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Oyster Point Pharma, Inc.

Clinical Protocol: OPP-004:

Phase 2, Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease
(The MYSTIC Study)

Statistical Analysis Plan
Version 2.0

December 23, 2019

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Revision History

Version	Version Date	Author	Summary of Changes Made
Draft 0.1	October 30, 2019	[redacted]	New Document
Draft 0.2	November 12, 2019	[redacted]	Modified based on Sponsor's comment
Draft 0.3	November 18, 2019	[redacted]	Modified based on Sponsor's comment: Added the percent of subjects who achieve ≥ 10 mm improvement in Schirmer's Test Score (STS)
Draft 0.4 (V2.0)	December 23, 2019	[redacted]	Modified based on Sponsor's comment: Delete the percent of subjects who achieve ≥ 10 mm improvement in Schirmer's Test Score (STS)

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Prepared by:

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Contents

[redacted]

1 Synopsis

Protocol Title:	Phase 2, Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray of Signs of Dry Eye Disease (The MYSTIC Study)
Protocol Number:	OPP-004
Investigational Product:	OC-01 Nasal Spray
Study Objective:	The objective of this study is to evaluate the chronic safety and effectiveness of OC-01 Nasal Spray as compared to placebo on signs of dry eye disease (DED)
Treatment Assignment	120 subjects will be randomized in a 1:1:1 and will be treated with OC-01 nasal solution delivered twice daily as a 50 microliter (µL)-intranasal spray in each nostril at the following formulations: • 0.6 mg/mL • 1.2 mg/mL • Placebo (vehicle)
Analysis Population	[redacted]
Sample Size and Power	[redacted]

[redacted]

2 Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
BID	twice daily
CAE®	Controlled Adverse Environment®
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DED	dry eye disease
EDS	Eye Dryness Score
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	institutional review board
ITT	intent-to-treat
LS	least square
MAD	mucosal atomization device
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
µL	microliter
mm	millimeter
nAChR	nicotinic acetylcholine receptor
PP	per protocol
SAE	serious adverse event
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization

[redacted]

3 Introduction

This statistical analysis plan (SAP), which is based on the amendment #4 of the study protocol dated March 7, 2019, defines the methods and analyses that Oyster Point Pharma, Inc. (henceforth, Oyster Point) plans to use to analyze the data from Protocol OPP-004. This SAP complies with guidance promulgated by the International Conference on Harmonization (ICH) and the US Food and Drug Administration (FDA). If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP prevails.

4 Study objective

The objective of this study is to evaluate the chronic safety and effectiveness of OC-01 Nasal Spray as compared to placebo on signs of dry eye disease (DED).

5 Study Design

This is a Phase 2, single-center, randomized, single-masked, placebo-controlled study designed to evaluate the safety and efficacy of OC-01 nasal spray in adult participants with DED. Approximately 120 subjects at least 22 years of age with a physicians' diagnosis of dry eye disease and meeting all other study eligibility criteria will be randomized to receive an application of OC-01 or placebo twice daily (BID) for 12 weeks.

Participants who terminate early during the application period will be asked to complete safety assessments (if the participants agree) prior to study exit. Participants who are terminated early from the study will not be replaced.

Approximately 120 participants will be enrolled at a single center in Mexico City, Mexico. Subjects will be randomized to receive one of the following three dose assignments:

- Placebo (vehicle) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 0.6 mg/ml OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 1.2mg/ml OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID

Appendix 1 describes the detailed study visits, measurements, and dosing information.

6 Primary Safety, Efficacy and Other measures.

6.1 Safety Measures

- Adverse Events

[redacted]

- Visual Acuity
- Slit-Lamp Biomicroscopy
- Intranasal Examination

6.2 Efficacy Endpoint

The primary efficacy endpoint in this phase II study:

- Mean change from baseline in the study eye on Schirmer's Test at Day 84 (Visit 6).

6.3 Other Efficacy Endpoints

[redacted]

6.4 Other Measures

Other measures include:

- Urine pregnancy test at Visit 1 and Visit6/ET if applicable.
- Concomitant medication

7 Sample Size

[redacted]

8 Statistical Hypothesis Testing

[redacted]

9 Statistical Analysis

9.1 General Consideration

Descriptive and inferential statistics will be used to summarize results of Protocol OPP-004. Continuous variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Categorical variables will be summarized using frequency counts and percentages. Baseline measures will be defined as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

All summaries for safety data and efficacy data will be presented by treatment group. For the baseline characteristics, all summaries will be presented by treatment group and overall. All collected data will be presented in listings which will be sorted by treatment, subject ID, and visit when it is appropriate. Summaries, data listings, and statistical analyses will be generated using SAS® Version 9.4 or higher.

