COMBINED CLINICAL and BIOSTATISTICS REVIEW

Application Type	NDA
Submission Number	22-436
Submission Code	N000
Letter Date	September 30, 2008
Stamp Date	October 1, 2008
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Clinical Reviewer Name	Kirk M. Chan-Tack, MD
Biostatistics Reviewer Name	Susan Zhou, PhD
Review Completion Date	June 29, 2009
Generic Name	Acyclovir 5% and Hydrocortisone 1% cream
Proposed Trade Name	Pending
Therapeutic Class	Antiviral/anti-inflammatory
Applicant	Medivir
Priority Designation	S
Formulation	Topical cream
Dosing Regimen	Five times per day for 5 days
Indication	Treatment of recurrent herpes labialis
Intended Population	Immunocompetent adults and adolescents (12 years of age and older)

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

Approval of this NDA is recommended. The efficacy and safety data presented in this submission support ME-609 (5% acyclovir and 1% hydrocortisone) cream for early treatment of signs and symptoms of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores in adults and adolescents 12 years of age and older.

The application includes three phase 3 trials. The efficacy and safety data from Study 609-04 are presented in support of ME-609 in adults. Study 609-06 provides additional safety data in immunocompromised adults. The safety data from Study 609-07 are presented in support of ME-609 in adolescents. Extrapolation of efficacy for ME-609 in adolescents is considered reasonable based on the available data since the course of recurrent herpes labialis and the effects of ME-609 are sufficiently similar in adults and adolescents.

In Study 609-04, ME-609 was superior to both placebo and acyclovir for reducing the incidence of ulcerative herpes lesions. Although the difference between ME-609 and acyclovir did not meet the predefined statistical significance level for demonstrating efficacy in a single registration study, evaluation of the totality of evidence regarding efficacy showed consistent benefit across subpopulations.

1.2 Risk Benefit Analysis

Overall, ME-609 cream appears tolerable for the proposed treatment dose and duration. No new or unexpected toxicities were observed with ME-609 cream compared to available safety data on its two approved principal constituents, 5% acyclovir cream and 1% hydrocortisone cream. Overall, the adverse event profile of ME-609 in adolescents was similar to adults. Additionally, the adverse event profile of ME-609 in a selected population of HIV-infected adults appears similar to immunocompetent adults.

In the three phase 3 trials, no deaths were reported and discontinuation rates were low. There was no evidence of an increase in discontinuation due to toxicity for ME-609 compared to acyclovir or vehicle. Most adverse events were mild. The most common adverse reactions (all grades, considered definitely, probably or possibly related to study treatment) were local skin reactions that occurred at the site of topical application. The adverse event profile was similar across trials.

1.3 Recommendations for Postmarketing Risk Management Activities

Routine risk mitigation activities are planned for ME-609 (i.e. product information, labeling and packaging). Specific risk mitigation programs for ME-609 are not proposed. Products containing the active ingredients in ME-609 have been marketed for several years with similar formulations and no significant risks have been identified with these products.

No new risks were observed in the clinical studies for ME-609. Therefore, routine risk mitigation strategies are considered sufficient.

1.4 Recommendation for other Postmarketing Study Commitments

No postmarketing study requests were proposed by the Applicant. However, due to the pathophysiology and epidemiology of the disease, this reviewer believes it is reasonable to conduct a clinical study of ME-609 cream in pediatric patients ages 6 to 11 years as a post-marketing commitment. To date, cold sores in this pediatric subpopulation are not commonly treated (Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol 2002; 4(3):231-237). Currently, only systemic acyclovir has been studied for use in pediatric patients with this disease condition. Therefore, current clinical practices could be more reflective of the limitations of approved agents for this pediatric population. Due to its topical application, negligible systemic absorption, and overall safety profile, it is possible that ME-609 could be used in pediatric patients ages 6-11 with recurrent herpes labialis.

The following post-marketing commitment (PMC) have been proposed and have been accepted by the Applicant:

Deferred pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric subjects from 6 to 11 years of age.

Protocol Submission Date: (b) (4)
Study Initiation Date: (b) (4)
Study Completion Date: (b) (4)
Final Study Report Submission Date: May 2013

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

The sponsor, Medivir AB, has submitted a 505(b)(2) application for ME-609 cream. ME-609 (5% acyclovir and 1% hydrocortisone) cream (b) (4) product that contains acyclovir (5.0% w/w), hydrocortisone (1.0% w/w), and the following inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water. The overall pH of the product is 5.

ME-609 cream is intended for treatment of signs and symptoms of recurrent herpes labialis. ME-609 cream is applied 5-times daily for 5 days in adults and adolescents (12 years of age and older).

ME-609 cream is packaged in plastic-laminated aluminum tubes. Tube sizes proposed for

marketing are 2 and 5 grams. The non-proprietary name for the proposed drug product is ME-609 cream. The proposed proprietary name was LIPSOVIR. Following review by the Division of Medication Error Prevention and Analysis (DMEPA). the proposed proprietary name was deemed unacceptable because it contains the United States Adopted Name (USAN) stem '-vir'. According to DMEPA review, the stem '-vir' is used by USAN to indicate an antiviral drug. Although LIPSOVIR is a proposed antiviral product and its use is consistent with the intended USAN meaning, the USAN Council uses this stem for established names only.

> The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs, which may compromise patient safety. Additionally, the USAN definition of the stem '-vir' is antiviral, although this defines one of the ingredients in Lipsovir, it does not reflect the other active ingredient, Hydrocortisone. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. We recommend you screen potential proprietary names against the USAN stem list and eliminate those that incorporate USAN stems.

Reference: Proprietary Name and Label Review for Lipsovir (DMEPA)

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no existing alternatives to the proposed combination product (5% acyclovir and 1% hydrocortisone cream) for the proposed indication (treatment of recurrent herpes labialis [cold sores] and to reduce the likelihood of ulcerative cold sores). However, there are several topical and systemic options for similar indications regarding treatment of recurrent herpes labialis:

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

There are numerous commercially available formulations of 1% hydrocortisone cream for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

2.3 Availability of Proposed Active Ingredient in the United States

ME-609 cream contains two approved principal constituents, 5% acyclovir cream and 1% hydrocortisone cream.

2.4 Important Issues With Consideration to Related Drugs

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

Adverse reactions with topical corticosteroids can include epidermal atrophy (usually reversible), dermal atrophy with development of striae, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Burning and itching may also occur at sites of application. Corticosteroids are pregnancy category C drug products.

Overall, no new or unexpected toxicities were observed with ME-609 cream compared to available safety data on its two approved principal constituents, 5% acyclovir cream and 1% hydrocortisone cream.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

An end-of-phase 2 meeting was held July 6, 2005. The purpose of the meeting was to obtain agreement on the proposed Phase 3 program and protocol outlines and concurrence on proceeding to Phase 3 clinical trials. Principal areas of discussion included efficacy parameters, sample size and planned statistical analyses, and safety parameters.

For pediatric studies, DAVP agreed with the proposed study outline to perform an open label safety study in 100 adolescents (12 to 17 years of age). Furthermore, DAVP stated that data in younger children (lower age limit to be determined) are needed and would be required under the Pediatric Research Equity Act. In addition, data in younger children are also needed in support of a Written Request in order to obtain pediatric exclusivity.

DAVP agreed that no additional non-clinical pharmacology or toxicology studies are needed to support the 505(b)(2) application.

A pre-NDA meeting with the Applicant was held May 22, 2008. An overview of efficacy and safety data from the phase 3 trials was presented. Medivir AB proposed to submit a request for deferral from studying ME-609 cream in patients 6 to 11 years of age, and a waiver from studying ME-609 cream in patients under 6 years of age, at the time of NDA submission. Medivir AB proposed to conduct a study in children 6 to 11 years of age (n=50). The study will be conducted according to the same parameters used in the adolescent study (Study No. 609-07). A draft protocol synopsis for this study was provided in Appendix 1 of the Pre-NDA meeting briefing package. FDA comments stated that the protocol synopsis was reasonable.

Reviewer Comment

This NDA submission included a request (b) (4) . According to the Applicant, this request is based on the safety

profile of ME-609 cream. Please refer to Sections 1.4 and 7.6.3 of this review for additional discussion.

Due to the pathophysiology and epidemiology of the disease, this reviewer believes ME-609 is unlikely to be used in pediatric patients younger than 6 years old. Herpes labialis in children under 6 years of age is generally a primary infection, and not a recurrence.

Due to the pathophysiology and epidemiology of the disease, this reviewer believes it is reasonable to request that the Applicant conduct a prospective study in pediatric patients ages 6-11 with recurrent herpes labialis. The annual prevalence of recurrent herpes labialis in children from 8 to 11 years has been estimated to be 11.75% in some studies. To date, cold sores in this pediatric subpopulation are not commonly treated (Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol 2002; 4(3):231-237). Currently, only systemic acyclovir has been studied for use in pediatric patients with this disease condition. Therefore, current clinical practices could be more reflective of the limitations of approved agents for this pediatric population. Due to its topical application, negligible systemic absorption, and overall safety profile, it is possible that off-label use might occur in pediatric patients ages 6-11 with recurrent herpes labialis.

In summary, this reviewer believes a partial waiver (for ages less than 6 years old) could be granted. This reviewer also believes that the Applicant should be asked to conduct a prospective study in pediatric patients ages 6-11 years old (n=50). As discussed during the May 22, 2008, Pre-NDA meeting, such a study could be conducted according to the same parameters used in the adolescent study (Study No. 609-07). The Applicant could submit a request for deferral of a pediatric study in patients ages 6-11 years old.

2.6 Other Relevant Background Information

ME-609 cream has not yet been approved in any country. Of note, EMEA granted the Applicant's request for a waiver from studying all age groups of children below 12 years.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

A routine consult was submitted to the Division of Scientific Investigations (DSI) on November 3, 2008, in response to this NDA submission. Please refer to the DSI review by Dr. Antoine El-Hage for further details. In Study 609-04, four clinical sites with high subject enrollment were inspected (Table 1).

Table 1: Study 609-04, Sites inspected

Name of PI and Center #,	City, State	Number of subjects randomized
Matthew G. Davis, MD Rochester Clinical Research, Inc. 500 Helendale Road – L20	Rochester, NY	127

Rochester, NY 14609 Center 10		
Jeffrey G. Geohas, MD Radiant Research, Chicago 515 North State Street, Suite 2700 Chicago, IL 60610 Center 17	Chicago, IL	149
James A. Hedrick, MD Kentucky Pediatric/Adult Research 201 South 5th Street, Suite 102 Bardstown, KY 40004 Center 21	Bardstown, KY	79
Michael J. Noss, MD Radiant Research, Inc. 11500 Northlake Dr, Suite 320 Cincinnati, OH 45249 Center 33	Cincinnati, OH	77

PI, principal investigator

In Study 609-04, the following deficiencies were identified during inspection of Center 17 (Chicago, IL, USA; 149 subjects randomized):

> Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation

These deficiencies are summarized in the following table.

Table 2: Study 609-04, Site 17 missing data

Subject ID (Visit#)	Source document	Case report form
0002 (start of treatment)	Investigator observation of stage as papule.	Investigator observation of stage as prodrome.
0013 (start of treatment)	Investigator assessment of treatment start date as 11/7/06.	Treatment start date is reported as 11/6/06.
0044 (start of treatment)	Investigator observation of stage as papule.	Investigator observation of stage as erythema.
0070 (Visit 6)	Subject diary documented mild tenderness (11/2/06).	Reported no tenderness.
0073 (Visit 1)	Subject reported some burning.	This adverse event information was not reported on the case report form.
0073 (Visit 3)	Subject diary documented moderate tenderness (11/19/06).	Reported mild tenderness.
0074 (recurrence)	Investigator assessment of recurrence endpoint of loss of hard crust as 10/23/06.	Date reported for recurrence endpoint of loss of hard crust is 10/22/06.
0094 (Visit 4)	Investigator observation of lesion dimensions as 5mm x 6mm.	Lesion dimensions are reported as 0mm x 0mm.
0095 (Visit 5)	Subject reported burning. Investigator observation described slight redness caused by meds.	This adverse event information was not reported on the case report form.
0108 (Visit 5)	Investigator observation of stage as hard crust. Overall Investigator recurrence assessment as an ulcerative recurrence.	Investigator observation of stage as residual abnormalities. Overall Investigator recurrence assessment as a non-ulcerative recurrence.
0149 (Visit 1)	Investigator observation of stage as prodrome. However, a lesion size is reported.	No information described in DSI report.

Reviewer Comment
Overall, Study 609-04 results are unaffected when the subjects from Site 17 with missing data are excluded from efficacy analyses. Additionally, these deviations did not adversely impact safety data analyses. The remainder of the data from the inspected sites is acceptable in support of this application.

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

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

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Jeffrey Medwid's CMC review for details. The contents of ME-609 cream are summarized in the following table.

Table 3: ME-609 ingredients

Names of ingredients	Percent Formula (%w/w)
Acyclovir*	5.0
Hydrocortisone*	1.0
Mineral oil (b) (4)	(b) (4)
Cetostearyl alcohol	
White petrolatum (b) (4)	
Isopropyl myristate	
Sodium lauryl sulfate	
Poloxamer 188	
Propylene glycol	
Citric acid	
Sodium hydroxide	
Sodium hydroxide/hydrochloric acid	q.s
Water. (b) (4)	(b) (4)

*Active ingredient; quantum sufficiat or satis (as much as suffices)

4.2 Clinical Microbiology

Please refer to Dr. Nalimbar Biswal's Microbiology review for details. Acyclovir resistance was assessed in Study 609-04 (immunocompetent adults) and Study 609-06 (immunocompromised adults). No acyclovir resistant samples were identified using both a genotypic analysis of TK- and DNA-polymerase genes and a phenotypic analysis (acyclovir resistance assay: Plaque Reduction Assay).

4.3 Preclinical Pharmacology/Toxicology

Please refer to Dr. Anita Bigger's Animal Pharmacology/Toxicology review for details of the preclinical program.

Topical acyclovir and hydrocortisone at the dosages used in ME-609 cream are approved for commercial use. This 505(b)(2) NDA relies on the FDA's previous determinations of safety and effectiveness of topical acyclovir [NDA 21-478 Zovirax® (acyclovir) cream 5% and NDA 18-604 Zovirax® (acyclovir) ointment 5%]; and that of hydrocortisone (Reference: Federal Register, "Proposed Amendment to the Tentative Final Monograph for External Analgesic Drugs Intended for Over-the-Counter Use", Vol. 55, No. 39, 2/27/90, pp. 6932-42, and "Hydrocortisone; Marketing Status as an External Analgesic Drug Product; Notice of Enforcement Policy", Vol. 56, No. 169, 8/30/91, pp. 43025-26).

Local (topical) toxicology was evaluated for ME-609 cream. Systemic toxicology studies were not required because systemic exposure following topical administration of acyclovir or hydrocortisone is minimal, and there are substantial data regarding the safety profiles of the active ingredients contained in ME-609 cream.

The objectives of the non-clinical studies in the Applicant's development program were:

- Assess the pharmacological effect of the acyclovir/hydrocortisone combination in a standard guinea pig model of primary cutaneous HSV infection and in a novel murine model, which was developed to more closely mimic recurrent HSV episodes
- Support the development of an optimized topical formulation
- Compare the penetration of acyclovir from the proprietary ME-609 cream formulation with that from the formulation used in the commercially available Zovirax® (5% acyclovir) cream
- Assess the local tolerance of ME-609 cream
- Assess the effects of glucocorticoids on HSV-1 replication *in vitro*

In guinea pigs, ME-609 cream reduced HSV titers compared to untreated controls. The reduction in viral titers with ME-609 cream was similar to results observed in animals given Zovirax® cream. There was no evidence of rebound or prolonged viral shedding in ME-609-treated animals compared to Zovirax®-treated animals. In mice, HSV titers were lower in both the ME-609 cream and Zovirax® cream groups at all time-points compared to untreated control and hydrocortisone groups. Also, the murine study showed that ME-609 cream was significantly more effective at reducing inflammation (as measured by ear thickness) compared to hydrocortisone cream, Zovirax® cream, and placebo.

A local toxicology study in rabbits showed that ME-609 cream had low acute dermal irritation potential. The selected formulation allowed sufficient skin penetration of hydrocortisone and retained or enhanced topical acyclovir penetration compared to Zovirax® cream. ME-609 formulation contains only well-characterized excipients known to have a high topical tolerance. The *in vitro* penetration of acyclovir from ME-609 cream was found to be similar to, or up to 2-fold better than that of 5% acyclovir formulated in a MAC

formulation similar to that of Zovirax® Cream through guinea pig skin. These factors were all considered when selecting the formulation of ME-609 cream to use in clinical trials.

In tissue culture, HSV replication was enhanced if the cells were pre-treated with dexamethasone, but not if dexamethasone was added at the time of HSV infection. Hydrocortisone administered concomitantly with acyclovir, did not promote HSV replication.

These results were discussed during the April 21, 2004, meeting between DAVP and the Applicant. At that time, it was agreed that no additional pharmacology/toxicology studies were needed in the development program. It was also agreed that no non-clinical photosafety studies were needed in the development program.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex. It is used topically for its anti-inflammatory effects which suppress the clinical manifestations of the disease in a wide range of disorders where inflammation is a prominent feature.

4.4.2 Pharmacodynamics

No pharmacodynamics data were provided or considered necessary for this submission.

Pharmacokinetics

No safety pharmacology studies were performed with ME-609 cream. Plasma concentrations of acyclovir and hydrocortisone were not measured following topical administration of ME-609 cream on cold sores because previous studies showed that systemic absorption of both drugs is minimal and without clinical consequences following topical administration.

5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

This review is primarily based on data from Study 609-04 (pivotal phase 3 trial in adults), Study 609-06 (phase 3 trial in immunocompromised subjects with HIV-1 infection), and Study 609-07 (phase 3 trial in adolescents).

Additionally, data from phase 1 dermatology specific supportive studies were reviewed in detail for safety by Dr. Trajkovic (FDA Division of Dermatology and Dental Products, DDDP).

5.1 Tables of Clinical Studies

The following table outlines the trial type, geographic location, numbers of subjects, and status of the phase 3 clinical trials submitted by the Applicant in support of this NDA.

