



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 8, 2005

To: Jules Mitchell, Ph.D.	From: Melinda Harris-Bauerlien, M.S. Project Manager
Company: Target Health for Summers Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (212) 681-2105	Fax number: (301) 827-2091 or 2075
Phone number: (212) 681-2100	Phone number: (301) 827-2020
Subject: IND 50,076 meeting clarification	

Total no. of pages including cover: 2

Comments: As stated on page 3 of the meeting minutes of August 30, 2005, (Agency's response to Sponsor's Question 1) two separate trials in which the sponsor's drug product demonstrates superiority to vehicle in both trials would be an acceptable approach provided that ethical concerns related to vehicle controlled studies are addressed (e.g., by early rescue of treatment failures).

Document to be mailed: • YES NO

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/s/

Melinda Harris-Bauerlien
9/8/2005 09:45:07 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 50,076

Summers Laboratories
Attention: Jules Mitchel, Ph.D.
President, Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 5% Lice Asphyxiator.

We also refer to your April 6, 2005, request, serial number 010, for a special clinical protocol assessment, received April 7, 2005. The protocol is entitled "A Multi-center, Randomized, Evaluator-Masked Clinical Trial to Evaluate the Efficacy and Safety of Summers Non-Pesticide Lice Asphyxiator (L.A.) Compared to NIX® Permethrin Crème Rinse 1% for the Treatment of Head Lice."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Clinical

1. The primary efficacy endpoint of having no live lice at 14 days is acceptable.
2. NIX® is an acceptable comparator medication.
3. A non-inferiority comparison with respect to NIX® is not adequate to establish efficacy; demonstration of superiority to NIX® will be necessary to establish efficacy.
4. Please modify inclusion criteria such that patients must have an active infestation with *Pediculus capitis*, the human head louse, with presence of nits and at least three live lice at baseline.
5. NIX® should be used according to the approved label; hence a second treatment should be given if live lice are observed seven days or more after the first application of this product.
6. If there is a valid risk with use of this product in pregnant or lactating women that necessitates their exclusion, then caretakers who will be applying the study drug who are pregnant or lactating would also need to be excluded from the study. This may result in restrictive labeling because pediculosis occurs in children and it is likely that caretakers of reproductive age may be exposed to the drug. The Sponsor is therefore requested to complete their non-clinical studies prior to the initiation of Phase 3, as was discussed in the teleconference of May 18, 2005, so that the Phase 3 study may be conducted in such a way that it would be consistent with the anticipated labeling for pregnant and lactating women.
7. The Sponsor should expand their planned safety monitoring to include assessing 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.

8. Please submit Form 1572 prior to study initiation. Additionally please provide the name and credentials of the M.D.s or D.O.s who will be responsible for study drug administration.
9. Please specify in which languages, in addition to English, the consent form will be available.

Biostatistics

At the End-of-Phase 2 meeting with the sponsor on September 9, 2004, the Agency provided detailed clinical and statistical comments which reflect the Division's thinking of the appropriate study design and efficacy evaluation required for establishing the efficacy and safety claim of the drug under investigation. The sponsor's current protocol appears to ignore to a large extent the Agency's comments. It should be noted that it might be difficult to establish efficacy or safety claims based on loose study design which does not address the Agency concerns as expressed by comments made at that meeting. The sponsor is encouraged to refer to these comments and implement them in their Phase 3 trial design for a successful drug development program. Specific reference is made to the following points which were given before at the September 9, 2004, meeting:

- a) The objective of Phase 3 trials should be establishing superiority of the 5% L.A. against Nix. In this regard the sponsor stated (page 19) 'CDC website where it states that treatment failure is common with Nix'. Later the protocol continues to state 'the goal of this study is to show that the treatment success rate in subjects treated with Summers 5% L.A. is within 10% (non-inferiority margin) of the treatment success rate in subjects treated with Nix'. Taking into account the nature of the indication and the availability of other treatments it might be difficult to justify efficacy claim based on non-inferiority comparison relative to a drug which the sponsor noted that its treatment failure is common.
- b) Details about randomization are requested including block size, as the protocol statement 'A balanced randomization, stratified by study site, will be used to ensure that treatment group balance is achieved' (page 18) is not sufficient.
- c) The protocol states (page 20) 'A logistic regression model will be used to test for the effect of the treatment controlling for baseline characteristics (age, gender, race and disease severity). An additional logistics regression model will fit to examine whether there is any evidence of study site difference with the main treatment effect'. From a scientific point of view, could the sponsor clarify how the logistic regression would be used to establish non-inferiority? It should be noted that randomization is expected to balance treatment allocation with respect to baseline factors. Furthermore, it might be difficult to interpret study findings if adjustment were made after checking for baseline imbalance. If the sponsor desires to adjust for baseline covariates then this needs to be pre-specified, at the protocol stage, and should be limited to a very small number of baseline covariates (or factors).
- d) The protocol should provide details of the statistical analysis methods for each of the primary and secondary endpoints, as general statements for analysis of continuous endpoint and categorical endpoints are not sufficient.

