CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203791Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Addendum

Date	
From	Kimberly A Struble, PharmD
Subject	Cross-Discipline Team Leader Addendum
NDA #	203791
Applicant	Bioalliance
Date of Submission	January 4, 2013
PDUFA Goal Date (new)	April 11, 2013
Proprietary Name / Established (USAN) names	Sitavig (acyclovir)
Dosage forms / Strength	Mucoadhesive Buccal Tablet 50 mg
Proposed Indication(s)	1. The treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients
Recommended:	*Approval – pending CMC inspection outcomes*

1. Introduction

This cross discipline team leader addendum summarizes the main issues regarding Bioalliance's response to the December 7, 2012 discipline review letter. This addendum review highlights the clinical and statistical findings regarding reanalyses of the assessment of the primary and secondary endpoints from the phase 3 trial (BA2005/21/02) and overall benefit risk assessment.

2. Background

This 505(b)2 application is based on reliance on FDA's previous findings of safety and efficacy for Zovirax cream, Zovirax capsule, tablet and suspension, published literature, a pharmacokinetic trial and one Phase 3 clinical trial. Sitavig is a new delivery system for acyclovir and is intended to provide a rapid and prolonged release of acyclovir in the buccal cavity following one single dose application. Sitavig is inserted to the upper gum just above the incisor tooth on the same side as the primary herpes labialis lesion. Bioalliance submitted this NDA for the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients (b) (4)

Based on the clinical and statistical review findings, FDA informed Bioalliance via a Discipline Review letter dated December 7, 2012, insufficient efficacy data were available to support the proposed treatment claims. The results for the primary endpoint, time to healing (TTH), did not meet the pre-specified clinical and statistical

benchmarks as communicated during the pre-NDA and subsequent meeting. Results from a single phase 3 trial could be supportive if the efficacy data were both clinically meaningful and statistically significant, specifically an improvement in TTH of > 0.5 days and p-value considerably smaller than 0.05. Data collection (infrequent collection of efficacy data by subjects and infrequent evaluation of subjects by investigators) impeded the ability to accurately calculate TTH. Additionally, data validation issues and protocol violations also led to lower efficacy results per the FDA analyses compared to those presented in the NDA.

Additionally, the other claims proposed by Bioalliance were either not sufficient because (b) (4) .

Bioalliance responded to the Discipline Review Letter seven days before FDA was ready to issue a Complete Response action. Based on Bioalliance's January 4, 2013 submission, the Division considered the submission a Major Amendment and extended the PDUFA review clock by three months. Of note, Bioallance removed the claims: (b) (4) from the NDA based on the comments received from the Discipline Review letter. Bioalliance's amended NDA only focuses on the treatment claim for recurrent orofacial HSV in immunocompetent patients. Below are the highlights of FDA's reanalyses and justification to base an approval action on duration of episode endpoint and consider the time to healing endpoint as secondary.

3. Clinical/Statistical- Efficacy

Bioalliance contends the Phase 3 trial is adequate to support the treatment claim for recurrent orofacial HSV infection. Bioalliance raised several issues with FDA's rationale considering the efficacy data for reduction in time-to-healing of ulcerative herpes labialis lesions based on the modified intent to treat population. Bioalliance's meeting minutes from the April 8, 2010 meeting state the intent-to-treat (ITT) population was considered the primary population and duration of episode was the primary endpoint. Additionally, FDA requested additional analyses based on modified intent-to-treat (mITT) for duration of episode and time to healing. The FDA meeting minutes from April 8, 2010 meeting do not explicitly state the primary endpoint would be changed from time to healing to episode duration nor do the minutes consistently state when the ITT vs the mITT population would be used for the various analyses. However, Bioalliance did submit the NDA based on the protocol defined primary endpoint time to healing for the mITT population. Of note, duration of episode based on ITT population was the protocol defined secondary endpoint.

Nevertheless, FDA re-reviewed the primary and secondary endpoints including definition for other oral HSV applications. As summarized in clinical/statistical

addendum, duration of episode based on the ITT population was used as the primary endpoint and time to healing based on the mITT population (those who developed vesicular lesion) as the secondary endpoint for acyclovir cream, of which this 505(b)2 application is based on. Therefore, we agree the same endpoints should apply. Admittedly, there is some confusion regarding the definitions/terminology for duration of episode and time to healing used in past applications. Also mean and median differences were not used consistently in reviews or labeling. FDA now considers duration of episode as the more clinically relevant endpoint because this endpoint takes into consideration the entire disease course (those who develop lesions and those who lesions do not progress to vesicular stage). This is particularly relevant for products which may increase the number of aborted lesions. We agree the duration of episode endpoint should be based on the ITT population.