Table 4: Phase 3 Clinical Trials

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/	Status
609-04 (Adults ≥18 years old)	Pivotal safety and efficacy	United States, Canada	Multi-center, randomized, double-blind, active and vehicle-controlled, three arm, subject initiated study	5 times per day for 5 days	1443 treated and evaluable subjects: ME-609 (n=601); 5% acyclovir in ME-609 vehicle (n=610); vehicle (n=232)	Completed
609-06 (HIV+ adults ≥18 years old)	Safety	Russia, Ukraine	Multi-center, randomized, double-blind, active-controlled, subject initiated study	5 times per day for 5 days	107 treated and evaluable subjects: ME-609 (n=77); 5% acyclovir in ME-609 vehicle (n=30);	Completed
609-07 (Adolescents 12-17 years old)	Safety and efficacy	Russia, Sweden	Open-label, multi-center, subject initiated safety study	5 times per day for 5 days	134 treated and evaluable subjects: ME-609 (n=134)	Completed

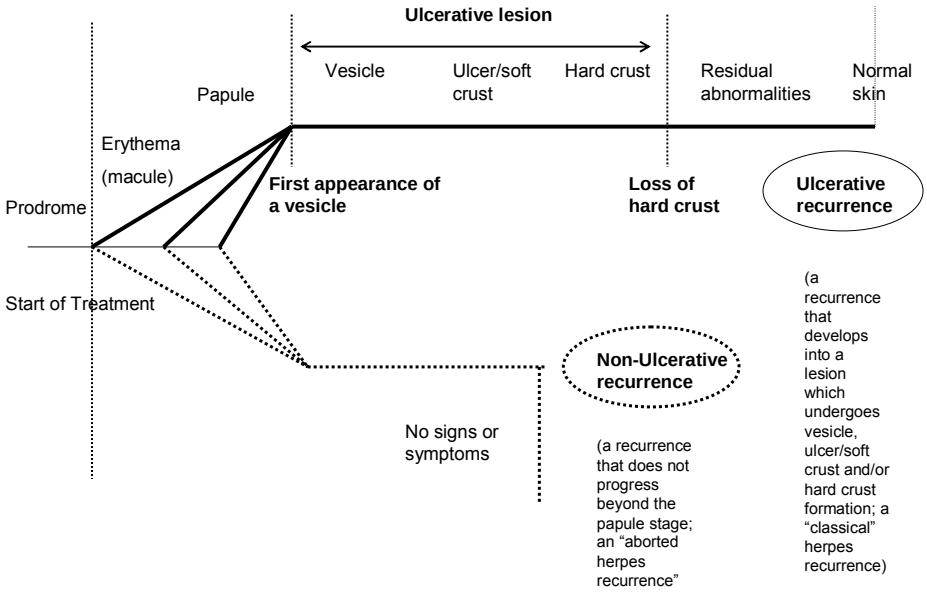
5.2 Review Strategy

Efficacy and safety data were reviewed for Study 609-04. Safety data were reviewed for Study 609-06 and Study 609-07. Safety data review included case report tabulations and case report forms when applicable. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. This MO reviewed study design, patient demographics, and adverse events. FDA clinical and statistical reviewers collaborated extensively throughout the review process, and a number of the efficacy analyses in this review were performed by the FDA statistical reviewer. Additionally, there was significant interaction with the FDA dermatology, CMC, pharmacology/toxicology, clinical pharmacology, and microbiology reviewers. Their assessments are summarized in this document, but complete details of their findings are available in the respective discipline reviews.

5.3 Discussion of Individual Studies

The clinical section of the NDA focuses on efficacy and safety data from Study 609-04 (pivotal phase 3 trial – adults), safety data from Study 609-06 (phase 3 trial –

immunocompromised patients with HIV-1 infection), and safety data from Study 609-07 (phase 3 trial – adolescents). The following figure illustrates the definitions used during Study 609-04, 609-06, 609-07:



Evaluation

- The first appearance of a herpes recurrence during the study is considered the primary recurrence for evaluation.
- Additional recurrences that appear on the same day are also considered part of the primary recurrence complex regardless of location. Herpes recurrences appearing on subsequent days but within 10 mm of the first study recurrence are considered part of the primary recurrence for evaluation.
- Other recurrences which develop in addition to, or on one or more days after the primary recurrence and are more than 10 mm from the primary recurrence are optional for treatment and not followed in the study.

Definitions

- **Non-ulcerative herpes recurrences (primary endpoint):** recurrence does not progress beyond the papule stage (investigator-assessed).

- **Episode duration (secondary endpoint):** measured from start of treatment to loss of hard crust for an ulcerative lesion (investigator-assessed), and from start of treatment to time of no signs or symptoms for a non-ulcerative herpes recurrence (investigator-assessed).

- **Episode duration to normal skin (secondary endpoint):** measured from start of treatment to normal skin for an ulcerative lesion (investigator-assessed), and from start of treatment to time of no signs or symptoms for a non-ulcerative herpes recurrence (investigator-assessed).

These phase 3 studies are summarized below

Study 609-04: a randomized, double-blind, active-controlled, vehicle-controlled, subject initiated trial comparing efficacy and safety of ME-609 versus acyclovir cream versus placebo (ME-609 vehicle) for treatment of recurrent herpes simplex labialis

This was a phase 3, multi-center, randomized, double-blind, active and vehicle-controlled, three arm trial to evaluate the safety and efficacy of ME-609 cream versus acyclovir cream versus placebo (ME-609 vehicle) for the treatment of recurrent herpes labialis. Immunocompetent adults, ages 18 years or older, who had a history of recurrent herpes labialis with at least three episodes during the last 12 months were eligible for the study. Up to 2500 subjects were planned to be randomized, of which 1270 were predicted to receive treatment in one of the study arms. Subjects were randomized to ME-609 (minimum of 535 evaluable subjects), acyclovir in ME-609 vehicle (minimum of 535 evaluable subjects), or ME-609 vehicle (minimum of 200 evaluable subjects). Study medications were administered five times daily for five days. Treatment was started within one hour of experiencing signs or symptoms of a herpes recurrence (prodromal symptoms or erythema), and prior to the first clinical sign of a cold sore (no swelling, blister or later stage lesion). Subjects were seen at the study clinic within 18 hours of treatment initiation and were followed daily at the clinic throughout the five-day treatment period and daily until loss of hard crust. Subjects recorded lesion stage, tenderness, and concomitant medications twice daily in a diary.

The trial was designed to show superiority of ME-609 compared to acyclovir and vehicle for the primary endpoint, proportion of subjects with non-ulcerative herpes recurrences. These comparisons are made in order to show the contribution of hydrocortisone and to show the overall effect is not due to the vehicle. Also, the study was designed to show superiority of ME-609 compared to vehicle for the secondary endpoint, episode duration. This comparison was made to show hydrocortisone does not adversely affect acyclovir antiviral efficacy.

Additional endpoints included episode duration to normal skin, cumulative lesion area of the primary ulcerative herpes, ulcerative lesion healing time, ulcerative episode duration, maximum lesion area, duration and severity of tenderness, and subject preference.

SYNOPSIS

- Study Initiation Date: July 5, 2006
- Study Completion Date: December 19, 2007
- Conducted at 55 investigational sites: USA (51 sites), Canada (4 sites)
- There were 2437 randomized subjects: ME-609 (n=1018); acyclovir in ME-609 vehicle (n=1033); vehicle (n=386)

- Subjects who experienced HSV recurrence and initiated treatment with study medication were included in safety and efficacy analyses.
- There were 1443 treated and evaluable subjects: ME-609 (n=601); acyclovir in ME-609 vehicle (n=610); vehicle (n=232)
- Study endpoints (investigator-assessed):
    - Primary: Proportion of subjects with non-ulcerative recurrences (proportion of patients in whom the study recurrences does not progress beyond the papule stage)
    - Secondary: Episode duration
- Key Inclusion Criteria
    - Male/Female 18 years and older
    - History of recurrent herpes labialis with at least 3 recurrences during the past 12 months and typically (>50% of episodes) associated with prodromal symptoms
    - History of at least half of the herpes recurrences producing ulcerative lesions (a recurrence that will lead to development of a lesion which undergoes vesicle, ulcer/soft crust and/or hard crust formation)
    - Females of childbearing potential must have a negative pregnancy test and practice a reliable method of contraception (intrauterine device or combined contraceptives) for at least 3 months prior to enrollment visits and during the remaining study period
    - Patients must agree to abstain from the use of anti-inflammatory medications (including aspirin and NSAIDS), systemic steroids and analgesics during the treatment period until healing occurs
    - Patients must agree to abstain from the use of any topical treatments in the lesion area (cosmetics, lip balms, sun screens, etc) during the treatment period until healing occurs
    - Patients must agree to abstain from any mechanical disruption of the prodromal area or lesion (i.e., scrubbing, lancing, shaving the area, rubbing with alcohol, etc.)
- Key Exclusion Criteria
    - Treatment with other systemic or topical antiviral agents or systemic corticosteroids within 4 weeks prior to study drug administration
    - Immunodeficiency disorders such as HIV or receiving cancer chemotherapy
    - Previous herpes vaccine
    - Significant skin disease (such as atopic dermatitis, acne, rosacea, eczema, psoriasis or chronic vesiculobullous disorders) that would interfere with assessment of lesions
    - Treatment with topical steroids in the oral area within four weeks prior to study drug administration
    - Unwillingness to refrain from using topical medical, OTC or cosmetic products in or around the oral area during the herpes recurrence

- Receipt of an investigational drug or immunomudulatory agent within four weeks prior to the study, or concurrently participating in another research study
- Pregnant, nursing and/or lactating females
- History of immediate hypersensitivity or serum sickness reaction to any nucleoside analogue antiviral agent or to any topical steroid
- History of hypersensitivity to any ingredient in vehicles of ME-609 or Zovirax cream
- Patients who have had infection with HSV-1 isolates known to be resistant to acyclovir, valaciclovir, famciclovir or ganciclovir

Study 609-04: Statistical Issues

1) Sample Size and Power

According to the Applicant, superiority of 3 hypothesis tests was required to demonstrate efficacy: proportion of subjects with non-ulcerative recurrences for ME-609 versus acyclovir and for ME-609 versus vehicle, and episode duration for ME-609 versus vehicle. Approximately 60 to 70% of enrolled subjects were predicted to have a herpes recurrence and initiate study drug treatment. Therefore, at least 2500 subjects would need to be randomized to reach the target of 1270 evaluable subjects.

2) Statistical Analyses

Study 609-04 was designed to show superiority of ME-609 compared to acyclovir and vehicle for the primary endpoint, proportion of subjects with non-ulcerative herpes recurrences. In addition, Study 609-04 was designed to show superiority of ME-609 compared with vehicle for the secondary efficacy endpoint, episode duration. Superiority for all three comparisons was required to demonstrate efficacy.

Reviewer Comment

Study design and statistical analysis issues were agreed between the Applicant and FDA during an end-of-phase 2 meeting held on July 6, 2005.

Study 609-06: a randomized, double-blind, active controlled, subject initiated trial comparing ME-609 to acyclovir cream for treatment of recurrent herpes simplex labialis in immunocompromised patients

This was a phase 3 multi-center, randomized, double-blind, active-controlled, trial to evaluate the safety and efficacy of ME-609 cream versus acyclovir in ME-609 vehicle for the treatment of recurrent herpes labialis in immunocompromised patients. HIV+ adults with stable infection (CD4 100-500 cells/mm^3), ages 18 years or older, who had a history of recurrent herpes labialis with at least two episodes during the last 12 months were eligible for the study. Other inclusion/exclusion criteria were similar to Study 609-04. A total of 230 subjects were randomized in a 2:1 ratio (ME-609:acyclovir), of which 80 were predicted to have evaluable data. Study medications were administered five times daily for five days. Treatment was started at the first signs or symptoms of a herpes recurrence.

The primary endpoint was episode duration and the secondary endpoint was time to next herpes recurrence. Additional endpoints included proportion of subjects with non-ulcerative recurrence, maximum lesion area, and episode duration to normal skin (defined as investigator assessment of time from treatment initiation to normal skin for ulcerative lesions, and time from treatment initiation to no signs/symptoms for non-ulcerative recurrence). Endpoints were assessed by study investigators. The study was designed as a non-inferiority study for episode duration. The non-inferiority limit was doubling of the median episode duration.

SYNOPSIS

- Study Initiation Date: December 25, 2006
- Study Completion Date: August 29, 2008
- Conducted at 25 investigational sites: Russia (19 sites), Ukraine (6 sites)
- The study population included 201 subjects, 136 randomized to treatment with ME-609 and 65 randomized to treatment with acyclovir.
- Subjects who experienced HSV recurrence and initiated treatment with study medication were included in safety and efficacy analyses.
- There were 107 treated and evaluable patients: ME-609 (n=77); acyclovir in ME-609 vehicle (n=30)
- Key inclusion criteria: HIV+ adults with stable infection (defined as CD4 100-500 cells/mm^3), ages 18 years or older, who have a history of recurrent herpes labialis with at least two episodes during the last 12 months were eligible for the study. Other inclusion/exclusion criteria were similar to Study 609-04.
- Other aspects of study design were similar to Study 609-04:
    - Study medications were administered five times daily for five days.
    - Treatment was started at the first signs or symptoms of a herpes recurrence.
- Study endpoints:
    - Primary: episode duration
    - Secondary: time to next herpes recurrence.

Reviewer Comment
No indication is being proposed for immunocompromised subjects.

Study 609-07: a phase 3, open-label, multi-center, safety trial of ME-609 for treatment of recurrent herpes simplex labialis in adolescents

This is a phase 3, open-label, multi-center, safety trial of ME-609 for the treatment of recurrent herpes simplex labialis in adolescents 12-17 years of age in which subjects initiated therapy at the first signs or symptoms of recurrent herpes simplex labialis. Immunocompetent adolescents who had a history of recurrent herpes labialis with at least two episodes during the last 12 months were eligible for the study.

SYNOPSIS

- Study Initiation Date: December 15, 2006
- Study Completion Date: September 19, 2007
- Conducted at 26 sites: Russia (20 sites), Sweden (6 sites).
- The study population included 254 subjects in this open-label, single-arm study.
- Subjects who experienced HSV recurrence and initiated treatment with study medication were included in safety analyses.
- There were 134 treated and evaluable subjects (all received ME-609).
- Key inclusion criteria: Immunocompetent adolescents, ages 12-17, who had a history of recurrent herpes labialis with at least two episodes during the last 12 months were eligible for the study. Other inclusion/exclusion criteria were similar to Study 609-04.
- Other aspects of study design were similar to Study 609-04:
    - Study medications are administered five times daily for five days.
    - Treatment with ME-609 was started at the first signs or symptoms of a herpes recurrence.
- There were no efficacy endpoints in Study 609-07.
- For safety evaluation, the following variables were assessed:
    - Adverse events, from treatment initiation until follow-up 3 weeks ± 1 week after last dose of ME-609.
    - Categorization of recurrence.
    - Maximum lesion area, measured as the maximum area of an ulcerative lesion. Lesion area is assessed for a recurrence that is in the papule or later stages until the hard crust is lost.

Reviewer Comment
Study 609-07 was designed to assess the safety of ME-609 in adolescent subjects. The Applicant proposes to extrapolate efficacy in adolescent subjects based on the results from Study 609-04. This reviewer believes the proposal is reasonable since the course of recurrent herpes labialis and the effects of ME-609 are sufficiently similar in adults and adolescents.

Compositions of ME-609, acyclovir in ME-vehicle, and ME-vehicle used in the phase 3 trials are presented in the following table.

Table 5: Composition of ME-609, Acyclovir, and Vehicle

Names of ingredients, Percent Formula (%w/w)	ME-609	Acyclovir	Vehicle
Acyclovir*	5.0	5.0	-
Hydrocortisone*	1.0	-	-
Mineral oil (b) (4)	(b) (4)		
Cetostearyl alcohol			
White petrolatum (b) (4)			
Isopropyl myristate			
Sodium lauryl sulfate			
Poloxamer 188			
Propylene glycol			

Citric acid	(b) (4)		
Sodium hydroxide			
Sodium hydroxide/hydrochloric acid	q.s	q.s	q.s
Water. (b) (4)		(b) (4)	

*Active ingredient; q.s., quantum sufficiat or satis (as much as suffices)

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

The efficacy analyses of Study 609-04 are based on data from 1443 immunocompetent adults ages ≥ 18 years who received ME-609 cream (5% acyclovir cream + 1% hydrocortisone + vehicle), acyclovir (5% acyclovir cream + vehicle) and vehicle (placebo) for treatment of recurrent herpes labialis. This study was conducted in the USA and Canada. The ITT population was 91% Caucasian, 72% female, with a median age of 44 years old and median frequency of 5 HSV episodes per year. At baseline, 65% of the subjects had only prodromal symptoms, 28% had erythema, and 7% had papules.

Overall, 42.6% of subjects in the ME-609 arm, 35.6% of subjects in the acyclovir (5% acyclovir cream + vehicle) arm and 25.4% of subjects in the vehicle (placebo) arm had non-ulcerative HSV recurrences. Thus, ME-609 was numerically superior to vehicle ($p<0.001$), and superior to acyclovir ($p<0.05$), for the reduction of ulcerative herpes lesions. The median episode durations were 4.77 days in the ME-609 and 5.09 days in the vehicle arm, respectively. The reduction in median episode duration (ME-609 - vehicle) using the Hodges-Lehmann's (H-L) approach was 0.38 days ($p>0.05$). Furthermore, subjects who were treated with ME-609 had a significant reduction in median duration to normal skin of 7 days, an approximate one day reduction compared to more than 8 days in the vehicle arm ($p <0.001$).

According to the protocol-defined success criteria, the efficacy results did not meet the statistical significance level of $p=0.001$ for demonstrating prevention of ulcerative herpes lesions (primary efficacy endpoint) with ME-609 versus acyclovir, nor for $p=0.05$ for the episode duration with ME-609 versus vehicle. Low-strength hydrocortisone preparations (0.5% or 1%) are used without a prescription for the temporary relief of (1) minor skin irritations, itching, and rashes caused by eczema, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry; (2) itchy anal and rectal areas; and (3) itching and irritation of the scalp. It is also used to relieve the discomfort of mouth sores[6]. Hence, the significance level of 0.001 may be reduced for demonstrating reduction of incidence of ulcerative herpes lesions with ME-609 versus acyclovir.

Other supportive evidence was obtained for six clinical endpoints among seven tertiary efficacy endpoints. The median duration to loss of hard crust was 5 days in the ME-609 arm, slightly shorter than 5.4 days in the acyclovir arm ($p>0.05$) but significantly shorter than 5.8

days in the vehicle arm (P<0.05). The median duration of tenderness was similar in the ME-609 arm and acyclovir arm, but was about 1 day shorter than that in the vehicle arm (P<0.05). The median reductions of average cumulative lesion area were 6.0 and 13.0 mm^2 respectively in the ME-609 arm, compared with that in the acyclovir and vehicle arms (p<0.05). Likewise, the median reductions of average maximum area were 2.0 and 4.0 mm^2, respectively, in the ME-609 arm, compared with that in the acyclovir and vehicle arms (p<0.05). Additionally, among subjects who developed ulcerative recurrence (UR) lesions, subjects who treated with ME-609 were more likely to feel better than those in the vehicle arm.

Primary efficacy analyses also show the contribution of both 5% acyclovir and 1% hydrocortisone to the prevention of ulcerative herpes lesions and the duration of time from lesion appearance to normal skin.

Extrapolation of efficacy for ME-609 in adolescents is reasonable since the course of recurrent herpes labialis and the effects of ME-609 are sufficiently similar in adults and adolescents.

Overall, efficacy analyses support approval of ME-609 (5% acyclovir and 1% hydrocortisone) cream for early treatment of signs and symptoms of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores in adults and adolescents (12 years of age and older).

6.1 Data Sources

As mentioned in Section 5, this submission contains the efficacy results of three Phase III studies:

- 609-04 for adult subjects 18 years and older with a history of at least three episodes of recurrent labial herpes during the prior 12 months;
- 609-06 for immuno-compromised subjects 18 years and older with at history of ≥2 episodes of recurrent labial herpes during the prior 12 months; and
- 609-07 among adolescents between 12-17 years age with ≥2 episodes of recurrent labial herpes during the prior 12 months.

The statistical review of the efficacy of ME-609 included the following three parts.

1. Reviewing protocols, statistical analysis plans, and efficacy results and conclusions in '609-0k-report-body.pdf' and other *.pdf files under three subdirectories '\609-0k', (k=4,6,7) of the CDER Electronic Document Room (EDR) directory \\Cdsesub1\evsprod\NDA022436\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\recurrent-herpes-labialis\5351-study-rep-contr

2. Downloading SAS programs and *.pdf files, and converting SAS transportable *.xpt and *.xpf files into SAS data files. All these files are stored under the CDER/EDR subdirectories of " \\Cdsesub1\evsprod\NDA022436\0000\m5\datasets".

Conducting sensitivity analyses on efficacy data for Study 609-04 to verify the Applicant's results.

6.2 Overview of Study 609-04

Study 609-04 was a phase 3, multi-center, randomized, double-blind, active and vehicle-controlled, three-arm trial to evaluate the safety and efficacy of ME-609 cream versus acyclovir cream versus placebo (ME-609 vehicle) for the treatment of recurrent herpes labialis in immunocompetent adults. This trial was of adequate design and sufficiently powered to study the safety and efficacy of ME-609 at a dose of 5-times daily for 5 days in subjects with recurrent herpes labialis.

