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2 EXECUTIVE SUMMARY

TITLE OF PROPOSAL: A Randomized, Double-Blind, Placebo- and Active-Controlled, Crossover Study to Evaluate the Abuse Potential of Oxymorphone Compared to Other Mu Opioid Agonists in Physically Dependent Opioid Users with Moderate-to-Severe Opioid Use Disorder

INVESTIGATIONAL PRODUCTS: Intravenous oxymorphone, oxycodone, and hydromorphone; oral morphine, and other opioids as appropriate

TOPICAL AREA: Application of novel or innovative clinical trial designs and data analyses (section 2.1.3C).

PHASE OF DEVELOPMENT: 2

INVESTIGATIONAL SITES/LOCATIONS: NYSPI (RFMH)/Columbia University and University of Kentucky, 2-sites, United States

2.1 OBJECTIVES

2.1.1 Primary Pharmacodynamic Objective

1. To evaluate the relative reinforcing effects (progressive ratio (PR) breakpoint value for drug and percent drug choice) of oxymorphone (1.8, 3.2, 5.6 and 10 mg/70 kg, intravenous, i.v.) compared to oxycodone (10, 18, 32, and 56 mg/70 kg, i.v.), and hydromorphone (3.2, 5.6, 10, and 18 mg/70 kg, i.v.) in active opioid users who are physically dependent on opioids and meet Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for moderate-to-severe opioid use disorder (OUD).

   We hypothesize that the PR breakpoint value and percent drug choice for oxymorphone will be significantly greater than placebo, but not oxycodone or hydromorphone.

2.1.2 Secondary Pharmacodynamic Objectives

To evaluate maximal subjective ratings (E_{max}) on individual visual analogue scale (VAS) items of Drug Liking, Take Drug Again, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Monetary Value of single i.v. doses of 1.8, 3.2, 5.6 and 10 mg/70 kg oxymorphone relative to single oxycodone (10, 18, 32, and 56 mg/70 kg, i.v.), and hydromorphone (3.2, 5.6, 10, and 18 mg/70 kg, i.v.) in subjects who are active, physically dependent opioid users who meet DSM-5 criteria for OUD.

We hypothesize that Drug Liking will be significantly greater for active doses of each drug compared to placebo, but Drug Liking will not be significantly different for oxymorphone compared to the other opioid agonists (because we are matching the doses of each drug on the Drug Liking measure).

2.2 STUDY DESIGN

This will be a 2-center, double-blind, randomized, placebo-controlled, and active-controlled cross-over study.

Pilot/Dose Finding Study:

We conducted a pilot/dose finding study (N=6) to examine dose equivalency and to ensure safety (See Table Below). For each drug, doses were administered in ascending order, but otherwise randomized. This study phase was single blind drug administration (participants will be blind to the dose; but not all physicians/study staff were blind in order to properly monitor safety).

The pilot study included the following intravenous doses (each dose was administered once):

Placebo (saline)

Oxymorphone: 1.8, 3.2, 5.6, 10, 18, 32, and 56 mg/70 kg

Oxycodone: 18, 32, and 56 mg/70 kg

Morphine: 18, 32, and 56 mg/70 kg

Hydromorphone: 1.8, 3.2, 5.6, 10, and 18 mg/70 kg

Oral morphine maintenance doses of 30 mg/dose was administered daily at 7 am, 1 pm, 6 pm, and 10 pm. On session days, the oral morphine doses scheduled for 1 pm and 6 pm were not be administered; the 10 pm dose was administered if the participant met all safety criteria (as determined by the criteria listed in below in section 2.2.1). Oral morphine doses were not weight-based (30 mg/dose for all participants).

PILOT/DOSE-FINDING STUDY

STUDY PHASE	STABILIZATION/QUALIFICATION							PILOT SESSIONS													
STUDY WEEK	Week 1***							Week 2							Week 3						
STUDY DAY	Q1	Q2	Q3	Q4	Q5	Q6	Q7	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Morphine Maintenance (mg, PO)*	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
	120	120	120	60	60	120	120	60	60	60	60	60	120	120	60	60	60	60	60	120	120
Agonist	Morphine Stabilization			Mor	Pbo			Pbo	Mor	Mor	Mor	Oxy			Oxy	Oxy	Hyd	Hyd	Hyd		
Dose (mg/70 kg, IV)**				56	0			0	18	32	56	18			32	56	1.8	3.2	5.6		

STUDY PHASE	PILOT SESSIONS											
STUDY WEEK	Week 4							Week 5				
STUDY DAY	15	16	17	18	19	20	21	22	23	24	25	26
Morphine Maintenance (mg, PO)	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri
	60	60	60	60	60	120	120	60	60	60	60	30-60
Agonist	Hyd	Hyd	Oxm	Oxm	Oxm			Oxm	Oxm	Oxm	Oxm	D/C
Dose (mg/70 kg)	10	18	1.8	3.2	5.6			10	18	32	56	

*Oral Morphine (30 mg) QID at 7am, 1pm, 6pm and 10pm
*For safety, the 1pm and 6 pm oral morphine dose will be withheld on session days; the 10 pm dose will be administered if all safety criteria are met
**All intravenous doses will be dosed by weight (mg/70 kg)
***Subjects will be stabilized on PO morphine for 3-7 days (3 days displayed above as an example - extra days [labeled with the Q prefix] can be added if needed).

PILOT STUDY
For each drug, doses will be administered in ascending order
Doses can be otherwise randomized, as long as the ascending rule is followed (doses for each drug are administered in ascening order).
IV doses will be administered at 11am. Sessions will end at 5 pm (for a total of 6 hrs post-dose monitoring).

Primary Study:

We have completed the pilot/dose finding study and the study team has reviewed the data and selected doses that were approximately equivalent/safe for the primary randomized study. The primary study is a randomized block-design, double-blind, placebo-controlled study. This study will include evaluations of drug/money self-administration and drug/drug choice procedures. We anticipate enrolling until there are approximately 10 completers per site (total approx. n=20). See Table 1 below for example study calendar.

TABLE 1: REPRESENTATIVE STUDY DESIGN

STUDY PHASE	QUALIFICATION							TREATMENT													
STUDY WEEK	Week 1***							Week 2							Week 3						
STUDY DAY	1Q	2Q	3Q	4Q	5Q	6Q	7Q	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Self-admin Procedure	NONE							DRUG VERSUS MONEY CHOICE													
Morphine Maintenance (mg, PO)*	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
	120	120	120	60	60	120	120	60	60	60	60	60	120	120	60	60	60	60	60	120	120
Agonist	Morphine Stabilization			Hyd	Pbo			Oxy	Oxm	Oxy	Hyd	Pbo			Hyd	Hyd	Oxm	Hyd	Oxy		
Dose (mg/70 kg, IV)**				18	0			32	3.2	10	18	0			10	5.6	10	3.2	18		

STUDY PHASE	TREATMENT (continued)																				
STUDY WEEK	Week 4							Week 5							Week 6						
STUDY DAY	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Self-admin Procedure	(continued)			DRUG VERSUS DRUG CHOICE																	
Morphine Maintenance (mg, PO)	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
	60	60	60	60	60	120	120	60	60	60	60	60	120	120	60	60	60	60	60	120	120
Agonist	Oxy	Oxm	Oxm	Oxm	Hyd			Oxm vs Hyd			Oxm	Oxy			Oxm vs Oxy			Oxm	Pbo		
Dose (mg/70 kg)	56	5.6	1.8	10	18			Choice	Choice	Choice	5.6	56			Choice	Choice	Choice	5.6	0		

STUDY PHASE	TREATMENT (continued)										
STUDY WEEK	Week 7							Week 8			
STUDY DAY	36	37	38	39	40	41	42	43	44	45	46
Self-admin Procedure	(continued)										
Morphine Maintenance (mg, PO)	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu
	60	60	60	60	60	120	120	60	60	60	60
Agonist	Oxm vs Pbo			Oxm	Hyd			Oxm vs Hyd			
Dose (mg/70 kg)	Choice	Choice	Choice	5.6	18			Choice	Choice	Choice	D/C

*30 mg QID at 7am, 1pm, 8pm and 10pm; check in on Day 1Q; subjects will be stabilized on PO morphine for 3-7 days; discharge on Day 46 ± 7 days; for safety, the 1pm oral morphine dose will be withheld on test days and the 8pm and 10pm dose will be withheld or given at the discretion of the investigators

**Test doses during Weeks 2-4 will be given at 11am and 3pm (the 3pm dose may be fractions of the 11am dose); during Weeks 4-8, Oxm, Hyd, Oxc, or Pbo will only be given at 11am on the 1st 2 days of that choice pair and participants can choose active or placebo doses or neither at 11am and 3pm on the subsequent 3 days of the week

***Test doses during Week 1 (18mg/70 kg hydromorphone and placebo) will be administered only at 11am and used to determine study qualification based on Drug Liking ratings
Oxm = oxymorphone; Oxc = oxycodone; Hyd = hydromorphone; Pbo = placebo (saline); D/C = Discharge

1. Study Qualification Phase (Week 1)

The study qualification phase is designed to assess the ability of subjects to distinguish the effects of i.v. hydromorphone (18 mg/70 kg) from placebo and to determine whether more Drug Liking is reported for hydromorphone based on pre-defined criteria. Subjects meeting these criteria will be entered into the Study Treatment Phase of the study. All study days preceding the first experimental session (including stabilization days, qualification sessions, and any other days preceding the first session) will be labeled with the Q prefix to denote that the participant is in qualification phase.

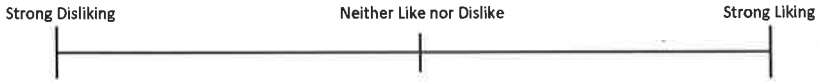
2. Experimental Session Phase (Weeks 2-8)

The study design is in accordance with the January 2017 United States (US) Department of Health and Human Services Food and Drug Administration (FDA) Center for Drug Evaluation and Research Guidance for Industry Assessment of Abuse Potential of Drugs.

The progressive ratio breakpoint value using a drug versus money choice procedure and percent drug choice using a drug versus drug choice procedure were chosen based on previous studies conducted by Drs. Comer and Walsh (Comer et al., 2008, 2013; Donny et al., 2005; Middleton et al., 2012). E_{max} on a 100-mm VAS to the question "Do you Like the Drug Effect you are feeling now?" (Drug Liking) was selected as a secondary pharmacodynamic endpoint of study, based on results of previous likeability trials and the 2017 FDA Guidance for Industry Assessment of Abuse Potential of Drugs.

At various time points after dosing, subjects will complete a VAS Questionnaire consisting of 7 questions and corresponding VAS for each question, presented with 1 question and 1 VAS per page and in the same order each time, to determine their subjective response to treatment. Subjects will indicate their response to the question "Do you Like the Drug Effect you are feeling now?" along the corresponding bipolar 100-mm VAS on which 50 mm is "Neither Like nor Dislike". We will also present other questionnaires at various times throughout the session (e.g., street value estimate, drug identification questionnaire).

1. Do you Like the Drug Effect you are feeling now?



2. Do you feel Any Drug Effects?

3. Do you feel High?

4. Do you feel Good Drug Effects?

5. Do you feel Bad Drug Effects?

6. Do you want to Take the Drug Again?

7. Do you have any Desire to use opioids?

The study will enroll subjects ≥ 18 and ≤ 55 years of age (≥ 21 years and ≤ 55 at Columbia site) who are physically dependent opioid users currently meeting DSM-5 criteria for moderate-severe OUD. Approximately 200 subjects will be screened to identify ~40 subjects to enter the Study Qualification Phase, with a target of 20 subjects across both sites to complete the study. Each site will screen ~100 subjects to identify ~20 subjects to enter the Study Qualification Phase, with a target of 10 subjects per site completing the study. The Institutional Review Board (IRB)-approved written Informed Consent will be obtained from all subjects prior to any study-related procedures. Screening can occur up to approximately 35 days prior to Day 1 of the Study Qualification Phase. Labs and ECG that are >30 days old will repeated on or before admission and will be cleared by a study physician prior to dosing.

Screening procedures include obtaining concomitant medication use, medical history, physical examination, vital signs, height, weight, laboratory safety tests, other drug use/psychological screening tests, urine drug screens, ethanol breath test, and 12-lead electrocardiogram (ECG). A naloxone challenge test/observation of opioid withdrawal symptoms during screening may also be used to confirm opioid physical dependence prior to Check-in. If a naloxone challenge test is used, typically, an intramuscular dose of 0.2 mg is the starting dose and is increased by 0.2 mg until we observe withdrawal symptoms. The maximum dose is 3 mg – this dose is occasionally needed due to heroin being cut with buprenorphine and those individuals require higher doses of naloxone in order to observe withdrawal symptoms.

Among these procedures:

Vital signs include blood pressure, pulse rate, respiratory rate, and hereafter referred to simply as vital signs

Laboratory safety tests include:

- Complete blood count with cell differential and platelet count
- Metabolic panel that includes aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, carbon dioxide, total bilirubin, blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, total protein, and uric acid
- Urine tests for blood, albumin/protein, and glucose
- These tests above are hereafter referred to simply as laboratory safety tests.
- Other screening tests may include:
    - Urine drug screen and ethanol breath test
    - Follicle stimulating hormone, if needed, to determine menopausal status
    - Serum pregnancy test in women of childbearing potential during screening
    - Urine pregnancy test in women of childbearing potential at admission

- Columbia-Suicide Severity Rating Scale (C-SSRS)

- Protocol inclusion and exclusion criteria will be reviewed.

During the screening/admission/training process, study staff will train potential subjects in the use of the self-administration procedures (Drug versus Money Choice using a progressive ratio schedule of responding and Drug versus Drug Choice using verbal responses) and VAS Questionnaire. Subjects must be able to demonstrate understanding of how to complete both self-administration procedures and the VAS Questionnaire prior to initiating each type of session.

To enter the Study Qualification Phase, all subjects must meet protocol eligibility criteria at both Screening and Check-in. Eligible subjects will be admitted to the Clinical Research Unit (CRU) and stabilized on oral morphine for at least 3 consecutive days (and up to 7 days if needed; i.e., days Q1 – Q7). Morphine (30 mg QID, p.o.) will be given daily at 7am, 1pm, 6pm, and 10pm throughout the study, with the exception of test days, when the 1pm and 6 pm dose will be withheld. The 10 pm dose will be administered at the discretion of the medical staff. Maintenance doses will be administered only if the participant meets all safety criteria for dose administration. Eligible subjects will continue on to the Study Treatment Phase (Day 1 through Day 46; extra days may be needed to account for holidays/variation in admission day). Participants will remain on the CRU for the full duration of their participation.

At Admission/Check-in, changes in concomitant medications and changes to medical status since the first Screening Visit will be recorded, vital signs will be obtained, and a urine drug screen, pregnancy test for females, and ethanol breath test will be performed. Changes from the first Screening Visit in medical history and physical examination will be recorded. Laboratory safety tests and 12-lead ECG will be repeated if the results are > 30 days old.

Participants will be weighed after admission and prior to the Qualification Phase to determine their IV doses (IV doses are based on body weight). Participants will be re-weighed every two weeks and doses will be adjusted as necessary.

2.2.1 Study Qualification Phase

Prior to dosing in the Study Qualification Phase, eligible subjects will be randomly assigned to 1 of 2 sequences of placebo and hydromorphone (18 mg/70 kg, i.v.) administration. A single i.v. dose of hydromorphone (18 mg/70 kg) or placebo (saline) will be administered according to the randomized assignment. Following a minimum 24-h post-dose washout, a single i.v. dose of the alternate treatment will be administered. Subjects who receive at least one dose of study drug in the Study Qualification Phase are considered enrolled in the study. The Qualification Phase will be conducted prior to randomization into the pilot study and the primary study. Each Qualification Session will last approximately 3.5 hrs (e.g., 30 minutes of baseline, 3 hrs post-dose safety monitoring and data collection).

The VAS Questionnaire will be administered before and at regular intervals after drug administration (e.g., every 5 minutes for the first 15 minutes and every 30 minutes

thereafter). To qualify for continued participation, participants must respond as follows after placebo administration: in response to the first question, "Do you Like the Drug?", the subject must have an $E_{max} \geq 40$ mm and < 60 mm on the bipolar 100-mm Drug Liking VAS on which a response of 0 mm is Strong Disliking, a response of 50 mm is Neutral/No Response, and response of 100 mm is Strong Liking. Following hydromorphone administration (18 mg/70 kg), the subject must have an $E_{max} \geq 60$ mm and ≥ 15 mm closer to "Strong Liking" than the placebo response on the Drug Liking VAS.

Vital signs will be taken prior to each dose. Blood pressure, pulse rate, respiration rate, oxygen saturation, and end tidal CO_2 will be measured and recorded approximately 15 min before drug administration and at the following approximate intervals after drug administration: immediately following, every 5 minutes for the first 15 minutes, and in 15 minute intervals thereafter for a total of 3 hrs post-dose monitoring. Pupil diameter measurements will follow this same schedule, but will also be measured approximately 2 minutes post-dose.

Participants will be monitored in the laboratory for 3 hrs and do not leave the session room until their vitals signs are at safe levels (e.g., oxygen saturation >95% with minimal sedation).

