CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206966Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077510

MEETING MINUTES

Hatchtech Pty Ltd
c/o Virtual Regulatory Solutions, Inc.
Attention: Lisa Jenkins, PhD
Vice President, Regulatory Strategy and Content Development
2401 Harrier Drive
Audubon, PA 19403

Dear Dr. Jenkins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Xeglyze (abametapir) topical lotion, 0.74%.

We also refer to the meeting between representatives of your firm and the FDA on January 21, 2015. The purpose of the meeting was to discuss the content and format of the proposed NDA submission for Xeglyze (abametapir) topical lotion, 0.74%.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 21, 2015 at 10AM
Meeting Location:	Building 22, Room 1415
Application Number:	IND 077510
Product Name:	Xeglyze (abametapir) topical lotion, 0.74%
Proposed Indication:	head lice infestation in patients 6 months of age and older
Sponsor Name:	Hatchtech Pty Ltd
Meeting Chair:	Jill Lindstrom, MD, FAAD
Meeting Recorder:	Cristina Attinello, MPH

FDA ATTENDEES
Amy G. Egan, MD, MPH, Acting Deputy Director, ODE III
Jill Lindstrom, MD, FAAD, Clinical Team Leader, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Angela Lu, PhD, Clinical Pharmacology Reviewer, DCP3
Yichun Sun, PhD, Acting Quality Assessment Lead, Branch V, DNDP II
Gene Holbert, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Erika Pfeiler, Microbiology Reviewer, OPS/NDMS
Kendra Worthy, PharmD, Team Leader, OSE/DMEPA
Roy Blay, PhD, Reviewer, OSI/DGCAB
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP
Omolara Laiyemo, PharmD, Regulatory Health Project Manager, DDDP
Stacy Blake, MPA, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEE
Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES
Hugh Alsop, BSc (Hons), MBA, Chief Executive Officer, Hatchtech
Sharon Hanegraaf, BSc, Regulatory Affairs Manager, Hatchtech

Tiina Ahveninen, BN (Hons), Clinical Manager, Hatchtech
(b) (6), US Agent and Consultant to Hatchtech, (b) (6)
(b) (6) Consultant to Hatchtech, (b) (6)
(b) (6) Toxicologist, Consultant to (b) (6)(attendance by phone only),
Vernon Bowles, PhD Chief Scientific Officer (attendance by phone only), Hatchtech
Michael Wheatcroft, PhD, Project Manager (attendance by phone only), Hatchtech
(b) (4) Consultant to Hatchtech (attendance by phone only), (b) (6)

Purpose of the Meeting:
To discuss the content and format of the proposed NDA submission for Xeglyze (abametapir) topical lotion, 0.74%

Regulatory Correspondence History

We have had the following meetings with you:
- August 1, 2012: End-of-Phase 2
- June 20, 2007: Pre-IND

We have sent the following correspondences:
- October 20, 2014: Advice
- August 22, 2014: Advice
- July 7, 2014: Advice
- May 8, 2014: PSP Agreement
- April 10, 2014: Proprietary Name Granted
- March 10, 2014 (2): Advice
- March 10, 2014: PSP Written Response
- December 4, 2013: Special Protocol Assessment Agreement
- December 3, 2013: Advice/Information Request
- October 31, 2013: Advice
- July 3, 2013: Advice
- October 27, 2011: Advice
- August 5, 2011: Advice
- February 3, 2011: Advice
- October 7, 2009: Advice
- April 30, 2009: Advice
- July 9, 2008: Remove Full Clinical Hold
- April 23, 2008: Full Clinical Hold

Regulatory

Question 24:
The overall TOC for the NDA has been provided in Appendix 1.

Does the Division have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

Response:
The overall Table of Contents (TOC) appears reasonable.

From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below.

1. FDA FORM 3674 should reside under m1.2 cover letter section, with a clear leaf title.

2. For archival purposes, also submit a pdf file of any labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.

3. The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

Cross referencing (m1.4.4)
Sponsor's options of cross referencing information submitted to another application, would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. nda, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that the sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf

Question 25:
Hatchtech is submitting a 505(b)(1) application. To the best of Hatchtech's knowledge, each of the clinical investigations included in this application meets the definition of a new clinical investigation as set forth in 21 CFR §314.108(a). In addition, the active, abametapir, meets the definition of a new chemical entity. As such, we anticipate that the product will be entitled to 5 years of market exclusivity.

Does the Agency concur with this assessment?

Response:
Five years of Waxman-Hatch exclusivity is granted upon approval of an NDA if a drug product contains a new chemical entity and was approved after September 24, 1984. Whether the data used to support the application is adequate for the approval of the NDA is a review issue. FDA does not award or grant exclusivity prior to approval of a drug product. We refer you to 21 CFR 314.108(b)(2) and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm for further information regarding exclusivity. You may also contact a member of the Orange Book Staff with any additional questions.

Question 26:
Hatchtech received a conditional approval for the brand name Xeglyze on 16 April 2014 and intends to include a copy of this letter in Module 1, Section 1.2 Cover Letter. Hatchtech does not propose to submit the full proprietary name submission to the NDA.

Does the Division agree with the sponsor's plan to only submit the conditional approval letter with the NDA and the proposed location of the letter?

Response:
No. You will need to submit a new request for proprietary name review with your NDA submission. Although your proposed proprietary name, Xeglyze, was found conditionally acceptable in the IND, the proposed name must be re-evaluated in the NDA review cycle. Refer to guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1].

Chemistry, Manufacturing and Controls (CMC)

Question 12:
Hatchtech submitted samples of drug product for dosage form evaluation to the IND (SN0058 submitted on 15 May 2014). The drug product is an oil in water emulsion that is pourable, has a viscosity of < (b) (4) cp @ (b) (4) °C and is intended for external application to the skin.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

Hatchtech believes that this fulfills the criteria for a lotion as defined in the FDA CDER Data Standards Manual (DSM CDER Data Element Number C-DRG-00201, Version 008) and the current US Pharmacopeia (USP <1151> Pharmaceutical Dosage Forms).
The composition of the drug product is provided in Table 44.

Does the Division agree that abametapir lotion 0.74% should be categorized as a lotion?

Response:
We agree that the product should be characterized as a lotion.

Question 13:
The available stability data at the time of submission is presented in Table 11. The formulation and manufacturing scale of the clinical batches, registration campaign 1 batches and registration campaign 2 batches are identical. The only difference between the batches is in the (b) (4) (Table 11). Further background on the evolution of the container closure system is provided in Section 10.2.3 .

Hatchtech proposes that all available stability data be submitted as primary data, as differences in the container closure systems are considered minor, and have no impact on the stability of the drug product. The ranges observed for each stability attribute at each condition to date are presented in Table 48.

Does the Division agree that the available stability data can be categorized as primary data, and will be sufficient to support an expiry date of 24 months in the proposed commercial container closure system?

Response:
Only the stability data obtained from the batches packaged in the proposed commercial container closure are considered as primary registration stability data. The rest will be considered as supportive stability data. We will consider all available stability information in review of the application. The expiration dating period will be granted based on available stability data during NDA review. We cannot commit to an expiry date of 24 months before fully reviewing the NDA.

Meeting Discussion:
The sponsor inquired whether they could submit additional stability data during the NDA review. The Agency responded that additional stability data could only be submitted within the first 30 days that follow application submission.

Question 14:
Hatchtech has continued to conduct microbiological examination of abametapir lotion throughout the development program, evaluating total aerobic microbial count (TAMC), total combined yeasts and molds count (TYMC) as well as specified organisms, *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Salmonella sp*. In addition, TAMC and TYMC are monitored in the drug substance at release and throughout stability testing.
Abametapir lotion 0.74% contains (b) (4)

[redacted] To date, there have been no observations of microbial growth in [redacted] drug product.

As such, Hatchtech proposes [redacted]

The proposed commercial drug product specification is provided in Table 46. Stability results for the primary drug product batches demonstrating no observations of microbial growth are summarized in Table 48.

