CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-478

MEDICAL REVIEW

Medical and Biometrics Review
Of NDA 21-478
Zovirax ® (Acyclovir) Cream 5%
For Treatment of Herpes Labialis

Dates Submitted:
NDA 21-122: 07/30/99
NDA 21-478: 03/29/02
Date Assigned: 04/11/02
Date Completed: 12/20/02

Reviewers: **Clinical:**
Joseph G. Toerner, M.D., Teresa C. Wu, M.D. Ph.D.

Statistical:
Andrei Breazna, Ph.D., Fraser Smith, Ph.D.

Applicant: GlaxoSmithKline
PO Box 13398
Research Triangle Park, NC 27709

Drug: Generic: Acyclovir 5% cream
Trade: Zovirax ® CS™
Chemical: 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one

Drug Class: Guanidine nucleoside analog

Dosage and Route of Administration: Five times a day for 4 days, topical application

Proposed Indication: Treatment of Recurrent Herpes Labialis in adults and Adolescents (≥ 12 years)

Related Formulations With Approved Indications:

Zovirax	Indication(s)
5% ointment	Initial herpes genitalis; limited non-life threatening mucocutaneous HSV infections in immunocompromised patients
Capsule, Tablets, Suspension	Herpes zoster, genital herpes, chickenpox
Sterile powder (intravenous infusion)	Mucosal and cutaneous HSV and VZV infections in immunocompromised patients, HSV encephalitis in patients >6 months of age, severe initial clinical episodes of herpes genitalis in immunocompetent patients

Related Drugs Approved for Herpes Labialis Indication:

Drug	Manufacturer	Year Approved
Denavir (penciclovir)1 % cream	Formerly SmithklineBeecham, now Novartis	1996
Valtrex (valacyclovir HCl)caplet	GlaxoSmithKline	2002

Review Category: Standard

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1. Introduction

The original NDA 21-122 which had been submitted on 07/30/99 was withdrawn by Glaxo-Wellcome on 4/28/00 as a consequence of the applicant's planned reorganization. Later in the same year, Glaxo/Wellcome and SmithKline Beecham merged to become GlaxoSmithKline (GSK). In October of 2001, GSK entered a business agreement with Biovail Pharmaceuticals wherein GSK would be responsible for the resubmission of the NDA (reassigned as NDA 21-478) and, pending FDA's regulatory decision, Biovail would be the sole commercial distributor of the product in the US.

The original NDA, which contained the core data in support of the effectiveness and safety of Zovirax cream, was reviewed by Joseph Toerner, Andrei Breazna and Fraser Smith. Additional safety information and a draft package insert were reviewed by Teresa Wu.

2. Executive Summary

2.1 Recommendations:

Zovirax® CS™(acyclovir) 5% cream for the treatment of recurrent herpes labialis in adults and adolescents ages 12 and higher is recommended to be approved. Two phase III, randomized, vehicle-controlled, double-blind clinical trials demonstrated acyclovir 5% cream's modest treatment benefit of approximately one-half day when compared to vehicle control cream. Although safety studies showed the potential to cause dermal irritation, the overall safety profile appeared similar to another marketed product in the same class, penciclovir 1% cream.

2.2 Summary of Clinical Findings:

The applicant submitted two large, randomized, vehicle-controlled clinical trials to provide the core support for acyclovir 5% cream for the episodic treatment of recurrent herpes labialis (RHL). Both trials demonstrated a modest treatment benefit in favor of acyclovir 5% cream. The vehicle may be exerting some clinical benefit because the mean time to healing for participants using the vehicle control was approximately five days, much shorter than time to healing reported in historical observational studies without treatment. Nevertheless, a modest treatment benefit in favor of acyclovir 5% cream was maintained regardless of the type of statistical analysis performed. Pivotal trials designed to examine the efficacy of another topical nucleoside analogue, penciclovir 1% cream, also utilized a vehicle control and resulted in the same modest treatment benefit of approximately 4.5 days versus 5 days in favor of penciclovir 1% cream. We

conclude that the applicant has demonstrated the efficacy of acyclovir 5% cream for the treatment of RHL.

The primary safety concern is the dermal irritation of acyclovir 5% cream and its vehicle. In fact, earlier clinical development was halted in the United States because a phase 1 study showed that acyclovir 5% cream is a dermal irritant. The applicant repeated dermal irritant and contact sensitivity studies, which demonstrated a high dermal irritation potential for acyclovir 5% cream. However, the application of the cream to approximately 1100 study participants resulted in local site reactions in 4.5%. This proportion is similar to the local site reactions observed in pivotal trials of penciclovir 1% cream. Nevertheless, the irritation potential when acyclovir 5% cream is applied to intact skin warrants emphasis in product labeling. Acyclovir 5% cream did not appear to prevent RHL lesions in two large clinical trials; the dermal irritation potential to intact skin may have been a contributory factor to the lack of efficacy in these trials.

There appear to be no significant concerns with the dose of the to-be-marketed formulation, and topical application of acyclovir 5% cream did not result in appreciable systemic absorption.

There is enough information in the NDA to conclude that the geriatric and adolescent (ages 12-18) populations have no differences in safety profiles when compared to the total study population.

3. Background:

Recurrent herpes simplex labialis (RHL) is reported to affect at least 30% of the population of the United States. The primary cause is due to Herpes Simplex Virus (HSV) type I, although HSV type II may occasionally cause orolabial infection. The infection is usually spread by direct contact during childhood or adolescence. Once primary infection has been established, HSV lies latent in sensory ganglia. The lesions of RHL likely result from reactivation of latent virus with migration to the skin. The recurrences are highly variable in number and character. Many individuals have severe and painful recurrent lesions just after initial infection with herpes simplex. The recurrent lesions often change in severity over time such that the lesions become significantly less severe.

Currently, there are two approved antiviral drugs for treatment of RHL: Denavir™ (penciclovir 1% cream) and Valtrex® (valacyclovir hydrochloride).

Two large phase 3 clinical trials of penciclovir 1% cream demonstrate a modest treatment benefit of approximately one-half day when compared to a placebo control cream, about 4.5 days versus 5.0 days.

. GSK had

application as a prescription product ;

Valtrex is rapidly converted to acyclovir after oral administration. Two double-blind, placebo-controlled trials were conducted in subjects ≥ 12 years of age with a history or RHL. Patients were randomized to Valtrex 2 grams twice daily on day 1 followed by placebo on day 2, Valtrex 2 grams twice daily on day 1 followed by 1 gram twice daily on day 2, or placebo on days 1 and 2. The mean duration of cold sore episodes was about 1 day shorter in treated subjects as compared to placebo. The 2-day regimen did not offer additional benefit over the 1-day regimen.

4. Foreign Marketing Experience:

Acyclovir 5% cream has received marketing approval in 116 countries, including Canada, Mexico, and all European countries, over the past 10-15 years. Many European countries permit behind-the-counter or over-the-counter (OTC) sales without a prescription. However, an OTC switch, and the an OTC switch application from

5. Disciplinary Reviews

5.1 Chemistry Manufacturing Control:

Please see Dr. Gu's review for further information

5.2 Microbiology:

The applicant neither submitted nor referenced information pertaining to a microbiology section.

5.3 Pharmacology/Toxicology:

All nonclinical pharmacology and toxicology data were referenced to NDA 18-604, acyclovir 5% ointment. Please see Dr. Bigger's review for further information.

