THROMBOCYTOPENIA	Moderate	1	0
VERTIGO	Moderate	0	1
VOMITING	Moderate	0	1

*generated by NO using ADAE dataset

7.4.2 Laboratory Findings

Laboratory assessments were performed infrequently because the ABT 50 product under study is a topical product with negligible systemic absorption and therefore unlikely to cause systemic toxicities. Assessments were performed prior to treatment (Day 0) at Visit 7 or Day 14. There was little change in any hematology or serum chemistry parameters between these visits on either treatment arm. The number and percentages of patients with normal values at baseline and abnormal values after treatment were comparable between treatment groups and were comparable to those with abnormal values at baseline and normal values at the end of treatment.

One patient, 3020007, a 63 year old French Caucasian female, who received ABT 50, developed thrombocytopenia classified as possibly related to treatment. The platelet count at baseline was normal at 274,000/mm³ and was abnormal at Day 14, 99000/mm³. The event was classified as moderate in severity and no action was taken. Concomitant medications included Orocal D3 for osteoporosis prophylaxis, Dacroserum, Almide, and Povidone for ocular pain, Hiru creme for venous insufficiency, and Tahor (atorvastatin) for hypercholesteremia. A review of these drugs revealed that atorvastatin can be associated with thrombocytopenia.

A review of the AE jmp dataset revealed 7 patients with serum chemistry abnormalities classified as TEAEs. As can be appreciated from the following table, none of the events were severe. Three patients with six events were classified as possibly related to study treatment. Four of the events were reported from a single patient. Both events that occurred in patients on ABT 50 were not clinically significant and were without relationship to the study treatment.

BA2005/21/02-1020003	UA INCREASED	MODERATE	WITHOUT RELATIONSHIP	ABT 50
BA2005/21/02-1020005	ALT INCREASED	MODERATE	WITHOUT RELATIONSHIP	PLACEBO
BA2005/21/02-1020005	AST INCREASED	MODERATE	WITHOUT RELATIONSHIP	PLACEBO
BA2005/21/02-1020005	GLUCOSE REDUCED	MODERATE	WITHOUT RELATIONSHIP	PLACEBO
BA2005/21/02-1020011	GGT INCREASED	MILD	WITHOUT RELATIONSHIP	PLACEBO
BA2005/21/02-1020016	OCCULT BLOOD +	MILD	WITHOUT RELATIONSHIP	ABT 50
BA2005/21/02-7060008	AST INCREASED	MODERATE	POSSIBLE	PLACEBO
BA2005/21/02-7060008	ALT INCREASED	MODERATE	POSSIBLE	PLACEBO
BA2005/21/02-7060008	GGTP INCREASED	MODERATE	POSSIBLE	PLACEBO
BA2005/21/02-7060008	MCH INCREASED	MODERATE	POSSIBLE	PLACEBO
BA2005/21/02-7100024	CREAT. INCREASED	MODERATE	POSSIBLE	PLACEBO
BA2005/21/02-7100031	CREAT. INCREASED	MILD	POSSIBLE	PLACEBO

In conclusion laboratory abnormalities were infrequent in patients treated with ABT 50. This is to be expected as there is minimal systemic absorption.

7.4.3 Vital Signs

There were minimal changes in systolic blood pressure, diastolic blood pressure, heart rate, temperature, weight or height between evaluations at Visit 2 (Day 0) and Visit 7. This is expected since ABT 50 study is a topical product with negligible systemic absorption, and therefore unlikely to cause any changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained in the assessment of the topical product with negligible systemic absorption and therefore unlikely to cause any cardiac-related toxicity.

7.4.5 Special Safety Studies

No specific special safety studies were performed. Study BA2004/21/01 entitled “Pharmacokinetic and tolerability study of single administration of acyclovir Lauriad® (50 and 100 mg), mucoadhesive buccal tablet 2, compared with single administration of oral tablet of acyclovir (200 mg) in healthy volunteers”, assessed the tolerability of the buccal tablet with regards to adhesion time, local and systemic adverse events.

The study was an open, randomized, single dose, three-way cross-over study in 12 healthy volunteers. The study was divided into three study periods of 2 days duration each. Overall, the expected duration of subject’s participation was about 6 weeks consisting of 2-week run-in period, followed by three 48-hour periods, separated by a one-week wash-out period and ending with a one-week follow-up.

