

Project/ Protocol # 20-DA-N014

Title: Biased opioid agonists for treatment of opioid withdrawal in OUD: A dose-finding pilot and within-subject randomized inpatient trial

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1. Précis

Background. Opioid-agonist medications (methadone and buprenorphine) are the most effective treatments available for opioid addiction. However, they are not effective in all cases, and with the vast number of people requiring treatment in the current crisis, even a modest increase in the percentage of people who respond to treatment would represent a substantial benefit in public health. Recent advances in neuropsychopharmacology have led to the discovery of a new class of opioid agonists that are functionally selective. That is, they are biased towards specific post- receptor pathways and in theory can produce therapeutic opioid effects (analgesia, withdrawal relief) while minimizing side effects (sedation, respiratory depression) that can lead people to discontinue treatment with methadone or buprenorphine.

Objective. Our goal is to assess the efficacy and tolerability of a biased opioid agonist for suppressing or reversing opioid withdrawal.

Participant population. Adults who are physically dependent on opioids and already receiving chronic daily methadone treatment (up to 64 enrolled; up to 30 completers, plus at least 3 to complete an initial unpowered dose-finding pilot). Target enrollment will include 40% women and 60% minorities (mostly African-American), reflecting the demographics of the relevant local population.

Experimental design. A double-blind within-subject randomized placebo-controlled experiment will be used to test whether a biased opioid agonist suppresses withdrawal when given about

52 hr after discontinuing methadone. TRV734 (capsule form), a biased opioid agonist with good oral bioavailability, will be compared to placebo and to oxycodone (positive control) in matching capsules. A signal of efficacy and safety in the proposed laboratory study will be our cue to embark on a larger clinical trial.

Methods. Participants in an unpowered dose-finding five-session pilot phase (up to 30 consecutive days, i.e., 29 consecutive nights) will receive placebo, oxycodone, and a range of doses of TRV734, starting on the high side of the analgesic dose range. The highest dose that relieves withdrawal symptoms with no appreciable adverse effects will be used as the higher of two doses for the participants in the main study. These participants will stay at the inpatient unit for up to 30 consecutive days to help ensure that participants use no additional opioids

52-76-hr prior to each test session.

Participants in the main phase will stay at the inpatient unit for up to 21 consecutive days (original timeline, likely to increase after the pilot is completed) to help ensure that participants use no additional opioids 52-76-hr prior to each test session. To help demonstrate that TRV734's effects are dose-related, we will also select a lower dose with withdrawal-relief efficacy intermediate between placebo and the higher dose. For participants in the main study, there will be four experimental sessions: one each with placebo, oxycodone, and the two doses of TRV734. Safety and research measures will be collected before (baseline) and for 4 hours after administration of study drugs. The participant's usual methadone dose will be administered after each session.

Outcome measures: The primary outcome will be suppression of withdrawal symptoms, to be assessed by the SOWS (Subjective Opioid Withdrawal Scale). Secondary outcomes will include safety, specificity of effects (e.g., absence of psychomotor slowing), tolerability, and suppression of objective signs of withdrawal. Instruments used for these assessments will include the COWS (Clinical Opioid Withdrawal Scale), scales for opioid effects, psychomotor assessments, and differential dropout across sessions. We hypothesize that the higher dose of TRV734 will be superior to placebo in therapeutic effects and have lower adverse effects (including effects on alertness and psychomotor performance) compared to oxycodone.

2. Table of Contents

1. Précis.....	2
2. Table of Contents	4
3. Introduction.....	6
3A. Biased agonists as a novel approach to treatment for opioid addiction	6
3B. Previous studies with the investigational drug	7
3C. The substitution procedure for assessment of withdrawal suppression	9
4. Study Objective.....	10
5. Subjects.....	10
5A. Description of Participants.....	10
5B. Inclusion Criteria.....	10
5C. Exclusion Criteria	12
6. Study Design and Methods.....	13
6A. Study procedures	13
6B. Recruitment.....	22
6C. Screening methods.....	23
6D. Follow-up / termination procedures	23
6E. Research Blood collection.....	23
6F. Plasma drug analysis and assay methodology.....	24
6G. Pharmacokinetics Analysis.....	24
6H. Other procedural issues.....	24
6H1. Research vs. Clinical Care.....	24
6H2. The IND sponsor is NIDA.....	25
6H3. No radiation is used in this protocol	25
6H4. The relationship of this study to other protocols	25
6H5. Storage of Data and Specimens: Future use and disposition	25
6H6. Data-sharing description	25
7. Risks and Discomforts	26
7A. Description of Risks	26
7B. Minimization of risks	28
8. Subject monitoring.....	29
8A. Parameters monitored.....	29
8B. Criteria for individual participant withdrawal/termination	29
9. Outcome measures	30
9A. Primary outcome measure	30
9B. Secondary outcome measures.....	30
10. Statistical Analysis.....	31
10A. Analyses	31
10B. Criteria for significance.....	33
10C. Power analysis and accrual-number request:.....	33
11. Human-Subjects Protection	34
11A. Equitability	34
11B. Justification for the exclusion of children under 18	34
11C. Justification for the inclusion or exclusion of other vulnerable subjects	34
11D. Justification of sensitive procedures.....	34
11E. Safeguards for vulnerable subjects	34
12. Assessment of risks and potential benefits	35
13. Consent documents and process	35
14. Data and Safety monitoring.....	36