5.4 Biopharmaceutics:

A single pharmacokinetic study was submitted. Application of Acyclovir 5% cream to the backs of healthy adult volunteers did not result in detectable levels of serum acyclovir. Please see Dr. Reynold's review for further information.

6. Clinical:

Table 1: Summary of Clinical Trials:

ZOVA 3003	Multicenter, vehicle control study, primary endpoint of time to healing RHL lesion; n=648
ZOVA 3004	Multicenter, vehicle control study, primary endpoint of time to healing RHL lesion; design identical to ZOVA 3003; n=637
ZOVA 3001	Multicenter, vehicle control study, primary endpoint of prevention of RHL lesion; application initiated at prodrome; n=421
ZOVA 3002	Multicenter, vehicle control study, primary endpoint of prevention of RHL lesion; application initiated at prodrome; n=432
ZOVA 3005	Open label safety study in adolescent population; n=113
ZOVA 4001	Single investigator, vehicle control study, primary endpoint of prevention of RHL lesion, secondary time to healing, viral culture, and PCR; n=47
ZOVA 1002	Single investigator safety study to examine the irritation potential of Acyclovir 5% and vehicle control; n=22
ZOVA 1003	Single investigator safety study to examine the contact sensitization of Acyclovir 5% and vehicle control; n=202
Miscellaneous studies	Actual use studies of acyclovir 5% cream (ZOVA 3007, ZOVA 30010) n=1044
Miscellaneous studies	European registrational studies and other clinical studies of acyclovir 5% cream, clinical studies of 5% ointment

6.1 Efficacy Review

6.1.1 Studies ZOVA 3003 and ZOVA 3004:

Both studies entitled "A multicenter, placebo-controlled evaluation of acyclovir cream for the treatment of herpes simplex labialis infection" were identical but were conducted by different sets of investigators in the US.

Objectives: The primary objective of each study was the determination of the duration of the episode of recurrent herpes labialis treated with acyclovir 5% cream in comparison to vehicle cream. Secondary objectives included the evaluation of aborted lesions, vesicle healing time, and duration of pain and tenderness.

Study Design: These were multicenter, randomized, double-blind, placebo-controlled studies to determine the efficacy of acyclovir 5% cream in comparison with placebo. Study participants were instructed to initiate application of the study cream within one hour of the first sign or symptom[1] of a herpes labialis lesion and report to the study center within 24 hours.

Study population: Study subjects were adults greater than 18 years of age, who had had at least three episodes of a typical herpes labialis lesion within the past year; experienced prodromal symptoms[2] at least 50% of the time; and experienced classical lesions at least 50% of the time (ulcer, vesicle, and/or hard crust). Participants also agreed to abstain from antiviral medications, other topical treatments, and mechanical disruption of the area. Participants were excluded for the following reasons: greater than 25% of untreated episodes

[1] Initial symptoms include papules or vesicles.
[2] Prodromal symptoms include burning or a sense of irritation.

aborted prior to vesicle formation; pregnancy; not willing to use birth control; people assumed to be unreliable; immunodeficiency syndromes; other conditions altering the susceptibility to HSV; allergy or sensitivity to acyclovir; use of antiviral medications. Culture confirmation of Herpes Simplex was not required.

Treatments administered: Participants were randomization to one of two treatments: acyclovir 5% cream or vehicle control. Subjects were instructed to apply the cream five times per day for four days, for a total of 20 applications. Identical tubes for acyclovir 5% cream and vehicle control cream were numerically coded at random. Four tubes of cream were packaged in a single box. Each tube was labeled with protocol number, treatment number, storage instructions and dosing instructions. The acyclovir 5% cream and vehicle control were identical in appearance, odor, and consistency. Participants reporting total application of the study drug 15 times or less during the four day dosing period were judged to be non-compliant.

Efficacy Endpoints: 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. Information about the clinician's assessment was not to be shared with the study subject. The clinician used all available information to determine the outcome measurement. Clinician-observed and subject-observed information was to be provided as supportive efficacy variables. Secondary variables include vesicle prevention, duration of pain, and duration of tenderness of the lesion areas. For the study participants whose lesions began as vesicles, the time until vesicle healing was included as a secondary efficacy endpoint.

Safety Endpoints: Adverse events were tabulated during the treatment period and follow-up. Regulatory definitions of adverse events were included in the protocol.

Determination of the sample size: The applicant determined the sample size for an intent to treat population using α=0.05 and β=0.20. A difference of 0.5 days was estimated to be a significant treatment difference with a standard deviation of 2.25 days. This is based on published data examining the healing times of RHL lesions with the use of penciclovir 1% cream (Spruance, SL, et al. JAMA 1997;277:1374-9).

$$N = \frac{2(1.96+0.84)^2}{(0.5/2.25)^2} = 318$$ per treatment arm, or 636.

The applicant estimated that 1000 persons would be required for each study in order to generate adequate numbers of subjects developing RHL lesions during the study period, aiming for 326 evaluable subjects per treatment arm in each study.

Study sites: Twenty-two study sites were involved in ZOVA 3003, and 23 sites for ZOVA 3004. Three sites each enrolled 120 subjects. The applicant states that no trends were identified in the classification of protocol violations among study centers.

Comment: this information was shared with the Clinical Investigations Branch, HFD-47, who inspected these three sites. The inspectors found no serious protocol violations and the data appear to be acceptable from these three inspected sites.

Extent of exposure: The study subjects applied the cream five times per day for four days.

Study patients: Overall, 2090 patients were enrolled into ZOVA 3003 and ZOVA 3004. A total of 694 participants did not initiate study medication because they did not have an RHL lesion during the study period ("not-treated" population). There were no demographic differences between the intention-to-treat population and the not-treated population. There were fewer total episodes within the past year, fewer episodes preceded by prodrome and fewer episodes producing classical lesions in the not-treated population. There was a trend towards a higher mean age in the not-treated population, but this did not reach statistical significance.

Protocol violations were prospectively identified and included initiation of study medication at the healing stages, not returning to the study site within 24 hours, lost to follow up after initiating treatment, and non-compliance with dosing. Fifty-six participants in the Acyclovir arm and 45 participants in the vehicle control arm were listed as having protocol violations, the most common being non-compliance with dosing, either non-compliant dosing at 48 or 96 hours or stopping the study drug before the end of dosing. No difference in demographic characteristics was identified between the two groups of study patients with regard to protocol violations as shown in Table 2.

Table 2: Demographic Parameters
(ZOVA 3003 and 3004, ITT)

Parameter	Acyclovir 5% cream N=682	Vehicle Control N=703
Gender		
Female	515	506
Male	167	197
Race		
White	640	663
Non-white	42	40
Age, in years		
Mean	38.5	38.5
Median	38	38
Range	18-87	18-81
Median years with RHL infection	20	20
Median number of episodes of RHL in last 12 months	5.0	5.0
Median number of RHL episodes producing classical lesions in last 12 months	5.0	5.0

There were 682 participants in the acyclovir 5% arm and 703 in the vehicle control arm. The baseline characteristics of the study population did not differ between the study groups. About 75% of the study participants were white female patients, with less than 6% minority representation. The age ranges vary widely, with the overall mean of approximately 38 years.
The history of RHL, including the duration of RHL, number of lesions in the past year, percentage of lesions that were "classical", and percentage associated with a prodrome, were not different between the treatment groups as shown in Table 3. Additional demographic descriptions can be found in APPENDIX 1, Table A.1 and Figure A.1

Table 3: Current RHL Lesion Evaluation, ZOVA 3003 and 3004

	Acyclovir 5% cream	Vehicle control cream
Number of subjects with available data on RHL lesion	665	692
Mean time from screening to onset of RHL lesion	43.9 days	48.5 days
Mean time from onset of lesion to application of study medicine	0.66 hours	0.64 hours
Mean time from onset of lesion to clinic visit	5.6 hours	6.4 hours

Results: In ZOVA 3003, the mean duration of RHL episode for the intent-to-treat population was 4.4 days for the Acyclovir 5% group and 4.8 days for the vehicle cream group. In ZOVA 3004, the mean duration of RHL episode for the intent-to-treat population was 4.7 days for the Acyclovir 5% group and 5.2 days for the vehicle cream group. The sponsor reports a significant p-value for both studies utilizing a t-test for the difference in means between the two groups.