FDA's results from the duration of episode endpoint from the ITT population analyses were similar to Bioalliances results. FDA's median difference between Sitavig and placebo for episode duration was 0.80 days (mean 0.66 days) with a p-value of 0.0049 (log rank test). The difference in FDA's and Bioalliance's results are due to five patients whose time to healing was recategorized and the patients who received prohibited antiviral medications were assigned a worst case duration of episode of 14 days. If the Hodges-Lehmann estimation is applied the median difference between treatment groups was 0.58 days (p-value 0.0289 from the Kruskal-Wallis test). These results exceed the clinical and statistical benchmark of at least a 0.5 day difference. In comparison the mean time to healing for acyclovir cream was approximately 0.5 days.

FDA also calculated time to healing based on the revised ITT population. Of note, FDA results differ from Bioalliance because the FDA analyses corrected the five patients time to healing, assigned a time to healing of 14 days for those 11 subjects who took a prohibited antiviral medication and assigned the 29 patients a time to healing of 14 days even though they were censored and considered not healed. Based on the KM method the median and mean difference between Sitavig and placebo were 0.94 and 0.87 days, respectively. Both the episode of duration and time to healing based on the ITT population showed a greater than 0.5 day benefit favoring Sitavig. Subgroup analyses for time to healing based on ITT population all showed a 0.89 to 1 day benefit in terms of median difference based on adhesion time (< 6 hours, 6-12 hours and > 12 hours) of first tablet using KM method. Given the consistency of the results for the ITT population, the review team considers this sufficient evidence to demonstration the efficacy of Sitavig.

4. Pediatrics

This product was discussed at the March 6, 2013, PeRC meeting. The PeRC agreed with the waiver request for 0 to less than 6 years. The PeRC asked the team to modify the reason for waiving the pediatric trials in this age group to "the product would be ineffective and/or unsafe in one or more pediatric groups(s) for

which a waiver is being requested." This is based on the risk of choking. As a result, the following language was included in the product labeling.

"Use in younger children is not recommended due to potential risk of choking."

The review team originally stated the trials in this age group were waived because necessary studies are impossible or highly impracticable and the product does not represent a meaningful benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. This is because of the pathophysiology and epidemiology of the disease. Herpes labialis in children less than 6 years of age is generally a primary infection, and not a recurrence.

Pediatric trials in ages > 6 years to ≤ 17 years are deferred. At the time of this addendum we are in negotiations with the applicant regarding the design and collection of data necessary for this trial. The applicant originally proposed to (b) (4) They propose to (b) (4) However, we do not agree with this approach because (b) (4) The PREA commitment will be to evaluate the safety and duration of episode in children ages greater than 6 years to ≤ 17 years of age in 100 treated subjects distributed among this age range.

5. Labeling

The applicant accepted all the changes proposed by the division. The major changes were to the Adverse Reaction and Clinical Trials sections. The Adverse Reaction section was updated to include adverse events without regard to causality. Typically only related events (adverse reactions) are included in this section. However, given the single dose nature of administration and limited events we decided to include all events in at least 1% of subjects.
The Clinical Trials section was updated to only include duration of episode as follows:

"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."

6. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

An approval action is recommended for this application pending CMC inspection and 505(b)2 assessment. The major amendment submitted by Bioalliance and FDA's reanalysis provides sufficient support to demonstrate Sitavig has a favorable impact on duration of orofacial herpes labialis infection and favorable safety profile.

- Risk Benefit Assessment

As noted in the original CDTL review and clinical/statistical review, the safety data presented are favorable and no new or unexpected findings were observed for the buccal administration of acyclovir. Local tolerance and complications from tablet dislodgement were initial concerns. The data presented do not indicate local tolerance was an issue. The safety profile for local adverse events was similar between treatment groups. Complications from tablet dislodgement were also not observed; however, these toxicities should be monitored postmarketing. FDA's reanalysis of time to healing and duration of episode based on the ITT population demonstrated consistent results of more than 0.5 days difference between Sitavig and placebo. The median difference in duration of episode was approximately 0.58 days with a p-value of 0.0289.

The Division requested the applicant to evaluate the efficacy in African Americans as a post marketing commitment (PMC). After discussions with BioAlliance we concluded additional data in African Americans were not needed. We could not find any published data on the incidence and prevalence of recurrent herpes labialis in African Americans adults. BioAlliance supplied references regarding the prevalence in children (0.57% in non-Hispanic black versus 1.72% in non-Hispanic white American children). They also reference a recent trial in Utah (b) (4), (b) (6) , personal communication) suggesting recurrent herpes labialis is less common in African-American adults. In the phase 3 trial all racial groups were permitted to enroll. Of the 775 patients recruited in the trial, 143 were American patients and 7.7% (11/143) were African American. Additionally, BioAlliance makes the argument that the mechanism of action is acyclovir salivary concentrations. The dose of acyclovir and release rate from the tablet is related to formulation and is independent of age, race or sex. The literature does not indicate salivary flow is different across races. Given this information a PMC was not further pursued.