Subjects received on Day 1 of each study period in a predefined order:

- 50 mg dose of acyclovir formulated as acyclovir Lauriad® (50 mg) MBT, or,
- 100 mg dose of acyclovir formulated as acyclovir Lauriad® (100 mg) MBT or,
- 200 mg dose of acyclovir formulated as a 200 mg oral tablet (Zovirax®).

Monitoring for the occurrence of adverse events (AE), changes in physical examination including buccal examination, vital signs (blood pressure, pulse rate) and electrocardiograms (ECG) were performed before and after each dose of the study drug to assess safety and tolerability.

Thirteen healthy volunteer subjects were eligible for safety assessments. One subject withdrew after one dose and was replaced. Five of the thirteen subjects (39%) reported a TEAE during the study. There were no deaths, SAEs or premature discontinuations due to TEAEs.

There were no serious TEAEs during the study. No AEs were reported prior to any treatment administration. Six TEAEs (headache and inflammation at the application site with acyclovir Lauriad® 50 mg and 100 mg MBT, nausea with acyclovir Lauriad® 100 mg MBT and oral soft tissue disorder with acyclovir 200 mg oral tablet) were reported by five subjects. The only TEAE classified as possibly related to the treatment was a headache of moderate intensity. The two cases of mild inflammation at the application site were classified as probably related to the treatment. The three other TEAEs were not related to the treatment, one of them was moderate in intensity and the two others were mild. All TEAEs resolved spontaneously without any corrective action.

Adhesion duration was slightly longer in the acyclovir Lauriad® 100 mg MBT group than in the acyclovir Lauriad® 50 mg MBT group. Specifically, in the acyclovir Lauriad® 100 mg MBT group ten out of the twelve randomized subjects kept their buccal tablet for more than 18 hours and five for more than 24 hours. The two remaining subjects kept their tablet respectively for ten and 12 hours. In the acyclovir Lauriad® 50 mg MBT group, the adhesion duration lasted more than 18 hours for two subjects. It ranged from ten to 16 hours in nine subjects and was only six hours in one subject.

Neither trends nor relevant changes from baseline were observed in vital signs, ECG parameters, physical examination, gingival index, and in any laboratory parameters assessed.

Comment: Both doses of the mucoadhesive buccal tablet were well tolerated in this study. The adverse event profile is similar to that seen in study BA2005/21/02 with headache and application site discomfort and mild inflammation seen in 2 subjects receiving each topical dose. Overall both topical doses as well as the oral acyclovir 200 mg dose were safe and well tolerated.

7.4.6 Immunogenicity

ABT 50 is considered unlikely to be immunogenic due to limited systemic absorption.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable as the same dose was used for all patients.

7.5.2 Time Dependency for Adverse Events

Substantive conclusions regarding time dependency for treatment-related AEs are precluded by the small numbers of AEs reported

7.5.3 Drug-Demographic Interactions

Twenty-three patients enrolled in the study were 65 years of age or greater. Fifteen received placebo and eight received ABT 50. Fifteen patients reporting TEAEs were aged 65 or greater. Two of these received ABT 50 and thirteen received placebo. Both events in the ABT 50 patients were mild, one patient complained of nocturia and one of dizziness. Neither event was considered related to treatment.

Overall there were too few patients ≥ 65 years of age to draw clinically meaningful conclusions regarding the safety of ABT 50 in this population.

The patients enrolled in this study were primarily Caucasian (95%). Therefore no clinically meaningful conclusions regarding the effects of race on the safety of ABT 50 could be drawn.

Similar percentages of patients on both treatment arms were female (67% ABT 50 and 69% placebo). Ninety seven of the female patients on the ABT 50 arm (26%) and 106 on the placebo arm (27%) developed a TEAE. Forty-eight of the male patients on the ABT 50 arm (13%) and 71 on the placebo arm (18%) developed a TEAE.

For the female patients headache was the most frequently reported TEAE (10 on each arm). Application site pain was reported by three ABT 50 and four placebo female patients. In the male patients the most frequently reported TEAEs were URI in five ABT 50 and four placebo patients followed by headache in three ABT 50 and two placebo patients.