The following are responses to the sponsor's specific questions:

Sponsor's Question 2: Study Endpoints/objectives:

Agency's Response:

Absence of lice at 14 days after the final treatment might be an acceptable primary endpoint (see clinical comments). However, evaluation of 5% L.A. against Nix is a vague statement for the Agency to concur with. For efficacy claim the superiority of the 5% L.A. against Nix in two well-controlled studies is required (see comment 'a' above).

Sponsor's Question 3: Study duration:

Agency's Response:

Each subject should be evaluated at day 22 of the study.

Sponsor's Question 4: Comparator Drug:

Agency's Response:

Use of Nix in the trial is acceptable as long as the goal is to establish superiority against Nix using two-sided significance level $\alpha=0.05$.

Sponsor's Question 5.1 Non-inferiority:

Agency's Response:

Non-inferiority is not an acceptable comparison to establish an efficacy claim, and further one-sided significance level $\alpha=0.05$ is not acceptable either.

Sponsor's Question 5.2: Power calculation:

Agency's Response:

The Agency does not concur with the non-inferiority power calculation. The sponsor should recalculate the sample size for a superiority comparison using two-sided $\alpha=0.05$.

Question 6: Study treatment (family members):

Agency's Response:

Sponsor's statements in different locations in the submission are inconsistent. Page 5 states 'Up to 2 family members will be treated with the goals of being included in the primary endpoint analysis' however, page 12 states 'Only one member of a household will be evaluated for efficacy'. The analysis should address correlation when 2 members are used for efficacy evaluation. Alternatively, the protocol might pre-specify one member of the household for efficacy assessment (such as the youngest member). Similarly, there is inconsistency about the number of subjects to enroll in the trial (the submission stated a total of 170 subjects in page 5 and page 19, but it states 'up to 200 males and females ...' in page 12.

Question 7: Study blinding:

Agency's Response:

Sponsor's description does not provide details about 'the sufficient steps have been taken to blind the evaluator' which the protocol refers to. Consequently, the Agency does not agree that blinding is ensured in this study.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Melinda Harris-Bauerlien, M.S., Project Manger, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jonathan Wilkin

5/18/05 05:21:55 PM

MEMORANDUM OF TELECON

DATE: 5/18/05, 2:00 P.M.

APPLICATION NUMBER: IND 50,076

DRUG PRODUCT: Lice Asphyxiator

BETWEEN:

Name: Jules Mitchell, MBA, PhD, President, Target Health
Glen Park, PharmD, Senior Director, Clinical Affairs
Erin Sharpe, CRA
Mike Precopio, President, Summers Laboratories
Representing: Summers Laboratories

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jill Lindstrom, MD, Team Leader, Clinical
Patricia Brown, MD, Clinical Reviewer
Barbara Hill, PhD, Pharmacology Reviewer
Melinda Harris-Bauerlien, MS, Regulatory Project Manager

SUBJECT: IND 50,076

The teleconference was requested by the Agency to request specific information from the sponsor concerning the submitted Special Protocol Assessment (SPA) for the IND.

1. The Agency stated that exclusion of pregnant or lactating subjects and caretakers from the phase 3 study will result in restrictive labeling. Because caregivers who apply the drug may be of reproductive age, the Agency is concerned that such labeling may have the unintended consequence of precipitating termination of otherwise desired pregnancies by caretakers who are inadvertently exposed to the drug in early pregnancy. The sponsor is therefore 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.
2. The Division asked the sponsor about the status of the recommended rodent and non-rodent embryofetal development studies for benzyl alcohol.

The sponsor informed the Division that subcutaneous dose range finding studies have been completed in rats and rabbits. In addition, subcutaneous doses of benzyl alcohol have been selected for the definitive rat and rabbit embryofetal development studies. The sponsor informed the Division that the definitive rat embryofetal

development study was initiated today (May 18, 2005) and that the definitive rabbit embryofetal development study will be initiated on May 22, 2005.

The Division recommended that the draft study reports for the subcutaneous rat and rabbit embryofetal development studies be submitted to the IND prior to initiation of the Phase 3 clinical study. The sponsor was informed that the results from the subcutaneous rat and rabbit embryofetal development studies would determine if it would be appropriate to include women of child bearing potential and/or pregnant women in the Phase 3 clinical study.

The sponsor replied that they will submit the draft study reports for the subcutaneous rat and rabbit embryofetal development studies to the IND prior to initiation of the Phase 3 clinical study.

The conversation ended amicably.

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/s/

Melinda Harris-Bauerlien
6/1/05 12:58:15 PM
CSO

Jill Lindstrom
6/1/05 02:11:26 PM
MEDICAL OFFICER