CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208694Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA CMC Meeting
Meeting Date and Time:	February 19, 2015 9:00 AM to 10:00 AM EST
Meeting Location:	Face to Face
Application Number:	IND 108558
Product Name:	Cetirizine HCl Ophthalmic Solution, 0.24%
Indication:	Treatment of ocular itching associated with allergic conjunctivitis.
Sponsor/Applicant Name:	Aciex Therapeutics, Inc.
Meeting Chair:	Thomas Oliver, Ph.D.
Meeting Recorder:	Navdeep Bhandari, Pharm.D.

FDA ATTENDEES

Wiley Chambers, M.D.	Supervisory Medical Officer
William Boyd, M.D.	Clinical Team Leader
Thomas Oliver, Ph.D.	Acting Division Director
Anamitro Banerjee, Ph.D.	CMC Lead
Shrikant Pagay, Ph.D.	Chemistry Reviewer
Neal Sweeney, Ph.D.	Microbiology Reviewer
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager

SPONSOR ATTENDEES

Nicox/Aciex Therapeutics, Inc.

Michael V.W. Bergamini, PhD	Chief Scientific Officer, Nicox SA, of which Aciex Therapeutics Inc. is a wholly owned subsidiary
[redacted] (b) (4)	
Gerald W. St. Peter	General Manager of Aciex Therapeutics, Inc.

Ora, Inc.

Matthew Chapin	VP, Corporate Development
Jeffrey Coderre, PhD	Director, Regulatory Writing (by phone)
Hal Patterson	Vice President, Quality Assurance, Ora, Inc. (by phone)

1.0 BACKGROUND

The Sponsor has evaluated cetirizine hydrochloride as a treatment for allergic conjunctivitis. A Physician investigational new drug application (IND) was originally filed for a

(b) (4)

An End-of-Phase 2 meeting was held with FDA on September 19, 2011. A subsequent meeting was held on March 11, 2013 to discuss the existing preclinical and clinical data package, and to obtain clarification regarding the contents of the planned 505(b)(2) NDA submission. At the latter meeting, the Agency recommended the Sponsor request a pre-NDA meeting to discuss potential CMC issues.

A recent Pre-NDA meeting was held with FDA related to clinical matters on December 16, 2014.

2.0 DISCUSSION

The objectives of the meeting are to discuss the CMC aspects of the development program for Cetirizine Ophthalmic Solution 0.24%.

The Agency sent preliminary responses on February 19, 2015 to the Sponsor. The Sponsor asked to focus on all subparts of question 3, and questions 6, 7, and 8.

3.0 QUESTIONS

Question 1:

Does the Agency agree that the proposed drug substance specification is sufficient for control of cetirizine HCl drug substance for NDA approval?

FDA Response

From the product quality microbiology perspective the proposed drug substance specification is sufficient.

The proposed specifications for the drug substance appear reasonable at this time. However, the final determination on the adequacy of the proposed cetirizine HCl drug substance specifications will be made during the NDA review.

Discussion: This topic was not discussed.

Question 2a:

Does the Agency agree that the proposed specification is sufficient for control of cetirizine ophthalmic solution, 0.24%?

FDA Response

From the product quality microbiology perspective the proposed drug product specification is sufficient.

The proposed specifications for the drug product appear reasonable at this time. However, the final determination on the adequacy of the proposed drug product specifications will be made during the NDA review.

Question 2b:

In particular, Aciex wishes to confirm that an endotoxin test is not required for this dosage form and intended indication (i.e., a topical ophthalmic solution intended for the treatment of ocular itching associated with allergic conjunctivitis).

FDA Response

Drug product bacterial endotoxin testing is not considered necessary for the proposed combination of dosage form (topical ophthalmic solution) and indication (treatment of ocular itching associated with allergic conjunctivitis).

Discussion: This topic was not discussed.

Question 3a:

Based on media reports (Attachment 1) indicating that (b) (4) has received 483 observations in an FDA inspection due to, among other things, data integrity issues, does the Agency have any comments on the strategy of seeking approval for (b) (4) as one of the drug substance suppliers?

FDA Response

All the manufacturing and testing facilities involved in the manufacture and controls of the proposed drug substance and drug product need to be in good GMP standing and be ready for inspection at the time of NDA submission.

Question 3b:

Are the equivalency attributes and stability program as laid out above, adequate to support (b) (4) as a second source of drug substance without impact on the PDUFA date?

FDA Response

The meeting information package described the (b) (4) ophthalmic bottles supplied by (b) (4) as being "comparable (identical)". If the critical dimensions of the (b) (4) and (b) (4) container/closure component interface surfaces are not identical then container/closure integrity should be demonstrated for the container/closure system from the new supplier.

One of the outcomes of the review process is to have meaningful drug substance retest dates and drug product expiries. In situations, where the applicant has sufficient drug product stability data sourced from one drug substance site and smaller amount of drug product stability data sourced from a second drug substance site, we strongly recommend good communication between the applicant and the sites involved. Note that in such situations, both the sites need to be in good GMP standing and be ready for inspection at the time of NDA submission. If good communication is not obtainable, we recommend that there is adequate drug product data generated from drug substance manufactured at each of the sites.

Table 3 in the submission shows one lot of drug substance manufactured by (b) (4) used in Phase 2 studies. Please list in the NDA all the drug substance lots, corresponding drug product batches and container closures, used in the clinical trials, throughout the clinical development program and proposed commercially. Also include other relevant information such as lot sizes of the drug substance and batch sizes of the drug product (number of vials filled) throughout the clinical development program.

Question 3c:

Aciex seeks permission to submit additional stability data for the drug product produced from (b) (4)-sourced drug substance and filled in (b) (4)-sourced container/closure systems during review to support establishing shelf life. Will the submission of data during NDA review impact the PDUFA date?