Additionally, at the time of this review the CMC inspection is pending and a final recommendation is not expected until April 11, 2013, one day before the action date.

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/s/

KIMBERLY A STRUBLE
03/28/2013

Cross-Discipline Team Leader Review

Date	December 11, 2012
From	Kimberly A Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA #	203791
Applicant	Bioalliance
Date of Submission	March 13, 2012
PDUFA Goal Date	January 11, 2013
Proprietary Name / Established (USAN) names	Sitavig (acyclovir)
Dosage forms / Strength	Mucoadhesive Buccal Tablet 50 mg
Proposed Indication(s)	1. The treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, [redacted] (b) (4)
Recommended:	Complete Response

1. Introduction

This cross discipline team leader review summarizes the main issues for Sitavig, a 50 mg mucoadhesive buccal tablet of acyclovir, for the local treatment of orofacial herpes [redacted] (b) (4). This review highlights the clinical and statistical issues regarding the assessment of the primary and secondary endpoints from the phase 3 trial (BA2005/21/02) and overall benefit-risk assessment.

2. Background

Acyclovir is a purine nucleoside analogue with activity against several human herpes viruses including herpes simplex types 1 and 2 (herpes labialis and genital herpes), and varicella zoster. Acyclovir (Zovirax) was first approved in 1982 and is now available in numerous formulations including 5% topical cream, 5% topical ointment, 200 mg capsules, 400 and 800 mg tablets, 200 mg/5 mL oral suspension and solution for injection.

Per Bioalliances' request, this 505(b)2 application is based on reliance on FDA's previous findings of safety and efficacy for Zovirax cream, Zovirax capsule, and tablet and suspension, the published literature, a pharmacokinetic trial and one Phase 3 clinical trial. Sitavig is a new delivery system for acyclovir and is intended to provide a rapid and prolonged release of acyclovir in the buccal cavity following one single dose

application. Sitavig is inserted to the upper gum just above the incisor tooth on the same side as the primary herpes labialis lesion. Bioalliance states this new delivery mechanism for acyclovir allows for high and sustained concentrations of acyclovir at the site of action and is expected to overcome the issue of the short intracellular half-life of acyclovir in other dosage forms. Bioalliance submitted this NDA for the treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, (b) (4) . The merits of this application were discussed at a pre-NDA meeting in April 2010 and during a follow-up type C meeting in July 2010. FDA concluded Bioalliance had enough data to submit an NDA; however, approvability was a review issue. During the April and July 2010 meetings, FDA raised several issues including:

- clinical and statistical benchmarks for the primary endpoint, time to healing (THH),
- methodology for calculating TTH,
- safety data for those subjects whose tablet dislodged,
- (b) (4),
- efficacy data by race and
- dose and drug delivery to site of action.

These issues are discussed in detail in the respective sections of this review.

FDA informed Bioalliance a single efficacy trial could be sufficient to support approval provided the results were both statistically significant and clinically meaningful. Specifically, the review team communicated the results needed to show statistically very persuasive findings and a very low-p-value for a single trial and quoted a $p<0.001$ for a single trial or $p<0.05$ for two trials. Further, the trial results must be robust to various sensitivity analyses and consistent across subgroups. The benchmark for clinically meaningful results is at least ½ day difference for TTH. This clinical benchmark is based on results from other topical treatments for herpes labialis. Based on the preliminary data submitted the TTH difference between Sitavig and placebo was approximately 0.3 days. FDA cautioned approvability in the first review cycle was questionable.

Additionally, FDA recommended Bioalliance not submit an application for the (b) (4) at this time. To support this claim, a (b) (4)

At the April and July 2010 meetings, Bioalliance did not indicate they were pursuing labeling for (b) (4) .

3. CMC/Device

Sitavig is an acyclovir 50 mg extended release tablet and is formulated with USP grade microcrystalline cellulose, povidone, sodium laurel sulfate, magnesium stearate, silicon dioxide, hypromellose and milk protein concentrate. The tablets are packaged in blisters with two tablets per blister. An expiration date of three years under controlled room temperature was supported by the submitted data.

A potential genotoxic impurity was found in a DMF review for the drug substance. However, CMC and pharm/tox determined this was low risk due to its extreme reactivity (low carryover) and downstream purification capability.

Drs. Pagay and Liu's review states adequate data to assure the identity, strength, purity and quality of the drug product were presented in the NDA. The DMF for acyclovir drug substance supporting this NDA is also adequate. However, final determination on the acceptablilty of a site inspection is still pending at this time. The inspection report is needed in order to determine if any CMC deficiencies were noted that would affect the overall CMC recommendation for an approval or complete response action.