For the 74% of study subjects who developed a vesicle, the vesicle healing time was evaluated by the sponsor. The overall difference between the mean healing time in ZOVA 3003 was –0.5 days, 4.2 days in the acyclovir arm and 4.7 days for the vehicle control arm (p-value= 0.028, two sample t-test). Similarly, in ZOVA 3004 the overall difference in vesicle healing time was –0.5 days, 4.6 for the acyclovir arm and 5.1 for the vehicle control arm (p-value 0.016).
The duration of pain was analyzed in the two studies. The duration of pain was 0.3 days shorter in the acyclovir arm of ZOVA 3003 and 0.4 days shorter in the acyclovir arm of 3004.

6.1.2 Studies ZOVA 3001 and ZOVA 3002

Both studies entitled "A multicenter, placebo-controlled evaluation of acyclovir cream for abortion of herpes simplex labialis lesions" were identical studies conducted by different sets of investigators. ZOVA 3001 and 3002 were to be used to

studies ZOVA 3001 and 3002 had as their primary endpoint the proportion of subjects with aborted lesions. Duration of the recurrent herpes labialis lesion was a secondary endpoint. Study subjects were instructed to initiate application of the study drug at the first indication, or prodrome, of a RHL lesion before the development of clinical signs of the lesion. Otherwise, studies ZOVA 3001, 3002, 3003, and 3004 were conducted in an identical manner with the collection of the same information about duration of healing. Although the results of ZOVA 3001 and 3002

, the studies contribute important safety as well as efficacy data. The applicant did not formally submit the efficacy results of ZOVA 3001 and 3002 to the NDA.

The sample size calculation assumed that false prodromes occur in 20% of study participants, and therefore the observed prevention rate is 20% higher than the actual prevention rate. The applicant used historical prevention data that a prevention rate of 60% would be anticipated in the acyclovir 5% arm, while the vehicle control arm would achieve up to a 40% prevention rate. Using an α of 0.05, a β of 0.20, and 5% of subjects lost to follow up, the sponsor estimates a sample size of 195 subjects per treatment arm. The applicant planned to enroll at least 600 subjects to ensure that 390 would develop a recurrent herpes labialis prodrome. The efficacy endpoint was the vesicle formation and the statistical analyses examined the proportion of subjects who failed to form a vesicle.

Study Population: A total of 1234 subjects were screened for both protocols, 14 were screen failures and therefore 1220 subjects were enrolled and randomized. Of the 367 study subjects who did not initiate therapy, most did not experience a lesion during the study period and returned unused study medications. Eighty-eight (7%) subjects developed a recurrent herpes labialis lesion, but could not attend clinic visits. Only 22 (2%) participants dropped out of the study without

returning study medications. Seventy-two (6%) subjects were prematurely withdrawn from the study and were listed as "other reasons". Only one stopped due to an adverse event.

Protocol violations were observed in 142 (12%) subjects: most initiated therapy after the papule stage, stopped study drug before the end of dosing, or were lost to follow up. These patients were included in the intent-to-treat analysis, and excluded from the applicant's evaluable patient population analysis.

The studies enrolled primarily white females, who comprised approximately 75% of the study population. The mean age was about 38 years. There were no significant differences in baseline characteristics between the treatment groups. As one might expect, those who did not experience an RHL lesion during the study had fewer reported episodes in the past 12 months. Over 90% of subjects were compliant with at least 16 study drug applications.

Results:

6.1.3 Integrated Efficacy Profile, Biometrics and Clinical Review Controlled clinical trials ZOVA 3001, 3002, 3003, 3004:

The following is a summary of FDA's statistical analyses. For a complete statistical review, please refer to Appendix 1.

Because ZOVA 3001, 3002, 3003, and 3004 were conducted in an identical fashion, the clinician assessed RHL episode duration may be assumed to be an endpoint for consideration in a pooled analysis. As such, the pooled data by the review teams is shown in Tables 4 and 5 below. Figures A.2 through A.6 in APPENDIX 1 show the distribution of time to healing among the four studies, and Table A.2 in APPENDIX 1 shows a supplemental endpoint review for combined data from ZOVA 3003 and 3004.

Table 4: Primary Efficacy Variable
(ZOVA 3001, 3002, 3003 and 3004)

Protocol	Treatment	Mean	Min	Max	Median	95% CI for the Mean
ZOVA3001						
ZOVA3001						
ZOVA3002						
ZOVA3002						
ZOVA3003	PLA	4.81	0.25	13.43	4.19	(4.56, 5.06)
ZOVA3003	ZOV	4.38	0.64	13.11	3.96	(4.14, 4.61)
ZOVA3004	PLA	5.20	0.58	14.99	4.51	(4.92, 5.49)
ZOVA3004	ZOV	4.74	0.29	15.01	4.13	(4.49, 4.99)
ZOVAALL						
ZOVAALL						

Note the mean time to healing for the vehicle control arms is approximately 5 days, which is relatively low in comparison to time to healing without treatment ("historical controls"). Therefore, the vehicle may be exerting a beneficial effect.

Table 5: Difference in Clinician Assessed Time to Healing
(ZOVA 3001, 3002, 3003, and 3004)

Protocol	Difference (Mean placebo-Mean Zovirax)	p-value (t-test)	95% Confidence Interval For Difference of Means
ZOVA3001			
ZOVA3002			
ZOVA3003	0.43456002	0.0135	(0.0902, 0.7789)
ZOVA3004	0.45998348	0.0176	(0.0804, 0.8396)
ZOVAALL			

When the data from all four studies are combined, the treatment effect is statistically significant at the 0.00125 level indicating that a true difference, albeit modest, is likely to exist for acyclovir 5% cream.

Non-parametric analyses to test the robustness of the data were performed. A Kaplan-Meier time to event (the event being in this case the clinician-assessed time to healing) analysis describes the difference between the two treatment arms. A Mann-Whitney test, comparing distributions of the time to healing in the two treatment arms, was also performed. Table 6 shows the results of these nonparametric analyses. All p-values for studies ZOVA 3003 and 3004 reach the significance level of 0.05 and demonstrate the superiority of the Zovirax arm. The p-values for the pooled results of the 4 studies combined were statistically significant or very close to being statistically significant at the 0.00125 level.