The primary endpoint was defined as the proportion of subjects with non-ulcerative recurrences (proportion of patients in whom the study recurrences does not progress beyond the papule stage), as assessed by study investigators. The secondary endpoint was episode duration (investigator-assessed). Overall, primary and secondary efficacy analyses suggest ME-609 is superior to placebo (vehicle) for the prevention of ulcerative herpes lesions, and superior to acyclovir (in ME-609 vehicle). Although the difference between ME-609 and acyclovir did not meet the predefined statistical significance level for demonstrating efficacy in a single registrational study, evaluation of the totality of evidence regarding efficacy showed consistency of results across subpopulations. FDA efficacy analyses, performed by Dr. Zhou and detailed in this section, are overall consistent with the Applicant's efficacy analyses.

6.2.1 Proposed Indication

The Applicant's proposed indication is as follows:

> *ME-609 cream, a combination of acyclovir (5%) and hydrocortisone (1%), is indicated for the early treatment of signs and symptoms of recurrent herpes labialis (cold sores) to prevent the development and reduce the duration of ulcerative cold sores in adults and adolescents (12 years of age and older).*

6.2.2 Efficacy Data from Study 604-04

Data from Study 609-04 were reviewed to assess the proposed indication. Pivotal phase 3 Study 609-04 was a multi-center, randomized, double-blind, active and vehicle-controlled, three arm trial to evaluate the safety and efficacy of ME-609 cream versus acyclovir cream and placebo (ME-609 vehicle) for the treatment of recurrent herpes labialis in immunocompetent adults. This trial was of adequate design and sufficiently powered to study the safety and efficacy of ME-609 at a dose of 5-times daily for 5 days in subjects with recurrent herpes labialis.

The primary endpoint was the proportion of subjects with non-ulcerative recurrences, defined as the proportion of patients in whom the study recurrences do not progress beyond the papule stage. The secondary endpoints were episode duration and duration to normal skin.

- Episode duration was defined as investigator assessment of time from treatment initiation to loss of hard crust for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.
- Episode duration to normal skin was defined as investigator assessment of time from treatment initiation to normal skin for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.

Tertiary efficacy endpoints included cumulative lesion area, lesion healing time to normal skin, lesion healing time to loss of hard crust, maximum lesion area, duration and severity of tenderness, and subject preference.

Pre-defined success criteria consisted of three hypotheses: 1) superiority of proportion of subjects with non-ulcerative recurrences in the ME-609 arm versus acyclovir arm at p=0.001; 2) superiority of proportion of subjects with non-ulcerative recurrences in the ME-609 arm versus vehicle arm at p=0.05; and 3) superiority of mean episode duration in the ME-609 arm versus vehicle arm at p=0.05.

Please refer to Section 5.3 for detailed discussion of study design.

6.2.3 Extrapolation of Efficacy in Adolescents

Efficacy outcomes in adolescents were extrapolated from the results of Study 609-04 obtained in adults. Extrapolation of efficacy for ME-609 in adolescents was considered reasonable since the course and pathophysiology of recurrent herpes labialis is known to be sufficiently similar in adults and adolescents.

6.3 Demographics

Study 604-04

In Study 609-04, the ITT population consisted of 1443 subjects. The majority of subjects were Caucasian (91%) and female (71.9%), with a mean age of 43.9 years. The mean number of recurrent herpes labialis episodes was 5.6 episodes during the preceding 12 months, and the majority of subjects had either prodrome (64.3%) or erythema (27.5%) at baseline presentation. As shown in Table 6, baseline demographics characteristics and baseline disease severity were balanced across treatment groups.

Table 6: 609-04: Subject Demographics and Baseline Characteristics (ITT Population)

	ME-609	(n=601)	Acyclovir	(n=610)	Vehicle	(n=232)	Total	(n=1443)
Age								
Mean (SD)	43.5	13.6	43.8	14.0	44.8	13.9	43.9	13.8
Median (range)	44	18,79	43	18,80	44	18,76	44	18,80
White	548	91.3%	556	91.3%	212	91.4%	1316	91.3%
Black	36	6.0%	36	5.9%	14	6.0%	86	6.0%
Other	16	2.8%	17	2.8%	6	2.6%	39	2.7%
Missing	1	0.2%	1	0.2%	0	0.0%	2	0.1%
Male	159	26.5%	182	29.8%	65	28.0%	406	28.1%
Female	442	73.5%	428	70.2%	167	72.0%	1037	71.9%
Women with Child–bearing Age								
Yes	256	57.9%	246	57.5%	94	56.3%	596	57.5%
No	186	42.1%	182	42.5%	73	43.7%	441	42.5%
Lesion Stage at Day 1								
Prodrome	391	65.1%	397	65.1%	140	61.0%	928	64.3%
Erythema	159	26.4%	164	26.9%	74	32.5%	397	27.5%
Papule	45	7.5%	42	6.9%	15	6.6%	102	7.1%
Vesicle or late stages	2	0.3%	5	0.8%	0	0.0%	7	0.3%
# of Episode Per Year								
Mean (SD)	5.5	3.3	5.5	2.9	5.9	3.3	5.6	3.1
Median (range)	4	3,40	5	3,30	5	3,24	5	3,40

Source: Applicant's September 30, 2008 submission

Study 609-06

Baseline demographics by treatment groups for the ITT population of Study 609-06 (n=107) are listed in Table 7. Age, gender, CD4+ cell counts, and number of episodes per year were evenly matched across treatment groups in Study 609-06. In the ITT population, 49 of 107 subjects (45.8%) were receiving highly active antiretroviral therapy (HAART) at baseline, including 36 (46.8%) in the ME-609 group and 13 (43.3%) in the acyclovir arm.

Table 7: 609-06: Subject Demographics and Baseline Characteristics (ITT Population)

	ME-609	(n=77)	Acyclovir	(n=30)	Total	(n=107)
Age						
Mean (SD)	31.5	7.8	32.5	9.1	31.8	8.2
Median (range)	29	19,55	30	21,64	30	19,64
White	77	100.0%	30	100.0%	107	100.0%
Male	46	59.7%	12	40.0%	58	54.2%
Female	31	40.3%	18	60.0%	49	45.8%
# of Episode Per Year						
Mean (SD)	3.7	1.7	3.7	1.2	3.7	1.6
Median (range)	3	2,10	3.5	2,6	3	2,10
CD4+ (cells/mm^3)						
Mean (SD)	328	111	321	116	326	112
Median (range)	344	100,500	346	116,500	344	100,500

Source: Applicant's September 30, 2008 submission

Reviewer Comment
In Study 609-06, 49 of 107 subjects (45.8%) were receiving highly active antiretroviral therapy (HAART) at baseline. In the ME-609 group, 36 of 77 subjects (46.8%) were receiving HAART at baseline. In the acyclovir group, 13 of 30 subjects (43.3%) were receiving HAART at baseline.

Study 609-07
Study 609-07 was an open-label, one-arm safety study among adolescents. All subjects received ME-609. The demographics and number of episodes per year in Study 609-07 are shown in the Table 8. The study population included 134 Caucasian subjects age 12-17. Please refer to Section 5 for additional details on the study design.

Table 8: 609-07: Subject Demographics and Baseline Characteristics (ITT Population)

	(n=134)
Age	
Mean (SD)	14.5 (1.7)
Median (range)	14.5 (12,17)
White	134 (100.0%)
Male	67 (50%)
Female	67 (50%)
# of Episode Per Year	
Mean (SD)	4.0 (2.2)
Median (range)	3.5 (2,15)

Source: Applicant's September 30, 2008, submission

6.4 Disposition

Study 609-04

Disposition for treated subjects is presented in Table 9. A total of 1443 subjects were treated with study drug: 601 (59.0%), 610 (59.1%), and 232 (60.1%) in the ME-609, acyclovir, and vehicle treatment groups, respectively. Of the 1443 treated subjects, 1398 (96.9%) completed the study endpoint assessment and 45 (3.1%) subjects were discontinued from the study. Four subjects (ME-609 – two subjects; acyclovir – one subject; vehicle – one subject) discontinued treatment due to adverse events considered related to study treatment by study investigators. Overall discontinuation rates were low across all treatment groups. Also, discontinuations due to adverse events were low across all treatment groups. Please refer to Section 7.3.3 for additional details.

Efficacy results in Study 609-04 were not substantively affected by subject dropouts.

Table 9: Subject disposition (as-treated) – Study 609-04

	ME-609	Acyclovir	Vehicle	Total
Subjects treated, n (%)	601	610	232	1443
Completed endpoint assessment, n (%)	582 (96.8)	591 (96.9)	225 (97.0)	1398 (96.9)
Discontinued, n (%)	19 (3.2)	19 (3.1)	7 (3.0)	45 (3.1)
Adverse event, n (%)	2 (0.3)	1 (0.2)	1 (0.4)	4 (0.7)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Loss to follow-up, n (%)	6 (1.0)	8 (1.3)	2 (0.9)	16 (1.1)
Consent withdrawn, n (%)	2 (0.3)	2 (0.3)	2 (0.9)	6 (0.4)
Pregnancy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject decision, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Investigator decision, n (%)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
Other protocol violation, n (%)	7 (1.2)	7 (1.1)	2 (0.9)	16 (1.1)

Source: Applicant's September 30, 2008, submission
Other includes: protocol violation, withdrawn per Sponsor request – noncompliant, subject had canker sore, subject dosed at wrong stage, cold sore occurrence inside nose, and did not return to clinic after start of study medication

Reviewer Comment
Overall, ME-609 is tolerable at the proposed treatment dose and duration (5 times daily for 5 days). Overall discontinuation rates were low across all treatment groups. Discontinuations due to adverse events were low across all treatment groups. As shown in the following sections, efficacy results in Study 609-04 were not substantively affected by subject dropouts.

Study 609-06
Disposition for treated subjects is presented in the Table 10.

Table 10: Subject disposition (as-treated) – Study 609-06

	ME-609	Acyclovir	Total
Subjects treated, n (%)	77	30	107
Completed endpoint assessment, n (%)	75 (97.4)	29 (96.7)	104 (97.2)
Discontinued, n (%)	2 (2.6)	1 (3.3)	3 (2.8)
Adverse event, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Loss to follow-up, n (%)	1 (1.3)	0 (0.0)	1 (0.9)
Consent withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Subject decision, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator decision, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other protocol violation, n (%)	1 (1.3)	1 (3.3)	2 (1.9)

Source: Applicant's September 30, 2008, submission

Reviewer Comment
No subjects discontinued due to adverse events in Study 609-06.

Study 609-07
Disposition for treated subjects is presented in Table 11. Of note, all subjects received ME-609 in this open-label safety study.

Table 11: Subject disposition (as-treated) – Study 609-07

	ME-609
Subjects treated, n (%)	134
Completed endpoint assessment, n (%)	132 (98.5)
Discontinued, n (%)	2 (1.5)
Adverse event, n (%)	1 (0.7)
Death, n (%)	0 (0.0)
Loss to follow-up, n (%)	0 (0.0)
Consent withdrawn, n (%)	0 (0.0)
Pregnancy, n (%)	0 (0.0)
Subject decision, n (%)	1 (0.7)
Investigator decision, n (%)	0 (0.0)
Other protocol violation, n (%)	0 (0.0)

Reviewer Comment
In Study 609-07, one subject (ID# 57001) discontinued treatment due to adverse event considered related to study treatment by study investigators. Please refer to Section 7.3.3 for additional details. One subject (ID# 05002), a 16-year-old female, decided to discontinue study medication treatment at the first clinic visit (second treatment day) after 5 applications. According to the case report form, "the subject felt tired now and again from her diabetes and she was too tired to continue in the study."

6.5 Evaluation of Primary Efficacy Endpoint

The FDA statistical reviewer conducted sensitivity analyses on the primary efficacy endpoints for Study 609-04. As shown in the following sections, FDA's efficacy analyses were generally consistent with the Applicant's efficacy analyses although different methods were used. In the text below, we refer to the non-ulcerative recurrence and ulcerative recurrence as NUR and UR, respectively, and percentage of subjects with NUR (UR) as PSNUR (PSUR) in estimation of primary efficacy endpoints.

6.5.1 Method

As shown in Table 9, in the ITT population, 19 subjects in ME-609 arm, 19 subjects in Acyclovir arm, and 7 subjects in Vehicle arm (total=45, 3.1%) discontinued from study. Among them, there were 28 subjects with missing data regarding the primary efficacy endpoint. Both the dropouts and the subjects with missing information for the primary efficacy endpoint were evenly distributed

among the three treatment arms. In addition, there were eight subjects with missing HSV labialis lesion stage at Day 1.

In order to verify the sponsor's efficacy results and examine the potential discontinuation differences among treatment arms, the FDA statistical reviewer imputed missing values in the primary efficacy endpoints using two methods: 1) Adjusting for baseline variables; and 2) Using 'Worst case scenario' approach. Other analyses were also performed, including the analyses 3) among completers (excluding those who discontinued from the study, 4) ignoring missing and 5) excluding Site 017 (analyses of the dataset excluding Site 017 were conducted due to data problems found during FDA's inspection at this site. Please refer to Section 3.1 of this review for additional details).

Detailed methodologies for these are as follows.

1. Imputation of Missing in Primary Efficacy Endpoint Adjusting for Baseline Variables

- First, the observed probabilities of NUR for subgroups of six baseline characteristics in addition to the treatment groups were computed using non-missing data (n=1415). The baseline characteristics were gender, age (≤ or >44), Caucasian versus other, number of episodes per year (≤ or >5), recurrence stage at Day 1 to be prodrome or not, and recurrence stage at Day 1 to be erythema or not.
- The missing values in Day 1 lesion stage were imputed three times as 'prodrome,' 'erythema' and 'vesicle or more advanced stages,' respectively. However, the imputed different lesion stages at Day 1 had a limited impact on the imputation of the primary efficacy endpoints, so only the imputation of 'prodrome' in missing Day 1 labialis stage is reported.
- The predicted probabilities of NURs were obtained for the 28 subjects with missing data regarding the primary efficacy endpoint according to those subjects with non-missing outcomes in the same treatment group.
- The summary statistics of the missing NURs were rounded to the nearest integers. The overall number of NUR was obtained for each of the three treatment arms and the corresponding treatment differences in PSNUR were estimated.

2. Imputation of Missing in Primary Efficacy Endpoint using 'Worst case scenario' Approach

For missing primary efficacy outcome data, UR for those subjects in the ME-609 arm and NUR for those in the acyclovir arm or vehicle arm were assigned, and the treatment differences in PSNUR were subsequently computed.

3. Completers

The analyses among 'Completers' consisted of 96.9% (1398/1443) of the subjects who did not dropout of Study 609-04.

4. Ignoring Missing

This method excluded subjects with missing UR or NUR status from both the numerators and denominators to estimate the PSNURs and treatment differences in PSNUR.

5. Excluding Site 017

Analyses of the dataset excluding Site 017 were conducted due to data problems found during FDA's inspection at this site.

6.5.2 Sensitivity Analyses

The results of FDA's sensitivity analyses of the primary efficacy endpoints are summarized in Table 12. The Applicant's results are also included in the last part of this table.

The Applicant reported PSNUR in 42.3% of subjects (254/601) treated with ME-609, 35.4% of subjects (216/610) treated with 5% acyclovir in ME-609 vehicle, and 25.9% of subjects (60/232) treated with vehicle. The PSUR was reported in 57.7% (347/601) of the subjects treated with ME-609, 64.6% (394/610) treated with acyclovir, and 74.1% (172/232) treated with vehicle.

Compared with the Applicant's results, FDA's sensitivity analyses showed similar results in four methods except for the 'Worst Case Scenario' (#4).

- The estimated PSNURs (ME-609 versus Acyclovir) were all within 0.3% and the significance levels (p-values) were well maintained to be <0.05 for the comparisons of PSNUR between ME-609 and Acyclovir.

- The estimated PSNURs (ME-609 versus Vehicle) were all within 0.9% and the significance levels (p-values) were well maintained to be <0.0001 for the comparisons of PSNUR between ME-609 and Vehicle.

Compared with the Applicant's results, FDA's results using the 'Worst Case Scenario' (#4) approach provided approximately 2% lower treatment differences in PSNUR ME-609 versus Acyclovir (p=0.09) and ME-609 versus Vehicle (p<0.0001).

Table 12: 609-04: Primary Efficacy Endpoint on ITT Population: Sensitivity Analyses*

ME-609			Acyclovir or Vehicle							
r_1	n_1	π_1(%)	r_2	n_2	π_2(%)	$\pi_1-\pi_2$(%)	SE($\pi_1-\pi_2$)	99.9% or 95% CI		P
1. Imputations of 'Prodrome' to Missing Day 1 Lesion Stage and Recurrence Types Adjusting for the Baseline Variables										
256	601	42.6	217	610	35.6	7.0	2.8	-2.2	16.2	0.012
			59	232	25.4	17.2	3.5	10.3	24.0	<0.00001
2. Worst Case Scenario										
251	601	41.8	226	610	37.0	4.7	2.8	-4.5	14.0	0.093
			63	232	27.2	14.6	3.5	7.7	21.6	<0.0001
3. Completers										
248	582	42.6	210	591	35.5	7.1	2.8	-2.3	16.4	0.0129
			57	225	25.3	17.3	3.6	10.3	24.2	<0.00001

4. Ignoring Missing										
251	589	42.6	214	598	35.8	6.8	2.8	-2.5	16.1	0.016
			59	228	25.9	16.7	3.5	9.8	23.7	<0.00001
5. Excluding Site 017 Due to Data Problems										
244	565	43.2	209	573	36.5	6.7	2.9	-2.8	1.2	0.021
			56	215	26.0	17.1	3.6	10.0	24.3	<0.00001
6. Sponsor's Results (Section 11.4.1.1 Primary Endpoint, Page 68, Clinical Study Report)										
254	601	42.3	216	610	35.4	6.9	2.8	-2.3	16.1	0.014
			60	232	25.9	16.4	3.5	9.5	23.3	<0.00001

*. Data Source: FDA analysis.
r_j - # of subjects with non-ulcerative recurrence, n_j – sample size$_t$ π_j -estimated PSNUR in the jth group, j=1,2.
First row: comparisons between ME-609 ($\pi_1=r_1/n_1$ *100) and Acyclovir ($\pi_2=r_2/n_2$ *100) with 99.9% CI;
Second row: comparisons between ME-609 and Vehicle ($\pi_2=r_2/n_2$ *100) with 95% CI.

6.5.3 Subgroup Analyses

Modified ITT Population (MITT)

Baseline and treatment information in four datasets 'adsl.xpt', 'adtg.xpt', 'adep.xpt' and 'adsm.xpt' were reviewed. It appears that 24 subjects (1.7%) may not be appropriately included in the ITT population (n=1443) due to reasons such as missing in lesion stage at Day 1 and/or missing in dose information. Table 13 lists the information for these subjects by treatment arm, including:

- 8 subjects with missing or unknown stage at treatment initiation (Day 1);
- 2 subjects with 2 episodes per year; and
- 14 subjects with no treatment dose information and/or no date of end of treatment.

In the subgroup analyses of the efficacy endpoints, the statistical reviewer refers to the ITT population excluding the above 24 subjects as 'Modified ITT' population (MITT, n=1419). The baseline demographics of the MITT population are similar to those from the ITT population excluding the 24 subjects.

Table 13: 609-04: Subjects with Inadequate Baseline Information*

	Acyclovir	ME-609	Vehicle	Total
1. Missing in Stage at Day 1				
	2	4	2	8
2. # Episodes <3	1	1	0	2
3. Missing in Dose or End Date of Treatment				
	4	8	2	14
Total	7	13	4	24

*Data Source: FDA analysis.