FDA Response

We strongly recommend providing the necessary amount of stability data in the original NDA to support the proposed shelf life. Three months of drug product stability data (b) (4) sourced drug substance and (b) (4) sourced container) at the time of submission would be acceptable if the (b) (4) drug substance site is found acceptable during the NDA review. If the (b) (4) site is the only drug substance site in the NDA, we recommend at least 12 months of long term stability data from 3 drug product batches using drug substance sourced from (b) (4). Refer to 3b response.

Question 3d:

Do the stability data sets, described above in Table 3, support a (b) (4) month shelf life for the (b) (4) 5 mL fill (in a 7.5 cc bottle)?

FDA Response

Shelf life assessment takes into consideration the amount and quality of the data submitted in the NDA. The drug product expiry will be determined during the NDA review.

Question 3e:

If (b) (4) ultimately is not an approvable source of drug substance, does the comparability information and stability data support (b) (4) as the sole source of drug substance with the same shelf life and same PDUFA date?

FDA Response

If (b) (4) is not an approved source of the drug substance, the data generated at this facility may not be considered during the evaluation of the NDA.

Discussion: The Sponsor will not seek approval of (b) (4) as a commercial drug substance supplier for the proposed NDA. The sponsor plans to utilize (b) (4) as the drug substance supplier but will seek a secondary supplier post approval. New stability batches with (b) (4) material will be submitted with the NDA. The Sponsor commented that there has been an independent audit of the (b) (4) facility and it was shown that the cetirizine was not involved in any of the 483 issues identified. The Sponsor has produced (b) (4) drug substance verification data using compendial methods. The agency is willing to review this information in the NDA. As any (b) (4) data would be supportive in nature, the applicant is encouraged to make a case (in the NDA) for why the (b) (4) data can be used to support their application, including any testing the Sponsor performed on (b) (4) batches.

The Agency stated that if (b) (4) is the only drug substance manufacturing site then more than the 3 months of drug product stability data sourced from that site would be needed.. The Agency recommended that 12 months of drug product stability data (using (b) (4) drug substance) be submitted in the proposed NDA (refer to Question 3c).

The Agency asked what amount of drug substance data had (b) (4) generated. The Sponsor believes that (b) (4) has at least 24 months long term data due to test dates of 2006 and 2007 and believes there may be more than 60 months of drug substance data. The amount of drug product stability data piece is what is lagging. Drug product lots are being made with 3 different batches of drug substance.

The Applicant stated that cetirizine is currently approved as tablets and an oral solution. The Agency asks if there has been a written request regarding pediatric data. The applicant stated no, but, the applicant is still thinking about their approach along this avenue.

The Sponsor wants to confirm that the phase 3 clinical trials made from (b) (4) are acceptable for clinical review. The Agency responds that this is not an issue.

Question 4:

Does the Agency agree that a comparability protocol submitted in the NDA for review and comment will be an acceptable means to describe and submit these planned post approval changes?

FDA Response

A Comparability Protocol is an acceptable method of describing the anticipated container/closure post approval changes. However, if either the composition of the container components or the critical dimensions of container/closure component interface surfaces are not identical to those approved in the NDA, then container/closure integrity should be demonstrated for the new container/closure systems. Provide clear diagrams. For the diagrams provided it was hard to determine differences; please consider making the diagrams larger and more legible.

While the attributes listed in the background information for Question 4 are reasonable, the comparability protocol will be reviewed in the NDA to determine if there are any concerns for the proposed post approval changes.

Discussion: This topic was not discussed.

Question 5:

Does the agency agree that the photostability study described in Table 29 will support the labeling for the (b) (4) 5 mL/7.5 cc (b) (4) container closure systems?

FDA Response

The test attributes provided in Table 29 appears to be appropriate for photo stability study.

Discussion: This topic was not discussed.

Question 6:

Does the Agency agree that these data will support labeling requirements for both the (b) (4) 5 mL/7.5 cc container closure systems submitted for approval?

FDA Response

The proposal for the photo stability and freeze-thaw study is acceptable with one of the fill volumes using the drug substance sourced from an acceptable supplier.

Discussion: The Sponsor asked in regards to Question 7 whether the currently available leachable study on (b) (4) and supplemented with (b) (4) data would be acceptable. The Agency responded that it should be acceptable. The FDA asked what temperature the Sponsor was using

for accelerated data. The Sponsor responded that the study is being conducted at (b) (4) degrees for (b) (4) months. The Agency asked about the impurity profile of the (b) (4) drug substance vs the (b) (4) drug substance. The Sponsor responded that the impurities are all below USP impurity specification (page 21 of briefing document referenced).

Question 7:

Does the Agency agree with the strategy of not performing a leachables study on stability?

FDA Response

We do not agree with your proposal. Leachable study for one primary stability batch should be included in the stability study protocol for the drug product (preferably the 5 mL fill). Extractable study test results should be included in the NDA with any available leachable study data from development and stability batches.

Discussion: See discussion for question 6 above.

Question 8:

Aciex will submit the following documentation to support the sterility assurance of the product:

a) Product-specific (b) (4) including bacterial retention, extractables data, compatibility with the drug product, and integrity testing (b) (4)

b) Sterilization of components (b) (4) sterilization of the container closure systems).

c) Sterilization of process equipment.

d) Facility design and room classification description.

e) Environmental monitoring program and historical data.

f) Media fills appropriate for the Cetirizine Ophthalmic Solution, 0.24% process.

g) Sterility testing methods and validation for Cetirizine Ophthalmic Solution, 0.24%.

h) Container closure integrity studies.

i) Evidence of written procedures.

Does the Agency have any comments on the completeness of the list described above for demonstration of sterility assurance for the NDA?

FDA Response to Question 8: In addition to the nine items listed for documentation of sterility assurance, the results from drug product antimicrobial effectiveness testing (i.e. USP <51>) should be submitted in the NDA. Antimicrobial effectiveness test results for product formulated

with less than the minimum benzalkonium chloride preservative content ((b) (4)% of the (b) (4) mg/mL) should be submitted.

