

rodent and nonrodent species to provide adequate data to address the teratogenic potential of benzyl alcohol (please refer to the ICH S5A document). It is recommended that the final study reports for both the rodent and non-rodent embryofetal developmental studies be included with an NDA submission.

*Discussion during the meeting:*

*The Sponsor stated that the final study reports for the rodent and nonrodent embryofetal developmental studies would be included with the NDA submission. The Sponsor asked if it would be possible to conduct the embryofetal developmental studies as topical studies. The Division informed the Sponsor that it might be possible to conduct the embryofetal developmental studies as topical studies if an adequate level of systemic exposure could be obtained in these studies or if maternal toxicity was exhibited in the high dose group. An independent representative for the Sponsor commented that benzyl alcohol metabolism in the skin might generate a unique metabolite which would argue for use of a topical embryofetal developmental study design. The Division stated that it might be possible to conduct one of the embryofetal developmental studies as a systemic study and one as a topical study. The Division recommended that the Sponsor submit their proposal for conduct of the embryofetal developmental studies, along with supporting data, to the IND for evaluation.*

**Sponsor's Question 3:**

Since L.A. is used for 10 minutes once per week for two weeks total, it is the intention of the Sponsor to use the 14-day toxicology studies to support the safety of the acute treatment with the product. Does the FDA agree?

**Agency's Response:**

Yes. Adequate nonclinical toxicology studies have been conducted with the lice asphyxiator drug product and benzyl alcohol to support the safety of the proposed Phase 3 clinical study contained in the briefing package.

**Clinical Pharmacology and Biopharmaceutics:**

There were no Clinical Pharmacology/Biopharmaceutics questions identified in the briefing document. The Clinical Pharmacology and Biopharmaceutics Comment is as follows:

Under 21CFR 320.21, you need to include either (1) evidence demonstrating the *in vivo* bioavailability of the drug product (see details below) or (2) provide information to permit the FDA to waive the submission of evidence demonstrating *in vivo* bioavailability.

(Details) You should conduct an *in vivo* bioavailability study in about 12 patients to monitor exposure of the active ingredient under the maximal usage conditions in patients using the highest strength of the final 'to-be-marketed' formulation (i.e., maximal dosing and frequency as well as maximal surface area that is consistent with the proposed package insert).

Discussion during the meeting:

*The Sponsor mentioned at the meeting that they will submit toxicokinetics (TK) data in animals who received benzyl alcohol in a clinical formulation up to 15% concentrations. They mentioned that no systemic benzyl alcohol levels were observed in 2 animal species. Therefore, they will be requesting a waiver of human bioavailability study. They will be submitting animal TK data to the Agency for review. Based on the Agency's review of this information, the Agency will determine whether the information submitted is adequate towards obtaining a waiver or the Sponsor would need to demonstrate the in vivo bioavailability of the drug in humans.*

**Clinical:**

1. Comments on Regulatory Status:

The regulatory pathway for the Sponsor's product will be a 505 (b) (1) application. Two pivotal trials will be needed to establish efficacy. Each pivotal trial should be independent of the other and should include multiple geographically-diverse centers that can achieve enrollment reflective of the population which will use the drug in the US (taking into account age, race, gender and disease prevalence).

2. Comments on the sponsor's drug and indication:

The Sponsor has identified benzyl alcohol as the active ingredient. Identification of the active ingredient(s) is essential for correct formulation of the vehicle. The vehicle success rate in the phase 2 study was reported to be 52.6%, but this appears to represent the success rate following either a single treatment with vehicle or a single treatment with vehicle followed by treatment with 5% LA. Success rate for vehicle alone was not found in the Sponsor's packet. Additionally, on page 12 of the briefing packet, the Sponsor states that the study drug, "stuns the spherical [sic] open and allows penetration of the study drug product which ultimately destroys the honeycomb structure and results in asphyxiation;" this raises the question of the contribution of the (b) (4) to the product's efficacy. Would 5% benzyl alcohol (b) (4) kill lice? Fixed combination prescription drug products require demonstration of the contribution made by each component to efficacy; see 21 CFR 300.50. Should the Sponsor determine that benzyl alcohol is the sole active ingredient, no claims may be made about any excipients.