Comment: TEAEs were reported more frequently in female patients on both treatment arms as compared to males. Headache was the most common TEAE in both genders. Definitive conclusions regarding differences in the frequency of TEAEs between the genders cannot be drawn given the small numbers of TEAEs reported.

7.5.4 Drug-Disease Interactions

Following discontinuation of study drug, secondary recurrences were reported in 149/267 (42%) of patients receiving ABT 50 as compared to 181/270, 73.6% of patients receiving placebo. The Applicant postulates that this difference is due to the rapid and high acyclovir concentrations achieved in the saliva and oral tissues with ABT 50. These high concentrations lead to a decrease in the reservoir of HSV and therefore a decrease in the recurrence rate.

7.5.5 Drug-Drug Interactions

Clinical experience with ZOVIRAX (5% acyclovir) cream has identified no interactions resulting from topical or systemic administration of other drugs concomitantly.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Dermal carcinogenicity studies were not conducted with ABT 50. Based on the information for ZOVIRAX (5% acyclovir) cream these studies are not necessary.

7.6.2 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with ABT 50 and are not considered necessary. No studies have been performed in pregnant or lactating women. Similar to ZOVIRAX cream systemic exposure of acyclovir following topical administration of ABT 50 is expected to be minimal.

The Applicant proposed the following labeling regarding pregnancy:

Pregnancy Category B

[REDACTED]

[REDACTED]

7.6.3 Pediatrics and Effect on Growth

There were numerous discussions with the Applicant regarding the submission of a waiver or a deferral depending on the pediatric populations studied. It should be noted that to date ABT 50 has not been studied in any patients less than 18 years of age.

[REDACTED]

A review of the Medical Officer review for Xerese, (acyclovir/hydrocortisone) in 2009 stated that “Due to the pathophysiology and epidemiology of the disease, this reviewer believes ME-609 is unlikely to be used in pediatric patients younger than 6 years old, but that ME-609 might be used in some pediatric patients ages 6-11 with recurrent herpes labialis. This reviewer believes it is important to prospectively evaluate the safety of ME-609 cream in younger

children (ages 6-11). Due to its topical application, negligible systemic absorption, and overall safety profile, it is possible that off-label use might occur in pediatric patients ages 6- 11 with recurrent herpes labialis.”

Based on the above, a partial waiver for ages less than six was requested for Xerese and the Applicant was asked to conduct a study in patients ages 6 – 11. A similar decision was reached for Oravig a miconazole containing mucoadhesive buccal tablet produced by the same Applicant as Sitavig. For that product, the Agency issued a deferral for children ages 6 – 17 and a waiver for those less than 5 years of age.

It seems reasonable to request that the Applicant follow a similar plan for ABT 50; that is that it should be studied for both efficacy and safety in children ages 7 – 11. A reasonable number of patients to be studied will be determined at the time of protocol submission with a greater number of younger patients given the potential choking hazards and the need for their assessment. A deferral would then be granted for this age group and a waiver is recommended for patients less than six years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Withdrawal or abuse potential for ABT 50 is considered unlikely.

7.7 Additional Submissions

Not applicable

8 Postmarketing Experience

Not applicable. ABT 50 has not yet been approved in any country and therefore there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

Not applicable

9.3 Advisory Committee Meeting

Not applicable

9.4 Tables:

T1: Demographics: Patients Enrolled by Site:

