

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

The sponsor agreed to test isolates of *P. acnes* obtained from a subset of acne patients who fail therapy by clinical criteria. The isolates would be tested against clindamycin and if possible against benzoyl peroxide. The sponsor raised the issue that benzoyl peroxide is not soluble in water and therefore it may not be possible to test it against the isolates. The sponsor agreed to investigate this further and to let the Agency know if it is or is not possible to test benzoyl peroxide against the isolates. The sponsor will submit their proposal for determining what acne patients will be cultured, how specimens will be obtained, and what method will be used to determine the isolates susceptibility to clindamycin and if possible, benzoyl peroxide, to the Agency for review. The Agency agreed that the sponsor's proposal was a satisfactory way to proceed.

2. Please provide information on the in vitro activity of clindamycin and benzoyl peroxide against *P. acnes*. If data is available on the concentration of the combination of clindamycin and benzoyl peroxide required to inhibit the growth of *P. acnes* that information should be submitted to the Agency. This information can be from recent laboratory studies (within the last 3 years) or from the recent literature (within the last 3 years).
3. The sponsor needs to be aware that because there will be no microbiology data being gathered during the Phase 3 clinical study the "Microbiology" section of the package insert will be limited in what is said about Clindaben from a microbiology perspective.

Clinical Pharmacology/Biopharmaceutics:

Sponsor's question 3 of February 4, 2005, Briefing Package: "A Phase 2 systemic absorption study is proposed to be conducted and submitted in the NDA. Does the Agency agree with the overall design of the protocol provided in Appendix 2?"

Agency:

No we do not agree. Please see comments below:

1. Frequency of dosing:

Please clarify the proposed once a day application for this study, particularly in light of the proposed Phase 3 Protocol 7002-E1HP-01-05 which has a twice a day frequency of dosing.

2. Duration of dosing:

Please provide a rationale for the proposed 14-day duration of dosing.

3. Use of the highest proposed strength:

Please provide a rationale for the application of the proposed 4 gram weighed dose of Clindaben (1/2.5) gel face, neck, back and chest. Comments are also needed to explain the protocols claim that this daily dose represents a four-fold increase over the anticipated typical upper clinical dose.

b(4)

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4. PK Sampling and Analytical methods:

Please clarify why the absorption by the skin of benzoyl peroxide is not being measured.

The sponsor acknowledged the above comments.

The sponsor stated that they do not intend to measure benzoyl peroxide in plasma because it is challenging in terms of assay development so they would like a waiver of this requirement. The Agency asked the sponsor to put together their rationale and request for a waiver in writing, which we would look at and provide them with the appropriate response.

The sponsor was also asked to remove the ceiling of $\frac{1}{2}$ as the maximum daily dose because clinically the patient may use more than $\frac{1}{2}$.

b(4)

Clinical

Sponsor's question 4 of February 4, 2005, Briefing Package: "Based on recent prior experience with large scale combination product acne trials, questions can be raised regarding the sensitivity of the static global acne scale to changes in non-inflammatory lesions and to its bearing on clinically meaningful improvement. The sponsor understands the Agency's rationale and agrees with the utilization of the static global acne scale as the primary endpoint when comparing the combination product to the vehicle. However, the sponsor proposes that the static global acne scale is a secondary endpoint when comparing the combination product to the monads due to the limited sensitivity and correlation to clinically meaningful outcomes. Does the Agency concur?"

Agency:

1. The Agency does not concur. The static global scale provides a clinically and regulatory useful evaluation of the subject as a whole with regard to severity of acne. The Agency continues to recommend that this be used as a co-primary endpoint along with the lesion counts for any evaluation of this acne product including for a superiority comparison of the dyad combination product to the monads. Achieving success in this manner is a clinically meaningful outcome.
2. The basis for the sponsor's assertion does not appear to be well-grounded. The sponsor is invited to provide evidence to support this assertion, to enable further discussion in this regard.

Sponsor's question 5 of February 4, 2005, Briefing Package: "The sponsor believes that, when comparing a combination acne product to its monads, the insensitivity of the static global acne scale results in unreasonable sample size requirements.