Does FDA agree, [redacted]

Response:

[redacted]

Question 15:

[redacted]

Response:

[redacted]

Question 16:
At the EOP2 meeting, FDA requested additional tests to be added to the specification:

Since the proposed formulation is a dispersed system of multiple phases, add the following tests with appropriate acceptance criteria to the drug product specification: microscopic appearance, droplet size, content uniformity in the container and package integrity

The proposed commercial drug product specification is provided in Table 46.

Does the Division find the proposed commercial drug product specification adequate to support the NDA?

Response:
The proposed drug product specification appears to be acceptable, however the final determination will be made during NDA review.

Pharmacology/Toxicology

Question 17:
Developmental and reproductive toxicity (DART) potential was assessed in in vivo models via oral administration of abametapir (Table 51). The potential for disruption of fertility and early embryonic development (Segment I), embryofetal development (Segment II), and peri-/post-natal development, including maternal function (Segment III), was assessed in rats. The potential for disruption of embryofetal development also was assessed in rabbits. DART study reports, including characterization of abametapir toxicokinetics in pregnant rats and rabbits in the embryofetal development studies, were submitted to the IND in SN0023 and SN0025. In the EOP2 Meeting Minutes, FDA agreed, in principle, that the submitted studies were adequate to support the marketing application.

Subsequently, Hatchtech identified a primary human metabolite, abametapir-COOH, and in the submission SN0055 proposed a program to characterize its toxicity potential. In an Advice letter dated 22 August 2014, FDA agreed that the proposed studies, which consisted of toxicokinetic characterization of the abametapir-COOH metabolite in non-pregnant rats after 14 days of abametapir dosing at the lowest no observed adverse effect level (NOAEL) as determined in the DART studies, appeared reasonable to support filing of an NDA. Hatchtech has since completed bioanalytical and toxicokinetic assessment of abametapir-COOH in pregnant rats using stored samples from the original embryofetal development study and in non-gravid rabbits using samples from a bridging study (Table 12). These new toxicokinetic data confirm both the rat and rabbit were exposed to the abametapir-COOH metabolite in the original embryofetal development studies.

Does FDA agree that the completed DART studies adequately support the marketing application of abametapir lotion 0.74% and that no additional DART studies are required?

Response:
Yes. The completed reproductive and developmental toxicology studies adequately support a marketing application of abametapir lotion, 0.74%. Abametapir and the abametapir-COOH metabolite are both considered well characterized. No additional reproductive and developmental toxicology studies are required.

The Agency develops multiples of human exposure for embryofetal development studies based on either body surface area comparisons, calculated using an average adult weight of 60 kg, or AUC comparisons using adult AUC values.

Question 18:
At the EOP2 meeting, FDA requested Hatchtech to characterize the metabolic pathway of abametapir, address the potential for drug-drug interactions, and characterize the ADME of abametapir. Hatchtech has since confirmed the presence of a major human metabolite; a mono-carboxylated derivative of abametapir (abametapir–COOH), which is observed in both pediatrics and adults and in all animal species of the toxicology program. Subsequent to the EOP2 meeting, Hatchtech conducted a number of nonclinical studies to characterize the PK of abametapir and submitted them to IND 77510 (SN0055 April 8, 2014). In an Advice letter dated 22 August 2014, FDA agreed, in principle, that the completed studies in SN0055 and the studies proposed for characterization of abametapir-COOH drug-drug interaction potential appeared reasonable to support filing an NDA.

Hatchtech has since completed studies characterizing the abametapir-COOH drug-drug interaction potential in vitro per the FDA 2012 draft guidance (Table 13). In addition, Hatchtech has conducted studies of abametapir stability in hepatic microsomes with metabolite identification and has explored aspects of Phase II metabolism both in vitro and in vivo.

Does FDA agree that Hatchtech has sufficiently characterized the ADME and drug-drug interaction potential of abametapir and abametapir-COOH to support the marketing application of abametapir lotion 0.74% and that no additional studies are required?

Response:
Yes. Hatchtech has sufficiently characterized the ADME and drug-drug interaction potential of abametapir and abametapir-COOH to support the marketing application of abametapir lotion, 0.74% from a Pharmacology/Toxicology perspective. See response to Question 3.

Question 19:
Hatchtech has assessed the dermal toxicity potential of the to-be-marketed formulation in a 28-day study in minipigs (20049509, Table 51). Females were administered the drug product and an enhanced strength formulation once or twice daily for 28 consecutive days. Males were dosed similarly for up to 13 consecutive days. Duration of dosing could not be extended in males due to protrusion of the penis down from the protective sheath; this clinical sign triggers early termination in laboratories due to ethical concerns for discomfort resulting from subsequent mechanical injury and low lymphatic clearance. The maximum tolerated dose (MTD) was reached in both sexes at the highest dose, as evident in clinical signs (tremors, decreased activity, inappetence, dermal reactions [erythema, edema]). Toxicokinetics of abametapir and abametapir-

COOH were characterized, although a full AUC curve was not described at the MTD due to ethical limitations on frequent blood collection from animals exhibiting toxicity.

Hatchtech believes the completed dermal toxicity program adequately characterizes the potential human risk associated with single-dose topical use of abametapir lotion and that the data provided in the 20049509 dermal toxicity study are adequate to support the marketing application. As such, Hatchtech does not propose to conduct any additional dermal toxicity studies. Refer to Section 10.3.3 for additional information.

Does the Agency agree that study 20049509 is sufficient to characterize the dermal toxicity potential of abametapir lotion 0.74% and that no additional dermal toxicity studies are required to support the marketing application of abametapir lotion 0.74%?

Response:
Yes. Study 20049509, which is a repeat dermal toxicity study in minipigs, is sufficient to characterize the dermal toxicity potential of abametapir lotion, 0.74%. No additional dermal toxicity studies are required to support the marketing application of abametapir lotion, 0.74%.

Question 20:
The systemic toxicity potential of abametapir and its abametapir-COOH metabolite was assessed in male and female adult and juvenile rats (Table 51). Abametapir was administered orally for 14 days to adults and 56 days to juveniles. MTDs and NOAELs were determined. The NOAEL in adult rats was 25 mg/kg/day based on kidney toxicity at 75 mg/kg/day, while the NOAEL in juvenile rats was 30 mg/kg/day based on an absence of adverse effects at this high dose.

At the EOP2 meeting, FDA agreed that the submitted toxicology studies and proposed studies were adequate to support the marketing application. In addition, FDA stated in an Advice letter dated 22 August 2014, that the studies proposed in SN0055 for characterization of abametapir-COOH safety appeared reasonable to support filing an NDA. Hatchtech since has completed bioanalytical and toxicokinetic assessments of abametapir-COOH in juvenile rats using stored samples from the original 56 day study and in adult rats using samples from a 14 day bridging study (Table 14). These new studies ((b) (4)-039; (b) (4)011, (b) (4)-034) verified the presence of abametapir-COOH in the original juvenile and general toxicity studies (70758 and (b) (4)0006). Hatchtech therefore believes the original toxicology studies conducted with oral administration of abametapir adequately assessed the toxicity potential of both abametapir and abametapir-COOH.

Since exposure to both abametapir and the abametapir-COOH metabolite was confirmed in these studies, Hatchtech does not plan to conduct any additional studies addressing systemic or juvenile toxicity potential. Refer to Section 10.3.4 for additional information.

Does FDA agree that the completed toxicology program outlined in Question 19 and Question 20 adequately supports the systemic toxicity potential of abametapir lotion 0.74% and that no additional systemic toxicology studies are required to support the marketing application?

Response:
Yes. The completed toxicology program adequately supports the systemic toxicity potential of abametapir lotion, 0.74%. No additional systemic toxicology studies are required to support the marketing application.

Question 21:
The genotoxicity potential of abametapir and abametapir-COOH was assessed using in vitro and in vivo models (Table 51). At the EOP2 meeting, FDA agreed that the submitted genotoxicity studies were adequate to support the marketing application, and in an Advice letter dated 22 August 2014, FDA agreed that the studies proposed in SN0055 for characterization of abametapir-COOH safety appeared reasonable to support filing an NDA. Subsequent to this, and consistent with the proposal presented in SN0055, Hatchtech assessed the mutagenicity of abametapir-COOH in an in vitro Ames test and confirmed that animals in the completed rat micronucleus assay were exposed to both abametapir and abametapir-COOH (Table 15).