Subgroup analyses of the primary efficacy endpoint (percentage of subjects with non-ulcerative recurrence [PSNUR]) were conducted for five baseline characteristics: gender, race (white, black

and other), age (≤33, 34-44, 45-53 and >53), labialis lesion stage at Day 1 (prodrome, etythema, papule or more advanced stages) and number of episodes per year (3, 4, 5, 6 and >6) in the MITT population. Difference in PSNUR between ME-609 and acyclovir arms denoted by (π_1–π_2) could also be referred to as the treatment effect of 1% hydrocortisone. Likewise, difference in PSNUR between ME-609 and vehicle arms denoted by (π_1–π_3) and that between acyclovir and vehicle arms denoted by (π_2–π_3) could be considered the overall treatment effect contributed by 1% hydrocortisone and 5% acyclovir, and by 5% acyclovir, respectively. In the analysis of primary efficacy endpoint for the overall population, only treatment difference in PSNUR between ME-609 and Acyclovir (π_1–π_2), and that between ME-609 and Vehicle (π_1–π_3) are of concern. Hence, the comparisons in PSNUR between acyclovir and vehicle (π_2–π_3) are post-hoc. Table 14 summarizes the treatment difference in PSNUR for these subgroups.

Comparing the treatment difference in PSNUR between ME-609 and acyclovir denoted by π_1–π_2, FDA analyses revealed the following:

- **Gender:** The majority of subjects (72%) enrolled were female. In general, treatment effects were greater in males than females. Male subjects had a treatment difference of 10.4%, greater than the 6.3% observed in female subjects.

- **Race:** Treatment differences in PSNUR were 8.6%, -8.8% and 12.7%, respectively for whites, blacks and "other" subjects compared with the population as a whole.

- **Age:** There was a significant downward trend in PSNUR for 1% hydrocortisone effect (See blue line in Figure 1). The youngest age group (age 33 or less) had the greatest treatment effect of 11.0%, followed by 8.5% for 34-44 year-olds, 5.6% for 45-53 year-olds, and 4.4% for the oldest age group (>53 year-olds).

- **Day 1 lesion stage:** Treatment effects were 6.7%, 4.8% and 21.4%, respectively, for subjects with Day 1 lesion stage of prodrome, erythema and papule or more advanced stages. Of note, no lesion stage- response trend was found. Those with Day 1 lesion stage papule or more advanced stages in Acyclovir group had a NUR of 14.3% (6/42), resulting in a greater treatment effect of 21.4%.

- **Number of episodes per year:** Treatment effects ranged between 5.9-13.4% for subjects with 3-6 episodes. However, no apparent treatment effect was observed for subjects with more than 6 episodes per year at baseline.

Comparing PSNUR between ME-609 and vehicle, subgroup analyses were conducted based on gender, age, baseline lesion stage and number of episodes per year, not race due to the small number of subjects in the vehicle arm: blacks (n=13) and other racial groups (n=6). Again, the treatment difference in PSNUR (π_1–π_3) measures the contribution of 5% acyclovir and 1% hydrocortisone.

- **Gender:** Treatment effect was greater in males than females. Male subjects had a greater treatment difference in PSNUR (26.1%) than female subjects (12.8%).

- **Age:** There was a significant upwards trend in PSNUR for 5% acyclovir and 1% hydrocortisone effects (See green line in Figure 3). The youngest age group age 33 or less had lowest treatment effect of 11.4%, followed by 13.2% for age between 34-44, 18.2% for age group 45-53, and 23.9% for the oldest age group (>53).

- **Day 1 lesion stage;** There was a significant upwards trend for 5% acyclovir and 1% hydrocortisone effects. The differences in PSNUR ($\pi_1-\pi_3$) were 14.4%, 18.4% and 22.4%, respectively for subjects with Day 1 lesion stage of prodrome, erythema and papule or more advanced stages.

- **Number of episodes per year:** Treatment effects ranged between 4.8-24.8% for number of episodes per year. However, no apparent treatment trend in PSNUR was observed.

Comparing the PSNUR between acyclovir and vehicle, subgroup analyses were conducted based on gender, age, baseline lesion stage and number of episodes per year, not race due to small number of subjects in the vehicle arm: blacks (n=13) and other racial group (n=6). The treatment effect $\pi_2-\pi_3$ measures the contribution of 5% acyclovir in PSNUR.

- **Gender:** Treatment effect was greater in males than females. Male subjects had a greater treatment difference in PSNUR (26.1%) than female subjects (12.8%).

- **Age:** There was a significant upwards trend in PSNUR for 5% acyclovir effects (See pink line in Figure 1). The youngest age group age 33 or less had almost no treatment effect of 0.4%, followed by 4.7% for age between 34-44, 12.6% for age group 45-53, and 19.5% for the oldest age group (>53).

- **Day 1 lesion stage:** 5% acyclovir may be more effective for subjects with Day 1 lesion of erythema than those with Day 1 lesion of prodrome. The differences in PSNUR were 7.7% and 13.6%, respectively, for subjects with Day 1 lesion stage of prodrome or erythema. In addition, 5% acyclovir appeared to have no effect among subjects with Day 1 stage papule or more advanced stages.

- **Number of episodes per year:** Treatment effects ranged between 7.5-30.6% for number of episodes per year. However, no apparent treatment trend was observed.

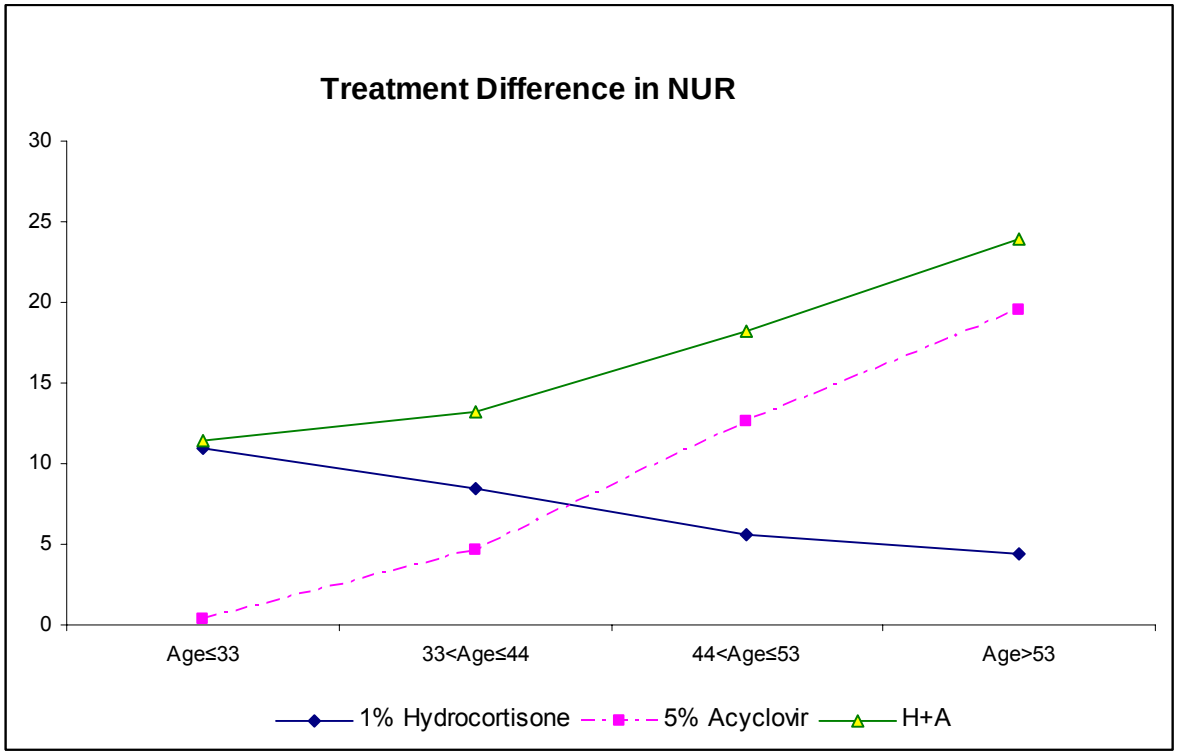


Figure 1. Treatment Difference in PSNUR by Age Groups

Table 14: 609-04: Primary Efficacy Endpoint: Overall and Subgroup*

	ME-609			Acyclovir			Vehicle					
	r_1	n_1	π_1(%)	r_2	n_2	π_2(%)	r_3	n_3	π_3(%)	$\pi_1-\pi_2$	$\pi_1-\pi_3$	$\pi_2-\pi_3$
Overall	249	588	42.4	211	603	35.0	59	228	25.9	7.4	16.5	9.1
Male	71	153	46.4	64	178	36.0	13	64	20.3	10.4	26.1	15.7
Female	178	435	40.9	147	425	34.6	46	164	28.1	6.3	12.8	6.5
Age≤33	56	150	37.3	41	156	26.3	14	54	25.9	11.0	11.4	0.4
33<Age≤44	67	157	42.7	55	161	34.2	18	61	29.5	8.5	13.2	4.7
44<Age≤53	64	150	42.7	49	132	37.1	12	49	24.5	5.6	18.2	12.6
Age>53	62	131	47.3	66	154	42.9	15	64	23.4	4.4	23.9	19.5
White	230	540	42.6	188	551	34.1	51	209	24.4	8.5	18.2	9.7
Black	12	34	35.3	15	34	44.1	4	13	30.8	-8.8	4.5	13.3
Other	7	13	53.9	7	17	41.2	4	6	66.7	12.7	-12.8	-25.5
Lesion Stage at Day1												
Prodrome	175	386	45.3	153	396	38.6	43	139	30.9	6.7	14.4	7.7
Erythema	59	158	37.3	52	160	32.5	14	74	18.9	4.8	18.4	13.6
Papule+	15	42	35.7	6	42	14.3	2	15	13.3	21.4	22.4	1.0
Number of Episodes per year												
3	58	118	49.2	47	115	40.9	11	42	26.2	8.3	23.0	14.7
4	75	182	41.2	52	161	32.3	9	55	16.4	8.9	24.8	15.9
5	36	89	40.5	36	104	34.6	15	42	35.7	5.9	4.8	-1.1
6	35	81	43.2	34	114	29.8	8	36	22.2	13.4	21.0	7.6
>6	45	118	38.1	42	109	38.5	16	53	30.2	-0.4	7.9	8.3

*. Data Source: FDA analysis. Excluding 24 subjects from ITT population.
r_j - # of subjects with non-ulcerative recurrence, n_j – sample size$_t$ π_j -estimated PSNUR in the jth group, j=1,2,3 for ME-609, Acyclovir and Vehicle, respectively. Papule+ includes any of the following: vesicle, ulcer (soft or hard crust).

6.5.4 Treatment-by-Baseline Characteristic Interaction

Treatment-by-Age Interaction

Significant treatment-by-age interactions on PSNUR were observed. As mentioned before, the comparisons of PSNUR between ME-609 and acyclovir, and between ME-609 and vehicle are protocol-defined primary comparisons. The comparisons of PSNUR between acyclovir and vehicle

are post-hoc because they are not protocol-defined. FDA's analyses using quartiles of baseline age as cut points to categorize age into four groups were also post-hoc.

There was a significant downward trend in NUR for 1% hydrocortisone effect (ME-609 - acyclovir) denoted by blue line in Figure 1. The youngest age group age 33 or less had greatest treatment effect of 11.0%, followed by 8.5% for age between 34-44, 5.6% for age group 45-53, and 4.4% for the oldest age group (>53).

There was a significant upward trend in NUR for the combined 5% acyclovir and 1% hydrocortisone effect (ME-609 - vehicle) denoted by green line in Figure 1. The youngest age group of age 33 or less had the lowest treatment effect of 11.4%, followed by 13.2% for age between 34-44, 18.2% for age group 45-53, and 23.9% for the oldest age group (>53).

There was a significant upward trend in NUR for 5% acyclovir effect (acyclovir-vehicle) denoted by pink line in Figure 1. The youngest age group of age 33 or less had almost no treatment effect of 0.4%, followed by 4.7% for age between 34-44, 12.6% for age group 45-53, and 19.5% for the oldest age group (>53).

6.6 Evaluation of Secondary Efficacy Endpoints

6.6.1. Method

In Study 609-04, the secondary endpoints were episode duration and episode duration to normal skin (Table 14). Episode duration was measured from start of treatment to loss of hard crust for an ulcerative lesion (investigator-assessed), and from start of treatment to time of no signs or symptoms for a non-ulcerative herpes recurrence (investigator-assessed). Episode duration to normal skin (secondary endpoint): measured from start of treatment to normal skin for an ulcerative lesion (investigator-assessed), and from start of treatment to time of no signs or symptoms for a non-ulcerative herpes recurrence (investigator-assessed). Superiority for mean episode duration in the ME-609 arm versus vehicle arm was required at a significant level of 0.05.

It appears that 'episode duration' and 'episode duration to normal skin' are deviated from normal distributions and therefore means would not be appropriate to use for comparisons. Figures 2 and 3 show histograms of duration to normal skin and episode duration. Both are exhibited skewed to the left with long-tails, and testing for normality were both rejected, $p<0.0001$ by Shapiro-Wilk tests. Table 13 summarizes basic statistics overall and those by treatment groups. In general, means are 0.6-0.9 days greater than medians. Please note that the univariate analyses on these two variables were performed on observed data. In other words, missing in these variables was ignored.

Hence, the FDA statistical reviewer applied Hodges-Lehmann's (H-L) approach[1,2] to estimate median treatment differences. The analyses were conducted on the ITT population and the missing 'time-to' parameters were imputed using the Applicant's approach.

Table 14. Study 609-04: Episode Duration and Duration to Normal Skin (ITT Population)

	n	mean	std	Median	Mean-median	minimum	maximum	p25	p75
Episode Duration to Normal Skin*									
	1397	8.03	4.70	7.45	0.58	0.00	51.13	4.65	10.65
ME-609	582	7.58	4.19	7.03	0.55	0.48	34.00	4.55	9.96
Acyclovir	591	8.01	4.55	7.44	0.57	0.20	36.42	4.74	10.59
Vehicle	224	9.24	5.97	8.47	0.77	0.00	51.13	4.83	12.26
Episode Duration*									
	1397	5.54	2.96	4.84	0.70	0.00	24.86	3.54	7.13
ME-609	582	5.45	3.04	4.72	0.73	0.48	24.86	3.43	6.98
Acyclovir	591	5.51	2.74	4.92	0.59	0.20	14.98	3.62	7.02
Vehicle	224	5.86	3.30	4.99	0.87	0.00	21.36	3.56	7.83

Source: FDA analyses. *. Excluding Missing.

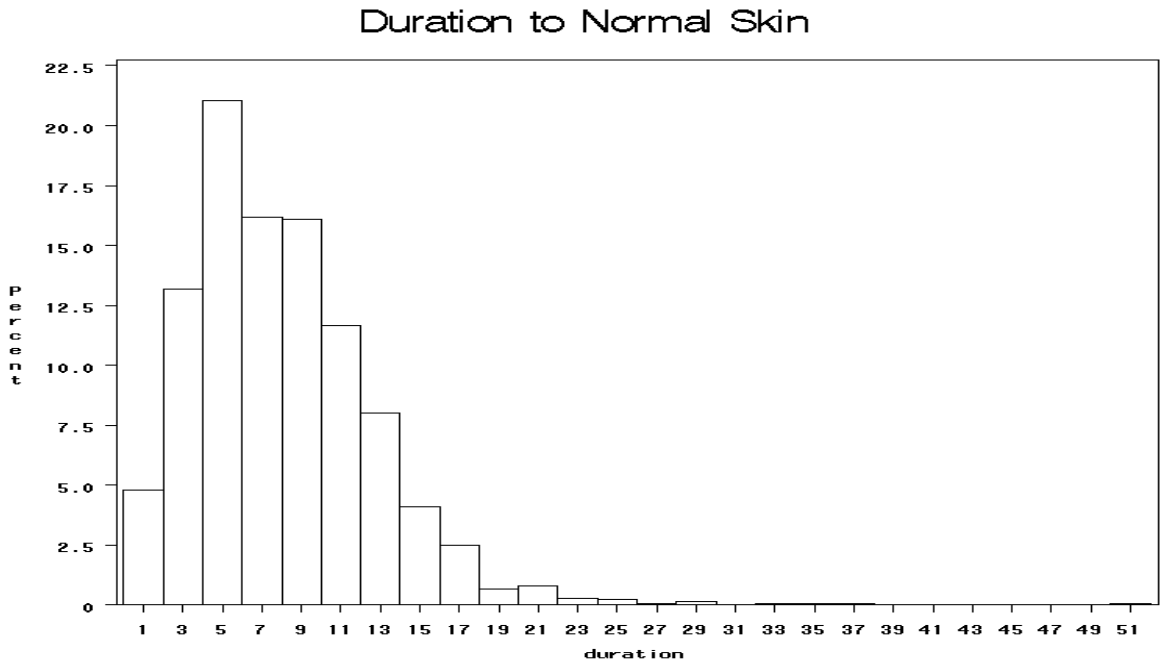


Figure 2. Histogram: Duration to Normal Skin

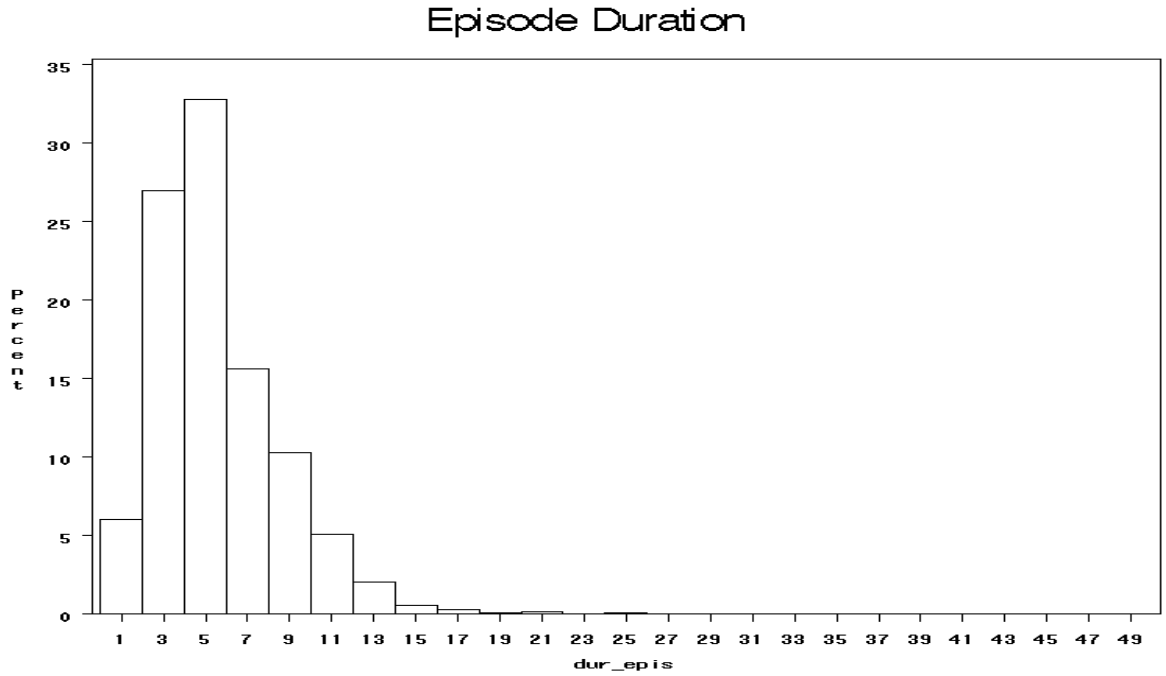


Figure 3. Histogram: Episode Duration

6.6.2 Results of Sensitivity Analyses of the Secondary Endpoints

The sensitivity analyses of the duration to healing for the overall ITT population, and for lesion stage at Day 1 (prodrome versus erythema) were performed. Missing values were imputed using the protocol-defined algorithm. The results are summarized in Table 15 for the comparisons between ME-609 and vehicle, in Table 16 for the comparisons between ME-609 and acyclovir and in Table 16 for the comparisons between acyclovir and vehicle.

