

MEMORANDUM OF MEETING MINUTES



Meeting Date: August 8, 2005 **Time:** 10:30 P.M.
Location: N225 **Meeting ID:** 15679
Topic: IND 50,076, for the treatment of head lice
Subject: Guidance meeting
Sponsor: Summers Laboratories, Inc.
Meeting Chair: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Meeting Recorder: Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
Patricia Brown, M.D./Clinical Reviewer, DDDDP, HFD-540
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDDP, HFD-540
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
Kathleen Fritsch, Ph.D./Biostatistician, DBIII, HFD-725
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

Sponsor Attendees:

Summers Laboratories

Mike Precopio/President
Maureen Vicaria/Global Health
Terri Meinking/President, Global Health

(b) (4)

Glen Park, Pharm.D./Regulatory Affairs, Target Health, Inc.
Jules Mitchel, Ph.D./Regulatory Affairs, Target Health, Inc.

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted July 8, 2005) provides background and questions (pp 2-4) for discussion. The sponsor requests input from the Agency on the submitted protocol.

Pharmacology/Toxicology:

It is recommended that the draft study reports for the subcutaneous rat and rabbit embryofetal development studies conducted with benzyl alcohol be submitted to the IND for evaluation prior to initiation of the proposed Phase 3 clinical study.

Clinical:

Sponsor's Question 1:

Does the Agency agree that two placebo controlled trials are appropriate to establish safety and efficacy of L.A. 5%?

Agency's Response:

Products for the treatment of head lice should demonstrate superiority over established products such as Rid or Nix. Significant resistance exists to these products, limiting their efficacy. In a study of a south Florida louse population, where permethrin resistant head lice have been reported, Meinking et.al. (Arch. Dermatol. 2002;138: pp220-224) found that after 3 hours of exposure Rid had produced 34% dead appearing lice and Nix (diluted 9 parts Nix to 1 part water) had produced 46% dead appearing lice. Use of a comparator arm is ethically preferable to use of a vehicle arm because subjects in a comparator arm would receive treatment with an approved product, albeit of low efficacy, whereas subjects in a vehicle arm would not receive effective treatment.

The sponsor stated that their proposed trials would offer rescue therapy within a day of determination of failure of either placebo or Lice Asphyxiator (L.A.). The sponsor also stated that L.A. is not a neurotoxic agent which makes it an alternative treatment to existing pesticidal pediculocides and would therefore have intrinsic value to the medical community.

The Agency then stated that three options exist for establishing efficacy provided that the ethical concerns related to vehicle controlled studies are addressed:

- A. One three arm study with two success criteria; L.A. demonstrates superiority to vehicle as well as non- inferiority to either RID or NIX. The latter comparison is with the product as it is currently labeled. If this option is elected, the data need to be convincing. The sponsor is referred to the FDA Guidance for Industry, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."
- B. Two separate trials; L.A. demonstrates superiority to RID or NIX in both trials.
- C. Two separate trials; L.A. demonstrates superiority to vehicle in both trials.

Sponsor's Question 2:

Does the Agency agree to have registered nurses provide the initial screen for irritation?

Agency's Response:

While it is acceptable to have registered nurses participate in some aspects of the trial it is necessary to have licensed prescribers determine the need for study drug administration and conduct safety evaluations.

The sponsor pointed out that the test products will be self administered and that the study has been designed to allow registered nurses to visit the study subjects at home for evaluations of both efficacy and safety. Furthermore, if adverse events are reported or observed, followup with the licensed prescriber will take place.

The Agency agreed that conditions of the study should replicate a real use situation with patients administering their own medicine. However, a licensed prescriber should verify the diagnosis of lice and make safety evaluations. The sponsor is requested to provide the rationale for the interval following study drug administration at which safety assessment will be performed.

Sponsor's Question 3:

Summers believes that 240 subjects exposed to 5% L.A. in the Phase 3 trials is sufficient for the safety evaluation. Does the Agency agree?