15. Adverse Events and Serious Adverse Events	39
15A. Definition of Adverse Event (AE).....	39
15B. Definition of Serious Adverse Event (SAE).....	39
15C. Classification of an AE	39
15D. Time period and frequency for event assessment and follow-up	41
15E. AE recording	42
15F AE reporting	42
15G. SAE reporting	43
15H. Events of special interest	43
15I. Reporting of pregnancy	43
15J. Reporting of protocol deviations and unanticipated problems	43
15K. Reporting to the Sponsor	43
16. Alternatives to participation or alternative therapies.....	45
17. Confidentiality	45
18. Conflict of Interest / Technology Transfer	45
19. Compensation	45
20. References.....	48
21. Abbreviations used in this document	53

3. Introduction

3A. Biased agonists as a novel approach to treatment for opioid addiction

Opioid addiction and overdose deaths have become, arguably, the most urgent public-health problem in the eyes of both providers and the lay public (Volkow & Collins, 2017; Epstein et al., 2018). Emergency-room visits, drug-related deaths, and untreated addiction each have a significant and negative impact on individual well-being, public health, and economic welfare (Kenan et al., 2012; Meyer et al., 2014; Compton et al., 2016). It is estimated that 11.5 million Americans used prescription opioids nonmedically in 2016 (Hedegaard et al., 2017) and 886,000 used heroin (2017 National Survey on Drug Use and Health, Mortality in the United States, 2016).

Until recently, it might have been tenable to suggest that opioid addiction is adequately addressable by the two FDA-approved agonists at mu opioid receptors (MORs), methadone and buprenorphine. The current epidemic changes the calculus: there are literally millions of new patients needing treatment, and even a small percentage of nonresponders or partial responders will mean a large amount of human suffering. For methadone, success is limited by restricted access and stigma as well as by prototypical mu-opioid side effects, of which the best- documented are sedation and constipation (Webster, 2013). Also frequently cited are sweating, effects on appetite and weight, and effects on sexual function (Hallinan et al., 2008; Dursteler- MacFarland et al., 2010). These effects, along with the risk of respiratory suppression, can prevent patients from being stabilized on doses high enough for full suppression of craving or full blockade of the effects of illicitly used opioids. Buprenorphine, with its partial-agonist action, is less liable to induce respiratory suppression, but its maximal efficacy is lower than that of methadone (Mattick et al., 2002), and its benefits are sometimes delayed because initial induction can be problematic (Ponizovsky & Grinshpoon, 2007; Gunderson et al., 2011). Even in countries that are not experiencing an opioid epidemic like the one in the US, treatment researchers are calling for clinical availability of MOR agonists that are better tolerated than methadone or buprenorphine and may improve longer term adherence and thereby improve longer term outcomes (Nordt et al., 2019).

We seek to address these problems by advancing the use of a novel class of MOR agonists. These agonists activate MORs but do so in a biased fashion by preferentially

(TRV130 (DeWire et al., 2013) and TRV734 [Trevena Inc., unpublished data]) or selectively (SR17018 (Schmid et al., 2017)) acting on G-protein signaling, with less or minimal, respectively, activation of beta-arrestin, an intracellular pathway that plays a critical role in three major side effects of MOR activation: analgesic tolerance, respiratory depression, and constipation (Bohn et al., 1999; Bohn et al., 2002; Raehal et al., 2005). In theory, this means that MOR biased agonists can combine the virtues of methadone (easy induction and essentially no ceiling on withdrawal suppression) with the virtues of buprenorphine (reduced incidence and severity of sedation, respiratory depression and constipation).

Our goal is to begin testing a novel hypothesis—the use of MOR biased agonists (already successful in preclinical and clinical studies for analgesia) as a new class of drugs for opioid agonist treatment. These drugs can complement buprenorphine and methadone, if they prove to have high efficacy, a more benign side-effect profile, and superior safety. As the following sections will clarify, we do not yet have a biased agonist with an ideal profile for this indication. We are starting with what we do have: a biased agonist that is currently approved for human use (as an investigational drug), whose profile is suitable for initial testing, and whose manufacturer (Trevena, Inc.) is eager to collaborate with NIDA so that an approved indication could ultimately include treatment of OUD. As drug companies have been fleeing behavioral medicine in general and addiction medicine in particular, opportunities for such collaboration have become woefully rare. This is a first step.

