Clinical Trial Protocol

Protocol Title:	An Open-Label, Single-Center, Randomized, 2-way Crossover Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 Nasal Spray as Compared to Varenicline Administered Orally as Chantix® (The ZEN Study)
Protocol Number:	OPP-100
Study Phase:	1
Product Name:	OC-01 (varenicline) Nasal Spray and Chantix®
[redacted]	[redacted]
Indication:	Healthy Volunteers
Investigators:	Single-Center
Sponsor:	Oyster Point Pharma, Inc. 700 Alexander Park Drive Suite 301 Princeton, NJ 08540
	Date
Original Protocol:	06 June 2019
Amendment #1	28 June 2019
Amendment #2	13 July 2019

Confidentiality Statement

SPONSOR PERSONNEL

[redacted]	[redacted]

SYNOPSIS

Protocol Title:	An Open-Label, Single-Center, Randomized, 2-way Crossover Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 Nasal Spray as Compared to Varenicline Administered Orally as Chantix®
Protocol Number:	OPP-100
Investigational Product:	OC-01 (varenicline) Nasal Spray
Study Objectives:	**Primary Objective:** To assess the relative bioavailability of varenicline administered intranasally at its highest intended clinical strength compared to varenicline administered orally at its highest oral tablet strength. **Secondary Objective:** To assess the clinical and laboratory safety of varenicline administered as a single dose orally and intranasally.
Overall Study Design	
Structure:	This is an open label, single dose, randomized, 2-way crossover study. Subjects will attend the unit for a screening assessment up to 28 days prior to the first dose. Subjects who are eligible for the study will return to the unit for 2 in-unit treatment periods, each separated by a minimum of 14 days. An End of Study visit will occur 7-14 days after the final dose. The two study treatments are: • Single oral dose of 1 mg varenicline (Chantix®). • Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril **Treatment Period 1:** Subjects will be admitted and will be randomly assigned to receive a single dose of varenicline either orally or intranasally. The administration dose will be delivered after an overnight fast by the subject. PK samples will be collected pre-dose and in an intensive sampling regimen up to 120 hours post-dose to allow for the assay of varenicline. **Treatment Period 2:** This period will be identical to Treatment Period 1 except that the administration of varenicline will be via the intranasal

	route for those subjects that previously received varenicline via the oral route. Those subjects that were previously administered oral varenicline during Treatment Period 1 will receive varenicline via the intranasal route. **End of Study Visit** will occur 7-14 days after the final period's dose of varenicline when follow-up assessments will be performed.
Duration:	10 study visits over a period of approximately 60 days: **Screening: Day -28 to -2** **Period 1: Day 1-3 (In-Unit Subjects will be confined in the Clinical Research Unit (CRU) from the morning of Day -1 until at least 48 hours post-dose (Day 3)); Day 4-6 (Out-Patient)** **Period 2: Day 15-17 (In-Unit Subjects will be confined in the Clinical Research Unit (CRU) from the morning of Day 14 until at least 48 hours post-dose (Day 17)); Day 18-20 (Out-Patient)** **End of Study: Day 27 + 7**
Control:	N/A
Dosing Regimen:	**Treatment A**: Single oral dose of 1 mg of Chantix® (varenicline) administered orally **Treatment B:** Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril
Collection Schedule:	**Treatment Period 1 and Treatment Period 2:** *All times are after study drug administration except for predose (time 0)* **In-Unit Blood PK Sampling** **Sample 1**: Predose (time 0) **Sample 2:** 5 minutes **Sample 3:** 15 minutes **Sample 4:** 30 minutes **Sample 5:** 1 hour **Sample 6:** 2 hours

	Sample 7: 3 hours **Sample 8:** 4 hours **Sample 9:** 6 hours **Sample 10:** 8 hours **Sample 11:** 12 hours **Sample 12:** 24 hours **Sample 13:** 36 hours **Sample 14:** 48 hours **Out-Patient Blood PK Sampling** **Sample 15:** 72 hours **Sample 16:** 96 hours **Sample 17:** 120 hours
Sample Collection and Storage:	Blood samples (4 mL in K_2EDTA tubes) are collected from an arm vein or catheter into Vacutainer tubes containing K_2EDTA. Blood samples are mixed gently and maintained chilled until centrifuged within 2 hours of collection. Plasma samples are separated into two equivalent aliquots and labeled appropriate with subject ID, site and nominal time point [redacted]
Study Population Characteristics	
Number of Subjects:	Approximately 22 healthy volunteer subjects will be enrolled such that approximately 18 subjects complete the relevant PK assessments.
Condition/Disease:	Healthy Volunteers
Inclusion Criteria:	Subjects **must**: [redacted] 2. Have a body mass index between 18.0 and 32.0 kg/m^2, inclusive. 3. Be healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical

	history, physical examination, ECG and laboratory tests with no clinically significant findings. 4. Have provided verbal and written informed consent. 5. If a female of childbearing potential who is not using an acceptable means of birth control (acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom, IUD, or surgical sterilization of partner), have a negative urine pregnancy test at the Screening Visit.
Exclusion Criteria:	Subjects must **NOT:** 1. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas. 2. Have a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction as confirmed by intranasal examination at the Screening Visit. [redacted] [redacted] 5. Any contraindication to varenicline according to the applicable label. 6. Have severe renal impairment (estimated creatinine clearance less than 30mL per minute). 7. Have current concomitant use of snuff, chewing tobacco, e-cigarettes or cigarettes/cigars during the study. [redacted] 9 [redacted] 10. Have any condition or history that, in the opinion of the investigator, may interfere with study compliance, outcome

	measures, safety parameters, and/or the general medical condition of the subject. [redacted] 12. Be a female who is pregnant, nursing an infant, or planning a pregnancy at the Screening Visit. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. 13. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days or 90 for investigational biologics prior to the Screening Visit. [redacted]

Evaluation Criteria	
Pharmacokinetic Endpoints:	Varenicline plasma $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, T_{max}, $T_{½}$, K_{el}
Safety Measures:	Adverse events, clinical chemistry, hematology and urinalysis, vital signs assessments, physical examinations, ECGs and intranasal examinations.
Statistical Methods:	**Pharmacokinetics** [redacted]
[redacted]	

[redacted]

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LIST OF ABBREVIATIONS

Term	Description
AE	adverse event
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BID	two times a day
BUN	blood urea nitrogen
CAE®	controlled adverse environment
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration observed
CRF	case report form
ECG	electrocardiogram
EDS	eye dryness score
EDTA	ethylenediaminetetraacetic acid
ENT	ear nose and throat
DED	dry eye disease
GGT	gamma-glutamyl transferase
HIPAA	health Information Portability and Accountability Act
IB	Investigator's Brochure
ID	identification
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intention to treat
Kel	elimination rate constant
Kg	kilograms
logMAR	logarithm of the minimum angle of resolution
LS	least square
M^2	meter square

Term	Description
MAD	mucosal atomization device
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
µL	microliter
mL	milliliter
mm	millimeter
nAChR	nicotinic acetylcholine receptor
PCSA	potentially clinically significant abnormalities
PK	pharmacokinetic
PP	per protocol
RBC	red blood cell count
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxalocaetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	standard of care
TEAE	treatment-emergent adverse event
T_{max}	time to reach the maximum concentration observed
US	United States
WBC	white blood cell count
WHO	World Health Organization

1. INTRODUCTION

[redacted]

2. STUDY OBJECTIVES

The primary objective is to assess the relative bioavailability of varenicline administered intranasally at its highest intended clinical strength compared to varenicline administered orally at its highest oral tablet strength.

The secondary objective is to assess the clinical and laboratory safety of varenicline administered orally and intranasally.

3. CLINICAL HYPOTHESES

No formal hypothesis testing will be performed.

4. OVERALL STUDY DESIGN

Protocol OPP-100 is a Phase 1, open-label, randomized, 2-way crossover study to evaluate the relative bioavailability of OC-01 (varenicline) Nasal Spray compared to varenicline administered orally as Chantix®. Approximately 22 healthy volunteer subjects between 18-65 years of age meeting all other study eligibility criteria will be randomized (Treatment Period 1) to receive an intranasal dose of 0.12 mg OC-01 (50 µL spray of 0.06 mg into each nostril) or a single 1 mg oral dose of Chantix®. Both administrations will be delivered while subject is in an overnight fasted state. Subjects then will return at least 14 days later (Treatment Period 2) to receive the alternate dose of varenicline that was delivered at Treatment Period 1. Again, this delivery will be performed while subject is in an overnight fasted state.

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.

5. STUDY POPULATION

5.1. Number of Subjects

Approximately 22 healthy volunteer participants will be enrolled at one site in the US. Subjects who are eligible for the study will return to the unit for two in-unit treatment periods, each separated by at least 14 days. The two study treatments are:

- **Treatment A**: Single oral dose of 1 mg varenicline (Chantix®) administered orally
- **Treatment B**: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril

5.2. Study Population Characteristics

All subjects must be between 18-65 years of age, inclusive of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3. Inclusion Criteria

Subjects must:

- [redacted].

