MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A randomized, open-label, parallel-group study to evaluate the efficacy of the digital therapeutic OXD01 (MODIA™) in combination with sublingual buprenorphine/naloxone for the treatment of opioid use disorder
Protocol Number:	OXD01-001
Protocol Version/Date:	1.0/ 19 April 2022
Investigational Product:	OXD01
Sponsor:	Orexo US, Inc. 150 Headquarters Plaza East Tower, 5th Floor Morristown, NJ 07960
SAP Version/Date:	2.0 / 01 May 2023

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
Weizhe Su, PhD ***Biostatistician*** ***Medpace, Inc.***	
Edward Kim, MD ***Chief Medical Officer*** ***Orexo US, Inc.***	

VERSION HISTORY

Version	Version Date	Description
1.0	17 February 2023	Original signed version
2.0	01 May 2023	Added clarification for the sensitivity analysis based on mFA Population. Updated language regarding PDs.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
BUP/NAL	Buprenorphine/naloxone
CDISC	Clinical Data Interchange Standards Consortium
CGI-S/I	Clinical global impression – severity/improvement
CRF	Case report form
CSR	Clinical Study Report
eCRF	Electronic case report form
GCP	Good Clinical Practices
ICF	Informed consent form
ICH	International Conference on Harmonization
IRS	Interactive response system
MAT	Medication Assisted Treatment
MedDRA	Medical Dictionary for Regulatory Activities
OUD	Opioid use disorder
PD	Pharmacodynamics
PK	Pharmacokinetics
QFI	Quantity-Frequency Index
QIDS-SR	Quick Inventory of Depression Symptoms, Self-Report
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SL	Sublingual
SDTM	Study Data Tabulation Model
SOC	Standard of care
TLFB	Timeline followback
UADE	Unanticipated adverse device effect
UDS	Urine drug screen
VAS	Visual analog scale
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number OXD01-001. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

2.1.1 Primary Objective and endpoint

The primary objective of the study is to determine whether the combination of sublingual (SL) buprenorphine/naloxone (BUP/NAL) standard of care (SOC) background therapy and the digital therapeutic OXD01 is superior to SL BUP/NAL alone to reduce opioid use, as measured by the treatment success rate. Treatment success is defined as the subject having ≥ 80% of urine drug tests negative for opioids plus negative self-reports for illicit opioid use (from the timeline followback (TLFB) interview at the same visit) from Week 6 to Week 25.

2.1.2 Secondary Objectives and Endpoints

Compare the treatment groups for the following outcomes:

- Cumulative response – The cumulative response rate over a period from Week 6 to Week 25 of treatment. Response is defined as the presence of both a negative urine drug test for opioids and a self-report negative for illicit use of opioids at a study visit.
- Illicit opioid use - The cumulative response rate over a period from Week 6 to Week 25 of treatment with respect to the percentage of urine drug tests negative for opioids.
- Self-reports of illicit opioid use - The cumulative response rate over a period from Week 6 to Week 25 of treatment with respect to the percentage of self-reports negative for illicit opioid use.
- Percentage of subjects abstinent - Abstinence is defined as a subject having a urine drug test negative for opioids as well as self-reports negative for illicit opioid use at Week 25.
- Proportion of subjects completing the study - A completer is defined as a participant who completed either the urine drug screen (UDS) or the self-report assessment at the Week 25 visit.
- Clinical global impression - This will be evaluated in two ways:
    - Score on the Clinical Global Impression-Improvement scale at Week 13 and Week 25
    - Change from baseline in the Clinical Global Impression-Severity score at Week 13 and Week 25
- Opioid cravings - Change from baseline in the opioid craving score using the Opioid Craving Visual Analog Scale from Week 4 to Week 25.
- Illicit use of non-opioid drugs of abuse - The cumulative percentage of subjects with urine drug tests negative for drugs of abuse (excluding opioids) plus self-reports negative for use of drugs of abuse for the period from Week 6 to Week 25.
- Number of hospitalizations, emergency department visits, and overdoses, and the ability to resume work, school, or other productive activity

- Adverse events (AE).