Based on these studies, the parent and metabolite both have been assessed in genetic toxicity studies, and Hatchtech does not intend to conduct any additional studies of genotoxicity potential. Refer to Section 10.3.5 for additional information.

Does FDA agree that the completed genotoxicity assessments sufficiently characterize the genotoxic risks associated with the single dose topical treatment of abametapir lotion 0.74% and that no additional nonclinical studies of genotoxicity are required?

Response:
Yes. The Agency agrees that the completed genotoxicity assessments characterize the genotoxic risks associated with the single dose topical treatment of abametapir lotion, 0.74% and that no additional nonclinical studies of genotoxicity are required.

Question 22:
Hatchtech has modified the original Question 21 that appeared in the 1.6.1 Meeting Request.

As previously stated, Hatchtech has calculated exposure-based safety margins for abametapir-COOH, using datasets from clinical studies as proposed in SN0055. These datasets enable calculation of PK parameters including AUC0-∞ in adults, but not in pediatrics, since t = Cmax in the majority of pediatric samples. Hatchtech has identified and assessed 2 independent methods for estimation of abametapir-COOH exposure and have selected the one that generates the largest (most conservative) pediatric exposures for use in safety margin calculations. This conservative approach utilizes a modified noncompartmental analysis method to calculate AUC0-∞ in adults. It also utilizes the Cmax ratio of parent:metabolite observed in adults to predict PK parameters in pediatrics, since t = Cmax in the majority of pediatric samples and AUC0-∞ could not be calculated via traditional noncompartmental analysis.

The approach employed to obtain the human AUCinf and Cmax values is detailed in the background section (Section 10.3.6). Exposure-based safety margins established in pivotal nonclinical studies are also presented in the same background section, Table 62 to Table 63, in addition to background Sections 10.3.1 and Section 10.3.3.

Does the Agency agree with the approach employed to obtain the human AUCinf and Cmax values utilized to calculate exposure-based safety margins for abametapir-COOH?

Response:
The approach employed to obtain safety margins for abametapir-COOH appears reasonable. See response to Question 3.

Question 23:
Are there any other aspects of the nonclinical development plan or nonclinical sections of the NDA that the Agency would like to comment on, or that Hatchtech should take into consideration?

Response:
No. The nonclinical development plan appears complete.

Clinical/Biostatistics/Clinical Pharmacology

Question 1:
Hatchtech has conducted 2 identical pivotal Phase 3 efficacy and safety studies (Ha03-001 and Ha03-002) in the US in 704 subjects (including 216 index subjects) 6 months of age and older. A summary of the available topline data is provided in Table 2 as well as Section 10.1.2 and Section 10.1.3.

Does the Agency agree that the available efficacy data obtained in the Phase 3 pivotal studies form an adequate basis for an NDA submission?

Response:
The summary data included in the briefing document regarding the Phase 3 trials provides an adequate basis for an NDA submission. However, the adequacy of that data to support approval of your drug product for the treatment of head lice infestation will be a review issue.

Question 2:
Hatchtech received an Advice letter from FDA on 20 October 2014 (1.6.3 Correspondence Regarding Meetings). FDA had the following comments:

1. In your "final" SAP for trial Ha03-001 and trial Ha03-002, while you stated that "for all main efficacy analyses, subjects without lice evaluation at the Day 14 visit will be considered as treatment failures," you listed the primary imputation method for the primary as well as the secondary endpoints as last observation carried forward (LOCF) on Table 3, page 18.

2. You are reminded of our previous comments that the method of handling missing data be consistent for the primary as well as for the secondary endpoints so that results can be reasonably interpreted (December 4, 2013 and March 10, 2014).

The Ha03-001 and Ha03-002 studies were clinically complete, the data were unblinded, and the clinical study reports were being prepared at the time Hatchtech received FDA's 20 October

2014 letter and clarification on the Agency's guidance regarding missing data imputation. In light of ICH E9 Statistical Principles for Clinical Trials, which clearly states that, "*Redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess*," Hatchtech intends to prepare the final study reports for the Ha03-001 and Ha03-002 pivotal studies in accordance with the efficacy analyses specified in the final protocols and SAPs that were submitted to the IND for these studies. However, to address the issues that FDA has raised around the imputation methods used for missing data, Hatchtech intends on providing a discussion and additional analysis on the pooled efficacy data from these studies in 2.7.3 Summary of Clinical Efficacy in the NDA using the LOCF sensitivity analysis as defined in the SAP for imputing missing data.

Does FDA agree with Hatchtech's approach to address FDA's concerns regarding the missing data imputation methods by conducting additional analyses of the pooled efficacy data and reporting this information in the NDA?

Response:
As the trials have already been unblinded, we do not see the utility of providing additional comments at this stage. Further, the goal of providing discussion and additional analysis on the pooled efficacy data from the Phase 3 trials is not clear. Note that you may include analyses based on pooled efficacy data in the integrated summary of efficacy (ISE).

For each Phase 3 trial, you may submit analysis based on the protocol-specified method and also submit additional analyses based on the Agency's recommendation. Determination of the adequacy of your approach will be a review issue which may be impacted by the magnitude of the dropout in the trials.

Question 3:
Hatchtech received an Advice letter from FDA on 7 July 2014 (1.6.3 Correspondence Regarding Meetings). FDA had the following comments and recommendation regarding Study Ha03-003:

Because systemic exposure to your drug product may be higher in the pediatric population age 6 months to 2 years than the adult population, you should conduct the pharmacokinetic assessment and safety evaluation in trial Ha03-003 under maximal use conditions in at least 16 evaluable subjects age 6 months to 2 years.

Study Ha03-003 was clinically complete prior to receiving the Advice letter. Study Ha03-003 has 4 evaluable subjects in the 6 months to 2 years age range with scalp erythema and evidence of excoriation or inflammation representing the upper level of disease severity. An additional 15 evaluable subjects in the 2 years to 17 years age range with scalp erythema and evidence of excoriation or inflammation representing the upper level of disease severity and 3 evaluable subjects in the 2 years to 3 years age range without evidence of excoriation (total of 22 evaluable subjects) were also treated (refer to Table 3).

Does FDA agree that the approach to pool the pediatric PK data obtained from these 2 pediatric PK studies is adequate to characterize the PK profile in the pediatric population under all conditions of use?

Response:
You may choose to pool the pediatric PK data as a supporting analysis in addition to the primary analysis of data from individual trials. It appears that systemic exposure was generally higher in trial Ha03-003 than trial Ha03-004. Provide in the NDA a table detailing the degree of erythema and excoriation for each subject in trials Ha03-003 and Ha03-004 and a discussion on what is the magnitude of increase in absorption that was observed in subjects with scalp erythema and excoriation.

Additional Clinical Pharmacology Comments

1. Provide in the NDA raw and calculated PK parameters for all trials with PK assessments in SAS Transport format (.xpt). Include a data definition file.

2. Provide in the NDA a table listing all clinical trials and the associated formulation used in each trial. Clarify the relationship among the terminologies used for the different formulations, e.g., Ha44 gel, Ha44 lotion, and abametapir lotion.

3. At the time of your NDA submission, you should include bioanalytical reports and associated method validation reports for all trials with PK assessment. The bioanalytical report for each trial should outline the duration of sample storage and supporting long-term storage stability information.

4. We noted that you submitted information regarding systemic exposure and drug interaction potential of the metabolite in the submission dated December 23, 2014. It has not been reviewed for this Pre-NDA Meeting.

Question 4:
Hatchtech received an Advice letter from FDA on 7 July 2014. FDA had the following comments and recommendations regarding Study Ha03-008:

For the proposed indication of the treatment of head lice infestation, the primary efficacy endpoint in protocol Ha03-008 should be the proportion of index subjects who are lice free 14 days after last treatment. As previously communicated August 7, 2012, the applicability of data from in vitro studies with head lice to support the indication of the "treatment of head lice infestation" is limited.