3B. Previous studies with the investigational drug

The safety of oral TRV734 in humans is supported by Phase 1 studies conducted by Trevena. One of the studies was a single ascending dose (SAD) study in 64 healthy men, conducted in a single-blind, parallel-group design with placebo control. The other was a multiple ascending dose (MAD) study in 62 healthy men and women, conducted in a double-blind, double-dummy design with both placebo and an active control (oxycodone). No serious adverse events (SAEs) were reported in either study. The most frequent AEs were somnolence, dizziness, and nausea. The frequency of AEs was similar between TRV734- and oxycodone- treated participants in the MAD study. No clinically significant findings were noted on electrocardiography, cardiac telemetry monitoring, vital signs, oxygen saturation, or clinical laboratory tests. There was a trend suggesting that the effects of TRV734 on the Bowel Function Index (a measure of opioid-induced constipation) were milder than those of

oxycodone; this is promising because constipation is the most common side effect of methadone in people being treated for OUD (Lugoboni et al., 2016; Haber et al., 2017). However, we are not hypothesizing that we will see a difference in constipation in this study, because the time course of administration (single doses on single occasions) will be not be of sufficient duration for testing that hypothesis.

The pharmacokinetics (PK) of TRV734, and the effect of food on its bioavailability, were examined in three open-label crossover studies in healthy men and women (N's = 12, 13, and 18 in these three studies). TRV734 was well-tolerated, with no AEs judged serious or leading to early discontinuation. Extended-release oral formulations of TRV734 showed bioavailability similar to that of an immediate-release formulation, suggesting that TRV734 is absorbed throughout the gastrointestinal tract. Food did not significantly alter the TRV734 bioavailability, an important finding that may facilitate patients' medication adherence.

Additional human studies by Trevena have established the tolerability and efficacy of TRV734 for analgesia. (For additional details on the in vitro, preclinical and human studies conducted by Trevena with TRV734, please see the Investigator's Brochure.) However, we do not know whether higher doses will be needed for suppression of withdrawal in highly tolerant patients with OUD. The likely clinical niche for MOR biased agonists in OUD will be for patients who need more agonist efficacy than buprenorphine can provide and who cannot tolerate the side effects of high doses of methadone. Therefore, we will focus on the high end of the dose range, and we will do some initial dose-finding work with our first few enrolled participants (as described below).

This protocol is the clinical portion of an approved Bench-to-Bedside project called "Maintenance treatment with novel biased mu agonists for opioid addiction"

<<https://clinicalcenter.nih.gov/ccc/btb/awards1.html>> The bench components of the project are being led by Bruce Blough (Research Triangle Institute, North Carolina), Laura Bohn (Scripps Research Institute, Florida), Sidney Negus (Virginia Commonwealth University), Charles Bradberry (NIDA IRP), and Yavin Shaham (NIDA IRP). Drs. Blough and Bohn are synthesizing new biased agonists, to be tested in nonhuman primates in the Negus and Bradberry labs, and in rats in the Shaham lab.

Results obtained in the Shaham lab, in experiments with the TRV734 analog TRV130 led by Dr. Jennifer Bossert, have informed the design of our human study. Dr. Bossert

showed, in rats, that chronic treatment with TRV130 via osmotic minipumps—a rodent model of maintenance treatment—suppressed relapse to oxycodone-seeking in rats in a manner similar to chronic treatment with buprenorphine (Bossert et al., 2020). During the experiments, Dr. Bossert noted that the rats maintained on TRV130 exhibited a generally healthier, more alert appearance than the rats maintained on buprenorphine. This was an informal observation, but one on which we want to follow up. In people with OUD, agonist treatment—especially with full agonists such as methadone—can produce subtle yet detectable decrements on memory performance, cognition, and alertness, either acutely after dosing, or in general (Curran et al., 2001; Verdejo et al., 2005; Savvas et al., 2012). These cognitive and psychomotor effects are small (Rass et al., 2014); they do not outweigh the overall benefits of methadone maintenance. Even so, a full agonist without such effects would be a welcome addition to the pharmacopoeia for treatment of OUD. We will assess whether TRV734 can be distinguished from a traditional mu agonist (oxycodone) on that basis, using short, sensitive tests of attention and processing speed (Millisecond Inquisit software) based on tasks used in Armstrong et al. (2012) and Nicholl et al. (1995).

