CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-436

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-436 SUPPL # N-000 HFD # 530

Trade Name

Generic Name Acyclovir and Hydrocortisone Cream 5%/1%

Applicant Name Medivir AB

Approval Date, If Known July 31, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-478 Zovirax (acyclovir) cream

NDA# 80-472 Hytone (hydrocortisone) cream

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 609-04: Pivotal Phase 3 trial
Study 609-06: Study in Immunocompromised patients
Study 609-07: Study in adolescents

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒

Investigation #2 YES ☐ NO ☒

Investigation #3 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 609-04: Pivotal Phase 3 trial
Study 609-06: Study in Immunocompromised patients
Study 609-07: Study in adolescents

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 58500 YES ☒ NO ☐
Explain:

Investigation #2

IND # 58500 YES ☒ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1

YES ☐ NO ☐
Explain: Explain:

Investigation #2

YES ☐ NO ☐
Explain: Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: David Araojo, Pharm.D.
Title: Regulatory Project Manager
Date: July 20, 2009

Name of Office/Division Director signing form: Jeffrey Murray, M.D., M.P.H.
Title: Deputy Director, DAVP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID E ARAOJO
08/06/2009

JEFFREY S MURRAY
08/06/2009

Medivir

Debarment Certification

Medivir AB hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Annelie Skagerlind, M.Sc.Pharm.
Director of Regulatory Affairs
Medivir AB

Sept. 3, 2008
Date

Elizabeth N. Dupras, RAC
Senior Project Manager
B&H Consulting Services, Inc.
US Agent for Medivir AB

16 Sept 2008
Date

Medivir AB
PO Box 1086
SE-141 22 Huddinge
SWEDEN

Telephone
Nat. 08-5468 3100
Int. +46 8 5468 3100

Facsimile
Nat. 08-5468 3199
Int. +46 8 5468 3199

Bankers
Sv. Handelsbanken
5425-5302
VAT SE 556238 4361.01

Internet
http://www.medivir.com
info@medivir.com

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-436	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Acyclovir and Hydrocortisone Cream, 5%/1% Dosage Form: cream Strengths:		
Applicant: Medivir AB		
Date of Receipt: October 1, 2008		
PDUFA Goal Date: August 1, 2009	Action Goal Date (if different): July 31, 2009	
Proposed Indication(s): For the treatment of early 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).		

b(4)

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
ZOVIRAX® (acyclovir) Cream	Efficacy and safety
HYTONE® (hydrocortisone) Cream	Efficacy and safety

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant relied on FDA's previous findings of safety and efficacy from NDA 21-478 and ANDA 80472 to obviate the need for repeating additional nonclinical studies. No BA/BE studies were done because the applicant's product is topical, as is the referenced approved products. Therefore, little to no systemic absorption is expected.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

APPEARS THIS WAY
ON ORIGINAL

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
ZOVIRAX® Cream	NDA 21-478	Y
HYTONE® Cream	ANDA 080472	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "**N/A**".*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph: Hydrocortisone Cream 1%

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
This application provides for a new combination indicated for, "For the treatment of early 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)."

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 22436	ORIG 1		ME-609 CREAM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID E ARAOJO
08/06/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-436 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Acyclovir and Hydrocortisone 5%/1% Dosage Form: Cream, topical		Applicant: Medivir AB Agent for Applicant (if applicable): B&H Consulting Services
RPM: David Araojo		Division: Division of Antiviral Products

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 21478 ZOVIRAX® Cream ANDA 80472 HYTONE® Cream Provide a brief explanation of how this product is different from the listed drug. This is a new combination of the active ingredients from both NDA 21478 and ANDA 80472. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☒ No changes ☐ Updated Date of check: July 20, 2009 **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	August 1, 2009 July 31, 2009
❖ Actions	AP
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

• Application[2] Characteristics	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	April 29, 2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
Copy of this Action Package Checklist[3]	Y
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 7/31/09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	Y
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	Y
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☒ DRISK 7/10/09 ☐ DDMAC ☐ CSS ☒ Other reviews 4/28/09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	4/28/09 Not acceptable 5/4/09
Administrative / Regulatory Documents	
Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	12/15/08
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	See Approval letter
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 6/19/08
• EOP2 meeting *(indicate date)*	☐ No mtg 7/29/05
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 7/31/09
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	7/21/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DDDP 6/22/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 7/2/09
Clinical Microbiology ☒ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 12/30/08
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 7/21/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/25/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6/25/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 7/31/09
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	7/31/09
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 7/31/09 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ^DRA.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: PREA PMR open-label multi-center, subject initiated safety study of ME-609 for treatment of recurrent herpes simplex labialis in immunocompetent patients, ages 6-11

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	[redacted]
Study/Clinical trial Completion Date:	[redacted]
Final Report Submission Date:	05/01/2013
Other:	

b(4)

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Various systemic and topical acyclovirs for the treatment of herpes labialis have been approved for over twenty years. Topical products have a well defined safety profile that has been demonstrated in patients down to the age of 12.

Currently, no topical products are approved for treatment of herpes labialis in patients under the age of 12. The annual prevalence of herpes labialis in 8-11 year olds is estimated at about 12%. Because of this, it is reasonable to expect that some off-label use will occur.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Characterize the safety of ME-609 in pediatric patients [redacted] years old.

b(4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open-label multi-center, subject initiated safety study of ME-609 for treatment of recurrent herpes simplex labialis in 50 immunocompetent patients, ages 6-11.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22436	ORIG 1	MEDIVIR AB	ME-609 CREAM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID E ARAOJO
07/31/2009

KENDALL A MARCUS
07/31/2009

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 1, 2009

TO: David Araojo, Regulatory Health Project Manager
Kirk Chan-Tack, M.D., Medical Officer
Division of Antiviral Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-436

APPLICANT: Medivir AB

DRUG: Lipsovir (ME- 609) Cream

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of early signs and symptoms of recurrent herpes labialis (cold sores)

CONSULTATION REQUEST DATE: November 3, 2008

DIVISION ACTION GOAL DATE: July 31, 2009

PDUFA DATE: August 1, 2009

I. BACKGROUND:

The sponsor has submitted a new drug application for marketing approval of Lipsovir for the treatment of early 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). The review division requested inspection of protocol 609-04 entitled "A randomized, double blind, active controlled, vehicle controlled, subject initiated study comparing efficacy and safety of ME-609 versus acyclovir cream for the treatment of recurrent herpes simplex labialis; a multinational, multicenter phase III study." The applicant submitted results from the above protocol in support of NDA 22-436.

The primary objective of the study protocol 609 was to evaluate the efficacy and safety of ME-609 for the treatment of herpes labialis recurrences compared with acyclovir in immunocompetent adults and adolescents, 12 years of age and older. The inspection targeted four domestic clinical investigators (CIs) who enrolled a relatively large number of subjects. The goals of the inspection included validation of submitted data and compliance of study activities with FDA regulations. The records inspected included, but were not limited to, 100% informed consent forms, source documents, drug accountability records, protocol inclusion/exclusion criteria, randomization procedures, efficacy end points and documentation of adverse events.

II. RESULTS (by protocol/site):

Name of CI and location	Protocol and # of subjects	Inspection Dates	Final Classification
Mathew Davis, M.D. Rochester, NY 14609	609-04 127 subjects	12/8-11/08	NAI
Jeffrey Geohas, M.D. Chicago IL 60610	609-04 149 subjects	12/16/08 and 1/13/09	VAI
James Hedrick, M.D Bradstown, KY 40004	609-04 79 subjects	1/5-12/09	NAI
Michael Noss, M.D. Cincinnati, OH 45249-1665	609-04 89 subjects	1/6-12/09	NAI

Key to Classifications
NAI = No deviation from regulations
VAI = deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol 609-04

1. Mathew G. Davis, M.D.
   Rochester Clinical Research, Inc.
   500 Helendale Road-L20
   Rochester, NY 14609

   At this site, a total of 129 subjects were screened, one subject was reported as a screen failure, 127 subjects were randomized, and 91 subjects completed the study. Thirty-six subjects discontinued and the reasons were documented. Eighteen subjects did not get cold sores, 8 subjects were lost to follow-up, and six subjects withdrew consent. The records for all subjects were reviewed to verify that subjects signed informed consent prior to screening and randomization into the study.

   The medical records for 80 subjects enrolled were reviewed in depth. Drug accountability records and source documents were compared to case report forms and data listings for primary efficacy end points and adverse events. Adverse events experienced by study subjects were reported to the sponsor and IRB within the required timeframes.

   The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

   The data appear acceptable in support of the pending application.

2. Jeffrey G. Geohas, M.D.
   Radiant Research, Chicago
   515 North State Street, Suite 2700
   Chicago, IL 60610

   At this site, 175 subjects were screened, 26 subjects were reported as screen failures, and 149 were randomized. Informed consent for all subjects was verified.
   The medical records for at least 75 subjects were reviewed, including case report forms, financial disclosure reports and drug accountability records. The FDA investigator reviewed the source documents and compared them to the data listings for primary efficacy endpoints and adverse events for the majority of the subjects.

   The inspection found inadequate and inaccurate records, protocol violations, and inadequate drug disposition. The review division may wish to consider the impact, if any, of the inspectional findings for subject numbers 0044, 094, 095 and 0108 in terms of data acceptability. Subject 0044 received prohibited medication ibuprofen; subject 095 received prohibited medication Fioricet; subject 094 had a lesion size of 5mm x 6mm in the source document changed to indicate that the lesion size was 0mm x0mm in the case report form; and for subject 0108, the investigator assessment of ulcerative recurrence was changed in the case report form to indicate that the subject did not have an ulcerative recurrence. It is

our understanding that these subjects were all randomized to receive active control rather than the investigational product. Overall, the data appear acceptable in support of the pending application.