Additionally, please refer to the 1994 FDA Guidance for Industry: "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products Center" for a comprehensive description of sterility assurance information expected for the NDA submission:
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf)

Discussion:

The Applicant requested confirmation that the currently available leachable data conducted on a single lot on stability that was made with (b) (4) drug substance and supplemented with (b) (4) drug product would be acceptable?

In general, the Agency stated the Sponsor should use (b) (4) material for studies to support the NDA. The Applicant can use accelerated material for storage conditions and six months for photostability studies. Additional data from (b) (4) will be provided to FDA as well.

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

/s/

OLGA SIMAKOVA
03/22/2015
Signed for Navdeep Bhandari

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

108558

MEETING MINUTES

Aciex Therapeutics, Inc.
c/o Ora Inc.
Attention: Donna Welch
Sr. VP & COO
300 Brickstone Square
Andover, MA 01810

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cetirizine ophthalmic solution 0.24%.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2014. The purpose of the meeting was to discuss the clinical program and contents for a 505(b)(2) application for the treatment of allergic conjunctivitis..

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 June Germain, Safety Regulatory Project Manager at 301-796-4024.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
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:	December 16, 2014, 1:00-2:00 PM, EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 108558
Product Name:	Cetirizine ophthalmic solution, 0.24%
Indication:	Allergic conjunctivitis
Sponsor:	Aciex Therapeutics, Inc. c/o Ora, Inc.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Judit Milstein

FDA ATTENDEES
Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William M. Boyd, Clinical Team Leader, DTOP
Martin Nevitt, Clinical Reviewer, DTOP
Andrew McDougal, Pharmacology/Toxicology Reviewer, DTOP
John Sinclair, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Yongheng (Eric) Zhang, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
Philip Colangelo, Clinical Pharmacology Team Leader, DCPIV
Abel Eshete, Biostatistics Reviewer, Division of Biometrics IV (DBIV)
Yan Wang, Biostatistics Team Leader, DBIV
Judit Milstein, Chief Project Management Staff, DTOP

SPONSOR ATTENDEES
Michael V.W. Bergamini, Chief Scientific Officer, Nicox SA
(b) (4)
Mark B. Abelson, Chief Scientific Officer, Ora, Inc.
Donna Welch, Senior VP, Chief Operating Officer, Ora, Inc.

Mathew Chapin, VP, Corporate Development, Ora, Inc.
Jeffery Coderre, Director, Regulatory Writing, Ora, Inc.
Paul Gomes, VP, Allergy Department, Ora, Inc.
Kirl Bateman, Director, Biostatistics, Statistics and Data Corporation
Misoo C. Ellison, Sr. Biostatistician, Statistics and Data Corporation

BACKGROUND

The Sponsor has evaluated cetirizine dihydrochloride for the treatment of ocular itching associated with allergic conjunctivitis. Since the March 11, 2013, meeting with the Agency, the Sponsor conducted three additional clinical studies: Study13-100-0002, which evaluated the onset of action (15 minutes) and duration of action (8 hours); Study 14-100-007, which evaluated pharmacokinetics and safety, and Study 14-100-006 which evaluated safety in adults and pediatric subjects 2 years and older.

The Sponsor requested this meeting to discuss the completed clinical and non-clinical studies and is seeking the Division's concurrence on the contents of a planned 505(b)(2) NDA application for cetirizine ophthalmic solution, 0.24%.

Preliminary comments on the questions posted in the briefing document dated November 17, 2014 were issued on December 11, 2014.

Based on these responses, the Sponsor indicated that during the meeting they would like to further discuss the supportive analyses of both Study 12-100-0006 and 13-100-0002, as well the combined dataset in order to make the case that the totality of the data supports an 8 hours duration of action, taking into consideration the safety data for cetirizine and its risk/benefit ratio. The meeting discussions focused on Questions 1 and 2 and a clarification on Question 3.

DISCUSSION

For the purposes of these minutes, the questions posted by the Sponsor in their briefing document are in **bold** format, the Division's preliminary responses are in *italics* and the meeting discussions in normal font.

Question 1.

The Sponsor believes that the clinical data are sufficient to warrant submission of an NDA for cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis. Does the Agency concur?

> *FDA Response: Yes; however, based on the summary information provided in the meeting package, study12-100-006 does not appear to demonstrate clinically significant efficacy at 8 hours. The duration of effect is unclear at this time.*
>
> Meeting Discussion:
> The Sponsor provided a handout that summarized the 8 hour ocular itching data from the two pivotal studies in both the ITT and PP populations, where the mean treatment

differences in the ITT populations range from 0.84 to 0.99. Also included in the hand out was a subgroup analysis of the mean treatment differences in the more severe responders in baseline itching scores. The Sponsor made the case that the 15 minute onset of action itching scores always meet the criteria for clinical effectiveness; that the 8 hour ocular itching scores are consistently in the upper 0.9 range; that analysis of subgroups (PP population, severe responders) produces mean differences at 8 hours in excess of the 1-unit threshold; and that together with the significant benefit/risk profile of cetirizine, this product represents a valuable addition to the agents available to treat ocular itching.

The Division responded that onset of action was not being questioned. It reiterated that the effectiveness decreases with time and that at 8 hours post administration the ocular itching scores consistently fall short of the established criteria for clinical effectiveness: ≥ 1-unit in 2 of 3 post-CAC time points. The Division further pointed out that these criteria set for demonstration of clinical effectiveness using the CAC model have been in place for many years and were the key to validation of the usefulness of the CAC model. The Division recommended that the Sponsor submit an NDA, where the totality of the data would be evaluated, but the effectiveness at 8 hours, and thus a proposed label claim for BID dosing, would be a review issue.

The Sponsor summarized some of the early studies with a lower cetirizine concentration formulated at a lower pH that did show greater than 1 unit differences at 16 hours, and asked whether those early studies, together with one additional study using the low-pH formulation, would be sufficient for NDA submission. The Division responded that the early data would have to be re-evaluated, but that those studies had low numbers of subjects per arm, and in one case did not include an onset of action arm. The Division cautioned that it was not obvious if one more study would be sufficient.