4. Nonclinical Pharmacology/Toxicology

Information regarding nonclinical pharmacology/toxicology is based on the published literature and FDA's previous findings from the Zovirax cream label. The nonclinical literature publications include studies on the acute, subchronic, chronic, mutagenicity, carcinogenicity, and reproductive toxicity of acyclovir. According to Dr. Lansita's review, these studies were performed using systemic dose routes which would likely over-predict the potential toxicity of Sitavig because systemic plasma exposure following buccal administration is likely to be minimal based on the clinical pharmacokinetic (PK) data of Sitavig. Bioalliance conducted a hamster single-dose tolerance trial with Sitavig 50 mg placed in the jugal mucosa of the hamster. No local or systemic pharmacokinetic or toxicokinetic analyses were done. However, this was not considered an approval issue by Dr. Lansita. No nonclinical issues were identified to preclude an approval action from the pharmaocology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Leslie Chinn reviewed dissolution data and results from a phase 1 trial BA2004/21/01 and a phase 3 trial BA2005/21/02. Trial BA2004/21/01 supported a biowaiver for the approval of a change in commercial manufacturing site.

The phase 1 trial evaluated the pharmacokinetics and tolerability of buccal administration of Sitavig 50 mg and 100 mg compared to Zovirax 100 mg tablet given orally. Acyclovir plasma and salivary concentrations were collected over 2 days. A single buccal application of Sitavig 50 mg and 100 mg dose showed rapidly detectable acyclovir concentrations in saliva at 30 minutes for both Sitavig 50 mg and 100 mg. The mean AUC/IC_{50} ratios were dramatically different between Sitavig 50 mg and 100 mg compared to Zovirax 200 mg oral tablet as shown in the table below.

Table 2 Pharmacokinetics of acyclovir in saliva

	ABT 50mg Single dose	ABT 100mg Single dose	Oral tablet 200mg Single dose
C_{max} (µg/mL)			
Mean ± SD	440 ± 241	576 ± 345	0.23 ± 0.28
Range	149 – 959	158 – 1200	0.02 – 0.95
Geo mean	387	484	0.11
T_{max} (h)			
Mean ± SD	7.95 ± 4.08	11.97 ± 4.6812	0.73 ± 0.50
Range	3.07 - 18.05	4.02 – 18.03	0.52 – 2.03
Geo mean	7	11	0.6
$AUC_{(0-t)}$ (µg•h/mL)			
Mean ± SD	2900 ± 2400	6320± 4750	0.25 ± 0.21
Range	849 – 9450	2100 – 16700	0.06 – 0.74
Geo mean	2320	4900	0.18
AUC_{0-t} / IC_{50}	103111	216000	7.9

IC_{50}: 22.5 ng/mL

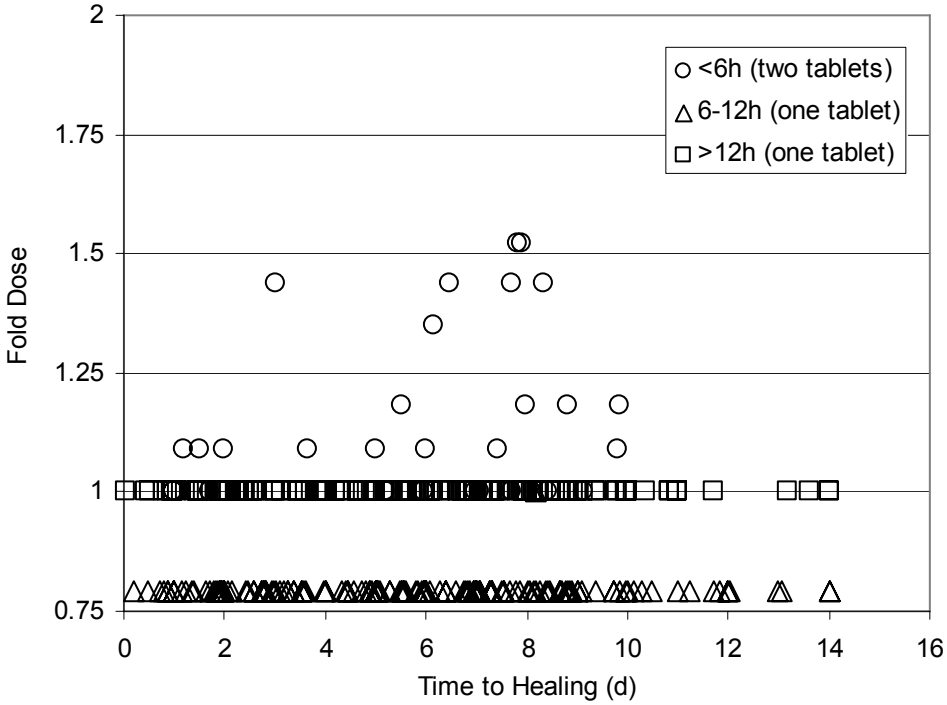
Source: BA2004/21/01 Table 9

Acyclovir concentrations following Sitavig 50 mg or 100 mg administration in labial mucosa were also evaluated and were significantly higher than acyclovir concentrations following Zovirax 200 mg oral tablet. Based on these data and the low plasma concentrations following buccal administration, the 50 mg dose was chosen for the phase 3 trial.