3. James A. Hedrick, M.D.
   Kentucky Pediatric/Adult Research
   201 South 5th Street, Suite 102
   Bardstown, KY 40004

   At this site, a total of 79 subjects were screened and randomized, and 63 subjects completed the study. Sixteen subjects were discontinued and the reasons were documented. Informed consent for all subjects was verified. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

   The medical records/source data for 28 subjects were reviewed in depth, including drug accountability records. The source data were compared to case report forms and data listings, primary efficacy measures and adverse events.

   The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

   The data appear acceptable in support of the pending application.

4. Michael J. Noss, M.D.
   Radiant Research, Inc.
   11500 Northlake Dr., Suite 320
   Cincinnati, OH 45249

   At this site, a total of 89 subjects were screened, 12 subjects were reported as screen failures, 77 subjects were randomized, and 48 subjects completed the study. Twenty-nine subjects discontinued and the reason(s) were documented. Fifteen subjects did not get cold sores, 10 subjects were dropped by the sponsor due to closure of site, and 4 subjects withdrew consent. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

   The medical records/source data for 48 subjects were reviewed in depth, including drug accountability records. The source data were compared to case report forms and data listings, including primary efficacy measures and adverse events.

   The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records were found to be in order and verifiable. There were no limitations to this inspection.

   The data appear acceptable in support of the pending application

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There was sufficient documentation to assure that all audited subjects at the sites of Drs. Davis, Hedrick and Noss did exist, fulfilled the eligibility criteria, received the assigned study medication and had their primary efficacy endpoint captured as specified in the protocol. Overall, the inspection of Drs. Davis, Hedrick, and Noss revealed no significant problems that would adversely impact data acceptability. The data generated and submitted from the above three inspected sites are acceptable in support of the pending application. However, the inspection of Dr. Jeffrey Geohas revealed objectionable findings: Inadequate and inaccurate records, protocol violations and inadequate drug disposition. Therefore, the division should evaluate the overall impact, if any, of the inspectional findings on the efficacy data from this site for the four subjects (0044, 094, 095 and 0108) discussed above.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Antoine El-Hage
7/2/2009 05:46:25 AM
PHARMACOLOGIST

Constance Lewin
7/2/2009 09:52:16 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-436

PROPRIETARY NAME REQUEST
- UNACCEPTABLE

Medivir AB
ATTENTION: Elizabeth N. Dupras, RAC
Senior Project Manager
B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, New Jersey 08876

Dear Ms. Dupras:

Please refer to your New Drug Application (NDA) dated September 30, 2008, received October 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ME-609 Cream (Acyclovir, 5% and Hydrocortisone, 1%).

We also refer to your October 28, 2008, correspondence, received October 29, 2009, requesting review of your proposed proprietary name, Lipsovir®. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable because it contains the United States Adopted Name (USAN) stem '-vir'. This stem 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.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "Pdufa Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Marlene Hammer, Regulatory Health Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0757. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
5/4/2009 10:28:30 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-436 Supplement # N-000 Efficacy Supplement Type SE-

Proprietary Name: Lipsovir
Established Name: acyclovir/hydrocortisone cream
Strengths: acyclovir 5% and hydrocortisone 1%

Applicant: Medivir
Agent for Applicant (if applicable): Beth Dupras, US Agent, B&H Consulting

Date of Application: September 30, 2008
Date of Receipt: October 1, 2008
Date clock started after UN:
Date of Filing Meeting: November 14, 2008
Filing Date: November 30, 2008
Action Goal Date (optional): User Fee Goal Date: August 1, 2009

Indication(s) requested:

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 58,500

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) July 6, 2005 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 22, 2008 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) February 2, 2006 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☒

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 14, 2008

NDA #: 22-436

DRUG NAMES: Lipsovir (acyclovir 5%/hydrocortisone 1%) cream

APPLICANT: Medivir

BACKGROUND: This is an original NDA 505(b)(2) indicated for treatment of early signs and symptoms of recurrent herpes labialis (cold sores) to prevent the development and reduce the dutation of ulcerative cold sores in adults and adolescents (12 years of age and older). As a 505(b)(2), the application identifies the reference listed drug products Zovirax® and Hytone® as the basis for the submission.

ATTENDEES: Debra Birnkrant, Jeff Murray, Scott Proestel, Kirk Chan-Tack, Greg Soon, Susan Zhou, Anita Bigger, Jeff Medwid, George Lunn, Steve Miller, Kellie Reynolds, Stanley Au, Nilambar Biswal, Lalji Mishra, Kendall Marcus, Jaewon Hong, Vicky TysonMedlock, Karen Winestock, David Araojo

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Chan-Tack, Kirk
Secondary Medical:	Proestel, Scott
Statistical:	Zhou, Susan
Pharmacology:	Bigger, Anita
Statistical Pharmacology:	
Chemistry:	Medwid, Jeffrey
Environmental Assessment (if needed):	
Biopharmaceutical:	Au, Stanley
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Biswal, Nilambar
DSI:	
OPS:	
Regulatory Project Management:	Araojo, David
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☐	FILE ☒	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX	N/A ☐	FILE ☒	REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY	FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

David Araojo
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 21478-Zovirax and ANDA 80472

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application combines two reference listed drugs in a proprietary cream base developed by the applicant.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☒

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s): 4963555

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☒ NO ☐

*If "**Yes,** what is the listed drug product(s)* Zovirax and Hytone Cream *and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug* preclinical, safety and efficacy
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☒

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☒

If "**Yes,**" please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Araojo
12/15/2008 02:49:21 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,500

B&H Consulting Services, Inc.
Attn: Elizabeth Dupras, RAC
Consultant and US Agent for Medivir AB
55 North Gaston Avenue
Somerville, NJ 08876

Dear Ms. Dupras:

Please refer to Medivir's Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ME-609 Cream (acyclovir and hydrocortisone).

We also refer to the meeting between representatives of your firm and the FDA on May 22, 2008. The purpose of the meeting was to discuss general, nonclinical, and clinical questions in preparation for the planned NDA submission.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: **May 22, 2008**

IND: **58,500**

Drug: **ME-609 cream (acyclovir + hydrocortisone)**

Sponsor: **Medivir**

Indication: **Treatment of recurrent herpes labialis**

Type of Meeting: **Type B**

Division of Antiviral Products (DAVP) Participants:

Debra Birnkrant, M.D., Director
Jeffrey Murray, M.D., M.P.H., Deputy Director
Kimberly Struble, Pharm.D., Medical Team Leader
Kirk Chan-Tack, M.D., Medical Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Susan Zhou, Ph.D., Statistics Reviewer
Anita Bigger, Ph.D., Pharmacology Reviewer
Jules O'Rear, Ph.D., Microbiology Team Leader
Nilambar Biswal, Ph.D., Microbiology Reviewer
Antoine El Hage, Ph.D., Division of Scientific Investigation
David Araojo, Pharm.D., Regulatory Project Manager

Medivir Participants:

Annelie Skagerlind, Director of Regulatory Affairs
Borje Darpo, M.D., Ph.D., Vice President Development
Bo Öberg, Vice President R&D Strategic Planning
Eva Arlander, PhD, Director Clinical Research
[redacted] b(4)

Elizabeth Dupras, RAC, Consultant and US Agent for Medivir AB

Background:

This meeting was held at the request of the sponsor, Medivir. The meeting was requested on March 6, 2008 and the meeting background package was submitted on April 23, 2008. Draft comments from the Division of Antiviral Products (DAVP) dated May 19, 2008, in response to the background package questions, were conveyed to Medivir prior to the meeting. Medivir provided a copy of presentation slides on May 22, 2008 (attached).

Objectives:

To discuss general, nonclinical, and clinical questions in preparation for the planned NDA submission.

Discussion: Sponsor's questions from the meeting package are listed in bold, followed by DAVP's response, as conveyed in the May 19, 2008 facsimile, in italics. Meeting discussion, if needed, immediately follows each question and response.

8.1 General

8.1.1 As previously agreed with the Agency, Medivir AB intends to submit the planned 505(b)(2) application in CTD format according to ICH guidelines. Medivir AB proposes to submit the planned submission as an electronic CTD (eCTD) NDA. Medivir AB's US Agent, B&H Consulting Services, will successfully complete an eCTD pilot prior to submitting the NDA.

Does the Agency agree with the proposed eCTD submission of the planned 505(b)(2) application?

FDA Reply: Yes, we agree.

8.2 Nonclinical
A summary of nonclinical information to be provided in the NDA is provided in Section 9 of the briefing package, and includes further supporting information for the nonclinical question provided below.

8.2.1 The formulation is a cream for topical application. All of the excipients in ME-609 Cream are listed on the FDA's Inactive Ingredients Database (IID). Two of these excipients, isopropyl myristate and Poloxamer 188, are present at levels greater than the IID listed maximum levels for topical cream formulations.

- **Isopropyl myristate is listed in the IID at a level of 10% for use in topical emulsion cream formulations. However, isopropyl myristate is also included in the IID at a level of 35% for use in topical ointments. The ME-609 Cream formulation contains ——isopropyl myristate. This level exceeds the current IID level for topical emulsion cream formulations, but is much lower than the level allowed in topical ointments.** b(4)
- **Poloxamer 188 is listed in the IID at a level of 0.0126% for use in topical emulsion cream formulations. However, Poloxamer 188 is also included in the IID at a level of 5.5% for use in topical gels. The ME-609 Cream formulation contains —— Poloxamer 188. This level exceeds the current IID level for topical emulsion cream formulations, but is much lower than the level allowed in topical gels.** b(4)

Although the levels of isopropyl myristate and Poloxamer 188 in ME-609 Cream exceed the IID listed for use in topical creams, both excipients are approved for use in other topical

formulations at significantly higher levels than those proposed in the ME-609 Cream formulation.
In the response to the previous meeting request, the Agency noted that it was not clear if repeated dosing for Poloxamer 188 and the use of these excipients on the lips, allowing ingestion of the excipients, are supported by topical formulations in the IID. Medivir AB contacted the FDA Office of Generic Drugs (OGD) to determine if the proposed levels of these excipients in a topical formation are supported by levels in currently approved products (Control No. 1099). OGD informed Medivir AB that the 5.5% level of Poloxamer 188 in a topical ointment listed in the IID is an error, and that 5.5% level is actually for a periodontal gel. OGD also confirmed that an isopropyl myristate level of —— (w/w) in a topical cream is supported by currently approved formulations. b(4)
Medivir AB conducted a review of scientific data available in literature for Poloxamer 188. Justification for the proposed level of Poloxamer 188 in the proposed formulation is provided in Appendix 4.