The sponsor would like to propose an approach to address this with a meta-analysis or integrated summary of efficacy method by combining the static global acne scale efficacy data from both Phase 3 studies and then apply inferential statistics to compare the combination product to the monads. Please comment on this approach."

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Agency:

The static global assessment provides useful information on the acne subject for the investigator and the Agency and should be retained. As information regarding this endpoint from two studies is needed for a single-ingredient product for approval, this is also needed for the dyad vs. each of the monad comparators. Dosing and power calculations should be based on Phase 2 studies. Please also see Biostatistics comments below.

The sponsor stated that the global has only 50% of the power as compared to lesion counts and needs more patients to allow for success.

Sponsor's question 6 of February 4, 2005, Briefing Package: "The sponsor would like to consider pursuing an indication for both 'acne' and '_____ ', depending on the outcome of the Phase 3 clinical studies. If the combination drug product beats both monads and vehicle in two out of three lesion counts, then an 'acne' claim would be possible. If the combination drug product beats both monads and vehicle in the inflammatory lesion count, then an ' _____ ' claim would be possible. Please comment on this approach."

b(4)

Agency:

1. Either an indication for 'acne' or ' _____ ' may be sought so long as the indication being sought is pre-specified and depending on the outcome of the clinical trials. Multiple analysis plans may result in an adjustment to preserve alpha (see Biostatistics comments below). The investigator's static global evaluation should be a part of the primary efficacy variable.
2. The sponsor is taking a risk as Phase 2 studies were not done with the proposed formulation. The sponsor is welcome to propose for discussion with the Agency an alternative statistical plan that would involve a nesting approach to evaluate "acne" and " _____ ". Please note the indication for ' _____ ' alone will likely be worded differently from that currently in the Duac label.

b(4)

Additional Agency Comments

1. For a 505(b)(2) application, the sponsor should conduct comparisons to the reference listed product(s) to provide clinical information on comparative bioavailability (i.e., 21 CFR 320.24(b)(4)). See guidance meeting minutes from November 12, 2003. With regard to a 505(b)(2), the sponsor should specify the informational pieces that are sought from the reference listed drug product with regard to the Agency's findings of safety and efficacy for that listed drug product.
2. Further, this is a fixed combination product as per 21 CFR 300.50. The sponsor should adequately demonstrate that the combination dyad product is superior to each of the monads in product vehicle and the vehicle alone for each of the primary endpoints. This could be accomplished via two adequate and well-controlled clinical studies that incorporate each of the needed arms.

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3. The Agency also commented on 2 point improvement on a 5 point acne global (0 to 4) as a potential evaluation of success. It was discussed that 2 point improvement could be taken as a measure of global success if the studies prespecified this endpoint as a win. Subjects who start the study as "severe" or 4 would need to improve to "mild" or 2. Subjects who start the study as "mild" would need to improve to "clear" or 0. Labeling in the Clinical Studies section would reflect the prespecified endpoints. If subjects who enter as "severe" do not "clear" or "almost clear" (0 or 1) then the Indications and Usage section would indicate that the drug product would not be indicated for severe acne.
4. With regard to resistance concerns, the Sponsor should demonstrate whether lack of efficacy can be correlated with drug resistance.
5. The sponsor should conduct dermal safety studies using the final to-be-marketed drug products. Generally, the required topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (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 is usually conducted in parallel with phase 3 studies. However, if Phase 1/2 studies should reveal an irritancy signal, and the product is to be labeled as an irritant, cumulative irritancy testing may not be needed. Phototoxicity and photoallergenicity studies may be waived by the Agency if there is no absorption in the 290 to 700 nm range.
6. The sponsor should address ICH E1A regarding long term safety assessment of their drug product for the chronic indication of acne vulgaris. The sponsor queried whether with a 505(b)(2) application, where the Agency used the findings of safety and efficacy for a reference listed product, the need for long term safety could be waived. The Agency replied that if the excipients and the active ingredients do not indicate potential serious concern regarding long-term safety, then potentially, the sponsor could put together an argument as to why such a study could be conducted as a Phase 4 study rather than as required pre-approval.
7. The sponsor should study an acne population that is relevant to that seen in the United States. The demographics with regard to race and gender of studies conducted should adequately address this need.

