CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217603Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 143686

MEETING PRELIMINARY COMMENTS

Tarsus Pharmaceuticals, Inc.
Attention: Jason Kato, PhD
Regulatory Affairs
15440 Laguna Canyon Rd.
Suite 160
Irvine, CA 92618

Dear Dr. Kato:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TP-03 (lotilaner ophthalmic solution), 0.25%. We also refer to your April 15, 2022, correspondence, requesting a meeting to discuss the upcoming NDA submission requirements.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please contact me at Dheera.Semidey@fda.hhs.gov or (301) 796-3009.

Sincerely,

{See appended electronic signature page}

Dheera Semidey, PharmD, RAC
Regulatory Health Project Manager
Ophthalmology
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 22, 2022, from 2pm to 3 pm EDT
Meeting Location: Teleconference

Application Number: IND 143686
Product Name: TP-03, lotilaner ophthalmic solution
Indication: Treatment of Demodex blepharitis
Sponsor Name: Tarsus Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 22, 2022, from 2pm to 3 pm EDT between Tarsus Pharmaceuticals and the Division of Ophthalmology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

DISCUSSION

The questions outlined in your meeting package are presented in **bold** font and our responses are in *italic* font.

Question 1: The NDA will be supported by two pivotal well-controlled studies (TRS-009 (Saturn-1) and TRS-010 (Saturn-2)) that, together, provide substantial evidence of safety and efficacy of lotilaner ophthalmic solution, 0.25% for the treatment of Demodex blepharitis. Does the Agency agree that the design of the pivotal studies and the results from these studies support filing a marketing application for this indication?

FDA Response to Question 1: Agree. The design of two Phase 3 studies should support filing of an NDA. However, whether or not an application is fileable can only be determined once a NDA is submitted.

Question 2: Does the Agency agree that the results from the two pivotal studies (TRS-009 (Saturn-1) and TRS-010 (Saturn-2)) support the proposed indication wording and the proposed efficacy analyses to be included in the Clinical section of the label (section 14)?

FDA Response to Question 2: This question is premature. Labeling can only be determined once an NDA is submitted and reviewed in its entirety.

Question 3: Does the Agency agree with the proposed content of the 120-day safety update?

FDA Response to Question 3: Acceptable.

Question 4: The Sponsor considers the safety and tolerability of lotilaner ophthalmic solution, 0.25% to be well defined and considers that routine pharmacovigilance and labeling will be sufficient to mitigate risks and preserve benefit, and therefore a Risk Management Plan or REMS is not needed. Does the Agency agree?

FDA Response to Question 4: The plan seems acceptable, but the Agency can only give a definitive response to this question once the NDA is submitted and reviewed.

Question 5: Does the Agency agree that the in vitro ADME studies, and assessment of clinical pharmacokinetics in the healthy volunteer study, TRS-012, as well as the assessment of systemic exposure after completion of drug administration in the pivotal studies (TRS-009 (Saturn-1) and TRS-010 (Saturn-2)) are adequate to characterize the pharmacokinetics of lotilaner after ophthalmic application within the prescribed dosing regimen and that no additional studies are needed for the NDA submission?

FDA Response to Question 5: Yes, overall, the plan appears reasonable. We note that QT assessment for lotilaner is ongoing and thus, we recommend you submit the study report at the time of NDA submission.

Question 6: Does the Agency agree that the nonclinical toxicology package is adequate to support a marketing application for lotilaner ophthalmic solution, 0.25%?

FDA Response to Question 6: Yes, we agree, pending review of the submission. All impurities and degradants should be qualified at the NDA submission.

Question 7: Does the Agency agree with the proposed NDA submission components that may be filed within 30 days of the original submission?

FDA Response to Question 7: We expect the NDA at the time of submission to include all the leachable data. Any data submitted during review may or may not be reviewed depending on resources available.

ADDITIONAL INFORMATION

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 27, 2022, 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 VI. 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 and, where applicable, the development of a Formal Communication Plan. 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.

Information on the Program is available at FDA.gov.[1]

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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[4] https://www.fda.gov/media/84223/download
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[6] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DHEERA K SEMIDEY
06/15/2022 03:18:38 PM
IND 143686 Meeting Preliminary Comments

PIND 143686

MEETING MINUTES

Tarsus Pharmaceuticals
c/o Ora, Inc.
Attention: Hal Patterson, Senior Vice President
300 Brickstone Square, Third Floor
Andover, MA 01810

Dear Mr. Patterson:

Please refer to your Pre-Investigational New Drug Application (PIND) file for TP-03 ophthalmic solution. We also refer to the meeting between representatives of your firm and the FDA on June 4, 2019. The purpose of the meeting was to discuss your clinical and nonclinical development plans.