Table 6: Nonparametric Analyses
(ZOVA 3001, 3002, 3003, and 3004)

Protocol	Mann-Whitney p-value	K-M logrank p-value	K-M Wilcoxon p-value
ZOVA3001			
ZOVA3002			
ZOVA3003	0.0140	0.0085	0.0139
ZOVA3004	0.0462	0.0120	0.0461
ZOVAALL			

Biometrics Comments:

- Treatment effects favored Zovirax in all 4 studies, and there was no statistical evidence of a treatment by study interaction.

- Given the small size of the treatment effect as measured by the primary efficacy variable, no subgroup analysis can produce remarkable findings, unless the difference between subgroups is very large. See Subgroup Analyses, starting with Table A.7 in APPENDIX 1.

- The clinician assessment of time to healing is unlikely to be so precise that values of 4.1 or 7.2 days are accurate. In order to test that no bias was hidden in the fractional part of the data, we re-analyzed the integer part of the time to healing. The results were similar to the original findings.

- A secondary efficacy analysis was done based on the duration of pain. The mean duration of pain appears to be reduced by less than half a day. Tables A.4 and A.5 in APPENDIX 1 show the difference of the means, the p-value yielded by the t-test, and the confidence intervals for the means.

- The nonparametric tests show results consistent with the ones for the primary efficacy variable.

Clinical Comments:

- The results of ZOVA 3001 and 3002 [redacted]

It appears that the above explanations would argue against the inclusion of efficacy data from studies ZOVA 3001 and 3002 in the pooled analysis. Nevertheless, with the inclusion of all participants in controlled clinical trials, we still conclude that a difference of approximately 0.4 days is a statistically meaningful difference that approaches "one-half day" of benefit.

- The data from studies ZOVA 3003 and ZOVA 3004 do not appear normally distributed. (See Figures A.2 to A.6 in APPENDIX 1) Therefore, additional nonparametric analyses may provide more statistically meaningful information. As such, converting the data to the dichotomous variable, healed or not healed at day 4, may be useful because the application of the product was for four days total. An assumption is made that no benefit is being obtained for the participants who did not heal by day four. For purposes of demonstrating another type of treatment effect, this type of analysis was done and again demonstrates the modest treatment benefit in favor of acyclovir 5% cream. (See Tables A.6 in APPENDIX 1)

- Even if one were to view these as studies utilizing an active-control arm (vehicle cream), the acyclovir 5% cream still results in a statistically significant difference. Therefore, we conclude that the results of this study show the modest treatment benefit of acyclovir 5% cream.

6.2 Integrated Safety Profile, ZOVA 3001, 3002, 3003, and 3004:

The most frequent adverse events were local site reactions, such as peeling, burning, dryness, or tingling on the lips near the site of study drug application. These adverse events occurred in 4.5% of study participants randomized to Acyclovir 5%, and 3.7% of participants randomized to vehicle control. The local reactions were classified as mild to moderate. Four study participants receiving acyclovir discontinued study due to adverse events. Of these 4 cases, one each reported local irritation, pruritis, and swollen lips and all were assessed as possibly related to study drug. The fourth case report was development of chest pain which was felt by the investigator to be unrelated to study medication.

Headache occurred in approximately 2% of study participants overall. There were no deaths in the studies. Other reported adverse events included cold and influenza-like symptoms, sinus headache, sore throat, gastrointestinal complaints, and arthralgias, which occurred in less than 1% of study participants. Overall, approximately 85% of study participants did not report an adverse event.

Table 7: Local Adverse Events
(ZOVA 3001, 3002, 3003, and 3004)

Adverse Event	Acyclovir 5% cream N=1100	Placebo vehicle control N=1138
Dry lips	10	4
Cracked lips	6	6
Irritation of lips	1	0
Edema of lip	1	1
Lip disorder	2	1
Erythema of lip	1	0
Oral and circumoral paresthesias/numbness	4	2
Tingling	2	1
Burning skin	8	7
Stinging skin	4	1
Pruritis	7	5
Desquamation	8	3
Flakiness of skin	5	8
Cracked/chapped skin	1	1
Dry skin	8	3
Rash	2	2
Painful skin	1	0
Contact dermatitis	0	1
Taste alterations	1	2
Total number with local adverse events*	**50 (4.5%)**	**42 (3.7%)**

*Study participants who reported more than one local adverse event were counted only once to arrive at the total number.

Safety Conclusions:

Phase I and II studies have demonstrated that the vehicle control cream and Acyclovir 5% cream both have potential to cause skin irritation. The safety profile observed in studies ZOVA 3001-3004 do not suggest a worsening severity of local skin site reactions with the application of acyclovir 5% cream. In general, the application of acyclovir 5% cream was well tolerated for the majority of study participants. In fact, study participants randomized to acyclovir 5% cream had a faster time to cessation of pain in comparison to vehicle control. Therefore, the product does not appear to worsen the clinical symptoms of a herpes labialis lesion. The patient who stopped treatment prematurely because of local site irritation was judged to have healed the day previously. The irritation potential for this cream likely contributed to the adverse event and the product should be applied only to the affected area. Headache was also a frequently reported adverse event and occurred in 2% or less of the study participants overall. Nausea or vomiting occurred in less than 1% of study participants. There were miscellaneous adverse events that were likely not associated with administration of the study drug, including symptoms resulting from influenza or other viral illness. In summary, the safety of this product does not appear to be problematic for prescription use when applied directly to the lesion. Product labeling should reflect that acyclovir 5% cream is not intended for use on intact skin and is not indicated for use in the prevention of herpes labialis.

6.3 Supportive Non-Registrational Trials

6.3.1 Study ZOVA 3005

"A multi-center, open-labeled evaluation of the safety of Acyclovir (acyclovir) 5% cream for the treatment of recurrent herpes labialis infections in an adolescent (12-17 years of age) population."

Objectives and Study Design: This was an open-label study with the primary objective of the collection of adverse events with open label use of the product in an adolescent population.

Study Population: The protocol investigators enrolled adolescents seeking care for recurrent herpes labialis lesions. The applicant aimed for enrollment of approximately 100 adolescents, who had an established diagnosis of recurrent herpes labialis and were otherwise healthy. Culture confirmation of herpes simplex was not required.

Treatments Administered: Each subject applied acyclovir 5% Cream to the herpes labialis lesion five times per day for four days. The subjects returned to the study site on a daily basis for collection of adverse event information.

Study Results/Safety Conclusions:
The study enrolled 113 adolescents ages 12-17, with an equal distribution of ages. The mean number of years since the first infection with herpes labialis was 6.9 years. There were more females (58%) than males. 96% of subjects were fully compliant with all 20 applications. No serious adverse events were noted in this study. Four percent of subjects had mild to moderate local site reactions, which was similar to that found in adults.

Clinical Comments:

- The study demonstrates that the safety profile of acyclovir 5% cream in adolescents is similar to adults.

- The study collected no efficacy data, and time to healing for this group of adolescents is unknown. We nevertheless expect recurrent herpes labialis lesions to respond similarly to acyclovir 5% cream in an adolescent population, and can extrapolate from the adult population.

