CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 138645

MEETING MINUTES

Oyster Point Inc
Attention: Loni da Silva, MS, RAC
Vice President Regulatory Affairs
700 Alexander Park
Suite 301
Princeton, NJ 08540

Dear Ms. Da Silva:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OC-01 (varenicline tartrate nasal spray). We also refer to the meeting between representatives of your firm and the FDA on February 25, 2019. The purpose of the meeting was to discuss phase 3 and NDA 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 Lois Almoza, M.S., Regulatory Health 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
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: End of Phase 2

Meeting Date and Time: February 25, 2019 from 1:00pm – 2:00pm (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 138645
Product Name: OC-01 (varenicline tartrate nasal spray)
Indication: dry eye disease
Sponsor Name: Oyster Point Inc

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

Wiley A. Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William M. Boyd, MD	Clinical Team Leader, DTOP
Rhea Lloyd, MD	Clinical Reviewer, DTOP
Lori Kotch, PhD	Pharmacology/Toxicology Supervisor, DTOP
Aling Dong, PhD	Pharmacology/Toxicology Reviewer, DTOP
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Qing Zhou, PhD	Statistics Reviewer, OB/DBIV
Chunchun Zhang, Ph.D.	Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Yushi Feng, PhD	Product Quality Reviewer, OPQ/ONDP
Lois Almoza, MS	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Jeffrey A. Nau, MMS, PhD	President and CEO
Michael Ackermann, PhD	Chairman of the Board
Loni da Silva, MS, RAC	Vice President, Regulatory Affairs
(b) (4)	(b) (4) Consultant, (b) (4)
(b) (4)	(b) (4) Consultant, (b) (4)
Patricia Johnson (on the phone)	Executive Director, Regulatory CMC

BACKGROUND

A December 19, 2019, submission from Oyster Point Inc (Oyster) requested a meeting to discuss phase 3 and NDA plans. A Meeting Request Granted letter issued on January 2, 2019. The Meeting Package was received on January 23, 2019, and Preliminary Comments were sent to Oyster via e-mail on February 21, 2019. On February 22, 2019, after reviewing the Meeting Preliminary Comments sent on February 21, 2019, Oyster e-mailed talking points. During the meeting on February 25, 2019, slides that were presented by Oyster are attached.

DISCUSSION

Following, in **bold font**, are the questions in the January 23, 2019, Meeting Package. The Agency responses, sent to Oyster Point Pharma(Oyster) via e-mail on February 21, 2019, are in *italic font*. Talking points sent via via-mail to the Agency from Oyster on February 22, 2019, are in ***bold italic*** font, and the meeting discussions are in regular font.

1. **Clinical**
   a. **Does the Division agree that the proposed Phase 3 endpoints in the attached Phase 3 protocol synopsis support approval of OC-01 for the signs and symptoms of dry eye disease?**

FDA Response: *No. It is recommended that the Phase 3 study include a 0.1 mg/mL dose arm and consideration be given to the Mean Change from Baseline in Schirmer's Score at Visit 4 (Day 28) and the Eye Dryness Score at Day 28 (Visit 5) as primary endpoints.*

Oyster Point Response Clarification to 1a.
Most importantly we would like to confirm that the same medium and high doses (0.1% varenicline tartrate salt=0.6 mg/mL free base and 0.2% varenicline tartrate=1.2 mg/mL free base) of varenicline tartrate that were used in the Phase 2b ONSET study will be used in Phase 3.

The Phase 3 Clinical Trial synopsis in the briefing package included a dosing regimen of "varenicline tartrate" 0.6 mg/mL and 1.2 mg/mL. These concentrations actually refer to the free base quantity of varenicline and are consistent with the doses delivered in the Phase 2b ONSET study. For clarity, the varenicline tartrate salt equivalent of the free base concentrations are noted below:

0.6 mg/mL free base = 0.1% tartrate salt
1.2 mg/mL free base = 0.2% tartrate salt

Although the Phase 2b ONSET study referred to the investigational drug in terms of % tartrate salt, the Phase 3 protocol will refer to the varenicline free base concentration in units of mg/mL to be consistent with potential future commercial labeling.