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 Derek Alberding, Regulatory Health Project Manager at (240) 402-0963.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	June 4, 2019, 3:00 p.m. – 4:00 p.m. ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Application Number:	PIND 143686
Product Name:	TP-03 ophthalmic solution
Indication:	Treatment of Demodex blepharitis
Sponsor Name:	Tarsus Pharmaceuticals
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Derek Alberding, PharmD

FDA ATTENDEES

Wiley A. Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William M. Boyd, M.D.	Clinical Team Leader, DTOP
Sonal Wadhwa, M.D.	Medical Officer, DTOP
Jennifer Harris, M.D.	Medical Officer, DTOP
Martin Nevitt, M.D.	Medical Officer, DTOP
Lori Kotch, Ph.D.	Pharmacology/Toxicology Supervisor, DTOP
Aaron Ruhland, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Chunchun Zhang, Ph.D.	Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products
Eric Adeeku, Ph.D.	Product Quality Microbiology Reviewer, OPQ/ Division of Microbiology Assessment
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Yunfan Deng, Ph.D.	Statistical Reviewer, OB/DBIV
Derek Alberding, PharmD	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Bobby Azamian, M.D., Ph.D.	Tarsus, Chief Executive Officer
Shawn Hickok	Tarsus, Director, Pharmaceutical Sciences
(b) (4)	Toxicology Consultant

Michael Ackermann, Ph.D.	Tarsus, Chairman
Mark Holdbrook	Tarsus, Vice President, Clinical Affairs
[redacted] (b) (4)	

BACKGROUND

Tarsus Pharmaceuticals (the Sponsor) is developing TP-03 (lotilaner) ophthalmic solution, an isoxazoline compound indicated for the treatment of *Demodex* blepharitis.

On April 3, 2019, the Sponsor submitted a Pre-IND meeting request to discuss clinical and nonclinical development plans to support the proposed indication. A face-to-face meeting was scheduled for June 4, 2019.

The Division sent Preliminary Comments on May 21, 2019, and the Sponsor provided preliminary responses on May 30, 2019.

DISCUSSION

For the purposes of these minutes, the questions submitted in the May 7, 2019, Meeting Package are in **bold** font, our May 21, 2019, preliminary responses are in *italics* font, and the June 4, 2019, meeting discussion is in normal font.

Non-clinical

1. **Does the Agency agree that the non-clinical systemic toxicity studies performed in support of the veterinary indication in combination with the proposed 28-day GLP ocular toxicity studies, the reports of which will be included in the IND, provide adequate support for the initiation of the proposed Phase 2b/3 and Phase 3 clinical studies?**

   FDA Response:
   The study summaries and study synopses provided in the briefing package appear sufficient in design and scope to support the proposed clinical studies. Ensure selected doses in your GLP animal studies provide an adequate safety margin for proposed clinical dose(s). If systemic exposure to lotilaner occurs following ocular administration, adequate safety pharmacology data should be provided.

   It appears that one of the studies in dogs cited in the briefing package assessed electrocardiography (Study [redacted] (b) (4) -13-010) and ECG is also proposed in the ocular toxicity study to be conducted in dogs. Please ensure that electrocardiography data includes measurement at Tmax. Additionally, respiratory and neurobehavioral safety

pharmacology data should be provided; data can be provided in the form of standalone studies or endpoints can be incorporated in your GLP ocular toxicity studies.

A final determination regarding the adequacy of your nonclinical data to support the proposed clinical trial will be made upon review of the full study reports and final clinical protocol.

Meeting Discussion: The Sponsor explained that the maximum feasible concentration of lotilaner that can be achieved in an aqueous solution is 0.25%. This is the planned concentration of lotilaner in TP-03 ophthalmic solution to be administered in clinical studies, one drop per eye twice daily. The Sponsor proposed three times daily dosing in the ocular toxicology studies, for a 1.5X safety margin (in addition to two lower doses). The Sponsor inquired if 1.5X was an adequate safety margin for the GLP ocular toxicity studies. The Division questioned the need to test doses lower than the clinical dose and recommended testing at least the proposed clinical dose and at two higher doses. The Division also discussed techniques for increasing dosing frequency in ocular toxicology studies.

