Recurrent Herpes Labialis: Developing Drugs for Treatment and Prevention

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Regina Alivisatos, MD, at 301-796-1500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Recurrent Herpes Labialis: Developing Drugs for Treatment and Prevention Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the development of drugs for the treatment and prevention of recurrent herpes labialis (RHL). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs to support the development of drug products with an antiviral mechanism of action used to prevent and/or treat RHL caused by either herpes simplex virus type 1 or 2 (HSV-1 or HSV-2) in immunocompetent subjects. This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.[2] This guidance does not address the development of drug products used to treat systemic, genital, or disseminated herpes virus infections, or herpes labialis in immunosuppressed subjects.

This guidance does not contain discussions of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs used to treat or prevent RHL.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Infections caused by viruses of the herpes virus family are increasingly frequent. One of the more common forms of such infections is RHL, which is primarily caused by HSV-1 but also caused by HSV-2, which is more commonly associated with genital herpes (Harmenberg, Öberg, et al. 2010; Cunningham, Griffiths, et al. 2012). From 2005 to 2010, the seroprevalence of HSV-1 was 53.9 percent, and the seroprevalence of HSV-2 was 15.7 percent in the United States (Bradley, Markowitz, et al. 2014). It is estimated that 20 to 40 percent of adults in the U.S. population experience RHL (Bader, Crumpacker, et al. 1978; Lowhagen, Bonde, et al. 2002).

The presentation of a primary herpes labialis episode in adults can vary from an asymptomatic presentation to an acute self-limiting gingivostomatitis often associated with posterior pharyngitis and tonsillitis (Arduino and Porter 2006). Fever, malaise, headache, and sore throat are presenting features and can be associated with vesicles on the tonsils and the posterior pharynx. These vesicles if present can rupture to form ulcerative lesions with grayish exudates. This type of primary infection that is associated with oral and labial lesions occurs in less than 10 percent of patients. Acute herpetic gingivostomatitis usually lasts 5 to 7 days, and the symptoms subside in 2 weeks. The virus then establishes latency in the sensory ganglia and, when reactivated, virus particles travel along sensory neurons to the skin and other mucosal sites and cause RHL (Harmenberg, Öberg, et al. 2010). A variety of stimuli can lead to reactivation, including exposure to ultraviolet light, fever, psychological stress, and menstruation. These recurrent episodes can be associated with lesions or asymptomatic viral shedding. When symptomatic, the episodes can be painful and disfiguring.

The outer edge of the vermilion border is the most common site of reactivation; on average three to five lesions are present. Episodes typically progress through sequential phases, including a prodromal stage followed by stages characterized by papules, or pustules (vesicles), and/or ulcers. The prodromal stage, comprised of sensory symptoms occurring in the absence of cutaneous lesions, generally resolves in 4 to 5 days.

Approximately 25 to 50 percent of RHL episodes do not progress beyond the prodromal or papule stage; these are referred to as aborted lesions (Spruance, Overall, et al. 1977). In the immunocompetent host, episodes that progress beyond the prodromal stage are self-limited and generally heal spontaneously within 8 to 10 days.

Herpes labialis recurrences are diagnosed primarily on the basis of clinical presentation. Diagnostic testing for HSV-1 or HSV-2, while available, is not used routinely in the clinical setting. Diagnostic confirmation, if needed, can be provided by isolation of HSV in tissue culture, indirect immunofluorescent staining of skin scrapings with monoclonal antibodies, or polymerase chain reaction.

There are a number of prescription topical and systemic drugs approved for the treatment of RHL. For antiviral drugs, the goal of therapy is to block viral replication in order to shorten the duration of symptoms and accelerate the healing of lesions leading to a return to normal skin. Because episodes of RHL are self-limited with an expected duration of 5 to 10 days, if treatment is either warranted or requested, it should be initiated as soon as possible to ensure an optimal and beneficial therapeutic effect. To date, no antiviral drug has been approved for the prevention of RHL.

III. DEVELOPMENT PROGRAM

A. General Considerations

General considerations pertinent to nonclinical development and early clinical development are outlined in this section. Sponsors can also obtain regulatory advice early in the development program, before submitting an investigational new drug application (IND), through the pre-IND consultation program.[4]

B. Nonclinical Development Considerations

1. Pharmacology/Toxicology Considerations

Pharmacology/toxicology development for HSV antivirals should follow existing guidances for nonclinical drug development with regard to study requirements, study duration, timing, and local tolerance, as well as fixed-drug combinations.[5]

If it is anticipated that a subject may be exposed to an HSV antiviral for prevention of recurrences, or for 26 weeks or longer (cumulative dosing over a calendar year), chronic toxicity and carcinogenicity studies are generally needed to support chronic dosing in subjects.