Subjects will be monitored for AEs and changes in concomitant medications throughout the Study Qualification Phase.

Dose Finding/Pilot Study Phase

We have completed a dose finding/pilot study. If pilot participants displayed appropriate responding during the qualification phase, they moved on to the pilot phase. Doses were administered in ascending order, but otherwise imposed on a randomized dose order. This phase lasted approximately 5 weeks. During this time, one single IV dose was administered during each session day (doses as listed above) with no self-administration/choice data collected. Data (e.g., subjective, physiological and observer-rated effects) was collected prior to and for approximately 6 hrs after each dose administration. Dose volume was standardized and contained approximately 20 mL of solution per injection and was infused at a standardized rate (approx. 30 seconds of drug infusion and approx. 30 second saline flush). Each Pilot Study Session lasted approximately 6.5 hrs (e.g., 30 minutes of baseline, 6 hrs post-dose safety monitoring and data collection).

Vital signs were taken prior to each dose. Blood pressure, pulse rate, respiration rate, oxygen saturation, and end tidal CO_2 were measured and recorded approximately 15 min before drug administration and at the following approximate intervals after drug administration: immediately following, every 5 minutes for the first 15 minutes, and in 15 minute intervals thereafter for a total of 6 hrs post-dose monitoring. Pupil diameter measurements followed this same schedule, but were also be measured approximately 2 minutes post-dose. Participants were monitored in the laboratory for 6 hrs post-dose and did not leave the session room until their vitals signs are at safe levels (e.g., oxygen saturation >95% with minimal sedation).

The VAS Questionnaire was administered approximately 15 min before and at regular intervals after drug administration (e.g., every minute for the first 10 minutes, at 15 and 30 minutes, and every 30 minutes thereafter, for a total of 6 hrs post-dose monitoring).

Subjects were monitored for AEs and changes in concomitant medications throughout the Pilot Phase.

Primary Study, Experimental Sessions

The first day of the Experimental Sessions will occur ≥ 24 h after the last dose of study drug in the Study Qualification Phase..

During Weeks 2-4 of the study, the Drug versus Money Choice procedure will be used to test the reinforcing efficacy of the opioid drugs (oxymorphone, oxycodone, hydromorphone, placebo; 4 doses tested per active opioid drug) versus money. During this procedure, subjects will receive $20 and a dose to "sample" in the morning (approximately 11 am). In the afternoon, participants will have the opportunity to work for the dose of drug sampled in morning (in $1/10^{th}$ increments), money (in $2 increments) or a combination of both by making finger presses on an iPad (drug administration at approximately 3 pm). All doses will be administered in randomized order. The sample portion of the Drug versus Money Choice Sessions will be approximately 2.5 hrs in duration (i.e., 30 minutes of baseline, 2 hrs of post-dose data collection and monitoring). The choice portion will last approximately 4 hrs in duration (approximately 2 hrs for baseline and completion of the self-administration program and 2 hrs of post-dose data collection and safety monitoring). All participants will remain in session for the full duration (until approximately 5 pm), regardless of their choice (money, drug, or money/drug combination).

During both portions of the Drug vs. Money session, blood pressure, pulse rate, respiration rate, oxygen saturation, and end tidal CO_2 will be measured and recorded approximately 15 min before drug administration and at the following approximate intervals after drug administration: immediately following, every 5 minutes for the first 15 minutes, and in 15 minute intervals thereafter for a total of 2 hrs post-dose monitoring. Participants will be monitored in the laboratory for a minimum of 2 hrs post-dose and do not leave the session room until their vitals signs are at safe levels (e.g., oxygen saturation >95% with minimal sedation).

During the sample portions of the Drug vs. Money session, the VAS will be administered on the following approximate schedule: prior to drug administration, every minute for the first 10 minutes after drug administration, at 15 and 30 minutes and in half hour intervals thereafter. During the choice portion of the session, the VAS will be collected at baseline and approximately 5, 10, 15 and 30 minutes post-dose and in half-hour intervals thereafter.

During Weeks 4-8 of the study, the Drug versus Drug Choice procedure will be used. Drug vs. drug comparisons will consist of 1) 5.6 mg/70 kg oxymorphone versus 56 mg/70 kg oxycodone, 2) 5.6 mg/70 kg oxymorphone versus 18 mg hydromorphone, 3) 10 mg/70 kg oxymorphone versus 18 mg/70 kg hydromorphone, and 4) 5.6 mg/70 kg oxymorphone versus placebo. To test preference between the drug pairs, subjects will

receive (in randomized order) a sample dose of drug on one day (Dose A) and a sample dose of another drug on the next day (Dose B). For the subsequent 3 days, subjects will be asked to choose between the drugs two times per day (drug administered at 11 am, 3 pm). For example, in the morning, they will be asked to select Dose A, Dose B, or Neither; they make the same choice in the afternoon (for a total of 6 choice opportunities per drug pairing). The Drug versus Drug Sample Sessions will be approximately 6.5 hrs in duration (i.e., 30 minutes of baseline prior to each dose, 6 hrs of post-dose data collection and monitoring). The Drug versus Drug Choice Sessions will last approximately 6.5 hrs in duration: approximately 2.5 hrs total for the morning portion [30 minutes of baseline, 2 hrs post-dose data collection and safety monitoring]; 1.5 hr break for a meal and rest; afternoon portion: approximately 2.5 hrs total [30 minutes of baseline, 2 hrs post-dose data collection and safety monitoring]). Participants will remain in session for the full duration (until approximately 5 pm) regardless of their choice (drug A/B or no drug).

During the Drug vs. Drug Sample Sessions, blood pressure, pulse rate, respiration rate, oxygen saturation, and end tidal CO_2 will be measured and recorded approximately 15 min before drug administration and at the following approximate intervals after drug administration: immediately following, every 5 minutes for the first 15 minutes, and in 15 minute intervals thereafter for a total of 6 hrs post-dose monitoring. Pupil diameter measurements will follow this same schedule, but will also be measured approximately 2 minutes post-dose. The VAS Questionnaire will be administered approximately 15 min before and at regular intervals after drug administration (e.g., every minute for the first 10 minutes, at 15 and 30 minutes, and every 30 minutes thereafter, for a total of 6 hrs post-dose monitoring).

During the Drug vs. Drug Choice Sessions, blood pressure, pulse rate, respiration rate, oxygen saturation, and end tidal CO_2 will be measured and recorded approximately 15 min before drug administration and at the following approximate intervals after drug administration: immediately following, every 5 minutes for the first 15 minutes, and in 15 minute intervals thereafter for a total of 2 hrs post-dose monitoring. The VAS will be administered on the following approximate schedule: prior to drug administration, every minute for the first 10 minutes after drug administration, at 15 and 30 minutes and in half hour intervals thereafter. Participants will be monitored in the laboratory for a minimum of 2 hrs post-dose and do not leave the session room until their vitals signs are at safe levels (e.g., oxygen saturation >95% with minimal sedation).

Subjects will be monitored for AEs and all concomitant medications will be recorded throughout the study.

Dose holding requirements

Oral or IV doses will be withheld if any of the following physiological criteria are met consistently across a 5-minute period. If an out-of-range value is obtained, measurements will be repeated and evaluated every minute for 5 minutes. Staff will contact a study physician when these criteria are met to determine when the dose can safely be administered.

Participant appears sedated or nodding (e.g., slow blinking, keeping eyes closed for several seconds at time; propping head up with arm; head is resting on the wall or table)

Systolic blood pressure: <85 or >170

Diastolic blood pressure: <50 or >100

Heart Rate: <45 or >130 beats per minute

Respiration Rate: ≤8 breaths per minute

O_2 Saturation: <95% on room air

Urine drug toxicology screens and breathalyzers will be conducted throughout the inpatient phase of the study.

Laboratory safety tests, urine drug screening, ethanol breath testing, and AE/concomitant medication assessments will be performed at discharge.

Subjects will be discharged from the CRU approximately 12-24 h after administration of the last dose of study drug (discharge planned for Day 53, although the exact study day/time of discharge may vary due to admission day differences/holiday schedules or the need for early discharge). If a participant has a PICC line inserted, it will be removed prior to discharge.

Concomitant medications will be recorded. Subject safety will be assessed prior to discharge from the CRU, including AEs, medical history, physical examination, vital signs, laboratory safety tests, and ECG. Urine drug screening and ethanol breath testing will also be performed prior to discharge from the CRU.

Subjects who discontinue the study before completing all experimental sessions will complete all discharge assessments (as described above) prior to discontinuation, unless consent is withdrawn.

Discharge: Treatment Referrals and Treatment Medication Options: Prior to study discharge, participants are asked if they are interested in treatment for substance use disorder and offered referrals for substance use disorder treatment if they indicate interest.

At the UK site, participants will be offered a standard 7-day buprenorphine/naloxone medication taper that will be prescribed and managed by Dr. Lofwall. The actual number of days may be based on clinical assessment and subject preferences. Subjects may receive their initial medication taper dose prior to discharge from the clinical research unit. We have used this procedure successfully for previous studies with opioid dependent subjects.

At the Columbia site, participants will receive counseling about the different treatment options for opioid use disorder (Vivitrol, buprenorphine, methadone, behavioral therapy etc.) prior to discharge. Additionally, the standard discharge procedure includes education about the risks of opioid overdose, how to identify opioid overdose, and how to use a naloxone kit provided to them as certified opioid overdose responders. For

those participants requesting outpatient treatment, appropriate arrangements will be made, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible, or participation in group therapy at STARS or Narcotics Anonymous. Induction onto Suboxone or Vivitrol treatment will also be available to all participants prior to discharge.

At both sites, participants are also counseled prior to discharge about the possibility that they are at increased risk and may be more sensitive to opioid effects as a result of the study. A research staff member reviews information with the participant and they are provided phone numbers for research staff/investigators if they have any questions. An example of the information provided to the participant:

"As a result of study participation, it is possible that you will be less tolerant to the effects of opioids at discharge. You should be aware that you may be more sensitive to the effects of heroin or other opioids upon completion of this study. This increased sensitivity to opiates could result in overdose and death. Thus, doses of heroin or other opiates that you used to take before entering the hospital could be enough to cause you to stop breathing and die. Fentanyl and carfentanil are powerful synthetic opioids that can be added to heroin without your knowledge and these further increase your risk of overdose. Extreme caution must be exercised after you leave the hospital, if you choose to use any opioid again."

Counseling about different treatment options and referrals to treatment are available to participants at any time before, during, or after their participation in our study. Subjects are informed that they do not have to participate in our study in order to receive a referral to treatment. For those requesting outpatient treatment, attempts are made to link them to an appropriate provider and all are offered naloxone kits and/or prescriptions for overdose reversal and made aware of local needle exchanges locations.

2.2.2 Safety Follow-Up (Approximately 2-4 weeks after study discharge)

A Follow-Up visit will be held approximately 2-4 weeks after discharge. Assessments of subject safety will include AEs, vital signs, and urine drug screens. Concomitant medications also will be recorded. Urine pregnancy tests will be performed for women of child-bearing potential.

2.3 MAIN CRITERIA FOR INCLUSION AND EXCLUSION

2.3.1 Key Inclusion Criteria at Screening including Check-In for Study Qualification Phase

1. ≥ 18 and ≤ 55 years of age at the time Informed Consent is signed. The Columbia site will enroll participants ages ≥ 21 and ≤ 55 years old.
2. Recent history of intravenous opioid use.
3. DSM-5 criteria for moderate-to-severe OUD.

4. At least 21 of the last 30 days of illicit opioid use with physical dependence for ≥ 1 month prior to Screening.
5. Positive for opioids on urine drug screening.

2.3.2 Key Exclusion at Screening including Check-In for Study Qualification Phase

1. DSM-5 diagnosis of any substance use disorders except for OUD requiring medical management.
2. Any of the following results on laboratory tests:
    a. A positive pregnancy test in women of childbearing potential.
    b. Hemoglobin < 12 g/dL for males and < 11 g/dL for females.
    c. Neutrophils < 1.0 $\times 10^9$/L.
    d. Platelets < 100 $\times 10^9$/L.
    e. Aspartate aminotransferase or alanine aminotransferase > 3.0 × upper limit of normal.
3. Any medical or psychiatric condition or concurrent medical therapies at Screening that may put the subject at greater safety risk, influence response to study drug, or interfere with study assessments.

2.3.3 Key Inclusion Criterion for the Study Treatment Phase:

1. During the Study Qualification Phase, on the bipolar 100-mm Drug Liking VAS, the subject must provide E_{max} ≥ 40 mm and < 60 mm following placebo and, following hydromorphone 18 mg/70 kg i.v., E_{max} ≥ 60 mm and ≥ 15 mm closer to "Strong Liking" than the E_{max} to placebo.

2.4 NUMBER OF SUBJECTS (PLANNED)

For the Primary Study, across the 2 study sites, approximately 200 subjects will be screened, 40 subjects will be enrolled in the Study Qualification Phase, and 20 subjects (approx. 10/site) will complete the Study Treatment Phase.

2.5 STUDY DRUGS, DOSAGE, AND MODE OF ADMINISTRATION

Study Qualification Phase: Subjects will receive, according to randomized assignment, hydromorphone 18 mg/70 kg or placebo, administered as a single, i.v. dose in two separate sessions in the qualification phase.

Study Treatment Phase: Participants receive doses in a double-blind, randomized, crossover sequence, according to a treatment sequence randomization schedule.

During sample sessions (morning portion of the Drug vs. Money sessions; sample sessions for the Drug vs. Drug Choice sessions), subjects will receive the assigned study drug administered in a fixed volume of solution (approximately 20 mL).

During the afternoon portion of the Drug vs. Money sessions, participants will receive none, some or all of the drug, depending on their behavior on the self-administration task. They can earn drug in 1/10 increments up to the full drug dose. The dose concentration will remain constant across all dose conditions, but the dose volume of the self-administered doses is dependent on the participant's choice behavior (e.g., 1/10th of the drug dose = 2 mL of solution; see below). The solution will be administered in a rate comparable to the other doses (approximately 1 mL/1.5 seconds). The pharmacists will prepare 20 mL of drug solution for each self-administration dose; RNs administer the appropriate amount (as below). Doses will be administered at the approximate rate of 1 mL/1.5 seconds. Participants can earn the following drug doses based on self-administration responses:

No drug earned = no drug/no solution administered

1/10th drug earned = 2 mL of drug solution administered

2/10th drug earned = 4 mL of drug solution administered

3/10th drug earned = 6 mL of drug solution administered

4/10th drug earned = 8 mL of drug solution administered

5/10th drug earned = 10 mL of drug solution administered

6/10th drug earned = 12 mL of drug solution administered

7/10th drug earned = 14 mL of drug solution administered

8/10th drug earned = 16 mL of drug solution administered

9/10th drug earned = 18 mL of drug solution administered

10/10th drug earned = 20 mL of drug solution administered

During Drug vs. Drug Choice sessions, participants will receive the full dose that they chose verbally (participants can also elect to receive no drug). The dose will be delivered in a fixed volume of solution (approximately 20 mL).

Full doses (20 mL) will be administered i.v. over approx. 30 sec.

The sample placebo solution will consist of approximately 20 ml of saline.

To preserve the medication blind, all doses will be administered to subjects by a blinded licensed medical professional. The pharmacist and one member of the research team will be unblinded.

IV Catheter/PICC Option: Participants who do not have adequate venous access for placement of a standard peripheral IV will be considered for placement of a peripherally inserted central catheter (PICC line). The risks of the PICC line are described to the participant in the study consent form and the clinical pre-procedure consent form. The primary risks include infection, bleeding and blood clot. These risks are managed with several safety precautions, including a specialized Vascular Access Team placing the

PICC line under sterile conditions, using ultrasound for proper placement, and 24/7 availability of RN staff who are familiar with PICC line care, dressing changes, and monitoring participants for infection or complications.

Participants will have the PICC line removed prior to study discharge. The risk of participants using the PICC line to inject drugs during enrollment is minimized with 24/7 nursing supervision, daily urine drug screens, no outside visitors permitted on the inpatient unit, presence of hospital staff escorts to observe participants if they leave the inpatient unit for any reason, only small amounts of controlled medications are present on the inpatient unit and are securely locked in an area in which participants cannot access. The overall risk of participants selecting to inject into a PICC line is similar to that of a standard peripheral IV that stays in place for several days.

The potential benefit of the PICC line is eliminating multiple needle sticks for peripheral IV placement and immediate access to deliver medication (e.g., naloxone) if needed in case of an emergency.

1) Stabilization PRNs
PRNs that are only available during stabilization (Q1-Q7)
PRNs from this list should not be administered within 24 hrs of the first session

Ambien: 5-10 mg PO QHS PRN insomnia. No doses after 3:00 am. **Columbia site only**: males receive up to 15 mg.

Clonazepam (Columbia site only): 0.5 mg PO every 4 hrs PRN opioid withdrawal symptoms. Maximum daily dose of 1.5 mg.

Clonidine: 0.1 mg PO every 6 hrs up to 3 times a day PRN increased blood pressure, pulse, anxiety, chills or piloerection. Hold for systolic BP <100, diastolic BP <60, HR <60, sedation or dizziness. Maximum daily dose of 0.3 mg.