The Sponsor inquired whether a 1X dosing frequency (one drop per eye, twice daily), a 2X dosing frequency (two drops per eye, separated by 10 minutes, twice daily) and a 3X dosing frequency (two drops per eye, separated by 10 minutes, three times daily) would be acceptable. The Sponsor stated each drop would be a 0.25% lotilaner solution. FDA stated this proposal would be acceptable.

The Division recommended that ECG testing at Tmax after ocular administration be included in the proposed dog study. The Sponsor clarified that ECG was evaluated in the oral administration studies and inquired if additional ECG data would be required if the systemic exposure after ocular administration is lower than with the oral administration. The Division stated that the ECG data in dogs after oral administration would satisfy the requirements if systemic exposure after ocular administration is shown to be lower than the exposure for oral administration.

The Sponsor also clarified that neurobehavior was evaluated in the 13-week, GLP oral rat toxicity study ((b) (4)-12-041), at pretest and Week 12 of dosing, by Functional Observational Battery. This information was inadvertently omitted from the briefing document. The Sponsor stated that no lotilaner-related CNS effects were observed at doses up to 40 mg/kg/day. The Division stated that if the review team made the same conclusions after reviewing the data, the completed CNS safety pharmacology would be sufficient.

Clinical

2. Does the Agency agree that the selected study population (presence of at least mild lid margin erythema; at least (b) (4) lashes with

collarettes/cylindrical dandruff present on upper lid; and Demodex density, upper and lower eyelids combined, of 1.5 mites or more per lash in at least one eye) is appropriate for the intended treatment of Demodex blepharitis?

FDA Response: Yes.

Meeting Discussion: None.

3. **Does the Agency agree with the proposed Phase 2b/3 study design to evaluate the efficacy and safety of TP-03 Ophthalmic Solution for the treatment of Demodex Blepharitis?**

FDA Response:
We recommend for the indication of blepharitis, studies be followed for at least 6 weeks after the initiation of treatment.

We recommend Corrected, distance, visual acuity (VA) (4 meters in distance or more) is recommended to be performed at every visit.

A slit lamp examination of the anterior segment is recommended to include the cornea, conjunctiva, anterior chamber, iris, lids and lashes. At a minimum, examinations are recommended to occur at baseline, day 3, 5 and 7.

An evaluation of patient comfort after the administration of the drug product is recommended to be completed.

A dilated fundus examination is recommended to be performed at baseline and at the end of the study.

Endothelial cell count examinations are recommended to be performed at baseline and at the end of trial in at least one study.

Systemic clinical and laboratory evaluations are recommended to be performed at baseline and at the end of the trial in at least one study.

Also see additional guidance regarding your Phase 2b/3 trial in our responses to Questions #5, #6, and #7.

For patients who withdraw from the study due to lack of efficacy or adverse events, you propose to use a multiple imputation approach to handle missing data. This approach imputes the missing data at a given study visit by using the observed data from the patients who are still on the Vehicle treatment. Without knowing the comparability of those study dropouts with the patients who adhere with the Vehicle treatment in terms of their efficacy outcomes, we cannot comment on your missing data handling approach. In the event that the TP-003 arm has a substantially higher

study dropout rate due to adverse events or lack of efficacy than the Vehicle arm, we recommend you consider alternative approaches such as the trimmed mean analysis (https://www.ncbi.nlm.nih.gov/pubmed/27523396) that treat those dropouts as having bad outcomes.

Because there is no better way to handle missing data than preventing them, we strongly recommend that your full study protocol specify measures to minimize missing data and to encourage patients who discontinue the study treatment early to stay in the study for efficacy and safety assessments at all scheduled visits.

Meeting Discussion: None.

4. **Does the Agency agree with the adequacy of the proposed scales and procedures for evaluating Demodex density and lash collarettes/ cylindrical dandruff (Appendix 1)?**

FDA Response: No, refer to response to Question #5 regarding the primary endpoint.

Meeting Discussion: None.