2. Have a body mass index between 18.0 and 32.0 kg/m^2, inclusive.
3. Be healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, ECG and laboratory tests with no clinically significant findings.
4. Have provided verbal and written informed consent
5. If a female of childbearing potential who is not using an acceptable means of birth control (acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom, IUD, or surgical sterilization of partner), have a negative urine pregnancy test at the Screening Visit.

5.4. Exclusion Criteria

Subjects must not:

1. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas.
2. Have a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction as confirmed by intranasal examination at the Screening Visit.

[redacted]

[redacted]

5. Any contraindication to varenicline according to the applicable label.
6. Have severe renal impairment (estimated creatinine clearance less than 30mL per minute).
7. Have current concomitant use of snuff, chewing tobacco, e-cigarettes or cigarettes/cigars during the study.

[redacted]

[redacted]

10. Have any condition or history that, in the opinion of the investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject.

[redacted]

12. Be a female who is pregnant, nursing an infant, or planning a pregnancy at the Screening Visit. Be a woman of childbearing potential who is not using an acceptable means of birth

control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner.

13. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days or 90 for investigational biologics prior to the Screening Visit.

[redacted]

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 treatment, but should attend the final follow up visit for safety evaluation.

Subjects may withdraw consent from the study at any time.

Sponsor and/or Investigator may discontinue any subject from study treatment for non- compliance or any valid medical reason during the course of the study (see Section 8.7.2 Discontinued Subjects).

6. STUDY PARAMETERS

6.1. Pharmacokinetic Parameters

The follow pharmacokinetic parameters will be calculated on the varenicline plasma levels:

- [redacted]
- [redacted]

[redacted]

6.2. Safety Measures

[redacted]

7. STUDY MATERIALS

7.1. Drug Supply

- Treatment A: Single oral tablet of 1 mg varenicline (Chantix®)

  Chantix® is supplied as 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

- Treatment B: OC-01 (varenicline) Nasal Spray delivered as a 50 µL spray (0.06 mg per each 50 µL spray) into each nostril for a total delivered dose of 0.12 mg.
  - OC-01 (varenicline) Nasal Spray will be formulated at the desired concentration in sodium phosphate buffers and sodium chloride as an aqueous solution and presented in an amber glass vial with a multi-use preservative-free nasal pump.
  - OC-01 (varenicline) Nasal Spray is preservative-free and intended for intranasal use only. The product should not be used if cloudy or if particulate matter are present.
  - OC-01 solution must be administered without dilution.

7.2. Other Study Supplies

- Intranasal speculums

8. STUDY METHODS AND PROCEDURES

8.1. Participant Entry Procedures

8.1.1. Overview

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

8.1.2. Informed Consent

Prior to a participant's enrollment in the trial (i.e., prior to any study-related procedures), the study will be discussed with each potential participant and participants 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

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4).

8.1.4. Procedures for Final Study Entry

Subjects must meet all inclusion criteria and none of the exclusion criteria.

8.1.5. Methods for Assignment to Treatment Groups

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent form (ICF) receives a unique subject identification number before any study-related activities/procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study.

Subjects who meet the eligibility requirements will be randomly assigned to receive Treatment A or Treatment B during Treatment Period 1. For Treatment Period 2, subjects will receive the alternate treatment not received during Treatment Period 1.

8.2. Concomitant Therapies

[redacted]

[redacted]

8.2.1. Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4)

8.2.2. Escape Medications

No escape medication is required for this study.

8.2.3. Special Diet or Activities

Subjects must be in a fasted state overnight and abstain from alcohol for 24 hours prior to each study period until after the last sample is collected from each study period.

8.3. Examination Procedures

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

The following procedures will be performed (see Appendix 2 for description). Repeat assessments can be performed at the discretion of the investigator.