Does the Agency agree that no additional nonclinical studies with isopropyl myristate and/or Poloxamer 188 are required to support the 505(b)(2) application?

FDA Reply: We agree that no additional nonclinical studies with isopropyl myristate and/or Poloxamer 188 are required to support the 505(b)(2) application.

8.3 Clinical

A summary of clinical information to be provided in the NDA is provided in Section 10 of this briefing package, and includes further supporting information for the clinical questions provided below.

8.3.1 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. As previously discussed, Medivir AB proposes 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 is provided in Appendix 1 of the meeting briefing package.

Does the Agency agree that the proposed study in pediatric patients 6 to 11 years of age is adequate to accumulate the recommended safety data?

FDA Reply: The protocol synopsis appears reasonable. Please submit a complete study protocol for DAVP review prior to initiating this study.

8.3.2 ME-609 Cream represents a new treatment concept for recurrent herpes labialis. The proposed drug product is a cream formulation containing 5% acyclovir and 1% hydrocortisone intended for topical episodic treatment. The principle of combining an anti-inflammatory drug with an anti-infective drug to improve clinical outcomes by reducing inflammation-related symptoms associated with the infection is well established in dermatology, and corticosteroids have been successfully combined with antibiotics or antifungals in approved topical products. A combination of an antiviral with a corticosteroid has successfully been used in the treatment of chronic herpetic stromal keratitis to counteract the visual impairment which can result from this disease. As a fixed-combination topical product, ME-609 Cream would combine the safety advantages of a topical product with the dual efficacy of an antiviral drug that blocks virus replication and a corticosteroid that reduces the symptoms.

The clinical program for ME-609 Cream consists of the 9 clinical studies as defined in Table 2 of the briefing package.

Table 2 (SN 086, letter date: April 23, 2008)

Study	Study description
Phase 1	
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 sensitisation.
Phototoxicity Study No. KGL 6201	Randomized, vehicle-controlled, double-blind study of the phototoxicity potential of ME-609 in healthy human subjects, (n=30). 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). Endpoint: Photoallergy reactions.
Phase 2	
Efficacy and Safety (Study No. 98-609-013)	Randomized, double-blind, vehicle-controlled study in subjects with recurrent herpes labialis. ME-609: n=190; vehicle: n=190. UV-light was used for induction of herpes

	labialis recurrences. **Primary endpoint: Healing time (time to loss of hard crust and normal skin).**
Phase 3	
Pivotal Study (Study No. 609-04)	**Randomized, double-blind, active- and vehicle-controlled in subjects with recurrent herpes labialis. 1270 treated and evaluable subjects: ME-609 n=535; acyclovir in ME-609 vehicle n=535; vehicle n=200. 2400 randomized.** **Primary endpoint: Proportion of subjects with non-ulcerative recurrences (proportion of subjects in whom the study recurrences does not progress beyond the papule stage)** **Secondary endpoint: Episode duration.**
Study in Immuno-compromised (Study No. 609-06)	**Randomized, double-blind study with ME-609 (n=50, at least) and acyclovir (n=25) in HIV subjects. 230 randomized.** **Primary endpoint: Episode duration.**
Study in Adolescents (Study No. 609-07)	**Open label study with ME-609 in 12 to 17 year old subjects with recurrent herpes labialis. 240 randomized to achieve 110 treated.** **Primary endpoint: Safety (adverse events).**

The primary endpoint of the pivotal phase 3 study (Study No. 609-04) was to show that treatment with ME-609 Cream prevents progression beyond the papule stage in recurrences of labial herpes. This endpoint has not previously been approved by the Agency for any other drug product. In addition, the episode duration was assessed as a secondary endpoint.

The comparator product used in the pivotal phase 3 study (Study No. 609-04) was acyclovir formulated in the ME-609 vehicle. In this study, ME-609 Cream was superior to placebo (vehicle) for the prevention of ulcerative herpes lesions (42% vs. 26%, $p < 0.0001$), and superior to acyclovir in the ME-609 vehicle (42% vs. 35%; p=0.014). The difference versus acyclovir, while statistically significant and internally consistent and robust, did not meet the predefined and requested statistical significance level for demonstrating efficacy in a single registration study ($p < 0.001$). Despite this, Medivir AB believes that the program has demonstrated that ME-609 Cream can provide patients with a clinically relevant and valuable preventive effect, which cannot be achieved with existing products on the market.

a. Does the Agency agree?

FDA Reply: 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. As noted, the predefined and requested statistical significance level for demonstrating efficacy in a single registration study ($p < 0.001$) was not achieved for ME-609 compared to acyclovir.

This is a review issue – evaluation of the totality of data provided in support of your registrational package may allow us to better evaluate your assessment of the potential clinical relevance and preventive effect of ME-609 Cream.

The phase 3 program that was the basis of approval for Zovirax® (acyclovir) Cream, 5% (NDA 21-478) failed to demonstrate prevention of ulcerative lesions. In contrast, Medivir AB's program has shown that acyclovir in the ME-609 vehicle provides a preventative effect (35% vs. 26% for placebo; p=0.011).
There are no marketed products available to patients for prevention of recurrent herpes labialis. Medivir AB believes that the comparison between ME-609 Cream and vehicle is more relevant to patients than the comparison between ME-609 Cream and acyclovir, which Medivir AB understands is necessary to meet the Agency's Combination Drug Policy.

b. Medivir AB would appreciate the Agency's view on this issue.

FDA Reply: We believe both comparisons (ME-609 Cream and vehicle; ME-609 Cream and acyclovir) provide useful information for clinical practice and regulatory decision making.

For subjects that developed an ulcerative herpes lesion while being treated with ME-609 Cream, the episode duration and episode duration to normal skin were comparable to that observed in subjects treated with acyclovir.

Summaries of the phase 3 clinical studies (Study Nos. 609-04, 606-06 and 609-07) are provided in Sections 10.3.1, 10.3.2 and 10.3.3, respectively.

Medivir AB believes the pivotal study supports the following proposed indication:

> **ME-609 Cream 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).**

c. Pending review, do the completed phase 3 clinical studies (Study Nos. 609-04, 609-06 and 609-07) along with other supportive information on dermal safety and efficacy support submission of a 505(b)(2) NDA for the proposed indication?

FDA Reply: This is a review issue – the adequacy of the studies and study endpoints (primary, secondary) depends upon the totality of data provided in support of your registrational package.

Meeting Discussion: Medivir presented several slides (attached) describing post hoc sub analyses and possible scenarios as to why the $p<0.001$ was not achieved for one of the primary hypotheses.

8.3.3 The phase 3 program included a study in an immunocompromised population (Study No. 609-06) with an extensive analysis of acyclovir susceptibility, including phenotyping [Plaque Reduction Assay (PRA)] and genotyping (sequencing for mutations in thymidine

kinase and DNA polymerase) of viral samples taken from cold sores. There were no samples identified with acyclovir resistance in either the ME-609 or acyclovir group. In the pivotal study (Study No. 609-04), analyses to date have included the frequency of virus positive lesions, which was similar between acyclovir and ME-609. As detailed in the protocol for Study No. 609-04, Medivir AB is currently analyzing viral samples from subjects who had longer episode duration than the median duration in the acyclovir treatment group. These samples will be analyzed by PRA for acyclovir susceptibility. In addition, viral shedding in the phase 2 study (Study No. 98-609-013) was shorter with ME-609 treatment in comparison to placebo.

> **Provided that no acyclovir resistance is demonstrated in the ME-609 group in the pivotal study, Medivir AB believes that the results from the described clinical program in conjunction with the available knowledge of acyclovir resistance in the treatment of recurrent herpes labialis makes emerging acyclovir resistance highly unlikely for the intended use, and that no additional risk minimization measures are needed.**

Does the Agency agree that no additional risk minimization measures are needed for viral resistance testing?

FDA Reply: This will depend on the results of the studies now being conducted for resistance testing.

8.3.4 Topical acyclovir and topical hydrocortisone have been used extensively in prescription and over-the-counter products, respectively. Both ingredients have well-known and relatively benign safety profiles. In Medivir AB's phase 3 program, the most commonly related adverse event in all treatment groups was local reactions at the site of application. There was no increase in frequency, severity or types of adverse events observed with ME-609 Cream as compared to acyclovir. Based on this, Medivir AB believe that no further risk minimization measures, beyond routine pharmacovigilance activities and dissemination of product risk information through appropriate professional and patient labeling, are needed.

Does the Agency agree?

FDA Reply: This is a review issue – our decision regarding risk minimization measures will be based on the findings from our safety analysis conducted during review of the NDA.

8.3.5 All Case Report Forms (CRFs) will be available at the time of NDA submission, and can be provided to the Agency upon request. In the previous meeting, Medivir AB proposed to limit CRFs in the original NDA to deaths and discontinuations due to adverse events. The Agency requested that Medivir AB also submit CRFs for all cutaneous reactions, and to include analyses on the timing of these events. Medivir AB proposes to evaluate the onset time and duration of cutaneous reactions, and separate line listings will be provided in addition to the CRFs.

Does the Agency agree with the proposed analyses (time and duration) of all cutaneous reactions?

FDA Reply: Yes, we agree. Please clarify if CRFs will be submitted for all application site reactions. Please also submit the CRF for the subject with face swelling.