The 2 Phase 3 pivotal efficacy studies, Ha03-001 and Ha03-002, were designed to establish abametapir lotion 0.74% as a pediculicide and provide direct evidence to support the indication of "treatment of head lice infestation". In both studies, the primary efficacy endpoint was the proportion of index subjects who were lice free through 14 days after treatment, an endpoint that was agreed to by FDA in the Ha03-001 SPA.

In contrast, the primary objective of study Ha03-008 was to demonstrate the ovicidal efficacy of abametapir lotion 0.74% using an "ex vivo" method. In vivo studies for the determination of ovicidal efficacy by direct observation of egg hatching on a human subject is extremely

challenging due to the difficulties of monitoring individual eggs on a head pre- and post-treatment over the full life cycle of the lice (Barker and Altman, 2011).

Various attempts have been reported in the literature to develop a more effective method where individual eggs can be tracked and measured for their hatchability. These methods range from harvesting of eggs from subjects then treating and incubating them in the laboratory, through to the development of laboratory based lice colonies from which eggs can be sampled and then treated with investigational products. The drawback with these methods is that the treatment process does not occur on a human subject, and thus is not representative of the proposed application procedure or the real life exposure to an investigational product.

Study Ha03-008 adopted a design termed an "ex vivo" method. This method was first described by Urcuyo and Zaias 1986, and then again by Barker and Altman 2011, and involves the collection of eggs from human subjects just prior to (pre) and then again immediately after (post) treatment with an investigational product. Subjects aged 3 years and older with an active head lice infestation were enrolled into the study. Prior to treatment (pre-treatment), louse eggs were harvested from each subject and set aside for evaluation. The subject was then treated with IP as per application instructions which involved a 10 minute application of sufficient product to fully saturate the hair. Following treatment, the subjects' hair was rinsed with warm water and eggs were again harvested (post-treatment) and set aside for evaluation.

Once collected, eggs were microscopically examined to determine whether they were viable. Viable eggs were placed in a laboratory incubator at controlled temperature and humidity conditions for 14 days. The selection of the incubator conditions simulated the conditions an egg would experience on the scalp, and since lice eggs take between 7 and 10 days to hatch, a period of 14 days was chosen for the incubation period. Ovicidal efficacy was then measured by comparing the hatch-rate of eggs collected pre-treatment with the hatch-rate of eggs collected post-treatment. This allows for any possible variation in natural hatchability to be taken into account, as it has been reported from a number of previous studies that between 5% and 30% of untreated lice eggs fail to hatch (Urcuyo and Zaias 1986, Meinking et al., 1986, Strycharz et al., 2011). This study provides additional ovicidal efficacy data from a vehicle-controlled study conducted in the proposed population and replicates data obtained in a number of in vitro studies using a laboratory based lice colony which previously demonstrated ovicidal efficacy.

(b) (4)

The "ex- vivo" method of assessing ovicidal activity involves the evaluation of the hatch rate after removal of the eggs from the subject (before and after treatment). The ovicidal activity observed ex-vivo may not predict the ovicidal activity observed in- vivo. Due to the difference in conditions (ex- vivo versus in- vivo), interpretation of the results is challenging. The adequacy of the data from trial Ha03-008 (b) (4) will be determined during the NDA review.

Meeting Discussion:
The sponsor proposed to include in the NDA a discussion of the differences between the conditions of the ex-vivo study and the in-vivo state.

Question 5:
Hatchtech intends to propose the following Indication Statement and Mechanism of Action in the label based on the results from studies Ha03-001, Ha03-002 (Table 2) (b) (4) (Table 7). The proposed draft label is provided in Appendix 2.

Indication Statement
Abametapir lotion 0.74% is a pediculicide (b) (4) indicated for the topical treatment of head lice infestation (b) (4) in patients 6 months of age and older. (b) (4)

Mechanism of Action
(b) (4)

Based on the positive results achieved in the pivotal Phase 3 efficacy & safety studies (Table 2), (b) (4) does FDA agree that the data provided are sufficient to support the proposed labeling?

Response:
Per 21 CFR 201.57(c), an appropriate indication involves the treatment, prevention, or diagnosis of a recognized disease or condition, important manifestation of a disease or condition, or relief of symptoms associated with a disease. Based on your Phase 3 clinical trials, the appropriate indication for your product is the treatment of head lice infestation. (b) (4) is a review issue. See response to Question 4.

Question 6:
At the End of Phase 2 meeting, FDA requested a summary of literature on the pharmacological effects of bipyridyl compounds in general and the role of metalloproteinases in normal physiological processes. Hatchtech has conducted this literature search, and will summarize the search methodology and provide a categorized citation list in Module 4.3. Hatchtech does not intend to conduct a literature search on abametapir lotion 0.74% or any other related key terms.

Does the Division agree that no additional literature searches are needed to support the NDA?

Response:
We agree that no additional literature searches are needed to file the NDA.

Question 7:
Hatchtech proposes to submit CSRs for the clinical studies that were originally submitted to the IND in paper format (Table 8) in eCTD format with E3 granularity.

Hatchtech also intends to submit CDISC (SDTM and ADaM) datasets for the 2 pivotal Phase 3 studies as well as the Ha03-008 study. For study Ha02-005, datasets were submitted to the IND (SN0028) and Hatchtech plans to provide only a cross-reference to these datasets in the NDA. Does the Division agree with this approach?

Response:
Your proposal to submit the clinical Study Reports (CSRs) in eCTD format with E3 granularity is acceptable.

Your proposal to submit CDISC (SDTM and ADaM) datasets for the Phase 3 trials is acceptable. In particular, include the following items for your Phase 2 and Phase 3 trials in your submission:

1. Submit the electronic datasets for clinical trials in SAS transport form (.xpt). You should submit both SDTM datasets (raw data directly from the CRF in standardized format) and analysis datasets. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.

2. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. The documentation should indicate which variables are derived.

3. Definition files for raw datasets modeled according to CDISC/SDTM and standards should be submitted as .xml file types (define.xml). Refer to CDISC's Define.XML page for assistance/guidance related to creating define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml.

4. Study protocols including the statistical analysis plan, all protocol amendments (with dates), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

5. If any subjects were enrolled in more than one trial, include a unique subject ID that permits subjects to be tracked across multiple trials.

You are encouraged to arrange a test submission, prior to actual submission. Refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm) for guidance on sending a test submission.

Meeting Discussion:
The sponsor proposed to submit some of their Phase 2 data sets in legacy data set format. The Agency responded that this appears reasonable at this stage.

Question 8:
A comprehensive summary of the efficacy of abametapir lotion 0.74% will be provided in Section 2.7.3 Summary of Clinical Efficacy and a comprehensive summary of safety will be provided in Section 2.7.4 Summary of Clinical Safety. As the development program for abametapir lotion 0.74% is relatively small, Hatchtech anticipates that the Module 2 Summaries will be within the ICH recommended page limitation of a total of 400 pages. As such, Hatchtech does not intend to submit an Integrated Summary of Efficacy or Integrated Summary of Safety in Section 5.3.5.3. The TLGs that are generated for the combined evaluations that will be reported in the Module 2 summaries will be provided in Section 5.3.5.3.

Does the Division agree with our request to waive the requirements for an ISE and an ISS in the NDA?

Response:
The integrated summary of efficacy (ISE) and integrated summary of safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports and are required by the regulations to be located in Module 5. If you believe section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and Module 5{21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a)}.

Note that the ISE generally includes comprehensive in-depth analysis of the total efficacy results, and discusses the extent to which the results of the relevant studies reinforce or do not reinforce each other. This may require additional discussion beyond individual study summaries and a pooled analysis. For additional information on the content of the ISE refer to guidance for industry *Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf).

Include such analysis and discussion in Section 2.7.3 should you elect not to submit an ISE. For additional information about the location of ISS and ISE in the CTD, refer to guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at the FDA website. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)

Question 9a:
Hatchtech intends to pool data from the 2 pivotal Phase 3 studies to represent the efficacy and safety profiles for abametapir lotion 0.74%. The primary Phase 3 efficacy studies, Ha03-001 and Ha03-002, have identical primary endpoints (PEs), study designs and patient populations (Table 9, Section 10.1.2 and Section 10.1.3). The Ha03-001 and Ha03-002 studies were both administered at home (not in the clinic) under normal clinical use conditions and thus best represent the safety and efficacy data to support the product label.

