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Protocol Number OPP-100

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)

Statistical Analysis Plan

Version 1.0

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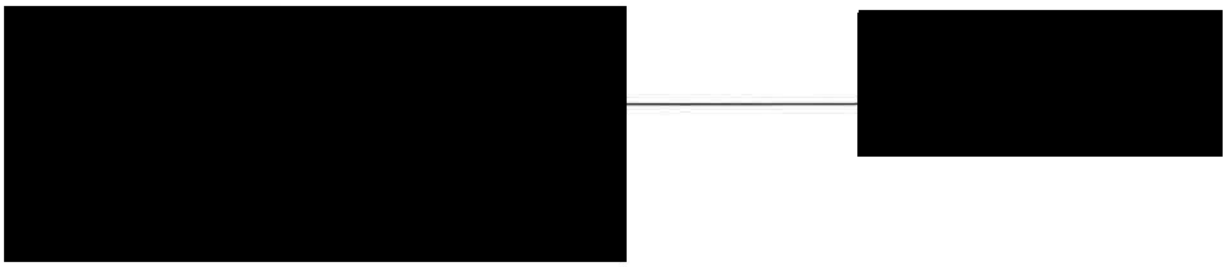

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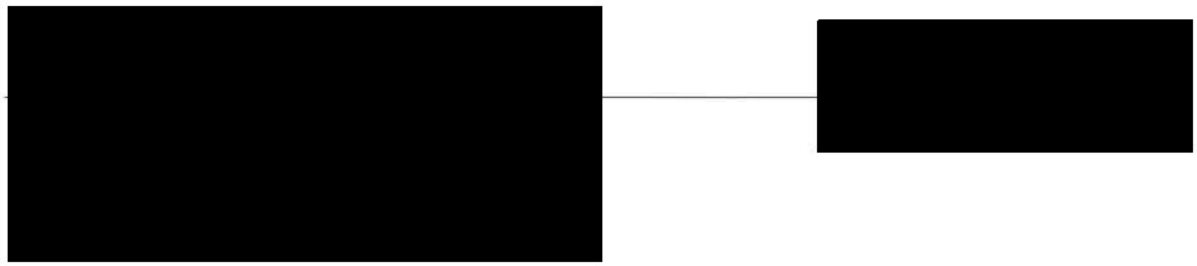

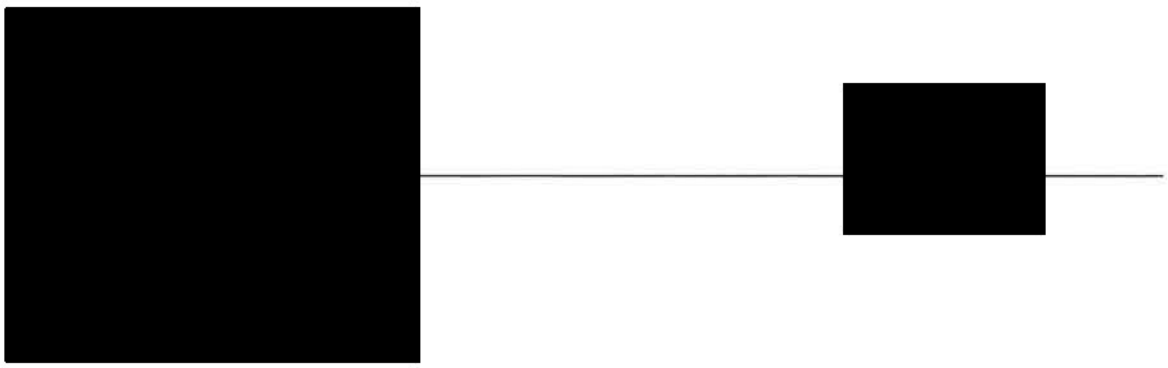

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List of Abbreviations and Definitions

AE	adverse event
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from 0 to the last measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve from 0 to infinity
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
C_{max}	maximum plasma concentration observed
CV	coefficient of variation
ECG	electrocardiogram
GM	geometric mean
Kel	elimination rate constant
LLOQ	lower Limit of Quantification
MedDRA	MedDRA
mg	milligrams
mL	milliliter
NCA	non-compartmental analysis
PK	pharmacokinetic
PT	preferred term
SAEs	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
$T_{½}$	terminal half-life
TEAEs	treatment-emergent adverse events
T_{max}	time to reach the maximum concentration observed

WHO	World Health Organization
µL	microliter

1. INTRODUCTION

This statistical analysis plan (SAP) contains the detailed technical specifications for the data analysis described in the OPP-100 protocol Amendment #2 (13 July 2019).

The reviewer can refer to the study protocol, and the case report form (CRF) for details of study design, conduct and data collection. Specifications of tables, figures, and data listings are contained in a separate document.

If the analyses described in the protocols differ from those in this SAP, the methods of the SAP prevail.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE(S)

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.

2.2 SECONDARY OBJECTIVE(S)

To assess the clinical and laboratory safety of varenicline administered as a single dose orally and intranasally.

3. STUDY DESIGN

3.1 OVERVIEW

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 the 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 the 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.

Table 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 (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 hours sample collection subjects will be discharged and return for remaining samples on an Out-Patient basis.

3.2 STUDY POPULATION

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.

