Clinical study protocol

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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

Sponsors' responsible medical officer

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PROTOCOL SYNOPSIS

Study 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.	
Study number: OXD01-001	**Product:** OXD01
Study phase: III	**Study population:** Male and female subjects
Number of subjects: 510 enrolled (approximately), 400 randomized	**Number of study centers:** 30-35
Sponsor: Orexo US, Inc.	
Background/Rationale: Medication-assisted treatment, the current standard for opioid addiction, is the use of medications in combination with counseling and behavioral therapies to provide a "whole-patient" approach to the treatment of opioid use disorder (OUD). However, patients may not have optimal access to face-to-face clinical behavioral health services. Digital therapeutics can help bridge the gap between accessible services and optimal treatment of OUD, the primary goal of which is to reduce the use of opioids. OXD01 is a device-based digital therapeutic, designed to offer individuals diagnosed with OUD quality psychotherapy intervention based on cognitive behavioral therapy and motivational interviewing. This study is being conducted to determine the value of OXD01 when combined with medication to change opioid use patterns in subjects with OUD.	
Objectives: *Primary Objective:* 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 TLFB interview at the same visit) from Week 6 to Week 25. *Secondary Objectives:* 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 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 12 and Week 25
    - Change from baseline in the Clinical Global Impression-Severity score at Week 12 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).

Treatments:

- 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.

Methodology: 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 OUD. Approximately 510 opioid dependent adults will be screened to randomize approximately 400 subjects. The study will include a screening visit and a randomization visit, followed by 24 weeks of study treatment. 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, then every other week from weeks 5 through 12, then monthly through week 25. Subjects will also return to the site for only a UDS and a self-report of drug use each week between the evaluation visits.
Statistical Considerations: 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 (chi-squared test). Approximately 510 opioid dependent males and females will be screened to randomize approximately 400 subjects.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/term	Definition
AE	Adverse event(s)
BUP/NAL	Buprenorphine/naloxone
CFR	Code of Federal Regulations
CGI-S/I	Clinical global impression – severity/improvement
CRF	Case report form
CYP	Cytochrome P450
ECG	Electrocardiography
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	Electronic case report form
FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional review board
IRS	Interactive response system
MAT	Medication-assisted treatment
OUD	Opioid use disorder
QFI	Quantity-Frequency Index
QIDS-SR	Quick Inventory of Depression Symptoms, Self-Report
SAE	Serious adverse event
SL	Sublingual
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TLFB	Timeline followback
UADE	Unanticipated adverse device effect
UDS	Urine drug screen
VAS	Visual analog scale

1. INTRODUCTION

1.1 Background

In 2017, 70,237 drug overdose deaths occurred in the United States. The age-adjusted rate of overdose deaths increased significantly by 9.6% from 2016 (19.8 per 100,000) to 2017 (21.7 per 100,000). Opioids, primarily synthetic opioids other than methadone, are currently the main driver of drug overdose deaths and were implicated in 47,600 overdose deaths in 2017 (67.8% of all drug overdose deaths). [2]

Effective and available treatment is the gateway to reducing the morbidity and mortality associated with drug addiction. Medication-assisted treatment (MAT), the current standard for opioid addiction, is the use of medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of opioid use disorder (OUD). Research shows that MAT can successfully treat opioid use disorder (OUD), and for some people can help sustain recovery. [3]

Successful MAT implementation requires the availability of varying levels and types of care in a range of settings, although all of the necessary services may not be available to all patients. Patients appropriate for outpatient care require access to office-based buprenorphine prescribing (or opioid treatment programs that provide methadone) and clinical behavioral health services. However, the National Center for Health Workforce Analysis estimates that between 40 million and 45 million individuals (roughly 20 percent of the U.S. 2013 population) may have needed but did not receive behavioral health care in 2013. The National Center completed a projection of US supply and demand for behavioral health practitioners in 2025 and identified six provider types that are tracking for shortage of more than 10,000 full-time equivalents: psychiatrists; clinical, counseling, and school psychologists; substance abuse and behavioral disorder counselors; mental health and substance abuse social workers; mental health counselors; school counselors. [4]

Clearly one challenge for healthcare providers working on the front of the current opioid crisis is to improve the availability and access to treatment, particularly behavioral health services. However, based on the National Center estimate, trained behavioral health professionals will not join the workforce in adequate numbers to meet the demand for services. The evidence is that many patients who require behavioral health services are not getting access, or chose not to engage in face-to-face therapy. New modes of service delivery are necessary to close the gap between patients and the treatment required for recovery from addiction.

Digital therapeutics, an innovative new category of mobile medical applications that help treat diseases by modifying patient behavior and providing remote monitoring to improve long-term health outcomes, are poised to improve the quality of healthcare across a broad spectrum of the market. Digital therapeutics implement treatment programs tailored to specific ailments, and the early evidence is that these digital health programs, often combined with human coaching/interaction, can effectively close service gaps and make a significant difference in health outcomes. In addition, digital health programs can be tailored and optimized for individual patients and delivered at scale via mobile devices, which can conceivably be transformative to the healthcare marketplace. With precise regimes and daily monitoring, digital therapeutics offer valuable data that can provide doctors insight into patient behavior and create feedback/optimization loops for individual patients. Enabling patients to take greater control over managing their chronic illnesses and preventing disease progression could yield substantial cost savings throughout the entire healthcare system, and evidence suggests that treatment adherence may be improved by new technologies. [5]

OXD01 is an individualized device-based digital therapeutic designed to be an adjunctive treatment tool for OUD. OXD01 is designed to offer individuals diagnosed with OUD quality psychotherapy intervention based on cognitive behavioral therapy and motivational interviewing, implemented through a smart application with artificial intelligence.

OXD01 has not been studied in patients with OUD receiving standard of care (SOC) MAT with sublingual buprenorphine/naloxone. The current study is being conducted to determine the value of OXD01 to reduce opioid use when combined with medication to treat OUD.

2. STUDY OBJECTVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of the study is to determine whether the combination of sublingual (SL) buprenorphine/naloxone (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 negative self-reports for illicit opioid use (based on the timeline followback [TLFB] interview at the same visit) from Week 6 to Week 25.