The preclinical studies did not include a direct test of whether biased mu agonists would prevent or relieve symptoms of opioid withdrawal. The known pharmacology of the compounds—e.g., the fact that biased mu agonists retain the reinforcing effects of traditional mu agonists (Austin Zamarripa et al., 2018)—seemed to render a specific test unnecessary. This is why we refer to our proposed human study as “proof of concept”: although the conclusion is not foregone, as in some situations where experimentation is uncalled for (Smith & Pell, 2003), a failure of TRV734 to suppress withdrawal would be surprising and noteworthy. Our secondary outcome measures assessing possible cognitive/psychomotor advantages for TRV734 are intended to increase the scientific contribution of the study.

3C. The substitution procedure for assessment of withdrawal suppression

The human laboratory procedure to be used in this study is an adaptation of one that was developed in the original Addiction Research Center in Lexington, Kentucky by William Martin, Donald Jasinski, and others (Jasinski et al., 1970). In the first versions of the procedure, participants were maintained on morphine until a designated test day, when the morphine was substituted with either a test drug or placebo to determine whether withdrawal symptoms would occur (Preston & Jasinski, 1991). In more recent refinements, maintenance

dosing is interrupted for one or two days to determine whether *emergent* symptoms of withdrawal can be *suppressed* by a test drug. The newer procedure (in versions that used maintenance on morphine or oxycodone) has successfully identified medications that suppress opioid withdrawal, such as tramadol (Lofwall et al., 2007), and medications that do not, such as dronabinol (Jicha et al., 2015).

4. Study Objective

To determine whether TRV734 decreases symptoms of opioid withdrawal in people with opioid-use disorder (OUD) who are physically dependent on opioids. This is a first step toward determining whether TRV734 or other biased MOR agonists are good candidates for treatment of OUD.

5. Subjects

5A. Description of Participants

The target for the protocol is 33 completers (3 for piloting, 30 for the main study) who are being treated with daily methadone for opioid-use disorder (OUD) at a community clinic or at the IRP's on-site research clinic. A current DSM diagnosis of OUD will not be required, because successfully treated patients will no longer meet DSM criteria. A lifetime DSM diagnosis will also not be required, because community clinics might not all use DSM criteria. Federal law requires that people enrolled in methadone clinics for maintenance must have OUD by established diagnostic criteria (of which the DSM criteria are one example). For purposes of this protocol, the only critical diagnostic feature is proneness to withdrawal symptoms on discontinuation; this is addressed in inclusion criterion 6.

For each participant, we will sign a guest-dosing agreement with the community clinic the participant attends. Guest-dosing agreements stipulate that that the clinic must resume its responsibility to treat its patient after the period of guest dosing (i.e., participation in this study).

In order to ensure that 33 participants complete the protocol, we are requesting approval to enroll up to 64 participants (12 for piloting, 52 for the main study).

5B. Inclusion Criteria

Participants will be eligible for inclusion in the study if they meet the following criteria:

- (1) Age between 18 and 75.

(2) Currently receiving daily treatment with methadone (dose range 60-150 mg/day) for opioid-use disorder (OUD) for at least 3 months prior to first study drug dose per participant's Opioid Treatment Program (OTP) and self-report. However, we will allow flexibility in the dose range during that 3-month period (such as an occasional missed methadone dose or a temporarily decreased methadone dose) if, in the judgement of the MAI, the candidate is stable on methadone overall and has not lost tolerance to methadone.

(3) Willing to miss two to three mornings' doses of methadone (without supplementing with other opioids), and reporting having done so in the past without severe withdrawal symptoms on the first day—with "severe" defined here as any of the following: repeated vomiting, repeated bouts of diarrhea, or any other symptoms so painful or uncomfortable that the participant would not want to experience them several times in this study.

(4) Willing to provide blood samples through an intravenous catheter to either upper extremity.

(5a) For women of childbearing potential: must have a negative serum or urine pregnancy test within 72 hours prior to the first study drug dose (active or placebo) AND agree to use an adequate method of contraception¹ to avoid pregnancy for a period of 3 months beginning from 30 days prior to first dose of study drug. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal.²

¹ Adequate methods of contraception for sexually active women are those who have a male sexual partner(s) who is surgically sterilized prior to inclusion; have a sexual partner(s) who is/are exclusively female; is using oral contraceptives (either combined or progesterone only) WITH a single-barrier method of contraception consisting of spermicide and condom or diaphragm; is using double-barrier contraception, specifically, a condom plus spermicide AND a female diaphragm or cervical cap; or is using an approved intrauterine device (IUD) with established efficacy.