Screening/Visit (Day -28 to -2):

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical history, concomitant medications
- Eligibility Criteria
- Urine pregnancy test (if applicable)
- Drug and Alcohol Screen
- Physical Examination
- 12-lead ECG
- Vital Signs
- Laboratory samples (hematology, chemistry)

- Urinalysis
- Intranasal Examination

Period 1 Check-In (Day -1)

- Serum pregnancy test (if applicable)
- Drug and Alcohol Screen
- Intranasal Examination
- Concomitant Medications

Period 1 (Day 1-6):

- Vital Signs (pre-treatment and 2 hours post treatment administration)
- Laboratory Samples (chemistry 2 hours post treatment administration)
- Randomization
- Administration of OC-01 (varenicline) Nasal Spray or Chantix®
- PK Sample Collection
- Concomitant Medications
- AE Query

Period 2 Check-In (Day 14)

- Serum Pregnancy Test (if applicable)
- Drug and Alcohol Screen
- Intranasal Examination
- Concomitant Medications
- AE Query

Period 2 (Day 15-20):

- Vital Signs (pre-treatment and 2 hours post treatment administration)
- Laboratory Samples (chemistry 2 hours post treatment administration))
- Administration of OC-01 (varenicline) Nasal Spray or Chantix®
- PK Sample Collection
- Concomitant Medications
- AE Query

End of Study/Early Termination (Day 27 + 7):

- Urine pregnancy test (if applicable)
- Physical Examination
- 12-lead ECG
- Vital Signs
- Laboratory Samples (hematology, chemistry)
- Urinalysis
- Intranasal Examination
- Concomitant Medications
- AE Query

8.4. Pharmacokinetic Sampling Schedule

PK samples should be collected according to the following schedule during Treatment Period 1 and Treatment Period 2:

All times are after study drug administration except for predose (time 0)

In-Unit Blood PK Sampling

Sample 1: Predose (time 0)
Sample 2: 5 minutes
Sample 3: 15 minutes
Sample 4: 30 minutes
Sample 5: 1 hour
Sample 6: 2 hours
Sample 7: 3 hours
Sample 8: 4 hours
Sample 9: 6 hours
Sample 10: 8 hours
Sample 11: 12 hours
Sample 12: 24 hours
Sample 13: 36 hours
Sample 14: 48 hours

Out-Patient Blood PK Sampling

Sample 15: 72 hours
Sample 16: 96 hours

Sample 17: 120 hours

8.5. Schedule of Visits, Measurements and Dosing

8.5.1. Scheduled Visits

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

8.5.2. Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source.

Evaluations that may be conducted at an Unscheduled Visit include:

- Intranasal Examination
- Physical Examination
- Vital Signs
- 12 lead ECG
- Laboratory assessments/urinalysis
- Urine pregnancy test (if applicable)
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator

8.6. Compliance with Protocol

Oyster Point Pharma, Inc. will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified in the protocol.

The investigator will conduct the trial in compliance with the protocol and approved by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Oyster Point Pharma, Inc. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact Oyster Point Pharma, Inc. Any departures from the protocol must be documented.

8.7. Subject Disposition

8.7.1. Completed Subjects

A completed subject is one who has completed both the Period 1 and Period 2 study visits and has received treatment with both OC-01 (varenicline) Nasal Spray and Chantix®.

8.7.2. 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:

- AEs
- Protocol violations
- Lost to follow-up
- Pregnancy
- Physician decision
- Subject non-compliance
- Sponsor termination of study
- Withdrawal by subject
- Other reasons

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

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor and/or its designee and will be clearly documented.

Discontinued subjects will not be replaced.

8.8. Study Termination

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

8.9. Study Duration

An individual subject's participation will involve ten visits over approximately 60 days.

8.10. Monitoring and Quality Assurance

[redacted]

9. SAFETY DEFINITIONS, SAFETY MONITORING AND REPORTING

9.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. 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 study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new AE.

Study drug includes the investigational drug under evaluation. Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, expectedness 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. AE collection will start following the first administration of study drug until the last follow up visit of the study.

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 to Study Drug

The relationship of each AE to the investigational product should be determined by the investigator using these explanations:

- *Definite:* When there are good reasons and/or sufficient documentation to demonstrate a direct causal relationship between investigational product and AE
- *Probable:* When there are good reasons and/or 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 IB 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 particular 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 "serious" (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.

- 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.
- Other medically important event

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/or its designee, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate source documents.

9.3.1. Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to the Sponsor and/or its designee 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 study drug, must be immediately reported. All information relevant to the SAE must be recorded. The investigator is obligated to pursue and obtain information requested by the Sponsor and/or its designee. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify the Sponsor and/or it's designee immediately; 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 and/or its designee 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.

Refer to the SAE form for additional reporting instructions.

9.4. 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-up will be documented in the subject's source document.