2.2 Secondary Objectives

The secondary objectives are to compare the treatment groups for the following outcomes:

- 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 negative self-report for illicit use of opioids at a study visit.
- 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.
- Self-report of illicit use of opioids - The cumulative response rate from Week 6 to Week 25 of treatment with respect to the percentage of negative self-reports for illicit use of opioids.
- Percentage of subjects abstinent - Abstinence is defined as a subject having a urine drug test negative for opioids as well as negative self-reports for illicit use of opioids at Week 25.
- 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.
- Clinical global impression - Will be evaluated by:
    - Score on the Clinical Global Impression-Improvement (CGI-I) scale at Week 12 and Week 25
    - Change from baseline in the Clinical Global Impression-Severity (CGI-S) score at Week 12 and Week 25

- Opioid cravings - Change from baseline in the opioid craving score using the opioid craving visual analog scale (VAS) from Week 4 to Week 25.

- 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 negative self-reports for illicit drug use 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)

3. INVESTIGATIONAL PLAN

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 in the treatment of subjects with OUD.

Approximately 510 opioid dependent adults will be screened to randomize approximately 400 subjects. 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).

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 to one of two treatment groups in a 1:1 ratio:

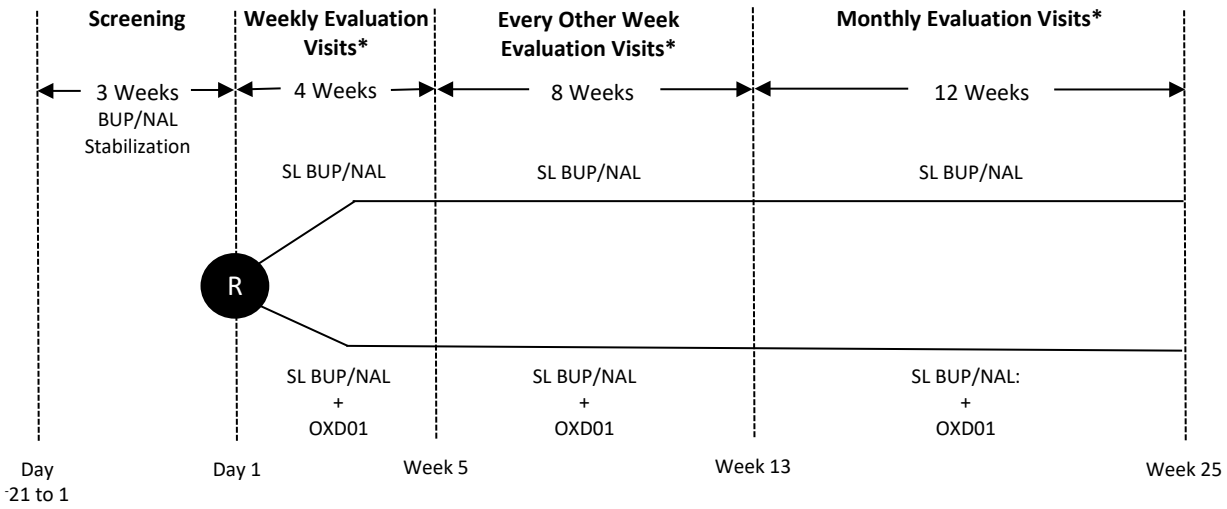
- SL BUP/NAL SOC background therapy
- SL BUP/NAL + OXD01 digital therapy

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.

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

Table 1. 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.

Table 2. Schedule of Events: 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.

3.1 Selection of Study Design

3.1.1 Overall Study Design

This is a prospective, open-label, randomized, parallel-group superiority study designed to determine whether the efficacy of OXD01 combined with SL BUP/NAL SOC background therapy is superior to BUP/NAL alone in the treatment of subjects with OUD. The study is comprised of a screening visit and a randomization visit, followed by 24 weeks of study treatment and 24 study visits (11 evaluation visits plus 13 visits to perform a UDS and collect a subject self-report of drug use).

A randomized, parallel-group design is selected to assure an adequately controlled study. An open-label design is necessary because there is not a placebo or sham validated for the OXD01 digital therapeutic.

3.1.2 Study Treatments

On study Day 1, subjects stabilized on SL BUP/NAL SOC background therapy will be randomized to SL BUP/NAL alone, or to SL BUP/NAL plus the OXD01 digital therapeutic. A stabilized subject will have completed SL BUP/NAL induction, with physical withdrawal symptoms reduced so the subject is able to fulling participate in OXD01 training, if randomized to that treatment group. Induction with SL BUP/NAL and titration to a maintenance dose that suppresses withdrawal signs and symptoms is described in the product information under Dosage and Administration and can be implemented in accordance with the Investigator's standard of practice. Note: No investigational product will be administered as part of this study.

Subjects randomized to SL BUP/NAL plus OXD01 will be trained to use OXD01 on Day 1 as directed in the OXD01 Clinician User Guide and will begin to access the therapeutic counseling modules for 15-30 minutes, 1-2 times per week as instructed. Randomization and OXD01 training should be conducted as soon as the subject is clinically stable, with physical withdrawal symptoms managed and the subject able to fully participate in the process, but no greater than 14 days from the first dose of SL BUP/NAL induction.

Subjects in both groups will use the assigned treatment for 24 weeks.

3.1.3 Subjects

Approximately 400 opioid dependent adults, seeking MAT for OUD, will be randomized. An eligible subject must be in generally good health, seeking MAT treatment for moderate or severe OUD (absent a moderate to severe use disorder for other psychoactive substances) and has not received MAT for OUD within 14 days prior to screening.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

A subject must meet the following criteria to qualify for the study.

1. Male or female 18 – 65 years of age at the screening visit, fluent in English and able to read, comprehend, and willingly sign the informed consent form (ICF).

2. Voluntarily seeking treatment for OUD.

3. In the judgment of the Investigator has the appropriate hearing, vision, manual dexterity, ability to understand instructions, and ability to use and understand internet-based applications.

4. Currently meets the criteria for moderate or severe opioid use disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-V (Appendix B).

5. Has a positive UDS for opioids at screening that is consistent with their drug use history.

6. In good health as determined by lack of clinically significant abnormalities in health assessments performed at screening.