In the phase 3 trial the relationship between estimated acyclovir dose delivered to the buccal cavity and TTH was evaluated. However, the exposure-response relationship for saliva viral titer, saliva acyclovir concentration and TTH was not assessed due to limited data collected. Therefore, a preliminary analysis using in vitro dissolution data and tablet adhesion time was conducted to approximate the amount of acyclovir released at the target site (refer to Figure 2 below).

Figure 2: Relationship between estimated fold dose of acyclovir and the time-to-healing of the primary vesicular lesion

Source: Dr. Chinn's review



Dr Chinn concluded, "Although local concentrations were not quantified, in theory, tablet adhesion time may be used as a surrogate for the amount of acyclovir delivered locally and subjects with longer adhesion times should have shorter TTH compared to those with shorter adhesion times. However, no relationship between adhesion time and TTH was observed, suggesting that local acyclovir exposures were either not sufficient to achieve significant antiviral activity or that the applicant's postulated mechanism of drug reaching the site of the cold sore (licking of the lips) is not well-supported. "

I agree with Dr. Chinn's assessments. At the pre-NDA meeting and throughout our review, we questioned the dose selection and delivery method. However, these data suggest a (b) (4) interval may not impact TTH. Bioalliance states acyclovir from the buccal tablet is delivered mostly from licking of the lips. Based on the data presented above we do not have convincing evidence of the delivery mechanism to the site of action. From the clinical perspective, this is one of the several issues impacting the regulatory review decision and why we concluded another trial is needed to demonstrate efficacy. Of note Dr. Chinn's review states a clearly demonstrated dose-response (or exposure-response) relationship is not needed to recommend approval providing robust efficacy is demonstrated. From the clinical pharmacology perspective Dr. Chinn recommended an approval action.

6. Clinical Microbiology

Bioalliance submitted published data on the mechanism of action of acyclovir, antiviral activity of acyclovir in cell culture against laboratory and clinical isolates, antiviral activity in animal models, acyclovir-resistance associated substitutions, susceptibility of acyclovir resistant isolates in cell culture and a virology report from Dr. Boutolleau at Pitie-Salpetrier University Hospital in Paris France. No notable issues were found. A comparison of salvia HSV-1 DNA in subjects treated with Sitavig compared to placebo showed Sitavig exhibited antiviral activity following a single dose. An 87% reduction in saliva HSV DNA was observed. No outstanding issues from a virology perspective. With respect to virology, Dr. Mishra's review recommends an approval action.

7. Clinical/Statistical- Efficacy

One phase 3 trial (BA2004/21/01) was submitted in the NDA. This trial was a randomized, double-blind, single dose, once daily administration of Sitavig 50 mg vs placebo for the treatment of recurrent herpes labialis in immunocompetent adult subjects. Subjects with a history of recurrent herpes labialis defined by at least 4 episodes in the preceding 12 months and accompanied by prodromal symptoms in at least 50% of recurrent episodes and at least 50% of previous episodes produced classical lesions to the vesicular stage were enrolled. Subjects were not permitted to receive any antiviral medications.

Subjects were to apply Sitavig or placebo on the side of the lesion on the upper gum in the canine fossa. Subjects were instructed to initiate treatment within one hour after onset of prodromal symptoms and before the appearance of any signs of lesions. The primary endpoint was time to healing (TTH). The endpoint was an investigator assessed endpoint; however, the investigator used all available data including patient diary to assess healing time. Subjects were seen by the investigator within 24 hours of treatment initiation and on days 1, 3, 5, 7 and 14. Subjects recorded their symptoms and stage of lesion (normal lip, erythema, papule, vesicle, crust) once daily. Of note, the original protocol submitted in 2006 and until August 2007 included provisions for subjects to make assessments of their lesions four times daily.

Treatment claim for recurrent orofacial herpes simplex virus infections in immunocompetent patients

Time to healing, the primary endpoint, as assessed by Dr. Wen Zeng is presented in the table below for the median difference between treatment groups using the Hodges-Lehmann method. Of note, Hodges-Lehmann method is preferred method and used in previous herpes applications. Please refer to the clinical and statistical review for further details.