5. **Does the Agency agree with the (b) (4) to support approval for the proposed indication of the treatment of Demodex blepharitis?**

FDA Response: We do not agree with your proposed primary endpoint. For your Phase 2b/3 trial you propose the following (b) (4) endpoints:

(b) (4)

We recommend a statistically significant difference between groups in the percentage of cured patients as a demonstration of efficacy. Superiority is recommended to be demonstrated in replicated studies with comparisons to the product's vehicle in the cure of the signs and symptoms of blepharitis (normal lids and no discharge) for the clinically infected patients who meet the inclusion criteria of the protocol. Clinical cure is recommended to be defined as the resolution of signs and symptoms (i.e. a score of 0).

Additionally, in trials which contain the product's vehicle as one arm of the study, it is recommended that the cure rate of the vehicle not be superior to the cure rate of the test product for the Intent-to-Treat population.

It is recommended that the replicated trials have the same time points for evaluation of the primary efficacy endpoints.

Meeting Discussion: The Sponsor proposed a modified primary endpoint of collarette cure rate for active vs. vehicle treatment groups. The Division stated that collarette cure rate would be an acceptable primary endpoint.

The Sponsor proposed a modified Collarette Grading Scale, where a Score of 0 is defined as (b) (4) or fewer collarettes on the upper lid of the analysis eye. The Division agreed to review a definition where 1, maybe 2 collarettes on the upper lid was considered normal and scored as 0, but stated that defining a Score of 0 as more than 2 collarettes would be unlikely and require additional justification.

The Sponsor proposed Demodex mite eradication as a secondary endpoint. The Sponsor clarified that this secondary endpoint would be defined as the proportion of patients with 0 mites/lash for the analysis eye. The Division agreed.

The Division requested an additional secondary endpoint of the proportion of subjects exhibiting both a Score of 0 for collarettes and a Score of 0 for lid erythema. The Division clarified that the Sponsor could add a symptom to the combination endpoint.

6. **Does the Agency agree that the proposed Phase 2b/3 study is an adequate and well-controlled study that, assuming it is conducted per protocol and the results are positive, could be considered a pivotal study towards approval/registration of TP-03 Ophthalmic Solution for the proposed indication?**

   FDA Response: Potentially a Phase 2b/3 study can be considered one of at least two adequate and well controlled trials to support approval. However, we cannot comment on the acceptability of your particular Phase 2b/3 trial because only a study synopsis is submitted. We would need to review a complete protocol to make additional comments.

   Meeting Discussion: None.

7. **The lifecycle of Demodex is approximately 2 weeks (Lacey et al., 2009). The Sponsor proposes a 4 week treatment period to ensure maximal efficacy of TP-03 Ophthalmic Solution (acarine GABACls inhibitor that leads to death of the Demodex mites). Does the Agency agree that a total of 300 exposed participants over the 28-day duration of treatment in the 2 proposed clinical trials is adequate and sufficient to assess the safety of the TP-03 Ophthalmic Solution?**

FDA Response: No, we recommend 6 week follow-up in the trials. Also, you are targeting your trials for the minimum number of patients for safety. It is recommended that the topical clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, it is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing.

Meeting Discussion: The Division agreed that a 4-week or 6-week treatment period is acceptable, as long as the follow-up and primary endpoint is at Week 6 or longer.

The Sponsor proposed that at least 300 subjects be included in the safety analysis over 2 pivotal studies. The Division agreed that a minimum of 300 subjects was acceptable, but emphasized that fewer than 300 subjects (e.g., 299 subjects) would not be acceptable.

The Sponsor inquired whether the 4-week treatment would be an acceptable treatment duration for the safety analysis, if a treatment duration of 4 weeks was selected. The Division agreed.

8. **The 0.25% concentration of the drug substance of TP-03 Ophthalmic Solution (lotilaner) is the maximum concentration that can be achieved with an aqueous solution. Given this is an anti-infective to kill Demodex, does the agency agree that clinical testing of lower concentrations is not necessary?**

FDA Response: Yes.

Meeting Discussion: None.

Additional FDA Comments:
It is noted that TP-03 Ophthalmic Solution is intended for multi-dose use and (b) (4) *is proposed as the preservative (* (b) (4) *ppm). As product development continues, it is recommended that you provide the results of antimicrobial effectiveness testing per USP <51> to support the preservative content in future clinical trial submissions.*

In preparation for marketing application submission, please refer to the Agency's 1994 Guidance document "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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 clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA

[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission. Additional information can be found at FDA.gov.[9]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

ATTACHMENTS AND HANDOUTS

- May 30, 2019, Sponsor Preliminary Comments: **"Discussion Focus for TP-03 Meeting 4 June 2019"**

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