2.2 Study Design

2.2.1 Overview

This is an open-label, randomized, parallel-group multicenter study designed to evaluate the efficacy of the digital therapeutic OXD01 combined with SL BUP/NAL SOC background therapy compared to SL BUP/NAL alone to change opioid use patterns in subjects with opioid use disorder (OUD).

The study will include a screening visit and a randomization visit, followed by 24 weeks of study treatment during which the subject will participate in 24 study visits (11 evaluation visits plus 13 visits to perform only a urine drug screen (UDS) and collect a subject self-report of drug use, *Figure 1*).

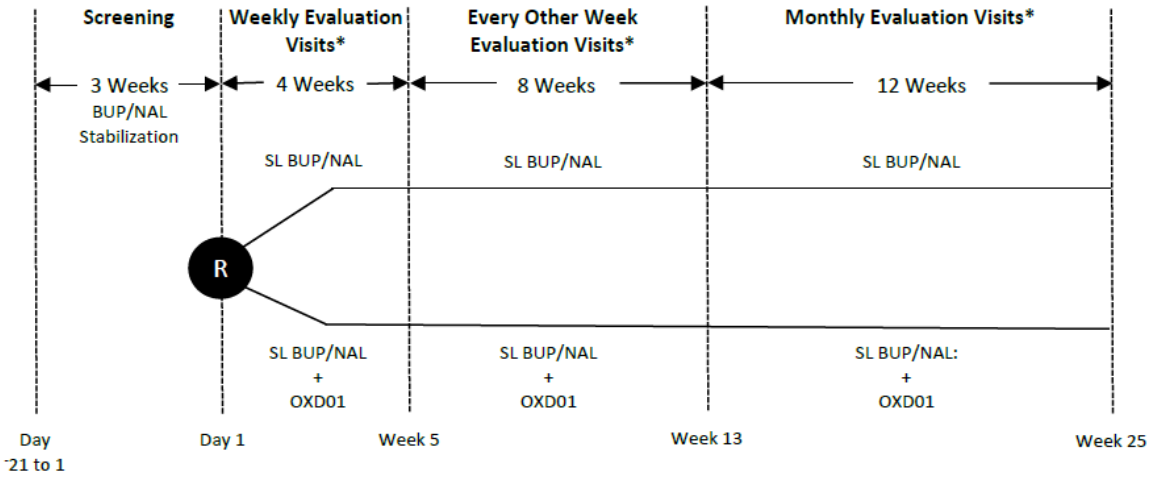
The screening visit will identify opioid dependent adults seeking MAT for moderate-to-severe OUD. Subjects who have received MAT for OUD within 14 days or those with a diagnosis of moderate to severe substance use disorder involving psychoactive substances other than opioids will be excluded.

Eligible subjects will be randomized with a 1:1 fashion into one of two treatment (SL BUP/NAL SOC background therapy or SL BUP/NAL + OXD01 digital therapy). Subjects in both groups will receive the assigned treatment for 24 weeks.

On study Day 1 all subjects will have been stabilized on SL BUP/NAL. Subjects randomized to BUP/NAL plus OXD01 digital therapy will use the OXD01 application as non-pharmacologic treatment for their OUD. OXD01 is a web-based software platform that can be used on a mobile phone, tablet, or computer with a compatible browser such as Google Chrome, Mozilla Firefox, Internet Explorer, or Safari.

Subjects will be scheduled for evaluation visits, which will include a UDS and a self-report of drug use, weekly during the first four weeks of treatment, every other week from weeks 5 through 12, and monthly through 24 weeks. Subjects will also return to the site for a UDS and a self-report of drug use each week between the evaluation visits.