Additionally, the patient population in the Ha03-001 and Ha03-002 studies make up the majority of the patient exposures (~72%). The other studies (Ha01-001, Ha02-002, Ha02-005, Ha03-003, Ha03-004, Ha02-003, Ha03-007 and Ha03-006) all have different study designs and/or PEs and/or populations and/or formulations than the 2 pivotal Phase 3 studies. There have been no product related SAEs in any of the clinical studies (refer to Section 10.1.1).

The sponsor plans on pooling the efficacy and safety data from the 2 pivotal Phase 3 studies, Ha03-001 and Ha03-002, and presenting the safety data from the remaining studies individually in Section 2.7.4 Summary of Clinical Safety since:

1. there have been no product related SAEs reported in the abametapir lotion 0.74% clinical program;
2. the pooled safety data (Ha03-001 and Ha03-002) best represents the safety data in the product label, and
3. the PEs and/or study design and/or study populations are very different among the studies.

A summary of the pooled analysis tables that the sponsor plans to provide in the NDA is presented in Table 10. The sponsor does not plan to provide the following pooled analyses for the reasons provided.
• TEAEs by Exposure – abametapir lotion 0.74% is a single application product and, as such, each patient received the same exposure.
• Discontinuations due to AEs – there were no discontinuations due to AEs for either of the Phase 3 studies.
• Summary of Laboratory Data (including shift tables) – tables were generated for each Phase 3 study. For both Phase 3 studies, the review of the hematology and biochemistry data did not present any trends nor were there any differences between the 2 treatment groups. Therefore, generation of a pooled analysis table would not be meaningful.
• Summary of Vital Signs – tables were generated for each Phase 3 study. For both Phase 3 studies, abnormal vital signs were limited and no trends were noted over time or between treatment groups. Therefore, generation of a pooled analysis table would not be meaningful.

Does FDA agree that it is acceptable to pool the efficacy data from the Ha03-001 and Ha03-002 studies [redacted](b) (4)?

Response:
While you plan to conduct analyses based on pooled efficacy data, the objective for such an approach is not clear. Generally, analyses based on pooled Phase 3 trials are used for ISE and

ISS. However, it should be noted that establishing an efficacy claim would be based on efficacy data from individual Phase 3 trials along with a replication of study findings.

Meeting Discussion:
The sponsor inquired whether subgroup analyses on the pooled Phase 3 data would be acceptable. The Agency responded that, to investigate the consistency of subgroup findings across the Phase 3 trials, we recommend subgroup analyses be conducted for each Phase 3 trial as well as on the pooled Phase 3 data.

Question 9b:
Does FDA agree that it is acceptable to pool the safety data from the Ha03-001 and Ha03-002 studies and present the safety data for the remaining studies individually?

Response:
Yes. Your approach appears reasonable.

In addition, provide the following:

- Pooled safety data from pediatric pharmacokinetic trials (study Ha03-003 and study Ha03-004).

- Pooled safety data from all vehicle controlled trials using the to-be marketed formulation (0.74%) with a single 10 minute application in subjects with head lice infestation [e.g. trials Ha03-001, Ha03-002, and Ha02-003 (0.74% and vehicle arms)].

- Provide a summary (including shift tables) of pooled data from the Phase 3 trials regarding of the evaluation of the scalp and skin for pruritus, erythema, excoriation, edema and pyoderma and the eye for irritation.

All pooled data also should be analyzed by age group (e.g., 6 months to 2 years, 3 years to 5 years 11 months, 6 years to 11 years 11 months, 12 to 16 years 11 months).

Meeting Discussion:
The sponsor proposed to analyze all pediatric data in the following age groups:
6 months to < 2 years
2 years to < 4 years
4 years < 12 years
12 years < 18 years

The Agency agreed to the above age ranges.

Question 9c:
Does FDA agree the pooled safety data from the Ha03-001 and Ha03-002 studies forms the basis of the safety information for the abametapir lotion 0.74% label?

Response:
We anticipate that the safety data from trial Ha03-001 and trial Ha03-002 will form the primary basis for labeling of abametapir lotion, 0.74%. However, all data from the safety database including local safety data collected under maximal use conditions will be evaluated and included in labeling if indicated.

Question 10:
Module 5: No deaths, SAEs related to study drug or discontinuations due to an adverse event related to study drug were reported in the clinical experience with abametapir lotion 0.74% (Section 10.1.1), and therefore, no CRFs or patient narratives are planned to be submitted in the NDA. In addition, Hatchtech does not intend to submit patient profiles for any study.

Does the Division agree with this approach?

Response:
No.

You should submit Case Report Forms (CRFs) and narratives for all serious adverse events (AEs) regardless of relationship to the study product, pregnancies, severe adverse events and all discontinuations regardless of the reason for all trials in the development program. In addition, provide narratives for subjects who experienced hair discoloration.

CRFs should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms." Also provide electronic links for:

a. all serious AEs
b. all patients discontinued regardless of reason
c. all pregnancies

Guidelines for narrative summary content are provided on page 26 of guidance for industry *Premarketing Risk Assessment* at http://www.fda.gov/cder/guidance/6357fnl.pdf.

Question 11:
Are there any other aspects of the clinical development plan or clinical sections of the NDA that the Agency would like to comment on, or that Hatchtech should take into consideration?

Response:

- We note that your vehicle contains (b) (4) benzyl alcohol, which is the active ingredient in an approved product for the treatment of head lice infestation. Per your briefing document, we note that response rates of 50.9% and 47.2% were observed in the vehicle arms of your Phase 3 trials. Provide your interpretation of this data.

    - Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

- Ensure that the adverse event (AE) data set contains the following:

a) Full MedDRA Hierarchy
b) Primary and secondary SOCs
c) All data in same version of MedDRA

- Per protocol, you evaluated the actual amount of the drug product administered to each subject by weighing the containers when dispensed and returned. Provide an evaluation of adverse events by actual exposure to your drug.

- Since accurate assessment of the primary efficacy variable, absence of live lice, is dependent (at a minimum) on adequate assessor training and sufficient time for examination, include documentation from the Case Report Forms and discussion of the total amount of time spent examining subjects for the presence of lice (e.g. at baseline and Day 14.) (End-of-Phase 2 Meeting Minutes dated August 7, 2012.)

- Include the full text version of any referenced articles.

- Submit a tabulated summary of ECG results from Phase 2 and Phase 3 trials to the NDA.

- To allow evaluation of cardiac safety data from pediatric subjects enrolled in Trial Ha03-003 provide the following :

  - Electronic copy of the study report
  - Annotated CRF
  - A data definition file which describes the contents of the electronic data sets
  - Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
  - Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
  - Data set whose QT/QTc values are the average of the above replicates at each nominal time point
  - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

- Include a 120 day safety update and a safety report from any worldwide use of the drug product (21 CFR 314.50(d)(5)(vi)(b)).

Meeting Discussion:
The Agency requested that the sponsor submit investigator training materials and a discussion of any training provided.

Administrative Comments

1. Comments shared 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 information submitted to the IND or NDA might identify additional comments or information requests.

2. 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 21 CFR 54 and 21CFR 314.50(k).