I concur with the conclusions by Dr. Alivisatos and Zeng that the efficacy data presented in the NDA are inadequate to support approval. The results did not meet the statistical and clinical benchmarks discussed during the April 2010 pre-NDA meeting for the primary endpoint TTH and did not consistently meet the predefined definition of clinically meaningful benefit of at least a half-day difference for TTH. The results at a 0.05 level were not robust to data validation for demonstrating efficacy in a single registration trial.

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 (6.7**2**, 7.**32**)	7.3**1** (**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). Source: clinical/statistical review

Several trial design and analysis issues led to our conclusions. First, the data collection for the primary endpoint was not optimal. Our ability to accurately calculate TTH was impeded by the infrequent evaluation by the investigator and infrequent collection of efficacy data by subjects. As previously stated, the TTH endpoint relied on investigator assessment. Additionally investigators used all available data, including subject dairy entries to better define the exact hour of loss of crust. Subjects

were only seen every other day during the trial by the investigator until Day 7, then were not seen again until Day 14. Also subjects only recorded lesion assessments once daily. As a result, the ability to accurately calculate time to healing and the ability to demonstrate at least a half-day benefit over placebo for TTH is severely limited by these trial design flaws.

Additionally, Dr. Zeng found errors in the TTH calculation for five subjects. Their TTH was calculated incorrectly because the next to the last visit date was used for the TTH calculation instead of the final disposition date. Dr. Zeng used the corrected TTH in the FDA analyses. FDA analyses also excluded 11 subjects from the efficacy evaluation due to protocol violations because these subjects received a prohibited antiviral medication during the trial. As a result the FDA efficacy results differ from those presented by Bioalliance in the NDA.

Three subjects in the Sitavig group and eight subjects in the placebo group received a prohibited medication. The time to healing for the eight subjects in the placebo group ranged from 3-14 days compared to 7-7.9 days for subjects in the Sitavig group. One would expect by excluding these subjects the treatment difference between trial arms would widen. The overall TTH results were sensitive to the TTH recalculation for 5 subjects and to the exclusion of 11 subjects for protocol violation and demonstrates the results are not robust.

The impact of delaying treatment beyond one hour of prodromal symptoms, adhesion time (< 6 hours, 6-12 hours or > 12 hours), tablet replacement (was the first table replaced or not), herpes history (at least 4 episodes in past 12 month or not) and lesion severity on TTH was also assessed by FDA.

Herpes history and lesion severity did not have a significant impact on TTH results. The sample size for those subjects who replaced a tablet was too small to make any conclusions. The median TTH difference for subjects who applied drug within one hour of onset of prodromal symptoms was -0.31 days (-0.90, 0.20 p-value 0.246; Hodges-Lehmann estimates). The goal of herpes treatment is to initiate treatment as soon as possible and within one hour of prodromal symptoms as stipulated in the protocol. The expectation is the TTH would be shorter for those who started treatment within one hour; however, the difference between Sitavig and placebo was minimal. A relationship between duration of tablet adhesion and TTH was not seen. The greatest difference in TTH was in the < 6 hour subgroup (0.79 and 1.06 days), followed by the > 12 hour subgroup (0.59 and -0.7 days), and finally the 6-12 hour subgroup (0.01 and 0.20 days). While subgroup analyses can produce spurious results, these subgroups were fairly large (approximately 40% of the population) and further highlight the lack of robustness in the data.

Another interesting finding is the difference between TTH observed in this trial compared to other trials used to support approval for acyclovir cream, acyclovir+hydrocortisone cream, penciclovir cream, docosanol (over the counter product) and oral Valtrex. The TTH in these trials is approximately 5 days compared

to approximately 7 days for Sitavig. Of note, the length of a herpes labialis cycle is approximately 7 days (5-12 days). For this 505(b)2 application, FDA is relying on our previous findings for acyclovir 5% cream. The difference in healing time across trials, (4.3 days for acyclovir vs 7 days for Sitavig), acknowledging the limitations of cross-trial comparisons, is another concern for the TTH assessment and further underscores a second trial is needed in support of approval.

Healing Time Outcomes for Approved Treatments for Herpes Labialis

	DRUG	**REGIMEN (OR PLACEBO)**	N	**OUTCOME (VS PLACEBO)**
				HEALING TIME
Oral	Valacyclovir*	2 g twice daily for 1 day	603	1.3 days ↓ (95% CI, –1.9 to –0.7) (4.8 vs 6.1 days)
			615	1.3 days ↓ (95% CI, –1.8 to –0.7) (5.1 vs 6.4 days)
	Acyclovir	400 mg 5 times a day for 5 days	174	
Topical	Penciclovir* 1%	Every 2 hours during waking hours for 4 days	3057	31% ↓ (HR=1.31; 95% CI, 1.20–1.42)
			1573	0.7 days ↓ (4.8 vs 5.5)
	Acyclovir 5%	5 times a day for 4 days	689	0.5 days ↓ (4.3 vs 4.8) (HR=1.23; 95% CI, 1.06–1.44)
	Docosanol* 10% (available OTC)	5 times daily	737	0.7 days ↓ (95% CI, 0.08–0.92 days) (4.1 vs 4.8 days)
	Acyclovir 5% + hydrocortisone 1% cream	5 times daily for 5 days		4.77 days vs 5.09 days