8.3.6 The one-year follow-up for Study No.609-06 (study in immunocompromised patients) will not be available until after NDA submission. Medivir AB proposes to submit an addendum to the report for Study No. 609-06 to include the one-year follow-up data during the NDA review period.

Does the Agency agree with Medivir AB's proposal to provide an addendum to the report for Study No. 609-06 to include the one-year follow-up data during the NDA review period?

FDA Reply: We agree with your proposal to provide an addendum for Study 609-06 to include one-year follow-up data. Please ensure this addendum includes cumulative data for Study 609-06. Please discuss your anticipated timeframe for submitting the data during the review.

Meeting Discussion: Medivir clarified the follow-up data for Study 609-06 is "time to follow-up" data. The " time to next occurrence" data will be submitted within one month of the NDA submission.

8.3.7 The results from the Plaque Reduction Assay (PRA) analysis of virology samples from Study No. 609-04 (pivotal study) will be completed in November 2008, and will not be available at the time of NDA submission. Medivir AB proposes to submit an addendum to the report for Study No. 609-04 to include the PRA analysis during the NDA review period.

Does the Agency agree with Medivir AB's proposal to submit an addendum to the report for Study No. 609-04 to include the PRA analysis during the NDA review period?

FDA Reply: For simplicity and to complete all the reviews in a timely manner, please plan to submit the virology test results at the time of the original NDA submission. It is expected that the virology data will include detailed analysis of the results on the incidence, phenotyping (by plaque reduction assay on culture positive samples), and genotyping (both HSV TK and DNA pol

genes using non-cultured samples) of HSV strains collected from all the patients (please refer to amendments 57, 64 and 67 to this IND).

Meeting Discussion: Medivir will provide virology data for Study 609-04 at the time of NDA submission. Medivir proposes to submit virology data for Study 609-06 as an addendum.

DAVP expressed concern of possible outgrowth of wild type virus and requested PCR testing to verify wild type virus and rule out resistance. Further, DAVP proposed a sub study of original samples, using subjects with the longest healing time.

Medivir will submit a sub study proposal.

8.3.8 In the response to the previous meeting request, the Agency requested clarification on the administration of ME-609 Cream, and asked Medivir AB to consider using wording found in the Zovirax® (acyclovir) Cream, 5% (NDA 21-478) label to describe the amount of cream applied to an affected area. Medivir AB has evaluated the administration information from US and foreign labeling for Zovirax® (acyclovir) Cream, 5%, and proposes the following administration instructions:

> **Adults and adolescents (12 years of age and older):**
> **Apply ME-609 Cream 5 times per day for 5 days. Treatment should be initiated as early as possible, preferably immediately after the first signs and symptoms** b(4)
>
> **For each dose, apply a quantity of ME-609 Cream sufficient to cover the affected area, including the outer margin. Avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection.**

Does the Agency agree with the proposed administration instructions for ME-609 Cream?

FDA Reply: Determination of labeling is a review issue. In your phase 3 trial (Study 609-04), treatment was started within one hour of experiencing signs 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). These instructions are also consistent with other products for the treatment of herpes labialis. [redacted] is a review issue. In the NDA, please provide a justification and supporting analyses to support [redacted] b(4

Response to question in the March 6, 2008 Meeting Request

8.1.2 In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review. A Priority Review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. Priority Review status can apply both to drugs that are used to treat serious diseases and to drugs for less serious illnesses.

Medivir AB believes the design of the clinical program for ME-609 Cream, assuming the pivotal phase 3 study endpoint of demonstrating that treatment with ME-609 Cream prevents progression beyond the papule stage in recurrences of labial herpes is met (which has not previously been approved by the Agency) qualifies the NDA for a Priority Review.

Does the Agency agree that the proposed 505(b)(2) application qualifies for a Priority Review?

FDA Reply: Herpes labialis is a non-life threatening disease and there are approved products for treatment of recurrent herpes labialis. These factors will be among several considerations for the FDA review team to discuss when deciding between Priority Review or Standard Review. This decision will be finalized at the filing meeting and communicated to you at that time.

Additional Comments

1. *For the immunocompromised study, data for the secondary efficacy endpoint (time-to-next recurrence) are being collected during an observation period lasting up to 12 months after study treatment and will be completed in August 2008. Please confirm these data will be included in the NDA submission.*

   Meeting Discussion: Medivir will submit the " time to next occurrence" data within one month of the NDA submission.

2. *Please submit resistance data in a SAS transport file following the format in the guidances for submitting resistance data for HIV, HBV, etc. We recommend submitting a sample dataset prior to NDA submission.*
   Please place the clinical virology summary in Section 2.7.2.4 Special Studies and the clinical virology study reports, data, and assay performance data/methodology in Section 5.3.5.4 Other Studies as outlined below:

   Other Study Reports (see http://www.fda.gov/cder/regulatory/ersr/ectd.htm see FDA eCTD Table of Contents Headings and Hierarchy (updated 7/7/2005))

   +Antiviral reports
   +*Cell culture and biochemical study reports*
   +Study report [identification] and related information
   -*Study report*
   -*Cell culture and biochemical data*
   +*Animal model(s) study reports*
   +Study report [identification] and related information
   -*Study report*
   -*Animal model(s) data*
   +*Clinical in vivo study reports*
   +Study report [identification] and related information
   -*Study report*
   +*Clinical in vivo data*

-Viral load
-Resistance
-Other
+In vivo (clinical) assays
-Viral load
-Genotype
-Phenotype
-Other

3. *Please ensure errors and oversights are corrected in the NDA submission. For example, the values in Table 3 (p. 18 of the meeting backgrounder) for Poloxamer 188 and cetostearyl alcohol were inadvertently reversed. Also, the p value (p=0.0.012) on page 28 of the meeting backgrounder contains an extra decimal point.*

4. *Please conduct adequate provocative human dermal studies with the final, to be marketed formulation. The cumulative irritation study should enroll sufficient subjects to obtain at least 35 evaluable subjects, and the sensitization should be conducted in at least 200 evaluable subjects. The phototoxicity and photoallergy studies have been conducted, but the final study reports have not yet been submitted. The numbers of subjects (30, and 45, respectively) appear adequate. Verification of the product formulation in these studies as the final, to be marketed formulation will be required at the time of NDA submission.*

   Meeting Discussion: Medivir reported enrollment of 30 subjects in the phototoxicity study and 47 subjects in the photoallergy study. These studies were conducted with the to-be-marketed formulation.

   Medivir also reported enrollment of 205 subjects in the sensitization study and obtained data on 33 subjects in the irritation study. However, the formulation used in these studies was not the final to-be-marketed formulation. The final formulation uses [redacted] citric acid but a [redacted] and [redacted] citric acid concentration was used in the sensitization and irritation study, respectively. Medivir reported the pH remained 5 in both formulations. This manufacturing error occurred during batch production and Medivir was unaware of it until after the completed safety studies. Medivir claimed it would take one and a half years to repeat the study using the final to-be-marketed formulation. Medivir stated the manufacturing issue has been resolved and no additional problems are foreseen. b(4)

   Medivir will submit their rationale to DAVP and the Division of Dermatology and Dental Products regarding their proposal that the completed dermal studies described above are sufficient for submission as part of the registrational package for ME-609 cream.

Additional Meeting Discussion:

Medivir stated their animal studies demonstrated efficacy and that the hydrocortisone component has an additive effect.

ME-609 Cream was superior to placebo (vehicle) for the prevention of ulcerative herpes lesions [redacted] vs. [redacted], $p < 0.0001$), and superior to acyclovir in the ME-609 vehicle [redacted] vs [redacted] $p=0.014$). The difference versus acyclovir, while statistically significant did not meet the predefined and requested statistical significance level for demonstrating efficacy in a single registration study ($p < 0.001$) [redacted]

b(4)

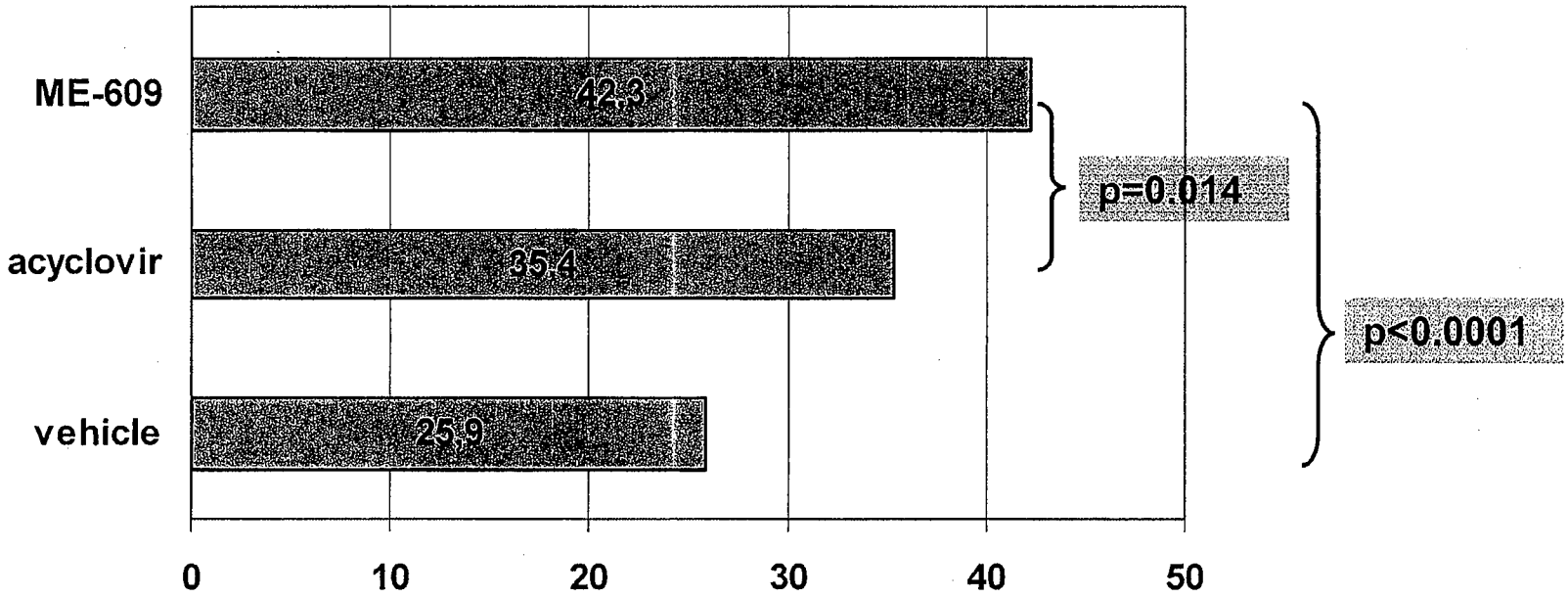
Action Items Summary:

- Medivir will submit a proposal for PCR testing to verify wild type virus and rule out resistance.
- Medivir will submit information regarding the use of higher citric acid concentration in its formulation for the sensitization and irritation safety studies, including rationale regarding their proposal that the completed dermal studies are sufficient for submission as part of the registrational package for ME-609 cream.
- Medivir was asked to submit animal data and their justification for the NDA submission.
- Medivir will submit the presentation slides officially to the IND.