For the purpose of summarization, medical history, concomitant medications, and AEs will be coded to MedDRA Version 20.1 and World Health Organization Drug dictionaries (Version WHODDB3Sep2017), as appropriate.

9.2 Analysis Populations

[redacted]

9.2.3 Safety population

The safety population will include all randomized subjects who received at least one dose of the investigational product. Subjects in the safety population will be analyzed as treated.

9.3 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the study eye as defined as the eye that meets all inclusion and exclusion criteria. If both eyes qualify, then the study eye will be the eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit. If there is no difference in stimulated tear production, the study eye will be the eye with the lower Schirmer's Test Score at screening. If there is no difference for either measure, the right eye will be used as the study eye.

For safety endpoints, both eyes will be analyzed.

9.4 Definition of Study Day or Dosing Day

Study and dosing days are defined as follows:

Study Day = [Event date – First dosing date + 1] if after randomization
[Event date – First dosing date] if before randomization

Dosing Day = [Dosing date – First dosing date + 1]

Note that with the definition above, days of "0" will not be used.

For subjects whose reference date is missing, the study day will also be categorized as missing.

9.5 Missing and Partial Data

Adverse event onset

If onset date is completely missing, date is set to date of first dose.
If year is present and month and day are missing or year and day are present and month is missing:

- If year = year of first dose, then set month and day to month and day of first dose.
- If year < year of first dose, then set month and day to December 31.
- If year > year of first dose, then set month and day to January 1.

If month and year are present and day is missing:

- If year = year of first dose and
  - month = month of first dose, then set day to day of first dose date.
  - month < month of first dose, then set day to last day of month.
  - month > month of first dose, then set day to first day of month.
- If year < year of first dose, then set day to last day of month.
- If year > year of first dose, then set day to first day of month.

For all other cases, set date to date of first dose.

Adverse event end date

If year is present and month and day are missing or year and day are present and month is missing, set end month and day to December 31.
If month and year are present and day is missing, set the day to last day of the month.
If fatal event, date is set to minimum of imputed end date and death date.
For all other cases, set date to missing.

For summaries that present distribution of time expressed in weeks and months, weeks will be defined as days divided by 7 and months as days divided by 30.4375.

9.6 Protocol Deviations

Important protocol deviations will be summarized by randomized treatment group.
Sensitivity analyses for the primary and secondary efficacy outcomes will be performed if the deviations have the potential to have a non-trivial impact on the analysis.

[redacted]

9.7 Subjects Disposition

The number and percentage of subjects randomized and included in each analysis population will be summarized by treatment and overall. Reasons for excluding subjects from the analysis populations will be presented in a by-subject listing.

The number of randomized subjects who completed the study, discontinued early from study drug, and reasons for discontinuation will be summarized by treatment group and overall. The Case Report Form (CRF) lists the following reasons why subjects may discontinue treatment before completing of the study:

- Non-fatal adverse event (AE)
- Pregnancy
- Protocol violation
- Lost to follow-up
- Physician decision
- Subject non-compliance
- Death
- Study terminated by sponsor
- Withdraw by subject

9.8 Demographics and Baseline Characteristics

Continuous variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Categorical variables will be summarized using counts and percentages. Summary data will be presented by treatment group and overall.

The following demographic and baseline characteristics will be summarized: age, gender, ethnicity, race, and ocular history.

Age in years will be calculated as the integer portion of the following:
[(Date of randomization - Date of birth) + 1] / 365.25.

Other baseline measurements such as baseline visual acuity will be summarized by treatment group.

9.9 Medical, Ocular and Dry Eye History

Medical history terms and ocular history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 20.1) and the number and percent of subjects with medical history will be summarized by (SOC) and Preferred Term (PT) for each treatment group and overall based on the safety population.

9.10 Treatment Exposure

Each randomized subject will receive an application of OC-01 (varenicline) Nasal Spray or placebo twice daily (BID) for approximately 12 weeks. Duration of exposure to study treatment, in days, will be summarized for all randomized subjects. Summary statistics for duration of exposure will be presented by visit and treatment group.

10 Ocular Assessments

Ocular assessments will occur at baseline and different study visits, the results will be collected in terms of grade, clinical significance, and relatedness to administration procedure and study drug. These results will be listed, summarized in tables, and presented in figures as appropriate.

10.1 Schirmer's Test

The Schirmer's Test without nasal stimulation will be performed prior to treatment and after corneal fluorescein staining and post treatment. At Visit 1, the first Schirmer's Test without nasal stimulation (concurrent with treatment), which should be performed after corneal fluorescein staining, will be used as the baseline Schirmer's Test score and performed at every visit post-treatment. A second Schirmer's Test with nasal stimulation using a cotton swab will be 10 minutes after the first Schirmer's test to assess tear production. Schirmer's Test will be summarized by visit, time point and treatment with descriptive statistics.