Ondansetron: 4-8 mg PO up to 3 times per day PRN nausea/vomiting. **Columbia site:** Maximum daily dose of 12 mg. **UK site:** Maximum daily dose of 24 mg.

2) Weekend Only PRN Medications
Available only on Friday and Saturday nights after sessions have been initiated (not available on Sunday evening if session occurs on Monday)

Ambien: 5-10 mg PO QHS PRN insomnia. No doses after 3:00 am. **Columbia site only**: males receive up to 15 mg.

3) PRN Medications Available Throughout Stabilization/Main Study
PRN Medications available during stabilization or after sessions have been initiated
Not available after midnight the evening preceding a session; doses available upon session completion (not available during sessions)

Milk of Magnesia (Columbia site only): 30 mL PO every 6 hrs PRN constipation, maximum daily dose 60 mL. **Magnesium Hydroxide (UK site only):** 5 mL (equivalent to 1200 mg) PO every 6 hrs PRN for constipation. Maximum daily dose of 20 mL (equivalent to 4800 mg).

Bismuth Subsalicylate: 30 mL PO every 4 hrs PRN for diarrhea/dyspepsia. Maximum daily dose 180 mL.

Colace: 100 mg PO twice daily PRN for constipation

Acetaminophen: 650 mg PO every 4 hours PRN for headache, pain. Maximum daily dose 2600 mg.

Ibuprofen: 400 mg PO every 6 hrs PRN aches/pain. Maximum daily dose of 1600 mg.

Nicotine gum (Columbia site only): 2 mg gum chewed every 1 hr PRN nicotine craving. Maximum daily dose of 16 mg.

Additional PRN medications can only be given if pre-approved by Drs. Manubay, Mogali, Comer, Lofwall or Walsh.

4) Standing Medications/Medications Available Daily

Multivitamin: 1 tablet PO once daily if participant requests to continue pre-admission vitamin regimen (not ordered for each participant)

Oral contraceptive: Continued as prescribed for women who have a standing prescription prior to admission

Nicotine transdermal patch (Columbia site only): Initiated during stabilization and maintained daily throughout the study. Patch strength (7, 14, or 21 mg) determined by study physician. Applied to skin in a location above the heart every morning. Remove at night before bedtime. PRN nicotine craving. Participants permitted to wear patches during laboratory sessions.

Topical diphenhydramine: 1% diphenhydramine cream applied topically to affected area up to 3-4 times per day PRN pruritus/hives. Available as needed throughout the study; permitted during laboratory sessions.

2.6 DURATION OF THE STUDY

- Screening: Approximately 35 days prior to admission
- Study Qualification Phase, including morphine stabilization for qualified subjects: A minimum of 3 and maximum of 7 days of morphine stabilization, 1 day of hydromorphone (18 mg/70 kg, i.v.) administration, 1 day of placebo

administration and at least ≥24 hrs between last qualification dose and first test dose in the testing during the Study Treatment Phase

- Study Treatment Phase: Approximately 46 days (the exact number of days is dependent on the day of admission/holiday schedule).
- Safety Follow-up: Approximately 2-4 weeks after discharge.

2.7 DISCONTINUATION OF TREATMENT

2.7.1 Removal of Subjects

For an individual subject, study drug will be discontinued and the participant discharged/withdrawn from the study if any of the following occurs:

- Subjects with positive urine drug screen after the initial wash-out except for those drugs administered experimentally or positive ethanol breath test
- Withdrawal of consent
- Pregnancy
- Any serious adverse event (SAE)
- Any life-threatening AE. NOTE: The term 'life-threatening' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Significant respiratory depression and/or requiring the use of naloxone administration

Subjects who have study drug permanently discontinued will be asked to complete the Discharge from CRU Visit and the Safety Follow-Up Visit, unless they withdraw consent.

2.7.2 Termination or Suspension of the Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. If any of the following events occur in a subject during enrollment, study entry randomization of new subjects into the study will be suspended until review of the event in question occurs:

- Any death during the study
- Any two serious adverse events (SAE)
- Determination of unexpected, significant, or unacceptable risk to subjects that contraindicates dosing of additional subjects, in the opinion of the study investigators/physicians.
- Any new information about the execution of the trial that, in the opinion of the study physicians/investigator, contraindicates further study entry and randomization of new subjects.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the Principal Investigator, with additional external expertise as needed, to make recommendations to the FDA whether screening, randomization, and/or dosing can resume or should be discontinued, whether the protocol should be modified, or whether the study should be discontinued permanently. Upon consideration of a cumulative review of safety and other data, the study can be discontinued permanently by the FDA.

Administration of study drug may continue during the time of review of subjects who are already receiving study drug, based on the judgment of the Study Physicians/Investigators.

Written notification, documenting the reason for study suspension or termination, will be provided by the FDA to the Principal Investigator and the local regulatory authorities (Institutional Review Board). If the study is suspended or prematurely terminated, the Principal Investigator will promptly inform the reviewing IRB and will provide the reason(s) for the suspension or termination. Review and approval by the reviewing IRB will be required for resumption of the study in the event the study is interrupted.

2.8 PRIMARY PHARMACODYNAMIC ENDPOINTS

- Progressive ratio breakpoint value for drug and percent drug choices

2.9 SECONDARY PHARMACODYNAMIC ENDPOINTS

- Progressive ratio breakpoint value for money
- E_{max} on the Drug Liking, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Monetary Value VAS
- Pupil diameter, oxygen saturation

2.10 PRIMARY SAFETY ENDPOINT

- Treatment-emergent adverse events with i.v. opioid and placebo treatment from inpatient admission through study follow-up visit.

2.11 SECONDARY SAFETY ENDPOINTS

- All AEs with onset after inpatient admission through the last study visit.
- Tolerability based on the clinical judgment of the physicians (defined by behavioral responsiveness combined with oxygen saturation levels [<90%])
- Change from baseline in medical history, as documented by adverse events reports
- Change from baseline in physical examination, as documented by adverse event reports

- Change from baseline in vital signs, as documented by vitals which are out-of-range, based on dose holding criteria
- Change from baseline in laboratory safety tests, as determined by clinically significant changes in lab values from baseline screening labs to labs collected at study discharge
- Positive pregnancy test
- Change from baseline in 12-lead ECGs, as determined by clinically significant changes in outcomes from baseline screening ECG to the ECG conducted at study discharge

2.12 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized before database locking and unblinding to treatment sequence in the Study Treatment Phase.

Data will be provided in data listings sorted by study drug and subject number. Summary data will be presented in tabular format by study drug and i.v. dose. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous data will be summarized by descriptive statistics including n, arithmetic mean, standard error, median, minimum, and maximum. All percentages will be rounded to 1 decimal place. The primary analytical strategy for the study will employ parametric testing and statistical significance will be 2-sided and accepted at a P value of ≤ 0.05.

We hypothesize that the PR breakpoint value and percent drug choice for oxymorphone will be significantly greater than placebo, but not oxycodone.

Primary Pharmacodynamic Analysis: Progressive ratio breakpoint value for drug and percent drug choice will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random effects and the remaining parameters fixed effects. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

We hypothesize that Drug Liking will be significantly greater for active doses of each drug compared to placebo, but Drug Liking will not be significantly different for oxymorphone compared to the other opioid agonists because we are matching the doses of each drug on the Drug Liking measure.

Secondary Pharmacodynamic Analysis: Progressive ratio breakpoint value for money, Emax on the VAS Drug Liking, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Monetary Value, and pupil diameter and oxygen saturation will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random effects and the remaining parameters fixed. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

2.12.1 Pharmacodynamic Statistical Analyses

The following sections describe the statistical methods. These methods may be revised based on regulatory requirements or need for additional clarifications. The finalized analysis plan may be documented formally in a statistical analysis plan (SAP) that will be finalized prior to data lock. The SAP will include additional details on how missing data will be handled and how data will be presented, as well as additional details on the analytical methods.

2.12.1.1 Determination of Sample Size

We propose to enroll 20 completers to assess adequately the primary outcome measures. Based upon previously published within-subject studies examining the pharmacodynamic responses to opioid agonists in humans (Comer et al., 2008; Babalonis et al., 2016), the ability to detect differences between active drug conditions and placebo for Drug Liking is achieved readily with small numbers of subjects. For example, Drug Liking, High, and progressive ratio breakpoint scores from Comer et al. (2008) for placebo versus oxycodone 50 mg/70 kg i.v., morphine 50 mg/70 kg i.v., and fentanyl 0.25 mg/70 kg i.v. yielded Cohen's d values ranging from 1.2 to 5.0 with power set at 0.8, alpha of 0.05 and a correlation among repeated measures where rho = 0.5 required approximately 9 subjects for detection of a large effect. Similar large effect sizes were observed by Babalonis et al. (2014) with Drug Liking, pupil diameter, and expired CO2 when comparing placebo versus oral oxycodone 40 mg and oxymorphone 40 mg (Cohen's d 3.8-7.3). However, analyzing these outcomes again for differences between active dose comparators produced more moderate effects. Oral oxycodone versus oxymorphone yielded small effects for Drug Liking (Cohen's d = 0.3), but large effects with pupil diameter and expired CO2 (both Cohen's d= 1.4). Taking into consideration the FDA guidelines and the data from previous within subject studies, we propose 20 subjects (10 per site) for the study. The sample size is well matched for these within-subject studies and laboratory-controlled environment, both features that minimize variance of the effect size estimate.

2.12.1.2 Interim Analysis

The pilot subject data were unblinded and the data examined by the study team in order to select the appropriate doses for the primary protocol. However, for the main study/randomized protocol, no interim analysis is planned. If carried out, the plan will be fully documented separately prior to its execution.

2.12.1.3 Analysis Populations

Two analysis populations will be used for this study.

- Pilot Population included data from approx. 6 subjects/dose condition who enrolled in the pilot study.
- Completer Population includes approximately 20 subjects, 10 from each of the two sites, who complete the main study.

2.12.1.4 Statistical Analyses

The analytical strategy for the study will employ parametric testing and statistical significance will be 2-sided and accepted at a P value of ≤ 0.05.

All data will be summarized by descriptive statistics and select data points will be displayed graphically as appropriate. Unless otherwise noted, continuous variables (e.g., progressive ratio breakpoint, percent drug choice, Drug Liking) will be summarized using number of non-missing observations, mean, standard error, minimum and maximum; categorical variables (e.g., drug choices) will be summarized using the frequency count and the percentage of subjects for each condition.

2.12.1.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics (e.g., age, sex, race, weight, and height) will be summarized for the overall population by descriptive statistics. Medical history, clinical laboratory tests, and ECG results will be listed. Prior and concomitant medications will be summarized by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

2.12.1.6 Pharmacodynamic Statistical Analyses

Pilot phase: Summary statistics (e.g., mean, standard error) were calculated to evaluate the similarities and differences between the drug and dose conditions. No statistical tests will be conducted due to the small sample size. However, relative potency equivalence for the highest test dose of each opioid were affirmed when the Emax difference score is ≤11pts. Dose response functions were compared across the test doses using the classic relative potency bioassay analysis described by Finney (Finney, 1978). For this assay, a multi-point parallel line will be used for each dose-effect function (4 doses per drug, including placebo). Relative potency estimates are determined only if analysis of variance comparing drug doses confirm the following: linearity, parallelism, no difference in drug preparation, and a significant regression coefficient. Conservative probability levels will be employed for the following: linearity $p>0.1$, parallelism $p>0.1$, drug preparation $p>0.1$, and regression $p<0.01$. Confidence intervals will be calculated at the 95% level for the potency estimates.

Primary Pharmacodynamic Analysis: Progressive ratio breakpoint value for drug and percent drug choice will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random effects and the remaining parameters fixed effects. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

Secondary Pharmacodynamic Analysis: Progressive ratio breakpoint value for money, Emax on the VAS Drug Liking, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Monetary Value, and pupil diameter and oxygen saturation will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random

effects and the remaining parameters fixed effects. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

2.12.1.7 Safety Statistical Analyses

All subject data will be listed with pertinent information (e.g., demographics, dosing condition, event details). Treatment-emergent adverse events (TEAE's) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing TEAEs, treatment-emergent SAEs (TESAEs), and TEAEs leading to study discontinuation will be summarized for each dose condition. No formal statistical analysis will be performed for safety endpoints.

2.12.1.8 Missing Data

Within-session missing data are expected to be less than 3% for each outcome. Inspection of missing data and correlates of missingness will be examined upon study completion. The use of Proc Mix as an analytic strategy obviates the need for interpolation of missing data.

3 INTRODUCTION – OVERVIEW OF THE PROJECT

3.1 RATIONALE FOR STUDYING OXYMORPHONE

Oxymorphone (14-hydroxydihydromorphinone) is a semisynthetic opioid agonist, structurally similar to oxycodone and hydromorphone, which displays a very high degree of mu opioid receptor specificity and intrinsic activity (Metzger et al., 2001; Carliss et al., 2009; Volpe et al., 2011). Oxymorphone is currently marketed in the United States as a prescription analgesic for the treatment of moderate-to-severe pain. Oxymorphone has a long history as an effective analgesic for anesthesia preparations and for the treatment of cancer-related pain (Coblentz and Bierman, 1956; Eddy and Lee, 1959; Ciliberti and Eddy, 1961; Beaver and Feise, 1977; Beaver et al., 1977). It was first approved by the US Food and Drug Administration in 1959, with oral, rectal and parenteral formulations marketed under the trade name Numorphan®. However, in the late 1970s, the drug manufacturer, Endo Pharmaceuticals, voluntarily removed the oral product from the market citing commercial reasons (United States Food and Drug Administration, Center for Drug Evaluation and Research, 2006), although there were indications that it was being readily abused, particularly via i.v. injection, prior to its removal (Watkins and Chambers, 1972).

After many years of absence from the US market, the manufacturer reintroduced the oral formulation in 2006 as both immediate- and extended-release (ER) products under a new trade name (Opana®, Opana ER®). In the years surrounding this reintroduction, several clinical trials, supported by the pharmaceutical sponsor, were conducted to assess the analgesic efficacy of the newly formulated oral products for cancer-related and non-cancer pain (i.e., chronic lower back pain, osteoarthritis, postoperative pain) (Gabrail et al., 2004; Gimbel and Ahdieh, 2004; Gimbel et al., 2005; Hale et al., 2005; Sloan et al., 2005; Aqua et al., 2007; Hale et al., 2007; Rauck et al., 2008). These studies concluded that oral oxymorphone was safe and effective in the management of acute and chronic pain and oxymorphone-induced analgesia was comparable with

standard therapeutic doses of oxycodone. Several of these studies, along with proprietary information held by the drug company, also helped establish the published relative analgesic potency and equianalgesic conversion ratios of oral oxymorphone, which state that oral oxymorphone is twice as potent as oral oxycodone and three times as potent as oral morphine for the treatment of pain (Gabrail et al., 2004; Hale et al., 2005; Endo Pharmaceuticals, 2010).

Although the analgesic effects of oxymorphone are well established, the abuse liability of oxymorphone has not been extensively examined. Schoedel et al. (2010, 2011) compared the behavioral effects of controlled-release (CR) formulations of oral oxymorphone (15, 30 mg ER) to oral oxycodone (30, 60 mg CR) in a single human laboratory study. This study, also industry-sponsored, reported that oxymorphone produced less cognitive and psychomotor impairment, decreased reports of sedation, lower ratings of abuse-related subjective effects (e.g., Drug Liking, High and Street Value), and fewer aversive effects (e.g., Bad Drug Effects, Nausea, and Dysphoria) relative to the comparator doses of oxycodone. Importantly, the oxycodone comparator doses were two-fold higher than doses of oxymorphone, selected on the basis of the analgesic equivalency tables; however, examination of several outcome measures clearly indicates that equipotent doses of oxymorphone and oxycodone were not compared. For example, oxycodone doses produced greater pupil constriction (a measure particularly sensitive to mu opioid receptor activation) than any test dose of oxymorphone, suggesting that oxycodone was substantially more potent than oxymorphone, thereby limiting the conclusions drawn regarding the relative abuse liability of oxymorphone. As oral oxymorphone prescribing and availability has increased over the past several years, rates of diversion, abuse, and overdose deaths involving oxymorphone have also increased (Garside et al., 2009; McIntyre et al., 2009; Butler et al., 2013; Crum et al., 2013).

In 2011, Endo Pharmaceuticals introduced a new version of the extended-release oral formulation for approval as an abuse-deterrent formulation (ADF). The FDA did not agree that there was sufficient evidence of abuse deterrence of this new formulation and declined the request to allow ADF language into the label. Nonetheless, Endo introduced the new formulation onto the market and simultaneously withdrew the original ER formulation describing the reasons for withdrawal as safety concerns. If accepted, this rationale would have led to withdrawal of all generic formulations as well; however, the FDA disagreed with the contention of the Sponsor, which allowed generic versions to continue to be marketed and sold (https://www.fda.gov/Drugs/DrugSafety/ucm351357.htm). At this time, the FDA also commented on the evidence related to the abuse deterrence features of the new formulation and expressed concern that it could be tampered with using rather simple methods for both intranasal and intravenous misuse.