If the Investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to the Sponsor and/or its designee within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10. STATISTICAL ANALYSIS

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. Sample Size and Power Considerations

[redacted]

10.2. Analysis Populations

- Pharmacokinetics
- Safety Population

10.3. Statistical Hypotheses

No formal hypothesis will be tested.

10.4. Statistical Analysis

This section briefly outlines the planned analyses. The 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.

10.4.1. General Considerations

[redacted]

Table 1: Interim Analysis Matrix

Outcome	Action
[redacted]	[redacted]

Outcome	Action
[redacted]	[redacted]
[redacted]	[redacted]

10.4.1.1. Subject Demographics and Baseline Characteristics

Continuous summary statistics will be generated for age in years by treatment group and for all subjects. Discrete summary statistics will be generated for the following qualitative demographic variables: age category, gender, ethnicity, race, and other baseline intranasal examination results, tabulated by treatment group and for all subjects. Individual subject data listings will support the Summary tables.

10.4.2. Pharmacokinetic Analysis

[redacted]

10.4.2.1. Safety Analysis

[redacted]

10.4.3. Interim Analysis

[redacted]

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

This study will be conducted in compliance with the 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 in the countries involved will be adhered to.

11.1. Protection of Human Subjects

11.1.1. Subject Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. 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. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record.

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 the Sponsor and/or it's designee 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 the Sponsor and provided in writing by 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 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 aforementioned 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 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 of Study Drug

11.5.1. Labeling/Packaging

[redacted]

11.5.2. Storage of Investigational Drug / Placebo

[redacted]

11.5.3. Accountability of Study Drug

OC-01/Chantix® must only be prescribed by the principal investigator or his/her named sub investigator(s) and is to only be used in accordance with this protocol. The study drugs must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drugs by maintaining a detailed inventory. This includes the amount of study drugs 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 Study Drug

OC-01 (varenicline) Nasal Spray will be returned to the Sponsor or their designee for destruction.

11.6. Recording of Data

All subject data will be captured in the subject source documents. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original

Data capture 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. Data will not be analyzed for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the database. After the end of the study and database lock, electronic copies of all applicable subjects' source documents will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7. Handling of Biological Specimens

Blood samples (4 mL in K_2EDTA tubes) are collected from an arm vein or catheter into Vacutainer tubes containing K_2EDTA. Blood samples are mixed gently and maintained chilled until centrifuged within 2 hours of collection.

Plasma samples are separated into two equivalent aliquots and labeled appropriate with subject ID, site and nominal time point [redacted]

All samples and associated results will be coded prior to being shipped from the site for analysis. Samples will be tracked using the unique identification number that is assigned to the subject.

11.8. Publications

The study will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or Investigator may publish or present any results from the study until the Sponsor completes a joint publication of the trial in conjunction with various participating Investigators and appropriate sites contributing data and comments. Subsequently, individual Investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the Clinical Trial Agreement will prevail.

12. REFERENCES

[redacted]

13. APPENDICES

APPENDIX 1. SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Screening	Period 1 Check-In	Period 1	Period 2 Check-In	Period 2	End of Study/Early Termination
	Day -28 to -2	Day -1	Days 1-6	Day 14	Days 15-20	Day 27 + 7 Days
Informed consent/HIPAA	X					
Demographics	X					
Medical history	X					
Eligibility criteria	X					
Urine pregnancy test[1]	X					X
Serum pregnancy test[1]		X		X		
Drug and Alcohol Screen	X	X		X		
Physical Examination[2]	X					X
12-lead ECG	X					X
Vital Signs[3]	X		X		X	X
Laboratory Samples (hematology, chemistry)[4]	X		X[4]		X[4]	X
Urinalysis	X					X
Intranasal Examination	X	X		X		X
PK Sample Collection[5]			X		X	
Randomization			X			
Administer OC-01 (varenicline) Nasal Spray/Chantix®			X		X	
Concomitant medications	X	X	X	X	X	X
AE Query			X	X	X	X

[1] For females of childbearing potential
[2]Weight and height collected at Screening Visit only
[3]Vital signs including heart rate, respiratory rate and blood pressure will be obtained at Screening, prior to treatment administration at Periods 1 and 2, and 2 hours post treatment administration at Periods 1 and 2, and End of Study/Early Termination.
[4]Clinical Chemistry to be performed at Screening, and 2 hours post treatment administration Periods 1 and 2, and End of Study/Early Termination. Hematology to be performed at Screening and End of Study/Early Termination.
[5]PK samples collected at the following timepoints post treatment administration (predose, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours). Samples collected up to and including 48 hours will be performed In-Unit. Following the 48 hour sample collection subjects will be discharged and return for remaining samples on an Out-Patient basis.