With respect to the comment from the Agency on the co-primary endpoints of Mean Change from Baseline in Schirmer's Score at Day 28 and Mean Change from Baseline in Eye Dryness Score at Day 28 in the Controlled Adverse Environment chamber, there are logistical challenges to assessing Schirmer's score on the same day as assessing Eye Dryness score in the Controlled adverse Environment chamber. We would propose to perform these two assessments on two separate days within the same Day 28 visit window. Please comment as to whether the Agency would find this acceptable.

Meeting Discussion:
The Agency suggested considering Eye Dryness Score as the symptom endpoint because its effect size may be stronger than the effect size of the Eye Dryness Score in the Controlled Adverse Environment Chamber: however, the Agency indicated that either endpoint would be acceptable for Phase 3.

The Sponsor asked for the Agency's insight regarding co-primary sign and symptom endpoints versus primary and secondary sign and symptom endpoints. The Agency stated that the sole primary endpoint, the percentage of subjects demonstrating statistically significant increases of ≧ 10mm in Schirmer score compared to vehicle, would be acceptable to support approval. This endpoint alone could support an application. The Sponsor could also choose sign and symptom endpoints. The Agency does not have a preference between a co-primary endpoint and primary/secondary endpoints as long as there is control of potential Type I error.

The Sponsor asked for the Agency's advice on most accurately representing 'sneezing' events, a common adverse event occurring immediately after administration of the investigational product. The Agency suggested that the Sponsor capture this information in a pre-planned manner with the intent of understanding its frequency and temporal relationship to time of administration of investigational drug. The package insert could include a section on sneezing.

b. Does the Division agree that the Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (ONSET) study suffice as one of two registration studies supporting NDA Approval of OC-01 for the signs and symptoms of dry eye disease? In addition, would one (1) additional Phase 3 study support a 505(b)(2) NDA filing of OC-01 for the signs and symptoms of dry eye disease?

FDA Response:
The ONSET study could be submitted in support of an application for the safety and efficacy of the 0.1% OC-01 nasal spray for the signs and symptoms of dry eye disease. At least one additional study which strongly supports the safety and efficacy of the 0.1% of OC-01 would be expected to support an NDA filing for the indication considering there is weak support of

a symptom in ONSET. The proposed Phase 3 study which does not include a 0.1% OC-01 treatment arm would be unlikely to support a 0.1% concentration.

Oyster Point Response Clarification to 1b.
We can confirm that the same medium and high doses (0.1% varenicline tartrate salt=0.6 mg/mL free base and 0.2% varenicline tartrate=1.2 mg/mL free base) of varenicline tartrate that were used in the Phase 2b ONSET study will be used in Phase 3; see the response to 1a

Meeting Discussion:
The Agency does not object with the proposed dose in the Phase 3 trial. The Agency recommended that if a USP monograph for varenicline is published by the time of filing a NDA for a nasal spray formulation, the Sponsor should follow the monograph terminology of free base or salt form and be consistent with dose throughout their entire submission going forward.

c. Given the totality of safety information with regards to varenicline tartrate:

Reference Data

- **Significant nonclinical, clinical trial and post-marketing experience with oral varenicline tartrate (Chantix®) under IND 58,994 (See table 1)**

Oyster Point Data

- **Toxicology: 7-day and 28-day intranasal toxicology studies in rat and rabbit with no significant findings. An intranasal 6-month chronic toxicology study in rabbits will commence in Feb 2019.**
- **Low systemic exposure to varenicline tartrate via the intranasal route of administration as compared to the oral delivery of varenicline tartrate [nominal daily dose comparison and rationale are provided in Section 9.1.3].**
- **Human intranasal delivery safety data available from the ONSET and one additional Phase 3 study that will include at a minimum at least 300 subjects would have completed at least 6 weeks of follow-up after the initiation of treatment and at least 100 subjects would have completed at least 12 months of follow-up after the initiation of treatment.**

Does the Division agree that these efficacy and safety data will be sufficient to support a 505(b)(2) NDA?