7. Agrees not to take any buprenorphine products other than those prescribed by the Investigator during participation in the study, and agrees to use OXD01 as directed if randomized to that treatment group.

8. Completed SL BUP/NAL induction, with physical withdrawal symptoms reduced so the subject is able to fulling participate in OXD01 training, if randomized to that treatment group, and is no greater than 14 days from the first dose of SL BUP/NAL induction.

4.2 Exclusion Criteria

A subject who meets any of the following criteria will not qualify for the study.

1. Unwilling or unable to comply with the requirements of the protocol or are in a situation or condition that, in the opinion of an Investigator, may interfere with participation in the study (e.g., does not have reliable internet access).

2. History of allergy or sensitivity to naloxone, buprenorphine or other opioids, or history of any drug hypersensitivity or intolerance which, in the opinion of an Investigator, would compromise the safety of the subject.

3. Used an investigational drug within 30 days or 5 half-lives (whichever is greater) prior to randomization.

4. Received prescribed medication-assisted treatment with buprenorphine, methadone, or naltrexone for opioid use disorder within 14 days prior to screening.

5. Past or present diseases that, judged by an Investigator and based on available medical history/records, may jeopardize the safety of the subject or impact the validity of the study results.

6. Tongue piercing, or piercings in the mouth or oral deformities that may affect sublingual absorption, in the opinion of an Investigator.

7. Hospitalization for a psychiatric disorder in the past 30 days, not including inpatient treatment for drug rehabilitation.

8. Schizophrenia, or other serious mental illness defined as a mental, behavioral, or emotional disorder

resulting in serious functional impairment which substantially interferes with or limits participation in the study.

9. A Quick Inventory of Depression Symptoms - Self-Report (QIDS-SR, Appendix C) score ≥ 16 (severe depression) or a rating of 2 or 3 for question 12 (Thoughts of Death or Suicide) at screening.

10. A current diagnosis, other than opioid use disorder, requiring chronic opioid treatment.

11. Chronic pain that is unremitting or unstable.

12. Current DSM-V diagnosis of moderate to severe substance use disorder for psychoactive substances other than opioids, caffeine, marijuana, or nicotine.

13. Requires current use of medications that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A4 (Section 4.3.1).

14. Any pending legal action that could affect participation or compliance in the trial.

15. Is an employee of the Investigator or the trial site, with direct involvement in the proposed trial or other trials under the direction of the Investigator or trial site, or is a family member of the Investigator or an employee.

4.3 Restrictions

4.3.1 Concomitant Medication

The following medications are prohibited during the study:

- CYP3A4 inhibitors - macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole); the non-nucleoside reverse transcriptase inhibitor antiretroviral delavirdine; the protease inhibitor antiretrovirals atazanavir and ritonavir

- CYP3A4 inducers - rifampin, carbamazepine, phenytoin; the non-nucleoside reverse transcriptase inhibitor antiretrovirals efavirenz, nevirapine, and etravirine

- Monoamine oxidase inhibitors

4.4 Withdrawal of Subjects

Every subject has the right to refuse participation in the study at any time and for any reason. A subject's participation must therefore be terminated immediately upon his/her request.

An Investigator or the sponsor may withdraw a subject from the study to protect the health of a subject. A subject will be withdrawn from the study for the following safety-related reasons:

- Subject experiences a serious adverse event (SAE) assessed as related to the study treatment by an Investigator or Orexo.

- Subject experiences other unacceptable AE(s) assessed as related to the study treatment by an Investigator.
- Subject requires a prohibited concomitant medication.
- Subject displays hypersensitivity reactions to BUP/NAL.
- Other significant subject safety issue as assessed by an Investigator or Orexo.

An Investigator will make every attempt to explain the reason(s) for discontinuation and to document this in the appropriate sections of the case report forms (CRFs) and in the source documentation, using the following as a guide:

- Subject requests discontinuation.
- Subject is non-compliant, defined as refusal or inability to adhere to the study procedures.
- Treatment failure, as defined by an Investigator, using any and all information including subject interview.
- Unacceptable or intolerable treatment-related AEs.
- Any illness or circumstance that would adversely affect the study procedures or outcome measures.
- At the request of Orexo, regulatory agencies, or institutional review board (IRB).
- Subject is lost to follow-up.

The final record will include reasons for withdrawal, AEs, and any necessary medical treatment.

Subjects who drop out of the study after randomization will not be replaced.

4.5 Safety Stopping Criteria for the Overall Study

The clinical study will be stopped if the sponsor determines the safety risks for study subjects exceed the anticipated risks, as described in the study protocol. The following occurrences (non-exclusive) will trigger a re-evaluation of the risk assessment for the study, which could lead to a stop of the overall study:

- Occurrence of an unexpected SAE in the study assessed as related to OXD01 by an Investigator or sponsor (serious unanticipated adverse device effect as defined in Sections 7.1.3 and 7.1.4.
- Occurrences of SAEs, assessed as related to OXD01, at a higher rate or severity than expected as assessed by an Investigator or the sponsor.
- Occurrence of other significant subject risks in the study.

5. STUDY TREATMENT

5.1 Treatment Regimen

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

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.

Prior to study Day 1 all subjects will have completed SL BUP/NAL induction, with physical withdrawal symptoms reduced so the subject is able to fulling participate in OXD01 training, if randomized to that treatment group. Study Day 1 should occur as soon as the subject is clinically stable, with physical withdrawal symptoms managed and the subject able to fully participate in the process, but no greater than 14 days from the first dose of SL BUP/NAL induction.

Subjects randomized to SL BUP/NAL plus the OXD01 digital therapeutic will be trained to use OXD01 on Day 1 as directed in the OXD01 Clinician User Guide and will begin to access the therapeutic counseling modules for 15-30 minutes, 1-2 times per week as instructed.

5.2 Sublingual Buprenorphine/Naloxone Medication Assisted Treatment

The subject will obtain buprenorphine/naloxone sublingual tablets from a retail pharmacy with a prescription from the Investigator. Prior to study Day 1 subjects will initiate SL BUP/NAL, complete induction, and have physical withdrawal symptoms reduced so the subject is able to fully participate in OXD01 training, if randomized to that treatment group. Subjects will take the prescribed dose daily of SL BUP/NAL from Day 1 through Day 169 as directed by the Investigator.