Created by MO from demographics and adde.xpt datasets

Italics = high enrollers

Site ID	# Rand	Country	#Treated ITT	#Missing	Lauriad	Placebo
101	4	AUS	1	0	1	0
102	103	AUS	53	2	21	30
103	123	AUS	62	0	28	34
201	31	CZE	10	0	4	6
202	27	CZE	13	0	6	7
203	41	CZE	16	0	7	9
204	65	CZE	33	0	17	16
205	42	CZE	22	0	10	12
301	34	FRA	14	0	7	7
302	45	FRA	19	0	9	10
303	64	FRA	15	0	6	9
304	10	FRA	3	0	1	2
305	34	FRA	16	0	10	6
307	2	FRA	1	0	1	0
308	20	FRA	1	0	1	0
309	12	FRA	6	0	3	3
310	20	FRA	9	1	2	6
311	1	FRA	0	0	0	0
401	66	DEU	28	0	15	13
402	118	DEU	36	0	18	18
403	93	DEU	37	0	17	20
404	76	DEU	7	0	5	2
405	24	DEU	9	0	3	6
406	40	DEU	15	0	7	8
407	31	DEU	8	0	4	4
408	12	DEU	4	0	3	1
409	18	DEU	3	0	2	1
410	49	DEU	0	0	0	0
502	19	POL	2	0	1	1
504	101	POL	49	0	24	25
506	32	POL	13	0	6	7
507	186	POL	54	0	29	25
508	39	POL	16	0	8	8
509	7	POL	1	0	0	1
601	23	GBR	14	0	8	6
602	7	GBR	0	0	0	0
603	25	GBR	6	0	3	3
701	12	USA	4	0	1	3
702	18	USA	8	0	4	4
703	12	USA	1	0	0	1
704	71	USA	16	0	10	6
706	54	USA	22	0	12	10
707	15	USA	6	0	3	3
708	26	USA	11	0	6	5
709	84	USA	44	0	24	20
710	32	USA	12	0	5	7
711	21	USA	7	0	1	6

T2: TTHPL by site
 Created by MO from ADDE dataset
 Only counted healed < 14 days

Site ID	TRTP	ITT	#heal	# h< 14	#>14	#H	#NH w/o date	#NH w date	heal %<14
101	LAURIAD 50mg	1	0	1	0	0	0	0	100%
102	LAURIAD 50mg	22	1	20	0	0	0	1	91%
102	PLACEBO	31	1	27	1	0	1	1	87%
103	LAURIAD 50mg	28	0	26	0	0	0	2	93%
103	PLACEBO	34	0	26	0	0	0	8	76%
201	LAURIAD 50mg	4	0	3	0	1	0	0	75%
201	PLACEBO	6	0	6	0	0	0	0	100%
202	LAURIAD 50mg	6	0	6	0	0	0	0	100%
202	PLACEBO	7	0	6	1	0	0	0	86%
203	LAURIAD 50mg	7	0	7	0	0	0	0	100%
203	PLACEBO	9	0	9	0	0	0	0	100%
204	LAURIAD 50mg	17	0	17	0	0	0	0	100%
204	PLACEBO	16	0	16	0	0	0	0	100%
205	LAURIAD 50mg	10	0	9	0	0	0	1	90%
205	PLACEBO	12	0	12	0	0	0	0	100%
301	LAURIAD 50mg	7	0	7	0	0	0	0	100%
301	PLACEBO	7	0	7	0	0	0	0	100%
302	LAURIAD 50mg	9	0	8	0	0	0	1	89%
302	PLACEBO	10	0	9	0	0	0	1	90%
303	LAURIAD 50mg	6	0	6	0	0	0	0	100%
303	PLACEBO	9	0	8	1	0	0	0	89%
304	LAURIAD 50mg	1	0	1	0	0	0	0	100%
304	PLACEBO	2	0	1	0	0	0	1	50%
305	LAURIAD 50mg	10	0	10	0	0	0	0	100%
305	PLACEBO	6	0	6	0	0	0	0	100%
307	LAURIAD 50mg	1	0	0	0	1	0	0	0
308	LAURIAD 50mg	1	0	1	0	0	0	0	100%
309	LAURIAD 50mg	3	0	2	0	0	0	1	67%
309	PLACEBO	3	0	3	0	0	0	0	100%
310	LAURIAD 50mg	3	1	2	0	0	0	0	67%
310	PLACEBO	6	0	6	0	0	0	0	100%
401	LAURIAD 50mg	15	0	15	0	0	0	0	100%
401	PLACEBO	13	0	12	0	0	0	1	92%
402	LAURIAD 50mg	18	0	16	0	0	0	2	89%
402	PLACEBO	18	0	16	1	0	0	1	89%
403	LAURIAD 50mg	17	0	17	0	0	0	0	100%
403	PLACEBO	20	0	19	0	0	0	1	95%
404	LAURIAD 50mg	5	0	2	0	0	0	3	40%
404	PLACEBO	2	0	2	0	0	0	0	100%

