Clinical Trial Protocol

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
Study Phase:	4
Study treatment Name:	Tyrvaya® administered with the Nasal Guide
IND Number:	138645
Indication:	Dry Eye Disease
Investigators:	Single-Center
Sponsor:	Oyster Point Pharma, Inc 202 Carnegie Center Suite 106 Princeton, NJ 08540

	Date
Original Protocol version 1:	02 May 2023

Confidentiality Statement

SPONSOR PERSONNEL

[redacted]:	[redacted]
[redacted]	[redacted]

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
Study Treatment	Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray Administered with the Nasal Guide
Study Objective:	**Primary 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
Overall Study Design	
Methodology:	This is a single center study. Subjects will be provided the nasal guide to utilize with Tyrvaya® administration. 30 subjects will participate in this study.
Duration:	This study will consist of two visits over 7 days.
Controls:	Not applicable this is an open-label sub-study
Dosing Regimen:	Subjects will administer Tyrvaya® BID with nasal guide for 7 days
Summary of Visit Schedule	Nasal guide will be used to aid in the administration of Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray At Visits 1 and 2, 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.
Measures Taken to Reduce Bias:	Not applicable. This is an open label study.

Study Population Characteristics	
Number of Subjects:	30 subjects
Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	**Subjects must:** 1. Be at least 18 years of age [redacted] 3. Have provided verbal and written informed consent. [redacted] 5. Willing to comply with all study related visits and procedures
Exclusion Criteria:	**None**
Study Endpoints:	**Primary endpoints** • Incidence of adverse events
Safety Measures:	• Adverse Events
Statistical Methods:	[redacted]
Summary of Known and Potential Risks and Benefits to Human Subjects Refer to the Tyrvaya® Package Insert regarding the risks and benefits to human subjects. There are no known risks associated with the use of the nasal guide	

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
BID	Twice a Day
CFR	Code of Federal Regulations
CRF	Case report form
eCRF	Electronic Case Report Form
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
PI	Package Insert
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States

1 NASAL GUIDE

[redacted]

2 STUDY OBJECTIVES

To determine the safety of the nasal guide during administration of Tyrvaya® (varenicline solution 0.03 mg) Nasal Spray.

3 CLINICAL HYPOTHESIS

This study is testing the hypothesis that the use of the nasal guide with Tyrvaya® does not introduce any additional safety concerns as compared to the safety of Tyrvaya® alone.

4 OVERALL 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.

5 STUDY POPULATION

5.1 Number of Subjects

30 subjects will be enrolled at one study site in the United States (US).

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, of any gender and race and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

1. Be at least 18 years of age.

[redacted]

3. Have provided verbal and written informed consent.

[redacted]

5. Willing to comply with all study related visits and procedures.

5.4 Exclusion Criteria

Not applicable

5.5 Withdrawal Criteria

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study, but will be followed for safety for the duration of the study, unless they refuse to attend follow-up visits.

A subject may withdraw consent from the study at any time.
The Sponsor and/or the Investigator may discontinue any subject from study treatment for non-compliance or for any valid medical reason during the study (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Primary Endpoint

- Incidence of adverse events

6.2 Safety Measures

- Adverse events

7 STUDY MATERIALS

7.1 Nasal Guide

Subjects will be provided the nasal guide for use when administering Tyrvaya®. See Appendix 1 for Instructions for Use.

7.2 Tyrvaya®

Please see Tyrvaya package insert for additional information.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Section 5.2, Section 5.3 and Section 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a subject's enrollment in the trial (i.e., prior to any study-related procedures), the study will be discussed with each potential subject and subject wishing to participate must be administered and provide written informed consent using an Institutional Review Board (IRB)-approved informed consent form (ICF). The ICF must be the most recent version that has received approval by a properly constituted IRB.

8.1.3 Washout Intervals

There are no washout intervals for this study.

8.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups

Not applicable as this is an open label study.

8.2 Concomitant Therapies

The use of any concurrent medication, prescription or over the counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

8.2.1 Prohibited Medications

There are no prohibited medications for this study.

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activity is required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objectives(s)

The following procedures will be performed (see Appendix 2 for description).