Summary of Phase3 Virology Data Being Collected

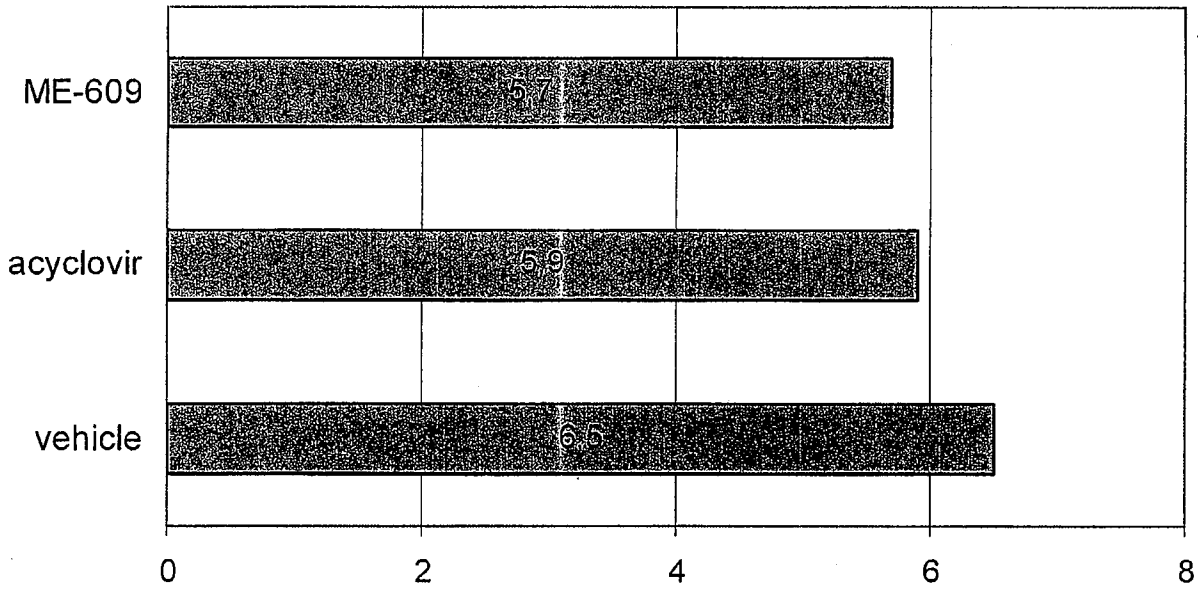
Study	Endpoints	Status
609-04 Pivotal study	•Culturing of swabs from ulcerative recurrences	•Completed
	•PRA for positive samples from subjects with healing time > median healing time in the ACV group	•On-going (To be completed and submitted in the NDA)
	•Genotyping will be conducted on any ACV resistant samples	•If applicable, will be submitted in the NDA
609-06 Immunocompromised	•Culturing of swabs from ulcerative recurrences	•Completed
	•Q-PCR on all samples	•Completed
	•PRA on all samples	•Completed
	•PCR (original sample) for TK- and DNA pol on all samples	•Completed

Primary Efficacy Endpoint - Prevention - ITT Population



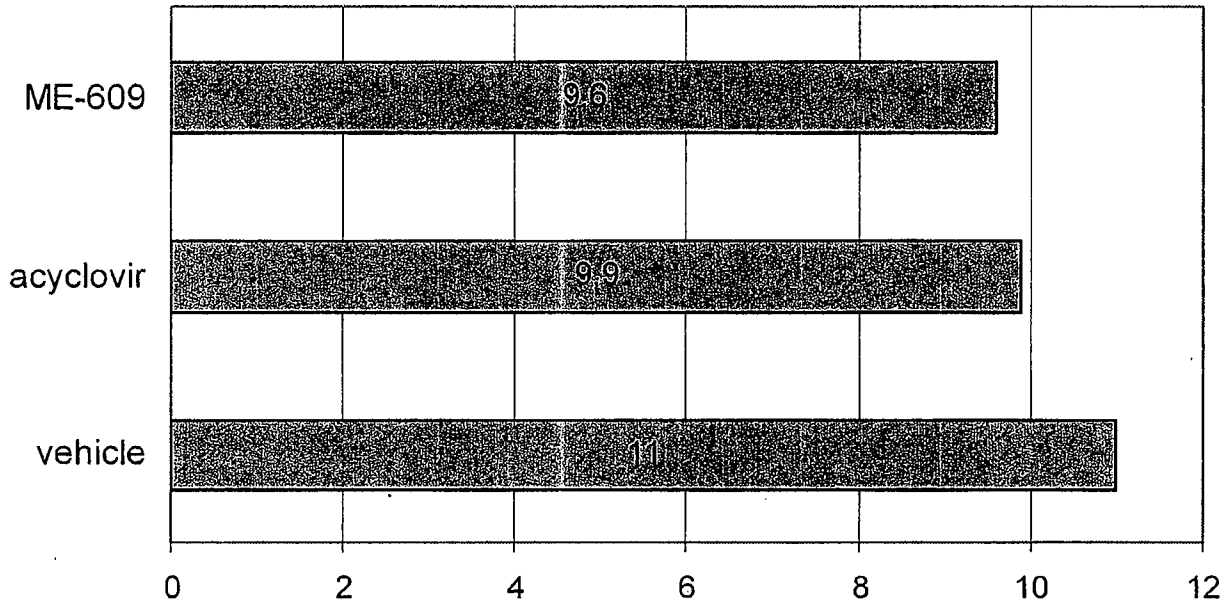
Prevention (%)	ME-609 (n=601)	acyclovir (n=610)	vehicle (n=232)
	42.3	35.4	25.9
Difference (p-value)		6.8% (0.0144)	16.4% (<0.0001)

Episode Duration: Ulcerative recurrences, ITT



Episode Duration (days) ULCERATIVE RECURRENCES	ME-609 (n=347)	acyclovir (n=394)	vehicle (n=172)
Mean (SD)	5.7 (2.85)	5.9 (2.63)	6.5 (3.27)
Median	5.0	5.5	5.8
Difference (p-value)		-0.2 (0.365)	-0.8 (0.011)

Secondary Efficacy Endpoint - Episode Duration to normal skin ulcerative rec., ITT



Episode Duration to NS (days) ULCERATIVE RECURRENCES	ME-609 (n=347)	acyclovir (n=394)	vehicle (n=172)
Mean (SD)	9.6 (3.77)	9.9 (4.32)	11.0 (5.66)
Median	9.1	9.2	10.1
Difference (p-value)		-0.3 (0.293)	-1.5 (0.002)