During this time and since approval of the newly formulated ER oxymorphone formulation, significant public health concerns have arisen from the misuse of Opana ER®. The first was a significant outbreak of HIV infection due to injecting-drug behavior in the small rural town of Austin, Indiana. Ultimately, more than 200 cases of HIV infection were identified in this small rural town (Peters et al., 2016). The second was the identification of numerous cases of Opana® injection-related blood disorders (i.e.,

thrombotic microangiopathy resulting in a thrombotic-thrombocytopenic purpura-like syndrome; Ban et al., 2017; Magro et al., 2015; Thakur et al., 2017). Both of these health complications were the result of crushing and preparing the oral formulation (with excipients) for intravenous use and confirmed absence of protection against intravenous preparation of this purported abuse deterrent formulation and a propensity for drug users to misuse this formulation specifically by the intravenous route.

These issues led the FDA to convene an independent advisory committee in March of 2017 to hear the evidence related to the public health harms of Opana ER®. Ultimately, the committee agreed that the data demonstrated a shift in abuse from the intranasal to the injection route and that the high cost and preparation strategy for injection set the stage for increased sharing of syringes. That committee voted 18 to 8 in support of the conclusion that the risks outweighed the benefits of this product (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf). In June 2017, the FDA asked the Sponsor to remove the product from the market, and the Sponsor quickly followed with a refusal to comply. The FDA put the Sponsor on notice that the Agency would be moving forward to remove the product from the market.

While it is clear that there have been significant unintended public health harms related to the misuse of oxymorphone by those with intent to misuse the drug, the factors contributing to these observations are incompletely known. There are a number of issues that could contribute to the observed shift from intranasal misuse to intravenous misuse of Opana ER® and its observed abuse potential. These may include availability in a particular region or drug-using network of Opana ER® compared to other full opioid agonists (immediate- and extended-release formulations), social lore amongst drug users, price, bioavailability, or intrinsic pharmacologic features unique to oxymorphone and this particular formulation of oxymorphone. Another possible contributing factor is the intrinsic activity of oxymorphone itself when administered by the intravenous route. Whether the abuse liability of i.v. oxymorphone is similar to or different from other full mu opioid agonists is unknown and is therefore the focus of this study.

3.2 RATIONALE FOR STUDY DESIGN, COMPARATORS, AND DOSES

3.2.1 Rationale for Study Design

This study design is based on the 2017 FDA Assessment of Abuse Potential of Drugs: Guidance for Industry [Center for Drug Evaluation and Research (CDER), 2017], which suggests use of a double-blind, positive- and placebo-controlled design that includes a qualification phase and VAS measure of Drug Liking. The proposed study also examines the reinforcing effects of oxymorphone and other mu opioid agonists using two different drug self-administration procedures, as described below.

3.2.1.1 Drug Self-administration Procedures

The reinforcing effects of oxymorphone, oxycodone, and hydromorphone will be assessed with two self-administration procedures: a Drug versus Money Choice procedure and a Drug versus Drug Choice procedure (based on previous studies by Drs. Comer and Walsh: Comer et al., 2008, 2013; Donny et al., 2005; Middleton et al., 2012).

These studies demonstrated that the two procedures can be used to show dose-related changes in reinforcing effects of a range of different drugs, as well as subtle differences in reinforcing effects between drugs. Two procedures will be used because they assess two different aspects of the reinforcing effects of a drug/dose: the Drug versus Money procedure measures relative reinforcing strength and the Drug versus Drug procedure measures relative preference for one drug or dose over another. The Drug versus Money procedure has the advantage of allowing an assessment of the relative reinforcing strength of a wide range of different drugs and doses within a short period of time (a complete dose-effect curve for one drug can be assessed in one week), while the Drug versus Drug procedure has the advantage of measuring potentially subtle differences in preference for one drug over another based on a pharmacodynamic measure of potency equivalence (Drug Liking).

During Weeks 2-4 of the Study Treatment Phase, the Drug versus Money Choice procedure will be used (oxymorphone, oxycodone and hydromorphone; placebo control), with four doses tested per active opioid drug (one dose will be tested per day). During this procedure, subjects will receive $20 and a sample dose of drug in the morning, and then in the afternoon they can choose to work for either the dose of drug sampled that morning or $20 by making finger press responses on a computer mouse. Subjects will have 10 opportunities to choose between drug and money. Each time an option is chosen, participants will be working for 1/10th of the sampled dose or $2 (1/10th of the sampled money amount). After they choose an option, subjects will begin responding. The ratio value for each option will begin at 25 responses for the first choice, and then increase to 50, 100, 200, 400, 800, 1600, 3200, 6400, and 12800 for subsequent choices for that option. The ratio requirement will increase independently for each option. Subjects will have up to approximately 1.5 hours to complete the task, after which they will receive whatever fraction of drug and/or money they earned. The amount of drug earned will be administered at approximately 3 pm. Session duration will be standardized and participants will remain in session until approximately 5 pm to allow for 2 hrs of post-dose monitoring. If no drug is earned, participants will still remain in session until approximately 5 pm.

On average, subjects make 7.5 responses per second during the task so it is possible for them to complete the task within about 1.5 hours if they choose one option on all 10 trials. We have used this procedure in several previous studies so we know that it is sensitive to different doses, drugs, and other pharmacological manipulations (Comer et al., 1999, 2005, 2008, 2013). In our previous studies, however, a different sequence of progressive ratio values was used (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800). With this sequence, it was relatively easy for subjects to complete the ratio requirements when they chose the drug option on all 10 trials. Therefore, we recently changed our PR values to maximize the chances of differentiating the reinforcing effects of an opioid in the presence and absence of a treatment medication (Metz et al., in press). We are proposing to use this "more difficult" sequence in the present study because we believe that it will more easily differentiate subtle differences in motivation to self-administer different opioids. After completion of the drug vs. money task, participants will receive the drug infusion and money (in cash) that they earned (approx. 10-15 minutes after completion of the task). However, the cash will be locked in a safe

until study completion for precautionary reasons and these earnings will be added to their paychecks at the end of the study. The participants are informed of these procedures during the consent process and reminded during training sessions.

During Weeks 4-8 of the Study Treatment Phase, the Drug versus Drug Choice procedure will be used. Comparisons will consist of:

5.6 mg/70 kg of oxymorphone versus 56 mg/70 kg oxycodone

5.6 mg/70 kg oxymorphone versus 18 mg/70 kg hydromorphone,

10 mg/70 kg oxymorphone versus 18 mg/70 kg hydromorphone

5.6 mg/70 kg oxymorphone versus placebo.

During this procedure, subjects will receive a sample dose of drug on one day (Dose A) and a sample dose of another drug on the next day (Dose B). For the subsequent 3 days, subjects will be asked to choose among Dose A, Dose B, or Neither in the morning and the afternoon (for a total of 6 choice opportunities per dose pairing). Responses will consist of verbal requests for Dose A, B, or Neither. Participants will be allowed to choose between the two options 6 times because, in our experience, it will provide a more accurate assessment of the relative abuse liability of two different drugs than a single choice. Participants will select between Drug A and Drug B (or neither) at approximately 11am and 3 pm. Session duration will be standardized and participants will remain in session until approximately 5 pm to allow for 2 hrs of post-dose monitoring after the 3 pm dose. If no drug is selected, participants will still remain in session until approximately 5 pm.

3.2.1.2 Subjective Responses

The Drug Liking VAS was selected as a secondary pharmacodynamic endpoint based on its use and the validity of results in previous likeability trials (Jasinski, 1977; Haertzen et al., 1963; Haertzen et al., 1987; Fischman and Foltin, 1991; Zawertailo et al., 2003) and the 2017 FDA Assessment of Abuse Potential of Drugs: Guidance for Industry (CDER, 2017). The VAS Questionnaire consists of 7 questions and corresponding VAS. Subjects will indicate their response to each question along the corresponding 100-mm VAS. We will also include other subjective outcome measures (e.g., street value estimates, drug identification assessments). An Opioid Symptom Scale that examines common opioid-related symptoms (Itchiness, Constipated, Dry Mouth, Drowsy, Headache, Lightheaded (Dizzy), Difficult to Pass Urine, Confused, Difficult to Concentrate) will also be used during the study. It will be administered during laboratory sessions and at bedtime each evening.

3.2.2 Rationale for Comparators

Oxycodone was selected as a comparator because illicit use of oxycodone is prevalent, even after the introduction of abuse-deterrent formulations of oxycodone (Cicero and Ellis, 2015). Studies suggest that oxycodone may be preferred over other opioid agonists because of the quality of the high (Cicero et al., 2013) and/or lower incidence of negative effects compared to other mu agonists (Comer et al., 2008). And finally,

hydromorphone was chosen as a comparator because it is consistently reported to be a highly abusable prescription opioid (e.g., Butler et al., 2015; Secora et al., 2017).

3.2.3 Rationale for Doses

The i.v. doses of oxymorphone for the pilot study were selected based on a previous study demonstrating comparable Drug Liking produced by the same doses of oral oxymorphone and oral oxycodone (Babalonis et al., 2014). While a separate previous study showed that i.v. doses of oxycodone (up to 50 mg/70 kg) were well tolerated by subjects with OUD who were maintained on 30 mg QID morphine (Comer et al., 2008), no data currently exist for the abuse liability of i.v. oxymorphone. The i.v. doses of oxycodone were selected based on a previous study of their abuse liabilities in subjects with OUD who were maintained on 30 mg QID morphine (Comer et al., 2008). The i.v. doses of hydromorphone were selected based on a recent study of intramuscular hydromorphone administered to subjects with OUD who were maintained on 30 mg QID morphine (Walsh et al., 2017). Slightly higher maximum doses of oxycodone (56 mg/70 kg rather than 50 mg/70 kg, were selected because the previous doses produced less-than-maximal effects on all of the study endpoints, including Drug Liking and drug self-administration using the Drug versus Money Progressive Ratio procedure.

The rationale for the dose selections/comparisons in the main study was based on the results of the pilot study as described below:

1. Taking into consideration the safety of administering each dose twice in one day with a 4-hr inter-dose interval and a desire to minimize carry-over effects, oxymorphone doses of 1.8, 3.2, 5.6, and 10 mg were selected. This was also the range that produced the clearest dose proportionality for Drug Liking Emax.
2. Hydromorphone doses of 3.2, 5.6, 10, and 18 mg most closely matched these oxymorphone doses on Drug Liking Emax ratings. In addition, the potency ratio of oxymorphone and hydromorphone for Drug Liking was close to 1 when using a valid assay with the widest dose range of each drug, so we tried to match the two drugs that way as closely as possible – again, taking into consideration a desire to minimize carry-over effects (hence our decision to NOT test oxymorphone 18 mg). And finally, the miosis produced by these two dose ranges was virtually identical.
3. Oxycodone doses of 18, 32, and 56 mg produced Drug Liking ratings that were similar to oxymorphone doses of 1.8, 3.2, and 5.6 mg. A lower dose of oxycodone 10 mg was added to obtain clearer dose-proportional effects for oxycodone.
4. The Drug vs. Drug doses were selected primarily by examining Drug Liking responses. Drug Liking ratings for oxymorphone 5.6 mg and hydromorphone 18 mg were comparable, as was Good Effect and Drug Effect (even though trough pupil diameter for oxymorphone 10 mg was comparable to hydromorphone 18 mg). So in order to compare oxymorphone and hydromorphone based on a commonly used endpoint (pupil constriction) and subjective measures (Drug Liking, Good Effect, Drug Effect), we decided to compare both 5.6 and 10 mg oxymorphone to hydromorphone 18 mg.
5. A dose of oxymorphone 5.6 mg was selected for comparison against oxycodone 56 mg because it produced Drug Liking that was more comparable to oxycodone 56 mg than oxymorphone 10 mg.

4 STATEMENT OF WORK

4.1 PRIMARY PHARMACODYNAMIC OBJECTIVE

To evaluate the reinforcing effects of oxymorphone (1.8, 3.2, 5.6, 10 mg/70 kg, i.v.) relative to placebo and oxycodone (10, 18, 32, 56 mg/70 kg, i.v.) and hydromorphone (3.2, 5.6, 10, 18 mg/70 kg, i.v.) in subjects who DSM-5 criteria for OUD and are physically dependent on opioids. The proposed test doses listed were selected based upon the results of the pilot/dose finding study (which included a broader range of doses and was designed to identify dose equivalence among the opioids on ratings of Drug Liking). The primary self-administration endpoints are drug breakpoint value for drug (highest ratio value completed for drug) using the Drug versus Money Choice Procedure and percent oxymorphone choice using the Drug versus Drug Choice Procedure.

4.2 SECONDARY PHARMACODYNAMIC OBJECTIVES

To evaluate breakpoint values for money, E_{max} on individual VAS of Drug Liking, Take Drug Again, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Monetary Value, and pupil diameter and oxygen saturation of single doses of oxymorphone (1.8, 3.2, 5.6, 10 mg/70 kg, i.v.) relative to placebo and oxycodone (10, 18, 32, 56 mg/70 kg, i.v.), and hydromorphone (3.2, 5.6, 10, 18 mg/70 kg, i.v.) in subjects who meet DSM-5 criteria for moderate-to-severe OUD and are physically dependent on opioids. The proposed test doses were selected based upon the results of the pilot/dose finding study (which included a broader range of doses and was designed to identify dose equivalence among the opioids on ratings of Drug Liking).

4.3 PRIMARY SAFETY OBJECTIVE

To evaluate treatment-emergent adverse events (TEAEs) associated with oxymorphone, oxycodone, morphine, hydromorphone, and placebo treatment from inpatient admission through the post-discharge follow-up visit.

4.4 SECONDARY SAFETY OBJECTIVES

1. To evaluate the tolerability of oxymorphone, oxycodone, hydromorphone, and placebo doses.
2. To evaluate changes in medical history, physical examinations, vital signs, laboratory safety tests, and ECGs associated with oxymorphone, oxycodone, morphine, hydromorphone, and placebo treatment from admission through discharge/last study visit.

4.5 STUDY DESIGN AND PLAN DESCRIPTION

This will be a 2-center, double-blind, randomized, placebo- and active-controlled, cross-over study with two phases during an inpatient period, a Study Qualification Phase and a Study Treatment Phase. The study will also include a Screening period (approx. 35 days prior to admission) and an approximately 2-4 week Follow Up period (Tables 1 and 2). The study events (Table 2) will be performed once weekly, with the exception of test drug administration (once or twice daily on test days), vitals (at each visit, daily, or

multiple times on test days), urine drug toxicology/breathalyzer (at each Screening visit or at least twice weekly or more frequently at random times during the inpatient stay), self-administration (once or twice daily on test days), VASs (repeatedly on test days), Concomitant Medications (once daily throughout the study), and AEs (once daily during the inpatient stay).

Table 2.

TABLE 2: STUDY EVENTS										
STUDY PHASE	SCREENING	QUALIFICATION	TREATMENT							FOLLOW UP
STUDY WEEK	Screening	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8/ Discharge	Week 12
Drug Administration		X	X	X	X	X	X	X	X	
Blood Chemistry Profile	X								X	
Liver Function Tests	X								X	
Hematology	X								X	
Urinalysis	X								X	
Electrocardiogram	X								X	
Physical Examination	X								X	
Suicide Assessments	X	X	X	X	X	X	X	X	X	X
Practice Session		X								
Vitals	X	X	X	X	X	X	X	X	X	X
Urine Drug Toxicology/Breathalyzer	X	X	X	X	X	X	X	X	X	X
STUDY PHASE	SCREENING	QUALIFICATION	TREATMENT							FOLLOW UP
STUDY WEEK	Screening	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8/ Discharge	Week 12
Participant:										
General Health Questionnaire	X									
Medical History Questionnaire	X									
Drug History Questionnaire	X									
Self-administration			X	X	X	X	X	X	X	
Visual Analog Scales		X	X	X	X	X	X	X	X	
Clinician:										
Psychiatric History/Mental Status Eval	X									
Drug History	X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events/Side-Effects		X	X	X	X	X	X	X	X	X

4.6 STUDY POPULATION

4.6.1 Target Population

The target population for this study will consist of adults with moderate-to-severe OUD who use opioids daily and have been physically dependent on opioids for ≥ 1 month immediately prior to Screening.

It is expected that ~200 subjects will be screened to identify a target population of ~40 eligible male or female subjects who will be enrolled, and 20 subjects will complete the study at 2 centers in the United States (~10 completers are expected per site). See Section 2.12.1.1 for a description of the sample size calculation.

4.6.2 Inclusion Criteria

4.6.2.1 Inclusion Criteria for Enrollment

Each subject enrolled in this study must meet **ALL** of the following inclusion criteria at Screening:

1. Able to understand and provide signed and dated written informed consent.
2. Recent history of intravenous opioid use
3. Self-reported opioid use for non-therapeutic purposes on at least 21 days in the 30 days prior to screening.
4. Positive urine drug screen for opioids during screening (those who are in a methadone or buprenorphine treatment program are ineligible; physical dependence on street methadone or buprenorphine are also exclusionary so participants must produce at least one methadone or buprenorphine negative urine during screening).
5. ≥ 18 and ≤ 55 years of age (Columbia site will enroll participants ≥ 21 and ≤ 55 years old).
6. Body mass index (BMI) ≥ 18 and ≤ 35 kg/m^2 and weight ≥ 50 kg (110 pounds).
7. Otherwise healthy as determined by the investigator/physician based on medical history, physical examination, vital signs, laboratory safety tests, and 12-lead ECG.
8. Women of childbearing potential must not be pregnant or breastfeeding at screening; women must be using an effective form of contraception during study participation.
9. Willing and able to comply with all testing requirements defined in the protocol.