The nasal guide will be used when administering Tyrvaya®. At Visits 1 and 2, subjects will attach the nasal guide and administer one spray Tyrvaya® 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.

Visit 1 (Day 1): Screening and Enrollment

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical history, prior medication (s), and ocular history
- Eligibility Criteria
- Enrollment
- Review Tyrvaya® Instructions for Use (IFU)
- Dispense nasal guide and IFU
- Subject Administration of Tyrvaya® with nasal guide
- Adverse Event Query

Visit 2 (Day 7)

- Subject administration of Tyrvaya® with nasal guide
- Concomitant Medications
- Adverse Events Query

Early Termination

- Concomitant Medications
- Adverse Event Query

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Assessment of AEs
- Any other assessments needed in the judgment of the Investigator.

8.5 Compliance with Protocol

Subjects will be instructed on the proper use and storage of the nasal guide and provided with written instructions for use at Visit 1.

8.6 Subject Disposition

8.6.1 Treatment Completed Subjects

A Completed Subject is one who has completed Visit 1 and Visit 2.

8.6.2 Discontinued Subjects

Subjects may be discontinued from treatment, or from involvement in the study at any time prior to their completion of the study due to:

- Non-fatal adverse event
- Protocol violations
- Disease progression
- Lost to follow-up.
- Physician decision
- Subject non-compliance
- Death
- Study terminated by the Sponsor
- Withdraw by subject (e.g., withdrawal of consent); and
- Other

Note: In addition, any subject may be discontinued from treatment or from study involvement for any sound medical reason at the discretion of the Investigator (after consultation with the Sponsor) or the Sponsor.

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor and will be clearly documented on the eCRF.

If a subject discontinues from treatment, the subject will be asked to be followed for safety for the duration of the study, unless they refuse to attend follow-up visits.

Discontinued subjects may be replaced.

8.7 Study Termination

The study may be stopped at any time by the Investigator and/or Sponsor, with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 2 visits over 7 days.

8.9 Monitoring and Quality Assurance

[redacted].

[redacted]

9 SAFETY DEFINITIONS, MONITORING AND REPORTING

9.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug or device in humans, whether the event is considered drug or device related or not. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the device, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the nasal guide will also be considered a new AE.

AE collection will start following the first administration of Tyrvaya® utilizing the nasal guide until the last follow up visit of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the Investigator or reported by the subject upon indirect questioning.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship

The relationship of each AE to the investigational product should be determined by the Investigator (in a blinded manner) using these explanations:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE
- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable

- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example, due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data, or poor documentation.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* An AE that is listed in the IB at the specificity and severity that has been observed.
- *Not Applicable:* Any AE that is unrelated to the study drug.

AEs that are mentioned in the Package Insert (PI) as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the drug under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered a serious adverse event (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include emergency room visits; outpatient/same day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

Note: Planned hospital admissions or surgical procedures for an illness or disease that was present before the patient received any study drug are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier than planned).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).

- A congenital anomaly/birth defect in an offspring of a study subject.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs are collected at the time the subject signs the Informed Consent Form until the last follow up visit of the study.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to the Sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the device, must be reported within 24 hours of the Investigator's knowledge. All information relevant to the SAE must be recorded on the appropriate CRFs. The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the Investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide the Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the SAE within their guidelines for reporting SAEs.

The SAE form must be completed and submitted to safety@oysterpointrx.com.

9.4 Procedures for Unmasking

Not applicable as this is an open label study.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The Investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-ups will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

New information relating to a previously reported serious adverse event must be submitted. All new information for serious adverse events must be submitted within 24 hours following the investigator's knowledge of new information. The investigator may be asked to provide additional follow-up information, which may include discharge summary or extracts from the medical record.

10 STATISTICAL METHODS

Statistical considerations and methods of analyses for this study are provided below; the accompanying Statistical Analysis Plan (SAP) contains complete details of the planned analyses.

10.1 Primary Endpoint

10.1.1 Primary Endpoint

- Incidence of Adverse Event

10.2 Analysis Populations

10.2.1 Safety Population

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

10.3 Statistical Analysis

This section briefly outlines the planned analyses. The statistical analysis plan (SAP) describes the methods to be used in detail. If the SAP and the protocol disagree, the details and methods of the SAP will prevail.