² Standard NIH Clinical Center criteria for menopause:

- Women over age 55 who have not had a period for 1 year will be considered menopausal and do not need a pregnancy test, FSH test, or contraception.
- Women between 50 – 55, who have not had a period for 1 year, should have an FSH test. If their FSH level is more than 20, they will be considered menopausal and do not need pregnancy testing or contraception. If their FSH level is less than 20, they will need pregnancy testing and contraception as required by the protocol.
- Women between 45 – 50 who have not had a period for 1 year will need both an FSH test and a pregnancy test. If they are not pregnant and their FSH level is more than 20, they will be considered menopausal, and will not require contraception or additional pregnancy testing. If their FSH test is less than 20, they will need pregnancy testing and contraception as required by the protocol.
- (5b) For men, unless surgically sterilized (vasectomy with documentation of azoospermia), must agree to practice abstinence or use barrier contraception, and not

donate sperm, for a period of 3 months beginning from first dose of study drug.

(6) Self-report of experiencing noticeable opioid withdrawal after missing just one or two days of methadone. This will be systematically assessed during screening.

(7) Participants must be able to speak, read, and understand English. Justification: This study uses scales and experimental procedures that are validated only in English. This includes the assessments conducted to test the primary and secondary outcomes and is therefore required to maintain the research integrity of the study.

5C. Exclusion Criteria

Applicants will not be eligible if they meet any of the following criteria:

- (1) A history of precipitated withdrawal after stopping opioid use and initiation onto buprenorphine or another partial or biased agonist, or self-reported prior inability to tolerate a moderate level of opioid withdrawal symptoms
- (2) History of DSM-5 psychotic or bipolar disorder
- (3) Current uncontrolled DSM-5 Major Depressive Disorder diagnosis.
- (4) Current physical dependence on alcohol or sedative-hypnotic, e.g. benzodiazepine, to avoid the risk of physical withdrawal from them. Other DSM-5 criteria for SUDs involving alcohol or sedative-hypnotics are not automatically exclusory. The MAI will determine whether the clinical profile suggests a risk of physical withdrawal from alcohol or sedative-hypnotics.
- (5) Inability to pass the NIDA Evaluation of Potential Research Participants' Ability to Consent questionnaire ("consent quiz") for 20-DA-N014.
- (6) Any condition that interferes with urine or blood sampling.
- (7) Clinically significant medical illness or medication use that, in the view of the investigators, would compromise safe participation in research, including but not limited to pulmonary disease, cirrhosis, nephrotic syndrome, thyroid disease, epilepsy, panhypopituitarism, adrenal insufficiency, ischemic heart disease, history of QTc prolongation, prolonged QTc on screening ECG (men, >450ms; women, >470ms, using the QTcF method), and potential causes of QTc prolongation (electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypocalcemia; medications such as certain antihistamines, antiemetics, antiarrhythmics, antidepressants, antibiotics, and

antipsychotics; and structural or functional heart disease such as congenital long QT syndrome).

- (8) Medications that could alter the effects of the opioid agonists being studied, including strong CYP3A4 inhibitors or inducers, or regular use of medications (such as alpha-2 agonists) that could attenuate signs or symptoms of opioid withdrawal.
- (9) For women: pregnancy or breastfeeding.
- (10) Any of the following lab values: Hb < 10.5 g/dl; Cr > 2.0mg/dL; AST or ALT > 3x upper limit of normal; total bilirubin > 2.0mg/dL.
- (11) Any other medical reason or clinical condition that the MAI or designee considers unsafe for participation in the study.

6. Study Design and Methods

6A. Study procedures

After providing informed consent, each participant will stay in the inpatient facility, the Clinical Research Unit (CRU) at Johns Hopkins Bayview Campus for up to 29 consecutive nights. (Participants in the dose-finding pilot will participate in 5 sessions at the outpatient treatment/research clinic at the NIDA IRP/BRC; participants in the main study will participate in 4 sessions at the outpatient treatment/research clinic at the NIDA IRP/BRC. Participants may be discharged and readmitted from the unit if necessary for personal or scheduling reasons. In that case, participant will be assessed and necessary tests will be repeated (e.g. breathalyzer, urine drug screen, pregnancy test) before study drug dosing takes place. Furthermore, urine and breath samples will be collected daily to ensure participants are not self-administering alcohol, opioids, or other drugs of abuse that are not part of the experimental protocol. Urine collection may be observed (by a staff member of the same sex as the participant); this will be stated in the protocol consent form. To obtain more fine-grained information on baseline patterns of drug use, we will administer a 30-day Timeline Followback (TLFB) survey (for alcohol, tobacco, and any illicit substances used by the participant) on the participant's day of enrollment.

On non-test days, participants will remain in the inpatient facility, where staff will provide them with their daily dose of methadone at approximately 8 am except when the dose is to be skipped. The SOWS, COWS, and pupil-diameter measurement will be completed on each non-session day, typically up to four times per day from morning through evening.