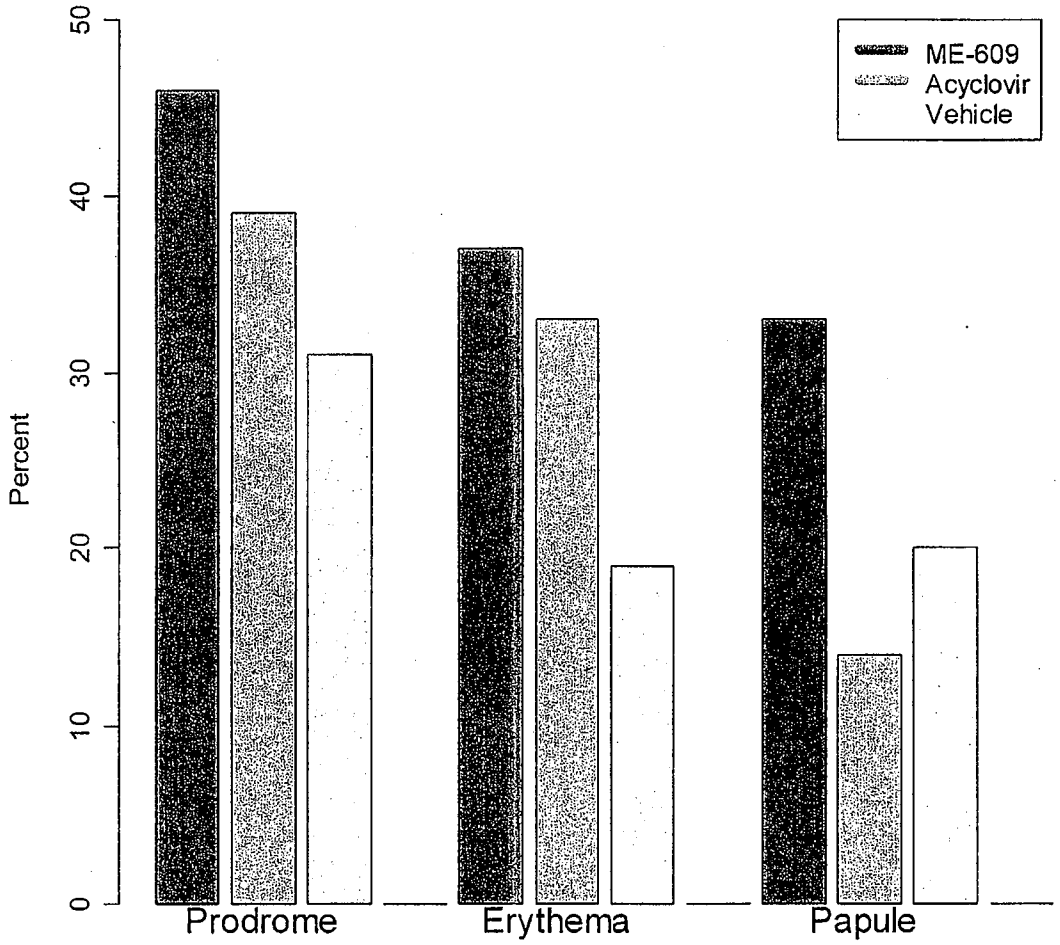
Statistical topics

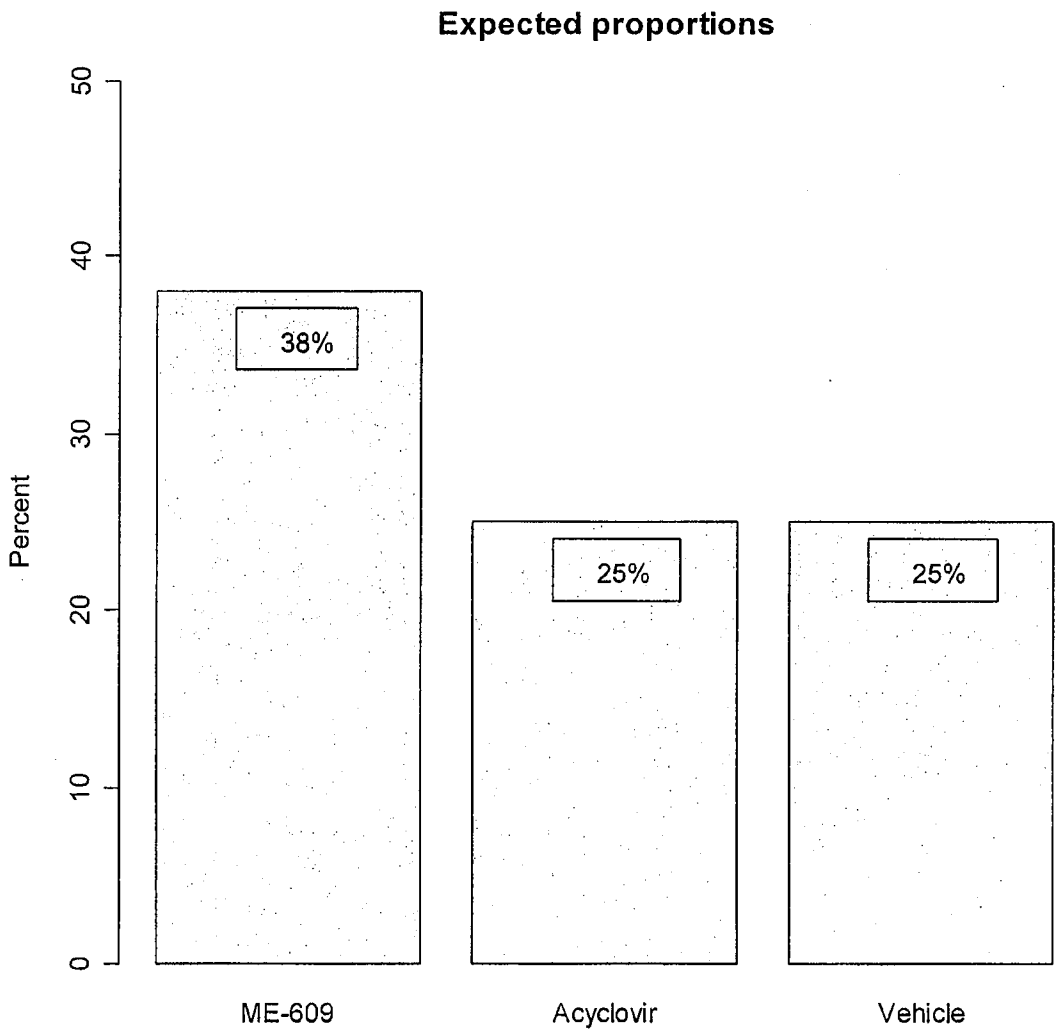
- Robustness of results
- Why the $p<0.001$ was not achieved for one of our primary hypotheses
- Complementary analyses
- Summary of the statistical evidence

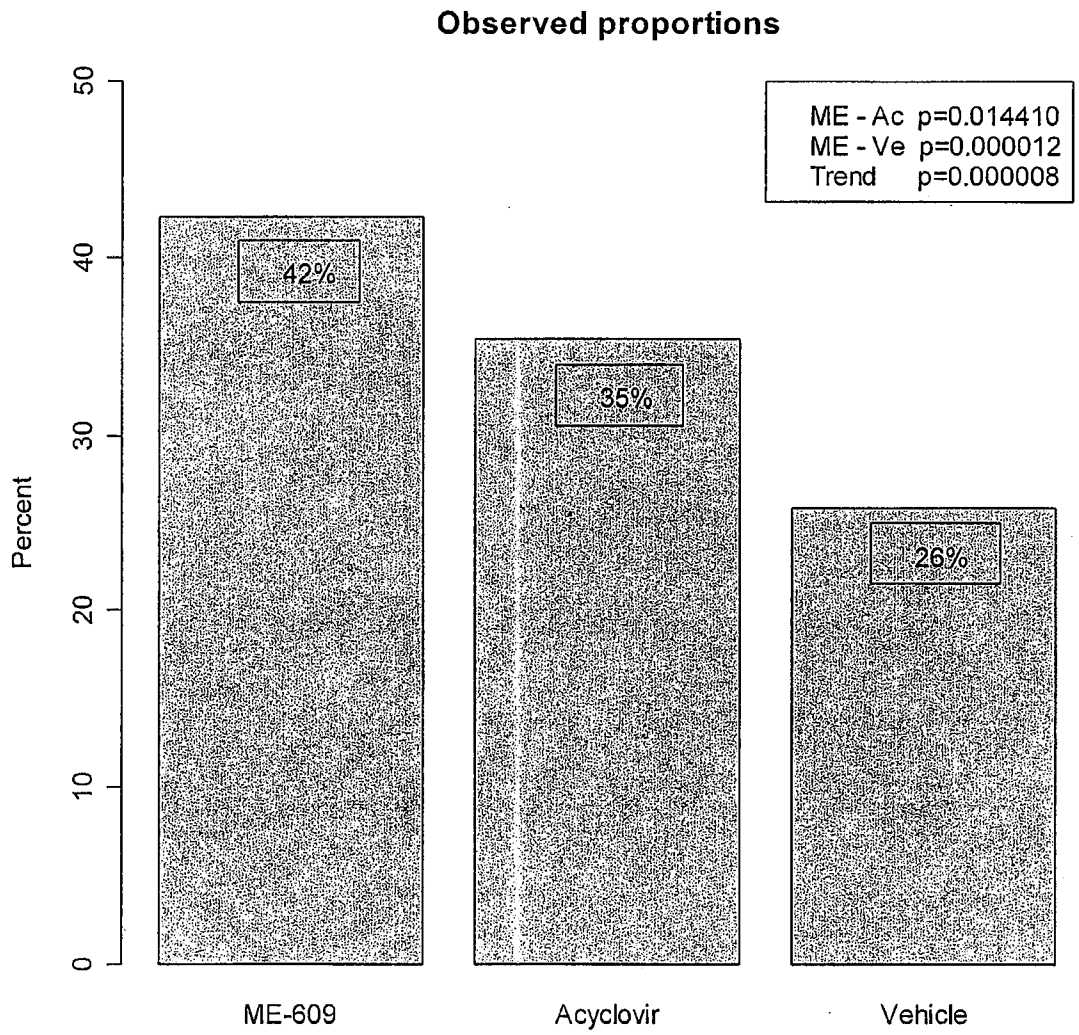
Examples of subanalyses

- Stage at start of treatment
- Study site
- Age
- Gender
- Efficacy by study day
- Critical lesion stage assessment