4.6.2.2 Inclusion Criteria for the Study Treatment Phase

Enrolled subjects must meet **ALL** of the following criteria to be eligible for participation in the Study Treatment Phase:

1. During the Study Qualification Phase, on the bipolar 100-mm Drug Liking VAS, the subject must provide E_{max} ≥ 40 mm and < 60 mm following placebo and, following hydromorphone 18 mg/70 kg, i.v., E_{max} ≥ 60 mm and ≥ 15 mm closer to "Strong Liking" than the E_{max} to placebo.
2. In the judgment of the investigators/physicians, the subject is able to tolerate the i.v. opioids administered in the study, including the ability to complete most pharmacodynamic assessments administered post-dose.
3. In the judgment of the investigators/physicians, the subject's general behavior during the Study Qualification Phase suggests the ability to successfully complete the Study Treatment Phase.

4.6.3 Exclusion Criteria

Individuals who meet ANY of the following criteria at Screening including Check-in are not eligible for enrollment:

1. History of a medical or psychiatric disorder that would prevent successful completion of the study.
2. Current DSM-5 diagnosis of substance use disorders requiring medical management other than OUD.
3. Suicidal ideation or intent with or without a plan at Screening or within 6 months prior to Screening (i.e., answering "Yes" to questions 4 and/or 5 on the Suicidal Ideation section of the Columbia - Suicide Severity Rating Scale).
4. Currently seeking or participating in treatment for substance use disorder.
5. Physically dependent on alcohol or drugs of abuse other than opioids, nicotine, or caffeine.
6. Clinically significant abnormality on physical examination, vital signs, screening laboratory tests, or 12-lead ECG. Those with screening/pre-drug baseline oxygen saturation <92% will be excluded.
7. Significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, or neurologic disorder.
8. Any surgical, or medical condition that may interfere with the absorption, distribution, metabolism, or excretion of the test drug.
9. Family history of long QT syndrome and/or unexpected sudden cardiac death or is known to have QTc > 450 ms (based on Fridericia correction formula) at screening.
10. Used an investigational agent within 30 days or 5 therapeutic half-lives of that agent, whichever is longer, prior to the first dose of study drug.
11. Hypersensitivity to opioids or any drug intended for use in this study.
12. Acute gastrointestinal symptoms (e.g., nausea, vomiting, fever, or diarrhea unrelated to opioid withdrawal) ≤ 7 days before Day 1.
13. Any of the following values for laboratory tests at Screening:
    a. A positive pregnancy test in women of childbearing potential.
    b. Hemoglobin < 12 g/dL in males and < 11 gm/dL in females.
    c. Neutrophil count < 1.0 × 109/L.
    d. Platelet count < 100 × 109/L.
    e. Creatinine clearance < 50 ml/min per modified Cockcroft-Gault equation.
    f. Aspartate aminotransferase or alanine aminotransferase > 3.0 × upper limit of normal.

4.7 WOMEN, MINORITIES, AND CHILDREN

Women and minorities will be recruited. Children will not be included because administering high doses of drugs of abuse i.v. to minors is not acceptable ethically.

4.8 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from advertising in local newspapers, subways, radio, social media, or word-of-mouth. Retention will be facilitated by conducting the study in a Clinical Research Unit (CRU).

4.9 SCREENING

Written informed consent will be obtained before any study-related procedure is performed for a subject. After obtaining written informed consent, eligibility for study enrollment is assessed using the protocol-defined inclusion and exclusion criteria.

Screening consists of an initial telephone screen, followed by approximately 1 to 5 in-person Screening visits. Screening can occur for up to approximately 35 days prior to inpatient admission.

During the screening/admission process, the site staff will train potential subjects on the self-administration task and VAS Questionnaire. Subjects must demonstrate understanding of how to complete the VAS Questionnaire to enter the Study Qualification Phase and understanding of the self-administration procedures prior to the Drug/Money sessions.

4.10 BLINDING

This study is double-blind to treatment sequence, with separate unblinding of treatment sequence for the Study Qualification Phase. Identical assessments and procedures will be followed during the study for subjects assigned to the different treatment sequences.

Subjects will be assessed in small groups (N ~1-4) during the Study Qualification Phase. When a subject completes the Study Qualification Phase, the Principal Investigator will request information on treatment sequence from the unblinded statistician. For the Study Treatment Phase, the blinding of treatment sequence must be maintained until all data entry and processing are complete and the database has been locked (unless required for medical/safety monitoring, as below).

All medical and clinical operations staff associated with this study will remain blinded to treatment sequence until after the database is closed. Study subjects and the study site staff, including the investigators who do safety and clinical assessments, qualified designees, study nurses, and study coordinators will be blinded to treatment sequence until after the database is closed. Exceptions are:

- Personnel as required for emergency unblinding or when needed for an adverse event/safety monitoring
- The Principal Investigator for treatment sequence for subjects in each small group in the Study Qualification Phase, after all subjects in that small group

complete the Study Qualification Phase, to determine subject eligibility for the Study Treatment Phase

- Pre-specified roles as outlined below:
    - An unblinded statistician who will generate random treatment sequences and provide these treatment sequences to the unblinded pharmacist
    - An unblinded pharmacist(s) who will prepare and label the study drug
    - A limited number of data management and programming personnel
    - An unblinded co-investigator to assist in decisions regarding safety and double-checking of all drug orders

These unblinded individuals are required not to reveal treatment sequence to others, unless a formal unblinding of treatment sequence for a given subject is undertaken for safety reasons.

4.11 TREATMENT ARMS AND SEQUENCE

For the Study Qualification Phase, subjects will be randomized in a crossover sequence to first receive either hydromorphone 18 mg/70 kg or placebo administered as a single i.v. dose (Table 3).

TABLE 3: TREATMENT ARMS (STUDY QUALIFICATION PHASE)

Sequence	Treatment
Placebo	Placebo i.v.
Active comparator	Hydromorphone 18 mg/70 kg i.v.

For the Study Treatment Phase, subjects will be randomized according to two separate William squares. One 4 x 4 square for drug sequence will be used and another 4 x 4 square for i.v. dose sequence (Table 4). Hydromorphone 18 mg/70 kg and placebo doses are also used during the Study Qualification Phase.

TABLE 4: TREATMENT ARMS (STUDY TREATMENT PHASE)	
Description	**Treatment**
Test Drug 1	Oxymorphone 1.8 mg/70 kg
Test Drug 2	Oxymorphone 3.2 mg/70 kg
Test Drug 3	Oxymorphone 5.6 mg/70 kg
Test Drug 4	Oxymorphone 10 mg/70 kg
Placebo	Placebo
Positive Control 1	Oxycodone 10 mg/70 kg
Positive Control 2	Oxycodone 18 mg/70 kg
Positive Control 3	Oxycodone 32 mg/70 kg
Positive Control 4	Oxycodone 56 mg/70 kg
Positive Control 5	Hydromorphone 3.2 mg/70 kg
Positive Control 6	Hydromorphone 5.6 mg/70 kg
Positive Control 7	Hydromorphone 10 mg/70 kg
Positive Control 8	Hydromorphone 18 mg/70 kg

4.12 OTHER ASSESSMENTS

For all female subjects of reproductive potential, a serum pregnancy test will be conducted during Screening. Urine pregnancy (hCG assays) will be conducted prior to each session at the University of Kentucky and at least weekly at Columbia University. Urine hCG tests will also be completed at the Follow-Up visit. Women of child-bearing potential will also be required to use an effective form of contraception throughout study participation.

4.13 EARLY DISCONTINUATION FOR INDIVIDUAL SUBJECTS

Subjects may be discontinued early from study drug or withdrawn from the study for reasons including, but not limited to: subject's request, withdrawal of consent, AE, protocol violation, subject noncompliance, loss to follow-up, and study termination by the FDA. An individual subject will not receive any further study drug if any of the following occur in the subject in question during the inpatient phases of the study:

- Subjects with positive urine drug screen after the initial wash-out except for those drugs administered experimentally or positive ethanol breath test
- Withdrawal of consent
- Pregnancy
- Any serious adverse event (SAE)
- Any life-threatening AE. NOTE: The term 'life-threatening' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Significant respiratory depression and/or requiring the use of naloxone administration

An individual subject who withdraws consent will be withdrawn from the study and may not receive any further study drug, assessments, or procedures after consent is withdrawn.

Participants who are discontinued permanently from study drug due to an AE will be followed until resolution or stabilization of the AE.

If a subject fails to return to the CRU for scheduled assessments, at least 3 attempts will be made to contact the subject by phone by a member of the research staff.

Subjects discontinued from dosing for any reason except withdrawal of consent will be evaluated at the time in the CRU or will be asked to return to the CRU for evaluation, for a Withdrawal Visit.

SUSPENSION OR PREMATURE TERMINATION OF THE STUDY

This study may be suspended or prematurely terminated by the FDA independently or at the request of a regulatory authority, with sufficient reasonable cause.

If any of the following events occur during the enrollment process, study entry and randomization of new subjects into the study will be suspended:

- Any death during the study
- Any two serious adverse events (SAE)
- Determination of unexpected, significant, or unacceptable risk to subjects that contraindicates dosing of additional subjects, in the opinion of the Medical Officer
- Any new information about the execution of the trial that, in the opinion of the study physicians/investigators, contraindicates further study entry and randomization of new subjects.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the Study Physicians and the Principal Investigator, with additional external expertise as needed, to make recommendations whether screening, randomization, and/or dosing can resume or should be discontinued, whether the protocol should be modified, or whether the study should be discontinued permanently. Upon consideration of a cumulative review of safety and other data, the study can be discontinued permanently by the FDA.

Administration of study drug may continue during the time of review of subjects who are already receiving study drug, based on the judgment of the Study Physicians/Investigators.

Written notification, documenting the reason for study suspension or termination, will be provided by the investigators and the regulatory authority. If the study is suspended or

prematurely terminated, the investigator will promptly inform his/her IRB and will provide the reason(s) for the suspension or termination. Review and approval by an investigator's IRB and the FDA may be required for resumption of the study at that site, in the event the study is suspended and then restarted.

4.14 DOSAGE PREPARATION AND ADMINISTRATION OF STUDY DRUGS

4.14.1 Study Qualification Phase

Subjects will receive, as randomized, either hydromorphone 18 mg/70 kg or placebo, each administered as a single, intravenous dose, during the qualification phase.

4.14.2 Study Treatment Phase

Subjects will receive 13 different single drug doses (including placebo) in a randomized, 6-way crossover sequence according to a treatment sequence randomization schedule. The first day of treatment will occur ≥ 72 h after the last dose of study drug in the Study Qualification Phase.

Each dose will consist of approx. 20 ml solution.

4.15 STUDY MEDICATION SUPPLY

Oxymorphone and oxycodone will be supplied by Prime Health Inc., a compounding pharmacy. Hydromorphone and saline (for placebo doses) for i.v. administration to humans will be purchased commercially and prepared and blinded by licensed pharmacists.

4.15.1 Packaging and Labeling

Oxymorphone, oxycodone, hydromorphone and placebo (or other opioid compounds as deemed appropriate) will be packaged in syringes that will be labeled in accordance with regulatory requirements.

4.15.2 Conditions for Storage and Use

At the site, bottles of study drug will be stored at room temperature away from temperature and humidity extremes, and, if relevant, under conditions appropriate for small quantities of Controlled Substances Act Schedule 2 substances.

4.16 UNBLINDING PROCEDURES

4.16.1 Emergency Unblinding Procedures

Except when small groups complete the Study Qualification Phase, breaks in blinding of treatment sequence assignment will occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of an individual subject and call for study drug discontinuation in that subject or is required by the reviewing regulatory authority. Unblinding of the treatment for an individual can be done in the case of: a medical emergency where knowledge of the treatment sequence is

necessary before the subject can be treated; a Suspected Unexpected Serious Adverse Reaction needing expedited reporting; and if requested by the investigator.

In circumstances other than an emergency, unblinding will be done only by the unblended pharmacist and only after discussion with the requesting investigator.

If the blind to treatment sequence is broken for a subject, this must be documented fully including the date and time, reason for unblinding, name and electronic signature of the person requesting the code break, and name and electronic signature of the person breaking the code.

The subject will have appropriate testing to evaluate the safety concern that caused the emergency unblinding, either at the time of a routine scheduled assessment, if due, or at an unscheduled visit as soon as possible after emergency unblinding. The subject should have a Withdrawal Visit when stable thereafter.

After emergency unblinding, the investigator will maintain the blind for that subject as far as possible. The actual treatment sequence allocation should not be disclosed to the subject and/or other study personnel including other site personnel, monitors, or project office staff. There should not be any written or verbal disclosure of the treatment sequence in any of the corresponding subject documents.

4.16.2 Study Completion Unblinding Procedures

After completion of the study, when all the study data are collected, all queries have been resolved, and the database has been locked, the study statistician will then generate a request to the unblinded statistician to break the treatment sequence code for all subjects, for purposes of data analyses. No Tables, Listings or Figures that reveal the treatment sequence assignment of any subject will be shared with any site or blinded personnel until the database is locked.

After the end of the study, the investigator(s) will be notified by e-mail that they or their qualified designees can obtain the treatment code for individual subjects at the site.

4.17 METHOD OF ASSIGNING SUBJECTS TO TREATMENT SEQUENCE

Separate randomly-generated treatment sequence schedules will be prepared by the unblinded statistician for the Study Qualification Phase and the Study Treatment Phase. The unblinded study pharmacist(s) or designee will prepare and label all study drugs according to the randomized treatment sequence schedule prior to each dosing period. The randomized treatment sequence schedules will be stored by the unblinded pharmacist in a double-locked cabinet or room.

4.18 DISPENSING, COMPLIANCE, AND ACCOUNTABILITY

4.18.1 Dispensing

The unblinded study pharmacist(s) will prepare and label all study drugs for administration.

4.18.2 Compliance

Each dose of study drug will be administered by a blinded qualified study staff member. A record of the dosing event will be kept by a qualified study staff member.

4.18.3 Accountability

The unblinded study pharmacist will be responsible for monitoring the receipt, storage, dispensing, and accounting of all study drugs according to accepted practices for a Schedule 2 drug. Accurate, original site records will be maintained of the drug inventory and dispensing activities. All records will be made available to appropriate regulatory agencies upon request.

The unblinded study pharmacist will check study drug shipments against the shipping contents form and complete a Master Drug Accountability Log with the date and time of delivery of the study drugs, lot numbers, and date and time of drug preparation. He/she will maintain a log of the amount of study drug provided to individual subjects and reconcile used and unused study drug supply. Documentation of study drug transfers from the pharmacy to the study center will be retained (in the pharmacy records or the research site records).

If any drug is lost or damaged, its disposition will be documented in the source documents and reported to the PI and government regulatory agencies, as appropriate.

At the end of the study, study drug will be disposed of by the site per their standard operating procedures and applicable federal regulations.

4.19 PRIOR AND CONCOMITANT THERAPY

Information about the concomitant medications and treatments given to the subject during the study will be recorded on the appropriate case report form.

4.20 PROHIBITED MEDICATIONS/ACTIVITIES

No investigational drug will be used within 30 days before administration of the study drug. On dosing days, subjects will be required to abstain from smoking or using any nicotine-containing substances for at least 30 min prior to and 60 min after dosing.

4.21 ADVERSE EVENTS

An AE is any symptom, sign, illness or experience or untoward medical occurrence that newly develops or a pre-existing condition that worsens in severity in a subject administered study drug and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries will be regarded as AEs.

This definition also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital, or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the study medication.

Abnormal results of any laboratory test or diagnostic procedure will be considered AEs if the event has any of the following characteristics:

- Results in study withdrawal.
- Is associated with a SAE.
- Is associated with clinically significant signs or symptoms.
- Leads to additional treatment or to further diagnostic tests.
- Is considered by the physician/investigator to be of medical significance. The investigator will assess all abnormal laboratory results for their medical significance. If any abnormal laboratory result is considered medically significant, the investigator must provide details about the action taken with respect to the study drug and about the subject's outcome.

Adverse events will be captured from inpatient admission to the end of the subject's participation in the study. Adverse events should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are recorded. One diagnosis/symptom should be entered per record. Adverse events will be captured by the standard method of querying patients and noting events reported to research and medical staff.

The primary safety outcome is the occurrence of TEAEs related to study medication and placebo. A TEAE is defined as an AE that is not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

Death and hospitalizations will be considered serious AEs (SAEs). A medication error is not an AE unless it is temporally associated with an unfavorable or unintended sign or symptom.

The investigator or qualified designee will report all directly observed AEs and all AEs spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about AEs.

All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study drug, and the subject's outcome.

4.21.1 Serious Adverse Events

Serious Adverse Events (SAE) are a subset of AEs. An SAE is defined as any untoward medical occurrence that meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. A new diagnosis of cancer during treatment should be considered as medically important.

An AE caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled. Serious AEs also include any other event that the investigator or the Study Physicians judge to be serious or which is defined as serious by regulatory authorities.