5.2.1 Assessment of 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. Any lapses in treatment compliance will be addressed with the subject during these visits.

5.3 OXD01

5.3.1 Initiation, Training

The Investigator/designee will receive instruction on initiating and training subjects to use OXD01 (see OXD01 Clinician Guide) prior to enrolling the first subject at the site.

On study Day 1 subjects randomized to SL BUP/NAL plus the OXD01 digital therapeutic will be trained by the Investigator or designee to use OXD01 (see OXD01 Clinician Guide and Patient Guide) and will begin to access the therapeutic counseling modules for 15-30 minutes, 1-2 times per week as instructed. OXD01 training should be conducted as soon as the subject is clinically stable, with physical withdrawal symptoms managed and the

subject able to fully participate in the process, but no greater than 14 days from the first dose of SL BUP/NAL induction. Training should include a discussion of the key concepts of recovery and working with OXD01 (OXD01 Clinician Guide, Getting Subjects Started with MODIA – Training and Registration).

5.3.2 Assessment of Compliance

Subjects must continue to use OXD01 for 15-30 minutes, 1-2 times per week from Day 1 (Section 5.3.1) through Day 169. Treatment compliance will be assessed through subject interviews at the following Visits: Weeks 2-5, 7, 9, 11, 13, 17, 21, and 25. Lapses in compliance with the recommended use of OXD01 will be addressed with the subject. The Investigator or designee will also record the following OXD01 usage information: typical number of sessions per week and duration of each session, and progress completing the chats since the previous evaluation. The Investigator or designee will reinforce the key concepts of recovery and working with OXD01 (OXD01 Clinician Guide, Maintaining Motivation and Monitoring Compliance).

6. STUDY PROCEDURES

6.1 Subject Informed Consent

An ICF approved by the IRB, that includes all of the relevant elements currently required by federal regulations (21 Code of Federal Regulations [CFR] Part 50) and applicable state and local regulations, will be provided to each prospective study subject at screening, before enrollment into the study. The requirements for participation, the type and method of study tests to be administered, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by an Investigator or designee. Once an Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the ICF. An Investigator or designee will also sign and date the form. A copy of the ICF will be provided to the subject.

The subject's signed and dated informed consent must be obtained before conducting any study specific procedures, including the following:

- Withholding or discontinuation of concomitant medical treatment for the purpose of the study
- Physical examination for the purpose of the study

6.2 Remote Visit Procedures

In the *Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards*[1] the Food and Drug Administration (FDA) recognizes that the COVID-19 public health emergency may impact the conduct of clinical trials. When circumstances such as quarantines, site closures, and travel limitations lead to difficulties in meeting protocol-specified procedures, sites may use telemedicine to perform procedures or collect endpoint evaluations, with

[1] https://www.fda.gov/media/136238/download

the exception of collecting a urine sample for the drug screen. Procedures conducted through telemedicine must be appropriately identified and the circumstance explained in the subject record.

6.3 Demographic Data, Medical History

Relevant medical and social history will be documented during the screening visit to assess eligibility.

The following demographic data will be collected:

- Date of birth
- Gender
- Ethnic origin

6.4 Opioid Use / Dependence

Opioid use over the past 30 days and the duration of OUD will be documented at screening. The criteria for moderate or severe opioid use disorder according to DSM-V will be verified at screening (Appendix B).

6.5 Previous Treatments for Opioid Use Disorder

A treatment history, including counseling, over the previous 2 years for OUD will be recorded at screening.

6.6 Concomitant Medications

Concomitant medications will be reviewed at screening, and subjects who require chronic treatment with strong inhibitors or inducers of CYP3A4 will not be eligible for the study (Section 4.3.1).

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.

6.7 Physical Examination

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.

6.8 Vital Signs Measurements

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

6.9 Drug Screen

A urine sample will be taken at screening, study Day 1, and at weekly visits during the study to test for the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cocaine metabolite, marijuana metabolite, methadone, opiates, phencyclidine, propoxyphene, and buprenorphine.

Precautions should be taken to prevent manipulation of the urine sample by the subject.

6.10 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 following two questions:

During the past 30 days:

1. How often do you have a drink containing alcohol?

(0) Never
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

The QFI will be completed on study Day 1 and at the visit on Week 25.

6.11 Timeline Followback Method – Drug and Alcohol Use

The 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. Subjects will be asked to estimate both drug and alcohol use during the 7 days prior to the study visit on Day 1 and Week 25. Subjects will be asked to estimate only drug use during the 7 days prior to the study visit on Weeks 2-24. The TLFB is a closed Yes or No question of drug or alcohol use (Appendix D, E).

6.12 Review Study Restrictions

Study restrictions (Section 4.3) will be reviewed with the subject at study screening, and at the visits on Weeks 1-5, 7, 9, 11, 13, 17, and 21.

6.13 Randomization and Allocation to Treatment, Subject Identification Number

Eligible subjects will be randomized on Day 1 through an IRT system (separate instructions will be provided).

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.

6.14 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 (Appendix F).

6.15 Quick Inventory of Depression Symptoms, Self-Report

Symptoms of depression will be assessed by the subject using the QIDS-SR (Appendix C) at screening and at the visit on Week 25. An overall score ≥ 16 (severe depression) or a rating of 2 or 3 for question 12 (Thoughts of Death or Suicide) at screening will exclude the subject from the study.

6.16 Review Behavioral Health Therapies

Participation 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.

6.17 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 following assessment scale:

> Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?
>
> 0 = Not assessed
> 1 = Normal, not at all ill
> 2 = Borderline ill
> 3 = Mildly ill
> 4 = Moderately ill
> 5 = Markedly ill
> 6 = Severely ill
> 7 = Among the most extremely ill subjects

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 following assessment scale:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his or her condition at admission to the project, how much has the subject changed?

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

6.18 End of Study Interview

The following information will be obtained from the subject at the visit on Week 25, addressing the time from Day 1 through Day 169 (or early termination):

- Number of emergency department visits
- Number of hospitalizations
- Number of overdoses
- Able to resume work, school, or other productive activity (Yes, No, or No Change)

7. ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

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.

