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Oyster Point Pharma, Inc.

Clinical Protocol: OPP-009:

A Phase 4, Single-Center, Open-Label Study Evaluating the Safety of the Nasal Guide Utilized During Administration with Tyrvaya®

Statistical Analysis Plan
Version 1.0

[redacted]

Date: July 13, 2023

Revision History

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Prepared by:

[redacted]

Approval Signatures:

[redacted]

[redacted]

Contents

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1 Synopsis

Protocol Title:	A Phase 4, Single-Center, Open-Label Study Evaluating the Safety of the Nasal Guide Utilized During Administration with Tyrvaya®
Protocol Number:	OPP-009
Investigational Product:	Nasal guide
Study Objective:	To determine the safety of the nasal guide when utilized to aid in the administration of Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray
Treatment Assignment	30 subjects will be provided the nasal guide to utilize with Tyrvaya® administration.
Sample Size and Power	[redacted]
Randomization and Stratification	Not applicable
Study Endpoints	Primary endpoints • Incidence of adverse events
Statistical Analysis for Primary Endpoint	The AE data collected from this study will be summarized with frequency and percentage. The profile of the adverse events will be made by comparing the results from this study with the external historical AE data collected for Tyrvaya® alone from OC-01 (varenicline solution) nasal spray Integrated Summary of Safety (ISS). The data comparison will be made without inferential statistics.
Analysis Population	[redacted]

[redacted]

Abbreviations

AE	adverse event
BID	two times a day
FDA	Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
MedDRA	medical dictionary for regulatory activities
mg	Milligram
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	treatment-emergent adverse event
US	United States

2 Introduction

This statistical analysis plan (SAP), which is based on the original protocol of the study protocol dated May 02, 2023, defines the methods, and analyses that Oyster Point Pharma, Inc. (henceforth, Oyster Point) plans to use to analyze and summize the data from Protocol OPP-009. 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.

3 Study objective

The objective of this study is to determine the safety of the nasal guide during administration of Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray.

4 Study Design

This is a single center, open-label study to evaluate the safety of the nasal guide during administration of Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray.
This study will consist of two visits over 7 days.

At Visits 1 and 2, the subjects will attach the nasal guide and administer one spray of Tyrvaya® (varenicline solution 0.03 mg) nasal spray in each nostril. In between study visits, subjects will administer one spray of the nasal spray in each nostril twice daily (BID) approximately 12 hours apart at home using the nasal guide.

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

5 Study Parameters

5.1 Primary Endpoint

The primary endpoint is the incidence of adverse events. The primary endpoint will be summarized based on the safety population.

5.2 Safety Measure

The safety measure is the adverse events. The safety measures will be summarized based on the safety population.

6 Sample Size Determination and Power Calculation

7 Randomization

Not applicable

8 Statistical Analysis

8.1 General Consideration

All data, including demographic and baseline characteristics and endpoint measures, will be summarized descriptively. 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 with frequency and percentage.

For the summaries, medical history and AEs will be coded using version 26.0 of the MedDRA dictionary.

All collected data will be presented in listings which will be sorted by subject ID and visit when it is appropriate. Summaries and data listings will be generated using SAS® Version 9.4 or higher.

8.2 Analysis Populations

8.2.1 Safety population

The safety population will include all enrolled subjects who received at least one Tyrvaya® administered with the nasal guide.

8.3 Definition of Study Day or Dosing Day

Study and dosing days are defined as follows:

Study Day = [Event date – Informed consent date + 1] if after informed consent date. [Event date – Informed date] if before informed consent date.

Dosing Day= [Event date – First dosing date + 1] if after first dosing date. [Event date – First dosing date] if before first dosing date.

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.

8.4 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.

8.5 Protocol Deviation

[redacted]

8.6 Subject Disposition

The number and percentage of subjects enrolled and included in sa
will be summarized. Reasons for excluding subjects from the analysis populations will be presented in a by-subject listing.

The number of enrolled subjects who completed the study, discontinued early from study, completed the treatment, discontinued early from the treatment, and reasons for discontinuation will be summarized.
The Case Report Form (CRF) lists the following reasons why subjects may discontinue treatment or discontinue study:

- Non-Fatal Adverse Event
- Protocol Violation
- Lost to Follow Up
- Pregnancy
- Disease Progression
- Physician Decision
- Subject Non-Compliance
- Death
- Study Terminated by Sponsor
- Withdrawal by Subject
- Other

8.7 Demographics and Baseline Characteristics

The following demographic will be summarized based on safety population:

- Age
- Gender
- Ethnicity
- Race

8.8 Medical History, Medical Procedure and Ocular History

Medical history terms, medical procedure terms and ocular history terms will be coded using the Medical Dictionaryfor Regulatory Activities (MedDRA) version 26.0 and the number and percent of subjects with medical history will be summarized by (SOC) and Preferred Term (PT) based on the safety population.

8.9 Treatment Exposure

Duration of exposure to study treatment, in days, will be summarized for all safety subjects.

8.10 Safety Analysis

8.10.1 Adverse Event

The investigator will promptly review each Adverse Event (AE) for accuracy and

completeness, and classify each AE according to its intensity, its re[redacted] administration procedure, and its seriousness. AEs will be coded using version 26.0 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. A TEAE is defined as an AE that is new or worsened in severity compared to the first dose of study drug.

TEAEs will be summarized by subject. In addition, the number of TEAE episodes that occurred during the study will be provided in the overall summary of AE table. All AEs will be presented in data listing with a flag indicating the event is a TEAE.

The following presentations of TEAEs will be generated:

- Overall adverse events summary (including any TEAEs, ocular TEAEs, resolved 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 treatment/study discontinuation)
- All TEAEs by SOC and PT
- All ocular TEAEs by SOC and PT
- All non-ocular TEAEs by SOC and PT
- Resolved ocular TEAEs by SOC and PT
- Serious adverse events (SAE) by SOC and PT
- Serious treatment-emergent adverse events (TESAE) by SOC and PT
- Related treatment-emergent serious adverse events (TESAE) by SOC and PT
- TEAEs by SOC and PT and by severity
- TEAEs by SOC and PT and by relationship
- TEAEs by SOC and PT leading to treatment discontinuation
- TEAEs by SOC and PT leading to study discontinuation

8.10.2 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (March 2023 version) and summarized in the safety population. 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 a concomitant medication for analysis.

[redacted]

Appendix 1 Schedule of Visits and Measurements

[redacted]