4.21.2 Procedures for Reporting AEs and SAEs

Throughout the duration of the study, the investigator or qualified designees will closely monitor each subject. All AEs (expected or unexpected), which occur during the study, whether observed by the investigator or by the subject, and whether or not thought to be related to study drug, will be recorded. The description of the AEs as recorded on the eCRF will include a description of event, start date, stopping date, intensity, if it was serious, relationship to study drug, what actions were taken with respect to the study drug, if treatment was required, and the subject's outcome.

Safety Reporting and Sharing:

Events that meet urgent IRB reporting will also be urgently reported to the FDA and to the PIs and primary study physicians at Columbia University and the University of Kentucky

Mild severity/expected adverse events will be reported to the FDA at least yearly and to the IRB during the yearly continuation review. Mild severity/expected adverse events will not generally be reported urgently between the sites, although this will occur at the discretion of the site investigators/physicians.

Moderate severity (expected or unexpected) adverse events that do not meet urgent reporting requirements will be shared with the PI and medically responsible physician at the other site. The report will contain a description of event, start date, stopping date (if established), intensity, if it was serious, relationship to study drug, what actions were taken with respect to the study drug, if treatment was required, and the subject's outcome (if established). No personally identifying information will be shared in the transmission of these reports. Participants will be referred to by subject number. If medical records need to be shared, PHI will be redacted. Reports will be shared through phone calls, secure email, and/or through an electronic email notification issued through the EDC system. This report sharing will occur approximately 14 days of site investigator becoming aware of the event. The PI, co-investigators, and the study physicians at both sites will address whether there is a need to redesign or amend the protocol, and/or to inform current and future subjects of a change in description of risk, either in the consent form and protocol, or by other written or verbal communication. These events will be reported to the FDA at least yearly, but more promptly at the discretion of the site investigators/physicians.

Serious adverse events (expected or unexpected) will be shared with the FDA and the PI and medically responsible physician (and others if needed) at the other site. The report will contain a description of event, start date, stopping date (if established), intensity, if it was serious, relationship to study drug, what actions were taken with respect to the study drug, if treatment was required, and the subject's outcome (if established). No personally identifying information will be shared in the transmission of these reports. Participants will be referred to by subject number. If medical records need to be shared, PHI will be redacted. Reports will be shared through phone calls, secure email, and/or through an electronic email notification issued through the EDC system. This report sharing will occur within 24 hrs of site investigator becoming aware of the event. The PI, co-investigators, and the study physicians at both sites will address whether there is a need to redesign or amend the protocol, and/or to inform current and future subjects of a change in description of risk, either in the consent form and protocol, or by other written or verbal communication.

4.21.3 AE Assessment and Follow-Up

Safety events will be assessed from the time of admission to the inpatient unit through the follow-up visit (if follow-up is not completed, we will assess through the last encounter [e.g., discharge/withdrawal visit]).

The investigator or qualified designee will record all reportable events with start dates occurring any time after a participant is admitted to the inpatient unit follow-up is completed (scheduled for approximately 2-4 weeks after discharge from the inpatient unit). At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. Adverse events related to study drug will be followed for outcome information until resolution or stabilization (if not serious and stabilized at the final follow-up visit and at the discretion of the study physician, AEs will be resolved by convention at the end of participation/follow-up visit).

4.21.4 Characteristics of an AE

4.21.4.1 Criteria for Defining the Severity of an Adverse Event

The following 3 grades will be used to measure the severity of AEs, including SAEs. Level of severity will be determined the physician/investigator.

- Mild: Mild symptoms, intervention not necessary; no disruption of normal daily activities.
- Moderate: Moderate symptoms, minimal, local or non-invasive intervention indicated; limits normal daily activities.
- Severe: Medically significant. Hospitalization/urgent intervention indicated; inability to perform daily activities.

4.21.4.2 Relationship to Study Intervention

After naming and grading the AE, the investigator must assign an attribution to the AE using the following categories (Table 5):

TABLE 5. RELATIONSHIP OF ADVERSE EVENT TO STUDY DRUG

Relationship	Attribution	Description
Unrelated to study drug	Unrelated	The AE is clearly **not related** to the study drug
	Unlikely	The AE is **doubtfully related** to the study drug
Related to study drug	Possible	The AE **may be related** to the study drug
	Probable	The AE is **likely related** to the study drug
	Definite	The AE is **clearly related** to the study drug

Adverse events listed as 'possibly, probably, or definitely' related to the study drug are considered to have a suspected 'reasonable causal relationship' to the study drug.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AEs. Suspected adverse reaction implies less certainty about causality than adverse reaction, which means any AE caused by the study drug.

4.21.4.3 Expectedness of Adverse Events

The PI will retain detailed records of all AEs reported by the subject or qualified personnel and perform an evaluation with respect to seriousness, causality and expectedness. Expected/unexpected is defined from the perspective of previously observed, not based on what might be anticipated from the pharmacological properties of a medicinal product. An "unexpected" adverse reaction is an event for which the nature or severity is not consistent with information in the relevant source document(s), including the package insert for each study drug.

Unexpected AE or unexpected suspected AE: An AE or suspected AE will be considered "unexpected" if it is not listed in the package insert. "Unexpected" also refers

to AEs or suspected AEs that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

4.21.4.4 Reporting Procedures

The reporting of the study will comply with all relevant regulatory authorities and site-specific requirements.

4.21.4.5 Periodic Drug Safety Update Reports

Periodic Drug Safety Update reports will be provided to the relevant regulatory authorities per their requirements.

4.21.4.6 Controlled Substance Reporting

As required, the study pharmacist(s) or investigator or designee will complete and keep a copy of controlled substance forms.

4.21.4.7 Unanticipated Problem Reporting to IRBs

All unanticipated problems should be reported to appropriate institutional officials as required by that institution's written reporting procedures. Serious unanticipated problems/treatment-related SAEs will be reported as below.

4.21.4.8 Reporting SAEs and AEs to Regulatory Agencies

The mandatory reporting of safety events to regulatory authorities will be followed, as outlined in 21 CFR 312.32 and the ICH Harmonised Tripartite Guideline Clinical Safety Data Management E2A. Reporting to regulatory agencies, IRBs, and investigators will be in accordance with all applicable global laws and regulations.

4.21.4.9 Other Reportable Information

The following events are considered SAEs in the way they must be reported to the Sponsor:

- Pregnancy exposure to study drug. If a pregnancy is confirmed then any further intake of i.v. study drug must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings.
- In addition, if a female subject becomes pregnant (at anytime from inpatient admission through the follow-up visit), the subject will be instructed to report this to the investigator for appropriate follow-up.
- Inadvertent or accidental exposure to study drug with or without an AE

4.21.5 Secondary Safety Variables

4.21.5.1 Tolerability

Tolerability is defined as discontinuation of study drug or "dropouts" (subjects that forfeit participation in the study) as the result of TEAE(s) that are probably- or definitely-related to study drug.

4.22 STATISTICAL METHODS

4.22.1 Planned Sample Size

Approximately 200 subjects will be screened across two sites with a goal of enrolling 40 subjects into the Study Qualification Phase, to obtain 20 subjects who complete all arms of the Study Treatment Phase and an additional 6 subjects who complete all arms of the pilot study. Subjects who discontinue during the Study Treatment Phase will be replaced with additional subjects who pass the Study Qualification Phase to ensure that 20 subjects complete the main study and 6 subjects complete the pilot study.

We propose to enroll 20 completers to assess adequately the primary outcome measures (see Section 2.12.1.1). Based upon previously published within-subject studies examining the pharmacodynamic responses to opioid agonists in humans (Comer et al. 2008; Babalonis et al. 2016), the ability to detect differences between active drug conditions and placebo for Drug Liking is achieved readily with small numbers of subjects. However, analyzing these outcomes for differences between active dose comparators produced more moderate effects. Comparing i.v. dosing of morphine versus oxycodone resulted in Cohen's d ranging from 0.4 to 1.0. Oral oxycodone versus oxymorphone yielded small effects for drug Liking (Cohen's d = 0.3), but large effects with pupil diameter and expired CO_2 (both Cohen's d = 1.4). Taking into consideration the FDA guidelines and the data from previous within-subject studies, we propose 20 subjects (10 per site) for the study. The sample size is well matched for these within-subject studies and laboratory-controlled environment, both features that minimize variance of the effect size estimate.

4.22.2 Populations for Analysis

Three study populations will be defined for analysis.

4.22.2.1 Enrolled Population

All subjects who sign the Informed Consent Form.

4.22.2.2 Safety Population

Subjects who have completed the Study Qualification Phase and become eligible for Study Treatment Phase and receive at least one dose of study drug in the Study Qualification Phase.

4.22.2.3 Completer Population

Subjects in the Study Treatment Phase who complete the entire Study Treatment Phase.

4.23 STATISTICAL ANALYSES

Descriptive statistics for continuous variables will include number of subjects (N), arithmetic mean, median, standard error, minimum, and maximum values. Means and medians will be presented to one more decimal place than the CRF data. Standard errors will be presented to two more decimal places than the CRF data. Minimum and maximum values will be presented to the same number of decimal places as the CRF data. Qualitative data will be tabulated by number of subjects (N) and percentages.

4.23.1 Subjects and Demographics

4.23.1.1 Disposition and Withdrawals

Subject disposition will be summarized using the number and percent of subjects who are in the Enrolled Population, Safety Population, and Completer Population.

Subjects who withdraw or are discontinued from the study, including the reason for discontinuation, will be listed by treatment sequence.

4.23.1.2 Protocol Deviations

Protocol deviations will be listed by subject and treatment sequence.

4.23.1.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population. No statistical comparisons will be made on demographic or baseline characteristics. The demographic and baseline characteristics will consist of age, sex, race, ethnicity, height (cm), weight (kg), and BMI (kg/m^2).

Demographic and baseline characteristics will be summarized by treatment sequence and overall population, independent of sequence. Demographic and baseline characteristics for all subjects including details of childbearing potential for female subjects will be listed by subject and treatment sequence.

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, standard deviation, min, median, and max. Frequencies and percentages will be used to describe categorical (discrete) variables including gender, race and ethnicity.

Evaluability status will be summarized by treatment sequence and listed.

4.23.1.4 Medical History

The presence or absence of any current medical condition or surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1, or higher.

The Reported Term, System Organ Class, and Preferred Term, start and end dates, and whether the condition is ongoing will be listed by subject and treatment sequence.

4.23.1.5 Concomitant Medications

Prior and concomitant medications will be recorded and coded

Medications will be listed by subject and treatment sequence including the indication including any linkage to AEs, dose, dose units, frequency, start and end dates, or whether the concomitant medication use is ongoing.

4.23.2 Exposure

Exposure to study drug in the Study Qualification Phase will be recorded and listed for the Enrolled Population. Study Treatment Phase exposure will be recorded and listed separately for the Safety Population.

Exposure to study drug will be listed by subject, treatment sequence and period will include information for the dose administered, date and time of study drug administration, and consumption of water administered with dosing. Any deviations from protocol-specified procedures will be documented.

4.23.3 Pharmacodynamic Analyses

Pharmacodynamic parameters including Progressive Ratio breakpoint, percent drug choice, and VAS Emax will be summarized by dose using descriptive statistics (n, arithmetic mean, median, standard error, minimum, maximum).

4.23.3.1 Primary Pharmacodynamic Analyses

Primary Pharmacodynamic Analysis: Progressive ratio breakpoint value for drug and percent drug choice will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random effects and the remaining parameters fixed effects. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

4.23.3.2 Secondary Pharmacodynamic Analyses

Secondary Pharmacodynamic Analysis: Progressive ratio breakpoint value for money, Emax on the VAS Drug Liking, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids, and Street Value, and trough pupil diameter and oxygen saturation will be analyzed in a mixed model including subject, drug condition, i.v. dose, site, drug sequence and i.v. dose sequence, where subject will be treated as random effects and the remaining parameters fixed effects. Paired t-test analyses will compare oxymorphone doses to placebo and to other active drugs at their comparable dose.

4.23.4 Safety and Tolerability Analyses

Adverse event information will be collected for all randomized subjects. Adverse events recorded after signing informed consent but prior to the first dose will be recorded as

baseline AEs and will be listed by subject but will not be included in the summary safety analysis.

The incidence of TEAEs will be summarized by treatment. All AEs will be summarized by relationship to study drug and by severity by treatment.

In addition, AEs categorized as Abuse-related AEs will also be summarized. These AEs are categorized according to MedDRA Preferred Terms which may provide abuse-related information about the drug. The list of Preferred Terms that will be included in this category of AEs will be determined prior to database lock and unblinding.

All AEs, including SAEs, reported will be coded and classified according to MedDRA (Version 19.1). AEs will be listed by Reported Term, System Organ Class and Preferred Term.

The numbers and frequencies of subjects reporting TEAEs including abuse-related AEs will be summarized. If the same AE (preferred term) is reported more than once for the same subject, it will only appear once in the summary tables and the highest severity grade and strongest relationship to treatment will be included in the summary. Any AEs leading to a study discontinuation will be summarized.

All deaths, other SAEs, and AEs will be listed.

4.23.4.1 Laboratory Safety Tests Assessments

Summary statistics, including n, mean, standard deviation, median, minimum and maximum values will be summarized for each quantitative laboratory safety test parameter by visit and treatment. Clinical laboratory test parameters, along with associated reference ranges provided by the laboratory, will be listed for individual subjects.

A listing of abnormal values will also be presented. Clinical laboratory test results outside the laboratory's reference ranges will be flagged with "L" for low and "H" for high and investigator's assessment of medical significance (clinically significant/ not clinically significant) will be noted.

4.23.4.2 Other Laboratory Test Assessments

Urine drug screen, ethanol breath test, and serum and urine pregnancy tests will be listed by subject and treatment.

4.23.4.3 Vital Signs

Vital signs measurements will be summarized using descriptive statistics (including n, mean, standard deviation, median, minimum, and maximum values) for each time point and treatment and listed for each subject. All parameters will be listed by subject and treatment sequence.

4.23.4.4 Physical Examination Findings

All physical examination data will be listed by subject.

4.23.4.5 Electrocardiograms

Electrocardiogram parameters of ventricular rate, PR interval, QRS duration, QT interval, QTcF interval will be summarized using descriptive statistics (including n, mean, standard deviation, median, minimum, and maximum values) for each time point and treatment and listed for each subject.

All parameters will be listed by subject with abnormalities and medical significance determined by the investigator noted.

4.23.4.6 Columbia Suicide Severity Rating Scale

Data from the C-SSRS administered at the Screening visit and prior to sessions will be listed by subject.

4.23.5 Handling of Missing Data (Imputation Methods)

For plotting the data, plasma concentration values that are below the limit of quantification and embedded between 2 measurable concentrations will be set to missing; however, below the limit of quantification values occurring after the last measurable plasma concentration will be set to zero.

4.23.6 Adjustments for Multiplicity

Not applicable. No adjustments for multiple comparisons are planned for this study.

4.23.7 Final Statistical Analysis Plans

The statistical analysis plan will be finalized prior to database lock at the end of the Study Treatment Phase.

4.24 STUDY OVERSIGHT

The Study PIs are responsible for providing the research staff with the information needed to conduct the investigation properly. The PIs will ensure: 1) proper monitoring of the investigation, 2) conduct of the study in accordance with the investigational plan and protocol, and 3) adherence to all pertinent regulations.

The PIs are responsible for ensuring the investigation is conducted per the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights and safety and welfare of subjects under the investigator's care; and for the control of study drug and supplies. Each PI is accountable to maintain records of disposition of study drug and assurance of IRB review at her site.

4.24.1 Medical Monitoring

Study Physicians have the responsibility to review and evaluate information relevant to the product safety throughout the development and implementation of the protocol. This data and safety review facilitates early detection of safety signals and maximizes the chances for continued appropriateness of the research and protection of human subjects. This oversight includes providing applicable recommendations about subject

safety. The Study Physicians will provide recommendations about subject safety to the PI, who, as appropriate, will report concerns about subject safety to the FDA.

4.24.2 Medical Care and Day-to-Day Safety of Subjects at the Site

The PI is responsible for all trial-related medical decisions at the site and will oversee the day-to-day safety of subjects at the site. In conjunction with the study staff, the PI will review all AEs, laboratory results, safety data regarding the subjects' clinical course and side effect profiles, for subjects at her site. She will regularly assess the number and type of AEs at that site.

Any qualified healthcare provider may provide medical care when necessary. The Study Physicians will advise subjects if medical care beyond the scope of the study is needed. Additionally, it is recommended that a subject's primary care physician be notified of a subject's participation in this research study if the volunteer consents to this notification.

4.25 DATA QUALITY

4.25.1 Source Data and Record Keeping

All investigators will keep accurate and well organized records to ensure that the conduct of the study is fully documented. The investigators or their qualified designee will ensure that the source documents and participant study files are legible and complete for each participant. The investigators will be responsible for the regular review of the conduct of the study, for verifying adherence to the protocol and for confirming completeness, consistency and accuracy of all documented data and accuracy of source documentation verification at his/her site.

4.25.2 Data Handling, De-Identification, and Source Records

The investigators and qualified designees will maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of subjects. All study documents will be maintained in accordance with local site policies and applicable regulatory requirements.