Proportion non-ulcerative recurrences by stage at start of treatment

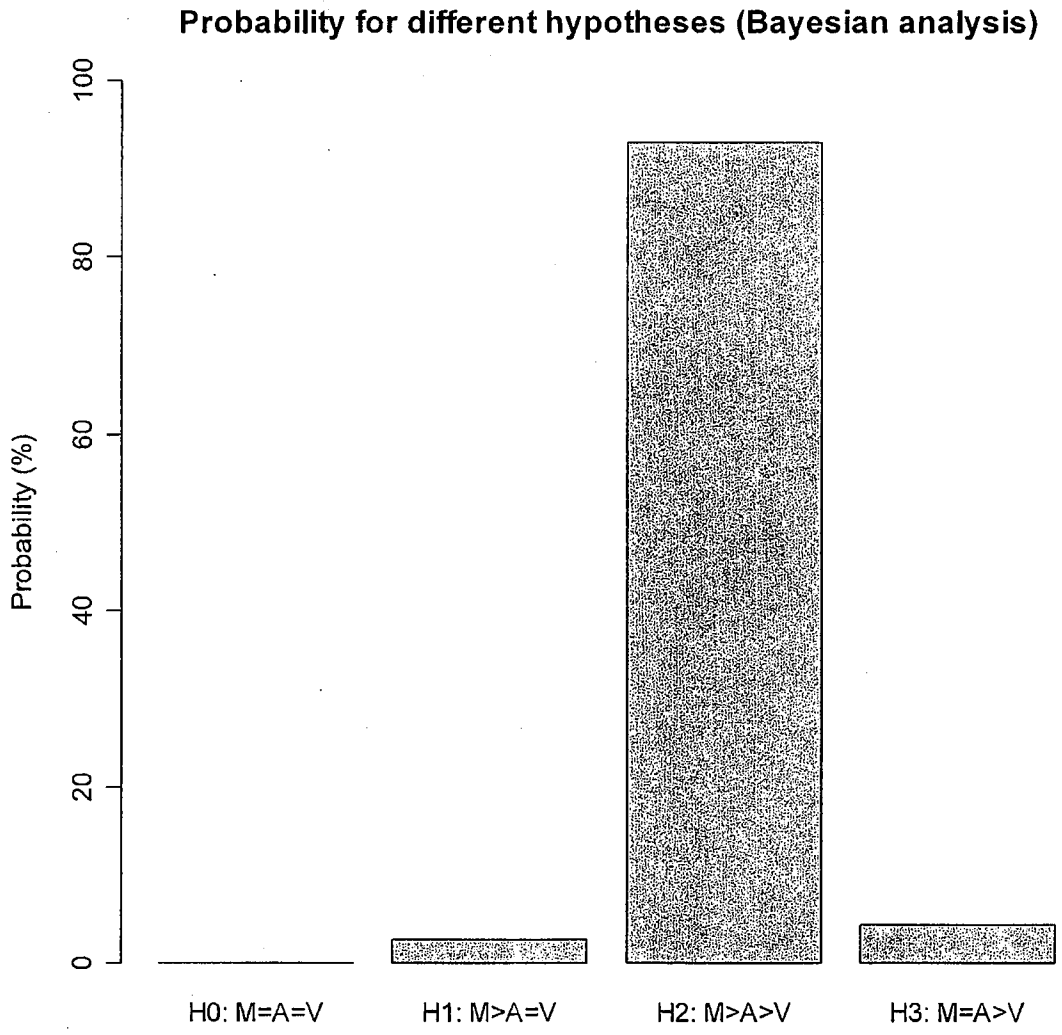



Expected proportions
Percent
0
10
20
30
40
50
38%
25%
25%
ME-609
Acyclovir
Vehicle


Observed proportions
ME - Ac p=0.014410
ME - Ve p=0.000012
Trend p=0.000008
Percent
0
10
20
30
40
50
42%
35%
26%
ME-609
Acyclovir
Vehicle

Possible hypotheses

- H0: ME-609 = Acyclovir = Vehicle
- H1: ME-609 > Acyclovir = Vehicle
- H2: ME-609 > Acyclovir > Vehicle
- H3: ME-609 = Acyclovir > Vehicle


Probability for different hypotheses (Bayesian analysis)
Probability (%)
0
20
40
60
80
100
H0: M=A=V
H1: M>A=V
H2: M>A>V
H3: M=A>V

Summary of statistical evidence

- Subgroup analyses and stratified analyses show that the results are robust and consistent.
- One of the primary analyses did not reach prespecified significance level ($p<0.001$) due to a higher than expected Acyclovir effect.
- The statistical evidence that ME-609 has a preventive effect is very convincing ($p<0.0001$).
- Complementary analyses strengthen the evidence that ME-609 has a better preventive effect than both Vehicle and Acyclovir.

Linked Applications	Sponsor Name	Drug Name
'ND 58500	MEDIVIR AB	ME-609 CREAM(ACYCLOVIR 5%/HYDROCORTISONE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
06/19/2008
for D.Birnkrant

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,500

Medivir
Attention: Mary L. Holland, Ph.D.
Vice President, US Program Management
361 Hacienda Way
Los Altos, CA 94022

Dear Dr. Holland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ME-609 (acyclovir and hydrocortisone).

We also refer to the meeting between representatives of your firm and the FDA on 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.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 827-2344.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D., M.P.H.
Deputy Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF FDA/INDUSTRY MEETING/TELECON

Date of Meeting: **July 6, 2005**

IND: **58,500**

Drug: **ME-609 cream (acyclovir + hydrocortisone)**

Sponsor/Applicant: **Medivir**

Indication: **Treatment of recurrent herpes labialis**

Type of Meeting: **Type B**

Division of Antiviral Drug Products (DAVDP) Participants:

Jeffrey Murray, M.D., M.P.H., Deputy Director
Kim Struble, Pharm.D., Acting Medical Team Leader
George Lunn, Ph.D., Chemistry Reviewer
Rafia Bhore, Ph.D., Acting Statistics Team Leader
Susan Zhou, Ph.D., Statistics Reviewer
Anita Bigger, Ph.D., Pharmacology Reviewer
Jules O'Rear, Ph.D., Microbiology Team Leader
Nilambar Biswal, Ph.D., Microbiology Reviewer
David Araojo, Pharm.D., Regulatory Project Manager

Medivir Participants:

Elisabeth Augustsson, Director Regulatory Affairs
Johan Harmenberg, M.D., Ph.D., Vice President Development
Prof. Bo Öberg, Vice President R&D Strategic Planning
Mary L. Holland, Ph.D., US Program Management
[redacted] b(4
[redacted]
Eva Arlander, PhD, Director Clinical Research
b(4

Background:

This meeting was held at the request of the sponsor, Medivir. The meeting was requested on May 6, 2005 (SN 025) and the meeting background package was submitted on June 6, 2005 (SN 031; for list of sponsor's questions, see Attachment A). Draft comments from the Division of Antiviral Drug Products (DAVDP) dated July 1, 2005, in response to the background package questions, were conveyed to Medivir prior to the meeting (see Attachment B).

Objectives:

To discuss the sponsor's proposed Phase 3 program and protocol outlines and to obtain concurrence on proceeding to Phase 3 clinical trials.

Discussion:

Formulation:

Dr. Struble opened the meeting by acknowledging Medivir's clarification that the formulation outlined in submission 023 is the final to be marketed formulation and is the formulation to be used in the phase 3 study.

Cumulative Irritation Study:

DAVDP agreed that the twenty-one day irritation study, which was done with the final to be marketed formulation, is sufficient to document the dermal safety of ME-609. DAVDP will forward a clarifying comment from the Division of Dermatologic and Dental Drug Products (DDDDP) regarding the results of this study.

Phototoxicity/Photoallergy Studies:

DAVDP conveyed the following preliminary feedback from DDDDP regarding the dermal safety studies:

Regarding the dermal safety studies, it was stated that the absorption spectra that were seen in the UVA, UVB, Visible range were the same as acyclovir. However, it was not shown that the sole mediator of this absorption is acyclovir in the ME-609 formulation.
Further, even if the formulation's absorption were a result of the acyclovir, we would need the provocative dermal safety study as we do not have results of any provocative phototoxicity and photoallerginicity studies for the currently marketed acyclovir cream to review.

DAVDP agreed to provide the above comments from DDDDP after the meeting.

Medivir agreed to submit absorption spectra data for both ME-609 and Zovirax cream for DDDDP's review.

Proposed Immunocompromised Study:

DAVDP suggested the study in immunocompromised subjects should evaluate safety and the development of resistance and any potential effect that hydrocortisone might have on episode duration. The Division stated that the study would need more than twenty subjects and that at least fifty subjects at the time of NDA submission would be necessary.

Medivir stated they intend to follow the Division's suggestion and will perform a randomized, double-blind, acyclovir-controlled study in immunocompromised subjects using the endpoint of

episode duration. For an NDA submission, Medivir proposed information on at least 50 subjects, 25 in each arm.

Further, DAVDP suggested Medivir power the study for non-inferiority and depending on the sample size, the required number of subjects for an NDA submission would be readdressed.

Medivir is considering including organ transplant recipients to facilitate recruitment. DAVDP stated this was acceptable; however, suggested excluding subjects receiving systemic steroid or anti-HSV drugs. DAVDP also suggested lowering the age limit for the study to facilitate recruitment.

In this study, Medivir will obtain virus swabs and test all positive isolates for resistance. Monthly follow-up by visit or phone will look at next recurrence/episode. Episode duration will be collected by patient data diary with subjects encouraged to visit during soft crust stages to collect viral swabs. The follow-up on subsequent recurrences would be reported as descriptive data only. Medivir agreed to submit a full draft protocol for DAVDP review.

Phase 3 Study:

DAVDP stated that the proposed Phase 3 study is sufficient for the single pivotal study for a 505(b)(2) application. Medivir agreed to implement comments regarding protocol clarifications made by DAVDP in a June 30, 2005 facsimile correspondence, since they reflect experience from other herpes labialis programs. Medivir also agreed to provide copies of the patient diary forms.

DAVDP agreed that the sizing and planned statistical analyses for the study are acceptable. Medivir agreed to provide clarification in the protocol that superiority must be demonstrated for the primary endpoints for both treatment comparisons as follows:

a. ME-609 > acyclovir in ME-609 vehicle
b. ME-609 > ME-609 vehicle

DAVDP agreed that the proposed plan for assessing changes in acyclovir susceptibility is acceptable and adequately addresses concerns for clinical relevant changes in acyclovir susceptibility.

Medivir will submit the final protocol for Special Protocol Assessment.

Clinical Safety Data:

DAVDP agreed that the clinical safety data in both adult and adolescents will be sufficient for 505(b)(2) submission.

DAVDP agreed that the safety of repeated use of ME-609 can be extrapolated from the extensive historical data on the long term topical use of each of the individual drugs and that additional clinical data on repeated use of ME-609 is not necessary for approval.

Pediatric Use Study:

DAVDP agreed with the proposed study outline to perform an open label safety study in 100 adolescents. Further, DAVDP 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 of Pediatric Exclusivity. DAVDP will clarify if the pediatric exclusivity would be linked to the use patent or the formulation patent.

Additional Pharmacology/Toxicology Studies:

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

CMC:

Medivir stated they received comments from DAVDP regarding a CMC update and will contact the division if additional discussion is needed.