Agency's Response:

We agree with randomization by household. Other clinically **infested** members of the household, who meet enrollment criteria, may receive the same treatment as the index patient but should only be included in safety evaluations. To ensure adequate screening for adverse events, the Agency recommends enrollment of at least 80 safety evaluable patients in the 6 month to 3 year age range and 100 safety evaluable patients in the 3 to 11 year age range. Please also see comments of biostat reviewer.

The sponsor agreed to study a total of 80 safety-evaluable patients between 6 months to 3 years, and 100 safety-evaluable patients, 3 to 11 years of age. The Agency pointed out that a different safety profile may be seen in infested patients who are symptomatic versus those infested patients who are not symptomatic. The Agency would prefer that the safety database include infested symptomatic patients.

Sponsor's Question 4:

Does the Agency agree clinical laboratory testing is not required for this product application?

Agency's Response:

Human pharmacokinetic data will be necessary under maximal use conditions, unless a waiver is requested and granted.

In response to sponsor's question the Agency stated that a waiver would be required before submission of an NDA and preferably before initiation of Phase 3 studies.

The sponsor also stated that a position paper will be written based on toxicokinetic studies to request a waiver for human pharmacokinetic data.

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 providing enrollment reflective of the population that will use the drug in the US (taking into account age, race, gender, disease prevalence, and resistance problems).

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

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 acceptable.

3. 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 early phase 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 (290-700 nm range), then phototoxicity and photoallergenicity studies may be waived (copies of the absorption spectra should be submitted to the IND).

The sponsor concurs with FDA comments on Topical Safety Studies.

4. Comments on protocols submitted:

Protocol number: SU-01-2005

Comments on overall study design:

- The sponsor proposes a multi-center, randomized, vehicle controlled, double blind clinical trial to evaluate the efficacy and safety of Lice Asphyxiator (L.A.) 5%. Subjects will be randomly assigned by household to one of two treatment groups. One member of the household, the youngest subject eligible to be treated, will be designated as the Primary Treatment Cohort and will be evaluated for efficacy and safety. All other members of each subject's household who have an active infestation of head lice will be eligible to receive the same treatment and will be designated the Secondary Treatment Cohort. The secondary cohort will be evaluated only for safety. Five geographically diverse study centers are projected.
- There are two study arms: Summers 5% L.A. applied for 10 minutes and Summers 5% vehicle without the active ingredient applied for 10 minutes.

- Establishment of efficacy will require demonstration of superiority versus an approved product such as RID or NIX in two clinical trials.

Please see also discussion to Sponsor's Question 1.

The sponsor stated that the index case for each family unit in the pivotal trials will be changed to the initial patient identified as having a lice infestation.

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).
- Please provide the scientific rationale for limiting enrollment to subjects 80 year of age and younger.
- The inclusion criterion, "Have an active infestation with *Pediculosis capitis*, the human head louse, with presence of nits and at least three live lice at baseline," reflects an appropriate population for treatment.

For inclusion criteria, the sponsor agrees to include "all comers" and will not exclude subjects over the age of 80.

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 6 (day 22), 14 days after the second treatment.
- No secondary efficacy variables are stated.

The sponsor stated that secondary efficacy endpoints will be the number of live and dead lice at Visits 3 and 4.

Comments on Safety:

- Safety will be assessed through the monitoring of adverse events. All subjects who receive at least one dose of study treatment will be included in the safety analysis.
- Subjects will be monitored for skin and eye irritation on Visits 2 (Day 2) and 4 (Day 9), one day after the first and second treatments.

General Comments:

- Please submit Principal Investigator and Institutional Review Board information prior to initiation of the proposed clinical studies.
- The sponsor is requested to complete their non-clinical reproductive toxicology studies prior to the initiation of Phase 3, so that the Phase 3 trials may be conducted in such a way as to be consistent with the anticipated labeling for pregnant and lactating women.

The sponsor stated that PI and IRB information will be submitted prior to the start of the Phase 3 study.

The sponsor also stated that nonclinical reproductive toxicology studies will be completed and the draft report will be sent to FDA prior to starting Phase 3.