The computations of episode duration and episode duration to normal skin involve the following three time-to-events components:

1) time from treatment initiation to loss of hard crust and time from treatment initiation to normal skin for an ulcerative lesion, both were defined as tertiary efficacy endpoints; and
2) time from treatment initiation to no signs or symptoms for a non-ulcerative lesion.

Episode Duration

Part 3 of Table 15 summarizes the observed median episode duration by treatment arms and the H-L median treatment difference. Using the H-L method, the median episode duration was 0.38 days shorter for the ME-609 arm (4.77 days) than the vehicle arm (5.09 days), p=0.062 by the Kruskal-Wallis test.

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

As shown in Part 3 of Table 16, the median H-L episode duration was 0.15 days shorter for the ME-609 arm (4.77 days) than the acyclovir arm (4.94 days), p>0.05 by Kruskal-Wallis test.

Of note, the Applicant reported mean episode duration of 5.4, 5.5 and 5.9 days, respectively in the ME-609, acyclovir and vehicle arms (Reference: Table 13, Study 609-04 Clinical Study Report, Page 71). The mean treatment differences were -0.079 (p>0.05) ME-609 versus acyclovir and -0.479 days ME-609 versus vehicle, p=0.0455 by the t-test.

Episode Duration to Normal Skin

Part 5 of Table 15 summarized the median episode duration to normal skin. The observed median episode duration to normal skin was 7.13 days in the ME-609 arm and 8.67 days in the Vehicle arm. The H-L median treatment difference (ME-609 - vehicle) was -1.30 days (p<0.001) by the Kruskal-Wallis test.

As shown in Part 5 of Table 16, the median H-L episode duration was 0.33 days shorter for the ME-609 arm (7.13 days) than the Acyclovir arm (7.50 days), p>0.05 by the Kruskal-Wallis test.

Of note, the Applicant reported mean episode duration to normal skin of 7.6, 8.1 and 9.3 days, respectively in the ME-609, Acyclovir and Vehicle arms (Reference: Table 14, Study 609-04 Clinical Study Report, Page 73). The mean treatment differences were -0.425 (p>0.05) ME-609 versus Acyclovir and -1.635 days ME-609 versus Vehicle, p=0.0001 by the t-test.

Table 15. Episode Duration and Duration to Normal Skin (ITT: ME-609 versus Vehicle)*

	ME-609		Vehicle		ME-609-Vehicle				
	n	median	n	median	$median_{H-L}$	95% CI		χ^2_{KW}	p_{KW}
1. Duration to No Symptom and Signs Among Those with Non-ulcerative Recurrence									
Overall	254	4.51	60	3.77	0.69	0.06	1.35	4.6814	0.0305
Prodrome	180	4.40	43	3.92	0.46	-0.33	1.19	1.5127	0.2187
Erythema	59	4.92	14	3.60	1.52	0.16	3.26	5.1842	0.0228
Papule	15	5.83	3	10.63	-3.23	-7.97	4.88	0.2842	0.5940
≤Erythema	239	4.49	57	3.71	0.70	0.07	1.35	4.947	0.0261
2. Duration of Return to Loss Hard Crust Among those with Ulcerative Recurrence***									
Overall	347	5.04	172	5.76	-0.61	-1.10	-0.13	6.4491	0.0111
Prodrome	211	5.23	97	5.55	-0.43	-1.09	0.21	1.8691	0.1716
Erythema	100	4.68	60	5.71	-0.68	-1.50	0.17	2.3345	0.1265
Papule	31	4.41	13	7.10	-2.10	-3.60	-0.36	6.3559	0.0117
≤Erythema	311	5.06	157	5.55	-0.48	-1.00	0.02	3.5697	0.0588
3. Episode Duration**									
Overall	601	4.77	232	5.09	-0.38	-0.79	0.02	3.4924	0.0617
Prodrome	391	4.72	140	4.88	-0.31	-0.82	0.18	1.4556	0.2276

Erythema	159	4.76	74	4.96	-0.17	-0.95	0.54	0.2768	0.5988
Papule	46	4.91	16	7.17	-1.96	-3.60	-0.19	4.8932	0.0270
≤Erythema	550	4.73	214	4.89	-0.27	-0.70	0.13	1.7721	0.1831
4. Duration of Reaching Normal Skin Among Those with Ulcerative Recurrence									
Overall	347	9.05	172	10.08	-1.02	-1.75	-0.27	7.3333	0.0068
Prodrome	211	9.09	97	9.57	-0.37	-1.33	0.58	0.521	0.4704
Erythema	100	8.81	60	11.02	-1.80	-3.11	-0.37	5.846	0.0156
Papule	31	10.00	13	10.28	-1.28	-3.44	0.82	2.0384	0.1534
≤Erythema	311	9.02	157	10.02	-0.93	-1.71	-0.10	5.0456	0.0247
5. Episode Duration to Normal Skin									
Overall	601	7.13	232	8.67	-1.30	-1.98	-0.60	13.117	0.0003
Prodrome	391	6.88	140	7.52	-0.78	-1.63	0.06	3.1515	0.0759
Erythema	159	7.52	74	10.02	-1.91	-3.23	-0.48	6.8812	0.0087
Papule	46	8.40	16	10.35	-2.18	-4.24	-0.06	4.3068	0.0380
≤Erythema	550	7.01	214	8.12	-1.17	-1.90	-0.46	9.85	0.0017

*Source: FDA analyses using imputed values for missing. **$median_{H-L}$ – Hodges-Lehmann's median treatment difference**
χ^2_{KW} and p_{KW} - Kruskal-Wallis chi-square statistic and p-value.
. Secondary Efficacy Endpoint. * Tertiary Efficacy Endpoints.

Table 16. Episode Duration and Duration to Normal Skin (ITT: ME-609 versus Acyclovir)*

	ME-609		Acyclovir		ME-609-Acyclovir				
	N	median	n	median	$median_{H-L}$	95% CI		χ^2_{KW}	p_{KW}
1. Duration to No Symptom and Signs Among Those with Non-ulcerative Recurrence									
Overall	254	4.51	216	4.54	0.08	-0.31	0.50	0.21	0.6502
Prodrome	180	4.40	155	4.32	0.14	-0.31	0.60	0.42	0.5194
Erythema	59	4.92	54	4.82	-0.16	-1.18	0.76	0.07	0.7893
Papule	15	5.83	6	5.84	0.07	-3.19	3.46	0.00	0.9379
≤Erythema	239	4.49	209	4.49	0.06	-0.34	0.47	0.11	0.7442
2. Duration of Return to Loss Hard Crust Among those with Ulcerative Recurrence									
Overall	347	5.04	394	5.50	-0.26	-0.62	0.08	2.19	0.1391
Prodrome	211	5.23	242	5.63	-0.23	-0.69	0.20	1.10	0.2935
Erythema	100	4.68	110	5.14	-0.42	-1.05	0.26	1.20	0.2741
Papule	31	4.41	41	4.77	-0.02	-1.19	0.88	0.00	0.9592
≤Erythema	311	5.06	352	5.55	-0.29	-0.67	0.08	2.26	0.1329
3. Episode Duration									
Overall	601	4.77	610	4.94	-0.18	-0.46	0.08	1.69	0.1934
Prodrome	391	4.72	397	4.95	-0.15	-0.50	0.17	0.88	0.3495
Erythema	159	4.76	164	4.97	-0.32	-0.89	0.22	1.13	0.2875
Papule	46	4.91	47	4.83	0.15	-0.85	1.09	0.07	0.7968
≤Erythema	550	4.73	561	4.95	-0.19	-0.50	0.08	1.92	0.1662
4. Duration of Reaching Normal Skin Among Those with Ulcerative Recurrence									
Overall	347	9.05	394	9.21	-0.12	-0.67	0.37	0.26	0.6118
Prodrome	211	9.09	242	8.96	0.04	-0.61	0.63	0.02	0.8896
Erythema	100	8.81	110	9.99	-0.68	-1.76	0.42	1.55	0.2136
Papule	31	10.00	41	9.00	0.35	-1.40	2.19	0.22	0.6369
≤Erythema	311	9.02	352	9.21	-0.19	-0.76	0.34	0.47	0.4926
5. Episode Duration to Normal Skin									
Overall	601	7.13	610	7.50	-0.33	-0.79	0.09	2.16	0.1412

Prodrome	391	6.88	397	6.96	-0.23	-0.79	0.30	0.67	0.4125
Erythema	159	7.52	164	8.18	-0.64	-1.54	0.25	2.00	0.1572
Papule	46	8.40	47	8.20	-0.23	-1.94	1.24	0.15	0.6951
≤Erythema	550	7.01	561	7.41	-0.35	-0.83	0.10	2.19	0.1385

*Source: FDA analyses using imputed values for missing. **$median_{H-L}$ – Hodges-Lehmann's median treatment difference.** χ^2_{KW} and p_{KW} - Kruskal-Wallis chi-square statistic and p-value.

Table 17. Episode Duration and Duration to Normal Skin (ITT:Acyclovir versus Vehicle)*

	Acyclovir		Vehicle		Acyclovir-Vehicle				
	n	Median	n	median	$median_{H-L}$	95% CI		χ^2_{KW}	p_{KW}
1. Duration to No Symptom and Signs Among Those with Non-ulcerative Recurrence									
Overall	216	4.54	60	3.77	0.63	-0.05	1.28	3.3294	0.0681
Prodrome	155	4.32	43	3.92	0.31	-0.60	1.08	0.487	0.4853
Erythema	54	4.82	14	3.60	1.76	0.36	3.42	6.4929	0.0108
Papule	6	5.84	3	10.63	-3.16	-9.77	9.09	0.6	0.4386
≤Erythema	209	4.49	57	3.71	0.65	0.00	1.31	3.8067	0.0510
2. Duration of Return to Loss Hard Crust Among those with Ulcerative Recurrence									
Overall	394	5.50	172	5.76	-0.36	-0.84	0.11	2.275	0.1315
Prodrome	242	5.63	97	5.55	-0.22	-0.88	0.43	0.4491	0.5028
Erythema	110	5.14	60	5.71	-0.23	-1.05	0.57	0.3522	0.5529
Papule	41	4.77	13	7.10	-1.82	-3.53	-0.34	5.4608	0.0194
≤Erythema	352	5.55	157	5.55	-0.21	-0.71	0.30	0.6894	0.4064
3. Episode Duration**									
Overall	610	4.94	232	5.09	-0.21	-0.63	0.19	1.0274	0.3108
Prodrome	397	4.95	140	4.88	-0.18	-0.73	0.35	0.4361	0.5090
Erythema	164	4.97	74	4.96	0.15	-0.56	0.85	0.1416	0.7067
Papule	47	4.83	16	7.17	-1.96	-3.77	-0.27	5.2786	0.0216
≤Erythema	561	4.95	214	4.89	-0.08	-0.52	0.33	0.1712	0.6790
4. Duration of Reaching Normal Skin Among Those with Ulcerative Recurrence									
Overall	394	9.21	172	10.08	-0.86	-1.57	-0.09	5.1606	0.0231
Prodrome	242	8.96	97	9.57	-0.30	-1.30	0.64	0.3706	0.5427
Erythema	110	9.99	60	11.02	-1.11	-2.44	0.17	2.8476	0.0915
Papule	41	9.00	13	10.28	-1.96	-3.88	0.38	2.7192	0.0991
≤Erythema	352	9.21	157	10.02	-0.67	-1.47	0.08	2.9126	0.0879
5. Episode Duration to Normal Skin									
Overall	610	7.50	232	8.67	-0.97	-1.67	-0.23	6.886	0.0087
Prodrome	397	6.96	140	7.52	-0.52	-1.41	0.35	1.352	0.2449
Erythema	164	8.18	74	10.02	-1.29	-2.56	0.06	3.4073	0.0649
Papule	47	8.20	16	10.35	-2.00	-3.93	0.32	2.9625	0.0852
≤Erythema	561	7.41	214	8.12	-0.83	-1.56	-0.06	4.5939	0.0321

*Source: FDA analyses using imputed values for missing. **$median_{H-L}$ – Hodges-Lehmann's median treatment difference.** χ^2_{KW} and p_{KW} - Kruskal-Wallis chi-square statistic and p-value.
**Episode duration (secondary endpoint) was measured from start of treatment to loss of hard crust for an ulcerative lesion ,and from start of treatment to time of no signs or symptoms for a non-ulcerative herpes recurrence, all were investigator-assessed.

6.7 Sensitivity Analyses of Selected Tertiary Efficacy Endpoints

Sensitivity analyses of tertiary efficacy endpoints were summarized in Tables 17-20 using the H-L approach for evaluation of continuous tertiary efficacy parameters and Table 20 for categorical tertiary efficacy parameters. The following findings were observed:

Among those with ulcerative HSV recurrence,

1) The observed median duration to loss of hard crust was 5.02 days in the ME-609 arm, 5.38 days in the acyclovir arm and 5.76 days in the vehicle arm. The median reduction of duration to loss of hard crust using the H-L's approach was -0.58 days ME-609 versus vehicle, p=0.018. No significant difference was found between ME-609 and acyclovir arms. For details please refer to Part 2 of Tables 15 and 16.

2) The median duration to reaching normal skin was 8.98 days in the ME-609, 9.01 days in the acyclovir arm, and 10.08 days in the Vehicle arm. The median reduction of duration to reaching normal skin using the H-L's approach was -1.01 days ME-609 versus vehicle, p=0.011. No significant difference was found between ME-609 and acyclovir arms. For details please refer to Part 4 of Tables 15 and 16.

For the overall population,

3) The observed median durations of tenderness were 4, 4 and 5 days, respectively, in the ME-609 arm, acyclovir arm and vehicle arm. The median reduction of duration of tenderness using the H-L's approach was -1 day ME-609 versus Vehicle, p=0.001. No significant difference was found between ME-609 and Acyclovir arms. For details please refer to Part 1 of Tables 18 and 19.

4) The median reductions of average cumulative lesion area (mm^2) were 6.0 and 13.0 respectively in the ME-609 arm, compared with that in the acyclovir arm and vehicle arm, p<0.01. See Part 2 of Tables 18 and 19.

5) The median reductions of Average Maximum Area (mm^2) were 2.0 and 4.0 respectively in the ME-609 arm, compared with that in the acyclovir arm and vehicle arm, p<0.01. See Part 3 of Tables 18 and 19.

6) Subjects treated with ME-609 were significantly less likely to have severe tenderness (4.8%) than those treated with vehicle (12.3%), p<0.01. 6.2% subjects in the acyclovir arm reported severe tenderness compared to 4.8% subjects in the ME-609 arm, p>0.05. See Part 1 of Table 20.

7) Among subjects with non-ulcerative recurrence, subjects' overall assessments of the treatment appeared to be similar across treatment arms with 92%-96% of the subjects reporting feeling 'better' (p>0.05). Among subjects with ulcerative recurrence, 73.8%, 68.0% and 58.7% subjects, respectively in the ME-609, acyclovir and vehicle arms reported 'better.' The overall assessment was significantly different between

ME-609 and vehicle arms ($p<0.01$), but not between ME-609 and acyclovir arms ($p>0.05$). See Part 2 of Table 20.

Table 18: 609-04: Tertiary Efficacy Endpoints (ME-609 versus Vehicle)*

	ME-609		Vehicle		ME-609-Vehicle				
	n	median	N	median	$median_{H-L}$	95% CI		χ^2_{KW}	p_{KW}
1. Duration of Tenderness in Days									
Overall	519	4.0	209	5.0	-1.0	-2.0	0.0	12.252	0.001
Prodrome	343	4.0	124	4.5	-1.0	-2.0	0.0	4.835	0.028
Erythema	139	4.0	71	5.0	-1.0	-2.0	0.0	4.394	0.036
Papule	37	3.0	14	4.0	-1.0	-4.0	1.0	2.615	0.106
≤Erythema	482	4.0	195	5.0	-1.0	-2.0	0.0	10.149	0.001
2. Average Cumulative Area (mm^2)									
Overall	588	31.5	228	49.0	-13.0	-24.4	-3.8	13.614	0.0002
Prodrome	386	29.5	139	34.0	-5.0	-15.5	0.3	3.252	0.071
Erythema	158	32.0	74	82.5	-32.0	-64.0	-8.0	9.559	0.002
Papule	43	45.0	15	97.0	-53.0	-95.0	-1.0	4.322	0.038
≤Erythema	544	30.0	213	47.0	-12.0	-23.0	-2.8	11.519	0.001
3. Average Maximum Area (mm^2)									
Overall	588	12.0	228	20.0	-4.0	-8.0	0.0	9.467	0.002
Prodrome	386	12.0	139	16.0	-2.0	-6.0	1.0	2.973	0.085
Erythema	158	15.0	74	24.0	-8.0	-14.7	0.0	5.800	0.016
Papule	43	16.0	15	25.0	-10.0	-24.0	5.0	1.950	0.163
≤Erythema	544	12.0	213	18.0	-4.0	-8.0	0.0	8.359	0.004

*. Source: FDA analysis. **$median_{H-L}$ – Hodges-Lehmann's median treatment difference.**

Table 19: 609-04: Tertiary Efficacy Endpoints (ME-609 versus Acyclovir)*

	ME-609		Acyclovir		ME-609- Acyclovir				
	n	median	N	median	$median_{H-L}$	95% CI		χ^2_{KW}	p_{KW}
1. Duration of Tenderness in Days									
Overall	519	4.0	544	4.0	0.0	-1.0	1.0	1.942	0.164
Prodrome	343	4.0	358	4.0	0.0	-1.0	1.0	1.897	0.168
Erythema	139	4.0	148	4.0	0.0	-1.0	1.0	0.103	0.748
Papule	37	3.0	38	4.0	-1.0	-3.0	1.0	3.166	0.075
≤Erythema	482	4.0	506	4.0	0.0	-1.0	1.0	0.930	0.335
2. Average Cumulative Area (mm^2)									
Overall	588	31.5	602	45.0	-6.0	-12.3	0.0	9.503	0.002
Prodrome	386	29.5	395	40.0	-3.0	-10.3	0.0	4.115	0.043
Erythema	158	32.0	160	49.0	-8.0	-21.4	0.7	3.268	0.071
Papule	43	45.0	47	68.0	-26.0	-65.0	2.0	3.336	0.068
≤Erythema	544	30.0	555	43.0	-4.0	-11.3	0.0	7.435	0.006
3. Average Maximum Area (mm^2)									
Overall	588	12.0	602	16.0	-2.0	-5.0	0.0	6.937	0.008
Prodrome	386	12.0	395	16.0	0.0	-4.0	1.0	2.908	0.088
Erythema	158	15.0	160	16.0	-4.0	-8.7	0.4	3.080	0.079

Papule	43	16.0	47	24.0	-5.0	-16.0	4.0	1.210	0.271
≤Erythema	544	12.0	555	16.0	-1.0	-5.0	0.0	5.939	0.015

*. Source: FDA analysis. **median$_{H-L}$ – Hodges-Lehmann's median treatment difference.**

Table 20. 609-04: Maximum Tenderness Severity and Subject's Overall Assessment*

	ME-609		Acyclovir		Vehicle	
	n_1	π_1(%)	n_2	π_2(%)	n_3	π_3(%)
1. Maximum Tender Severity						
None	69	11.3	57	9.5	19	8.3
Mild	264	44.9	282	46.8	95	41.7
Moderate	227	38.6	226	37.5	86	37.7
Severe	28	4.8	37	6.2	28	12.3
p-value			>0.05		0.0013	
2. Subject's Overall Assessment						
Subjects with Non-ulcerative Recurrence						
Better	239	96.0%	195	92.4%	56	94.9%
Same	8	3.2%	12	5.7%	2	3.4%
Worse	1	0.4%	1	0.5%	0	0.0%
Missing	1	0.4%	3	1.4%	1	1.7%
			>0.05		>0.05	
Subjects with Ulcerative Recurrence						
Better	245	73.8%	261	68.0%	98	58.7%
Same	62	18.7%	91	23.7%	49	29.3%
Worse	25	7.5%	28	7.3%	20	12.0%
Missing	0	0.0%	4	1.0%	0	0.0%
p-value			>0.05		0.0027	

*. Source: FDA analysis.
π_j .-proportions in the jth group, j=1,2,3 for ME-609, Acyclovir and Vehicle, respectively.