Nonclinical studies to support a change in the route of administration (e.g., oral to topical) or reformulation of an already approved drug substance may be needed if existing data do not support trials in subjects.[6] Similarly, if systemic absorption following a change in the route of administration is higher than previously observed, additional pharmacology/toxicology studies may be needed. The need for such studies can be further discussed with the DAVP.

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[4] See the FDA Web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm.

[5] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.

[6] See the guidance for industry and review staff *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route*.

2. Virology Considerations

Nonclinical virology studies can facilitate dose selection and study design to provide proof of concept and data supporting an antiviral claim. Additional recommendations for general antiviral drug development can be found in the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*. Sponsors can seek advice regarding the appropriate nonclinical virology assays through the pre-IND program mentioned previously.

a. Mechanism of action

The mechanism by which an anti-HSV investigational drug specifically inhibits HSV-1 and/or HSV-2 replication or a virus-specific function should be investigated using cell culture, biochemical, structural, and/or genetic studies that include evaluation of the effect of the drug on relevant stages of the virus life cycle. Mechanism-of-action studies should include appropriate controls for assessing the specificity of anti-HSV activity, which may include assessments of activity against HSV-1 and/or HSV-2 proteins that are targeted by the investigational drug, relevant host proteins, and other viruses.

b. Antiviral activity in cell culture

HSV-1 and HSV-2 are closely related but distinct viruses and both cause RHL. The antiviral activity of oral, parenteral, and topical drugs should be characterized in cell culture to assess the anti-HSV-1 and/or HSV-2 activity and to identify a target plasma concentration for evaluation of oral- or parenteral-administered drug products in HSV-infected subjects. Anti-HSV activity studies should include assessments against several (greater than or equal to 20 each) geographically and temporally distinct isolates of HSV-1 and HSV-2, the vast majority of which should be U.S. isolates. Additional isolates should be obtained from relevant countries if non-U.S. sites will be used in clinical studies. The effective concentration at which virus replication is inhibited by 50 and 90 percent (EC_{50} and EC_{90} values) should be determined for each isolate using a quantitative assay. Sponsors should consider and discuss with the DAVP the merits of developing an investigational drug showing significantly greater activity for HSV-2 compared to HSV-1 given the relative proportions of each in the U.S.-infected population.

c. Cytotoxicity and mitochondrial toxicity

The cytotoxic effects of the drug should be quantified directly in the cells used for assessing anti-HSV activity, and a 50 percent cytotoxic concentration (CC_{50}) and a therapeutic index (CC_{50} value/EC_{50} value) should be calculated. Cytotoxicity should also be assessed using various cell lines and primary cells cultured under proliferating conditions for several cell divisions and nonproliferating conditions. Deoxynucleoside/deoxynucleotide analogs should be assessed for bone marrow precursor cell toxicity with appropriate controls.

Mitochondrial toxicity for all drugs should be evaluated in glucose-containing medium and galactose-containing medium (Marroquin, Hynes, et al. 2007). Mitochondrial toxicity assessments should be evaluated with drug exposures for several cell divisions. Positive controls

for mitochondrial toxicity studies should be relevant to the class of the investigational drug whenever possible. The active triphosphate of nucleoside analog inhibitors also should be evaluated in biochemical assays with mitochondrial DNA and RNA polymerases (Arnold, Sharma, et al. 2012).

These biochemical and cell-based assessments for potential cellular and mitochondrial toxicity should be conducted as a complement to in vivo toxicology assessments and not in lieu of in vivo studies. Results from these studies should be interpreted in the context of the in vivo toxicology, nonclinical, and clinical pharmacokinetic data to help assess clinical risk.