6.3.2 Additional Safety Studies:

ZOVA 1002
"A single-center, single-blind, controlled evaluation of the primary irritation potential of acyclovir cream 5% in normal healthy subjects"

This study enrolled 22 subjects. Acyclovir 5% cream, vehicle cream, sodium lauryl sulfate 0.05% controls, and saline controls were placed on the skin of the back of each subject using occluded and "semi-occluded" patches and left on for a two-day period. The skin sites were evaluated at 24 and 48 hours. At both 24 and 48 hours, over 90% of the study subjects had mild to moderate irritation of the skin site after removal of the semi-occluded patch; 77% showed moderate irritation. The occluded patch yielded mild to moderate irritation in 82% of subjects at 48 hours. The sodium lauryl sulfate 0.05% control acted similarly, with 90% of study subjects experiencing mild to moderate irritation at 48 hours. The results of this study demonstrated a high dermal irritation potential for acyclovir 5% cream and its vehicle control.

ZOVA 1003
"A single-center, single-blind, controlled evaluation of the contact sensitization potential of acyclovir cream 5% in healthy subjects using the Draize Modification of the Human Repeated Insult Patch Test."

The primary objective of the study was to evaluate the potential for acyclovir 5% cream and the vehicle control cream to cause sensitization. The "reporting of any noted irritation" was a primary endpoint and reporting of adverse events was a secondary endpoint. The Draize procedure involved repeated application of a series of occlusive patches to a single skin site for three weeks, followed by a two-week rest period, then a challenge application of test substance at a new site. The modified procedure permitted changing application sites of the serial occlusive patches. The study used the modified procedure because of the high dermal irritation of acyclovir 5% cream and its vehicle. Each study subject received both acyclovir 5% cream and vehicle control cream applied via occlusive patch three times per week for three weeks (nine repetitive applications). The patch was applied by study personnel and removed by the subjects after 24 hours. A blinded evaluator scored the skin site reactions at the time of the subsequent visit. The study enrolled healthy adults. Women of child bearing potential were included if a pregnancy test was negative. Subjects were excluded if they were using anti-inflammatory medications, antihistamines, or dermatological creams.

Two-hundred-two (202) subjects completed the study. During the course of the repeated occlusive patch applications, 77% of subjects required a move to at least one new skin site due to moderate or severe skin site reactions. Overall, 41% required two new skin sites (a total of three sites for application of the occlusive patches) due to moderate or severe skin site reactions at the original site and the first move site. For nearly all of the study subjects, the skin site inflammatory scores (1=mild, 2=moderate, 3-severe) were identical for both the acyclovir 5% cream and vehicle control. The applicant reports that four (2%) subjects demonstrated contact hypersensitivity to the application of both acyclovir 5% and vehicle control after the two-week rest period. A review of the

data's line listings show that 17 (8%) demonstrated moderate or severe irritation scores to the application of either acyclovir 5% or vehicle cream or both after the two week rest period.

The self-reporting of adverse events by the study subjects were all related to the application of study drug, and included itching, rash, or burning sensation of skin at the site of application. These adverse events were reported for 30 (15%) of the study subjects.

Clinical Comments:

ZOVA 1003 demonstrated the high dermal irritation potential for acyclovir 5% cream and its vehicle when applied to healthy skin under exaggerated exposures. An unusually high rate of contact sensitization of acyclovir 5% cream was observed in this study. Such information should be included into the label to warn against the application of the product to healthy skin.

6.3.3 Study ZOVA 4001

"Evaluation of Acyclovir 5% cream in subjects with recurrent herpes labialis (RHL)"

This was a phase 4, single-center, double blinded study conducted in Europe. The primary objective of the study was to determine the proportion with aborted RHL vesicles. Secondary objectives included the comparison of the staging of lesions via thermographic imaging techniques. The study enrolled adults with RHL who were otherwise healthy. Over two hundred subjects were screened for enrollment, and 47 developed a prodrome of an RHL lesion, documented by thermographic imaging to minimize false prodromes, for inclusion into the study. Thermographic imaging and clinical staging of the lesions were done at daily visits to the study center. Subjects were randomized to either acyclovir 5% cream or vehicle control with application of the cream five times per day for five days.

Twenty four were randomized to the acyclovir 5% arm, and 23 to the vehicle arm. The prevention of a vesicle occurred in — in the acyclovir arm and — in the vehicle arm, which did not represent a statistically significant difference. The clinician-assessed time to healing of the RHL lesions was — hours for acyclovir 5% and — hours for vehicle control. Viral cultures and herpes simplex PCR were obtained from the affected area on a daily basis. The only difference was observed at the 24 hour visit:

Table 8: Virologic Data, Study ZOVA 4001

	Proportion with positive HSV viral culture (%)	Proportion with HSV identified by PCR (%)
Acyclovir 5% cream	29	33
Vehicle	39	52

No differences in these virologic endpoints were observed between the two arms at other time points in the study. The HSV killing effect of acyclovir is expected to be the highest during the first 24 hours which explains why timepoints after 24 hours showed no differences in virologic endpoints.

Five subjects (11%) reported local irritation adverse events during the study, such as erythema and stinging.

Clinical Comments:

This study is not large enough to draw significant efficacy conclusions. The trends, however, are similar to the larger phase III studies showing a shorter average time to healing in the acyclovir 5% arm. The types of reported adverse events are similar to those reported in the larger phase 3 studies.

While the phase III pivotal studies did not collect virologic information to prove that herpes simplex, the virus responsible for herpes labialis, was the causative agent, it is reassuring that at least one study in this NDA application has collected virologic information to ensure that herpes simplex is the virus being treated with this product. The design of the phase 3 studies ZOVA 3003 and 3004 mimic what is done in a clinical setting, where most often viral cultures are not obtained. Given that the enrollment was based on clinical diagnosis without virologic confirmation, the statistically significant difference in favor of acyclovir cream in a likely 'diluted' HSV-infected population further strengthens the conclusion of the effectiveness of acyclovir treatment.

6.3.4 Other studies:

Study by Shaw, et al, "Trial of topical acyclovir 5% (AMC-P) cream in herpes labialis", used a very similar study design to The difference is that Shaw collected baseline time to healing for subjects presenting for inclusion into the study. All subjects were required to have culture-positive herpes simplex from this initial lesion. The next two subsequent RHL lesions would be treated, in a randomized fashion, with either acyclovir 5% cream or vehicle control. The median time to healing for the initial episode in 72 subjects, without application of study medications, was 13 days. The median time to healing was 9 days when using acyclovir 5% and 10 days when using vehicle control. This study showed a treatment benefit of acyclovir 5% when compared to no treatment, a median of 9 days versus 13 days, respectively, and also showed a treatment benefit for the vehicle control, 10 days versus 13 days.

Clinical Comment:

The results of this study show that the vehicle control and acyclovir 5% cream demonstrated similar treatment benefits. Therefore, the vehicle may be contributing to the clinical benefits. However, a modest treatment benefit in favor of acyclovir 5% cream is demonstrated in this study as well as studies ZOVA 3003 and 3004.

Other Studies:

There were additional small studies, and Gibson, et al., which demonstrated a modest benefit to acyclovir 5% cream for the treatment of RHL.

small safety studies, Klaher-Gibson,et al., Fawcett, et al., found local skin site irritation to be the most common adverse events associated with the use of acyclovir 5% cream.

7. Geriatric Evaluation:

Studies 3001, 3002, 3003, and 3004 enrolled a total of 101 study participants aged 65 or greater. There are too few numbers of patients to demonstrate differences in time to healing because of the large variation in the times. The safety data show that local skin site reactions occurred in 3% of geriatric subjects from these studies. Overall, 88% of geriatric subjects did not report an adverse event. In comparison, approximately 85% of total study subjects did not report an adverse event. The safety profile for a geriatric population does not appear to differ from the general population.