*Discussion during the meeting:*

*The Sponsor stated that benzyl alcohol is the active ingredient and mineral oil is an excipient.*

The Sponsor seeks an indication for treatment of head lice. The proposed primary efficacy endpoint, treatment success, defined as the absence of live lice at 14 days after final treatment, is supportive of the proposed indication but may be insufficient. Please explain how the presence of new or viable nits will be assessed for at the primary time point (or later).

3. Comments on demonstration of adequate safety information to proceed with human trials:

In Phase 2, 125 subjects were enrolled and 85 were exposed to active. There were no serious adverse events. However, the AE tables (appendix 16) were omitted from both the study report SU-02-2003 and amended study report SU-02-2003A submitted in the briefing packet. The inclusion of this

information would have been helpful. No active assessment of safety variables was performed, such as clinical assessment for cutaneous or ocular irritation, and no laboratory evaluations were obtained.

4. Comments on dose ranging:

The Sponsor conducted a Phase 2 dose-ranging study. Eighty one subjects were enrolled into four arms: 5% LA (N=20), 10% LA (N=21), vehicle (N=20), and RID shampoo (N=21); treatment duration was 10 minutes. A second phase enrolled forty-three subjects: 5% LA for 10 minutes (N=21), and 5% LA for 30 minutes (N=23). Comparable efficacy was seen with the 5% LA and 10% LA formulations, as well as with application times of 10 and 30 minutes; the Sponsor selected the 5% dose and 10 minute application for their Phase 3 trial. Ideally the Sponsor will explore a range of doses that will include concentrations and durations at which lesser efficacy is observed.

5. Comments on topical safety studies:

Topical safety studies will be needed at the time of NDA submission. 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 are usually conducted in parallel with phase 3 studies. However, if phase 1/2 studies reveal an 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 Sponsor's product absorbs in the UVA, UVB, or visible light spectra, then phototoxicity and photoallergenicity studies may be waived (copies of the absorption spectra should be submitted to the IND).

6. Comments on protocols submitted:

Protocol number: SU-01-2004

Comments on overall study design:

- A single protocol is submitted; two trials will be needed to establish efficacy.
- The study seeks to be evaluator-masked; subjects will not be blinded. There do not appear to be sufficient measures in place to protect the evaluator blind. Study personnel with knowledge of treatment assignment who will dispense CTM, instruct subjects on study drug use, and answer subject questions related to study drug use have not been identified. Subjects are not given specific instructions not to discuss their treatment with the evaluator. Please address odor.
- There are two study arms: RID used as labeled, and Summers 5% LA applied for 10 minutes.
- If the Sponsor chooses RID as the active comparator, establishment of efficacy will necessitate demonstration of superiority of the Sponsor's product versus RID in two clinical trials.

Comments on Inclusion/Exclusion criteria:

- In general, Phase 3 studies should include patients that will be similar to those who will use the product once it is approved and marketed (i.e., all-comers).
- While it may be reasonable to exclude patients less than two years of age in early studies, these patients may be infested with lice and should not be excluded from Phase 3 trials.
- The Sponsor has not identified how viability of eggs is to be determined (see inclusion criterion #2 for protocol SU-01-2004).
- If there is a valid risk with use of this product in pregnant or lactating women necessitating their exclusion, the Sponsor may wish to complete their non-clinical studies prior to the initiation of Phase 3. Additionally, if there is a valid risk with use of this product in pregnant or

lactating women necessitating their exclusion, then subjects whose caretaker (who will apply study drug) is pregnant or lactating should also be excluded. The Sponsor can ensure that risk information is communicated to subjects and caretakers by obtaining informed consent.