The Sponsor initiated a general discussion of possible proposed product label wording that could take advantage of the 8 hour effectiveness in more severe responders, the assumed (but not demonstrated) effectiveness at 6 hours, and the long-term safety of the product (demonstrated with BID dosing, (b) (4) dosing). The Division stated that there are no long-term safety data to support repeated dosing at 6 hours intervals and if the Sponsor should decide to conduct an additional safety study supporting a claim for "BID, every (b) (4) 8 hours" treatment, this study would be considered as supportive information.

Question 2.

The Sponsor believes that the existing clinical safety data are sufficient to submit an NDA for cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis in subjects 2 years of age and older? Does the Agency concur?

FDA Response: See response to Question #1 above. Based on the summary information provided in the meeting package, there appears to be adequate safety data to file an NDA once there is adequate clinical data to support efficacy.

Meeting Discussion: See Question 1

Question 3.

Does the Agency have any comments on the approach for ISS/ISE study integration and analyses?

• Are the pooling and analyses strategies acceptable?

FDA Response: Yes. Although we do not object to the pooling of the data for preparing the ISE and ISS, we expect to see the efficacy summaries for each pivotal study provided separately in their individual study reports.

Please provide the safety summaries from the studies which used lower concentrations of cetirizine.

• Are the planned subgroup analyses sufficient and acceptable?

FDA Response: No. The Agency recommends the subgroup analyses include analyses by iris color. If applicable, include analyses by geographic regions, i.e. US versus the rest of the world.

Meeting Discussion: The Sponsor agreed to provide in the NDA, the safety summaries and full CSRs from all studies. The Sponsor also agreed to include a subgroup analysis by iris color.

Question 4.

The Sponsor plans to submit raw data in SDTM format for the individual studies included in the ISE/ISS, and the Sponsor also plans to submit analysis datasets in ADaM format for the individual studies included in the ISE/ISS. Pooled analysis datasets in ADaM format for the ISE and ISS will also be submitted. A Define.xml file will be included with each SDTM and ADaM submission.

Is this data submission strategy acceptable?

• We will follow the current eCTD guidance (version 2, dated June 2008) and portable document format (PDF) specifications (version 4.0, dated September 2014) for submission of the NDA. We welcome any comments regarding the submission that would facilitate FDA's review of the application.

FDA Response: Acceptable. The Agency has no additional comments at this time.

Meeting Discussion: None

Question 5.
The Sponsor believes that the nonclinical studies, utilizing topical ocular dosing, conducted by Aciex, as well as a summary of safety pharmacology and systemic toxicology data on cetirizine in the public domain, are adequate to support review of the nonclinical safety of cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis. Does the Agency concur?

FDA Response:
Yes, FDA concurs with your general approach. The adequacy of the data will be a review issue. Please note:

a. *Neither a summary basis of approval (SBA) nor published FDA discipline reviews can be relied upon to support a 505(b)(2) application. Pending review of your comparative PK data, however, reliance on the Agency's finding of safety and effectiveness for Zyrtec® Hives Relief, Zyrtec®, Zyrtec® Allergy, and/or Zyrtec-D® 12 Hour (Zyrtec) may be appropriate. In the nonclinical Pharmacokinetics summary, please provide a summary of comparative PK data to establish that such reliance is scientifically justified.*
b. *The comment from the March 11, 2013 meeting is reiterated, "Your application should summarize the oral use of cetirizine from the literature, and we recommend that you summarize the applicability or lack of applicability of oral data to your topical ophthalmic formulation."*
c. *Additionally, we have the following comments regarding submission of published literature:*
    i. *The nonclinical summaries are typically organized to address each of the required nonclinical elements (e.g. pharmacology, safety pharmacology, pharmacokinetics, ocular and systemic toxicity following topical ocular dosing, ocular toxicity following oral dosing, genotoxicity, carcinogenicity, fertility, reproductive toxicity). For each element being fulfilled with literature, the relevant data should be adequately summarized within the appropriate subsection of the integrated summary ('Nonclinical Written and Tabulated Summaries'). A copy of each cited article should be provided.*
    ii. *Please note that review articles cannot be relied upon to support an application; the relevant source articles which contain full study data should be provided.*
    iii. *Published data is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.*
    iv. *Please identify any listed drug(s) described in the submitted published literature [e.g. any trade name(s)].*
d. *Please be aware that the publications regarding clinical use of cetirizine (e.g. during pregnancy; related to oculogyric crisis) are generally outside the scope of the*

nonclinical review, but may be important to review of your application. Please ensure that the literature review is up-to-date, and that the data cut-off date is noted.

Meeting Discussion: The Sponsor agreed with the Division's recommendations and no further discussion followed.

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.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on

FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will issue the minutes of the meeting within 30 days

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/s/

WILEY A CHAMBERS
01/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108558

MEETING MINUTES

Aciex Therapeutics, Inc.
c/o Ora, Inc.
Attention: Donna Welch, RN BSN
Sr. Vice President & COO
300 Brickstone Square
Andover, MA 01810

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cetirizine HCl Ophthalmic Solution.

We also refer to the meeting between representatives of your firm and the FDA on March 11, 2013. The purpose of the meeting was to discuss the clinical program and the expectations regarding the contents of a 505(b)(2) NDA for Cetirizine for the treatment of allergic conjunctivitis.