Figure 1. Study schema



R – randomization; SL BUP/NAL – sublingual buprenorphine/naloxone
*Evaluation visits: Weeks 2-5, 7, 9, 11, 13, 17, 21, 25
*Urine drug screen/drug use interview only: Weeks 6, 8, 10, 12, 14-16, 18-20, 22-24

2.2.2 Randomization

Eligible subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- SL BUP/NAL SOC background therapy
- SL BUP/NAL + OXD01 digital therapy

Eligible subjects will be randomized on Day 1 through an IRT system.

Each subject will be identified by a unique randomization number assigned by the IRS system on Day 1. Prior to randomization, subjects will be identified by a screening number, assigned when the subject signs the ICF.

2.2.3 Study Treatment and device

- SL BUP/NAL SOC background therapy
- SL BUP/NAL + OXD01 digital therapy for 15-30 minutes, 1-2 times per week

Subjects in both groups will receive the assigned treatment for 24 weeks. Note: No investigational product will be administered as part of this study. Subjects in both groups may also be encouraged to participate in behavioral health therapies in accordance with the Investigator's standard of practice.

2.2.4 Sample Size Determination

Treatment success is defined as the subject having ≥ 80% of urine drug tests negative for opioids plus ≥ 80% of self-reports negative for illicit opioid use (from the TLFB interview at the same visit) from Week 6 to Week 25 of the study. Current literature suggests that the proportion of subjects likely to be successful by this measure while under treatment with the control agent may be approximately 12%. [1] If OXD01 is effective in improving this percentage to 25%, approximately 200 subjects will be required to receive each treatment to provide 90% power to

detect such a difference at an α = 0.05 level (Fisher's Exact Test). Approximately 510 opioid dependent males and females will be screened to randomize approximately 400 subjects.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first use of study device. The day of the first use of study device will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the electronic case report form (eCRF). Unscheduled visits recorded on the eCRF will not be re-assigned and will remain labeled as unscheduled.

Early termination (ET) visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 2	8	2	11
Week 3	15	12	18
Week 4	22	19	25
Week 5	29	26	32
Week 6	36	33	39
Week 7	43	40	46
Week 8	50	47	53
Week 9	57	54	60
Week 10	64	61	67
Week 11	71	68	74
Week 12	78	75	81
Week 13	85	82	88
Week 14	92	89	95
Week 15	99	96	102
Week 16	106	103	109
Week 17	113	110	116
Week 18	120	117	123
Week 19	127	124	130
Week 20	134	131	137
Week 21	141	138	144
Week 22	148	145	151
Week 23	155	152	158
Week 24	162	159	165
Week 25	169	166	

3.1.3 Definition of Baseline

Baseline is defined as Study Day 1. Subject with missing baseline value will be considered as missing and will be excluded from the analysis for the change from baseline endpoints.

3.1.4 Summary Statistics

In general, categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of observations), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

Corresponding with the primary efficacy objective of the study, the primary inference for hypothesis testing is the treatment difference between the combination of SL BUP/NAL SOC background therapy and the digital therapeutic OXD01, and SL BUP/NAL alone to reduce opioid use, as measured by the treatment success rate from Week 6 to Week 25. The hypothesis testing is based on a two-sided test with significance level at 0.05.

3.1.6 Evaluation of Site Effect

This is a multicenter study. Sites will not be pooled for any planned inferential analysis.

3.2 Analysis Populations

3.2.1 Full Analysis (FA) Population

The primary efficacy analyses will be based on FA Population that consists of all randomized subjects.

3.2.2 Modified Full Analysis (mFA) Population

The modified FA Population that consists of randomized subjects who were not considered with any data reliability issues. A sensitivity analysis of the primary endpoint and key secondary endpoints will be performed based on mFA Population.

The mFA Population will exclude the following subjects due to data reliability issues:

- 13 subjects enrolled in Site 25 (##-###, ##-###, ##-###)
- 24 subjects enrolled in Site 35 (##-###, ##-###, ##-###)

3.2.3 Safety Population

The Safety analyses will be based on Safety Population that is consistent of all randomized subjects.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were randomized, discontinued early from the study, and completed the study will be summarized by treatment on all randomized subjects (FA Population). Reasons for early discontinuation will also be summarized.