Biostatistics:

Sponsor's question 4 of February 4, 2005, Briefing Package: "Based on recent prior experience with large scale combination product acne trials, questions can be raised regarding the sensitivity of the static global acne scale to changes in non-inflammatory lesions and to its bearing on clinically meaningful improvement. The Sponsor understands the Agency's rationale and agrees with the utilization of the static global acne scale as the primary endpoint when comparing the combination product to the vehicle. However, the Sponsor proposes that the static global acne scale is a secondary endpoint when comparing the combination product to the monads due to the limited sensitivity and correlation to clinically meaningful outcomes. Does the Agency concur?"

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Agency:

The Agency disagrees with the sponsor proposal to use the static global acne scale as a secondary endpoint when comparing the combination product to the monads. The global acne scale takes into account both inflammatory and non-inflammatory lesions, yet it places more weights on inflammatory lesions compared to non-inflammatory lesions. Estimates of lesion counts (inflammatory or non-inflammatory) tend to be inaccurate especially when lesions counts are large.

Sponsor's question 5 of February 4, 2005, Briefing Package: "The sponsor believes that, when comparing a combination acne product to its monads, the insensitivity of the static global acne scale results in unreasonable sample size requirements. The sponsor would like to propose an approach to address this with a meta-analysis or integrated summary of efficacy method by combining the static global acne scale efficacy data from both Phase 3 studies and then apply inferential statistics to compare the combination product to the monads. Please comment on this approach."

Agency:

For replication of study findings efficacy results for each of the co-primary endpoints should be established for each study independently. A possible approach for reducing the sample size is to use unequal treatment allocation for the different treatment arms based on the sponsor's experience with the efficacy for the various treatment arms. Other approaches for reducing the sample size include seeking a specific acne type indication or disease severity based on efficacy results from sponsor's previous studies.

Sponsor's question 6 of February 4, 2005, Briefing Package: "The sponsor would like to consider pursuing an indication for both 'acne' and '_____', depending on the outcome of the Phase 3 clinical studies. If the combination drug product beats both monads and vehicle in two out of three lesion counts, then an 'acne' claim would be possible. If the combination drug product beats both monads and vehicle in the inflammatory lesion count, then an '_____' claim would be possible. Please comment on this approach." b(4)

Agency:

Efficacy results from the sponsor's previous trials might be utilized in forming the statistical hypotheses to be tested so that the sponsor achieve their objective above and Type I error rate remains controlled. However, for the validity of this approach a pre-specification of the statistical hypotheses to be tested is required.

Additional Biostatistics comments:

1. The protocol indicated that "a sensitivity analysis will be conducted to investigate the impact of data imputation on the dichotomized global severity", however, no method is specified. The protocol should pre-specify the planned method to be used in the sensitivity analysis, as selection of the method after the data collected does not ensure efficacy results are not driven by the method of data imputation.

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2. The protocol stated that "an overall treatment test (using the data from all treatment groups under consideration) will be presented, and then to carry pairwise comparison only when the overall test is significant." The goal of this overall comparison is not clear. Furthermore, the proposed approach might not control Type I error rate.
3. The protocol indicated that pooling will be carried out to achieve a minimum of 8 subjects in each active treatment arm. The Agency recommends the study be planned to have minimum of 5 subjects in the vehicle arm (i.e., 10 subjects per active arm) to avoid problems in the analysis of cell with 0 frequency. The protocol might pre-specify an approach for pooling small centers if actual enrollment did not meet the above criteria for some centers.

The sponsor is referred also to the Agency comments made at the Guidance meeting conducted November 12, 2003.

Project Management:

1. Comments shared with you today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or informational requests.
2. For applications submitted after February 2, 1999, you are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
4. You are encouraged to request and attend an End of Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

The meeting ended amicably.

Minutes preparer: Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Project Manager

Concurrence Chair (or designated signatory): Jonathan K. Wilkin, M.D., Division Director

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

/s/

Jonathan Wilkin
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