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 Ms. June Germain, Senior Regulatory Project Manager at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: guidance

Meeting Date and Time: March 11, 2013, 12:00 PM TO 1:00 PM EDT
Meeting Location: Teleconference

Application Number: IND 108558
Product Name: Cetirizine HCl Ophthalmic Solution

Indication: treatment of allergic conjunctivitis
Sponsor/Applicant Name: Ora, Inc. On behalf of Aciex Therapeutics, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: June Germain, MS

FDA ATTENDEES

Renata Albrecht, MD	Director
Wiley Chambers, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Lucious Lim, MD	Medical Reviewer
Jennifer Harris, MD	Medical Reviewer
Martin Nevitt, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Sonal Wadhwa, MD	Medical Reviewer
Yan Wang, PhD	Statistical Team Leader, OB/DBIV
Abel Eshete, PhD	Statistical Reviewer, OB/DBIV
Lori Kotch, PhD	Pharmacology/Toxicology Team Leader
Andrew McDougal, PhD	Pharmacology/Toxicology Reviewer
Eric Zhang, PhD	Clinical Pharmacology Reviewer, DCP4
Phillip Colangelo, PharmD PhD	Clinical Pharmacology Team Leader, DCP4
Balajee, Shanmugam, PhD	Product Quality Team Leader, ONDQA
Celia Cruz, PhD	Product Quality Reviewer
June Germain, MS	Senior Regulatory Project Manager

SPONSOR ATTENDEES

Mark Abelson, MD	Ophthalmologist, Ora
Donna Welch, RN	Sr. VP/ COO, Ora
Matthew Chapin	VP Corporate Development, Ora
Paul Gomes	VP Allergy, Ora
Jeffrey Coderre, PhD	Manager Regulatory Writing, Ora
Hal Patterson	VP Quality and CMC, Ora
Kirk Bateman, MS	Director, Biostatistics, SDC

Les Kaplan, PhD	Chairman of the Board, Aciex Therapeutics
Tom Cavanagh	President, Aciex Therapeutics
[redacted]	(b) (4)

1.0 BACKGROUND

On December 12, 2012, Ora, Inc. on behalf of Aciex Therapeutics, Inc. requested a Type C meeting to discuss the proposed clinical program and the expectations regarding the contents of a 505(b)(2) NDA for Cetirizine for the treatment of allergic conjunctivitis.

The face to face meeting was granted for March 11, 2013. The preliminary comments were emailed to the sponsor on March 6, 2013. On March 8, 2013 the sponsor indicated that they were seeking further clarification on questions 2, 8 and 12 at the meeting and requested the meeting be converted to a teleconference.

2.0 DISCUSSION QUESTIONS

Q1. Is the package of completed studies with cetirizine sufficient to support efficacy for the intended indication of prevention of itching associated with allergic conjunctivitis with BID dosing, or would you require further data?

FDA Response: *The package is not sufficient. To demonstrate efficacy, the Agency expects cetirizine to be statistically and clinically superior to placebo in at least two adequate and well-controlled trials. Based on the summary information provided in this meeting package, it appears that the effect of cetirizine on ocular itching has worn off by 16 hours post-challenge and is only marginally effective 8 hours post-challenge. To demonstrate clinical significance in a CAC study, the difference between treatment groups should be at least one unit on a scale from 0-4 at a majority of the time points evaluated. This endpoint should be replicated in at least two trials. It is recommended that an additional study be conducted which demonstrates continued efficacy at 8 hours.*

Aciex Email Reply March 8, 2013: No further discussion required.

Q2. If a second pivotal study is needed, would results similar to, or better than, the result in the 8-hr CAC study (12-100-0006) be acceptable?

FDA Response: *See response to Question #1. An additional study demonstrating greater efficacy than study 12-100-006 is recommended or consideration should be given to demonstrating a duration of efficacy of 6 hours.*

Aciex Email Reply March 8, 2013: We thank the Agency for this recommendation and will give serious consideration to including a duration of efficacy visit at 6 hours. We assume that the 8-hr efficacy data from Study 12-100-0006 would still serve as the first pivotal trial. If the second, multi-center trial shows clinically significant results at 6 hours, we would propose

(b) (4)

(b) (4) Would this be acceptable?

Meeting discussion:

- The sponsor asked whether is would be acceptable if the second, multi-center trial showed clinically significant results a (b) (4) hours, (b) (4) The Division stated it would not be acceptable, but instead the (b) (4)
- The Division stated that in order to be labeled BID every 8 hours, the results of the trial should show at least a one unit difference over 8 hours. The Division also noted that if a second trial demonstrated efficacy over both 6 hours and 8 hours then it would probably be labeled 8 hours BID.

Q3. Is the proposed safety study sufficient to complete the safety requirements for NDA?

FDA Response: *The proposed study appears to be sufficient, although you may wish to consider dosing tid to provide an additional option if replicated efficacy can only be demonstrated at 6 hours.*

Aciex Email Reply March 8, 2013: No further discussion required.

Q4. Is the proposed PK study sufficient?

FDA Response: *Yes, the proposed Phase 1 clinical PK study is acceptable from a clinical pharmacology perspective.*

Aciex Email Reply March 8, 2013: No further discussion required.

(b) (4)

Does the Agency agree?

FDA Response: We *disagree. The study reports of both studies should be included in the NDA.*

Aciex Email Reply March 8, 2013: No further discussion required.

Q6. Understanding it is subject to review of the completed dataset and final report by FDA, if there are no unexpected drug-related findings, is the completed chronic ocular toxicology study in rabbits sufficient and acceptable to support the NDA?

FDA Response: *It is not clear that the formulation tested in the ongoing chronic ocular toxicology study in rabbits is the clinical formulation. If the clinical formulation is being tested in the chronic rabbit study, then the chronic rabbit study appears adequate to support an NDA for the indication described in the briefing package (up to twice daily bilateral dosing with 0.24% cetirizine). The adequacy of the submitted nonclinical information to support the proposed 505(b)2 NDA will be a review issue.*

Meeting Discussion:

- The sponsor clarified that the formulation used in the chronic ocular toxicology study was the clinical formulation and is now completed.

Q7. We propose to conduct one additional preclinical study in parallel with the clinical safety study. This preclinical study will be an ADME study with radiolabelled cetirizine product according to the attached detailed outline. Is this proposed study design acceptable?

FDA Response: *Yes, presuming that 0.24% cetirizine will be tested and that the clinical formulation will be used, the design appears adequate.*

Aciex Email Reply March 8, 2013: No further discussion required.

Q8. Is the existing preclinical package (with the conduct of the proposed ADME study) sufficient to complete the preclinical requirements for this product?