3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 18, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
Regulations and related guidance documents
A sample tool illustrating the format for Highlights and Contents, and

The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will

consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

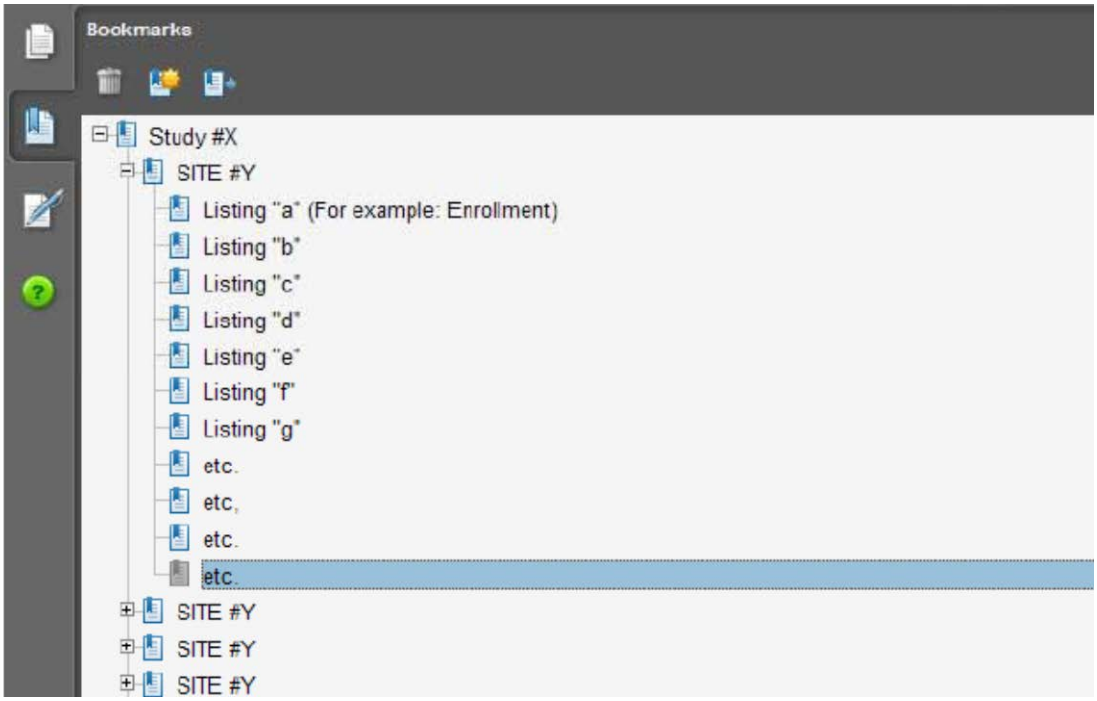
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

JILL A LINDSTROM
02/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077510

MEETING MINUTES

Hatchtech Pty Ltd
c/o Biologics Consulting Group, Inc.
Attention: Kelly T. Boyle
Chief Financial Officer
400 N. Washington Street, Suite 100
Alexandria, VA 22314

Dear Ms. Boyle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ha44 Gel, 0.74%.

We also refer to the meeting scheduled on August 1, 2012 between representatives of your firm and the FDA. The purpose of the meeting was to discuss the clinical development plan for IND 077510. Your premeeting briefing package (submitted June 15, 2012) provides background and questions for discussion.

We acknowledge the email on August 1, 2012, notifying us that after receipt and review of the premeeting communication consisting of Agency responses to your questions, Kelly Reich determined that the responses to your questions are sufficient and additional discussion is not necessary.

This letter and the enclosed final responses represent the official record.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure – Written Responses

WRITTEN RESPONSES

IND 077510

Product: Ha44 Gel

Regulatory Path: 505(b)(1)

Sponsor: Hatchtech Pty. Ltd

Proposed Indication: for the topical treatment of head lice infestation in patients 6 months of age and older

Type of Meeting: End-of-Phase 2

Meeting Date: August 1, 2012

Introductory Comment:

This material includes the Agency's written responses to the questions submitted for your meeting scheduled for August 1, 2012 at 10:30AM in White Oak Building 22 between Hatchtech Pty. Ltd and the Division of Dermatology and Dental Products. This material was shared to promote a collaborative and successful discussion at the meeting. After receipt of the preliminary responses, you had two options:

- If these answers and comments were clear to you and you determined that further discussions were not required, you had the option of canceling the meeting.
- If you determined that discussion was needed for only some of the original questions, you had the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecon).

Kelly Reich conveyed to Cristina Attinello via email on August 1, 2012 that the responses to your questions were sufficient and additional discussion was not necessary. As such, the below responses represent our final responses to your questions.

Purpose of the Meeting:
The purpose of this meeting is to discuss the clinical development plan for IND 077510.

Regulatory Correspondence History

We have had the following meeting with you:
- June 20, 2007: Pre-IND Meeting

We have sent the following correspondences:
- October 27, 2011: Advice

- August 5, 2011; Advice
- February 3, 2011: Advice
- October 7, 2009: Advice
- April 30, 2009: Advice
- July 9, 2008: Remove Full Clinical Hold
- April 23, 2008: Full Clinical Hold
- June 25, 2007: Pre-IND Meeting Minutes

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Hatchtech will be using a new drug substance manufacturer for the Phase 3 clinical product and for future commercial drug product. To support use of the new supplier, Hatchtech plans to conduct a comparability study that will be detailed in the Briefing Package. Does the FDA find the proposed comparability study adequate to support use of the drug substance from the new supplier in the Phase 3 clinical study and for future commercial drug product?

Response:
It is adequate to support Phase 3. To support future commercial drug product, you should submit comparative analytical and spectral data for drug substance sourced from both suppliers for structure confirmation, and discuss potential differences in process impurities.

Question 2:
The starting material for the manufacture of the drug substance is presented in the briefing package. Does FDA agree with the proposed starting material?

Response:
We agree that (b) (4) can be designated as the starting material for the synthesis of Ha44 drug substance.

Question 3:
The proposed drug substance specifications are presented in the briefing package along with the justification for these specifications.
a. Does FDA find the proposed specifications adequate to support use in Phase 3?
b. Does FDA find the proposed specifications adequate to support the NDA submission?

Response:
The proposed drug substance specification is acceptable both for Phase 3 and for NDA submission; however, you should provide a justification for the proposed (b) (4) limit of (b) (4) ppm.

Question 4:
Hatchtech will include drug substance stability data at the time of NDA submission to support the proposed re-test date. Does FDA find this acceptable?

Response:
Yes.

Question 5:
Hatchtech plans to scale-up the drug manufacturing process from the current (b) (4) L to (b) (4) L for the Phase 3. Following the planned scale-up for Phase 3, Hatchtech plans to scale-up to (b) (4) L for the commercial product.
a. Does FDA find the scale-up plan for Phase 3 acceptable?
b. Does FDA find the scale-up plan for commercialization acceptable?

Response:
Your proposed scale-up plan is acceptable. However, if warranted, you may need to demonstrate batch equivalence between the scale (b) (4) L) used in Phases 1 and 2 and the scale (b) (4) L) proposed for Phase 3 since the scale difference between them is greater than (b) (4) fold. SUPAC-SS contains examples of bridging studies for scale-up of semi-solid dosage forms and lotions.

Question 6:
The proposed drug product specifications are presented in the Briefing Package along with the justification for these specifications.
a. Does FDA find the proposed specifications adequate to support use in Phase 3?
b. Does FDA find the proposed specifications adequate to support the NDA submission?

Response:
No, it is not adequate to support either the Phase 3 or the NDA submission. Since the proposed formulation is a dispersed system of multiple phases, add the following tests with appropriate acceptance criteria to drug product specification: microscopic appearance, droplet size, content uniformity in the container, and package integrity.

With reference to the Identity test, clarify what you mean by "UV absorption." Note that HPLC retention time alone is not considered to be a specific identity test (ICH Q6A).

Addendum:
Package integrity is a visual examination of the interior and exterior surfaces of the immediate container/closure system for signs of deterioration, leakage, discoloration, bulging, shedding particles, cracking, etc.

Question 7:
Hatchtech will include stability data for drug product manufactured at the (b) (4) L scale in the NDA at the time of filing to support the proposed expiration dating period. Does FDA find this acceptable?

Response:
You should submit stability data obtained on a minimum of 3 batches of drug product manufactured by the proposed commercial process at a scale greater than one tenth of the commercial scale and stored in the proposed to-be-marketed container/closure system.

The amount of stability data that you presented in Table 19 of the briefing package is adequate for filing, provided that the (b) (4) L and (b) (4) L batches are packaged in the to-be-marketed container/closure system.

Additional CMC Comments

1. Submit a representative sample of the drug product for dosage form evaluation.

2. You state that the container closure system consists of amber Type (b) (4) glass bottles with (b) (4) caps. This is acceptable for Phase 3, but unacceptable for commercialization. To reduce the risk for medication errors due to accidental ingestion, we strongly recommend that you choose a container/closure design for commercialization which is more in line with topical products, and refrain from using a design which is typical for oral liquids. We encourage you to include a consideration of child resistance when selecting the to-be-marketed container/closure system for this product.

