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Oyster Point Pharma, Inc.

Clinical Protocol: OPP-002-01EXT

Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET Study)-Long Term Safety Follow-up

Statistical Analysis Plan
Version 1.0

October 25, 2019

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Prepared by:

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Contents

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1 Synopsis

Protocol Title:	Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET Study)-Long Term Safety Follow-up
Protocol Number:	OPP-002-01EXT
Investigational Product:	Subjects were previously treated in the OPP-002 study with one of the following formulations of OC- 01 (varenicline tartrate) nasal spray: 0.12 mg/mL (low dose), 0.6 mg/mL (medium dose), 1.2 mg/mL (high dose) or Placebo.
Study Objective:	The objective of this safety long-term follow-up study is to evaluate the safety of OC-01 Nasal Spray at 6 months and 12 months post treatment in the OPP-002 study.
Treatment Assignment	180 subjects were randomized in a 1:1:1:1 into one of four treatment groups in OPP-002: • OC-01 (varenicline) Nasal Spray, 0.12 mg/mL [low dose] • OC-01 (varenicline) Nasal Spray, 0.6 mg/mL [medium dose] • OC-01 (varenicline) Nasal Spray, 1.2 mg/mL [high dose] • Placebo (vehicle) [control]
Sample Size	Approximately 100 subjects previously enrolled in the OPP-002 study

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2 Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
BID	twice daily
CAE®	Controlled Adverse Environment®
CMH	Cochran-Mantel-Haenszel
CFR	Code of Federal Regulations
eCRF	Electronica case report form
CI	confidence interval
CRF	case report form
DED	dry eye disease
EDS	Eye Dryness Score
FDA	Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
ITT	intent-to-treat
logMAR	logarithm of the minimum angle of resolution
LS	least square
MAD	mucosal atomization device
MAR	missing at random
MCAR	missing completely at random
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MMRM	mixed model for repeated measures
MNAR	missing not at random
µL	microliter
mm	millimeter
nAChR	nicotinic acetylcholine receptor
OSDI©	Ocular Surface Disease Index©
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan

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SD	Standard deviation
STS	Schirmer's Test Score
TEAE	treatment-emergent adverse event
US	United States

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3 Introduction

This statistical analysis plan (SAP), which is based on the original study protocol dated January 21, 2019, defines the methods and analyses that Oyster Point Pharma, Inc. (henceforth, Oyster Point) plans to use to analyze the data from Protocol OPP-002-01EXT. 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 safety long-term follow-up study is to evaluate the safety of OC-01 Nasal Spray at 6 months and 12 months post treatment in the OPP-002 study.

5 Study Design

Protocol OPP-002-01EXT is a long-term follow-up study of those subjects that have previously participated in the OPP-002 study. The OPP-002 study was a Phase 2, multicenter, randomized, double-masked, placebo-controlled study designed to evaluate the safety and efficacy of OC-01 nasal spray in adult participants with DED. The first scheduled visit will occur 6 months after the first treatment of OC-01 Nasal Spray/Placebo in the OPP-002 study. The second scheduled visit will occur 12 months after the first treatment of OC-01 Nasal Spray/Placebo in the OPP-002 study.

6 Primary Safety Measures

- Intranasal Exam at Months 6 and 12
- Slit Lamp Examination at Months 6 and 12
- Adverse Events (AE) at Months 6 and 12

7 Statistical Analysis

7.1 General Consideration

Descriptive and inferential statistics will be used to summarize results of Protocol OPP-002-01EXT. 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 are defined in the OPP-002 protocol as the last measure prior to the initiation of study treatment.

All summaries for safety data will be presented by treatment group. For the subject characteristics at Visit 1, all summaries will be presented by treatment group and overall. All

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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.

7.2 Unit of Analysis

For safety endpoints, both eyes will be analyzed.

7.3 Analysis Populations

[redacted]

7.4 Missing and Partial Data

[redacted]

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.

7.5 Definition of Study Day or Dosing Day

[redacted]

7.6 Protocol Deviation

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7.7 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 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)
- Protocol violation
- Lost to follow-up
- Physician decision

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- Subject non-compliance
- Death
- Study terminated by sponsor
- Withdraw by subject

7.8 Demographics

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 at Visit 1 will be summarized: age and gender.

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

8 Ocular Assessments

Ocular assessments will occur at Visit 1 and Visit 2, 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.

8.1 Slit Lamp Biomicroscopy

The slit lamp biomicroscope will be performed at Visit 1, Visit 2, and the early termination. 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 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

9 Intranasal Examination

Intranasal assessments collected at Visit 1, Visit 2, 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.

10 Safety Analysis

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10.1 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 the MedDRA dictionary version 20.1. 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 and presented in the data listing. TEAE is defined as AE is new or worsened in severity after the first dose of study drug.

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.

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10.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODDB3Sep2017). A prior medication is defined as any medication taken within 60 days before dosing on Day 1 and stopped prior to the first dose of the study medication in the study. 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.

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Table 1 Classification of prior and concomitant medications			
End date / Start date	Taken within 60 days before dosing on Day 1	Taken during the treatment period until the last day of the study	Missing
Taken within 60 days before dosing on Day 1	Prior	Prior/ Concomitant	Prior/ Concomitant
Taken during the treatment period until the last day of the study	–	Concomitant	Concomitant
Missing	Prior	Prior/ Concomitant	Prior/ Concomitant

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Appendix 1 Schedule of Visits and Measurements

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