7.1.2 Adverse Reaction

An adverse reaction is all noxious and unintended responses in a subject using a medical device. The phrase related to a medical device means that a causal relationship between a device and an adverse event is at least a reasonable possibility; i.e., the relationship cannot be ruled out.

7.1.3 Unanticipated Adverse Device Effect

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.

7.1.4 Serious Adverse Event

An 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)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject's health or may require intervention to prevent one of the other outcomes listed in the definitions above. These AEs should also usually be considered as serious.

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.

7.2 Adverse Event Reporting Period

The AE reporting period will start after signing the informed consent form and will end at discharge from the study.

7.3 Collection of Adverse Event Data

The subjects will be monitored throughout the study for any AEs, including abnormal, clinically significant, laboratory values, clinically significant findings at physical examinations, vital signs measurements or electrocardiogram (ECG) measurements, spontaneous reports by study subjects and observations by the study personnel. AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) Version 14.1 or later AE dictionary. The subjects will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by an Investigator based on observation and questioning of the subject.

7.4 Recording of Adverse Events

All AEs should be recorded in the CRFs. Although an AE can initially be acknowledged by anyone in the study team, an Investigator will always be responsible for reporting and assessments of AEs. All AEs should be reported separately (i.e. one record per event). Reporting of AEs are event based, (i.e., an ongoing event will not be closed until resolved or at the end of study). At least the following will be recorded for each AE:

Description of adverse event: Adverse event description should be provided in English. Diagnosis is to be preferred over symptoms. If no diagnosis could be made, each symptom will be reported as a separate AE. Abbreviations should be avoided. Descriptive words should be used for ongoing conditions as applicable (e.g. “exacerbation of herpes genitalis”, “worsening of eczema” etc.).

Serious adverse event: Yes or no (definition of SAE in section 7.1.4). If Yes, an SAE Report Form needs to be completed.

Maximum intensity: Maximum intensity of the AE during the complete course of the event should be recorded in accordance with the following definitions:

- Mild – Awareness of sign and symptoms but easily tolerated
- Moderate – Discomfort sufficient to cause interference with normal activities
- Severe – Incapacitating, with inability to perform normal activities

Duration: The duration of the AE will be recorded by start and stop date and time.

Relatedness to medical device (causality): Relatedness to the medical device will be assessed by an Investigator according to the below categories.

- *Not related*: A causal relationship between the medical device and the AE is assessed as not possible (e.g. due to onset in relation to use of the device or that another cause of the AE has been identified)
- *Related*: A causal relationship between the medical device and the AE is assessed as at least possible

Actions taken: Actions taken in relation to the AE with respect to use of the medical device, should be recorded as:

- Use of the medical device withdrawn
- Use of the medical device interrupted
- Use of the medical device is reduced
- Use of the medical device is increased
- Use of the medical device not changed
- Not applicable
- Unknown

Any medication given to treat the AE will be recorded separately on the concomitant medication list of the CRFs.

Outcome: The outcome of the AE should be recorded.

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae
- Fatal
- Unknown – lost to follow-up

7.5 Serious Adverse Event Reporting/ Unanticipated Adverse Device Effects – Procedures for Investigators

7.5.1 Initial Reports

All SAEs/UADEs occurring from the time of informed consent until discharge from the study must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After discharge from the study, any SAE/UADE that the Investigator considers related to study drug must be reported to the Medpace Clinical Safety or the Sponsor/designee.

To report the SAE/UADEs, complete the form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper form to Medpace (contact information listed in Section 7.5.2) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible.

7.5.2 Follow-up Reports

The Investigator must continue to follow the patient until the SAE/UADE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs/UADEs.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

The Investigator is primarily responsible for ensuring proper care of study subjects. Medical queries with regards to the management of subjects with SAEs and AEs may also be addressed to the medical monitor at Orexo.

7.6 Reporting Responsibilities

Orexo will report UADEs to the FDA. Medpace will be responsible for submitting reports of UADEs to sites and Central IRBs according to applicable regulations and stipulated timelines. Sites will be responsible for reporting to local IRBs as required.

In the event an SAE is reported as related to BUP/NAL (SOC background therapy), Medpace will forward this information to the manufacturer for postmarketing reporting to the FDA as required.

7.7 Pregnancy

A confirmed pregnancy does not require withdrawal of the subject from the study. The Investigator should consider the risk-benefit analysis for the individual subject and either continue or discontinue BUP/NAL treatment based on their clinical judgement.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject was discontinued from the trial.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.

8. MEDICAL SAFETY

8.1 Expected Side Effects

8.1.1 OXD01

Since OXD01 is a non-systemic therapy for OUD, the likelihood of adverse events is low. However, the following emotions may occur when using the application:

- Disappointment if there is no benefit
- Distress when presented with particular topics.
- Frustration, or other distressing emotions, if the content is found to be confusing, overwhelming, or unsuitable.

Subjects should be directed to contact the Investigator if any of these feelings become significant.

9. STUDY DOCUMENTS, RECORD KEEPING, SOURCE DATA AND CASE REPORT FORMS

9.1 Protocol and Informed Consent Form

The study will be performed in accordance with this study protocol. The Investigator indicated on Form FDA 1572 will act as the Principal Investigator. Copies of the signed Form FDA 1572 and protocol will be provided to the sponsor.

Based on the study protocol, Medpace will develop a written ICF that includes all of the relevant elements

currently required by FDA (21 CFR part 50) or state regulations (see section 6.1).

The protocol and the ICF must be approved by the relevant IRB prior to study conduct per 21 CFR part 56.

9.2 Protocol and Informed Consent Changes

Changes to the protocol or the ICF will be implemented as amendments to the original document and must be approved by the applicable IRB prior to implementation. Protocol amendments are normally agreed between Orexo and the Investigator prior to finalization, however, urgent changes needed to protect the safety of study subjects should be implemented directly and the sponsor and IRB should then be notified as soon as possible. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the sponsor. Any addendum, amendment, or revision that substantially alters the study design or increases potential risk to the subject requires the subject's consent to continue in the study.