d. Combination antiviral activity

Early in development, combination antiviral activity relationships of the investigational drug and approved drugs for HSV should be characterized in cell culture to identify any combinations where the antiviral activity is antagonistic if future combination therapy is anticipated. Each component of a combination drug that will contain at least one novel drug substance should be assessed for antagonism between the components.[7] For all combination antiviral activity assessments, sponsors should provide combination index values or synergy scores when the two drugs are combined at their individual EC_{50} values, and studies should include controls for cytotoxicity. Combination antiviral activity relationships for nucleos(t)ide and deoxynucleos(t)ide HSV investigational drugs for which there will be systemic exposure should also be assessed with approved drugs for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus-1, as appropriate, before testing combinations of the drugs in co-infected subjects.

e. Activity in animal models

Demonstration of HSV-1 and HSV-2 antiviral activity in an animal model is not needed for drug approval. However, if such studies are conducted and provided in support of an HSV therapy program, we recommend including the HSV type, time course plots of viral load data for each animal, and an assessment of resistance development.

f. Resistance and cross-resistance

Amino acid substitutions associated with the development of resistance to the investigational drug can be identified by genotyping the target gene and the conferred fold-shift in susceptibility determined using appropriate cell culture assays. Results from these studies can be used to: (1) identify resistance pathways; (2) validate resistance assays for use in clinical trials; (3) determine whether the genetic barrier for resistance development is high or low; (4) predict whether the genetic barrier for resistance may vary as a function of concentration of the investigational drug; (5) assess the potential for cross-resistance with other anti-HSV drugs, particularly acyclovir; and (6) support the drug's hypothesized mechanism of action. Resistant viruses selected in cell culture provide important controls for phenotypic assessment of clinical isolates.

[7] See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*.

Resistance studies can include evaluation of the potential for cross-resistance, both to approved drugs and also to drugs in development when possible, particularly focusing on those in the same drug class and other classes targeting the same protein or protein complex. The antiviral activity of the investigational drug can be assessed against mutant viruses that are resistant to drugs within the same drug class as the investigational drug as well as against a representative sample of viruses resistant to other approved anti-HSV drugs.

Deoxynucleoside analogs for the treatment of herpes viruses have been found to have antiviral activity against human immunodeficiency virus-1 (HIV-1) and can select for resistant variants (Tachedjian, Hooker, et al. 1995; McMahon, Siliciano, et al. 2008; Lisco, Vanpouille, et al. 2008). Developers of such drugs for HSV should determine the cell culture antiviral activity of the active moiety against HIV-1. If the drug demonstrates antiviral activity, development of resistance to the investigational drug should be determined genotypically and phenotypically by selecting resistant HIV-1 variants. Resistance studies should include evaluation of cross-resistance to approved nucleo(t)side reverse transcriptase inhibitors for HIV-1.

3. Early Phase Clinical Considerations

The extent of this development phase depends on whether the treatment under study is a new molecular entity or a previously approved drug seeking a new indication with or without a new route of administration or a new formulation. In all cases, DAVP will consult with the Division of Dermatology and Dental Products to assess the need for dermatologic safety studies for drugs being developed for topical administration.

a. Investigational drugs

The development program for orally or topically administered investigational drugs should include the standard phase 1 safety studies as specified in the guidance for industry, investigators, and reviewers *Exploratory IND Studies*. Following phase 1, progression to proof-of-concept and dose-ranging phase 2 trials is strongly advised to establish a sufficiently well-tolerated and active dose for phase 3 trials. The phase 2 trials can be of similar design to phase 3 trials, albeit smaller. The primary objective should be a reduction in the duration of the episode of RHL by at least 1/2 day. The number of phase 2 trials needed to proceed to phase 3 clinical development depends on the treatment under study, and the safety and efficacy results observed in at least one such trial.

Of note, a phase 2 dose-response trial is one type of adequate and well-controlled trial that, if measuring appropriate endpoints in appropriate populations, can contribute to substantial evidence of effectiveness (21 CFR 314.126). In addition, dose- or exposure-response analyses within trials can provide additional support for approval of different doses or dosing regimens.

b. Previously approved drugs with a new formulation and/or route of administration

The early clinical development program for previously approved drugs with a new formulation and/or route of administration should be discussed with the FDA. A drug previously approved for oral administration and now being developed for a new indication and/or dosage likely will not need an extensive phase 1 development program. However, as discussed previously, an oral drug product now being developed as a topical drug product may need to undergo dermatologic safety testing. A proof-of-concept phase 2 clinical trial may be needed depending on the formulation, route of administration, and dose under study.