FDA Response: An *assessment of melanin binding is expected for the NDA (i.e. either as part of or separate from the ocular pharmacokinetic study). The package otherwise appears adequate to support a 505(b)2 NDA.*

Aciex Email Reply March 8, 2013: We would like to clarify for FDA that the GLP 6month chronic ocular toxicology study was performed in pigmented Dutch belted rabbits. Do we still need to conduct the melanin binding study? If so, would this be an in vitro melanin binding study to satisfy the FDA request?

Meeting Discussion:

- The Division stated that an assessment of melanin binding is expected for the NDA, and that an *in vitro* melanin binding study would suffice.
- The sponsor agreed

(b) (4)

Aciex Email Reply March 8, 2013: No further discussion required.

Q10. Cetirizine, as oral/systemic Zyrtec®, has over thirteen hundred publications in the peer-reviewed literature describing other clinical indications and animal pharmacology. Given that the FDA has a long experience with oral use of cetirizine, Aciex proposes that the literature review to be included in the NDA for the cetirizine (b) (4) ophthalmic solution be limited to ophthalmic dosing of cetirizine. Does FDA agree?

FDA Response: *No. Your application should summarize the oral use of cetirizine from the literature, and we recommend that you summarize the applicability or lack of applicability of oral data to your topical ophthalmic formulation.*

Aciex Email Reply March 8, 2013: No further discussion required.

Question 11. Are the supportive stability data for the (b) (4) fill volume provided in this document and proposed stability plan for the 5mL fill volume for the cetirizine 0.24% ophthalmic solution product sufficient for NDA submission given the expected NDA timeline?

FDA Response: *Stability data for the (b) (4) fill volume from three batches (two of the three batches should be at least pilot scale) can be used as supportive data. The proposed storage conditions (long-term and accelerated) and quality attributes to be tested on stability for the (b) (4) mL fill volume (supportive) and 5 mL (primary batches) appears reasonable. Horizontal orientation of samples may be acceptable if this represents the worst case scenario and should be supported with data from other orientations (inverted and upright). If the NDA will provide for a (b) (4) configuration, this sample configuration should also be placed on stability per protocol outlined for the commercial configuration. Please note that we expect the NDA at the time of submission to include 12-months long-term and 6-months accelerated stability data for three registration batches. Any data submitted during review may or may not be reviewed depending on resources available.*

Aciex Email Reply March 8, 2013: (b) (4) Aciex noted they will conduct a stability study on three batches of drug product in the to-be-used container-closure at both long term and accelerated storage conditions.

Concerning orientation of the stability samples, Aciex plans to propose a study protocol to demonstrate that the horizontal orientation is a suitable worst case orientation. This study protocol will be sent to the FDA for its review prior to initiating this study.

Q12. Freeze-thaw cycling and photostability studies are planned for the (b) (4) 5mL commercial configurations. Each study will use a single batch of cetirizine ophthalmic solution, 0.24%. Are these special stability studies sufficient to support product labeling?

FDA Response: *While the proposal to use one batch for freeze-thaw cycling and photo stability studies appears to be reasonable, we recommend that you refer to ICH Q1B for further guidance especially on the need for additional testing when results are equivocal and on batch selection.*

Aciex Email Reply March 8, 2013: Aciex will conduct a photostability study on one batch each of the (b) (4) and 5mL commercial product as well as control samples in compliance with ICH Q12B. If these study results are equivocal, Aciex will conduct an additional study to address equivocal results. Aciex will conduct a freeze-thaw cycling study to establish whether a caution relating to freezing is required in the product labeling.
Aciex wishes to confirm that no simulated patient use study is required as a special stability study

Meeting discussion:

- Aciex inquired if no simulated patient use study is required as a special stability study.
- The Division agreed it was not.

Additional FDA CMC Comments:

1. *A test for identity should be included in the drug product specification. Please note that per ICH Q6 (A), identification solely based on a chromatographic system is not considered specific. It is recommended that a specific identity method or two chromatographic procedures, where separation is based on different principles be used. Also, propose suitable acceptance criteria for related substances, osmolality, and viscosity. For particulate matter, we recommend setting limits per USP <789>, Table 2. All proposed acceptance criteria should be adequately justified with data.*

Aciex Email Reply March 8, 2013. Concerning a test for identity, Aciex will propose for FDA review an additional test for cetirizine identity in addition to the retention time of cetirizine in a (b) (4) method prior to its implementation.

Concerning proposing acceptance criteria for cetirizine related substances, osmolality, and viscosity, Aciex will propose acceptance criteria for these as additional stability data with these 2 packaging configurations becomes available and no later than a pre-NDA meeting. A justification for acceptance criteria for these test parameters will be prepared.

Concerning particulate matter, Aciex has set limits in accordance with USP <789>, Table 2.

2. *The following one-time tests are recommended to be conducted as drug development proceeds towards a NDA.*
   a. Weight loss through expiry on primary stability batches
   b. Leachables/extractables on container/closure by using screening analytical methods (such as HPLC, GC etc) and studies on at least one stability batch through expiry.
   c. Droplet volume evaluation from multiple container batches

Aciex Email Reply March 8, 2013. Aciex will conduct studies to evaluate weight loss, leachable & extractables, and drop volume in accordance with FDA's recommendations.

3. *Information on container closures can either be provided by referencing a DMF with a letter of authorization from the DMF holder or by providing all appropriate information in the NDA.*

Aciex Email Reply March 8, 2013. Aciex will provide information concerning the container-closure system either by reference to DMF(s) or inclusion in the NDA of the relevant information.

We recommend that you request a Pre-NDA meeting to discuss potential CMC issues.

Meeting discussion:

- The sponsor agreed to request a separate CMC meeting to discuss product quality issues.

Q13. In what electronic format would FDA like the individual patient data listings for each of the studies submitted in the NDA?

FDA Response: *We recommend that you submit your raw data using SDTM Model and analysis data using ADaM model. For implementation and submission of study data in a standardized format, please refer to CDER website:*

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

Aciex Email Reply March 8, 2013: Agreed. No further discussion required.