3. Weight loss should be monitored in the registration stability studies.

4. (b) (4)

Pharmacology/Toxicology

Question 8:
The nonclinical safety program conducted to date includes assessment of safety pharmacology (cardiovascular, respiratory, and central nervous system), metabolic stability (*in vitro* hepatocytes), general toxicity (14-day oral rat and dermal minipig with parent toxicokinetics (TK)), juvenile toxicity (8-week oral rat with TK), developmental and reproductive toxicity (oral rat Seg I, II, and III and oral rabbit Seg II; Seg II studies with TK), genotoxicity (complete ICH battery), and local tolerance (primary ocular and dermal irritation, skin sensitization). Final study reports of each of these studies either have been submitted to the IND previously or will be submitted by end of June 2012. Summaries of each of these studies are provided in this EOP2 Briefing Package.

Does FDA agree that the completed nonclinical studies adequately support the conduct of Phase 3 clinical trials of Ha44 Gel (0.74%) for the topical treatment of head lice in adult and pediatric subjects as young as 6 months of age and that no additional nonclinical studies are required?

Response:
The completed nonclinical studies listed above appear acceptable to support the conduct of Phase 3 clinical trials with Ha44 for the topical treatment of head lice infestation in adult and pediatric subjects. We acknowledge the recently submitted developmental and reproductive toxicity studies conducted with the drug substance, but note that the definitive peri- and post-natal

development study (b) (4) 0005) was not included in the submission sent on 6-21-12. The final determination concerning the adequacy of these recently submitted nonclinical studies to support conduct of Phase 3 clinical trials will be made after review of the complete study reports. In addition, you should provide the Investigator's Brochure for your drug product that contains an updated nonclinical section for review.

Question 9:
In addition to the completed studies described above, Hatchtech intends to support the 505(b)(1) NDA with the studies described in Table 1.

Table 1: Planned Nonclinical Studies

Study Category	Duration or Type of Study	Route of Administration	Test System	Test Article	GLP[a]
Metabolism	Metabolite Profiling[b]	Dermal, Oral	Human, Minipig, Rat, & Rabbit Plasma	Ha44 Gel, Ha44	No
General Toxicity	28 days	Dermal	Minipig	Ha44 Gel	Yes

[a] GLP = Good Laboratory Practices.
[b] If the human blood contains a metabolite at levels ≥10% of parent, the plasma of nonclinical species will be analyzed to confirm suitability of the animal model to assess exposure to any major human metabolite.

Does FDA agree that the nonclinical program outlined in Questions 8 and 9 sufficiently characterize the safety of Ha44 Gel (0.74%) for the topical treatment of head lice in adult and pediatric subjects as young as to 6 months of age and that no additional nonclinical studies are required to support the approval of the 505(b)(1) NDA?

Response:
The nonclinical program outlined in Questions 8 and 9 appears acceptable to support a 505(b)(1) NDA submission. The final determination concerning the adequacy of the conducted nonclinical studies to support the safety of your drug product will be made after review of the submitted nonclinical final study reports, including study (b) (4) 0005 which was not included in the submission sent on 6-21-12. In addition, we request that you submit a summary of the literature concerning the pharmacological effects of bipyridyl compounds in general and the role of metalloproteases in normal physiological processes to support the safety of your drug product.

Clinical Pharmacology

Question 19a:
In order to assess systemic exposure and safety of Ha44 Gel in the youngest age group planned for licensure, Hatchtech plans to conduct a pediatric safety and PK study.

a. Is the design of the proposed PK study satisfactory with respect to age ranges, number of subjects, open-label design, and inclusion and exclusion criteria?

Response:

1. You should revise your enrollment criteria to include subjects with at least 3 live lice as per your Phase 3 study plan.
2. We recommend that you stratify enrollment by age ranges (e.g. 6 - 12 months, 1 - 2 years, and 2 - 3 years) to ensure that there is sufficient number of subjects in the lowest age range enrolled in this trial.
3. You should ensure that there are at least 16 evaluable subjects.
4. We recommend that you use the to-be-marketed formulation in this trial.
5. We recommend that you evaluate the systemic exposure of benzyl alcohol in this trial.

Question 19b:

b. Does FDA have any comments on the sampling schedule or planned pharmacokinetic analysis?

Response:

The proposed PK sampling plan appears reasonable.

Question 20a:

For the maximal use study, Hatchtech proposes to evaluate the safety and PK of the planned labeled dose of Ha44 Gel in children.

a. Is the design of the proposed maximal use study satisfactory with respect to age ranges, number of subjects, and inclusion and exclusion criteria?

Response:

1. Revise your inclusion criteria to include subjects with at least 3 live lice as per your Phase 3 trial plan.
2. You have proposed to administer 200 mL of the formulation to the hair and scalp in all subjects. It is unclear if administration of this amount will be feasible in the pediatric population in the lower age range due to hair not long enough to warrant application of this amount. Alternatively, you could consider applying enough formulation to saturate the scalp and hair and record the amount of formulation used per subject.
3. You should ensure that sufficient number of subjects in the lowest age range is enrolled in this study (e.g. via stratification of enrollment by age). You should also ensure proper representation of sex and race in the maximal use PK trial.
4. We recommend that you use the to-be-marketed formulation in this trial.
5. We recommend that you evaluate the systemic exposure of benzyl alcohol in this trial.

Question 20b:

b. Does FDA have any comments on the sampling schedule or planned pharmacokinetic analysis?

Response:

The proposed PK plan appears to be reasonable.

Additional Clinical Pharmacology Comments

1. You should characterize the metabolic pathway of Ha44 in humans and address the potential for drug-drug interactions. For further information, you are referred to *"Draft Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* February 2012.
2. You should characterize the Absorption Distribution Metabolism and Excretion of Ha44.

Addendum:
The Agency recommends that the sponsor determine the route(s) of elimination and metabolic pathway of Ha44. It is anticipated that systemic exposure in pediatrics (particularly the younger subjects) will be similar to or higher than that to be evaluated in the thorough QT study. It is important to understand the route of elimination and metabolic pathways of this new molecular entity (NME) to assess the potential for drug interactions and/or intrinsic factors (e.g., hepatic or renal impairment) that may lead to increased systemic exposure of the drug.

Clinical/Biostatistics

Question 10:
The proposed indication for Ha44 Gel is (b) (4) treatment of head lice infestation in patients 6 months of age and older." Does FDA have any comments regarding this proposed indication?

Response:
We understand you to be pursing an indication for your product for treatment of head lice infestation in patients 6 months of age and older. The recommended dose would be conveyed in the Dosage and Administration section of product labeling. The final wording of labeling will be determined during the review of your NDA.

Question 11:
Given that most head lice products require two applications and the strong tendency for over-treatment in this indication, Hatchtech wishes to avoid the unnecessary exposure of a second application by providing provide reassurance to both prescribers and the parents of children with head lice that a single application of Ha44 Gel is sufficient for effective treatment. Although it may be self-evident to those who know the life-cycle of head lice that clinical significant ovicidal activity logically follows from the demonstration of effectiveness after a single treatment, the abundance of other products requiring more than one application and the proclivity of parents to over-treat to ensure eradication of head lice and the social stigmatization attached to this condition, would be advantageously countered by emphasis in the labeling on the sufficiency of one application and the evidence underpinning this assertion. In addition to Phase 2 clinical data in which success with one application demonstrates the consequence of successful, relevant ovicidal activity, (b) (4) .

(b) (4)
to advise against more than one routine application, including any suggestions by FDA for additional studies.

Response:

(b) (4)
will be a review issue.

Question 12:
Based on the Phase 2 data for Ha44 Gel, a single application of Ha44 Gel 0.74% w/v for 10 minutes has been selected for the Phase 3 pivotal studies in children and adults. Does FDA concur?

Response:
Based on the summary data submitted in the meeting package, the selection of a single application of your drug product for 10 minutes appears to be acceptable.