Source: Chon, T, Nguyen L, Elliott TC. Clinical Inquiries. What are the best treatments for herpes labialis J Fam Pract. 2007 Jul;56(7):576-8. Acyclovir+hydrocortisone source: FDA Decisional Memorandum assessed December 7, 2012: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022436s000_SumR.pdf

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8. Safety

Based on over 20 years of experience with topical and systemic acyclovir formulations, the overall safety database of 378 subjects who received ABT 50 mg in the phase 3 trial is adequate to assess the safety profile. Limited plasma concentrations are expected following a single buccal administration; therefore, the main safety concern prior to phase 3 trials was tablet dislodgement and local tolerance. A total of 783 subjects from the phase 1 and phase 3 trial are available to assess the safety issues related to tablet dislodgement (of note 395 subjects received matching placebo buccal tablet).

No deaths or serious adverse events were reported for Sitavig 50 mg. The most commonly reported adverse events were similar between Sitavig 50 mg and placebo and include headache (3% each), application site pain (1% each) and nasopharyngitis (1% each). The majority of these events were mild or moderate in severity. Few events were considered severe and were not likely related to study medication.

The safety data were reviewed in detail by Dr. Alivisatos to determine local tolerability. Overall, 14 subjects (4%) in the Sitavig 50 mg group and 12 subjects (3%) in the placebo group developed an application site reaction or reaction related to the lips or oral cavity. This analysis is presented in Table 40 of the clinical/statistical review. All these events were considered mild, with the exception of one event in each group which were moderate in severity. No severe events were reported. Based on this analysis, the local tolerance of Sitavig was acceptable and similar to placebo.

The main concern for a dislodged tablet includes cough, choking, pain, suffocation, respiratory complication or esophageal/pulmonary infections. As shown by the adverse event profile no increased incidence of these events were noted. Additionally, Bioalliance reviewed their internal safety database and literature for their buccal tablet Oravig. No evidence was identified for these types of adverse reactions. Based on the phase 3 trial data and experience with Oravig, the risk for dislodgement and adverse consequences appears low. Bioalliance recommends subjects consume a glass of water following accidental ingestion.

Overall, treatment emergent adverse events were numerically higher in females compared to males and included headache: 3.5% for females vs 2.5% for males and, application site pain: 1.2% for females vs 0.8% for males. Slightly larger differences were seen in the placebo group. GI disorders were observed more frequently in males receiving Sitavig 50 mg compared to placebo (5.3% vs 3.2%). A gender effect is not likely due to Sitavig 50 mg. An assessment of safety by race could not be evaluated because 95% of the trial population was White/Caucasian.

Minimal laboratory abnormalities were observed. This was expected for a topically administered product with minimal systemic absorption and assessments were only performed before treatment and on study day 14.

Overall the safety profile of Sitavig is favorable and no concerns with local tolerance or tablet dislodgement were observed which require further assessment. Bioalliance has an adequate plan in place to address tablet dislodgement issues.

9. Advisory Committee Meeting

An advisory committee meeting was not held and not necessary for an acyclovir given the twenty plus years of marketing experience in various topical and systemic formulations.

10. Pediatrics

Because the clinical and statistical review team recommended a complete response action this application was not discussed with the PeRC. Bioalliance proposed [redacted] (b) (4) Due to the pathophysiology and epidemiology of herpes labialis I recommend safety data are obtained in pediatric subjects ages 7 to 17 years of age. A waiver could be granted for less than 7 years of age due to both potential risks for choking, inability to comply with administration instructions and low likelihood this product will be used in this subgroup. This recommendation is also consistent with the pediatric requests for Xerese.

[redacted] (b) (4)

11. Other Relevant Regulatory Issues

No additional regulatory issues aside from those listed in section 13 below.

12. Labeling

The trade name Sitavig was deemed acceptable. However, given the complete response action, the trade name must be submitted for re-evaluation with the resubmission. Review of the label by all disciplines was deferred until the deficiencies are addressed in the resubmission.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Insufficient data were provided to recommend approval at this time. I agree with the statistical and clinical review team's assessment regarding the need for additional trial data to support approval for the various claims proposed by Bioalliance. A complete response action is recommended. The section below describes the deficiencies identified by the review team and data needed to resolve these issues.