Time points may vary and missing data although expected, will be minimized, we do expect that we will not always be able to collect all planned data (an example of a scenario is missing blood samples due to problems with the cannula, hemolysis, and other technical problems; other examples include schedule conflicts including e.g. week-ends, holidays, etc.).

Nonetheless, every effort is made to minimize these unforeseen problems with equipment or study procedures. If one should occur, we may ask the participant to repeat a specific experimental procedure (if allowed by the overall study schedule, if it is feasible and if the participant agrees) in order to avoid having to discard other usable data from a participant. The goal is to achieve reasonable coverage of the participant's daily experience. To reduce participant burden: the SOWS assessment may begin with a screening question such as "has anything changed since the last SOWS?" Participants can thereby opt out of answering the full set of SOWS questions when they feel that their status has been stable, and the SOWS score can be recorded as unchanged.

Withdrawal-related criteria to begin the first withholding of daily methadone

Because some participants may have been using fentanyl or other opioids along with their provider-prescribed methadone before they begin daily methadone guest dosing at the CRU, we want to ensure that they are not in acute withdrawal from those opioids when we begin the first period of methadone withholding. The following criteria must be met prior to the first period of methadone withholding: (1) A SOWS score <11 with no individual subscore being indicative of severe symptoms (no score of 3 or 4 on any SOWS item) (2) A COWS score <13 (a reflection of observable signs rather than symptoms), and (3) MAI written approval to proceed with methadone-dose withholding. Although COWS is not the primary study outcome, requiring that the participant not score above the mild withdrawal range of 5-12 on COWS is intended to help ensure that we do not initiate methadone-dose withholding for a participant who may be underreporting their symptoms on the SOWS. Pupillometry readings will be collected; however, scoring will not determine participant readiness for methadone-dose withdrawal. Pupillometry data will be used to facilitate objective pupil size assessments for the COWS scoring.

Withdrawal-related criteria to proceed with Session 1

Once the MAI or designee has confirmed the individual is not in acute opioid withdrawal per criteria outlined above, Session one, first withholding of daily methadone

dose will take place. The participant will be assessed four times per day. The SOWS score must increase to at least 11 (a SOWS score of 11-20 is considered moderate withdrawal) before Session 1 can occur. This criterion could be met with a small increase (e.g., from 10 to 11); that possibility is acceptable because symptoms will probably continue to increase after the decision is made to have the session. For the COWS, there will be no score cutoff. Instead, to help corroborate the SOWS, any one of these signs will suffice:

- Resting pulse rate score of ≥ 2 (101-120)
- Sweating score of ≥ 2 (observably flushed or moist)
- Tremor score of ≥ 1 (can be felt, even if not seen)
- Restlessness score of ≥ 3 (observable restlessness)
- Yawning score of ≥ 1 (any yawning noted during assessment)
- Pupil score ≥ 1 (possibly larger than normal for room light)
- Anxiety/irritability score ≥ 2 (participant obviously irritable or anxious)
- Bone or joint aches score ≥ 4 (observably rubbing self, or other signs of pain)

If a participant's SOWS score decreases from 11+ to the range of 0-2, suppression criteria will be satisfied. If a participant's SOWS score decreases from 11+ to the range of 3-5, partial-suppression criteria will be satisfied. The decision to proceed, or not, with Session 1 will generally be made by approximately 6:00 PM on the preceding day per MAI or designee so study staff will have adequate time to prepare. Participants who have not met withdrawal criteria by the evening of the second day of dose withholding (i.e., after approximately 58 hours since a their regular 8:00 AM methadone dose) will not qualify for Session 1 and will thereby not qualify to continue in the study. They will be administered their regular dose and then discharged back to their regular methadone program per the guest dosing agreement in place with the respective community clinic. If the 7AM SOWS assessment on the morning of Session #1 is borderline (8-10) but not yet above the threshold value of 10, we will recheck SOWS/COWS/pupils at 09:30 AM when the patient arrives to BRC before doing any other procedures.

For later sessions (#2-5 for pilot or #2-4 for main study), the session schedule from Session # 1 will be "locked in" and will not be altered or canceled regardless of the 7AM SOWS/COWS readings on the mornings of later sessions *unless the MAI decides that the*

risk:benefit ratio does not justify proceeding with the session. This could include instances where withdrawal symptoms do not appear to be present at all.

On session days, the participant will be escorted from the inpatient CRU facility to the outpatient research site at the NIDA IRP/BRC. On each session day, they will be fed a standardized breakfast in the morning and remain fasted until after the session (approximately 4 hours). Although the sites are at most a ten-minute walk from each other, transport will be provided by car or shuttle to reduce variability in what participants experience before sessions (e.g., a walk in the sun versus a walk in the rain or snow).