For subjects that discontinued early from study, treatment success by treatment group will be investigated with a Kaplan-Meier survival plot, censored to when the subjects dropped out over the course of the study.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on the clinical protocol as described in the Protocol Deviation Plan to align with ISO 14155:2020 (Clinical investigation of medical devices for human subjects – Good Clinical Practice). Protocol deviations will be identified prior to unblinding the database.

Counts and percentages of subjects with major protocol deviations by deviation category will be summarized by treatment based on FA Population.

3.3.3 Analysis Populations

Counts and percentages of subjects will be summarized by treatment based on FA Population.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Baseline craving Visual Analog Scale (VAS)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment based on FA Population.

3.3.5 Opioid Use History/ Treatment

A treatment history, including counseling, over the previous 2 years for OUD will be recorded at screening. Opioid use history and treatment including main drug of abuse and primary route used, will be summarized by treatment based on Safety Population.

3.3.6 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment based on the Safety Population.

3.3.7 Concomitant Medications

Concomitant medications that are ongoing on study Day 1 will be recorded. Additions, deletions, or changes to concomitant medications after Day 1 will not be recorded.

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary version March 2021G B3. For summary purposes, medications will be considered prior medications if they stopped prior to the first use of study device (Day 1) and concomitant medications if they were taken at any time after the first use of study device (i.e. started prior to Day 1 and were ongoing or started after Day 1).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for

missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking concomitant medications by ATC class and a preferred term will be summarized by treatment based on the Safety Population.

3.3.8 Study Device Compliance

Dosing instructions will be reviewed and subjects will be interviewed to assess treatment compliance at the following Visits: Weeks 2-5, 7, 9, 11, 13, 17, 21, and 25.

Percent compliance of study device OXD01 will be calculated as the number of OXD01 sessions taken / the number of expected OXD01 sessions taken. Percent compliance to the study device regimen will be summarized based on the Safety Population with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <50%
- 50-80%
- 80-100%
- >100%

3.4 Efficacy Assessment

Efficacy data will be summarized by randomized treatment based on the FA Population. The primary efficacy endpoint will also be summarized based on the mFA Population.

3.4.1 Primary Endpoints Analysis

The primary objective of the study is to determine whether the combination of SL BUP/NAL SOC background therapy and the digital therapeutic OXD01 is superior to SL BUP/NAL alone to reduce opioid use, as measured by the treatment success rate. Treatment success is defined as the subject having ≥ 80% of urine drug tests negative for opioids plus ≥ 80% of self-reports negative for illicit opioid use (from the TLFB interview at the same visit) from Week 6 to Week 25. Each subject will be evaluated as a success or failure for this metric and the proportion of subjects in each group demonstrating ≥ 80% of urine drug tests negative for opioids plus negative self-reports for illicit opioid use (from the TLFB interview) will be tested using chi-squared test. Count and percentage of the subjects with treatment success will be summarized by treatment based on FA Population.

If the subject withdrew the study, then the urine drug tests for opioids and self-reports for illicit opioid use after withdrawal will be imputed as positive. If the subject completed the study with any missing visit, then the urine drug tests for opioids and self-reports for illicit opioid use for the missing visit will be imputed as positive.

<u>Sensitivity analysis 1</u>

As supportive analyses to the primary analysis for the primary endpoint, sub-group analysis using a similar chi-squared test as described above will be repeated for the following factors:

- Percentage of subjects meeting primary endpoint by reported compliance rate or who achieved greater than 80% completion of the visits during Week 6 to Week 25
- Subjects who took the dose of buprenorphine versus retention.
    - Target dose or lower: ≤ 16 mg buprenorphine for Suboxone or equivalent formulation; or ≤ 11.4 mg Zubsolv
    - Higher dose than target dose: > 16 mg buprenorphine for Suboxone or equivalent formulation; or > 11.4 mg Zubsolv
- Subjects who received additional behavioral health services

Sensitivity analysis 2

As supportive analyses, the primary endpoint and key secondary endpoints will be performed using the similar statistical methods based on mFA Population.