#### Comments on Endpoints

- The primary efficacy variable is the presence of live lice. The primary efficacy endpoint is treatment success, defined as the absence of live lice. The primary time point for efficacy evaluation is visit 4 (day 22), 14 days after the second treatment. The Sponsor is asked to address how subjects will be assessed for the presence of viable nits (see p 86 of Sponsor's briefing packet, protocol SU 01-2004, p.9, section 11.3 subpoint 1: "viable or non-viable nits"), or how the likelihood of false negatives can be reduced.
- It is not clear whether the primary efficacy variable, the presence of live lice, is to be assessed by examination of the scalp before shampooing with (b) (4), after shampooing with (b) (4), or both. The Sponsor is requested to clarify the rationale for shampooing by study personnel at visits 2 (day 8), 3 (day 15) and 4 (day 22). Study procedures in phase 3 trials should conform as closely as possible to expected real-world use, and may affect labeling.
- The secondary efficacy variables include numbers of live lice, dead lice, live nymphs, and dead nymphs. It is not clear whether these variables will be assessed before or after shampooing, or will include counts from rinse water (visit 2).
- The Sponsor is asked to clarify the rationale behind the collection of rinse water at visit 2.

#### Comments on Safety:

Safety monitoring is limited to assessment of adverse events.

The Sponsor is requested to actively assess for local safety by evaluating cutaneous and ocular irritation within 24 hours of treatment, such as at days 2 and 9, one day after the first and second treatments. Safety evaluation for the phase 3 trials should include laboratory assessments (e.g. CBC, chemistries).

#### **Biostatistics:**

The sponsor indicated that they plan to conduct two Phase 3 trials against RID. The following are comments concerning the sponsor's proposed Phase 3 trial (#SU-01-2004). The sponsor is encouraged to submit revised Phase 3 study protocols with detailed statistical analysis plan for the Division's comments.

1. Per the Division's recommendation, the study objective should be the superiority of Lice Asphyxiator to RID. Consequently, the study size needs to be re-calculated. The calculations should address the issue that two patients could be enrolled in the study from the same household.
2. Both the intent-to-treat (ITT) and per-protocol (PP) analyses should be submitted for establishing efficacy claims of the study drug. For superiority trials, hypothesis testing at two-sided significance level of 0.05 is recommended and the ITT analysis should be the primary. The Division recommends that the ITT population be defined as all randomized patients who are dispensed drug medication, regardless of having any post-baseline outcomes.

The proposed missing data handling based on the last observation carried forward (LOCF) is acceptable. A sensitivity analysis based on different imputation methods should be conducted to evaluate the robustness of the efficacy results.

3. Comments on the sponsor's proposed statistical methods:
  - a. The sponsor indicated that no more than 2 subjects would be enrolled to the study from the same household, and consequently, data from the two subjects (from the same household) are expected to be correlated. Analysis methods accounting for such a correlation should be proposed. The sponsor is reminded to pre-specify the patients from the same household if they are included in the study.
  - b. The draft protocol listed several methods for the analysis of the primary efficacy endpoint. The primary method should be pre-specified. As the study is multi-center, the treatment-by-site interaction effect should be evaluated. In the case there is a significant interaction effect, a sensitivity analysis should be conducted to ensure that efficacy results are not driven by extreme study sites. Such a sensitivity analysis should be pre-specified in the protocol.
  - c. For analyses based on the logistic regression and analysis of covariance, the number of baseline covariates to be included in the models should be few and limited to those that have strong influence on the response variable. These covariates need to be pre-specified in the protocol and statistical analyses should include all these covariates.
4. The sponsor proposed two secondary efficacy endpoints at three time points which constitute a total of 6 endpoints. Secondary efficacy endpoints intended for labeling should be clinically relevant and in agreement with the Division. For efficacy claims over multiple time points, an adjustment for multiplicity might be needed.
5. The sponsor indicated that the randomization is household basis and based on balanced block randomization stratified by study site. Details on how to apply block randomization to patients from the same household should be provided. The sponsor is reminded that the randomization codes that show treatment assignment should be prepared and documented prior to initiation of each study. The time/date of enrollment for each subject should be included in patient demographic database.
6. Subgroup efficacy results by age, gender, race, and baseline characteristics should be planned for each study.

### **Administrative Comments**

1. For applications submitted after February 2, 1999, the applicant is 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).
2. The Sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires 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."

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