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/s/

WILEY A CHAMBERS
04/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEETING MINUTES

IND 108558

Aciex Therapeutics, Inc.
c/o ORA, Inc.
Attn: Donna L. Welch, RN, BSN
Sr. Vice President & COO
300 Brickson Square
Andover, MA 01810

Dear Ms. Welch:

Please refer to the End-of-Phase 2 meeting between representatives of your firm and FDA on September 19, 2011. The purpose of the meeting was to discuss the completed Phase 2/3 data of Cetirizine Ophthalmic (b) (4) for treatment of allergic conjunctivitis.

The official minutes of that meeting of teleconference is enclosed for your information. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LT June Germain, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Minutes of the Meeting

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: September 19, 2011 Start: 9:05, End: 9:30
Meeting Location: Teleconference

Application Number: IND 108558
Product Name: Cetirizine Ophthalmic (b) (4)
Indication: for the treatment of allergic conjunctivitis

Sponsor/Applicant Name: Aciex Therapeutics, Inc.
c/o ORA, Inc.

Meeting Chair: Wiley Chambers, M.D.
Meeting Recorder: Raphael R. Rodriguez

FDA ATTENDEES
Wiley A. Chambers, M.D., Deputy Director, DTOP
William Boyd, M.D., Clinical Team Leader
Rhea Lloyd, M.D., Clinical Reviewer
Martin Nevitt, M.D., Clinical Reviewer
Lucious Lim, M.D., Clinical Reviewer
Janice Lansita, Ph.D., Nonclinical Reviewer
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology Team Leader
Dongliang Zhuang, Ph.D, Acting Statistics Team Leader
Mushfiqur Rashid, Ph.D., Statistical Reviewer
Raphael Rodriguez, Regulatory Project Manager

SPONSOR ATTENDEES
Ora:
Mark Abelson, MD, Chief Scientific Officer
Donna Welch, RN, BSN, Sr VP & COO
Matt Chapin, MBA, VP Business Development
Paul Gomes, VP, Allergy
Jeffrey Coderre, Manager, Regulatory Writing

Statistics and Data Corporation:
Katie Kennedy, Director, Biostatistics

Aciex:
Tom Cavanagh, President
Les Kaplan, PhD, Chairman of the Board

BACKGROUND

Aciex has recently completed a single-center Conjunctival Allergen Challenge (CAC) study to support the indication of allergic conjunctivitis. Aciex would like to present these results to the Division, review the results from the cetirizine arms from two previously completed CAC studis (b) (4) cetirizine, and obtain concurrence on the planned clinical studies in support of the intended indication.

Preliminary responses to the Sponsor's questions posted in the briefing package submitted on August 19, 2011, were provided via email September 17, 2011. This meeting served to clarify those responses.

For the purposes of these minutes, the questions posted by the Sponsor are described in **bold** format, the Division's preliminary responses are in *italics*, and the meeting discussion in normal font.

TOXICOLOGY

A chronic ocular toxicity study outline will be included in the briefing package.

Question 1: Is the proposed toxicity study acceptable?

FDA Response: No, the study should include systemic and ocular toxicokinetic (TK) endpoints. Alternatively, a stand-alone ocular distribution study can be conducted to address the ocular PK of cetirizine. Please also provide scientific justification for the selected high dose of 0.24%, BID. The acceptability of the overall study is a review decision and will depend on the study results and data quality.

Meeting Discussion: The Sponsor indicated that they will incorporate TK measurements in the chronic ocular toxicology study, and proposed collecting blood samples following the first dose on Day 1, Month 1, 3 and 6 for assay of cetirizine. The Sponsor also indicated that they will conduct a separate study to assess the ocular distribution following a single ocular administration. Details on both protocols will be submitted to the Division for review.

The Sponsor also clarified that they intend to use 0.24% BID as the (b) (4) dose in the toxicology study as this represents a dose frequency higher than the one intended in the clinical dosing (0.24%, bilateral, (b) (4) The Division stated that from a daily systemic exposure point of view, a rabbit dose of 0.24% unilateral, BID, is equivalent to the proposed clinical dose of 0.24%, bilateral, (b) (4) The Division agreed that a 0.24% dose, (b) (4) would be acceptable.

Question 2: Is submission of a 2-month interim report on the toxicity study prior to initiating the proposed 6-week safety study acceptable?

FDA Response: Yes, submitting an interim report 30 days prior to starting the 6-week safety study appears to be acceptable. Please ensure that the interim report is complete and contains all of the data up to 2 months for the ophthalmic examinations (including slit lamp, fluorescein staining, fundoscopy, and tonometry).

Meeting Discussion: None

Question 3: Does the FDA agree that given the systemic experience with marketed cetirizine products, that the proposed chronic ocular toxicology study in rabbits will complete the necessary toxicology requirements for the proposed ophthalmic product?

FDA Response: Yes, however, if nonclinical or clinical safety issues arise that are not fully addressed in the 6-month ocular rabbit study additional nonclinical studies may be warranted.

Meeting Discussion: None

CLINICAL

Question 4: Is the proposed Phase 3 clinical plan acceptable to support the proposed product?

FDA Response: Complete protocols were not submitted in the briefing package. The Agency will likely have further comments when the complete protocols are submitted and reviewed.

In addition to what has been proposed in the clinical trial outlines, the Agency recommends the following:

1) *Perform drop comfort assessment at all study visits in the Phase 3 trials*

2) *Perform endothelial cell count evaluation in a study of at least 3 months duration (i.e., evaluation at baseline and at month ≥3) at some point in your drug product development plan.*

Regarding the Crossover study:
a) We do not recommend crossover trial designs because of the potential for unequal baselines at the crossover.
b) We recommend that you pre-specify the primary analysis model and its assumptions (fixed effects, random effects, covariance structure of the error vector and etc.). We also recommend that you add a statistical considerations section addressing these issues.