3.4.2 Secondary Endpoints Analysis

The secondary objectives are to determine whether the combination of SL BUP/NAL SOC background therapy and the digital therapeutic OXD01 is superior to SL BUP/NAL alone with respect to the following variables. Note that the secondary objectives are listed in priority order for potential gatekeeping statistical approaches. The second test will only be conducted if the first test is statistically significant, and the following tests will only be conducted if the previous test is statistically significant.

The following secondary endpoints will be tested in a hierarchical fashion to protect the family-wise type I error:

- Cumulative response – The cumulative response rate from Week 6 to Week 25 of treatment. Response is defined as the presence of both a negative urine drug test for opioids and a self-report negative for illicit use of opioids at a study visit.

  To compare the two treatment groups with respect to their cumulative distribution functions of the proportion of subjects responding, the Kolmogorov-Smirnoff methodology will be used.

- Illicit use of opioids - The cumulative response rate from Week 6 to Week 25 of treatment with respect to the percentage of urine drug tests negative for opioids will be the primary metric for this variable. To compare the two treatment groups with respect to their cumulative distribution functions of the proportion of subjects responding, the Kolmogorov-Smirnoff methodology will be used.

- Self-reports of illicit use of opioids - The cumulative response rate from Week 6 to Week 25 of treatment with respect to the percentage of self-reports negative for illicit use of opioids will be the primary metric for this variable. To compare the two treatment groups with respect to their cumulative distribution functions of the proportion of subjects responding with self-reports negative for illicit opioid use, the Kolmogorov- Smirnoff methodology will be used.

- Percentage of subjects abstinent - Abstinence is defined as a subject having urine drug tests negative for opioids as well as self-reports negative for illicit use of opioids at Week

25. Each subject will be scored as abstinent or non-abstinent and the groups will be compared using a chi-squared test.

- Proportion of subjects completing the study - A completer is defined as a participant who completed either the UDS or the self-report assessment at the Week 25 visit. The groups will be compared with respect to the proportion of completers using a chi-squared test.

- Clinical global impression - This will be evaluated in two ways
    - Score on the CGI-I scale at week 13 and Week 25
    - Change from baseline in the Clinical Global Impression-Severity score at Week 13 and Week 25

  CGI scores will be evaluated using General Linear Model (GLM) methodology with treatment as categorical covariate. If substantial deviations from the model assumptions are observed, then supportive analyses such as non-parametric assessments including a Mann–Whitney U test will be performed.

- Opioid cravings - Change from baseline in the opioid craving score using the Opioid Craving VAS from Week 4 to Week 25. Opioid Craving scores will be evaluated using GLM methodology with treatment as categorical covariate. If substantial deviations from the model assumptions are observed, then supportive analyses such as non-parametric assessments including a Mann–Whitney U test will be performed.

- Use of illicit non-opioid drugs of abuse - The cumulative percentage of subjects with urine drug tests negative for illicit drugs of abuse (excluding opioids) plus self-reports negative for illicit drug use for the period from Week 6 to Week 25 will be evaluated using the Kolmogorov-Smirnoff methodology.

- Number of hospitalizations, emergency department visits, and overdoses, and the ability to resume work, school, or other productive activity. descriptive statistics (count and percentage) will be summarized by treatment.

3.4.3 Exploratory Analysis

- Percentage of subjects with longer abstinent – Longer abstinence is defined as a subject having urine drug tests negative for opioids as well as self-reports negative for illicit use of opioids at Week 22 – Week 25. Each subject will be scored as abstinent or non-abstinent and the groups will be compared using a chi-squared test.

3.5 Safety Assessment

Safety data will be summarized by actual treatment received based on the Safety Population.