9.3 Records

Adequate records will be maintained for the study as required by International Conference on Harmonisation (ICH) Good Clinical Practices (GCP). This will include volunteer medical records, CRFs, laboratory reports, work sheets, signed ICFs, drug dispensing records, AE reports, information regarding volunteers' discontinuation and similar.

Following completion of the study, Medpace will supply the sponsor with originals of the CRFs (or a copy if electronic CRFs are used) and copies of laboratory reports and ECGs. CRF copies and original laboratory reports and ECGs will be retained for archiving by Medpace. No study related essential documents, records or data should be destroyed without prior written authorization by Orexo.

9.4 Source Data and Case Report Forms

Subjects will be identified by screening number prior to randomization and a subject number after the first dose of study medication. Source documents will be used to record all study-related data.

Source document entries will be used to complete CRFs. A set of CRFs will be completed for each subject randomized in the study. All data and CRFs will be reviewed, evaluated, and signed by the Investigator, as required. An electronic CRF (eCRF) system will be used in this study.

All changes to the eCRF data will be traced by an audit trail incorporated in the eCRF system.

10. DATA MANAGEMENT

Each investigative site will maintain source documentation and enter subject data into the CRFs as accurately as possible and will respond to any reported discrepancies rapidly.

Electronic case report forms are accessed at the investigative sites. This electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, Investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There is an internal quality review audit of the data

and additional reviews by a clinical monitor.

Each CRF is presented as an electronic copy, allowing data entry by clinical unit personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling clinical unit personnel to resolve and manage discrepancies in a timely manner.

Paper copies of the CRFs and other database reports may be printed and signed by the Investigator. This system provides clinical unit personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and Investigator comment information.

11. STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

Prior to the database lock, a detailed statistical analysis plan will be completed and placed on file. The statistical analysis plan will contain a more comprehensive explanation of the methodology used in the statistical analyses than that described below. The statistical analysis plan will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries will present data by treatment arm and overall. The data listings will include all available efficacy and safety data.

11.1 Study Populations

The primary efficacy analyses will be based on full analysis population that consists of all randomized subjects. The safety analyses will be based on safety population that is consistent of all randomized subjects.

11.2 Study Disposition

Demographic and baseline characteristics for the enrolled subjects will be summarized separately by treatment assignment. Summary statistics will be used to describe these two groups. No hypotheses will be tested with respect to baseline characteristics.

11.3 Primary Objective

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.

11.4 Secondary Objectives

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.

- 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 12 and Week 25
  - Change from baseline in the Clinical Global Impression-Severity score at Week 12 and Week 25

  CGI scores will be evaluated using general linear model methodology or non-parametric analogs.

- 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 general linear model methodology or non-parametric analogs.

- 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.

11.5 Safety Analyses

Adverse events - Safety will be assessed by recording and monitoring adverse events. Rates of adverse events will be summarized overall and by organ system class, preferred term, severity, and suspected relationship to the medical device by treatment assignment.

11.6 Determination of Sample Size

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.

12. STUDY REPORT

The clinical, statistical and bioanalytical report will be generated by Medpace.
Medpace will integrate the different parts of the report so that it is in an ICH E3 and electronic common technical document compliant format suitable for sponsor submission to Health Agencies.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Quality Control

13.1.1 Quality Control Procedures

Appropriate Quality Control measures in critical processes will be employed for the conduct of the study, in data management, in the statistical analysis and in the report writing, to ensure that data reported from the study is true and reliable.

13.1.2 Monitoring

The study will be adequately monitored in accordance with ICH Harmonised 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.

The clinical monitor, as a representative of the sponsor, will follow the study closely. In doing so, the monitor will visit the principal Investigator and sub-Investigator at the clinical site at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal Investigator, sub-Investigator, or clinical unit staff.

13.2 Quality Assurance Audits and Inspections

Orexo (or designee) may conduct audits at the clinical site at their discretion. Audits may include, but are not limited to, study procedures including the informed consent process, study drug accountability, regulatory aspects of study conduct, source documentation and CRF transcription for compliance with GCP. A Quality Assurance Statement of items audited will be provided in the final report. Sponsor audits, when applicable, will be documented by an audit certificate.

The trial site may also be subject to inspections/audits by a regulatory authority or an IRB. The Investigator is required to inform Orexo immediately of any inspection requested.

The clinical site will facilitate auditing and inspections by cooperating with auditors/inspectors and will make documentation, source data and staff available as needed.

13.3 Training of Staff

Before inclusion of subjects Orexo and/or the monitor will perform a trial initiation visit to inform and train relevant trial staff. All Investigators and staff carrying out observations of primary or other major variables involved in the trial should provide curriculum vitae. The principal Investigator will keep a list of all personnel involved in the trial together with their function and trial related duties delegated. The Investigator will ensure that appropriate trial related training is given to the staff involved in the trial, and that new information of relevance to the performance of this trial is appropriately forwarded.

14. ETHICAL CONSIDERATIONS

14.1 Risk-Benefit Assessment

Opioid dependence is associated with decreased quality of life and increased morbidity and mortality. Medication-assisted treatment, a combination of an opioid agonist or partial agonist with psychosocial intervention, has been shown to be more effective than detoxification and abstinence in reducing the frequency and quantity of opioid use as well as the risk of overdose, improving social functioning, and decreasing criminal activity.[24]

The current study is not expected to provide data which will alter the safety profile of buprenorphine used for MAT.

14.2 Ethical Conduct of the Study

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions and in accordance with ICH GCP. It is the duty of the Investigator to protect the life, health, privacy and dignity of the subjects.

14.2.1 Voluntariness, Subject Information, and Consent

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of this study and that he voluntarily consents to participate in the

study in writing according to section 6.1. Subjects will have the right to withdraw from the study at any time without consequences on their continued treatment, and must be properly informed of these rights.

14.2.2 Subject Safety

The Investigator's duty is first and foremost to safeguard the life and health of study subjects. When in conflict, considerations related to the well-being of the human subject should take precedence over the performance of the study.

14.2.3 Subject Data Protection

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential in accordance with national data legislations. This is detailed in the written information provided to the subject and an agreement for disclosure of any such information will be obtained in writing and is included in both copies of the volunteer ICF signed by the subject.