APPENDIX 2. EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

The following examination procedures, tests, equipment and techniques are listed in this Appendix:

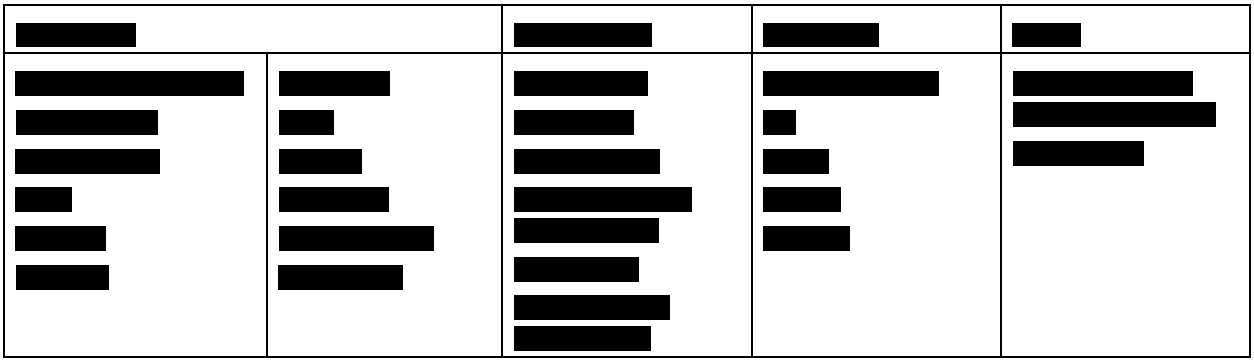
A1. Intranasal Examination

Qualified participants for the study must undergo an intranasal exam to make the final eligibility determination (e.g. severe nasal airway obstruction such as, severe septal deviation or inferior turbinate hypertrophy, or vascularized polyp seen on examination are reasons for exclusion). To monitor nasal mucosal integrity during the study for participant safety, an examination of the nasal cavities via an intranasal exam will be performed at the Screening Visit (after all other screening procedures have been completed), Periods 1 and 2 Check-in, and at the End of Study/Early Termination Visit. This examination will be performed by an Ear Nose and Throat (ENT) specialist, otolaryngologist or other suitably qualified medical practitioner (i.e. one who has been trained to perform intranasal exam). The procedure used for the intranasal exam can be conducted either by endoscopic examination or nasal specula.

A2. Laboratory Samples

The Schedule of Visits and Measurements (Appendix 1) defines the timepoints when each analyte should be collected. Table 2 below outlines the specific analytes to be tested:

Table 2: Laboratory Analytes



A3. Physical Examination

A physical examination will be conducted as per Standard of Care (SOC). Breast, genital and rectal examinations are not required unless specific evaluation is warranted. Physical examination findings should be recorded on the appropriate source document (e.g., medical history). Body

height and weight will be collected at screening. Height should be measured in centimeters (without shoes). Weight should be measured in kilograms (without shoes).

A4. Vital Signs

Vital signs, including heart rate, respiratory rate and blood pressure will be obtained. Subjects must be in supine or sitting position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same that is used throughout the study. Vital sign assessments should be performed prior to blood sample collection.

A5. Electrocardiogram

A 12-lead ECG will be obtained during Screening and End of Study/Early Termination. Subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible.

The principal investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. ECG should be performed prior to blood sample collection.

APPENDIX 3. SPONSOR APPROVALS

Protocol Title: An, Open-Label, Single-Center, Randomized, 2-way Crossover Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 Nasal Spray as Compared to Varenicline Administered Orally as Chantix® (The ZEN Study)

Protocol Number: OPP-100

Signed: [redacted] Date: [redacted]

APPENDIX 4. INVESTIGATOR'S SIGNATURE

Protocol Title: An, Open-Label, Single-Center, Randomized, 2-way Crossover Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 Nasal Spray as Compared to Varenicline Administered Orally as Chantix® (The ZEN Study)