C. Phase 2 and Phase 3 Clinical Development

1. Drug Development Population

The drug development population should include immunocompetent adults or adolescents at risk for developing recurrent episodes of herpes labialis, defined as individuals experiencing at least four recurrent episodes per year. Enrollment of a population that has experienced multiple recurrences is preferred for the treatment indication to allow early initiation of treatment at the first symptoms or signs of recurrence. For a prevention indication, the enrollment of a population with a greater likelihood of recurrence is critical to demonstrate a preventative effect. It may be possible to enroll children 12 years of age or younger (ages 6 to 12) depending on the formulation under development and its safety profile (i.e., a drug product for topical use) in either the adult trials or in separate concurrently run trials. Sponsors are advised to discuss this possibility with the FDA.

Given estimates of disease prevalence in the United States, we recommend that there be adequate representation of U.S. subjects within the application to support approval. If trials are conducted outside the United States, sponsors are strongly encouraged to refer to the recommendations outlined in the guidance for industry *Acceptance of Foreign Clinical Studies* and the requirements in the final rule "Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application" for the relevant considerations.[8]

2. Efficacy Considerations

For investigational drugs, sponsors are strongly encouraged to conduct two adequate and well-controlled phase 3 trials (superiority) to support the intended indication. However, a single persuasive and clinically meaningful study for each indication (treatment and prevention) submitted together may provide substantial evidence of effectiveness sufficient for approval of both indications. In circumstances where a drug previously approved for RHL treatment is being developed for the prevention indication, a single superiority study may be considered to provide substantial evidence of effectiveness for the intended indication. In addition if a drug was previously approved for a disease caused by HSV-1 or HSV-2 and is now being developed for RHL, one adequate and well-controlled trial may suffice. For a prevention-only indication, data

[8] 73 FR 22800, April 28, 2008

from two phase 3 trials is strongly recommended. See section III.C.4., Specific Efficacy Trial Considerations, for details. Sponsors should also refer to the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products*.

a. Treatment indication

In general, treatment trials should be designed to demonstrate a decrease in the duration of episode (DOE) of RHL by at least 1/2 day relative to a control. Spontaneous resolution of RHL can occur in 5 to 10 days and approved antiviral drugs that reduce the duration of RHL episodes by at least 1/2 day are considered clinically beneficial. Sponsors can consider secondary endpoints, such as a reduction in the number of ulcerative lesions, pain reduction, or an increase in the number of aborted lesions for labeling claims; however, discussion with the FDA and agreement before designing pivotal trials is strongly encouraged. See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products* for details on the number of controlled clinical efficacy studies needed to support the effectiveness of a new treatment.

In general, as noted above, trials for the RHL treatment indication should be placebo-controlled superiority trials although an actively controlled superiority trial also can be considered.

b. Prevention indication

Prevention of RHL denotes no recurrences or less-frequent recurrent episodes in at-risk individuals. Currently, no drug is approved for the prevention of RHL; therefore, a trial for this indication should be a placebo-controlled superiority trial.

While designing a prevention trial(s), consideration should be given to the duration of observation (preferably 12 months) and the determination of the primary endpoint. An appropriate primary endpoint for prevention studies is either the number of confirmed recurrences observed in subjects on suppressive therapy over a 12-month period or the time to first recurrence, defined as the time from randomization until the onset of an episode of RHL. However, it is strongly recommended that the number of recurrences over a 12-month period be provided.

Drugs in development for the treatment and/or prevention of RHL in immunocompetent hosts are not eligible for consideration under 21 CFR part 312, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses, breakthrough therapy designation, fast track, or priority review because of the non-life-threatening and self-limited nature of the disease.

3. Safety Considerations

Generally, sponsors are advised to discuss the size of an appropriate safety database for their drug product at the end-of-phase 2 meeting. Consideration should also be given to the route of administration in determining the size of the safety database for either the treatment or the prevention indication. The safety database can include both adults and pediatric subjects.

For topical treatments, the safety database may need topical safety studies. Sponsors are advised to discuss the need for such studies with the DAVP.

The number of subjects that should be studied to have an acceptable safety database for a new previously unapproved drug product that will be used chronically for a prevention indication should be discussed with the DAVP. We anticipate that a minimum of 1,000 subjects treated with the proposed dose for oral drugs or topicals with systemic absorption will be studied. However, a topical drug with no systemic absorption may have a safety database between 500 and 1,000 subjects.