In order to maintain anonymity, subjects will be identified by a special subject number in lieu of the subject's name in all subject data handling outside the clinical unit. The code list connecting the subject numbers to the identity of the subjects will be kept by the Investigator and will only be disclosed to external parties for the purpose of quality control, quality assurance, and IRB or regulatory inspections.

14.3 Ethical Review

The study protocol, ICF, subject information, Investigator's brochure (or package insert as applicable), and any specific advertising will be submitted to an independent IRB for review before the start of the study. A form signed by the chairman or designee of the IRB noting approvals of the study must be obtained before enrollment of any subject. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the sponsor. The IRB will be informed of any serious AEs occurring during the study.

Substantial amendments to the study protocol and/or subject information/ICF should be submitted to the IRB and may not be implemented until approved, unless immediate actions are required to protect the safety of study participants.

15. REFERENCES

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

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APPENDIX A: PROTOCOL SIGNATURES

Protocol Signature – Sponsor´s Responsible Medical Officer

Document

Doc ID:	Clinical study no:	Version:	Status:	Product:	IND no:
NA	OXD01-001	1.0	Final	OXD01	NA

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

Issued by:	Date:
David Capano	19 April 2021

Signature

Date: April 19TH 2021

Signature:

Michael Sumner, MB, BS MRCP (UK), MBA

Address:

Orexo US, Inc.
150 Headquarters Plaza
East Tower, 5th Floor
Morristown, NJ 07960

orexo

Protocol Signature – Study Statistician

Document

Doc ID:	Clinical study no:	Version:	Status:	Product:	IND no:
NA	OXD01-001	1.0	Final	OXD01	NA

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

Issued by:	Date:
David Capano	19 April 2021

Signature

Date: 19APR2021

Signature:

Miao Yang, PhD

Address:

Medpace
5375 Medpace Way
Cincinnati, Ohio 45227

Protocol Signature – Principal Investigator

Document

Doc ID:	Clinical study no:	Version:	Status:	Product:	IND no:
NA	OXD01-001	1.0	Final	OXD01	NA
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					
Issued by: David Capano				**Date:** 19 April 2021	

I agree to the terms of this study protocol. I will conduct the study in accordance with the procedures specified in the study protocol, the ethical principles in the Declaration of Helsinki, ICH Good Clinical Practice and all other applicable regulatory requirements.

Signature

Date: _____

Signature: _____

Address:

APPENDIX B: DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS – 5TH EDITION – CRITERIA FOR MODERATE OR SEVERE OPIOID USE DISORDER

Opioid Use Disorder requires at least 2 criteria be met within a 12 month period:

1. Opioids are often taken in larger amounts or over a longer period of time than intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire to use opioids.
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
10. * Tolerance, as defined by either of the following:

    (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect

    (b) markedly diminished effect with continued use of the same amount of an opioid
11. * Withdrawal, as manifested by either of the following:

    (a) the characteristic opioid withdrawal syndrome

    (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

* This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Severity:
Mild: presence of 2-3 symptoms
Moderate: presence of 4-5 symptoms
Severe: presence of 6 or more symptoms.

APPENDIX C: QUICK INVENTORY OF DEPRESSION SYMPTOMS, SELF-REPORT

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

0 - I never take longer than 30 minutes to fall asleep.
1 - I take at least 30 minutes to fall asleep, less than half the time.
2 - I take at least 30 minutes to fall asleep, more than half the time.
3 - I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:

0 - I do not wake up at night.
1 - I have a restless, light sleep with a few brief awakenings each night.
2 - I wake up at least once a night, but I go back to sleep easily.
3 - I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

0 - Most of the time, I awaken no more than 30 minutes before I need to get up.
1 - More than half the time, I awaken more than 30 minutes before I need to get up.
2 - I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
3 - I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

0 - I sleep no longer than 7-8 hours/night, without napping during the day.
1 - I sleep no longer than 10 hours in a 24-hour period including naps.
2 - I sleep no longer than 12 hours in a 24-hour period including naps.
3 - I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:

0 - I do not feel sad.
1 - I feel sad less than half the time.
2 - I feel sad more than half the time.
3 - I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

0 - There is no change in my usual appetite.
1 - I eat somewhat less often or lesser amounts of food than usual.
2 - I eat much less than usual and only with personal effort.
3 - I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR –

7. Increased Appetite:

0 - There is no change from my usual appetite.
1 - I feel a need to eat more frequently than usual.
2 - I regularly eat more often and/or greater amounts of food than usual.
3 - I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (within the last two weeks):

0 - I have not had a change in my weight.
1 - I feel as if I have had a slight weight loss.
2 - I have lost 2 pounds or more.
3 - I have lost 5 pounds or more.

- OR –

9. Increased Weight (within the last two weeks):

0 - I have not had a change in my weight.
1 - I feel as if I have had a slight weight gain.
2 - I have gained 2 pounds or more.
3 - I have gained 5 pounds or more.

During the past seven days...

10. Concentration / Decision Making:

0 - There is no change in my usual capacity to concentrate or make decisions.
1 - I occasionally feel indecisive or find that my attention wanders.
2 - Most of the time, I struggle to focus my attention or to make decisions.

3 - I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

0 - I see myself as equally worthwhile and deserving as other people.
1 - I am more self-blaming than usual.
2 - I largely believe that I cause problems for others.
3 - I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

0 - I do not think of suicide or death.
1 - I feel that life is empty or wonder if it's worth living.
2 - I think of suicide or death several times a week for several minutes.
3 - I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest:

0 - There is no change from usual in how interested I am in other people or activities.
1 - I notice that I am less interested in people or activities.
2 - I find I have interest in only one or two of my formerly pursued activities.
3 – I have virtually no interest in formerly pursued activities.

14. Energy Level:

0 - There is no change in my usual level of energy.
1 - I get tired more easily than usual.
2 - I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).
3 - I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

0 - I think, speak, and move at my usual rate of speed.
1 - I find that my thinking is slowed down or my voice sounds dull or flat.
2 - It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
3 - I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

0 - I do not feel restless.
1 - I'm often fidgety, wringing my hands, or need to shift how I am sitting.
2 - I have impulses to move about and am quite restless.
3 - At times, I am unable to stay seated and need to pace around.