Protocol Number: OPP-100

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: _____

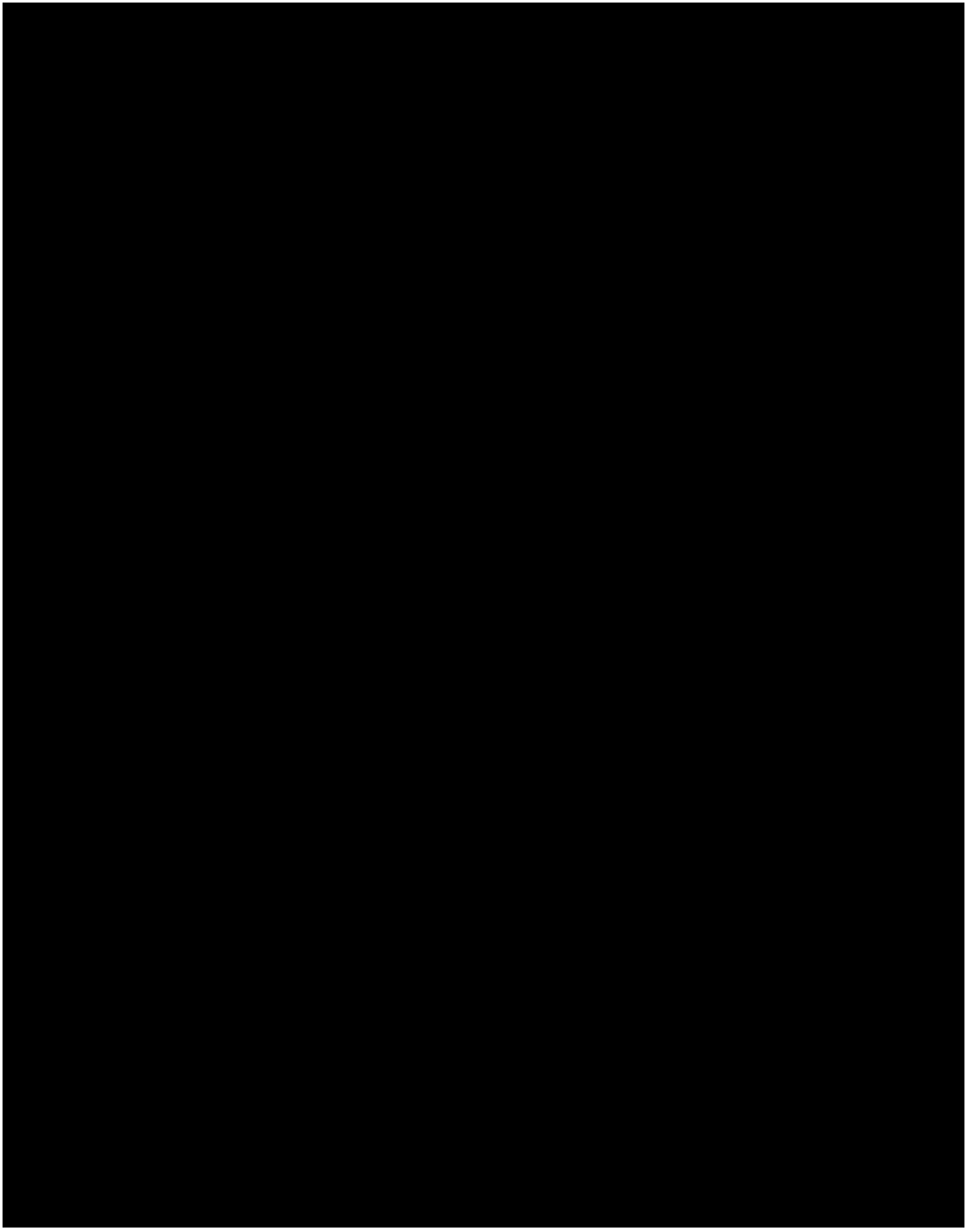
APPENDIX 5. [redacted]

[redacted]

behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. The healthcare provider should

[redacted]

[redacted]



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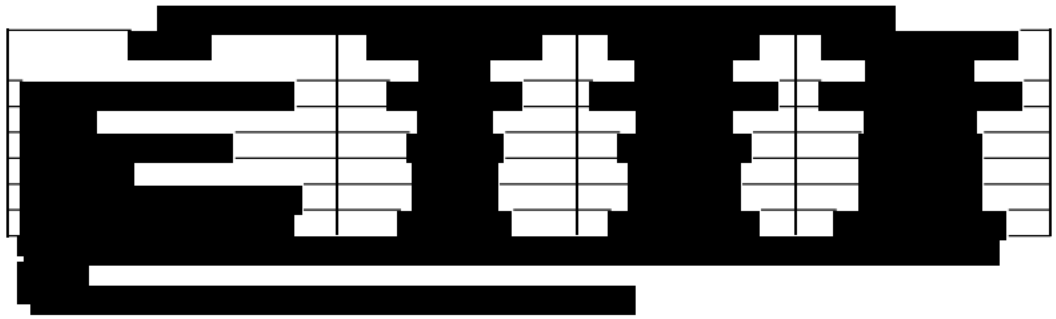