3.5.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a subject or clinical trial subject caused by, or associated with a device and which does not necessarily have to have a causal

relationship with the device. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the device, whether or not considered related to the intended use of the device.

Pre-existing conditions will not be regarded as AEs if the condition follows a normal course of recovery, unless it worsens after exposure to the device. Medical procedures will not be regarded as AEs, but the cause of the procedure may be.

The AE reporting period will start after signing the informed consent form and will end at discharge from the study. All AEs will be coded to system organ class and preferred term using MedDRA version 24.0.

Adverse events with missing start dates will be considered as device related AE unless the partial date excludes that possibility. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months. If the causality for an adverse event is missing, the adverse event will be assumed to be related.

A Serious Adverse Event (SAE) is an AE that:

- results in death
- is life threatening
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event (e.g., convulsions not leading to hospitalization)

SAEs will only be considered when there is an underlying AE. For example, a hospitalization due to a pre-existing condition which is not due to an aggravation of the condition after exposure to any study treatment will not be considered to be an SAE.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the device; or any other unanticipated serious problem associated with a device that relates to the safety or welfare of subjects.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any AEs (overall and by maximum severity/intensity)
- Any AE related to medical device (causality) (overall and by maximum severity)
- Any AE related to protocol-required Medicinal Background Therapy (sublingual buprenorphine/naloxone) (overall)
- Any serious AEs (SAEs)
- Any unanticipated adverse device effect (UADE)
- Any TEAEs leading to discontinuation of Investigational Device
- Any TEAEs leading to discontinuation of study

- Any AEs leading to death

Counts and percentages of subjects will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for SAEs and AEs leading to discontinuation of Investigational Device.

3.5.2 Urine Drug Screen

Descriptive statistics for UDS test will be presented from Week 6 to Week 25 by treatment.

A urine sample (urine dipstick) will be taken at screening, Week 1 to Week 5 during the study to test for the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cocaine metabolite, marijuana metabolite, methadone, opiates, phencyclidine, propoxyphene, and buprenorphine. Individual data listings of Urine Dipstick results will be presented for each subject and visit of collection.

3.5.3 Vital Signs

Vital signs will be measured after resting in the supine position for at least 5 minutes at screening and on study Day 1, including body temperature, respiratory rate, heart rate, and blood pressure.

Summary statistics for vital signs values will be presented by treatment group for each visit of collection.

3.5.4 Physical Examinations

A physical examination will be performed by the Investigator at screening. The following areas will be included:

- General inspection
- Neck veins / pulses
- Oral cavity / teeth (for assessment of abnormalities possibly affecting sublingual absorption)
- Palpation of precordium and auscultation of the heart
- Auscultation of chest
- Abdominal examination (liver, spleen, and lower abdomen)
- Peripheral pulses (radial and foot)
- Assessment of reflexes (biceps, knee, and ankle)

Any abnormalities will be recorded. Individual data listings of physical examination results will be presented for each subject and visit of collection.

3.5.5 Quantity-Frequency Index

The Quantity-Frequency Index (QFI) is a self-assessment of the frequency and quantity of alcohol consumption over the previous 30 days. The QFI is comprised of the two questions and will be completed on study Day 1 and at the visit on Week 25.

Individual data listings of QFI will be presented for each subject and visit of collection.

3.5.6 Timeline Followback Method – Drug and Alcohol Use

The Timeline Followback Method – Drug and Alcohol Use (TLFB) is a self-assessment used to document recent use of opioids, other illicit drugs of abuse, and alcohol. A TLFB assessment will be completed on study Day 1, and at weekly visits while on study treatment. The TLFB is a closed Yes or No question of drug or alcohol use.

Individual data listings of TLFB – drugs and TLFB – alcohol will be presented for each subject and visit of collection, separately.

3.5.7 Opioid Craving Visual Analog Scale

Cravings for opioids will be assessed by the subject through the use of a VAS, where 0 mm represents “no cravings” and 100 mm represents “the most intensive craving I have ever had.” The baseline craving VAS assessment will be collected on study Day 1 and at the visit on Weeks 5, 9, 13, 17, 21 and 25.

