Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment

Guidance for Industry

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

May 2018
Clinical/Medical

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry for establishing clinical effectiveness of drugs for the treatment of acne vulgaris (acne).[2] The recommendations in this guidance are based on the FDA's assessment of issues raised in the review of clinical trials for acne.

This guidance does not address systemic retinoid therapies because they may not have appropriate risk-benefit profiles for non-nodular acne therapy. Sponsors should discuss development programs for systemic retinoids with the review division before trial initiation. This guidance also does not address clinical safety, clinical pharmacokinetics, nonclinical issues, or chemistry, manufacturing, and controls issues.

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 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

Acne is a chronic disease of sebaceous follicles that is multifactorial in etiology. It can wax and wane in severity according to lesion types, numbers, and extent of involvement and can result in

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

[2] For the purposes of this guidance, all references to *drugs* include human drugs and not therapeutic biological products unless otherwise specified.

scarring. Acne occurs more frequently on the face, but can also occur on nonfacial skin (e.g., trunk).

There are two major types of acne lesions:

1. **Noninflammatory:** Noninflammatory lesions are the open (blackheads) or closed (whiteheads) comedones.

2. **Inflammatory:** Inflammatory lesions include papules, pustules, and nodules.

Although most drug products for acne are intended for the broad indication of acne vulgaris, some drug products have been developed that only target one of these two lesion subsets.

Acne is primarily a disease of adolescence and young adulthood, but can persist past the third decade of life.

III. CLINICAL TRIAL DESIGN FEATURES — KEY CONSIDERATIONS

A. Enrollment Criteria

The study population should be defined by the following criteria:

- A minimum number of each type of lesion: inflammatory and noninflammatory.

- A baseline score on an Investigator's Global Assessment (IGA) severity scale that is consistent with the baseline lesion counts.

- An age of enrollment reflective of the onset of acne relative to adrenarche.

B. Study Design and Efficacy Endpoints

In the assessment of efficacy, sponsors should consider the following:

- To demonstrate efficacy, we recommend conducting randomized, double-blind, well-controlled trials that include a placebo arm.

- Although acne occurs on the face and trunk, efficacy assessment should be limited to the face because it is the most frequent site of involvement. However, topical drug products can be applied to all affected areas during clinical trials.

- We recommend that the IGA be a static evaluation of overall acne severity.

  – The IGA should be an ordinal scale with approximately five severity grades (reported only in whole numbers (e.g., 0 to 4)). Each grade should be defined by a distinct and clinically relevant morphologic description to minimize interobserver variability. The

definitions of the severity grades should not include numerical ranges of lesions because the IGA scale is intended to be a qualitative assessment of the subject's condition.

  - The IGA scale should be dichotomized to success or failure, with success defined as clear or almost clear (grade 0 or 1) and at least a two-grade improvement from baseline; this represents a clinically meaningful outcome.

  - There is no single, standardized grading system for severity of acne. We encourage sponsors to discuss their IGA scales and study designs with the FDA before trial implementation.

- Inflammatory and noninflammatory lesions should be counted and reported separately. All lesions on the face should be counted, including those on the nose.

- The assessment of treatment effect should be based on both changes in lesion counts and success on the IGA. Endpoints based on changes in lesion counts and IGA success provide both quantitative and qualitative assessments of acne, and thus provide useful complementary information.

  - A reduction in lesion counts may indicate improvement of acne severity; however, it does not account for the variable expression of acne (e.g., size of lesions, intensity of inflammation, and location of lesions). The IGA considers the quality and quantity of the acne lesions.

  - Although subjects are considered as success or failure based on the IGA with improvement of two grades, this endpoint is not a precise measure of the magnitude of improvement. The changes from baseline in lesion counts provide a quantitative assessment of the improvement.

C. General Analysis Considerations

The statistical analysis should address the following:

- The analysis of lesion counts can be influenced by a few extreme outliers, which may cause difficulty in interpretation of the clinical trial findings. The statistical analysis plan should consider alternative approaches for analysis of lesion counts if extreme outliers are anticipated (such as analyses based on ranks).

- For assessment of the treatment effect on inflammatory and noninflammatory lesion counts, analysis of absolute change and percentage change from baseline are both relevant and complementary. Absolute change in lesion counts can be affected by subjects with large numbers of lesions at baseline, while percent change in lesion counts can be affected by subjects with relatively small numbers of lesions at baseline. The absolute change in lesion counts is expected to have better analysis properties, such as a less skewed distribution. Therefore, we recommend absolute change in lesion counts for

the primary endpoint analysis, and percentage change in lesion counts for the secondary endpoint analysis.