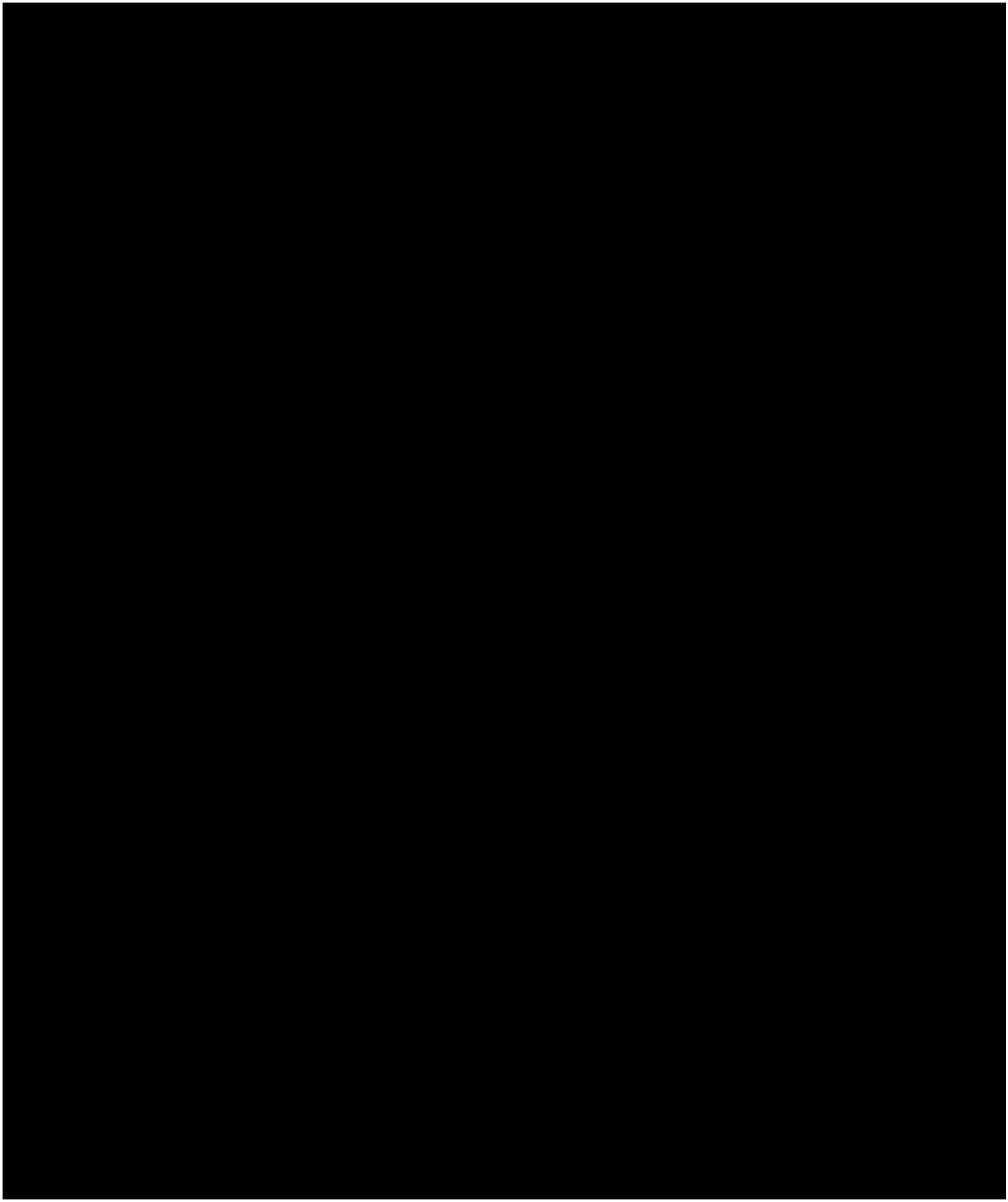

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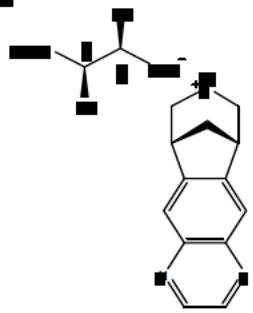

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