6.8 Summary and Conclusions

6.8.1 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the FDA efficacy analyses for Study 609-04, the reviewers agree that ME-609 at a dose of 5-times daily for 5 days in adults and adolescents (12 years and older) with recurrent herpes labialis is efficacious.

6.9 Statistical Issues

6.9.1 Validation of Hypotheses

To provide evidence of efficacy for regulatory approval of this product, superiority of three hypothesis tests were required; Proportion of subjects with non-ulcerative recurrences for ME-609 vs. acyclovir and ME-609 vs. vehicle, and episode duration for ME-609 vs. vehicle. (Source: Section 9.7.2 Sample size and hypotheses, 609-04-protocol.pdf). Three hypotheses were proposed as shown below.

1. Hypothesis 1 would test null $H_{10:}\ \pi_M=\pi_A$ against the alternative $H_{11:}\ \pi_M\neq\pi_A$; where π_M and π_A denote the population percentage of subjects with non-ulcerative recurrence, respectively for ME-609 arm and acyclovir arm. Hypothesis 1 will be tested at the significance level 0.001 (p_1) by the Chi-square test to fulfill the requirement of one registration Phase III trial design.

2. Hypothesis 2 would test null $H_{20:}\ \pi_M=\pi_V$ against the alternative $H_{21:}\ \pi_M\neq\pi_V$; where π_M and π_V denote the population percentage of subjects with non-ulcerative recurrence, respectively for ME-609 arm and vehicle arm. Hypothesis 2 will be tested at the significance level 0.05 (p_2) by the Chi-square test.

3. Hypothesis 3 would test null $H_{30:}\ \mu_M=\mu_V$ against the alternative $H_{31::}\ \mu_M\neq\mu_V$ where μ_M and μ_V denote the population mean episode durations, respectively for ME-609 (M) arm and Vehicle (V) arm. Hypothesis 3 will be tested at the significance level 0.05 by the two-sample t-test.

where subscripts M, A and V denote ME-609 arm, acyclovir arm and vehicle arm, respectively.

It appears that the treatment difference in SPNUR between ME-609 and vehicle (Hypothesis 2) should always surpass that between ME-609 and acyclovir (Hypothesis 1). The comparisons between ME-609 arm and acyclovir arm show the contributions by 1% hydrocortisone; and between ME-609 arm and vehicle arm show the contributions by 1% hydrocortisone and 5% acyclovir.

- The treatment differences in PSNUR were 4.7%~7.1% between ME-609 arm and acyclovir arm, and 14.6%~17.3% between ME-609 arm and vehicle arm, using different methods in FDA's sensitivity analyses (Table 12).

- The significance levels for the comparison of PSNUR between ME-609 arm and acyclovir arm (p_1) were systematically lower (larger p-value by the Chi-square test) than the corresponding value (p_2) for the comparison of PSNUR between ME-609 arm and vehicle arm ($p_2 < p_1$), regardless of different methods used in estimation of PSNUR.

If a pre-assigned value p_1 for H_{10} versus H_{11} should be at 0.001, then the pre-assigned value p_2 would be at least 0.001 for Hypothesis 2 since $p_2< p_1<0.001$. As a result, the pre-defined success criteria p_2 at 0.05 level for the Hypothesis 2 should be revised.

6.9.2 609-04 Efficacy Data Do Not Meet Pre-defined Success Criteria

The efficacy data of 609-04 show that ME-609 cream is numerically superior in treatment of herpes labialis compared with acyclovir and vehicle. However, the significance levels do not meet success criteria pre-defined for a single registration study: p=0.001 for demonstrating

prevention of ulcerative herpes lesions with ME-609 versus acyclovir, and p=0.05 for a decrease in episode duration with ME-609 versus vehicle.

For the primary efficacy endpoint defined as the percentage of subjects with non-ulcerative recurrence (PSNUR), we have the following comments.

- At the design stage of 609-04, acyclovir arm (5% acyclovir in ME-609 vehicle) was assumed to have no effect in prevention of developing an ulcerative recurrence. Numerically, the acyclovir arm was expected to have a PSNUR of 25%, the same as that in the ME-609 vehicle[3,4].

- The efficacy data in 609-04 showed that the PSNUR in the acyclovir arm was much greater at approximately 36%, resulting in a lower than expected treatment effect in PSNUR ME-609 versus acyclovir. This implied that 5% acyclovir in ME-609 vehicle may have a different effect in the prevention of an ulcerative recurrence compared to 5% acyclovir in Zovirax vehicle.

For the secondary efficacy endpoint defined as mean episode duration, we have three comments.

- 'Time to event' parameters such as 'episode duration,' 'episode duration to normal skin' and other related components are 'long tailed' and are likely different from normal distributions. Hence, summarizing treatment difference using mean and t-test may not be appropriate.
- The Applicant reported a significant mean reduction of 0.5 days in episode duration ($p<0.05$), and the reviewer reported a median reduction of 0.35 days using the H-L approach ($p>0.05$).
- Although 'Episode Duration' has been used as one of the key efficacy endpoints for 609-04, but the two components 'duration to no symptoms and signs' for those with NUR and 'duration to loss hard crust' for those with UR appear to be at different stages clinically. Perhaps the 'Episode Duration to Normal Skin' used for evaluation of other herpes labialis trials[5] may be considered as a key efficacy endpoint as it would have the same lesion healing stage as 'Normal' for both NUR and UR groups.

In summary, to avoid the need for post-hoc changes of decision rules, the strength of supportive evidence should be carefully considered to define success criteria in the design stage.

6.9.3 References used in Statistical Review

1. Hodges, J. L and Lehmann E. L. (1963). Estimates of location based on rank tests, The Annals of Mathematical Statistics, 34: 598:611.

2. Lehmann E. L. (1975). Nonparametrics: Statistical methods based on ranks, Holden-Day, San Francisco.

3. FDA review of NDA 21-478 Zovirax cream.

4. Spruance, S.L., et al., Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinicaltrials. Antimicrob Agents Chemother, 2002. **46**(7): p. 2238-43.

5. Evans, T.G., et al., Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. Antimicrob Agents Chemother, 2002. **46**(6): p. 1870-4.

6. Hydrocortisone Topical. Medline Plus.
Web address: http://www.nim.nih.gov/medlineplus/druginfo/meds/a682793.html.

6.10 Additional Efficacy Analyses/Statistical Issues

Efficacy results for Study 609-06

The FDA reviewer conducted sensitivity efficacy analyses for Study 609-06. The analyses were performed for the ITT population which consisted of 77 subjects in the ME-609 arm and 30 in the acyclovir arm. The results are summarized in Tables 21 and 22. The Percentage of Subjects with Non-ulcerative Recurrence (PSNUR) was 42.1% and 37.9%, respectively, for the ME-609 arm and acyclovir arm (Table 21). The treatment difference between ME-609 and acyclovir was 4.2% (95% CI -15.6, 25.6%), indicating that the subjects in the ME-609 arm were doing slightly better, $p>0.05$. This endpoint is the tertiary efficacy endpoint in Study 609-06.

Table 21: 609-06: Percentage of Subjects with Non-ulcerative Recurrence*[1]

ME-609 (n=77)		Acyclovir (n=30)		ME-609-Acyclovir			
r_1	π_1(%)	r_2	π_2(%)	π_1-π_2(%)	95% CI		p
32	42.1	11	37.9	4.2	-15.6	25.4	0.640

*. Data Source: FDA analysis on ITT population.
1. Tertiary Efficacy Endpoint, π_j: estimated PSNURs , j=1,2 for ME-609 and Acyclovir groups.

Table 22: 609-06: Other Efficacy Endpoints

ME-609 (n=77)		Acyclovir (n=30)		ME-609-Acyclovir			
n	median	N	median	$Median_{H-L}$	95% CI		p_{KW}
1. Episode Duration[1]							
77	6.38	30	6.61	-0.07	-1.06	1.00	0.835
2. Duration to Normal Skin[2]							
All Recurrence (Observed Data)							
77	8.05	30	8.83	-0.01	-1.63	1.85	0.986
Ulcerative Recurrence (Observed Data)							
45	9.69	19	10.46	0.05	-1.81	2.51	0.901
3. Maximum Lesion Area (mm^3)							

All Recurrence							
76	4	29	4	0	-4	3	0.864
Ulcerative Recurrence							
44	22	18	20	0	-8	15	0.720
4. Time to Next Herpes Recurrence (days)[3,b]							
44	150.5	14	121.0				

a. Data Source: FDA analysis on ITT population.
b. Applicant's Addendum, Table 14.2.5.1, ME-609/No. 609-06, October 2008.
1. Primary Efficacy Endpoint.
2. Tertiary Efficacy Endpoint, π_j (j=1,2): estimated PSNURs.
3. Secondary Efficacy Endpoint.
median$_{H-L}$ – Hodges-Lehmann's median treatment difference.

7. INTEGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

The safety analysis in Study 609-04 provides safety data for immunocompetent adults ages ≥ 18 years who received ME-609 cream for treatment of recurrent herpes labialis. The safety analysis in Study 609-06 provides safety data for HIV-infected adults ages ≥ 18 years who received ME-609 cream for treatment of recurrent herpes labialis. The safety analysis in Study 609-07 provides safety data for adolescents ages 12 to 17 years who received ME-609 cream for treatment of recurrent herpes labialis. Overall, the safety data provided in this submission are adequate for evaluation of exposure with regard to the size of the safety database and the duration of administration.

As discussed in Section 5.3, the major differences among Studies 609-04, 609-06, and 609-07 were study design (Studies 609-04 and 609-06 were randomized controlled trials; Study 609-07 was an open-label, single-arm trial), definitions of patient population (especially age at enrollment and immune status) and history of recurrent herpes labialis (Study 609-04: at least three episodes during the last 12 months; Studies 609-06 and 609-07: at least two episodes during the last 12 months). These factors complicated attempts for pooling data between studies. Although other elements of study design were similar, the safety analyses presented below were performed separately on each study.

Overall, no new or unexpected toxicities were observed with ME-609 cream compared to available safety data on its two approved principal constituents, 5% acyclovir cream and 1% hydrocortisone cream. Overall, the adverse event profile of ME-609 in adolescents was similar to adults. Additionally, the adverse event profile of ME-609 in a selected population of HIV-infected adults appears similar to immunocompetent adults.

No deaths were reported in any of these trials. There was no evidence of an increase in discontinuation due to toxicity for ME-609 compared to acyclovir or vehicle, respectively (please refer to Section 7.3).

Serious adverse events (SAEs) were reported in 3 subjects in Study 609-04, one subject in Study 609-06, and zero subjects in Study 609-07. In Study 609-04, SAEs included coronary artery disease (ME-609 – 1 subject), chest pain (ME-609 – 1 subject), and pneumonia (acyclovir – 1 subject). In Study 609-06, one subject (acyclovir group) reported pneumonia. None of these SAEs were considered related to study treatment by study investigators.

In Study 609-04, moderate-to-severe intensity of AEs were reported in 14 (2.3%) subjects receiving ME-609, 5 subjects (0.8%) receiving acyclovir, and 4 subjects (1.7%) receiving vehicle. Overall rates were less than 1% for each of these adverse reactions. Adverse reactions of severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in 2 subjects receiving ME-609 (lip swelling, application site irritation), and one subject receiving vehicle (dry lips).

In Study 609-06, adverse reactions of moderate-to-severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site hypersensitivity). In Study 609-07, adverse reactions of moderate-to-severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site inflammation).

In Study 609-04, treatment-related AEs (all grades, considered definitely, probably or possibly related to study treatment by study investigators) were reported in 28 (4.7%) subjects receiving ME-609, 18 (3.0%) subjects receiving acyclovir, and 10 (4.3%) subjects receiving vehicle. Most AEs were mild and included dry lips; chapped lips; cheilitis; dysgeusia; drying or flaking of the skin; transient burning or tingling following application; erythema; pigmentation changes; application site reaction including signs and symptoms of inflammation. Dry lips occurred in 1.2% of subjects receiving ME-609, 0.3% of subjects receiving acyclovir, and 1.3% of subjects receiving vehicle alone. All other AEs occurred in less than 1% of subjects in each treatment group.

In Study 609-06, treatment-related AEs (all grades, considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site hypersensitivity). In Study 609-07, treatment-related AEs (all grades, considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site inflammation). Please refer to Sections 7.3 and 7.4 for additional details.

Of note, no clinical laboratory evaluations were performed in the phase 3 trials for ME-609 cream. The absence of clinical laboratory data is reasonable since ME-609 is a topical product with minimal systemic absorption.

Reviewer Comment
The Applicant's common AE frequencies were overall similar to the review team's analyses. This reviewer also agrees with the Applicant's assessments of causality of adverse events.

Overall, ME-609 appears safe for the proposed treatment indication in the proposed patient population.

Of note, in Study 609-04 there were 43 subjects (7.2%) aged 65 and over who received ME-609. In Studies 609-06 and 609-07, there were no subjects aged 65 and over.

To date, no clinical trials have been conducted with ME-609 in patients less than 12 years old. Due to the pathophysiology and epidemiology of the disease, this reviewer believes ME-609 is unlikely to be used in pediatric patients younger than 6 years old, but it might be used in pediatric patients ages 6-11 with recurrent herpes labialis. This reviewer believes it is important to prospectively evaluate the safety of ME-609 cream in younger children (ages 6-11).A partial waiver (for ages less than 6 years old) should be granted. However, the Applicant should be asked to conduct a prospective study in pediatric patients ages 6-11 years old. The Applicant could submit a request for deferral of a pediatric study in patients ages 6-11 years old. Additional discussions between FDA and the Applicant regarding the timeline for this study could then be further discussed.

7.1 Methods

Clinical Studies Used to Evaluate Safety

Pivotal data

The applicant proposed to use the safety results from Studies 609-04 and 609-07 in the label for approval. Therefore, FDA analyses of key safety signals were performed using safety data from Studies 609-04 and 609-07. The safety results from these trials were reviewed, which included review of the datasets, clinical study reports, case report tabulations, and selected case report forms.

Supporting data

The safety results from Study 609-06 were reviewed, which included review of the datasets, clinical study reports, case report tabulations, and selected case report forms. These data contributed useful supportive data for evaluation of the overall safety profile of ME-609.

Reviewer Comment

No indication is being considered for immunocompromised subjects, such as the HIV-infected patient population evaluated in Study 609-06. Therefore, descriptions of Study 609-06 should be included in Section 8 (Use in Specific Populations) instead of Section 14 (Clinical Studies). Safety data from Study 609-06 should be described in Section 6 (Adverse Reactions in Clinical Studies) of the label.

7.1.2 Adequacy of Data

The data from Studies 609-04 and 609-07 were overall adequate to evaluate safety, tolerability, and efficacy of ME-609 cream for adults and adolescents (12 years and older). The data from Study 609-06 provided some additional supportive safety data in a subgroup of HIV-infected patients with stable infection (CD4 100-500 cells/mm^3). These trials were

conducted in accordance with GCP. The data sources used in the safety assessment were adequate, and the Applicant's methods of safety assessment were appropriate. In Study 609-04, 24 of 1443 subjects (1.7%) were excluded due to missing data (ME-609: 7/601 [1.2%]; acyclovir 13/610 [2.1%]; vehicle 4/232 [1.7%]). Please refer to Section 6 for additional details. Ten of these subjects were also identified by DSI audits (please refer to Section 3.1 for additional details). Of note, excluding these subjects from analyses did not affect the overall efficacy or safety findings.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The patient populations were considered too different to pool data across trials.

7.2 Adequacy of Safety Assessments

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

In Study 609-04, Study 609-06, and Study 609-07, exposure data at appropriate doses and duration were overall adequate.

- In general, adequate numbers of subjects were exposed to the drug, including adequate numbers of various demographic subsets and subjects with pertinent risk factors.
- The doses and durations of exposure were adequate to assess safety for the intended use.
- The design of Study 609-04 (multi-center, randomized, double-blind, active and vehicle-controlled, three arm study) was adequate to answer important questions in the safety review. Overall, 601 subjects received the proposed dose (5 times per day) and duration (mean duration of dosing was 5.4 days) of ME-609.
- The design of Study 609-06 (multi-center, randomized, double-blind, active-controlled, study) provided some additional supportive safety data in HIV-infected subjects with stable HIV infection (defined as CD4 100-500 cells/mm^3). Overall, 77subjects received the proposed dose (5 times per day) and duration (mean duration of dosing was 4.6 days) of ME-609.
- The design of Study 609-07 (open-label, multi-center, subject initiated safety study) was adequate to provide safety data in the adolescent population. Overall, 134 subjects received the proposed dose (5 times per day) and duration (mean duration of dosing was 5.6 days) of ME-609.

Of note, exclusion of patients with chronic cutaneous conditions could limit the relevance of some safety assessments (such as local site reactions) observed in these studies.

Study 609-04

Overall 1443 adult subjects were treated with study drug (ME-609 – 601 subjects, acyclovir – 610 subjects, vehicle – 232 subjects). However, dosing records were not received for 15

subjects (ME-609 – 7 subjects, acyclovir – 5 subjects, vehicle – 3 subjects). Table 23 shows study drug exposure based on 1428 subjects with available dosing records.

Table 23: Study Drug Exposure by Study Day (ITT Population[a]) – Study 609-04

	ME-609 (n=594)		Acyclovir (n=605)		Vehicle (n=227)	
	N	Mean # of doses (SD)	N	Mean # of doses (SD)	N	Mean # of doses (SD)
Treatment Day	N	Mean # of doses/day (SD)	N	Mean # of doses/day (SD)	N	Mean # of doses/day (SD)
Day 1	594	4.0 (1.5)	605	3.7 (1.6)	229	3.9 (1.5)
Day 2	588	5.0 (0.5)	599	5.0 (0.5)	226	5.0 (0.4)
Day 3	585	5.0 (0.5)	598	5.0 (0.5)	226	5.0 (0.3)
Day 4	582	4.9 (0.4)	594	5.0 (0.4)	226	5.0 (0.2)
Day 5	579	4.9 (0.5)	592	4.9 (0.5)	224	5.0 (0.4)
	N	Mean # of days (SD)	N	Mean # of days (SD)	N	Mean # of days (SD)
Total	594	5.4 (0.7)	605	5.5 (0.7)	229	5.4 (0.7)

[a]Dosing records were not received for 15 subjects (ME-609 – 7, acyclovir – 5, vehicle – 3). The data in this table represent subjects with available dosing records.
ITT, intent-to-treat; SD, standard deviation
Source: Applicant's September 30, 2008, submission

Reviewer Comment
Overall, 1428 subjects were exposed to at least one application of study drug (ME-609 – 594 subjects, acyclovir – 605 subjects, vehicle – 229 subjects). The extent of exposure, mean number of exposure days, number of doses applied per day, and the total number of applications were similar across treatment groups. The reported high compliance rates suggest that ME-609 was tolerable in this adult population.

Study 609-06
Overall 107 HIV-infected adult subjects were treated with study drug (ME-609 – 77 subjects, acyclovir – 30 subjects). Dosing records were received for all subjects. There were no discontinuations of study treatment.