8. Pediatric Evaluation:

While the results from an adolescent safety study, ZOVA 3005 support the safety of acyclovir 5% cream in children between 12 and 17 years of age, there has been no safety information in children less than 12 years of age. During the original NDA review, the Division recommended a safety study of a minimum of 100 children 6 to 12 years of age. A lower limit of 6 years was chosen because children younger than 6 years of age would not be practical to the topical application of medication. However, no agreement between the Division and the applicant was reached on this issue due in part to the prospective corporate merger. During the review of the present resubmission, the issue of safety study in younger children was revisited. Because RHL in children of less than 12 years of age are rarely treated in clinical practice, the pediatricians in the Division agree that the requirement of a safety study in children between 6-12 years old may not be warranted. Prior to the submission of this application, a similar determination had been made for Valtrex.

9. Financial Disclosure Information:

One investigator, a former employee of the applicant, disclosed financial holdings in a retirement account originally established by the applicant. This investigator enrolled 77 (3%) subjects in studies ZOVA 3002 and 3004. The time to healing reported by the investigator was 4.1 days for the acyclovir 5% group and 4.4 days for the vehicle control group. Removing the 77 subjects from the analysis did not change the results of the study.

10. Overall Efficacy Conclusions:

The application of acyclovir 5% cream to herpes labialis provides a modest benefit in comparison to vehicle control cream. The modest treatment benefit was statistically significant for studies ZOVA 3003 and 3004 that were designed to examine the endpoint of time to healing of a RHL lesion. Summaries from additional studies, which were used as registrational studies in European countries, also demonstrated a modest treatment benefit in favor of acyclovir 5% cream. One useful aspect of these studies is the incorporation of time to healing without application of either the product or the vehicle control. The observation of shorter time to healing associated with the application vehicle control in these studies highlights the difficulties in interpreting the results of trials ZOVA 3003 and 3004, which utilized a vehicle control for comparison. Even if the vehicle control is considered an "active control", the results of ZOVA 3003 and 3004 represent a modest benefit in favor of acyclovir 5% cream that is statistically significant. The average time to healing of approximately 5 days in the registrational studies appears to be much faster than the reported time to healing based on previous observation of recurrent herpes labialis. This again suggests that the vehicle control may be providing some benefit to the healing of a RHL lesion.

Acyclovir 5% cream did not prevent RHL lesions, and studies ZOVA 3001 and 3002 did not show a significant treatment benefit in time to healing. The dermal irritation potential of acyclovir 5% cream when applied to intact skin may have resulted in the failure to demonstrate efficacy for the prevention of RHL lesions.

11. Overall Safety Conclusions:

Local irritation has emerged as a consistent adverse event associated with acyclovir 5% cream, occurring in about 4% of participants enrolled in clinical trials. These local reactions include erythema, burning sensation, dry skin, peeling skin, and pruritis. The vast majority of these adverse reactions were reported to be resolved in a short period of time after discontinuing the study medication. In addition, the RHL lesion itself may be giving rise to the local irritation reactions. However, it is clear from the additional phase 2 studies performed that the vehicle is a dermal irritant. The application of the cream to healthy skin under exaggerated conditions causes moderate irritation in a majority of patients. It should also be noted that the product has been approved for marketing internationally with over 10 years of post-marketing safety experience. Serious adverse events have not been reported with great frequency. An important safety concern is the dermal irritation when applied to healthy skin and should be emphasized in product labeling.

12. Package Insert:

12.1 Safety Update

The only new information included in this resubmission is a safety update. This update report includes all reports to the GSK spontaneous adverse event database for topical acyclovir (cream and ointment) during the period July 1999 through 31 December 2001.

There were 124 spontaneously reported adverse events for Zovirax 5% cream during this period. The majority of these events were local application-site reactions including signs and symptoms of inflammation, eczema, and cracked and dry lips. There were 8 reports of burning sensation in eyes all described as medication errors.

There were 12 cases of serious adverse events with 5% cream during the time period covered by the update. These 12 cases included reports of anaphylaxis (1), neutropenia (1), leukocytoclastic vasculitis (1), and erythema multiforme (1). The other 8 reports involved contact dermatitis and/or eczema, pruritis, rash and pain. Seven of the 8 cases required hospitalization.

There were 71 spontaneously reported adverse events for Zovirax 5% ointment during this update period. As was observed with the cream formulation, many of these cases involved local application-site reactions including signs and symptoms of inflammation. There were 3 reports of burning sensation in eyes described as medication error.

There were 7 cases of serious adverse events with Zovirax 5% ointment during the period of this update. These 7 cases included reports of eye irritation due to medication error (2), general disorders (5) (4 of 5 these subjects received concomitant systemic medications.)

12.2 Hypersensitivity/Contact dermatitis

Hypersensitivity[3] was first observed in ZOVA1003 study designed to evaluate the potential for hypersensitivity to Zovirax 5% cream in healthy subjects. (Please refer to Section 6.3.2 of this review.) Under the exaggerated use conditions, 2% (n=4) subjects exhibited a reaction to both Zovirax 5% cream and vehicle treatment indicative of a sensitization reaction. However, the incidence of hypersensitivity was not observed in other clinical studies including both treatment use (5 times daily for 4 days) and repeated use of the product (4 times daily for 32 weeks for prophylaxis.[4])

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[3] Hypersensitivy reactions were defined as edema of face, angioneurotic edema, eczema, contact dermatitis, peri-orbital edema., some were tested with cutaneous patch test with Zovirax cream.

[4] Gibson, JR et al: Prophylaxis against Herpes labialis with acyclovir cream-a placebo-controlled study. Dermatologica 1986; 172: 104-107.
Fawcett, HA et al: Prophylactic topical acyclovir for frequent recurrent herpes simplex infection with and without erythema multiforme. Br. Med J 1983; 287: 798-799.

Of the 942 spontaneous adverse experience reports reported with Zovirax 5% cream during the period of April 1996 to December 2001, 57 were identified as serious possible hypersensitivity cases. Most of the cases involved skin reactions (rash, contact dermatitis, erythema, eczema); some cases involved other body systems (angioneurotic edema, anaphylactoid reactions, and dysphagia). A positive cutaneous test to either acyclovir or the excipients in Zovirax cream was positive in 30 instances.

Because spontaneous reports are made voluntarily from a population of unknown size, an estimate of the frequency of hypersensitivity event can not be made. Given the fact that more than 200 million packs of Zovirax cream have been distributed internationally since product introduction, the number of hypersensitivity cases associated with Zovirax cream (or its excipients) is concluded as a rare adverse event.

13. **Labeling Comments:**

- Incidents of medication errors, though rare, were reported in subjects who had applied Zovirax 5% cream to areas such as eye, genital area, or other mucous areas resulting in local site irritation reactions. We therefore recommend that a prominent display of 'for cold sores only' be incorporated in Zovirax's package insert, the 2-g tube, and its packaging box.

- Under Precautions, General,

- Lines 160, 161. The sponsor should clarify the sentence,

- Before line Insert '

Delete the sentence " an additional study....".

- After line insert " The sensitizing ingredient (s) has not been identified.

- Patients should be informed that Zovirax 5% cream is not a cure for cold sores. (to be consistent with Valtrex labeling)

- Delete lines 153, 154 because this paragraph does not provide added information to Table 1.

- Delete [redacted] and describe the results in text.