3.3 SAMPLE SIZE AND POWER CONSIDERATIONS

This study is designed to test the relative bioavailability of 2 treatments (single oral dose of 1 mg varenicline [Chantix®] and Intranasal dose of 0.12 mg varenicline [OC-01]).

[redacted]

Table 2: Interim Analysis Matrix

[redacted]

3.4 RANDOMIZATION

Subjects will be randomized in a 1:1 ratio to receive treatment sequence 1 or 2. Treatment sequence 1 is treatment A: Single oral dose of 1 mg varenicline (Chantix®) administered orally in Period 1 and treatment B: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril in Period 2. Treatment sequence 2 is treatment B: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril in Period 1 and treatment A: Single

oral dose of 1 mg varenicline (Chantix®) administered orally in Period 2. This study will be open-label and no blinding procedures will be necessary.

4. ANALYSIS SETS

4.1 PHARMACOKINETICS ANALYSIS SET

[redacted]

4.2 SAFETY ANALYSIS SET

[redacted]

5. ENDPOINTS

5.1 PHARMACOKINETICS ENDPOINTS

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

- [redacted]

5.2 SAFETY ENDPOINTS

- [redacted]

6. GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

All statistical analyses and data summaries will be performed using SAS® (version 9.4). Tables and listings will be prepared in accordance with the current ICH Guidelines. [1] [2] In general, data will be summarized using descriptive statistics.

[redacted]

6.1 STUDY DAY

Study day is calculated as assessment date minus date of first dose of study drug + 1 if the assessment occurred after the date of first dose of study drug. For assessments that occurred before the first dose of study drug, study day is calculated as assessment date minus date of first dose of study drug. Date of first dose is defined as study Day 1.

6.2 BASELINE

Unless otherwise specified, the baseline value is defined as the last assessment prior to administration of the first dose.

7. PATIENT DISPOSITION

The number of subjects who complete the study, and who discontinue the study will be tabulated for the Safety Analysis Set by treatment sequence.

8. PROTOCOL DEVIATION

Major protocol deviations will be summarized by treatment sequence for Safety Analysis Set.

9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and other baseline characteristics for the Safety Analysis Set and Pharmacokinetic Analysis Set will be summarized using descriptive statistics by treatment sequence.

Continuous demographic and baseline variables include age, BMI, weight, and height; categorical variables include gender, ethnicity, and race.

10. MEDICAL HISTORY

Medical history (recorded at the screening visit) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and will be summarized by system organ class (SOC) and preferred term (PT). The summary will be presented by treatment sequence for the Safety Analysis Set.

11. PRIOR AND CONCOMITANT MEDICATION

- [redacted]

[redacted]

12. PHARMACOKINETIC ANALYSES

12.1 General Considerations

Pharmacokinetics parameters will be calculated by NCA (Non-compartmental analysis) and evaluated for the PK analysis set.

[redacted]

12.2 Primary Analysis

[redacted]

[redacted]

12.3 PK CONCENTRATION

[redacted]

12.4 PK PARAMETERS

[redacted]

12.5 HANDLING OF MISSING VALUES AND OUTLIERS

[redacted]

13. SAFETY ANALYSIS

13.1 EXTENT OF EXPOSURE

Dose and time of dosing will be listed per subject. The number of subjects who received each treatment will be summarized by treatment sequence.

13.2 ADVERSE EVENTS

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

A treatment-emergent AE is any AE occurring after the administration of the study drug and within 5 days after study drug administration, or a pre-treatment AE or pre-existing medical condition that worsens in intensity after start of the study drug and within the time of residual drug effect in both periods.

All AE data will be listed by subject. Only treatment-emergent AEs will be presented in summary tables by treatment.

For treatment emergent AEs overview summary table, by treatment and overall, will be prepared and including number of subjects reporting an AE, the percentage of subjects (%) with an AE and the following categories:

- Any Treatment-emergent adverse events (TEAEs)
- Deaths
- Serious TEAEs
- Study drug related TEAEs
- TEAEs leading to withdrawal
- TEAEs leading to death

Summaries of the following TEAEs will be provided by system organ class (SOC) and preferred term (PT):

- All TEAEs
- Study drug related TEAEs
- Serious adverse events (SAEs)
- TEAEs by severity

13.3 LABORATORY EVALUATIONS

Hematology and chemistry laboratory results will be classified as low (L), normal (N), or high (H) according to the laboratory-supplied reference range. Shift tables will be presented for each laboratory test for post-baseline assessments.

13.4 URINALYSIS

Urinalysis results will be listed by subject. Urinalysis results will be classified as normal or abnormal according to the laboratory-supplied reference range. Shift table from baseline to end of study will be presented for each laboratory test.

13.5 PREGNANCIES

Pregnancy test results will be presented in by-patient listing for further medical review.

13.6 VITAL SIGNS

Period baseline for all vital sign analyses will be the last assessment prior to the period study drug administration.

For each period, change from period baseline, will be derived for 2 hours post treatment. These changes from baseline values will also be summarized descriptively for each assessment time by treatment.

13.7 ECG

ECGs results will be listed by subject and summarized descriptively by overall subjects.

13.8 PHYSICAL EXAMINATION

Significant findings for physical examination will be collected as medical history and adverse events. They will be reported in the listings of medical history and adverse events.

13.9 INTRANASAL EXAMINATION

Intranasal examinations abnormal results will be listed by subject.

14. REFERENCE