Sponsors should provide a toxicity grading scheme for clinical trials. Commonly used schemata can be used (e.g., AIDS Clinical Trials Group, National Cancer Institute, or World Health Organization), with the understanding that toxicities with a relatively low grade assignment may be less acceptable in healthy populations commonly enrolled in RHL clinical trials compared to populations in clinical trials of drugs for diseases such as cancer or human immunodeficiency virus.

4. Specific Efficacy Trial Considerations

a. Study design

Study designs appropriate for the study of the treatment or prevention of RHL can be found below:

- **Treatment trials**

  To date, the most successful applications for a treatment indication of RHL have included double-blinded, placebo-controlled trials that focused on early treatment intervention by prospectively dispensing the investigational drug (or placebo) for subject-initiated treatment at the first sign or symptom of a recurrent episode. Given the self-limited nature of RHL, such placebo-controlled superiority trials are considered the most direct route to providing evidence of efficacy.

  Noninferiority trials have not been considered feasible for an RHL treatment indication because of the modest and variable treatment effects observed to date with available treatments (1/2 day difference in the duration of episode endpoint). Expected outcomes cannot be predicted well enough to support an adequate noninferiority margin.

  In addition to placebo-controlled trials, superiority trials against an active control (i.e., an approved antiviral drug for RHL) could also be considered. A single-arm, open-label trial design is not considered appropriate for a treatment indication.

  Duration of treatment depends on the formulation under study and can range from single to multiple doses.

- **Prevention trials**

  Currently no drug is approved for the prevention of RHL; therefore, a trial for this indication should be a placebo-controlled superiority trial. A placebo-controlled trial is considered feasible given the self-limited nature of RHL. Similar to trials designed for a treatment indication, a single-arm, open-label trial design is not considered an appropriate alternative for evaluating prevention of RHL.

b. Study population

As mentioned above, RHL affects a substantial percentage of the U.S. population. Phase 3 trials should focus on RHL in healthy immunocompetent adults and adolescents. See section III.C.4.e., Special populations, for discussion of pediatric and adolescent subjects.

c. Inclusion and exclusion criteria

Generally, trials to assess the treatment (or prevention) of RHL should be conducted in a population of subjects highly experienced with the disease under study. This enables subjects to rapidly identify recurrences and to self-initiate treatment as soon as possible during the prodrome phase. The inclusion criteria should specify:

- Enrollment of experienced subjects with a history of at least 4 episodes of RHL in the previous 12-month period
- At least half of these episodes should be vesicular in nature
- At least half of the episodes should be preceded by prodromal symptoms
- Immunocompetent subjects

Note: Culture or serologic documentation is not needed for the RHL indication. The diagnosis is a clinical one based on previous history of recurrences. However, HSV-1 and HSV-2 could respond differently to an investigational drug product, which could affect efficacy results (see section III.C.4.l., Clinical virology considerations, for further discussion).

Subjects who have received even one dose of any treatment active against HSV (current episode) should be excluded. This includes both nonprescription as well as prescription medications.

Also subjects should be excluded if they have evidence of active malignancy or immunodeficiency disease, require chronic use of immunosuppressive drugs (e.g., systemic steroids) or topical steroids, or chronically use antiviral medication with activity against HSV. Subjects who cannot be reliably expected to comprehend or satisfactorily assess a herpetic lesion, who have abnormal skin conditions (e.g., acne, eczema, rosacea, psoriasis, albinism, or chronic vesiculo-bullous disorders) that occur in the area ordinarily affected by RHL, or who have had a vaccine for HSV-1 (typically oral herpes) or HSV-2 (typically genital herpes) should also be excluded.

d. Randomization, stratification, and blinding

It is important for sponsors to consider double-blinding, if possible, given the self-limited nature of RHL and the subjectivity of a number of the endpoints, such as time to pain resolution, or symptom improvement.

e. Special populations

Special populations in which RHL can be studied are listed below:

- **Pediatrics**

  Decisions regarding pediatric development may vary depending on various issues including, but not limited to, formulation and safety profile. Therefore, sponsors are encouraged to begin discussions about their pediatric formulation and clinical development plan early because sponsors are required to submit pediatric study plans under the Pediatric Research Equity Act (PREA).[9] The following discussion is based on situations where the antiviral drug is expected to act similarly in adults and pediatric patients. Other situations should be discussed with the FDA on a case-by-case basis.