405	LAURIAD 50mg	3	0	3	0	0	0	0	100%
405	PLACEBO	6	0	5	0	0	0	1	83%
406	LAURIAD 50mg	7	0	5	0	2	0	0	71%
406	PLACEBO	8	0	6	1	1	0	0	75%
407	LAURIAD 50mg	4	0	4	0	0	0	0	100%
407	PLACEBO	4	0	3	0	0	0	1	75%
408	LAURIAD 50mg	3	0	3	0	0	0	0	100%
408	PLACEBO	1	0	1	0	0	0	0	100%
409	LAURIAD 50mg	2	0	1	0	0	0	1	50%
409	PLACEBO	1	0	0	0	0	0	1	0
502	LAURIAD 50mg	1	0	1	0	0	0	0	100%
502	PLACEBO	1	0	1	0	0	0	0	100%
504	LAURIAD 50mg	24	0	24	0	0	0	0	100%
504	PLACEBO	25	0	25	0	0	0	0	100%
506	LAURIAD 50mg	6	0	5	1	0	0	0	83%
506	PLACEBO	7	0	7	0	0	0	0	100%
507	LAURIAD 50mg	29	0	29	0	0	0	0	100%
507	PLACEBO	25	0	25	0	0	0	0	100%
508	LAURIAD 50mg	8	0	8	0	0	0	0	100%
508	PLACEBO	8	0	8	0	0	0	0	100%
509	PLACEBO	1	0	0	0	0	0	1	0
601	LAURIAD 50mg	8	0	7	0	0	0	1	86%
601	PLACEBO	6	0	6	0	0	0	0	100%
603	LAURIAD 50mg	3	0	3	0	0	0	0	100%
603	PLACEBO	3	0	3	0	0	0	0	100%
701	LAURIAD 50mg	1	0	1	0	0	0	0	100%
701	PLACEBO	3	0	3	0	0	0	0	100%
702	LAURIAD 50mg	4	0	3	0	1	0	0	75%
702	PLACEBO	4	0	3	0	0	0	1	75%
703	PLACEBO	1	0	1	0	0	0	0	100%
704	LAURIAD 50mg	10	0	10	0	0	0	0	100%
704	PLACEBO	6	0	6	0	0	0	0	100%
706	LAURIAD 50mg	12	0	12	0	0	0	0	100%
706	PLACEBO	10	0	9	1	0	0	0	90%
707	LAURIAD 50mg	3	0	3	0	0	0	0	100%
707	PLACEBO	3	0	3	0	0	0	0	100%
708	LAURIAD 50mg	6	0	6	0	0	0	0	100%
708	PLACEBO	5	0	5	0	0	0	0	100%
709	LAURIAD 50mg	24	0	22	1	0	0	1	92%
709	PLACEBO	20	0	17	3	0	0	0	85%
710	LAURIAD 50mg	5	0	4	0	0	0	1	80%
710	PLACEBO	7	0	6	0	0	0	1	86%
711	LAURIAD 50mg	1	0	1	0	0	0	0	100%

711 PLACEBO 6 0 5 1 0 0 0 83%

Drug	missing	ABT50	Placebo
ABREVA	1	13	12
ACICLOVIR	0	2	2
ACYCLOVIR	1	13	11
DENAVIR	0	1	1
DOCOSANOL	1	5	5
FAMVIR	0	1	0
GEN ACICLOVIR	0	0	1
LAMIVUDINE	1	0	0
OTHER AVIRALS	0	0	1
PENCICLOVIR	0	1	1
VALACICLOVIR	0	7	6
VALTREX	2	6	2
ZELITREX	0	0	2
ZOVIRAX	0	1	4