- Risk Benefit Assessment

The safety data presented are favorable and no new or unexpected findings were observed for the buccal administration of acyclovir. Local tolerance and complications from tablet dislodgement were initial concerns. The data presented do not indicate local tolerance was an issue. The safety profile for local adverse events was similar between treatment groups. Complications from tablet dislodgement were also not observed; however, if approved in the future, these toxicities should be monitored.

Despite the favorable safety profile, insufficient efficacy data were available to support approval. The results for the primary endpoint, TTH, did not meet the pre-specified clinical and statistical benchmarks as communicated during the pre-NDA and subsequent meeting. Results from a single phase 3 trial could be supportive if the efficacy data were both clinically meaningful and statistically significant, specifically an improvement in TTH of > 0.5 days and p-value considerably smaller than 0.05. Data collection (infrequent collection of efficacy data by subjects and infrequent evaluation of subjects by investigators) impeded the ability to accurately calculate TTH. Additionally, data validation issues and protocol violations also led to lower efficacy results per the FDA analyses compared to those presented in the NDA. The trial results were sensitive to the five subjects TTH recalculation and 11 censored subjects due to protocol violations (received prohibited antiviral medication) and therefore underscores our conclusions the data presented from one phase 3 trial were not robust. Additionally, results from subgroup analyses were not consistent compared to the results from the overall population. Again, questioning the robustness of the trial results. For these reasons, the review team could not support approval for treatment of recurrent herpes labialis. An additional trial with at least twice daily lesion assessment by subjects and daily evaluation of subjects by investigators is needed. A significance level of 0.05 for TTH is also needed for a resubmission.

The claim to [redacted] (b) (4)

(b) (4)

The claim to (b) (4)

The review team did not specifically discuss with Bioalliance the criteria for (b) (4)

In summary, the data presented from the phase 3 trial for the primary endpoint, TTH, were not robust to data validation for demonstrating efficacy in a single registration trial. Data validation and protocol violations led to lower efficacy results by the review team compared to the results presented in the NDA. For the other claims, insufficient data were provided to support an approval action. One or two additional phase 3 trials are needed depending on which claims Bioalliance requests in a subsequent NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Given the self-limiting nature of herpes labialis and the acceptable safety profile of Sitavig postmarketing risk management plans are not necessary.

- Recommendation for other Postmarketing Requirements and Commitments

Discussions on postmarketing trials were deferred. Depending on the data contained in the resubmission targeted trials in certain racial subgroups may be necessary.

- Recommended Comments to Applicant

This section includes the deficiencies identified. In addition, I have incorporated my own recommendations to further address the identified safety and efficacy issues. This section serves as a draft for the complete response letter and will be further revised in the upcoming month. Please consult the final complete response letter.

CLINICAL and STATISTICAL

Deficiency 1: Claim for treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients

We have determined the efficacy data presented in your NDA 203,791 submission were inadequate to support this claim due to the deficiencies described in the Discipline Review (DR) letter dated December 7, 2012. The trial results did not consistently meet the predefined definition of clinically meaningful benefit of at least a half day difference in the primary efficacy endpoint time to healing (TTH). Additionally, the results at a 0.05 level were not robust to data validation for demonstrating efficacy in a single registration trial. Trial design deficiencies and analysis issues led to this conclusion. The ability to accurately calculate TTH was impeded by the infrequent collection of efficacy data by subjects (one daily) and infrequent evaluation of subjects by the investigator (every other day until Day 7, then on Day 14). Additionally, data validation issues and protocol violations (use of prohibited antiviral medication) also led to lower efficacy results per the FDA analyses compared to those presented in the NDA.

Data needed to resolve deficiency #1:

Please conduct another phase 3, randomized, placebo-controlled clinical trial in patients with herpes labialis. The trial results should show at least a half day difference for TTH. Additionally, the results must attain statistical significance at the 0.05 level and should be robust to data validation with multiple statistical methods.

In your protocol please ensure subjects are evaluated daily by the investigators during the active treatment period and subjects complete diary assessments of lesions at least twice daily. Please ensure subjects do not receive other antiviral treatments during the active lesion phase of the trial. As noted in the DR letter the population studied in your initial NDA application was 95% Caucasian thus precluding an assessment of Sitavig across races. Please ensure the phase 3 trial includes a more racially balanced population including a substantial number of subjects of Black race as there are concerns regarding decreased effectiveness of herpes antiviral treatments in this subgroup.

Deficiency #2: Claim for [redacted]

[redacted]

Data needed to resolve deficiency #2

[redacted]

Deficiency #3: Claim for [redacted]

[redacted]

Data needed to resolve deficiency #3:

[redacted]

Deficiency #4: Claim for [redacted]

[redacted]

Data needed to resolve deficiency #4:

[redacted]

(b) (4)

Deficiency #5: Indication for (b) (4)

(b) (4)

Data needed to resolve deficiency #5:

(b) (4)

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/s/

KIMBERLY A STRUBLE
12/20/2012