  Because the course and pathophysiology of RHL is similar in adults and pediatric patients (ages 6 to younger than 18 years), and the effect of the antiviral drug product is expected to be the same in adults and children, extrapolation of efficacy from adults to children is generally acceptable. In this situation, pharmacokinetic (if systemically absorbed) and safety studies may be considered adequate to extend the indications to these pediatric age groups.

  The annual prevalence of RHL in children from 8 to 11 years has been estimated to be 12 percent in some studies. The annual prevalence of RHL in adolescents between 12 and 17 years of age has been estimated to be 17 percent in some studies. Therefore, studies in the pediatric population are required under PREA.[10] Herpes labialis in children younger than 6 years of age is generally a primary infection, and not recurrent in nature (Rioboo-Crespo Mdel R, Planells-del Pozo P, et al. 2005; Arduino, Porter, et al. 2008). Therefore, a partial waiver to conduct studies in subjects younger than 6 years of age generally will be granted. Pediatric studies should evaluate subjects aged 6 to 17 years as described below:

[9] See PREA (Public Law 108-155; section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144). See also the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

[10] See PREA (Public Law 108-155; section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355B) as amended by FDASIA (Public Law 112-144).

- Antiviral drugs with favorable risk-benefit assessment should be evaluated in pediatric patients aged 6 to 11 years. A minimum of 50 pediatric patients (aged 6 to 11 years) should be studied to adequately characterize dosing and safety of the drug product.

- Antiviral drugs with favorable risk-benefit assessment should be evaluated in adolescent subjects aged 12 to younger than 18 years. A minimum of 50 adolescent subjects (subjects aged 12 to younger than 18 years) should be studied to adequately characterize dosing and safety of the drug product.

- **Other special populations**

  The determination of the efficacy and safety of the treatment under study in other special populations should be discussed with the DAVP. The route of administration and the degree of systemic absorption for a topical drug product will be factors in determining the need for further assessment.

f. Dose selection

Animal studies and human dose-ranging trials can contribute to dose selection for phase 3 clinical trials. Exposure-response relationships can be used to help guide dose selection. Various pharmacodynamic parameters, such as those relating to viral clearance and healing time, should be explored. As previously noted, sponsors should conduct adequate phase 2 trials before designing the phase 3 trials.

For some drugs, more than one route of administration can be considered. Different dosing, safety, and efficacy issues may arise with different routes of administration. For example, certain drugs may be available for both oral and topical use and appropriate dosing should be established for both routes.

g. Choice of comparators

RHL is a self-limited disease. Therefore, a placebo comparator arm is considered ethical and most appropriate in a superiority trial design for either the treatment or the prevention indication. Other approved treatments for RHL also can be used as comparators in a superiority trial for the treatment indication.

h. Efficacy endpoints

Efficacy endpoints for both the treatment and prevention indications are discussed below:

- **For the treatment indication**

  The DOE endpoint provides the most accurate assessment of the effectiveness of RHL treatments to date because it measures the effect of the treatment under study on the full spectrum of the RHL episode (i.e., all stages of lesion evolution).

DOE is defined as the time from treatment initiation to the healing of primary lesions (loss of crust) for subjects who experienced a vesicular lesion. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last.

- For the DOE endpoint, the protocol should provide:
  - How often the acute episodes will be assessed
  - Daily investigator follow-up during the acute episodes until complete healing has occurred
  - Subject diary where subjects can record their lesion status at least twice daily, so that time of assessment and lesion or disease status can be accurately documented
- For the DOE endpoint, the mean and median values should be provided. A study evaluating treatment of RHL should show clinically meaningful as well as statistically significant results to make a claim of decreased episode duration. A clinically meaningful difference in DOE has been determined to be a difference between treatment arms of at least 1/2 day for both mean and median values.
- Secondary endpoints can include:
  - Investigator-assessed prevention of progression to a classical lesion (aborted lesions)
  - Subject-assessed duration of lesion pain
  - Subject-assessed severity of lesion pain
  - The incidence of recurrence and time to recurrence following treatment

  For labeling claims based on secondary endpoints, the results should be clinically meaningful and statistically significant. A testing strategy should be included a priori in the protocol and statistical analysis plan (SAP) to control the overall type I error rate.

  Note: For incidence of recurrence, all enrolled subjects should continue to be followed for the prespecified time period and the follow-up population should be defined a priori.