10.2 BCVA

Best corrected visual acuity will be performed and collected at Visits 1, 2, 3, 4, 5 and 6 (pre- and post-treatment). Visual function of the study and fellow eye will be assessed using the best corrected ETDRS protocol starting at 10 feet. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be performed consistently using the same lighting conditions and same correction, if possible, during the entire study. If the same correction cannot be used (e.g., a

subject broke his/her glasses), the reason for the change in correction should be documented. BCVA will be summarized by visit and by treatment group for both study and fellow eyes. Abnormal clinically significant findings will be described. Shifts from baseline including normal to abnormal (not clinically significant), and normal to abnormal (clinically significant) will be presented using counts and percentages

10.3 Corneal Fluorescein Staining

Corneal fluorescein staining will be performed, and data will be collected at Visits 1 and 5. Corneal fluorescein staining will be assessed for both the study and fellow eye. Staining will be graded using the National Eye Institute (NEI)/Industry Workshop Scale. Examiners will score each of five areas on the cornea of each eye: 1 – Central; 2 – Superior; 3 – Temporal; 4 – Nasal; 5 – Inferior. A standardized grading system of 0-3 will be used for each of the five areas. The corneal fluorescein staining score will be described by visit, treatment, study eye, and fellow eye with summary statistics. Specifically, scores will be presented by each of the five cornea areas and total scores for all corneal areas.

10.4 Slit Lamp Biomicroscopy

The slit lamp biomicroscope will be performed at Visit 1, Visit 2, Visit 3, Visit 4, Visit 5 and Visit 6. A slit lamp will be used for external examination and biomicroscopy. The eyelids, cornea, conjunctiva, anterior chamber, iris, and lens will be examined at each visit. Slit lamp biomicroscopy results will be summarized for each treatment group for the study and fellow eye by visit using discrete summary statistics. Abnormal clinically significant findings will be described. Shifts from baseline including normal to abnormal (not clinically significant), and normal to abnormal (clinically significant) will be presented using counts and percentages

11 Intranasal Examination

Intranasal assessments collected at the screening visit (Visit 1) and at Visit 6, and the early termination visit will be summarized by treatment group with counts and percentages. Shifts from baseline of normal to abnormal (not clinically significant) and normal to abnormal (clinically significant) will be presented using counts and percentages.

12 Efficacy Analysis

12.1 Primary Efficacy Endpoint

The primary efficacy endpoint is mean change from baseline in Schirmer's Test at Day 84 (Visit 6).

[redacted]

12.2 Other Efficacy Endpoints

[redacted]

[redacted]

12.3 Missing Efficacy Data Handling

[redacted]

13 Safety Analysis

The safety population will be used for all safety analyses. All recorded safety parameters will be listed by treatment, subjects ID and visit or visit date.

13.1 Adverse Events

The investigator will promptly review each Adverse Event (AE) for accuracy and completeness, and classify each AE according to its intensity, its relationship to study drug or administration procedure, and its seriousness. AE will be coded using version 20.1 of the MedDRA dictionary. AEs will be monitored throughout the study and documented on the appropriate AE form. AEs will be categorized as ocular and non-ocular events as well as by system organ class (SOC) and preferred term (PT), seriousness, severity, and relation to study medications.

All treatment-emergent adverse events (TEAEs) will be summarized. TEAE is defined as AE is new or worsened in severity compared to the first dose of study drug. All AEs will be presented in the data listing with a flag as the indication of TEAE.

TEAEs will be summarized by subject level. In addition, # of TEAE episodes occurred during the study will be provided in the overall summary of AE table.

The following presentations of TEAEs will be generated:

- Overall adverse events summary (including any TEAEs, ocular TEAEs, resolved ocular TEAEs, non-ocular TEAEs, ocular TEAEs, non-ocular TEAEs, SAEs, treatment-emergent SAEs, treatment-related treatment emergent SAEs, TEAEs by maximum severity, TEAEs by relationship to study drug, AEs leading to study discontinuation);
- Serious adverse events (SAE) by SOC and PT;
- All ocular TEAEs by SOC and PT;

[redacted]

- All non-ocular TEAEs by SOC and PT;
- TEAEs related to the study medication;
- TEAEs leading to study discontinuation.

13.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODDB3Sep2017) and summarized for each treatment group based on the safety population. Prior medication is defined as any medication taken and stopped prior to the first dose of the study medication in the initial treatment period. Any medication taken from the day of first dose of the study treatment up to the day of last date of the study will be considered as concomitant medication for the treatment analysis.

Table 1 describes the classification of prior and concomitant medications.

[redacted]

13.3 Other Safety Endpoints

Other safety endpoints including visual acuity, slit-lamp biomicroscopy and intranasal examination will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.