Action Items Summary:

- DAVDP agreed to provide comments regarding the dermal safety studies from DDDDP.
- Medivir agreed to submit absorption spectra data for both ME-609 and Zovirax cream.
- Medivir agreed to submit a full draft protocol of the immunocompromised study for DAVDP review.
- Medivir agreed to provide copies of the Phase 3 study patient diary forms.
- Medivir will submit the Phase 3 study final protocol for Special Protocol Assessment.
- DAVDP will clarify if the pediatric exclusivity of a Written Request would be linked to the use patent or the formulation patent.

Post-meeting Note:

Please submit a draft protocol for the immunocompromised study. In the protocol please provide a non-inferiority margin and supporting rationale and documentation. We will follow-up with you in a timely manner regarding the proposed non-inferiority margin following review of the requested submission.

Attachment A

Meeting Package Questions

Clinical

1. As described in Section 7.2, the Sponsor has performed one cumulative irritation study in 36 healthy volunteers and one contact sensitizations study in 236 healthy volunteers. These studies are believed to be sufficient to document the dermal safety of ME-609. Does the FDA agree?

2. As described in Section 7.2.3, the Sponsor proposes that no clinical studies on phototoxicity or photoallergy need to be performed since the risk for photoadverse effects with ME-609 is low and these studies are unlikely to provide new information. Does the FDA agree with this position?

3. As described in Section 8, the Sponsor proposes that a study in 20 immunocompromised subjects is conducted to evaluate safety in this population as well as acyclovir susceptibility in virus isolates. Does the FDA agree that this study addresses the relevant safety concerns for the potential inadvertent use of the combination in this higher risk population?

4. As described in Section 9, and as previously agreed with FDA, the Sponsor proposes to conduct one single pivotal Phase 3 study in 1270 subjects, with the objective of demonstrating the superiority of ME-609 vs. acyclovir in ME-609 vehicle and vs. its vehicle. Based on the background provided in Section 6, virus isolates will be obtained from all treated subjects and analyzed as described in Section 9.4.
   a) Does the FDA agree that this study is adequately designed to provide evidence of efficacy of ME-609 and to constitute the single pivotal study for this 505(b)(2) application?
   b) Does the FDA agree that the sizing and planned statistical analyses in this study are adequate?
   c) Does the FDA agree the proposed plan for assessing changes in acyclovir susceptibility is acceptable and adequately addresses any concerns for clinical relevant changes in acyclovir susceptibility after ME-609 treatment?

5. As described in Section 9.6, the Sponsor proposes that the clinical safety data obtained from treatment of at least 500 subjects in the pivotal phase 3 study and 100 adolescents in a separate safety study, together with supportive safety data from phase 1 dermal safety studies and the phase 2 study, will be sufficient for the 505(b)(2) submission. The Sponsor believes that the safety of repeated use of ME-609 can be extrapolated from the extensive historical data on the long term topical use of each of the individual drugs, thus additional clinical data on repeated use of ME-609 is not necessary for approval. Does the FDA agree with this position?

6. As described in Section 9.5, and as previously agreed with FDA, the Sponsor proposes to perform an open label safety study in 100 adolescents to document pediatric use. Does the FDA find the proposed study outline (Section 9.5.1) acceptable?

Non-clinical Questions

7. As described in Section 4, and as previously agreed with FDA, the Sponsor proposes that no further non-clinical pharmacology or toxicology studies are needed to support the 505(b)(2) application. Does the FDA agree?

CMC Questions

8. The Sponsor received the fax memorandum from the Division containing feedback on the CMC update submitted by Medivir on April 15, 2005 and will respond in a separate communication.

Attachment B

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 58,500

Drug: ME-609 Cream (acyclovir + hydrocortisone)

Date: June 30, 2005

Sponsor: Medivir

From: David Araojo, Pharm.D., Regulatory Project Manager

Through: Kimberly Struble, Pharm.D., Senior Clinical Analyst
Debra Birnkrant, M.D., Division Director

Subject: Draft Comments for July 6, 2005 meeting

Based on our review of your briefing package for the July 6, 2005, End-of-Phase-2 Meeting, we have the following comments and discussion points.

Formulation:

We acknowledge in serial submission 023 your intent to change the formulation and ——— b(4)
——— Please clarify if the formulation as outlined in submission 023 is the final to be marketed formulation. Please also clarify if the final to be marketed formulation is used in the phase III study. As previously stated, we recommend you use the final to be marketed formulation in the phase III study.

Dermal Safety Studies:

Per our discussions with DDDDP, the final to be marketed formulation should be used in the dermal safety studies. As a result, the completed 21-day cumulative irritation patch test and sensitization study are not sufficient to document the dermal safety of ME-609. We recommend you conduct another 21-day cumulative irritation patch test and sensitization study using the final to be marketed formulation.

At this time we are not able to rely on historical data to waive the requirement for phototoxicity or photoallergy studies. Please refer to the April 21, 2004 meeting minutes. During the meeting we recommended the following:

Generally, the required topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergy (not less than 50 evaluable subjects) and phototoxicity (not less than 30 evaluable subjects). These studies should be conducted with the final to be marketed formulation and are usually conducted in parallel with phase 3 studies. However, if phase 1 or 2 studies should reveal an apparent irritancy signal, and the product is to be labeled as an irritant, cumulative irritancy testing may not be needed. Additionally, if no component of the product absorbs in the UVA, UVB or visible light spectra, then phototoxicity and photoallergy studies may be waived (copies of the absorption spectra of the complete product from ——— should be submitted to the IND). b(4

Please provide information regarding if ME-609 absorbs in the UBVA, UVB, or visible light spectra. Depending on the results of these data, phototoxicity and photoallergy studies may be waived.

Proposed Immunocompromised Study:

We appreciate your efforts in proposing a study to evaluate ME-609 in immunocompromised subjects to address the concerns regarding the possibility of changes in acyclovir susceptibility and the impact of acyclovir and hydrocortisone use in this population. You proposed a single-arm, open-label safety study. The proposed primary endpoint is ——— Although ——— b(4)
in this patient population is important, our main concerns about the safety of hydrocortisone component in ME-609 cream relates to the potential for prolonged healing times and the risk for developing resistance. Your study as proposed is not sufficient to address this issue. We would like to discuss with you an alternative study design as outline below.

Please consider a two-arm study (ME-609 versus acyclovir) with a primary endpoint of episode duration. This endpoint will enable us to determine if the hydrocortisone component adversely affects acyclovir efficacy. Our concern is prolonged healing times with ME-609, for example, episode duration is twice as long compared to acyclovir. Therefore, we would like to discuss sample size proposals for this study. In addition, we recommend a similar follow-up plan as proposed in the immunocompentent study.

We recognize the sample size for this study is likely to be larger than your proposed 35 patients study and recruitment may be slower than an immunocompetent study. At this time, completion of this study prior to an NDA submission is not required; however, information on 50 subjects (minimum) is needed for the NDA submission.

In addition, we would like to hear your thoughts on following subjects in this study for subsequent recurrences to evaluate the time to next recurrence and episode duration of subsequent recurrences. Please note, we are not requesting a study powered to evaluate these endpoints.

Phase III Immunocompetent Study:

1. Previous studies included provisions for subjects to call the study clinic or a central number at the earliest prodromal symptom(s) and before the development of any clinical signs of a cold sore. Once confirmation of the outbreak was obtained, subjects were instructed to initiate treatment immediately and begin to record information in the diary. Please consider including similar provisions in the study. These provisions can help reinforce study procedures and recording of information in the diary, especially for subjects whose recurrences occur several months after recruitment into the study.
2 The study procedures require subjects to visit the clinic within 18 hours for evaluation. In other studies, subjects are required to visit the clinic no later than 24 hours for evaluation. For feasibility reasons, please consider the time point of no later than 24 hours for evaluation in order to avoid protocol violations.
3 Please submit the patient diary forms for review. In addition, a record for the following information in the patient diary is recommended:
    - Start and end time of prodromal (early) symptoms
    - Date/time of first visible sign (macule/papule) of a cold sore appeared
    - Date/time vesicle (blister) formed
    - Date/time of complete loss of crust
    - Date/time skin returned to normal
    - Date/time of cessation of tenderness
4. Clarification in the protocol is needed to ensure clinicians assess the herpes recurrence before reviewing the subject's diary. In addition, please clarify in the protocol that information about the clinicians' assessment is not shared with subjects.
5. We recommend the following staging for recurrence evaluations; therefore, please specify in the protocol if a lesion crust is dislodged or manually removed and the lesion beneath is weepy/red then the clinician should continue to stage the lesion as a "crust" until the lesion is considered healed.
6. Please revise the protocol and explicitly state the following in the inclusion criteria:
    - Subjects 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.
    - Subjects 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.
    - Subjects 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)
7. Regarding the exclusion criteria, please expand the definition of significant skin disease to include eczema, psoriasis or chronic vesiculobullous disorders.
8. In addition, we recommend the following exclusion criteria: subjects who have had infection with HSV-1 isolates known to be resistant to acyclovir, valaciclovir, famciclovir or ganciclovir.
9. Please clarify in the protocol if pregnant or nursing women are eligible for the study.
10. Please clarify in the protocol superiority must be demonstrated for the primary endpoint for both treatment comparisons as follows:
    a. ME-609 > acyclovir in ME-609 vehicle
    b. ME-609 > ME-609 vehicle

Pediatric Development:

The proposed open-label safety study in 110 adolescents is reasonable and likely to yield useful information for product labeling. Please clarify if you intend to propose a Written Request for Pediatric Exclusivity.

We look forward to a productive meeting on July 6, 2005.

If you have any questions or concerns please contact me at (301) 827-2344 or by fax at (301) 827-2523.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

David Araojo, Pharm.D.
Regulatory Health Project Manager
Division of Antiviral Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
7/29/05 02:42:09 PM