- **For the prevention indication**

  The recommended primary endpoint should be either the number of confirmed recurrences observed in subjects on suppressive therapy over a 12-month period or the time to first recurrence defined as the time from randomization until the onset of an episode of RHL. It should be stressed that for this indication the duration of observation is paramount. Shorter observation periods, such as 6 months, may be inadequate to collect an appropriate amount of clinically meaningful events.

i. Study procedures and timing of assessments

Enrolled and randomized subjects should be provided with study treatment and directions to start treatment as soon as possible after the appearance of their prodromal symptoms.

Of primary importance for the treatment indication is the frequency of clinical assessments and by whom assessments are made. For the treatment indication, subjects should be assessed by the investigator within 12 to 24 hours of the start of the prodromal symptoms and treatment initiation (self-initiation) and then observed daily thereafter (or as often as possible) by the investigator or a subinvestigator until healing of the primary vesicular lesion or return to normal skin for those subjects without a vesicular lesion. In addition, subjects should be provided with a subject diary in which they should record, at a minimum of twice daily, their symptoms, such as pain, tenderness, tingling, itching, and discomfort and the stage of their herpes lesions (e.g., normal lip, erythema, papule, vesicle, ulcer, crust).

For the prevention indication, subjects should be assessed within 24 to 48 hours of the development of prodromal symptoms or an active lesion. Consideration should be given to the treatment of such subjects. One option is to continue the drug under study and to assess the duration of episode as well as other secondary endpoints. The treatment of subjects who develop a recurrence should be discussed with the DAVP at the time of protocol development.

j. Endpoint adjudication

Generally, the drug development of RHL treatment has been straightforward with a well-defined primary endpoint and it is unlikely that adjudication will be necessary. The same is expected for the prevention indication.

k. Statistical considerations

Sponsors should provide a protocol with a detailed SAP stating the trial hypotheses and the analysis methods before trial initiation.

- **Treatment studies**

  The primary endpoint in RHL treatment studies in adults should be the decrease in DOE. The primary efficacy analysis should be based on the differences in the time to DOE among groups, and appropriate statistical methods for event-time data should be

employed. Both the mean and median DOE should be assessed. Minimizing missing data is paramount, and there should be an explicit plan to handle missing data. A strategy should be included a priori in the SAP to control the overall type I error rate for any secondary endpoints that may form the basis of labeling claims.

The primary efficacy analysis should be performed on the intent-to-treat (ITT) population defined as all randomized subjects who initiated treatment. Safety analyses should be conducted on all randomized subjects. It should be noted that all subjects with RHL should be assessed and not only those subjects who develop vesicular lesions.

- **Prevention studies**

In prevention studies the primary endpoint should be either the number of confirmed recurrences observed in subjects on suppressive therapy over a 12-month period or the time to first recurrence defined as the time from randomization until the onset of an episode of RHL. However, as noted in section III.C.2.b, Prevention indication, it is strongly recommended that the number of recurrences over a 12-month period be provided.

Minimizing missing data is important, and investigators should be diligent in obtaining the final status of subjects either on or off the assigned treatment, either in the study or if terminated from the study. The primary analysis should be performed on the ITT population and all subjects lost to follow-up/missing and drop outs should be considered to have had a recurrence (i.e., a treatment failure). Appropriate sensitivity analyses should be performed to assess the robustness of the results to the strategy for handling missing data.

l. Clinical virology considerations

HSV-1 and HSV-2 have distinct viral proteins and may exhibit differential responses to an investigational drug, which could affect efficacy results in clinical trials if the drug is only effective against one type of HSV and the clinical study population was infected with both types. Therefore, sponsors may want to consider determining the type of HSV infection present at baseline to determine if the investigational drug exhibits antiviral activity against both HSV types. The assay used to genotype the HSV type in enrolled subjects should be included with the clinical trial protocol and the performance characteristics of the assay provided. However, the diagnosis of RHL is clinical; therefore, virologic confirmatory studies are not considered mandatory.

In general, the HSV-1 or HSV-2 present in recurrent lesions is not likely to persist at the site of the lesion in a latent state; therefore, resistance analysis of virus from immunocompetent subjects is considered optional. Sponsors may want to consider performing resistance analysis in a subset of subjects who failed treatment (failure of lesions to heal) to determine if baseline or emergent substitutions that occur in the targeted genome region correlate with resistance.