**T3: Visit Information for Six Patients with recalculated TTH
 Study BA2005/21/02**

USUBJID	VISIT	STDT	ENDT	AVALC	STDT	SVSTDT	ADTM	ADT	SVDISPDT	CRIT1FL
BA2005/21/02-2010005	VISIT 7 (DAY14)	-08-05T17:00	-08-1	HEALED						
BA2005/21/02-2010005	VISIT 6 (DAY7)	2007-08-05T17:00:00		NOT HEALED	8/5/2007	8/13/2007		8/13/2007		Y
BA2005/21/02-2010005	VISIT 5 (DAY5)	2007-08-05T17:00:00		NOT HEALED	8/5/2007	8/10/2007		8/10/2007		
BA2005/21/02-2010005	VISIT 4 (DAY3)	2007-08-05T17:00:00		NOT HEALED	8/5/2007	8/8/2007		8/8/2007		
BA2005/21/02-2010005	VISIT 3 (DAY1)	2007-08-05T17:00:00		NOT HEALED	8/5/2007	8/6/2007		8/6/2007		
BA2005/21/02-3070002	VISIT 3 (DAY1)	2008-04-08T10:00:00		HEALED	4/8/2008	4/9/2008		4/9/2008		Y
BA2005/21/02-406001	VISIT 7 (DAY14)			HEALED		11/12/2007			11/12/2007	
BA2005/21/02-406001	VISIT 4 (DAY3)	2007-11-06T08:15:00		NOT HEALED	11/6/2007	11/8/2007		11/8/2007	11/12/2007	Y
BA2005/21/02-406001	VISIT 3 (DAY1)	2007-11-06T08:15:00		NOT HEALED	11/6/2007	11/6/2007		11/6/2007	11/12/2007	
BA2005/21/02-4060019	VISIT 7 (DAY14)			HEALED		10/1/2007			10/1/2007	
BA2005/21/02-4060019	VISIT 6 (DAY7)	2007-09-19T06:40:00		NOT HEALED	9/19/2007	9/26/2007		9/26/2007	10/1/2007	Y
BA2005/21/02-4060019	VISIT 5 (DAY5)	2007-09-19T06:40:00		NOT HEALED	9/19/2007	9/24/2007		9/24/2007	10/1/2007	
BA2005/21/02-4060019	VISIT 4 (DAY3)	2007-09-19T06:40:00		NOT HEALED	9/19/2007	9/21/2007		9/21/2007	10/1/2007	
BA2005/21/02-4060019	VISIT 3 (DAY1)	2007-09-19T06:40:00		NOT HEALED	9/19/2007	9/19/2007		9/19/2007	10/1/2007	
BA2005/21/02-4060024	VISIT 7 (DAY14)			HEALED		6/10/2008			6/10/2008	
BA2005/21/02-4060024	VISIT 3 (DAY1)	2008-03-08T21:30:00		NOT HEALED	3/8/2008	3/10/2008		3/10/2008	6/10/2008	Y
BA2005/21/02-7020010	VISIT 7 (DAY14)			HEALED		12/29/2007			12/29/2007	
BA2005/21/02-7020010	VISIT 5 (DAY5)	2007-12-23T10:00:00		NOT HEALED	12/23/2007	12/28/2007		12/28/2007	12/29/2007	Y
BA2005/21/02-7020010	VISIT 4 (DAY3)	2007-12-23T10:00:00		NOT HEALED	12/23/2007	12/26/2007		12/26/2007	12/29/2007	
BA2005/21/02-7020010	VISIT 3 (DAY1)	2007-12-23T10:00:00		NOT HEALED	12/23/2007	12/24/2007		12/24/2007	12/29/2007	

T4: Patients Who Took Prohibited Concomitant Medications during the Study
BA2005/21/02