The AE data collected from this study will be compared with the historical AE data collected for Tyrvaya® alone from OC-01 (varenicline solution) nasal spray Integrated Summary of Safety (ISS). The data comparison will be presented descriptively without inferential statistics comparison.

10.3.1 General Considerations

No formal sample size calculation will be made in this pilot study. All data, including demographic and baseline characteristics and endpoint measures, will be summarized descriptively. Continuous variables will be summarized with mean, median, and standard deviation. Categorical variables will be summarized with frequency and percentage.

10.3.2 Safety Analysis

The investigator will promptly review each Adverse Event (AE) for accuracy and completeness, and classify each AE according to its intensity, its relationship to drug or administration procedure, and its seriousness. AEs will be coded using version 22.0 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.

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 treatment/study discontinuation)
- Serious adverse events (SAE) by SOC and PT;
- All ocular TEAEs by SOC and PT;
- All non-ocular TEAEs by SOC and PT;
- TEAEs leading to treatment discontinuation;
- TEAEs leading to study discontinuation

10.3.3 Interim Analysis

No interim analysis is planned for this study.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with this protocol, Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs/devices in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Sponsor prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Sponsor and provided in writing by Sponsor prior to the consent process.

11.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations [U.S. 21 Code of Federal regulations (CFR) Part 56.103]. The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the informed consent form will be used.

11.2 Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions so as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of the Sponsor, the IRB approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the above listed individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as photographs, X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the CRFs serves as the Investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal

11.5.1 Labeling and Packaging

Commercially available Tyrvaya® will be utilized in this study. Please refer to the Tyrvaya® package insert for additional information.

The nasal guide will be provided individually wrapped and sealed in plastic storage bag. Please refer to the nasal guide package insert for additional information.

11.5.2 Storage of Nasal Guide

The nasal guide can be stored ambient temperature at 20°C to 25°C (68°F to 77°F).

11.5.3 Accountability of Nasal Guide

The nasal guide is only prescribed by the principal Investigator or his/her named sub investigator(s) and is to only be used in accordance with this protocol. The nasal guide must only be distributed to subjects properly qualified under this protocol. The Investigator must keep an accurate accounting of the nasal guide by maintaining a detailed inventory. This includes the

amount o received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4 Return or Disposal of Nasal Guide

You may be requested to destroy the nasal guides at the end of the study. If site regulations do not permit destruction, the nasal guides will be returned to the Sponsor or their designee for destruction.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. A recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff who have been trained on the system and have access to the system. Minimal data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, electronic copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7 Handling of Biological Specimens

Not applicable.

12 REFERENCES

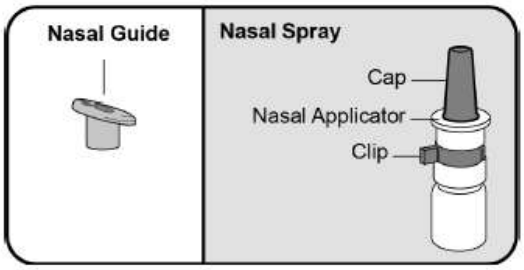
13. APPENDICES

Appendix 1: Nasal Guide Instructions for Use

Nasal Guide

Intended Purpose: Nasal Guide is an optional accessory that helps you administer TYRVAYA® (varenicline solution) Nasal Spray by pointing the spray tip in the correct direction inside the nose and ensuring the tip doesn't go too far into the nose. For use only with TYRVAYA, as prescribed by your doctor.