FDA Response:
See response to question 1b and question 2.

Meeting Discussion: None

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FDA Response:
This labeling question is a review issue.

Meeting Discussion: None

2. Nonclinical

Oyster Point has completed two 7-day and two 28-day intranasal toxicity studies in rat and rabbit and plans to conduct a 6-month intranasal toxicity study in rabbit. Does the Division agree that no additional nonclinical studies are needed for a 505(b)(2) New Drug Application (NDA), relying in part upon FDA's prior review of nonclinical data for the reference listed drug, Chantix®?

FDA Response: We agree, presuming you can establish an adequate bridge between your product and the listed drug. Please note FDA discipline reviews cannot be relied upon to support an 505(b)(2) NDA application. If you intend to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate. You should establish a "bridge" (e.g., via comparative pharmacokinetic data, via comparative dose) between your proposed formulation and the listed drug. If exposure levels following nasal spray administration of your final clinical formulation are less than or equal to that of the listed drug (at approved dose/route), then reliance upon the listed drug(s) would be considered scientifically justified. If exposure levels following nasal spray administration of your clinical formulation exceeds those of the listed drugs, then additional toxicity studies may be needed to support the increased exposure.

See 'General 505(b)(2) NDA advice' provided below.

General 505(b)(2) NDA advice

1. All recommended nonclinical elements should be provided to the NDA, either directly (studies conducted by you, or data for which you have right of reference) or by reliance on literature or FDA's findings of safety and effectiveness for a listed drug(s). Reliance on data that you do not own or have right of reference to will require an adequate bridging strategy (e.g., comparative ocular and/or systemic PK, comparative dose). We advise that you provide information (summary or Table) in the NDA detailing which data you intend to rely on for each nonclinical element, and how you intend to bridge that data.

2. If literature is being relied upon to support the NDA, published literature relevant to your product should be considered, and relevant data should be summarized in the NDA.

a. Include a summary of all published nonclinical literature being relied upon and a copy of all publications cited.

b. The nonclinical summary is typically organized to address each of the nonclinical elements (e.g., pharmacology, pharmacokinetics, ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.).

c. A copy of each cited article should be provided. Please note that review articles cannot be relied upon to support an application; the source articles which contain full study data should be provided or incorporated by reference.

d. 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.

e. Please also identify any listed drug(s) described in the published literature (e.g., trade name(s)). Reliance on published literature describing a listed drug(s) may be considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s).

f. You will need to be able to bridge (e.g. via comparative dose or PK) any published safety data that you plan to rely on to fulfill nonclinical requirements. We advise that you provide information in the NDA discussing how you intend to bridge data contained in each of the published studies you plan to rely on. A discussion regarding the impact of formulation differences between your product and those used in published studies would also be helpful. The adequacy of the published data to support your 505b2 NDA application will be a review issue.

3. Please note that non-US labeling or non-US regulatory authority assessments may not be relied upon as they are considered summary data.

4. FDA discipline reviews cannot be relied upon to support an 505(b)(2) NDA application. FDA finding of safety and efficacy is captured in the product labeling, and may include findings that can be inferred from fact of approval. If you intend to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate. You should establish a "bridge" (e.g., via comparative pharmacokinetic data, via comparative dose) between your proposed formulation and each listed drug. If exposure levels following topical administration of your final clinical formulation are less than or equal to that of the listed drugs (at approved dose/route), then reliance upon the listed drugs would be considered scientifically justified. If exposure levels following topical administration of your clinical formulation exceeds those of the listed drugs, then additional toxicity studies may be needed to support the increased exposure.

5. Impurity specifications that exceed qualification limits specified in the ICHQ3 guidances should be adequately qualified and safety data supporting duration of use should be provided in the NDA submission.

6. Novel excipients should be qualified, and safety data supporting duration of use should be provided in the NDA submission.

7. For the NDA, labeling should comply with the Pregnancy and Lactation Labeling Rule (PLLR). For more information, please see the final rule.
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm

Meeting Discussion: None

Attachment: Slides presented by Oyster Point Inc. during, February 25, 2019 meeting

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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/

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