Source data/records contain all the information, which is necessary for the reconstruction and evaluation of the study. The primary source document for this study will be the subject's medical record on site, stored in paper form or in an electronic medical record. If separate research records are maintained by the investigator, both the medical records and the research records will be considered the source documents for the purposes of auditing the study.

Data recorded on source documents will be transcribed by study staff onto CRFs.

Source data/records are: 1) original records; 2) certified copies of original records; 3) observations; 4) laboratory reports; and 5) CRFs and/or data sheets. Source data/records are to be kept by investigators until the end of the regulatory retention period. All clinical findings, observations, laboratory results, subject correspondence, SAE reports, and other information related to subject participation in the study must be

maintained in subject binders that contain source documents and other data collection instruments designed specifically for this investigation.

The investigator will permit study-related monitoring, audit(s), EC review(s) and regulatory inspection(s), with direct access to all the required source documents. Study staff will permit authorized representatives of the EC and government regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Consented subjects who meet eligibility for the study will receive a unique subject identification number, which will be used to de-identify subject data for storage in study files. This number will be linked only through a secure log that connects each subject to his/her data.

4.25.3 Privacy and Confidentiality of Subject Information

Privacy and confidentiality of a subject will be respected throughout the study. Each subject will be assigned a subject identification number and these numbers rather than names will be used during collection, storage, and reporting of subject information.

Information about subjects will be kept confidential and managed per the requirements of the relevant regulatory authority. These regulations require a signed subject authorization informing the subject of the all the following:

- What protected health information will be collected from subjects in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their protected health information.

If a subject revokes authorization to collect or use protected health information, the PI, by regulation, will retain the ability to use all information collected prior to the revocation of subject authorization.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, the investigator is obligated to obtain such permission in writing from the appropriate individuals.

4.25.4 Data Management Responsibilities at the Site

Data collection and accurate documentation are the responsibility of the investigator and study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Each site will monitor the study to ensure the data are collected and maintained correctly and in compliance with GCP.

4.25.5 Data Capture Method

Data capture on CRFs will be used with data quality checks. It is expected that the CRFs will be submitted coincident with the subject visit or within 7 business days.

4.25.6 Types of Data

Data will be collected on subject demographics, concomitant medications, AEs, medical history, physical examination, vital signs, screening laboratory tests, C-SSRS, laboratory safety tests, ECGs, tolerability, and pharmacodynamic data.

4.25.7 Protocol Deviations and Reporting

The investigators and research staff are responsible to follow the written protocol as approved by their IRB. The investigator or qualified designee shall prepare and submit complete, accurate, and timely reports of all protocol deviations.

A protocol deviation is an excursion from the protocol that is not implemented or intended as a systematic change and that has not received prior approval by the reviewing IRB. There are several types of protocol deviations with different requirements for reporting each type of deviation.

An emergency protocol deviation occurs in an emergency when an excursion from the protocol is required to protect the life or physical well-being of a participant. The Study Physicians and the reviewing IRB must be notified as soon as possible, but not later than 5 days after the emergency occurred.

A major protocol deviation occurs in a non-emergency when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Major protocol violations for this study include, but are not limited to, any of the following:

- Failure to comply with GCP guidelines
- Failure to meet eligibility criteria at randomization
- Use of a prohibited concomitant medication
- Failure to query the subject about potential AEs
- Failure to obtain self-administration and VAS responses at the scheduled time points unless the subject is unable to be assessed for safety reasons, for example, hospitalization or withdraws consent.

Major protocol deviations must be reported to the IRB within that IRB's guidelines.

A minor or administrative protocol deviation is an excursion from the protocol that does not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects. Examples of minor or administrative deviations could include: assessments that occurred outside the protocol required time frame because of the participant's schedule, or assessments obtained at times close to but not precisely at

the time points specified in the protocol. If a protocol deviation occurs which meets this definition, the deviation should be reported to the reviewing IRB (if reporting is required) at the time stipulated, such as the continuing review application is submitted.

4.25.8 Schedule and Content of Report

Reports will be generated by the PI or designee to monitor enrollment and study conduct. The final study report will be generated separately and only after the database is locked. The final study report that will be generated will be stipulated in the final statistical analysis plan.

4.26 QUALITY CONTROL AND ASSURANCE

4.26.1 Study Monitoring Plan

The investigator will monitor data quality from his/her site on a regular basis throughout the study and monitor for compliance with the protocol, applicable government regulations, Good Clinical Practice, the site's standard operating procedures, and the local IRB, when applicable. The investigator will allocate adequate time for these monitoring activities.

The investigator and institution involved in the study will permit study-related monitoring by staff at both sites, government agencies and other regulatory groups, if requested and provide direct access to all study records at the site and to the facilities. Adequate time and space for monitoring visits should be made by the investigator or other site staff.

The investigator or a member of the study team must be available to the monitor during monitoring visits to review data, resolve queries and review the subjects' records (e.g., medical records, hospital charts, etc.) for source data verification.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that any problems noted during monitoring are resolved.

4.26.2 Audit and Inspection of Site

Participation by the investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices. The investigators and institutions involved in the study will permit such study-related audits and provide direct access to all study records. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is not part of the electronic medical record and that is suitable for inspection by Quality Assurance monitors, IRB representatives, and representatives of government regulatory bodies. The investigators agree to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities or representative from IRBs may also perform inspections either during or after the study. The investigators agree to cooperate fully

with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records.

4.27 RECORD RETENTION

The investigator must ensure that the following records and documents pertaining to the conduct of the study and the distribution of study drug are retained for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval): copies of the study specific documents and other sources of information such as original medical documents, data and records (such as hospital records, clinic and office charts, laboratory notes, memoranda, documents regarding subject treatment and study drug accountability, and original signed informed consents). All IRB records related to this investigation will be retained by the site for as long as required by the local IRB.

4.28 CONFIDENTIALITY OF SUBJECT DATA

To maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

4.29 REPORTING AND PUBLICATION

4.29.1 Confidentiality of Study Data

Any information relating to the study drug or the study, including any data and results from the study, will be the exclusive property of the site institution. The investigators and any other persons involved in the study will protect the confidentiality of this information.

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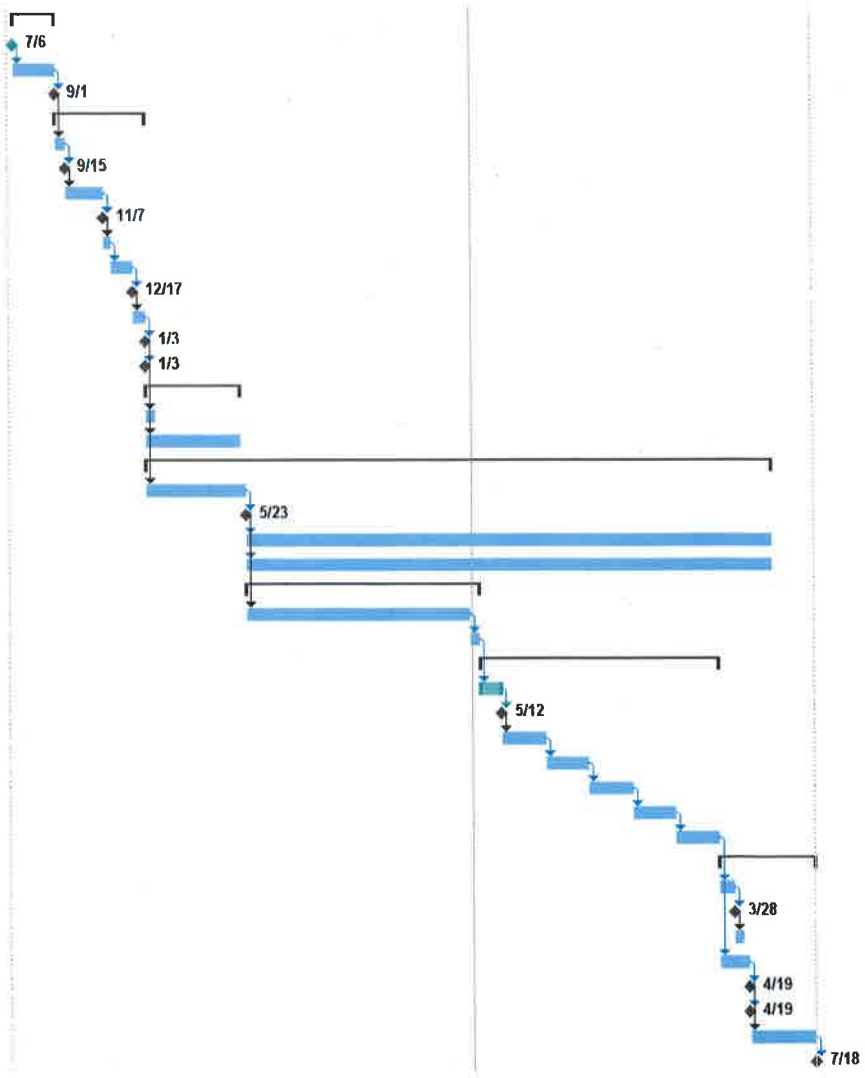
5 GANTT CHART WITH MILESTONES

Obtain funding	**58 days**	**7/6/17**	**9/1/17**
Submit grant application	0 days	7/6/17	7/6/17
Grant review	58 days	7/6/17	9/1/17
Receive grant award	0 days	9/1/17	9/1/17
Obtain protocol approval	**124 days**	**9/2/17**	**1/3/18**
Revise protocol	14 days	9/2/17	9/15/17
Submit protocol to IRBs	0 days	9/15/17	9/15/17
IRB review	53 days	9/16/17	11/7/17
Receive conditional IRB approvals	0 days	11/7/17	11/7/17
Prepare and submit IND application	10 days	11/8/17	11/17/17
IND review	30 days	11/18/17	12/17/17
Receive IND approval	0 days	12/17/17	12/17/17
Revise IRB protocol	17 days	12/18/17	1/3/18
Receive final IRB approvals	0 days	1/3/18	1/3/18
Register study on clinicaltrials.gov	0 days	1/3/18	1/3/18
Prepare study	**132 days**	**1/4/18**	**5/15/18**
Develop CRFs	14 days	1/4/18	1/17/18
Obtain study medication	132 days	1/4/18	5/15/18
Enroll subjects	**870 days**	**1/4/18**	**5/22/20**
Begin recruitment	140 days	1/4/18	5/23/18
First pilot subject in	0 days	5/23/18	5/23/18
Ongoing recruitment	730 days	5/24/18	5/22/20
Enroll subjects	730 days	5/24/18	5/22/20
Run pilot subjects	**324 days**	**5/24/18**	**4/12/19**
Pilot subjects 1-9	310 days	5/24/18	3/29/19
Analyze pilot data	14 days	3/30/19	4/12/19
Run main study subjects	**330 days**	**4/13/19**	**3/7/20**
Obtain IRB approval for main study	30 days	4/13/19	5/12/19
First main study subject in	0 days	5/12/19	5/12/19
Subjects 1-8	60 days	5/13/19	7/11/19
Subjects 9-16	60 days	7/12/19	9/9/19
Subjects 17-24	60 days	9/10/19	11/8/19
Subjects 25-32	60 days	11/9/19	1/7/20
Subjects 33-40	60 days	1/8/20	3/7/20
Prepare manuscript	**133 days**	**3/8/20**	**7/16/20**
Clean up data	21 days	3/8/20	3/28/20
Lock database	0 days	3/28/20	3/28/20
Analyze data	14 days	3/29/20	4/11/20
Prepare manuscript	43 days	3/8/20	4/19/20
Submit manuscript	0 days	4/19/20	4/19/20
Submit final study report to FDA	0 days	4/19/20	4/19/20
Manuscript review and revision	90 days	4/20/20	7/16/20
Manuscript published	0 days	7/16/20	7/16/20



6 DELIVERABLES SCHEDULE

The following milestones are planned/anticipated for the primary study (Table 6):

TABLE 6: PLANNED/ANTICIPATED MILESTONES	
Milestone	**Date**
First main study subject in	06/15/19
Lock database	05/15/20
Submit manuscript	07/01/20
Submit final study report to FDA	07/28/20
Manuscript published	08/30/20

7 SECURITY PLAN

This is study will abide by the Security Policies in place for the University of Kentucky IRB, Safety/Security Department, and Technology and Information Systems.

8 INTELLECTUAL PROPERTY

Not applicable. No patents will be submitted for the proposed study.

9 BIOSKETCHES

See Appendices

10 PREVIOUS GOVERNMENT-RELATED CONTRACTS

See Appendices

11 QUAD CHART

See Appendices

12 PROTECTION OF HUMAN SUBJECTS

See Appendices

13 LABORATORY LICENSE REQUIREMENTS

Prior to study initiation, the PI, co-Investigators, pharmacists, and contractors have or will obtain all licenses required by federal law.

14 ANIMAL USE

Not applicable. No laboratory animals will be used in the proposed study.

15 USE OF SELECT AGENTS

Not applicable. Select agents will not be used in the proposed study.

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

1.1. Human Subjects Involvement and Characteristics: Approximately 40 volunteers will be enrolled in this inpatient study, allowing for the designated number of completers [n=20 in the primary study (10 per site) and n=6 in the pilot/dose finding study (3-4 per site)] and attrition [approx. 25-35% of enrolled participants]. It is estimated that ~ 200 volunteers will need to be screened across the two sites. Volunteers will be otherwise healthy female and male physically dependent opioid users between the ages of 18 and 55 years.

Volunteers will complete a drug-use history questionnaire that will determine types, quantities, and patterns of drug use. Volunteers must be able to produce a sufficient number of supervised urine samples with results supporting their self-report. Potential research volunteers for the studies proposed in this application who are seeking treatment for substance abuse/dependence will be excluded from research participation but will be referred to an appropriate treatment program. All volunteers for the studies proposed in this application must report 1) previous opioid use through the intravenous route, 2) recent daily/near daily non-medical opioid use, with physical dependence for ≥ 1 month immediately prior to study screening, and 3) provide an opioid-positive urine drug screen (collected under staff observation). If a urine drug screen is negative for opioids, participants must be in frank withdrawal (e.g., Clinical Opioid Withdrawal Scale (COWS) score ≥ 5). We have extensive experience making these determinations and our multi-day screening process provides us with an opportunity to observe and collect multiple self-report measures and urine tests to assess veracity of the drug use history. All participants must meet DSM-5 criteria for moderate-to-severe OUD.

Exclusion criteria include DSM-5 diagnosis of any substance use disorders (except for OUD) requiring medical management. Participants with any of the following results on laboratory tests will be disqualified: 1) positive pregnancy test (urine or serum hCG), 2) Hemoglobin < 11 g/dL for males and < 10 g/dL for females, 3) Neutrophils < 1.0 $\times 10^9$/L, 4) Platelets < 75 $\times 10^9$/L, and 5) aspartate aminotransferase or alanine aminotransferase > 3x upper limit of normal. Subjects with any medical or psychiatric condition or concurrent medical therapies that may put him or her at greater safety risk, influence response to study drug, or interfere with study assessments will be excluded.

Screening procedures for all volunteers will include psychiatric questionnaires (e.g., Beck Depression Inventory that screens for depression, CSSR-S that screens for suicidal ideation, and drug-use questionnaires), medical/psychiatric history and physical examination by the study physician, laboratory chemistries (e.g., blood chemistry with liver function tests, complete blood count, urinalysis), and 12-lead ECG. Any potential subject with an acute medical problem (e.g., infection) or chronic medical problem requiring daily medication or ongoing medical care (e.g., significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic disorder), abnormal ECG, clinically significant laboratory findings (e.g., liver function tests >3x the upper limits of normal), current or past histories of psychiatric disorder that would limit compliance or participation in the studies (e.g., bipolar disorder), or physical dependence on alcohol, benzodiazepines or sedative hypnotics requiring medical detoxification will be excluded from research participation.

Female volunteers must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, intrauterine device (IUD), barrier method, cervical cap with a spermicide or abstinence) in order to participate and must not be pregnant or lactating/breastfeeding. Pregnancy tests will be conducted during screening, upon admission, and at minimum each week during the study to ensure female volunteers do not continue in the study if pregnant.

Study Timeline: This project requires start-up time to complete all regulatory requirements (FDA, IRB, Certificate of Confidentiality, Operating Procedures Manual Development and Staff Training). The study will also be registered on clinicaltrials.gov in order to comply with the new NIH regulations and revised definition of clinical trials. The timeline assumes a consistent bed occupancy rate and an attrition rate of ~35%. Each site has ample capacity to allow several subjects to participate concurrently to achieve the enrollment timeline (see Table 6).

1.2. Sources of Material: All sources of research material will be obtained specifically for research purposes. Urine and blood samples will be collected at screening prior to a subject's participation in the experimental protocol. These urine samples will be tested for the presence of a full range of drugs of abuse. Blood samples will be used for the laboratory chemistries. Females will have a urine and serum pregnancy (hCG) test at the time of screening; post-menopausal status may have status confirmed by serum follicle stimulating hormone assay. Urine drug screens will be conducted at least twice weekly and urine pregnancy tests for women will be conducted at least weekly on the inpatient unit. These samples must be negative for all drugs, except experimentally administered drugs (i.e., samples may be positive due to carryover from previous sessions) and negative for pregnancy for sessions to proceed. Expired air samples will also be taken at these times to detect the presence of recent alcohol consumption. Other research materials obtained from the volunteers include demographic information, the psychiatric and physical health screening information, experimental data and non-intrusive staff observations. Research and nursing staff will have access to individually identifiable private information in the research records. Two sets of records are kept; those requiring individually identifying information (e.g., hospital laboratory results, consent forms) and those with only a subject number assigned (e.g., all experimental data collection). Records with identifying information are kept locked and stored separately from experimental data (see below).