Regarding the Single-center study:
a) If a third arm is added to the trial, we recommend that you plan to adjust for multiple hypotheses due to multiple doses.
b) Last Observation Carried Over (LOCF) should be implemented within the same study visit. Data should not be carried forward from the previous visit.
c) Besides LOCF method for handling missing data, please consider additional methods (including multiple imputation method) in sensitivity analyses.

Regarding the Multi-center study (efficacy):
a) You have proposed two primary endpoints without a plan to adjust for multiplicity. To be consistent with the single center CAC study, we recommend that you use a two-sided significance level of 0.025 for testing each primary efficacy endpoint.
b) LOCF should be implemented within the same study visit. Data should not be carried forward from the previous visit.
c) Besides LOCF method for handling missing data, additional methods (including multiple imputation method) should be considered in sensitivity analyses.

Meeting Discussion:
The Division accepted the Sponsor's proposal to evaluate drop comfort at all visits of the proposed safety study and/or in a separate 1-drop comfort study but not in the CAC study. The Sponsor clarified that the comfort trial will be of parallel design.

The Division also accepted the Sponsor's proposal to carry out endothelial cell counts (ECC) in a subset of at least 100 subjects in the proposed 6-week safety study that stop treatment at 6 weeks and follow-up for ECC evaluation 6 weeks later, at Month 3.

The Division indicated that if itching and redness are specified as primary efficacy endpoints, and if clinical success is defined as > 1 unit at 2 of 3 time points in both, then no further correction for multiplicity was required and $P<0.05$ was the appropriate threshold for statistical significance for each individual endpoint.

The Division also stated that it was acceptable to define clinical success as one endpoint only (i.e., itching OR redness), but this was not the preferred definition. The Division further stated that if a second drug arm was added, appropriate multiplicity corrections would be required and that specifying $P<0.025$ would be acceptable.

The Division stated that it was preferable not to impute missing data, and that if the imputation was used, the last observation carried forward could be used within a single visit but not between separate visits. The Division further stated that the Markov Chain Monte Carlo imputation method in the sensitivity analysis is acceptable.

Question 5: If the two proposed additional CAC studies with cetirizine 0.24% VS. vehicle demonstrate clinical significance (1 unit difference) in the prevention of ocular itching at 16 hours, can Study 3 (11-100-0004) serve as the dose-ranging study?

FDA Response: *Study 3 (11-100-004) is acceptable as a dose-ranging study.*

Meeting Discussion: None

Question 6: Given the extensive systemic use of cetirizine products in the market, is the proposed 6-week study sufficient to support the safety of the proposed product, and are the specified patient numbers acceptable?

FDA Response: Acceptable.

Meeting Discussion: None

Question 7: Given the baseline imbalance observed in the Visit 2 ocular itching data in the dose-ranging study (Study 11-100-0004), we propose to stratification subjects in future CAC studies based on baseline ocular itching scores as described in the attached clinical trial outline.

Is this an acceptable approach?

FDA Response: Acceptable.

Meeting Discussion: There was an extended discussion with regard to the problems of baseline imbalance. FDA agreed that an imbalance at baseline was a significant problem and accepted the Sponsor's proposal to try to minimize imbalances by using stratification in future studies.

The Sponsor pointed out that when the baseline correction suggested by the FDA in their preliminary comments was applied, the outcome of the 11-100-0004 study reached the Division's standard for clinical relevance. FDA stated that a correction for a baseline imbalance was not acceptable for determining clinical significance.

In the context of what comprises evidence of efficacy, FDA stated that it was the totality of data that would be reviewed. Data from this study, burdened by a statistically significant baseline imbalance (treatment differences of -0.8, -0.8, -0.5 uncorrected; -1.0, -0.9,-0.8, corrected), should be included and would be reviewed as part of the total submission.

Question 8: Does the Agency have alternate suggestions to account for any baseline? imbalance?

FDA Response: We recommend that you plan to adjust your primary analysis using the stratification variables as covariates.

Meeting Discussion: See above in question 7

Additional Agency Comments

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

Meeting Discussion: The sponsor indicated that they plan to implement CDISC standards for their NDA submission.

ADDITIONAL DISCUSSION

The Sponsor requested the Division's guidance with regard to minor formulation modifications that would be acceptable for a second pivotal study. The Division indicated that there is no way to determine what would be a minor formulation change, and that it would prefer to see the impact of individual formulation changes in each study. The Division further clarified that it is preferable to conduct two studies with the final formulation.

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/s/

WILEY A CHAMBERS
04/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108558

MEETING MINUTES

Aciex Therapeutics, Inc.
c/o Ora, Inc.
Attention: Donna L. Welch, RN, BSN
Sr. Vice President & COO
300 Brickstone Square
Andover, MA 01810

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cetirizine (b) (4) (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on October 5, 2010. The purpose of the meeting was to discuss plans for the development of the product as a treatment for (b) (4) of allergic conjunctivitis.

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

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	October 5, 2010, 1:00 – 2:00 PM
Meeting Location:	10903 New Hampshire Avenue, Silver Spring, MD 20993 Building 22, Room 1415
Application Number:	108558
Product Name:	Cetirizine (b) (4) (b) (4)
Indication:	Treatment of allergic conjunctivitis
Sponsor/Applicant Name:	Aciex Therapeutics, Inc.
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Alison Rodgers

FDA ATTENDEES
Division of Anti-Infective and Ophthalmology Products
Wiley Chambers, MD, Acting Director
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
William Boyd, MD, Clinical Team Leader
Lucious Lim, MD, Medical Officer
Rhea Lloyd, MD, Medical Officer
Martin Nevitt, MD, Medical Officer
Mushfiger Rashid, PhD, Statistical Reviewer
Alison Rodgers, Project Manager
Wendy Schmidt, PhD, Pharmacology and Toxicology Team Leader
Yan Wang, PhD, Statistical Team Leader
James Wild, PhD, Pharmacology and Toxicology Reviewer
Yongheng Zhang, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES
Aciex Therapeutics
Tom Cavanagh, President

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/s/

WILEY A CHAMBERS
11/01/2010