For resistance analyses, any changes, including mixtures, in the amino acid sequence of the target protein present in on-treatment or follow-up samples, but not in the baseline sample, can be reported as having developed during therapy. In addition, baseline samples should be analyzed to identify HSV genetic polymorphisms that are associated with differential antiviral activity against the investigational drug. The DAVP should be consulted for the most current format for submission of resistance data.

For virologic assessments in clinical trials, the use of FDA-approved assays, when available, and a central laboratory are recommended. Sponsors can collect results from local lab tests, identifying the assay(s) used. If investigational assay(s) are used, performance characteristics with geographically and temporally distinct isolates should be provided.

m. Accelerated approval (subpart H) considerations

The regulations in 21 CFR part 314, subpart H (accelerated approval based on a surrogate endpoint considered reasonably likely to predict clinical benefit in subjects with a serious or life-threatening disease), have not been used for approval of antivirals used to treat RHL, and are unlikely to be appropriate in most instances, because RHL is not considered a serious or life-threatening disease.

n. Risk-benefit considerations

The overall risk-benefit assessment should be considered in the context of disease, which in this case is a nonserious and self-limited condition. RHL in immunocompetent individuals is also not associated with life-threatening complications and several approved antivirals are available for treatment. For the treatment indication, clinically meaningful benefits should outweigh toxicity risks. As discussed previously, demonstrating large efficacy improvements over currently approved drugs is challenging. A favorable safety and tolerability profile is critical for the target population. In addition, other advantages over current standard of care, such as shorter duration dosing, or convenient administration resulting in improved adherence are considerations in the overall assessment.

Likewise for the prevention indication, a favorable drug safety profile is critical because the target population consists of immunocompetent individuals with a relatively benign recurrent condition. For a chronic suppressive drug, safety with cumulative or chronic dosing should be emphasized. Because there are no approved drugs for prevention of RHL, the overall assessment should rely on the level of clinical benefit the drug offers in reducing the frequency of recurrences or the recurrence-free period.

D. Other Considerations

1. Risk Management Considerations

Given the self-limited nature of RHL, risk minimization strategies usually are not considered necessary.

2. Relevant Nonclinical Safety Considerations

In general, it is anticipated that the nonclinical toxicology studies for drugs active against RHL will be similar to studies for other antimicrobial drugs. One question that can be asked is whether animal toxicology data to support chronic administration are needed. Although RHL treatment is usually for 5 to 10 days, the possibility of multiple courses of treatment or long-term prevention should be taken into account in determining the nature and duration of nonclinical safety studies.

For instance, if the indication for a drug is treatment of RHL, long-term carcinogenicity studies in rodents usually are not needed. If, on the other hand, the drug is indicated for the prevention of RHL, carcinogenicity studies in rats and mice as well as 6-month toxicology studies in a rodent and a nonrodent species should be conducted before approval. Longer duration studies may be needed when the duration of life time exposures to drugs used frequently in an intermittent manner in the treatment and prevention of chronic or recurrent conditions generally exceed 6 months. The ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* provides detailed information concerning the conditions under which carcinogenicity studies should be conducted. The sponsor should also refer to the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* when designing its studies.

3. Pharmacokinetic/Pharmacodynamic Considerations

Various administration routes have been considered for RHL drugs: oral, topical, and buccal. For oral administration, plasma drug concentrations are presumed to be correlated with concentrations at the site of action, although prediction of clinical effect cannot be assumed. However, for topical and buccal administration, drug concentrations at the dermal layer of the skin may better correlate with the antiviral activity. Generally, comparing concentrations in a targeted organ to cell culture EC_{50} values or antiviral activity data from animals with similar concentrations in a targeted organ may help select doses for initial clinical trials.

Clinical endpoints can be used as response metrics in the exposure-response evaluations. For prevention trials, the clinical endpoint should be used. Relationships between each of these assessments and the principal efficacy endpoints should be assessed based on all available data.

Any drug exposure-related toxicity should be explored to assess the relationship between drug concentration and the adverse event, to identify the highest tolerable dose, and to determine the probability of an adverse event with a given drug exposure. This information can also guide dose adjustments for specific populations and drug interactions.

4. CMC Considerations

We anticipate that the chemistry, manufacturing, and controls (CMC) data for RHL drugs will be comparable to the CMC data for other drugs with similar uses and administration.

5. Labeling Considerations

There are no specific labeling considerations for the RHL indications.

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