Question 13:
The proposed Phase 3 study is a randomized, double-blind, 2-arm, vehicle-controlled study of Ha44 Gel, 0.74% w/v. Does FDA have any comments regarding the study design?

Response:
You propose to conduct two Phase 3 trials with identical protocols. We have the following comments regarding the proposed protocol(s):

- Phase 3 clinical trials should be multicenter, well-controlled, randomized and geographically diverse. Geographical diversity is important because resistance patterns vary by locale.

- Since accurate assessment of the primary efficacy variable, absence of live lice, is dependent (at a minimum) on adequate assessor training and sufficient time for examination, then the protocol should specify the minimum time required to evaluate the scalp (actual time should be documented on the CRF).

- The protocol stated that the randomization would be stratified by household strata (≤3 vs. >3 subjects per household). However, whether this stratification factor is the most relevant factor will need to be determined. Our preference is to assess the treatment effect by site so as to check the site-to-site variability. As such, study sites should enroll a minimum number of subjects per treatment arm per site (e.g. 8 subjects per treatment arm per site) so that estimates of treatment effect are meaningful. The analysis should follow randomization (e.g. CMH test stratified by site) and your protocol should also plan to test treatment-by-site interaction to address such interaction if it arises, by proposing a sensitivity analysis to ensure that efficacy results are not driven by extreme investigative

sites. In addition, the protocol should pre-specify an algorithm for pooling small sites if actual enrollment does not meet the minimum number of subjects per site. Furthermore, the protocol should specify the number of sites and whether the sites will be in the U.S.

- Your proposed secondary endpoints are to be evaluated at multiple time points that would yield a total of 7 secondary endpoints. Secondary endpoints intended for a labeling claim should be clinically meaningful, limited in number and adjusted for multiplicity.

- For the primary imputation method, you stated that subjects without follow-up lice evaluations at the Day 14 visit will be considered as treatment failures. As there is no single universally acceptable approach for handling missing data, we recommend that you refer to the recent publication *"The prevention and treatment of missing data in clinical trials"* by the National Academies. Further, propose sensitivity analyses so as to ensure that efficacy results are not driven by the imputation method used.

- You proposed to power the Phase 3 trials based on your completed Phase 2b trial. While the trials might be powered for superiority over vehicle, for establishment of an efficacy claim, the trials will need to achieve a certain level of efficacy that is clinically meaningful.

- As the population in the Phase 2 trial (age 2 and above) differs from that proposed for the Phase 3 trials (6 months of age and older), and because the Phase 2 trial was only conducted in 2 centers, you should consider the impact of these factors when powering the Phase 3 trials.

Question 13a:
a. Use of a vehicle control

Response:
Your proposal to use a vehicle- control in your Phase 3 trial(s) to establish the safety and efficacy of Ha44 is acceptable.

We note that your vehicle contains (b) (4) benzyl alcohol, which is the active ingredient in an approved product for the treatment of head lice infestation, and we note that a response rate of 23.4% was observed in the vehicle arm of your Phase 2b trial. Please provide your interpretation of this data, and address the function of the benzyl alcohol in your formulation.

Question 13b:
b. Population ≥ 6 months of age with active head lice infestation

Response:
The study population as defined by the inclusion criteria (e.g. index subjects must have at least 3 live lice and household members must have at least 1 live louse) is acceptable. However, based on the data submitted in the meeting package, systemic exposure to Ha44 increased as the subject's age and weight decreased and because the higher exposure is anticipated in the

population 6 months – 2 years, you might consider completing the thorough QT (TQT) study before initiating the Phase 3 clinical trials (which would enroll subjects 6 months of age). Refer to the response to Question 13e, regarding cardiac safety monitoring.

Question 13c:
c. Home administration of a single dose of Ha44 Gel 0.74% w/v or vehicle with an administered volume of up to 200 mL

Response:
Home administration of a single dose of Ha44 Gel 0.74% w/v or vehicle is acceptable as it reflects real world conditions.

Question 13d:
d. Sample size

Response:
Refer to the general comments above.

Question 13e:
e. Safety assessments

Response:
The proposed safety monitoring [including physical examinations, vital signs, urine pregnancy testing, active local safety assessments (e.g. irritation scores from the scalp, skin and eyes) and adverse events] is acceptable.

In the absence of complete data from the TQT trial and maximal use pharmacokinetic trial in the youngest pediatric subjects, systemic safety assessment should include cardiac safety monitoring (e.g. 12 lead ECG at baseline and steady state) and laboratory evaluation (e.g. hematology and chemistry).

Clarify your rationale for requiring highly effective methods of birth control for female subjects of child bearing potential and excluding pregnant subjects during the Phase 3 trial(s). Per protocol, an adult is required to administer (by hand and massaged until saturated) the study drug to household member <18 years of age and it is recommended that all household members >18 years of age have study drug administered by another adult. Address how you intend to limit exposure of caregivers who are females of child bearing potential.

Question 13f:
f. Primary efficacy endpoint

Response:
Your proposal to assess efficacy as the proportion of index subjects who are lice-free at all follow-up visits through the Day 14 visit is acceptable.

Question 13g:
g. Management of treatment failures

Response:
You propose to treat all subjects with live lice at any follow-up visit with rescue therapy (RID). Your proposed management of treatment failures is acceptable, however, RID should be used as labeled. Because RID is recommended for the treatment of head lice infestation in patients age 2 years and above, your protocol should also include rescue therapy for subjects age 6 months to 2 years of age.

Question 14:
Ha44 Gel has been well tolerated in Phase 1 and 2 studies in a total of 133 subjects with head lice. Hatchtech proposes a total safety database for the NDA submission of approximately 950 subjects, of which approximately 600 will receive Ha44 Gel. Does FDA concur with the size of the total safety database?

Response:
Your proposal appears to be reasonable. The adequacy of the safety database for the proposed indication and the intended population will be a review issue.

Question 15a:
In regard to the pediatric development of Ha44 Gel, the Phase 2b study included children down to 3 years of age. Hatchtech proposes to conduct the Phase 3 pivotal studies in subjects with active head lice infestation ≥ 6 months of age.
a. Does FDA have any comments regarding the pediatric development plan for Ha44 Gel?

Response:
See response to Question 13b.

Question 15b:
b. Hatchtech plans to request a pediatric waiver for the 0-6 month age group. Does FDA concur with this proposed pediatric waiver?

Response:
A waiver for subjects under 6 months of age appears reasonable. Submit your request for a partial waiver and your rationale according to 21 CFR 314.55(c)(3) with your NDA.

Question 16:
Hatchtech plans to conduct a cumulative irritation study since no clinically significant skin irritation has been reported in the clinical studies to date or is predicted by repeat dose dermal nonclinical studies. Does FDA have any comments regarding this study?

Response:
The meeting package contains limited information regarding the planned study. You are encouraged to submit the full protocol prior to conducting the study with sufficient time for Agency review.

Question 17:
Since Ha44 Gel is planned as a single application treatment for head lice, (b) (4)

Response:
(b) (4) we recommend that you conduct a dermal sensitization study for the following reasons:

- Ha44 is a new molecular entity
- non-clinical sensitization studies are poorly predictive of human sensitization
- your product may be applied more than once (re-infestation)
- dermal safety studies are provocative: they are conducted under exaggerated (occlusive) conditions, which allow evaluation for cutaneous safety signals to be accomplished with fewer subjects (e.g. 200 subjects for sensitization), than would be needed under normal (non-occlusive) conditions

Question 18:
Since no ingredients in the Ha44 Gel product absorb light in the range of 290 – 700 nm, Hatchtech proposes a waiver for the requirement of the photoallergy and phototoxicity dermal studies. Does FDA have any comments regarding this proposed waiver?

Response:
A waiver of phototoxicity and photoallergenicity studies appears reasonable. Submit a waiver request to the NDA at the appropriate time.

Administrative Comments

1. Comment shared in this document are based upon the contents of the briefing document, which is considered to be an informational aid. Review of information submitted to the IND or BLA might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA

should be submitted directly to the project manager.

3. 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).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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

/s/

SUSAN J WALKER
08/07/2012