14. Recommended Regulatory Action:

The reviewers recommend that Zovirax 5% Cold Sore Cream for the treatment of recurrent herpes labialis in adolescents and adults be approved.

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Mathematical Statistician, DAVDP

Concurrences:
Katie Laessig, M.D.
Team Leader, DAVDP

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Team Leader, DAVDP

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Division Director, DAVDP

CC:
Orig NDA
HFD-340
HFD-530:
MO/WuT
Chem/Gu
Micro/Biswal
Biopharm/Reynolds
Pharm/Bigger
Biometrics/SmithF
/AnelloC
/HuqueM
/Soon
PM/Belouin

APPENDIX 1

Table A.1 Age distribution for studies ZOVA 3001-3004

Protocol	Treatment	Mean	Min	Max
ZOVA3001	PLA	39.273631841	18	82
ZOVA3001	ZOV	40.886363636	19	74
ZOVA3002	PLA	37.837606838	18	77
ZOVA3002	ZOV	37.833333333	18	71
ZOVA3003	PLA	38.536931818	18	81
ZOVA3003	ZOV	38.571856287	18	79
ZOVA3004	PLA	38.515669516	18	74
ZOVA3004	ZOV	38.548850575	18	87
ZOVA_ALL	PLA	38.516695958	18	82
ZOVA_ALL	ZOV	38.894545455	18	87

Figure A.1, Age distribution of combined ZOVA 3001-3004:

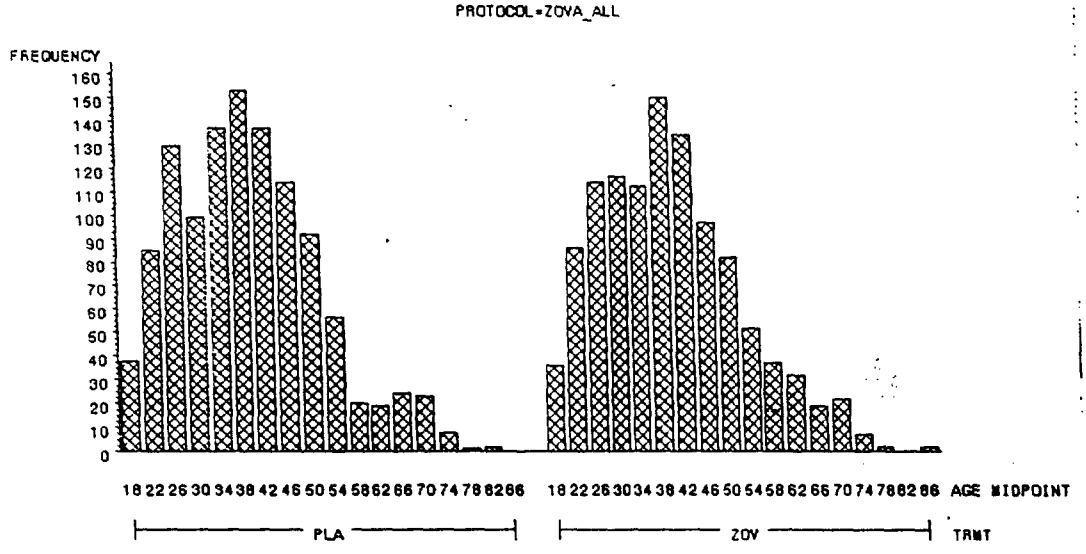

Figure A.2: Distribution of Time to Healing ZOVA 3001

Figure A.3: Distribution of Time to Healing ZOVA 3002

Figure A.4: Distribution of Time to Healing ZOVA 3003

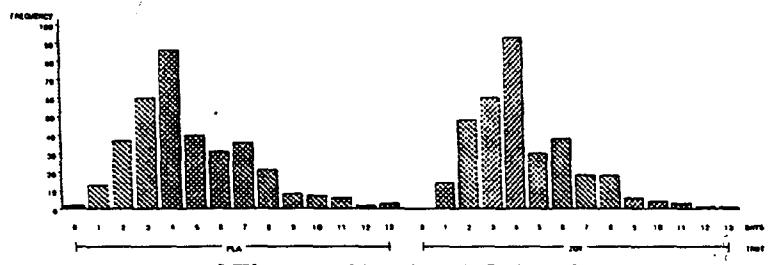

Figure A.5: Distribution of Time to Healing ZOVA 3004

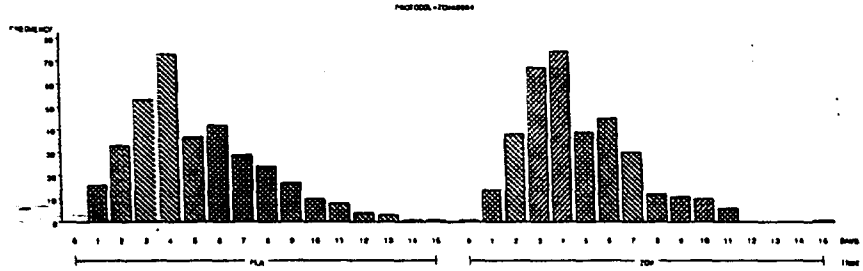

Figure A.6: Distribution of Time to Healing Combined ZOVA 3001-3004

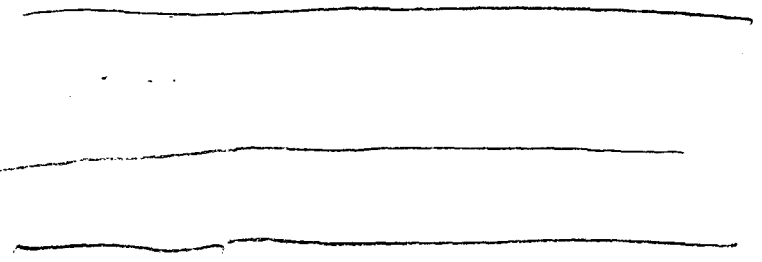

Table A.2: Supplemental summary of the sponsor's statistical analysis of efficacy, Medical Officer Review of combined ZOVA 3003 and 3004:

Parameter	ZOVA 3003	ZOVA 3004	Combined 3003/3004#
Duration of RHL lesion, Acyclovir	4.4 days	4.7 days	4.56 days
Duration of RHL lesion, vehicle control	4.8 days	5.2 days	5.00 days
Difference* in duration of RHL	0.4 days	0.5 days	0.44 days
==========	======	======	======
Vesicle healing time, Acyclovir	4.2 days	4.6 days	4.46 days
Vesicle healing time, vehicle control	4.7 days	5.1 days	4.92 days
Difference* in duration of vesicle healing time	0.5 days	0.5 days	0.46 days
==========	======	======	======
Duration of pain, Acyclovir	2.9 days	3.1 days	3.0 days
Duration of pain, vehicle control	3.2 days	3.5 days	3.4 days
Difference* in duration of pain	0.3 days	0.4 days	0.4 days

data from combined studies derived from electronic datasets submitted by the applicant

*all p-values < 0.05 (for two sample t-test for the difference in mean days)

Table A.3: Imputation Strategy for Missing Values

Populations	Duration of RHL Episode Vesicle Healing Time	No. patients Placebo arm/ No. patients Zovirax arm			
		3001	**3002**	**3003**	**3004**
ITT with complete data	Data	181 / 192	201 / 179	312 / 275	328 / 283
ITT with incomplete data	Assigned 3rd Quartile (75th Percentile) without regard to treatment	11 / 15 3rd Q= 5.52 days	18 / 13 3rd Q= 6.86 days	6 / 10 3rd Q= 5.87 days	8 / 20 3rd Q= 6.49 days
ITT with no data	Assigned 2nd Quartile (50th Percentile) without regard to treatment	0 / 0	0 / 0	0 / 0	0 / 0

Figure A.7 to A.11 show the survival curves for the four studies and for all the combined data.