1.3. Potential Risks: The behavioral and physiological assessment procedures employed in these studies are relatively benign. During the screening process, it is possible that subjects may feel uncomfortable answering personal questions about their health, psychiatric and drug use histories. However, they may stop answering questions at any point (as described during informed consent). During screening and at study follow-up, all subjects will have venipuncture in order to draw blood for testing purposes. It is possible that this could lead to bruising, infection or a blood clot, but this risk is minimal and limited by the sterile procedures and well-trained staff. An indwelling venous catheter will be inserted (typically the antecubital vein in the participant's non-dominant arm) by nursing staff; if a venous catheter is not a good option due to poor venous access, a peripherally inserted central catheter will be inserted by a specialized team. Both of these options allow for dosing and as a precautionary measure to ensure immediate venous access in the event of an emergency. The catheter will be kept

patent by a saline drip/flush as needed per hospital protocol. Both catheter options will reduce the number of needle sticks required and improve participant comfort. Catheters will be flushed and maintained regularly according to hospital practice. Risks of catheter placement include inflammation, bleeding, bruising, infection, light-headedness, thrombosis or fainting. Therefore, catheters will be placed by trained professionals under sterile conditions to significantly reduce the risk of any deleterious effects.

The primary risks to the study volunteers are those related to the administration of the study medications. Most of the doses of each substance to be administered in the proposed research have been administered safely to humans in previous studies and/or used clinically. During the test sessions, a board-certified anesthesiologist or licensed medical professional will administer the intravenous opioid and will provide monitoring of respiratory depression, physiological signs, and vital signs. Naloxone syringes are present at the time of drug administration in case of emergency. Nursing staff will be present during each test session and will assist in physiological monitoring. Participants are never left unattended and nurses continue to monitor their safety after sessions have ended. The relative safety as well as the contraindications and possible side effects of these compounds are well known and documented. However, oxymorphone doses will be administered in ascending order in the pilot phase to ensure that all doses are well tolerated. Randomized doses of all drugs will be administered during the primary study. The administration of any drug involves some risks simply because individuals differ in their reactions to drugs. Individuals with known allergies/hypersensitivity to the study drugs/substances will be excluded.

The short-acting opioids that will be administered in the proposed study produce the typical side effect profile of mu opioid agonists, and these may include nausea, vomiting, headache, dry mouth, itchiness, drowsiness, sweating, dizziness, stimulation, somnolence, lightheadedness, restlessness, a feeling of well-being, talkativeness, urinary retention and constipation. More serious side effects may include allergic reaction and respiratory depression. The doses were selected with care to preclude those that produce clinically relevant respiratory depression and most are doses that have been administered in prior studies without serious adverse events. The effects of i.v. oxymorphone have not been carefully assessed (and this is the primary aim of the current study); however, we will administer oxymorphone doses in ascending order during the pilot phase and doses will be adjusted if necessary.

It is possible that during the initial morphine maintenance stabilization phase, some participants may experience opioid withdrawal. These symptoms include nausea, vomiting, teary eyes, runny nose, loose stool, stomach cramps, shakiness, anxiety/irritability, increased heart rate, sweating/chills, restlessness, and body aces/discomfort. Oral morphine dosing (30 mg, four times/day) will be extended for up to 7 days for those participants who require additional stabilization. Participants who are not able to achieve stabilization during this time and experience discomfort/withdrawal will be discharged from the protocol and offered a buprenorphine taper (details below).

UK Site only: At discharge, subjects are offered an optional, standard 7-day buprenorphine taper to help alleviate opioid withdrawal symptoms. Subjects sign a Suboxone Taper Agreement, documenting their agreement to take the Suboxone as indicated by the instructions on the form. Induction is completed under nurse supervision prior to discharge from the hospital, usually the day after the final session.

Subjects must have a COWS score of >5 to receive the first dose of 4 mg Suboxone (given as two 2 mg/0.5 mg sublingual films). After 90 minutes, if the COWS score is <10, subjects receive an additional 4 mg dose, for a total of 8 mg prior to leaving the hospital. Subjects are discharged with their remaining doses. Additionally, subjects are scheduled for a follow-up appointment with a physician for 2-3 days after discharge and asked to bring their remaining films. During this appointment, opioid withdrawal is assessed, subjects are queried for any adverse events, and compliance with the Suboxone dosing instructions is verified.

Columbia Site Only: Participants will receive counseling about the different treatment options for opioid use disorder (Vivitrol, buprenorphine, methadone, behavioral therapy etc.) prior to discharge. Additionally, the standard discharge procedure includes education about the risks of opioid overdose, how to identify opioid overdose, and how to use a naloxone kit provided to them as certified opioid overdose responders. For those participants requesting outpatient treatment, appropriate arrangements will be made, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible, or participation in group therapy at STARS or Narcotics Anonymous. Induction onto Suboxone or Vivitrol treatment will also be available to all participants prior to discharge.

At both sites, participants are also counseled prior to discharge about the possibility that they are at increased risk and may be more sensitive to opioid effects as a result of the study. A research staff member reviews information with the participant and they are provided phone numbers for research staff/investigators if they have any questions.
An example of the information provided to the participant:

"As a result of study participation, it is possible that you will be less tolerant to the effects of opioids at discharge. You should be aware that you may be more sensitive to the effects of heroin or other opioids upon completion of this study. This increased sensitivity to opiates could result in overdose and death. Thus, doses of heroin or other opiates that you used to take before entering the hospital could be enough to cause you to stop breathing and die. Fentanyl and carfentanil are powerful synthetic opioids that can be added to heroin without your knowledge and these further increase your risk of overdose. Extreme caution must be exercised after you leave the hospital, if you choose to use any opioid again."

Counseling about different treatment options and referrals to treatment are available to participants at any time before, during, or after their participation in our study. Subjects are informed that they do not have to participate in our study in order to receive a referral to treatment. For those requesting outpatient treatment, attempts are made to link them to an appropriate provider.

Overall, there are numerous precautionary measures in place including 1) the rigorous screening process, 2) our well-trained research and medical staff, 3) inpatient 24-hour nursing supervision and daily physician examination with progress note documentation

while subjects are inpatient, 4) emergency intervention equipment and treatment available on-site, and 5) carefully considered medication dosing and safety criteria.

As part of the study design, a side effect checklist will be developed that is used throughout the course of the study and will include a list of symptoms drawn directly from the FDA-approved package inserts for the study drugs; each questionnaire will also include an open-ended query about symptoms. This is one strategy that we use to monitor subjects for untoward and/or unexpected side effects. There is a theoretical risk that volunteers might choose to seek out illicit sources of drugs they received experimentally and liked. However, this risk is minimal because all drugs are administered under blind conditions and because all volunteers will have histories of non-medical opioid use. Alternatives to participation will be provided and, if subjects express interest in treatment during the screening process, they will be assisted with referrals (both in-house and external referrals are available), but will not be included in the study. If a subject previously disinterested in treatment completes the study and expresses a desire for treatment at the end, we will assist in their referral. There is also the risk that others may see a subject's Protected Health Information (PHI). The following PHI will be collected as part of this project: names (individual, employer, relatives, etc.), address, telephone number, Social Security number, dates (birth, admission, discharge), medical record numbers, driver's license numbers, psychiatric and physical health history, drug use history, results from psychiatric and physical health screening, and data from experimental measures.

2. Adequacy of Protections Against Risks

2.1 Recruitment and Informed Consent: Potential volunteers will be recruited from the community via newspaper, radio, and subway advertisements, billboards, posted flyers, online sources (e.g., Craigslist), and word-of-mouth. IRB approval will be obtained for all advertisements. Sober, written informed consent will be obtained from all individuals prior to their screening for and participation in the experimental protocol. Prior to obtaining informed consent, each potential subject must pass a field sobriety test, have no signs of active intoxication (e.g., nodding) and have an expired breath alcohol content (BAC) of 0.00. The site PI or her designated Co-Investigator will obtain consent for this project. The consent form will provide the potential volunteer with information about the study (e.g., who is conducting it, contact information for the investigators and medical staff, how it is funded, where it will take place, the purpose of the study), about what will be required of the volunteer (e.g., time commitment, dietary, drug use and post-drug activity restrictions, drug administrations), the risks to the subject (e.g., what drugs could be administered, drug side effects), the rights of the volunteer (e.g., confidentiality, voluntary participation) and the benefits of participating (e.g., health screening). The informed consent document will be explained thoroughly and signed. The subject is given ample time to ask questions of the investigator at the time of consent and any time thereafter. Each subject will receive a copy of their informed consent document and will sign a form indicating its receipt.

2.2. Procedures to Minimize Risk: Study physicians (or their designee) will screen all potential volunteers to ensure they meet medical inclusion/exclusion criteria. Other physician coverage is available, as back up, and the Attending Psychiatry service will cover daily rounds on the CCTS Inpatient Unit for these inpatient volunteers. Nurses will provide 24-hour/7-day supervision. Urine samples will be monitored throughout the

study to ensure that female volunteers are not pregnant and that all volunteers are adhering to the drug use restrictions. All volunteers in these studies will be thoroughly informed of the various drug side effects that they might experience and will be appropriately cautioned concerning their activities in the hours after drug administration. Because participation is voluntary, participants can withdraw at any time. The drug doses to be administered in the present study were chosen to minimize the chance of any SAEs from occurring. We anticipate that careful subject and dose selection, subject monitoring will greatly reduce, if not eliminate, the occurrence of serious side effects. The investigative team at each site will train their staff on this project, and all staff will complete the appropriate trainings (i.e., human subjects' protection, the Health Information Portability and Accountability Act (HIPAA), universal precautions). These studies will be conducted under an investigator-held IND (to be filed). The FDA will review this IND to evaluate the study design, safety and pharmacy manufacturing plans. The IRB at each site will review the study protocol and associated consent forms.

Physiological and behavioral effects will be monitored during experimental sessions. Volunteers who experience an SAE following administration of any of the drugs will be excluded from further research participation. Vital signs will be monitored frequently throughout sessions. While it is possible that volunteers may experience an allergic reaction to the study drugs, this is unlikely to occur because these volunteers will all be experienced drug users who are familiar with opioid effects. However, if a volunteer experiences an allergic reaction, diphenhydramine will be available for oral or parenteral administration. Lastly, while the risk of significant respiratory depression is limited by the careful dose selection in this study, naloxone will be administered if clinically indicated. The primary study physicians (or a designated ACLS-certified physician) will provide medical oversight for each test session and will carefully review respiratory outcomes for safety. Continuous monitoring by qualified staff and physiological monitoring equipment occurs throughout all sessions. A crash cart with oxygen is on site. Naloxone is present for reversal of if needed. All study activities take place within a fully functional hospital setting with emergency code response available. We do not anticipate needing to employ these methods for reversal but they are available in the event of emergency. The study physicians will also participate in discussions of outcomes obtained from the pilot ascending oxymorphone dose study and will assist in evaluation of those findings to inform proceeding to the randomized study. During test sessions, we will employ standard criteria for nursing staff and research personnel during the monitoring of individuals. If oxygen saturation drops below 90% accompanied by sedation, volunteers are simply prompted verbally to breathe. In our experience, physical and verbal stimulation are often sufficient to prompt breathing and restore a normal respiratory rate. Participants are monitored carefully with a watch-and-wait approach; they are accompanied continuously by nursing personnel and can be evaluated promptly by an anesthesiologist. If clinical evaluation determines that a participant's level of sedation is increasing, naloxone can be administered parenterally to produce immediate reversal of opioid effects. Should opioid-induced sedation persist, repeat naloxone administration or naltrexone may be administered for more prolonged opioid receptor blockade. In our extensive experience administering opioids to human volunteers, even at high doses, there have been very few incidents requiring actual intervention (naloxone/naltrexone), although our medical/nursing staff are always prepared for this possibility.

All volunteer PHI is confidential and will be protected according to the guidelines established by HIPAA. This allows the investigators on this project to use or share health information with the U.S. Department of Health and Human Services representatives, the IRB at each site, Office of Research Integrity/similar entity at each site, the FDA, other research collaborators, or when required by law. A Certificate of Confidentiality will be obtained from the FDA for this study. Files will not contain the name of the subject. Instead, each subject will be assigned a unique identifying number. Data containing volunteer names are kept separately from coded data so that the two cannot be joined. All written documents, including PHI, will be stored in locked cabinets at the each site's office facility. Key access will be limited to immediate laboratory personnel. Electronic information will reside on a stand-alone, password-protected computer. Electronic transmission via e-mail or fax with volunteer PHI will have a statement of confidentiality.

3. Potential Benefits of the Proposed Research to Human Subjects and to Others: The degree of risk to which individual study volunteers are exposed as a consequence of their research participation is relatively low under these closely supervised medical conditions with expert medical staff. In contrast, the potential and probable benefits to be derived by society in general and by drug-abusing individuals specifically appear to be considerable. The major benefits of this study are scientific and related to the knowledge gained concerning the relative risk of oxymorphone administration - a prescribed opioid analgesic that is frequently abused via the i.v. route, but for which little controlled data has been collected. Individual volunteers are expected to benefit personally from the provided medical and psychiatric evaluations and from referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this study seems well justified.

4. Importance of Knowledge to Be Gained: These studies will provide important fundamental information on the abuse potential of i.v. oxymorphone. There have been significant unintended public health harms related to the misuse of oxymorphone and the factors contributing to these observations are not well understood. One possible contributing factor is the intrinsic activity of oxymorphone itself when administered by the i.v. route. Whether the abuse liability of i.v. oxymorphone is similar to or different from other mu opioid agonists is unknown and the focus of this study.

Initial Data and Safety Monitoring Plan (DSMP): The purpose of this research is to characterize the relative reinforcing effects of oxymorphone compared to morphine, hydromorphone, and oxycodone. Volunteers will be ~40 men and women (completers and non-completers across both sites) aged 18-55 years, of varying race/ethnicity, who are physically dependent on opioids. Volunteers must not be seeking treatment for their drug use and must provide informed consent to participate. The PIs at each site will monitor the safety and effective implementation of this project, forming the DSMB, if required, and complying with the reporting requirements. The PI will provide a summary of progress to the FDA on a monthly basis. The report will include the volunteers' demographic characteristics, expected versus actual recruitment rates, retention rates, any quality assurance or regulatory issues that occurred during the past month, summary of AEs and SAEs, and any actions or changes with respect to the protocol.

Data Monitoring Plan: Data will be collected using a computerized data collection and management system wherever possible. This system automates the collection of data,

which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard drive of the computer. In all instances, the data files do not contain the name of the subject, but instead, a unique identifying number for each subject. A computer file linking the unique number with the subject's name will be kept on a stand-alone, password-protected computer. All data requiring hand entry (e.g., urinalysis results) will be double entered by two staff members and comparison macros conducted to ensure accuracy. Primary outcome measures will include performance on self-administration procedures (drug breakpoint values and percent drug choice) to evaluate the reinforcing effects of each opioid. Secondary outcomes will include evaluation of E_{max} on VAS items, as well as trough pupil diameter and oxygen saturation. Physiological safety outcomes (with a focus on measures of respiratory depression) will also be collected. Data will be analyzed using Proc Mix for repeated measures designs along with other statistical analyses. The quality of manipulated data and data analyses will be monitored by random inspection by the PI and/or Co-Investigators.

Safety Monitoring Plan: Potential volunteers will provide information regarding their drug use history and undergo an extensive screening to determine their eligibility and safety of their participation. Any potential subject with a history of clinically significant physical disease or psychiatric disorder will be excluded from participation. Women must be using an effective form of birth control or confirm abstinence and will not be pregnant or breastfeeding in order to participate. AEs will be monitored via observations by the medical and research staff, spontaneous report by the volunteers, and regular measurements of vital signs. Volunteers will not receive study drug if they have any signs or symptoms that may contraindicate its administration. All AEs occurring during the course of the study will be collected, documented, and reported to the PI each week. An SAE will be reviewed immediately. The study investigators will follow all AEs to the point of a satisfactory resolution. Volunteers may be withdrawn from the study if the medically responsible investigator determines it is the best decision in order to protect the safety of the subject. Any SAE, whether or not related to the study drug, will be reported to the IRB and FDA. In the event that a volunteer either withdraws from the study or the investigator decides to discontinue him or her, appropriate follow-up monitoring will occur and continue until the problem has resolved or stabilized with no further change expected or results in death. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to the FDA.

Data and Safety Monitoring Board (DSMB): DSMBs are implemented for 1) multi-site clinical trials involving interventions that entail potential risk to the volunteers and 2) for most Phase III clinical trials. This project meets the first of these definitions and, therefore, it is likely that a DSMB will be required. This is up to the discretion of the funding agency and the local IRB. In this event, we are prepared to create a DSMB.