Table 24: Study Drug Exposure by Study Day (ITT Population[a]) – Study 609-06

	ME-609 (n=77)		Acyclovir (n=30)	
Treatment Day	N	Mean # doses/day (SD)	N	Mean # doses/day (SD)
Day 1	77	3.3 (1.5)	30	3.7 (1.3)
Day 2	77	5.0 (0.1)	30	5.0 (0.0)
Day 3	77	5.0 (0.3)	30	5.0 (0.0)
Day 4	77	4.9 (0.5)	29	5.0 (0.0)
Day 5	76	5.0 (0.0)	29	5.0 (0.0)
	N	Mean # of days (SD)	N	Mean # of days (SD)
Total	77	4.6 (0.5)	30	4.5 (0.7)

[a]Total doses of applied equals the extent of exposure for the 5-day treatment period.

ITT, intent-to-treat; SD, standard deviation
Source: Applicant's September 30, 2008 submission

Reviewer Comment
The mean number of exposure days, number of doses applied per day, and the total number of applications were similar across treatment groups. The high compliance rates reported in this study suggest that ME-609 was tolerable in this HIV-infected patient population.

Study 609-07
Overall, 134 adolescent subjects were treated with ME-609 in this single-arm safety study. Dosing records were received for all subjects. Two subjects discontinued before completing the 5-day treatment course. Subject No. 57001 discontinued study medication due to application site inflammation after 9 applications. Subject No. 05002 discontinued study medication due to the occurrence of diabetes after 5 applications.

Table 25: Study Drug Exposure by Study Day (ITT Population[a]) – Study 609-07

	ME-609 (n=134)	
Total # doses applied/day	N	Mean # of doses/day (SD)
Day 1	134	3.7 (1.5)
Day 2	132[b]	5.0 (0.4)
Day 3	130	5.0 (0.3)
Day 4	130	5.0 (0.3)
Day 5	130	5.0 (0.4)
	N	Mean # of days (SD)
Total # of exposure days	134	5.6 (0.6)

[a]Total doses of applied equals the extent of exposure for the 5-day treatment period.
[b]Two subjects discontinued before completing the 5-day treatment course.
ITT, intent-to-treat; SD, standard deviation
Source: Applicant's September 30, 2008 submission

Reviewer Comment
Overall, subjects generally completed dosing as outlined in the protocol. The high compliance rates reported in this study suggest that ME-609 was tolerable in this adolescent population.

Geriatric Use
In Studies 609-06 and 609-07, there were no subjects aged 65 and over. In Study 609-04, there were 43 subjects (7.2%) aged 65 and over who received ME-609. In subjects aged 65 and over who received ME-609, seven adverse events (all causality, all grades) were reported in six subjects:

- Secondary HSV recurrence: Subjects 026-0040, 045-0053, and 057-0004*
- Flakiness around cold sore: Subject 026-0065
- Viral upper respiratory tract infection: Subject 027-0003
- Sinusitis: Subject 031-0019
- Chest pain: Subject 057-0004*

*Note: Subject 057-0004 had two AEs (secondary HSV recurrence; chest pain).

Reviewer Comment
The relatively small number of subjects aged 65 and over precludes any significant efficacy or safety analyses in this age group. Overall, no specific safety signals were identified in this subpopulation. The available efficacy and safety results are similar to lower age subjects.

7.2.2 Explorations for Dose Response

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

7.2.3 Special Animal and/or In Vitro Testing

Appropriate pre-clinical testing was performed. Please refer to Section 4.3 and Dr. Anita Bigger's Animal Pharmacology/Toxicology review for details of the preclinical program.

7.2.4 Routine Clinical Testing

The extent and frequency of routine clinical testing of this topical product was appropriate for Studies 609-04, 609-06, and 609-07. In these studies, subjects who developed ulcerative lesions visited the clinic daily until loss of hard crust, but at a minimum for five days during the treatment period. After the loss of hard crust, subjects visited the clinic every other day until return to "normal skin." Subjects with non-ulcerative recurrences were followed daily until no signs or symptoms, but at a minimum for five days during the treatment period. All subjects had a follow-up visit 2-4 weeks after the skin had returned to normal (no signs or symptoms). For this visit, subjects were contacted via telephone.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

This is a new combination product comprised of two currently approved constituents, 5% acyclovir cream and 1% hydrocortisone cream. Anticipated adverse reactions at the site of topical application with both of these topical products include dry lips, cracked lips, desquamation, dryness or flakiness of the skin, transient burning or tingling or stinging following application, pruritus, cheilitis, dysgeusia, erythema, pigmentation changes, contact dermatitis, eczema, or application site reaction including signs and symptoms of inflammation.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

No deaths occurred in the development program for ME-609 cream.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were reported in 3 subjects (ME-609 – two subjects; acyclovir – one subject) in Study 609-04, one subject in Study 609-06 (received acyclovir), and zero subjects in Study 609-07. None of these SAEs were considered related to study treatment by study investigators.

Table 26: Serious adverse events (SAEs) in Phase 3 studies for ME-609

Study	Subject	Study drug	SAE
609-04	0027-0014	ME-609	coronary artery disease
	057-0004	ME-609	chest pain
	042-0032	Acyclovir	pneumonia
609-06	3802T004	Acyclovir	pneumonia
609-07	None		

In Study 609-04, SAEs included coronary artery disease (Subject 0027-0014: ME-609 group), chest pain (Subject 057-0004: ME-609 group), and pneumonia (Subject 042-0032: acyclovir group). The narratives for subjects who received ME-609 are provided below:

- Subject 0027-0014 was a 57-year-old, white, female who was randomized to the ME-609 treatment group. She administered 5 applications/day of study medication from 28 September 2006 to 01 October 2006. The subject had a stress test for chest pain on 28 September 2006 and was diagnosed with coronary occlusions. She had a catheterization and angiogram on (b) (6). Three coronary stents were placed without incident and the subject was admitted to the hospital for observation. She was discharged on (b) (6) and this event was considered to be resolved. The Investigator considered the event to be moderate in severity and not related to ME-609. No action was taken with regards to the study medication and the subject completed the study. The subject's medical history included undiagnosed chest pain (since 2004); hypertension; hypercholesterolemia; and type 2 diabetes. Concomitant

medications at the time of the SAE included atorvastatin, irbesartan-hydrochlorothiazide, atenolol, gemfibrozil, acetylsalicylic acid, glucosamine, and omega 3 fish oil.

- Subject 057-0004 was a 75-year-old, white male who was randomized to the ME-609 group. He administered 5 applications/day of study medication from 19 February 2007 to 24 February 2007. On (b) (6), the subject experienced chest pain/tightness in his left anterior chest with associated nausea, lightheadedness, and dizziness. The subject went to the emergency room where he was treated with aspirin and nitroglycerin paste, and was admitted to the hospital for observation and evaluation. Diagnostic examinations performed included an ECG and chest x-ray, both of which showed no evidence of acute cardiopulmonary disease. An exercise echocardiogram with spectral Doppler revealed exercise induced atrial and ventricular arrhythmias and no inducible left ventricular wall motion abnormalities. He was diagnosed with non-cardiac chest pain and discharged from the hospital on (b) (6). He recovered with no further complications reported. The Investigator considered this event to be moderate in severity and not related to ME-609. No action was taken with regards to the study medication and the subject completed the study. In addition to recurrent herpes simplex labialis, the subject's medical history included hypertension, osteoarthritis, obstructive sleep apnea, gastroesophageal reflux disease, esophagogastric ring (ie, Schatzki's ring), pancreatitis, mild carotid stenosis, bilateral knee replacement, lumbar stenosis, benign prostatic hypertrophy, and actinic keratosis. Concomitant medications at the time of this SAE included benazepril HCl, zolpidem, propoxyphene, omeprazole, oxybutynin, and doxazosin mesylate.

No SAEs were reported in Study 609-07.

Reviewer Comment
The case report forms and narratives were reviewed for all SAEs. This reviewer agrees with the Applicant's assessment that these SAEs were not related to study treatment.

7.3.3 Dropouts and/or Discontinuations

In Study 609-04, four subjects (ME-609 – two subjects; acyclovir – one subject; vehicle – one subject) discontinued treatment due to toxicity considered related to study drug, as assessed by study investigators. Discontinuations related to toxicity were due to cheilitis (Subject 004-0010: ME-609), lip swelling (Subject 045-0032: ME-609), application site erythema (Subject 026-0050: acyclovir), and dry lips (Subject 045-0057: vehicle).

Table 27: Discontinuations due to toxicities in Phase 3 studies for ME-609

Study	Subject	Study drug	AE
609-04	004-0010	ME-609	cheilitis

	045-0032	ME-609	lip swelling
	026-0050	Acyclovir	application site erythema
	045-0057	Vehicle	dry lips
609-06	None		
609-07	57001	ME-609	application site inflammation

The case report forms and narratives were reviewed in detail and are presented below:

- Subject 045-0032 was randomized to receive ME-609. She administered 5 applications/day of study medication from 26 September 2006 to 29 September 2006. On the 3rd treatment day, the subject experienced mild swelling of the upper lip (MedDRA preferred term/verbatim: swelling face/swelling on upper lip) and noticed small bumps on the lower lip. Both events were considered to be possibly related to study medication by study investigators. Over the next 2 days, swelling of the upper lip worsened with some swelling also above the lip (largest diameter of swelling was 27 mm by 11 mm) and numbness. The AE of swelling was then considered to be severe. Blisters were observed on the inside of both the upper and lower lip. Study medication was discontinued on treatment Day 4. The patient was treated with Benadryl and local cooling with ice and the swelling of the upper lip was resolved without sequelae on 02 October 2006. The small bumps on the lower lip were resolved by 03 October 2006. The subject completed the study.

- Subject 004-0010 (ME-609 group) experienced mild cheilitis after using study drug for 4 days. The Investigator considered this event to be mild in severity and possibly related to ME-609. Study drug was stopped and the AE resolved without any intervention. The subject completed the study.

- Subject 026-0050 (acyclovir group) experienced application site erythema after using study drug for 2 days. The Investigator considered this event to be mild in severity and probably related to acyclovir. Study drug was stopped and the subject was discontinued from the study. The event was resolved with no further complications reported.

- Subject 045-0057 (vehicle) experienced dry lips after using study drug for 5 days. The Investigator considered this event to be moderate in severity and probably related

to study drug. Study drug was stopped and the AE resolved with no further complications reported. The subject completed the study.

No treatment discontinuations due to toxicity were reported in Study 609-06.

In Study 609-07, one subject (ID# 57001) who received ME-609 discontinued treatment due to toxicity (application site inflammation). The narrative is provided below:

- Subject No. 57001, a 14-year-old female, developed an application site inflammation (localized inflammatory reaction at the application site) on the second day of treatment. The adverse event was of moderate intensity and was assessed by the Investigator as definitely related to study medication. The subject discontinued the study due to the adverse event. The event lasted for 2 days and the subject had recovered at the follow-up visit.

Reviewer Comment
The case report forms and narratives were reviewed for all subjects who discontinued treatment due to toxicity. This reviewer agrees with the Applicant's assessment of causality.

7.3.4 Significant Adverse Events

Please refer to Section 7.4.1

Submission Specific Primary Safety Concerns

The primary safety concern is local skin reactions in the area of the application site.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

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

Overall, clinical toxicities reported with ME-609 cream appear similar to the clinical toxicities reported with ZOVIRAX cream. In Study 609-04, Study 609-06, and Study 609-07, most adverse reactions considered by investigators to be definitely, probably or possibly related to study treatment were mild. Analyses of common AEs reported with ME-609 cream are presented below.

Study 609-04

All adverse events (AEs) – all grades, regardless of causality

In Study 609-04, AEs (all grades, regardless of causality) were reported in 111 (18.5%) of subjects receiving ME-609, 100 (16.4%) of subjects receiving 5% acyclovir in ME-609 vehicle, and 45 (19.4%) of subjects receiving ME-609 vehicle. As shown in the following table, the most commonly reported AEs (all grades, regardless of causality, ≥1% incidence in any treatment group) were herpes simplex recurrences, nasopharyngitis, dry lips, application site dryness, and headache. Most AEs were mild and most were considered unrelated to study treatment.

Table 28: AEs (all grades, regardless of causality) observed in ≥ 1.0% of patients in any treatment group

Preferred Term	ME-609 (n=601)	Acyclovir (n=610)	Vehicle (n=232)
	N (%)	N (%)	N (%)
Total # of subjects with AE, n (%)	115 (18.5)	100 (16.4)	45 (19.4)
Herpes simplex	33 (5.5)	43 (7.0)	17 (7.3)
Nasopharyngitis	7 (1.2)	3 (0.5)	5 (2.2)
Upper respiratory tract infection	2 (0.3)	4 (0.7)	3 (1.3)
Lip dry	8 (1.3)	2 (0.3)	3 (1.3)
Application site dryness	4 (0.7)	4 (0.7)	3 (1.3)
Headache	13 (2.2)	9 (1.5)	4 (1.7)
Pharyngolaryngeal pain	6 (1.0)	2 (0.3)	2 (0.9)

Source: September 30, 2008 submission, FDA analysis adverse events dataset, and Table 14.3.1.4

Treatment-related adverse events (AEs)

In Study 609-04, treatment-related AEs (all grades, considered definitely, probably or possibly related to study treatment by study investigators) were reported in 28 (4.7%) subjects receiving ME-609, 18 (3.0%) subjects receiving acyclovir, and 10 (4.3%) subjects receiving vehicle. Most AEs were mild and included dry lips; chapped lips; cheilitis; dysgeusia; drying or flaking of the skin; transient burning or tingling following application; erythema; pigmentation changes; application site reaction including signs and symptoms of inflammation. Dry lips occurred in 1.2% of subjects receiving ME-609, 0.3% of subjects receiving acyclovir, and 1.3% of subjects receiving vehicle alone. All other AEs occurred in less than 1% of subjects in each treatment group.

Table 29: Treatment-Related[a] AEs (all grades) observed in each treatment group

Preferred Term	ME-609 (n=601)	Acyclovir (n=610)	Vehicle (n=232)
	N (%)	N (%)	N (%)
Total # of subjects with ≥1 AE, n (%)	28 (4.7)	18 (3.0)	10 (4.3)
Lip dry	7 (1.2)	2 (0.3)	3 (1.3)

Chapped lips	1 (0.2)	3 (0.5)	1 (0.4)
Cheilitis	3 (0.5)	0 (0.0)	1 (0.4)
Nausea	2 (0.3)	0 (0.0)	0 (0.0)
Vomiting	1 (0.2)	0 (0.0)	0 (0.0)
Hypoaesthesia, oral	0 (0.0)	1 (0.2)	1 (0.4)
Lip disorder (swelling)	1 (0.2)[b]	0 (0.0)	0 (0.0)
Oral discomfort	0 (0.0)	0 (0.0)	1 (0.4)
Paresthesia, oral	0 (0.0)	0 (0.0)	1 (0.4)
Dysgeusia	3 (0.5)	0 (0.0)	0 (0.0)
Swelling face (upper lip)[c]	1 (0.2)[b]	0 (0.0)	1 (0.4)
Skin exfoliation[d]	0 (0.0)	1 (0.2)	0 (0.0)
Application site reactions[e]	11 (1.8)	12 (2.0)	5 (2.2)
Application site dryness	3 (0.5)	3 (0.5)	3 (1.3)
Application site irritation	4 (0.7)	4 (0.7)	0 (0.0)
Application site erythema	1 (0.2)	2 (0.3)	0 (0.0)
Application site anaesthesia	0 (0.0)	1 (0.2)	1 (0.4)
Application site paresthesia	2 (0.3)	1 (0.2)	0 (0.0)
Application site exfoliation[f]	1 (0.2)	0 (0.0)	0 (0.0)
Application site pain	0 (0.0)	1 (0.2)	1 (0.4)

[a]FDA medical reviewer's assessment of causality
[b]Reported in the same subject (ID# 045-0032)
[c]Swelling of upper lip
[d]Skin peeling at fingertips
[e]Application site reactions encompass the following terms: application site dryness, application site irritation, application site erythema, application site anaesthesia, application site paresthesia, application site exfoliation, and application site pain
[f]Flaking or peeling skin around the cold sore
Source: September 30, 2008 submission, FDA analysis adverse events dataset, and Table 14.3.1.5

In Study 609-04, moderate-to-severe intensity of AEs were reported in 14 (2.3%) subjects receiving ME-609, 5 subjects (0.8%) receiving acyclovir, 4 subjects (1.7%) receiving vehicle. Overall rates were less than 1% for each of these adverse reactions.

Table 30: Treatment-Related[a] AEs of moderate to severe intensity observed in each treatment group

Preferred Term	ME-609 (n=601)		Acyclovir (n=610)		Vehicle (n=232)	
	N (%)		N (%)		N (%)	
Number of events (%)	Moderate	Severe	Moderate	Severe	Moderate	Severe
Lip dry	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Chapped lips	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cheilitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Vomiting	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lip disorder (swelling)	1 (0.2)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling face (upper lip)[c]	0 (0.0)	1 (0.2)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Application site reactions	4 (0.7)	1 (0.2)	3 (0.5)	0 (0.0)	2 (0.9)	1 (0.4)
Application site dryness	3 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.4)[e]
Application site irritation	1 (0.2)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Application site anaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)[e]	0 (0.0)
Application site pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)[e]	0 (0.0)

[a]FDA medical reviewer's assessment of causality
[b]Reported in the same subject (ID# 045-0032)
[c]Swelling of upper lip
[d]Application site reactions encompass the following terms: application site dryness, application site irritation, application site erythema, application site anaesthesia, application site paresthesia, application site exfoliation, and application site pain
[e]Reported in the same subject (ID# 047-0021)
Source: September 30, 2008 submission, FDA analysis adverse events dataset, Listing 16.2.7.1

Adverse reactions of severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in 2 subjects receiving ME-609 (lip swelling, application site irritation), and one subject receiving vehicle (application site dryness). Each of these reactions occurred once. The narratives are provided below:

- Subject 045-0032 in the ME-609 group experienced a severe AE of worsening face swelling/swelling on upper lip that resulted in discontinuation of study drug. Please refer to Section 7.3.3 for the complete narrative.

- Subject 047-0045 was randomized to the ME-609 group. She administered 5 applications/day of study medication from 31 December 2006 to 04 January 2007. On 03 January 2007, she experienced 1 day of severe application site burning considered to be definitely related to study medication by study investigators. The AE resolved on 04 January 2007 and the subject completed the course of study medication.

- Subject 047-0021 was randomized to the vehicle group. She administered 5 applications/day of study medication from 05 November 2006 to 10 November 2006. On 07 November 2006, the subject experienced 1 day of application site dryness considered to be moderate in severity and definitely related to study medication by study investigators. On 10 November 2006, the subject experienced 2 days of application site dryness, considered to be severe and definitely related to study medication. The AE of severe application site dryness was considered to be resolved on 12 November 2006. During this same course of study medication, this subject also experienced moderate application site anesthesia (numbness around the lesion) and moderate application site pain (pain at lesion site). The Investigator considered both

of these AEs to be probably related to the study medication; the events resolved. No action was taken with the study medication. The subject completed the course of study medication.

Study 609-06

In Study 609-06, adverse reactions of moderate-to-severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site hypersensitivity). The narrative is provided below:

- A 41-year-old female (subject 0714T001), developed an application site reaction that was reported by the Investigator as "probably related to study medication." The subject was treated with ME-609. She was diagnosed HIV positive in 2005 and started antiretroviral treatment with Combivir (zidovudine/lamivudine) and Stochrin (efavirenz) in February 2007. In 2006 she also became HCV seropositive and past medical history also included uterine leiomyoma. Her CD4+ T-cell count was 170 cells/mm^3 at screening and 250 cells/mm^3 approximately a month later during study treatment. Itching occurred in the area of application in the morning of the 4^{th} day of treatment, after a total of 14 applications of study medication. The symptoms worsened and at the end of the day the subject complained of edema and severe itching. The application of study medication was not stopped as the Investigator could not exclude that the symptoms were caused by the herpes lesion. Viral swab for HSV analyses was not done. The subject described increased edema and itching during a clinic visit on Day 5, the lesion area was measured to be 375 mm^2. On Day 6, hard crust with severe edema was noted and the treatment was completed with the last application of the study medication by noon. By the end of this day the subject noted reduction of symptoms. During follow-up, the Investigator noted pigmentation and desquamation in the area to which study medication had been applied. Normal skin was recorded 21 days after start of the application site reaction. No other medication was given to treat the application site reaction. This adverse event was reported by the Investigator as "skin allergic reaction at site of study drug application."

