



connetics®
Connecting Science Skin and Lives™

0951 5 DEC 20 A10:56

December 19, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Rm. 1061)
Rockville, MD 20852

Re: Docket No. 2005D- 0340
Draft Guidance for Industry- Acne Vulgaris: Developing Drugs for Treatment

Dockets Management Staff,

Connetics supports the development of innovative agents for the treatment of acne vulgaris, and appreciates the opportunity to comment on the Draft Guidance for Industry – Acne Vulgaris: Developing Drugs for Treatment (made available for comment September 19, 2005, Docket No. 2005D-0340).

Connetics agrees that specific Guidance from the Agency that embraces clinically meaningful and reliable endpoints will help applicants design clinical trials, collect relevant data for analysis, and perform appropriate analyses to convincingly demonstrate safety and efficacy in support of approval of investigational drugs for the treatment of acne vulgaris. Clear and appropriate guidance from the Agency can expedite the development of new agents and minimize the time required to get advances in therapy into the hands of patients who will benefit from them.

In that spirit, Connetics would like to offer the following comments on the draft guidance, and propose revisions for Agency consideration:

1. Baseline lesion counts (Sec. III.A.2): It is stated that “Applicants are encouraged to investigate the optimal range of baseline lesion counts to demonstrate success before initiation of Phase 3 study”. Connetics agrees that clear definition of Phase 3 patient populations as reflected in baseline lesion counts is an important objective. However, it is very important that baseline lesion counts be reliably correlated with acne severity as defined by the Investigator’s Static Global Assessment (ISGA). This would contribute to the consistency of the conclusions drawn by different sponsors from their respective clinical trials with regard to the study drug efficacy. We suggest that FDA recommend

2005 D-0340

C3

specific baseline lesion count ranges (for both inflammatory or noninflammatory lesions) that FDA will accept as being consistent with respective ISGA scores.

2. Targeted Acne Therapy (Sec. III.A.3): It is stated that “For drugs specifically intended to treat either inflammatory or noninflammatory lesions, it is appropriate for both lesion counts and the ISGA to be assessed.” It is not clear how the ISGA as it is described in the guidance, can be applied to one lesion type without consideration of the other, as ISGA grades include by definition both lesion types. A lesion-specific ISGA would have to be developed to accurately and uniquely define acne severity for inflammatory lesions and for noninflammatory lesions, respectively. As “pure” cases of either inflammatory or noninflammatory acne are quite rare, it is not clear how to use a lesion-specific ISGA scale in a patient with both types of lesions on the face. It may be appropriate to set a maximum criteria for either baseline inflammatory or baseline noninflammatory lesion counts such that patients with greater than criteria for either lesion type would not be appropriate to enroll in studies designed to assess the utility of treatments for single lesion types.

3. Fixed combination Drug Products for Acne Vulgaris (Sec. III.A.4): If an applicant desires to utilize a Reference Listed Drug (RLD) safety database only in support of their 505(b)(2) application, and if the applicant plans to establish efficacy in two controlled well-designed Phase 3 studies, then the following conditions should be sufficient to establish a clinical bridge between test product and RLD: the test drug does not exhibit superior efficacy to the RLD; the test drug does exhibit similar or better safety than the RLD; the test drug exhibits similar or lower bioavailability than the RLD; and the test combination drug product exhibits superiority to each of its components alone.

4. Primary Endpoints (Sec.IV. A): The draft guidance appears to recommend that absolute reduction in lesion counts be used as one of the co-primary endpoints. It states: “... clinical perception of a given lesion count reduction, e.g., 50 lesions or less is different for various baseline lesion counts, e.g., 100 vs 53 lesions”. This example reflects why we believe that %reduction in lesion counts from Baseline to end of treatment and/or assessed over time, is more appropriate than absolute change in lesion counts. Use of %reduction of lesion counts as a co-primary endpoint is especially meaningful when a specific range of lesion counts at Baseline defines severity at study start and is a component of the protocol inclusion criteria. Absolute lesion counts can be used as an important secondary endpoint.

5. ISGA: It has been noted that efficacy outcomes associated with ISGA are well correlated with those expressed as %reduction in lesion counts. Additionally, it has been noted that patients who tend to be categorized as success based on ISGA often have lower lesion counts at baseline, while patients who demonstrate substantial %reduction in lesion counts, often have a higher lesion count at baseline. Given the differential sensitivity of these endpoints to baseline status, it does not appear that ISGA and %reduction of lesion counts consistently compliment one another across the range of disease severity commonly studied. As such, linking these two endpoints as required co-

primary outcomes may not provide the measure of internal consistency and hence confirmatory evidence that is generally sought through the use of co-primary endpoints.

We further note that ISGA is a subjective and categorical measure of treatment success. Broad categorical assessment of patient improvement as required by ISGA fails to exploit the full range of drug response that quantitative analysis by %reduction allows; in contrast, %reduction analysis fully utilizes the available data to draw quantitative conclusions. Another advantage of %reduction as a co-primary endpoint is that it is not subject to investigator differences when they are forced to choose between two ISGA grades when in their clinical judgment, the patient's actual response lies somewhere between the ISGA categories. A dichotomous definition of treatment success or failure compounds this lack of precision and reliability as investigators are often forced to evaluate a patient as a "failure" even when they see a dramatic overall improvement in acne severity.

Finally the ISGA scale proposed in the draft guidance does not make a clear distinction between "clear" (grade 0) and "almost clear" grades. This may significantly increase the variability of outcomes across study sites and contribute to erroneously low success rates and hence inappropriate rejection of potentially useful new agents. Given the sensitivity of statistical power to small changes in ISGA success rates (especially for low success rates), sample size calculations based on this endpoint often leads to prohibitively high subject numbers. Even high subject numbers cannot guarantee sufficient power because of the exaggerated impact of small changes in success rate on power and p-value when a dichotomous-only measure is used. Therefore, Connetics proposes that while ISGA may have value as a secondary endpoint, it should not be required as a co-primary endpoint.

Connetics appreciates this opportunity to comment on the Draft Guidance and hopes our input will contribute to the formulation of a final Guidance that is both clinically meaningful and experimentally robust.

Sincerely yours,



Alex Yaroshinsky, Ph.D.
Connetics
Vice President, Clinical Operations and Biostatistics



Michael S. Eison, Ph.D.
Connetics
Vice President, Regulatory Affairs