Figure A.7: ZOVA 3001

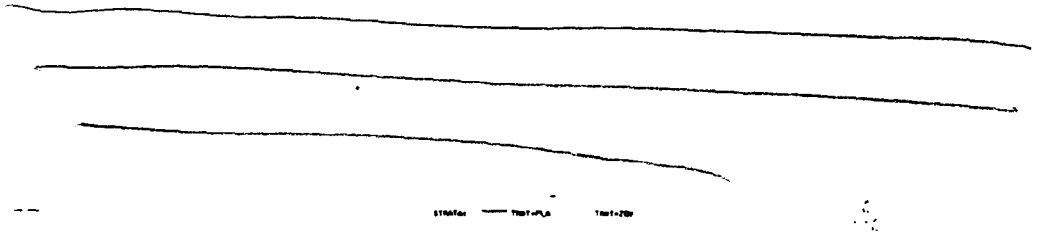

Figure A.8: ZOVA 3002

Figure A.9: ZOVA 3003

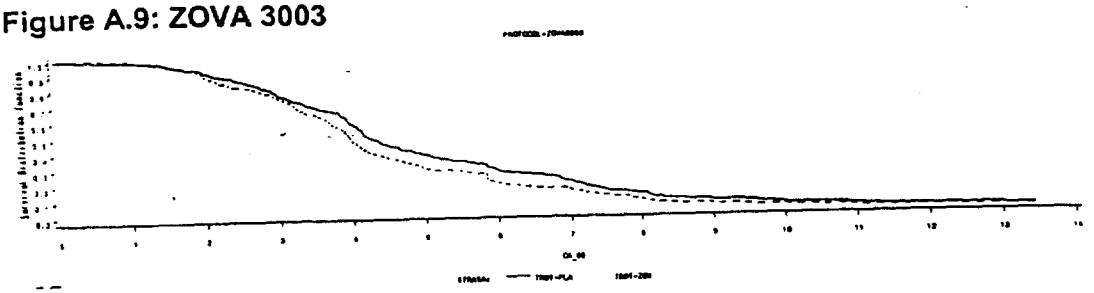

Figure A.10: ZOVA 3004

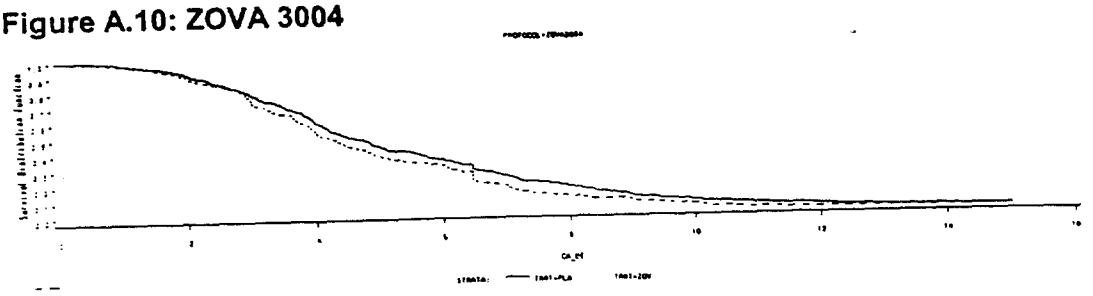

Figure A.11: Combined ZOVA 3001-3004

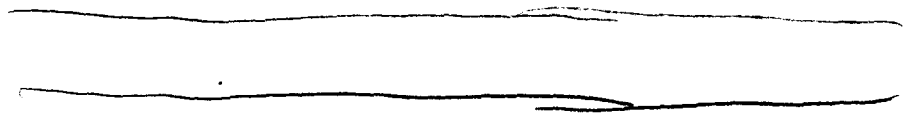

Table A.4: Duration of Pain, Studies ZOVA 3001-3004

Protocol	Treat - ment	Mean	Min	Max	95% CI for the Mean
ZOVA3001	PLA				
ZOVA3001	ZOV				
ZOVA3002	PLA				
ZOVA3002	ZOV				
ZOVA3003	PLA	3.2481060606			(3.00, 3.50)
ZOVA3003	ZOV	2.8607493347			(2.63, 3.09)
ZOVA3004	PLA	3.5483469848			(3.26, 3.83)
ZOVA3004	ZOV	3.1299608876			(2.90, 3.36)
ZOVAALL	PLA				
ZOVAALL	ZOV				

The mean duration of pain appears to be reduced by less than half a day. The Table A.4 shows the difference of the means and the p-value yielded by the t-test. Confidence intervals for the mean are also listed. The nonparametric tests show results consistent with the ones for the primary efficacy variable.

Table A.5: Difference in Duration of Pain, Studies ZOVA 3001-3004

Protocol	Difference (Mean. placebo-Mean Zovirax)	p-value (t-test)	95% Confidence Interval For Difference of Means
ZOVA3001			
ZOVA3002			
ZOVA3003	0.38735673	0.0239	(0.0515, 0.7233)
ZOVA3004	0.41838610	0.0255	(0.0513, 0.7854)
ZOVAALL			

Table A.6

Healed at or before day 4, ZOVA 3003

	YES	NO	
Acyclovir 5%	193	131	324
Vehicle control	155	191	346
	348	322	670

X^2= 14.62, p=0.000

Healed at or before day 4, ZOVA 3004

	YES	NO	
Acyclovir 5%	167	181	348
Vehicle control	144	207	351
	311	388	699

X^2= 3.43, p=0.064

Healed at or before day 4, Combined ZOVA 3003 and 3004

	YES	NO	
Acyclovir 5%	360	312	672
Vehicle control	299	398	697
	659	710	1369

X^2= 15.6, p=0.000

Subgroup Analyses:

Table A.7: The clinician-assessed episode duration between those with compliance versus those not compliant with therapy: Compliance defined as greater than or equal application of 16 doses in 4 days

	Acyclovir 5% cream	Vehicle control
Compliant	4.5 days (n=648)	5.0 days (n=682)
Non-compliant	5.7 days (n=34)	4.9 days (n=21)

Male patients in ZOVA 3003, a total of 177 with 83 in the Acyclovir 5% group averaged 4.2 days to healing and 94 in the vehicle control group averaged 5.3 days to healing, for a difference of –1.1 (pvalue=. 0012, two sample t-test). This larger difference did not hold for male patients in ZOVA 3004, with 187 subjects demonstrating a 0.5 day difference in duration of RHL episode. Pooling the results of both studies, there is a 0.79 day difference in duration of RHL lesions for male participants in favor of acyclovir 5% cream, which is similar to the total population of study participants.

Separating the analysis on White and Non-White patients we see no treatment effect in the Non-White group. This may be due to the fact that racial minorities were not properly represented in the trial cohorts. There was no notable difference based on gender or interaction between gender and treatment. Given the small size of the treatment effect as measured by the primary efficacy variable, no subgroup analysis can produce remarkable findings, unless the difference between subgroups is very large.

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