Scoring:

Total QIDS scores range: 0 to 27

- No depression: ≤ 5
- Mild depression: 6 to 10
- Moderate depression: 11 to 15
- Severe depression: 16 to 20
- Very severe depression: ≥ 21

APPENDIX D: TIMELINE FOLLOWBACK METHOD – DRUGS AND ALCOHOL

Instructions for Filling Out the Timeline Drug and Alcohol Use Calendar

To help us evaluate your drug and alcohol use, we need to get an idea of what your use was like in the past days. To do this, we would like you to fill out the attached calendar.

- ✓ Filling out the calendar is not hard!
- ✓ Try to be as accurate as possible.
- ✓ We recognize you won't have perfect recall. That's OKAY.

✓ WHAT TO FILL IN

- The idea is that for **each day** on the calendar we want you to indicate whether you "used" or "did not use" drugs or alcohol. Specifically indicate whether you have used any of the following: amphetamines (uppers), barbiturates, benzodiazepines (for example, Xanax, Ativan, Valium), cocaine, marijuana, methadone, opiates (for example, oxycodone, hydrocodone), phencyclidine (PCP), or alcohol in any form.
- On days when you **did not use drugs or alcohol**, you should write a "0" in the box.
- On days when you **did use drugs or alcohol**, you should put a **"✓"** in the box for drugs or alcohol.

It's important that something is written for <u>every</u> day for both drugs and alcohol, even if it is a "0".

✓ YOUR BEST ESTIMATE

- We realize it isn't easy to recall things with 100% accuracy.
- If you are not sure whether you used a certain drug or alcohol on a Thursday or a Friday of a certain week, **give it your best guess**! The goal is to get a picture of how many days you were using drugs and your patterns of use.

✓ HELPFUL HINTS

- Holidays such as Thanksgiving and Christmas are marked on the calendar to help you better recall your use. Also, think about whether you used drugs or alcohol on personal holidays and events such as birthdays, vacations, or parties.
- If you have **regular drug or alcohol use patterns** you can use these to help you recall your use. For example, you may have weekend/weekday changes in your drug use or your drug use may be different depending where you are or whom you are with.

✓ COMPLETING THE CALENDAR

- A blank calendar is attached. **Each day** should contain a "0" for no drug use or a **"✓" for drug and alcohol use**.
- The time period we are talking about on the calendar is from _____ to _____ .
- In estimating your drug use, be as accurate as possible.

- DOUBLE CHECK THAT ALL DAYS ARE FILLED IN BEFORE RETURNING THE CALENDAR.
- Before you start look at the **SAMPLE CALENDAR** below.

✓ **SAMPLE CALENDAR SEPTEMBER 3-9**

2000	SUN	MON	TUES	WED	THURS	FRI	SAT
						1	2
S	3 Drugs 0 Alcohol 0	4 Labor Day Drugs 0 Alcohol 0	5 Drugs 0 Alcohol ✓	6 Drugs 0 Alcohol ✓	7 Drugs ✓ Alcohol ✓	8 Drugs 0 Alcohol 0	9 Drugs 0 Alcohol 0
E	10	11	12	13	14	15	16
P	17	18	19	20	21	22	23
T	24	25	26	27	28	29	30

APPENDIX E: TIMELINE FOLLOWBACK METHOD – DRUGS

Instructions for Filling Out the Timeline Drug Use Calendar

To help us evaluate your drug use, we need to get an idea of what your use was like in the past days. To do this, we would like you to fill out the attached calendar.

- ✓ Filling out the calendar is not hard!
- ✓ Try to be as accurate as possible.
- ✓ We recognize you won't have perfect recall. That's OKAY.

✓ WHAT TO FILL IN

- The idea is that for **each day** on the calendar we want you to indicate whether you "used" or "did not use" drugs. Specifically indicate whether you have used any of the following: amphetamines (uppers), barbiturates, benzodiazepines (for example, Xanax, Ativan, Valium), cocaine, marijuana, methadone, opiates (for example, oxycodone, hydrocodone), phencyclidine (PCP).
- On days when you **did not use drugs**, you should write a "0" in the box.
- On days when you **did use drugs**, you should put a **"✓"** in the box.

It's important that something is written for <u>every</u> day, even if it is a "0".

✓ YOUR BEST ESTIMATE

- We realize it isn't easy to recall things with 100% accuracy.
- If you are not sure whether you used a certain drug on a Thursday or a Friday of a certain week, **give it your best guess!** The goal is to get a picture of how many days you were using drugs and your patterns of use.

✓ HELPFUL HINTS

- Holidays such as Thanksgiving and Christmas are marked on the calendar to help you better recall your use. Also, think about whether you used drugs on personal holidays and events such as birthdays, vacations, or parties.
- If you have **regular drug use patterns** you can use these to help you recall your use. For example, you may have weekend/weekday changes in your drug use or your drug use may be different depending where you are or whom you are with.

✓ COMPLETING THE CALENDAR

- A blank calendar is attached. **Each day** should contain a "0" for no drug use or a **"✓" for drug use**.
- The time period we are talking about on the calendar is from _____ to _____ .

- In estimating your drug use, be as accurate as possible.
- DOUBLE CHECK THAT ALL DAYS ARE FILLED IN BEFORE RETURNING THE CALENDAR.
- Before you start look at the **SAMPLE CALENDAR** below.

✓ **SAMPLE CALENDAR SEPTEMBER 3-9**

2000	SUN	MON	TUES	WED	THURS	FRI	SAT
						1	2
S	3 Drugs 0	4 Labor Day Drugs ✓	5 Drugs 0	6 Drugs 0	7 Drugs ✓	8 Drugs 0	9 Drugs 0
E	10	11	12	13	14	15	16
P	17	18	19	20	21	22	23
T	24	25	26	27	28	29	30

APPENDIX F: VISUAL ANALOG SCALE – OPIOID CRAVINGS

Please draw a perpendicular mark through the line between No Cravings and The Worst Possible Cravings to describe the intensity of your opioid cravings in the last 24 hours.

No cravings _____ The worst possible cravings