The procedures to be conducted on session days are summarized in the Times and Events Table (Figure 1, below). Participants will provide urine and breath samples prior to other testing. Participants who smoke will be permitted to smoke ad lib (cigarettes, e-cigarettes, or other products, subject to CRU policy) until 1 hour before the session, but they will not be permitted to smoke during the session. Participants who smoke will also be offered the opportunity to use a nicotine-replacement product, both during and between sessions, as desired. (Smoking on the residential unit is limited to one designated room.)

The first 3 to 12 participants will be enrolled in an unpowered dose-finding single-blind pilot, in which we will test a range of doses of TRV734 in capsule form. The procedure will be the same for the pilot participants and subsequent participants, except for the doses of TRV734 tested. Placebo and oxycodone will be administered in the randomized order in the first two sessions. TRV734 will be administered in sessions 3-5 as described below.

The goal of the pilot study is to identify two TRV734 test doses to be used in the randomized main trial: one dose that completely or almost completely suppresses withdrawal (high dose) and a lower dose that is demonstrably less effective. The purpose of using two dose levels is to show evidence for an orderly dose-response relationship; ideally, this would be done with additional dose levels to generate a detailed dose-response curve, but we are limited by the need to keep participants on a residential unit; additional dosage conditions would require more sessions and longer stays, thereby interfering with enrollment and retention.

The proposed doses for the pilot portion of the study may include any dose up to and including 250 mg, for example: 65, 90, 125, 175, and 250 mg. These example doses will be the initial doses we evaluate, because these increments represent approximately equal log-

scale changes of 0.137 to 0.147. The highest of the proposed doses, 250 mg, is the highest dose for which human safety data are available.

For the first pilot participant who is able to complete all sessions, the sequence of dosing for the pilot sessions will be as follows: the initial dose will be 175 mg. If withdrawal is completely or almost completely suppressed, the second and third doses will be lowered to 125 mg and 90 mg. If withdrawal is not almost completely suppressed by the 175 mg dose, the second dose will be raised to 250 mg and third dose will be 125 mg.

For the second subsequent pilot participant, the starting dose will be the lowest dose that produced complete or almost complete suppression in the first participant; that dose will then be increased or decreased, depending on the level of suppression. For example, if 90 mg produced complete or almost complete suppression in the first participant, the second participant would start at 90 mg, and the second dose would be adjusted up to 125 mg or adjusted downward to 65 mg, depending on the level of suppression. The third dose would be determined based on the response to the first two doses, for example either increasing to 75 mg if the 65 mg dose did not produce withdrawal suppression, or decreasing to 45 mg if the 65 mg dose did produce withdrawal suppression. Other doses could be used during the pilot, but no doses will exceed the maximum approved dose of 250 mg.

For the third subsequent participant, the starting dose will be the lowest dose that produced complete or almost complete suppression in both of the first two participants, and then adjusted to increase or decrease, depending on the level of suppression, within the 0-250 mg dose range approved for the study.

Determination of complete or almost complete suppression will be based on the SOWS (Subjective Opioid Withdrawal Scale). SOWS scores from the dose ranging session for each dose will be compared to the mean SOWS score obtained 4 hours after methadone dosing on each of the first two non-session days. If a participant's SOWS score decreases to the range of 0-2, suppression criteria will be satisfied. If a participant's SOWS score decreases to the range of 3-5, partial-suppression criteria will be satisfied. COWS and pupil diameter will be considered for confirmation purposes.

Main study

The doses chosen for the main study will be determined based on our results from the pilot phase. The goal is to test one dose that completely or almost completely suppresses

withdrawal (high dose) and a lower dose that is demonstrably less effective.

Participants in the main phase of this study will undergo a within-subject double-blind placebo-controlled experiment, to be conducted up to 21 days for each participant. Each session (4 in total) will be conducted after 52-76 hours of abstinence from opioids. The session timeline is shown in the Time and Events Table (Figure 1). At the start of the session, baseline measures will be collected. Approximately one-half hour later, a capsule containing placebo, oxycodone (30mg), or one of the two doses of TRV734 will be administered. Each participant will receive all four treatments, one per session day, with the order counterbalanced across participants.

Figure 1: Time and Events Table (for both Pilot Study and Main Study)

(NOTE: Times are approximate and may be adjusted based on practical scheduling needs)

will be by car or shuttle to reduce variability in what participants experience before sessions (e.g., a walk in the sun versus a walk in the rain or snow).