Instructions for Use: Before using Nasal Guide, read these instructions and the Instructions for Use supplied with TYRVAYA. Do not discard these instructions. If you have questions, please ask your doctor or your pharmacist. Keep accessory out of the reach of children. **Prepare TYRVAYA for use including priming steps per the Instructions for Use.**



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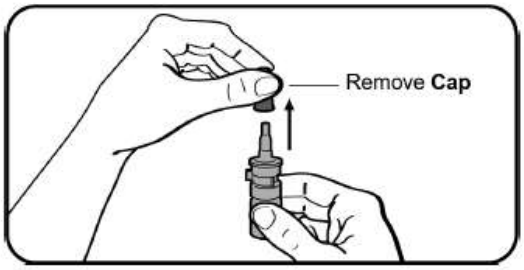
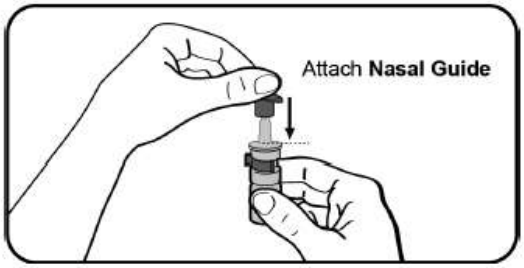
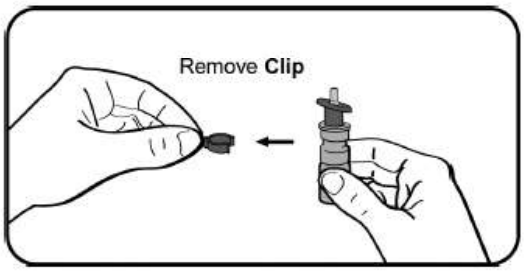
1 Attach Nasal Guide to TYRVAYA.

- Remove the blue cap from the Tyrvaya nasal applicator.
- Ensure the clip is on prior to attaching the Nasal Guide.
- Slide Nasal Guide down over the tip of the nasal applicator to sit flat against the base of the nasal applicator.
- Remove the clip.

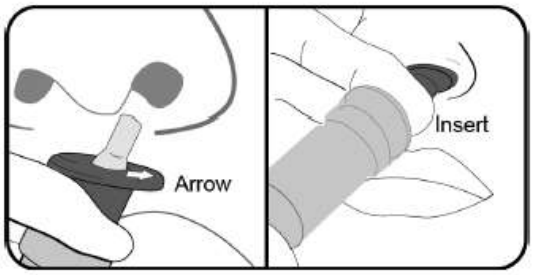






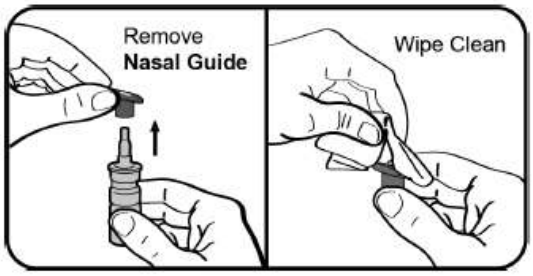
2 Position TYRVAYA correctly.

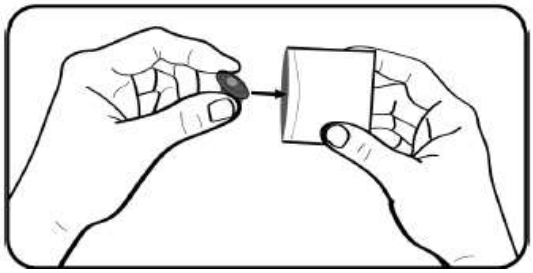
- When ready to spray TYRVAYA into your nostril, point the arrow on Nasal Guide towards the ear on the same side as your nostril.
- Insert TYRVAYA into the nostril until Nasal Guide touches the bottom of the nose. Administer TYRVAYA per the Instructions for Use.



3 Remove and store Nasal Guide.

- Slide Nasal Guide up from the nasal applicator.
- Wipe Nasal Guide with a clean tissue.
- Store Nasal Guide in its bag until the next use.
- Wipe the TYRVAYA nasal applicator with a clean tissue. Replace the clip and the cap as per the TYRVAYA Instructions for Use.
- The Nasal Guide can be cleaned weekly by soaking for 15 minutes in a mild solution of liquid dish detergent and lukewarm water. Agitate gently. Rinse with clean water and dry with a clean tissue. **DO NOT PLACE IN DISHWASHER**.





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APPENDIX 3: SPONSOR APPROVALS

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

APPENDIX 4: INVESTIGATOR'S SIGNATURE

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

Protocol Number: OPP-009

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed: _____ Date: _____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____