USUBJID	TRTP	TTH	EVNTDESC	MITTFL	drugname
BA2005/21/02-4010058	LAURIAD 50mg	7	HEALED BEFORE 14 DAYS	Y	ACICLOVIR
BA2005/21/02-4050007	LAURIAD 50mg	7	HEALED BEFORE 14 DAYS	Y	ACICLOVIR
BA2005/21/02-1020001	LAURIAD 50mg	7.91	HEALED BEFORE 14 DAYS	Y	VALTREX
BA2005/21/02-7100004	PLACEBO	3	NOT HEALED -min(14,TIME OF EVENT)	Y	ZOVIRAX
BA2005/21/02-7060023	PLACEBO	3.13	HEALED BEFORE 14 DAYS	Y	ABREVA
BA2005/21/02-1020050	PLACEBO	5.95	HEALED BEFORE 14 DAYS	Y	ZOVIRAX
BA2005/21/02-7110005	PLACEBO	9.05	HEALED BEFORE 14 DAYS	Y	VALACICLOVIR
BA2005/21/02-3020037	PLACEBO	13	HEALED BEFORE 14 DAYS	Y	ZELITREX
BA2005/21/02-3040002	PLACEBO	13	NOT HEALED -min(14,TIME OF EVENT)	Y	ZELITREX
BA2005/21/02-2020001	PLACEBO	14	HEALED -min(14,TIME OF EVENT)	Y	ACYCLOVIR
BA2005/21/02-7090037	PLACEBO	14	HEALED -min(14,TIME OF EVENT)	Y	ACYCLOVIR
BA2005/21/02-1020039					FAMVIR
BA2005/21/02-4020093					ACICLOVIR
BA2005/21/02-7060025					VALTREX
BA2005/21/02-7090033					ABREVA

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/s/

M R ALIVISATOS
12/03/2012

WEN ZENG
12/03/2012

GUOXING SOON
12/03/2012

KIMBERLY A STRUBLE
12/03/2012
I concur

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-791

Applicant: Bioalliance Stamp Date: March 12, 2012

Drug Name: Sitavir

NDA/BLA Type: Adult

Acyclovir Lauriad™ Mucoadhesive
buccal tablet; ABT 50

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comments
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Acyclovir
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: BA2004/21/01 Study Title: A Phase 2, Open, single-centre, randomized, cross-over, with 1-week wash out, 3 periods in 12 healthy volunteers to determine the PK/PD profile of ABT and define the optimal dose Sample Size: N = 13 Arms: three arms ABT 50 mg, SD, application to the gum ABT 100 mg, SD, application to the gum Acyclovir tablet 200 mg, SD, oral route	x			Ph 2 OL crossover study to determine PK/PD and dosing. Both 50 and 100 mg achieved high local concentrations No proven benefit from 100 mg dose over 50 mg as per the Sponsor.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comments Formatted Table
	Location in submission: Section 5				
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 A Randomized, Double-Blind, Single dose, One-Day Early Administration, Multicenter 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</p> <p>Indication: SITAVIG is indicated in adults and children above 12 years of age for the treatment of recurrent orofacial herpes simplex virus infections in immunocompetent patients, (b) (4)</p>	x			<p>One phase 3 study was required for this 505b2 NDA to show efficacy and safety of the buccal acyclovir containing product. Acyclovir has previously been shown to be efficacious in the treatment of HSV infections. In addition acyclovir cream is approved for the treatment of HL. Applicant informed that they must show st. sign (p <= 0.001) results for TTHPL. In addition TTHPL results must be clinically relevant and at a min ½ day.</p> <p>NOTE Applicant requesting approval for (b) (4)</p> <p>EMEA granted deferral for 10 - 17 and waived lower ages.</p>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			<p>Consistent with Agency policy the primary endpoint was to demonstrate the efficacy of a single dose of ABT 50 mg versus a single dose of matching placebo on the time to healing (TTH) of the primary vesicular lesion of labial herpes.</p> <p>Secondary objectives were:</p> <ul style="list-style-type: none"> • To compare the efficacy of ABT 50 mg versus placebo on: <ul style="list-style-type: none"> o The evolution of prodromal symptoms to aborted lesions (herpes lesions that did not progress beyond the papule stage, preceded by recorded prodromal symptoms); o The healing of non primary lesions; o The duration of herpes episode; o The duration of symptoms; o The healing of aborted primary lesions; o The healing of intra-oral and mucosal non primary lesions; o The incidence of and time to recurrence during 9 months following treatment (ancillary study in selected centers);

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comments Formatted Table
					<ul style="list-style-type: none"> • 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 centers) 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.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	No additional studies performed for this 505b2 application.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comments
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver requested
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Previously assessed for innovator product
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	Of note there were no deaths, SAEs or discontinuations
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Applicant should revise deferral and waiver requests to be consistent with regards to age cut-offs.

Regina Alivisatos, MD	April 18, 2012
Reviewing Medical Officer	Date

Kimberly Struble, PharmD	
Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

M R ALIVISATOS
05/29/2012