Study 609-07

In Study 609-07, adverse reactions of moderate-to-severe intensity (considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (ID# 57001, application site inflammation). The narrative is provided in Section 7.3.3.

Reviewer Comment
This reviewer agrees with the investigator assessments of causality.

7.4.2 Laboratory Findings

No clinical laboratory evaluations were performed in Studies 609-04, 609-06, or 609-07. Laboratory evaluations were not considered necessary since study agents were topical products with negligible systemic absorption, and unlikely to cause any systemic toxicities.

7.4.3 Vital Signs

Aside from the screening visit, no vital signs were obtained in Studies 609-04, 609-06, or 609-07. Laboratory evaluations were not considered necessary since study agents were topical products with negligible systemic absorption, and unlikely to cause any changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

Baseline electrocardiograms were not included as part of the routine safety monitoring plan in Studies 609-04, 609-06, or 609-07. Electrocardiogram monitoring was not considered necessary since study agents were topical products with negligible systemic absorption, and unlikely to cause any cardiac-related toxicities.

7.4.5 Special Safety Studies

Data from phase 1 dermatology specific supportive studies were reviewed in detail for safety by Dr. Snezana Trajkovic (Division of Dermatology and Dental Products, DDDP). Please refer to Dr. Trajkovic's review for additional details of the following dermatology-specific, Phase 1 supportive studies:

Table 31: Dermatology-specific, Phase 1 supportive studies

Study	Description
Skin Blanching (Study No. 99-609-005)	Randomized, double-blind, study in healthy subjects of the topical activity of two ME-609 formulations (ME-609 and ME-609B) and hydrocortisone cream 1% (n=20). Primary endpoint: Vasoconstriction (skin blanching).
21 Day Cumulative Irritation Patch Test (Study No. 604598)	Randomized, double-blind, vehicle- and active controlled study in healthy subjects with ME-609, ME-609 vehicle and commercial Zovirax cream, (n=29). Primary endpoint: Skin irritation.
Human Repeat Insult Patch Test (Study No. 604603)	Randomized, double-blind, vehicle-controlled study in healthy subjects, (n=205). Primary endpoint: Skin sensitization.
Phototoxicity Study No. KGL 6201	Randomized, vehicle-controlled, double-blind study of the phototoxicity potential of ME-609 in healthy human subjects, (n=30).

	Primary endpoint: Phototoxicity reactions.
Photoallergy Study No. KGL 6202	Randomized, vehicle-controlled, double-blind study of the photocontact allergenicity potential of ME-609 in healthy human subjects, (n=45). Primary endpoint: Photoallergy reactions.

DDDP Reviewer Conclusions
The results of trial 604598 are adequate to conclude that there is high irritation potential of the study drug ME-609.

The results of Trial 604603 are adequate to conclude that ME-609 may be sensitizing. Hydrocortisone and vehicle components of the test drug are probably responsible for the sensitization. There is no evidence that acyclovir is the sensitizing component in the reactions seen.

Review of Trials KGL 6201 and KGL 6202 revealed no phototoxic or photoallergic potential of study drug ME-609.

DDDP Reviewer Labeling Recommendations (in bold font)

> Contact dermatitis following application has been observed when applied under occlusion in dermal safety studies. Where contact sensitivity tests have been conducted, the reactive substances were hydrocortisone or a component of the cream base.
>
> A study enrolling 225 healthy adults was conducted to evaluate the contact sensitization potential of ME-609 using repeat insult patch testing methodology. Of 205 evaluable subjects, one confirmed case (0.5%) of sensitization to hydrocortisone and 2 additional cases (1.0%) of possible sensitization to the ME-609 cream base were identified. **Additionally**, one subject developed a contact allergy in the photosafety studies to propylene glycol, one of the inactive ingredients of the cream base.
>
> Dermal tolerance was assessed in a 21-day cumulative irritation study in 36 healthy subjects. ME-609, its cream base and Zovirax® (acyclovir) Cream 5% all showed a high and cumulative irritation potential under occlusive and semi-occlusive conditions.
>
> **Photoallergic potential** and phototoxicity were assessed in two studies in 50 and 30 healthy volunteers, respectively. No **photoallergic** or phototoxicity potential was identified for ME-609.

7.4.6 Immunogenicity

ME-609 is considered unlikely to be immunogenic due to limited systemic absorption.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

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

7.5.2 Time Dependency for Adverse Findings

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

7.5.3 Drug-Demographic Interactions

The majority of subjects (91%) were Caucasian and no clear differences were seen across racial categories.

No clear safety differences were identified by gender. However, definitive conclusions regarding safety by gender are precluded by relatively smaller numbers of male subjects and small numbers of AEs observed in the overall study population.

In Studies 609-06 and 609-07, there were no subjects aged 65 and over. In Study 609-04, there were 43 subjects (7.2%) aged 65 and over who received ME-609. In subjects aged 65 and over who received ME-609, seven adverse events (all causality, all grades) were reported in six subjects. Only one of these AEs was considered by investigators to be possibly related to study drug. Overall, no specific safety signals were identified in this subpopulation. However, the small number of subjects aged 65 and over precludes any conclusive safety analyses in this age group. Please refer to Section 7.2.1 for additional details.

7.5.4 Drug Disease Interactions

Following discontinuation of study drug, secondary recurrences were reported in 28 (4.7%) subjects receiving ME-609, 35 (5.7%) subjects receiving acyclovir, and 17 (7.3%) subjects receiving vehicle.

7.5.5 Drug-Drug Interactions

Clinical experience with ZOVIRAX (5% acyclovir) cream has identified no interactions resulting from topical or systemic administration of other drugs concomitantly. Clinical experience with 1% hydrocortisone cream has identified no interactions resulting from topical or systemic administration of other drugs concomitantly.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Dermal carcinogenicity studies were not conducted with ME-609. Based on the information for ZOVIRAX (5% acyclovir) cream and 1% hydrocortisone cream, these studies are not necessary.

7.6.2 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with ME-609 and are not considered necessary. Pregnancy was an exclusion criterion in the Phase 2 and 3 studies, and pregnancy was also a discontinuation criterion in these studies. No studies have been performed in pregnant or lactating women. Similar to ZOVIRAX cream and approved 1% topical hydrocortisone products, systemic exposure of acyclovir and hydrocortisone following topical administration of ME-609 is expected to be minimal.

The Applicant proposed the following labeling regarding pregnancy:

> **8.1 Pregnancy**
> **Category B**
> *Teratogenic Effects:*
> Acyclovir was not teratogenic in the mouse, rabbit or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy between 1984 and 1999 followed 749 pregnancies in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximated that found in the general population. However, the size of the registry was insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.
>
> Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.
>
> Animal reproduction studies have not been conducted with (b) (4). No studies have been performed in pregnant women. Systemic exposure of acyclovir and hydrocortisone following topical administration of (b) (4) is minimal.

Reviewer Comment
Zovirax (5% acyclovir) cream is designated as Pregnancy Category B. Hydrocortisone cream (1%) is designated as Pregnancy Category C. Topical corticorticosteroids have class labeling regarding pregnancy category designation. Of note, hydrocortisone 1% cream is classified as Class 7 (least potent) topical corticosteroid.

The Applicant's proposed Pregnancy Category B seems overall reasonable, since the acyclovir concentration is identical to Zovirax (5%), and the hydrocortisone component of ME-609 is one of the least potent topical corticosteroids.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

Assessment of effect on growth was not performed as part of the clinical development program. Of note, Study 609-04 enrolled immunocompetent adults ≥18 years old. Study 609-06 enrolled HIV-infected adults ≥18 years old. Study 609-07 enrolled adolescents ages 12 to 17 years. To date, pediatric studies in subjects less than 12 years old have not been conducted.

During May 22, 2008, Pre-NDA meeting, the following issues were discussed:

> As previously agreed with the Agency, Medivir AB will submit a request for deferral from studying ME-609 Cream in patients 6 to 11 years of age, and a waiver from studying ME-609 Cream in patients under 6 years of age, at the time of NDA submission. Medivir AB understands the Pediatric Review Committee (PeRC) will review and evaluate these requests. In the responses to the previous meeting request, the Agency acknowledged the potential for limited use of ME-609 Cream (or any topical antiviral) in the 3 to 9-year old age group, and suggested that it could still be useful to prospectively and systematically accumulate some safety data on ME-609 Cream in younger children. In response to FDA feedback, Medivir AB proposed to conduct a study in children 6 to 11 years of age. The study will be conducted according to the same parameters used in the adolescent study (Study No. 609-07). A draft protocol synopsis for this study was provided in Appendix 1 of the Pre-NDA meeting briefing package. FDA comments stated that the protocol synopsis appeared reasonable.

However, the NDA submission included a request for a (b) (4) According to the Applicant, ME-609 is unlikely to be used in pediatric patients younger than 12 years old. The Applicant suggested the following rationale:

I. Proposed Indication

ME-609 cream is proposed for the early treatment of signs and symptoms of recurrent herpes labialis to prevent the development and reduce the duration of ulcerative lesions in adults and adolescents (12 years of age and older) with recurrent labial herpes (RHL).

(b) (4)

(b) (4)

Reviewer Comment
Due to the pathophysiology and epidemiology of the disease, this reviewer believes ME-609 is unlikely to be used in pediatric patients younger than 6 years old, but that ME-609 might be used in some pediatric patients ages 6-11 with recurrent herpes labialis.

II. Clinical manifestations of HSV-1 Infections
The clinical picture and the severity of the HSV-infections are influenced by age-dependent factors. The clinical manifestations of HSV-1 infection in different populations are summarized in the following table. Herpes labialis is the most common clinical manifestation of HSV-1 infection. It either occurs as primary gingivostomatitis or recurrent herpes labialis (upon reactivation).

Table 32: Clinical manifestations of HSV-1 Infections

Type of infection	Symptoms	Patient Population
Primary infection	Gingivostomatitis	Children
	Tonsillitis	Adolescents
	Pharyngitis	Children and adolescents
	Keratoconjunctivitis	Adolescents
	Eczema herpeticum	Atopics (all age groups)
Recurrent infection	Herpes labialis	Children and adults
	Keratoconjunctivitis	Children and adults
	Encephalitis	Children and adults

Source: September 30, 2008 submission, Module 1, Table 1; Harrison's Principles of Medicine, 17th Edition; Mandell Principles and Practices of Infectious Diseases, 6th Edition.

Primary herpes simplex virus type 1 (HSV-1) infections usually occur during childhood. As shown in the above table, the clinical manifestations of primary HSV-1 infection are variable. Of note, most cases of primary HSV-1 infection are asymptomatic. Primary gingivostomatitis generally occurs in young children and less frequently in adolescents. When it is symptomatic, it often includes buccal and gingival mucosa. Lesions occur on lips, gingiva, tongue, buccal mucosa and on the hard and soft palate. The differential diagnosis of primary gingivostomatitis in children includes aphthous stomatitis, herpangina (coxsackie virus), herpes zoster and the mucosal vesicles of hand-foot-and-mouth disease (Harrison's Principles of Medicine, 17th Edition; Mandell Principles and Practices of Infectious Diseases, 6th Edition; Rioboo-Crespo Mdel R. Med Oral Patol Oral Cir Bucal. 2005 Nov-Dec;10(5):376-87; Kolokotronis A. Clin Microbiol Infect. 2006 Mar; 12(3):202-11; Arduino PG. J Oral Pathol Med. 2008 Feb; 37(2):107-21).

During primary infection, HSV-1 virus particles are transported to the trigeminal ganglia and remain there, often without causing further disease. Antibodies to HSV-1 are a sign that a primary infection has occurred. Despite the immune response induced by primary infection, HSV-1 can reactivate later in life and cause recurrent labial herpes with vesicles (cold sores). Even if recurrent herpes labialis is observed in children less than 6 years old, primary HSV-1 infections generally predominate (Harrison's Principles of Medicine, 17th Edition; Mandell Principles and Practices of Infectious Diseases, 6th Edition).

The annual incidence of primary HSV-1 infection as determined by serology has been reported to be 7-13% at 2 years, 5-10% at 4 years, and 1-4% at 5 years (Fatahzadeh M. J Am Acad Dermatol 2007;57(5):737-63). Only a small fraction of the children with a primary infection develop recurrent herpes labialis (Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol 2002; 4(3):231-237). Young children with HSV-1 infections generally do not receive treatment; those children who receive treatment are typically given oral acyclovir formulations (Spruance W. Herpes 2007;14 Suppl 1:13A-18A; Spruance W. J Fam Pract 2007;56(1):30-6). Of note, the Applicant states that primary HSV-1 episodes should not be treated with ME-609 cream. The proposed indication and supporting data for ME-609 cream is based on studies in subjects with recurrent herpes labialis episodes.

Recurrent herpes labialis differs from primary HSV-1 infection by having a shorter duration of viral replication, which is considered likely due a primed immune system. The pathophysiology and clinical manifestations of recurrent herpes labialis are thought to be the same in populations of different ages (Fatahzadeh M. J Am Acad Dermatol 2007; 57(5):737-63). It may not always be possible to delineate a primary episode from a recurrent episode. Diagnostic challenges could lead to the possibility of misdiagnosing childhood diseases with similar symptoms. Clinicians may misdiagnose the ulcerations of recurrent aphthous stomatitis, which are twice as prevalent as herpes labialis in school children 4-14 years of age. Additional infections that can pose diagnostic difficulties include hand-foot-and-mouth disease, herpes zoster, mononucleosis, chickenpox, and impetigo (Harrison's Principles of Medicine, 17th Edition; Mandell Principles and Practices of Infectious Diseases, 6th Edition).

Recurrent herpes labialis is often preceded by prodromal symptoms, such as burning, tingling and itching in the area where vesicles subsequently appear. Patients eventually learn to recognize these early prodromal symptoms. The Applicant suggests that younger children, who have experienced fewer episodes, and may not be capable to adequately describe and communicate these sensations to their parents, may have age-related limitations when considering the opportunity to provide antiviral therapy.

III. Recurrent HSV in Children Aged 0-12 Years

Herpes labialis in children under 6 years of age is generally a primary infection, and not a recurrence. In many children, the primary infection does not result in any recurrent episodes (Rioboo-Crespo Mdel R. Med Oral Patol Oral Cir Bucal. 2005 Nov-Dec; 10(5):376-87; Kolokotronis A. Clin Microbiol Infect. 2006 Mar; 12(3):202-1; Arduino PG. J Oral

Pathol Med. 2008 Feb;37(2):107-21). The annual prevalence of recurrent herpes labialis in children from 8 to 11 years has been estimated to 11.75% (Shulman JD. Community Dent Oral Epidemiol 2004; 32(6):402-9). In clinical practice, episodic treatment of recurrent episodes is often considered as not warranted in childhood. Consequently, cold sores in children of less than 12 years of age are not commonly treated (Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol 2002; 4(3):231-237; Nasser M. Cochrane Database Syst Rev. 2008 Oct 8; (4): CD006700; Porter SR. Evid Based Dent. 2008; 9(4):117).

(b) (4)

Reviewer Comment
Due to the pathophysiology and epidemiology of the disease, ME-609 is unlikely to be used in pediatric patients younger than 6 years old. Herpes labialis in children under 6 years of age is generally a primary infection, and not a recurrence.

Due to the pathophysiology and epidemiology of the disease, it is reasonable to request a prospective study in pediatric patients ages 6-11 with recurrent herpes labialis. The annual prevalence of recurrent herpes labialis in children from 8 to 11 years has been estimated to be 11.75% in some studies. To date, cold sores in this pediatric subpopulation are not commonly treated (Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol 2002; 4(3):231-237). Currently, only systemic acyclovir has been studied for use in pediatric patients with this disease condition. Therefore, current clinical practices could be more reflective of the limitations of approved agents for this pediatric population. Due to its topical application, negligible systemic absorption, and overall safety profile, it is possible that off-label use of ME-609 might occur in pediatric patients ages 6-11 with recurrent herpes labialis.

IV. Recurrent HSV in Pediatric Age Group 12-17 Years
The annual prevalence of recurrent herpes labialis in adolescents between 12 and 17 years of age has been estimated to be 16.8% (Shulman JD. Community Dent Oral Epidemiol 2004;32(6):402-9; Whitley RJ. Semin Pediatr Infect Dis. 2002; 13(1):6-11; Whitley RJ. Curr Treat Options Neurol. 2002; 4(3):231-237).

In Study 609-07, the safety of ME-609 cream in the adolescent pediatric population (ages 12-17 years) was evaluated in 134 subjects in an open-label study design. Subjects were instructed to self-initiate treatment at early signs and symptoms of a herpes recurrence (prodrome or erythema). As discussed in Section 7 of the clinical review, ME-609 cream was

well tolerated in the adolescent population. Adverse events considered definitely, probably or possibly related to study treatment by study investigators) were reported in one subject receiving ME-609 (application site inflammation). No other local adverse events were recorded. Of note, some of the features of recurrent herpes labialis, such as pain, erythema and irritation, can be difficult to distinguish from local application site adverse events.

Efficacy of ME-609 cream in adolescents was extrapolated based on the efficacy findings in adults (Study 609-04) and the overall similarities in pathophysiology and clinical presentation in these patient populations.

V. Reviewer Comment and Summary

Due to the pathophysiology and epidemiology of the disease, this reviewer believes ME-609 is unlikely to be used in pediatric patients younger than 6 years old, but that ME-609 might be used in some pediatric patients ages 6-11 with recurrent herpes labialis. This reviewer believes it is important to prospectively evaluate the safety of ME-609 cream in younger children (ages 6-11). Due to its topical application, negligible systemic absorption, and overall safety profile, it is possible that off-label use might occur in pediatric patients ages 6-11 with recurrent herpes labialis.

In summary, this reviewer believes a partial waiver (for ages less than 6 years old) should be granted. However, the Applicant should be asked to conduct a prospective study in pediatric patients ages 6-11 years old. As discussed during the May 22, 2008, Pre-NDA meeting, such a study could be conducted according to the same parameters used in the adolescent open-label safety study (Study No. 609-07). A draft protocol synopsis for this study was provided in Appendix 1 of the Pre-NDA meeting briefing package to collect safety data on 50 evaluable subjects. FDA comments stated that the protocol synopsis appeared reasonable.

Reviewer Comment

The pediatric development plan was discussed internally and with the Pediatric Review Committee (PeRC) as part of the review process.

The DAVP review team and the PeRC agreed to grant a partial pediatric waiver (for ages less than 6 years old), and also agreed that the Applicant should request a deferral for a pediatric study in children ages 6-11 years old. The Applicant submitted the following timeline for the proposed pediatric study in children ages 6-11 years old (50 evaluable subjects):

Protocol Submission Date: (b) (4)
Study Initiation Date:
Study Completion Date:
Final Study Report Submission Date: May 2013

The proposed timeline for the study in children ages 6-11 years old is acceptable to the FDA review team and to the PeRC.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

Withdrawal or abuse potential for ME-609 is considered unlikely.

7.7 Additional Submissions

Not applicable.

8. POSTMARKETING EXPERIENCE

Not applicable. ME-609 cream has not yet been approved in any country and therefore there is no postmarketing experience at this time.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Literature reviewed for this sNDA is cited in relevant sections of this document.

9.2 Labeling Recommendations

A summary of the major changes is provided in Appendix 1.

9.3 Advisory Committee Meeting

Not applicable.

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