Individual data listings of opioid craving VAS will be presented for each subject and visit of collection.

3.5.8 Quick Inventory of Depression Symptoms (Self-Report)

Symptoms of depression will be assessed by the subject using the Quick Inventory of Depression Symptoms Self-Report (QIDS-SR) at screening and at the visit on Week 25.

Individual data listings of QIDS-SR will be presented for each subject and visit of collection.

3.5.9 Review Behavioral Health Therapies since The Previous Visit

Subjects in behavioral health therapies since the previous visit, including 12-step programs, will be recorded at the visits on Weeks 1-5, 7, 9, 11, 13, 17, and 21 in eCRF.

Individual data listings of behavioral health since previous visit will be presented for each subject and visit of collection.

3.5.10 Clinical Global Impression

Clinical Global Impression (Severity) – Severity of opioid dependence will be assessed by the Investigator on study Day 1 and at the visit on Week 13 and Week 25 using the assessment scale (rate from 0 to 7).

Clinical Global Impression (Improvement) – Improvement in severity of opioid dependence from baseline (study Day 1) will be assessed by the Investigator at the visit on Week 13 and Week 25 using the assessment scale (rate from 0 to 7).

Individual data listings of Clinical Global Impression severity/ improvement (CGI-S/I) will be presented for each subject and visit of collection.

4 DATA SAFETY MONITORING

The study will be adequately monitored in accordance with ICH Harmonized Tripartite Guideline for GCP. Monitoring is performed to ensure that the study is conducted in accordance with the study protocol, applicable laws and regulations and ICH GCP. The clinical site will facilitate monitoring of the study by cooperating with the monitor and will make documentation, source data and staff available to the monitor.

5 ANALYSIS TIMING

5.1 Draft Analysis/Blinded Data Reviews

Draft analysis tables, figures, and listings (TFLs) for blinded data reviews will be provided prior to the scheduled database lock for final review.

Draft TFLs will include text to indicate that they are draft and use dummy treatment assignments (e.g., a watermark on the output with text of 'DRAFT').

5.2 Interim Analysis

No interim analysis is planned for this study.

5.3 Pre-Final Analysis

After the database is locked, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 3 weeks after database lock.

5.4 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include: annotated case report forms (eCRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

This SAP does not deviate from the statistical analysis described in v1.0 of the protocol.

Addition to the protocol, an exploratory analysis on 'percentage of subjects with longer abstinent' is performed as an exploratory purpose. Longer abstinence is defined as a subject having urine drug tests negative for opioids as well as self-reports negative for illicit use of opioids at Week 22 – Week 25.

Addition to the protocol, a sensitivity analysis for primary endpoint and key secondary endpoints will be performed based on mFA Population. The modified FA Population that consists of randomized subjects who were not considered with any data reliability issues.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

8 REFERENCES

[1] F. Dang, "Clinical Review: Application Number 209819Orig1s000 (Sublocade (Buprenorphine) extended -release injection)," Center for Drug Evaluation and Research, Beltsville, 2017.