Biostatistics:

The sponsor's current submission calls for 2 Phase 3 superiority trials over vehicle, each of size 120 subjects randomized in 1:1 ratio to active and vehicle. The following are biostatistics comments on the sponsor's protocol:

1. There may be more than one study design pathway that could be used to establish the efficacy of the lice asphyxiator. If the sponsor provides evidence that vehicle controlled studies could be ethically conducted, then it might be possible to demonstrate efficacy via (1) two vehicle-controlled trials, or (2) one three arm study demonstrating the superiority of lice asphyxiator to its vehicle and the non-inferiority of lice asphyxiator to RID or NIX. If it is not ethical to include a vehicle arm, then two studies demonstrating the superiority to RID or NIX would be needed, as it would not be possible to assess non-inferiority without a concurrent control to assess assay sensitivity. If the sponsor intends to establish efficacy based on a single three-arm study, the sponsor should note that to provide convincing evidence of efficacy, the study should have results which are internally consistent across subgroups and have a convincing p-value.
2. Although in the current study proposals, only 60 subjects are planned to be treated with the active in each trial the protocol counts for every subject treated and evaluated for efficacy another member of the household to be treated with the active and evaluated for safety (i.e., total of 120 subjects in each trial). It is not clear whether this assumption is realistic or whether the subjects not included in the efficacy evaluation will necessarily have the same pattern of AEs and exposure as the youngest family member infested. The adequacy of the safety information from the non-index cases will depend on the actual numbers enrolled, the age of the patients, baseline symptoms, etc. (see clinical comments).
3. Although randomization is stratified by study site, the primary efficacy analysis does not consider stratification. In general, analysis should take into account stratification factors when they are used for randomization. Regardless of whether the analysis used stratification or not, the protocol should plan subgroup analysis by center along with testing for center by treatment interaction. The Division generally uses a p-value of 0.10 for assessing treatment by center interaction. For significant center by treatment interaction, the protocol should plan a sensitivity analysis to ensure efficacy results are not driven by an extreme center. In addition, to reduce problems with the analysis and interpretation of findings from small centers, the division recommends that studies be planned to enroll at least 8 subjects per treatment arm per center and to have plan for pooling small centers if actual enrollment did not meet this criteria.
4. The protocol stated (page 13) that in order to guarantee balance within each study site, randomization will be performed using a variable block size scheme. It is not clear how treatment allocation and blinding would be ensured with the variable block design as no details

have been given about randomization. The Division prefers a fixed block design as it is easier with this design to generate treatment allocation prior to study enrollment and ensuring treatment blinding.

5. Under additional analysis, the protocol calls for the analysis of covariance with adjustment for several factors with the sponsor's objective 'to add precision to treatment effect estimates'. Per previous division's comments the number of covariates should be very limited, in particular for this relatively small study. It should be noted that the sponsor might carry out any additional analyses as long as it is understood that no efficacy claim can be made about findings from these analyses.
6. The ITT population should be defined as all patients randomized and dispensed drug medication, regardless of whether they had at least one outcome measurement or not. Subjects with no post-baseline follow-up could be managed as treatment failures. For superiority comparisons, the ITT population should be the primary analysis population. For non-inferiority comparisons, the Division considers both the ITT and per protocol analyses as primary.
7. It may be reasonable to classify all subjects with missing data at the 14-day post-treatment visit as failures. In addition to the primary approach for handling missing data the protocol should plan a sensitivity analysis using a different imputation method to ensure efficacy results are not influenced by the method of handling missing data.
8. The sponsor has not proposed any secondary endpoints in the current version of the protocols. The sponsor noted at the meeting that they are considered adding some secondary endpoints. The Division noted that secondary endpoints should be clinically relevant and limited number. If more than a small number of secondary endpoints are proposed, than an adjustment for multiplicity may be necessary.

The sponsor is encouraged to submit revised Phase 3 protocols which incorporate the Division comments for the Division concurrence on study design and analysis.

Administrative Comments

1. 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."
2. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
3. The Sponsor is encouraged to submit its revised protocol for the treatment of head lice as a Special Protocol through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
4. The Sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.

IND 50,076 8/8/05 meeting

Minutes Preparer: _____
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540

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/s/

Jonathan Wilkin
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