APPENDIX A: SCHEDULE OF EVENTS

Schedule of Events: Screening, Weeks 1-12

Evaluation	Screening	*Treatment*									
	Day -21 to 1	Week 1 Day 1	Week 2/3/4 Day 8/15/22	Week 5 Day 29	Week 6 Day 36	Week 7 Day 43	Week 8 Day 50	Week 9 Day 57	Week 10 Day 64	Week 11 Day 71	Week 12 Day 78
Window	NA	NA	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day
Informed consent	X										
Demographics	X										
Inclusion/exclusion criteria review	X	X									
Medical history	X										
Opioid use history	X										
Confirm diagnosis - OUD[1]	X										
Previous treatments for OUD	X										
Concomitant medications[2]	X	X									
Physical examination	X										
Vital signs	X	X									
Urine drug screen	X	X	X	X	X	X	X	X	X	X	X
QFI		X									
TLFB interview – drugs and alcohol		X									
TLFB interview – drugs			X	X	X	X	X	X	X	X	X
Review study restrictions with subject	X	X	X	X		X		X		X	
Randomization - IRS[3]		X									
OXD01 – subject training[3]		X									
Opioid craving VAS		X		X				X			
QIDS-SR	X										
CGI-S		X									
CGI-I											
Review behavioral health therapies			X	X		X		X		X	
MAT compliance assessment/counseling			X	X		X		X		X	
OXD01 compliance assessment/counseling			X	X		X		X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X

OUD – opioid use disorder; QFI – Quantity-Frequency Index; TLFB – timeline followback method; IRS – interactive response system; MAT – medication-assisted treatment; VAS – visual analog scale; QIDS-SR – Quick Inventory of Depression Symptoms, Self-Report; CGI-S/I – clinical global impression severity/improvement

1. The subject must meet the criteria for moderate or severe opioid use disorder based on DSM-V (Appendix B).
2. Concomitant medications ongoing on Day 1 will be recorded.
3. As soon as the subject is clinically stable on SL BUP/NAL with physical withdrawal symptoms managed, and the subject able to fully participate in OXD01 training, but no greater than 14 days from the first dose of SL BUP/NAL induction.

Schedule of Events (Continuous): Weeks 13-25, Early Termination

Evaluation	*Treatment*							Early Termination
	Week 13 Day 85	Week 14/15/16 Day 92/99/106	Week 17 Day 113	Week 18/19/20 Day 120/127/ 134	Week 21 Day 141	Week 22/23/24 Day 148/155/162	Week 25 Day 169	
Window	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Day	± 1 Days	± 1 Day	
Informed consent								
Demographics								
Inclusion/exclusion criteria review								
Medical history								
Opioid use history								
Confirm diagnosis - OUD[1]								
Previous treatments for OUD								
Concomitant medications[2]								
Physical examination								
Vital signs								
Urine drug screen	X	X	X	X	X	X	X	X
QFI							X	X
TLFB interview – drugs and alcohol							X	X
TLFB interview – drugs	X	X	X	X	X	X		
Review study restrictions with subject	X		X		X			
Randomization – IRS[3]								
OXD01 – subject training[3]								
Opioid craving VAS	X		X		X		X	X
QIDS-SR							X	X
CGI-S	X						X	X
CGI-I	X						X	X
Review behavioral health therapies	X		X		X		X	X
MAT compliance assessment/counseling	X		X		X		X	X
OXD01 compliance assessment/counseling	X		X		X		X	X
End of study interview							X	X
Adverse Events	X	X	X	X	X	X	X	X

OUD – opioid use disorder; QFI – Quantity-Frequency Index; TLFB – timeline followback method; IRS – interactive response system; MAT – medication-assisted treatment; VAS – visual analog scale; QIDS-SR – Quick Inventory of Depression Symptoms, Self-Report; CGI-S/I – clinical global impression severity/improvement

1. The subject must meet the criteria for moderate or severe opioid use disorder based on DSM-V (Appendix B).
2. Concomitant medications ongoing on Day 1 will be recorded.
3. As soon as the subject is clinically stable on SL BUP/NAL with physical withdrawal symptoms managed, and the subject able to fully participate in OXD01 training, but no greater than 14 days from the first dose of SL BUP/NAL induction.

APPENDIX B: SAS Programming Example

The sample SAS code for Chi-Squared test is included below:

```
PROC FREQ DATA=DATA;
TABLES RESPONSE * TREATMENT / CHISQ;
 RUN;
```

The sample SAS code for Kolmogorov-Smirnov (KS) test is included below:

```
PROC NPAR1WAY DATA=DATA WILCOXON EDF;
CLASS TREATMENT;
VAR CUMULATIVE_RESPONSE;
 RUN;
```