Hour: ^a	-5.00	-4.5	-4.0	-3.5	-2.0	-1.5	-1.00	-0.5	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0	10.0
Clock time	7:00	7:30	8:00	9:30	10:00	10:30	11:00	11:30	12:00	12:15	12:30	12:45	13:00	13:30	14:00	14:30	15:00	15:30	16:00	16:30	17:00	18:00	19:00	20:00	22:00
Unit	CRU	CRU	CRU	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	NIDA	CRU	CRU	CRU	CRU
Awaken	X																								
Standardized breakfast		X																							
Transfer ^d				X																X					
Symptom Checklist				X																					
Fast ^b																									
Leisure ^b			X																						
Smoking permitted ^a	X	X	X	X	X	X																			
Urine/breath tests ^c					X																				
IV Insertion					X																				
Drug administration									X																
CBC/CMP						X																			
ECG						X				X	X	X	X	X	X	X	X	X	X						
SOWS	X							X		X	X	X	X	X	X	X	X	X	X		X		X		X
Craving								X		X	X	X	X	X	X	X	X	X	X						
VAS								X		X	X	X	X	X	X	X	X	X	X						
COWS ^f	X							X		X	X	X	X	X	X	X	X	X	X		X		X		X
Pupil diameter	X							X		X	X	X	X	X	X	X	X	X	X		X		X		X
Vital signs ^g	X							X		X	X	X	X	X	X	X	X	X	X		X		X		X
Psychomotor task ^h								X			X			X		X		X							
PK ⁱ								X ^j		X	X	X	X		X		X		X			X		X	
End session; after-session survey																			X						
Snack																				X					
Methadone dose ^l																			X	X					

Dinner																					X			
AE assessments ^k																								

^aAll assessments times are relative to the time of drug administration. Actual times will differ, depending on the time of drug administration.

^bFasting and leisure time will last from 8:00 am until 9:00 am (-5 h to -4 h).

^c Urine and breath samples will be collected daily to ensure participants are not self-administering alcohol, opioids, or other drugs of abuse that are not part of the experimental protocol.

^dTransport will be by car to reduce variability in what participants experience before sessions (e.g., a walk in the sun versus a walk in the rain or snow).

^eParticipants who smoke will be permitted to smoke ad lib until 1 hour before the session, but they will not be permitted to smoke during the session.

^fClinical opioid withdrawal scale (COWS) assessments require a 30-min time frame.

^gVital signs will include SBP, DBP, respiration, O₂ saturation and temperature. Patient weight will also be collected on admission, on each session day, and at discharge.

^hThe tasks will be attention, speed, and dexterity.

ⁱPK samples should be taken \pm 2 minutes of the scheduled time. If other assessments need to be performed at the same time as a scheduled PK sample, the PK sample should be taken last. Additional PK assessments will occur at hours 6, 8, and 10.

^jBlood will be sampled within 30 minutes before capsule administration.

^kAdverse event (How do you feel?) assessments will be done prior to dosing and regularly post-dose.

^l Methadone will not be given, or will be given later, if the participant exhibits or reports adverse opioid effects at the time that the post-session methadone is scheduled.

At the end of each session (approximately 4 hours after the test capsule), the participant will be administered his or her usual dose of methadone before being discharged from the test session and returned to the inpatient unit. In previous studies, we have found that 200% of the prescribed methadone dose does not produce adverse effects (Preston et al., 1984), so we do not expect that the usual dose of methadone will interact adversely with the single dose of TRV734 or oxycodone that will have been given during the session. Nonetheless, CRU staff will monitor for any such effects, affording an opportunity to detect any potential interactions between TRV734 and methadone. Methadone will not be given, or will be given later, if the participant exhibits or reports adverse opioid effects at the time that the post-session methadone is scheduled.

Also at the end of each session, the participant will be asked to guess whether the pill given for that session was placebo, oxycodone, or the study drug, and the degree of confidence in the guess. On or shortly before the day of discharge from the study, the participant will be asked again to guess the conditions for all sessions, and will also be asked exit-interview questions about satisfaction with the study, the residential unit, and the staff (After-Session Survey and Exit-Interview Survey).

Subjective, observational, and task measures will be taken just before the capsule is administered, then at intervals throughout the session for 4 hours. Study Instruments will include the SOWS (Subjective Opioid Withdrawal Scale), the COWS (Clinical Opioid Withdrawal Scale), visual-analog scales for opioid effect, and Psychomotor testing. Blood will be sampled at the timepoints shown in in the Time and Events Table (Figure 1).

Pilot Study: Vital signs, CBC, CMP, oxygen saturation, and continuous 12-Lead ECG will be collected for safety monitoring for the duration of each experimental session and on final study day or day of discharge.

Main Study: Vital signs, CBC, CMP, oxygen saturation and a 12-Lead ECG will be collected for safety monitoring at baseline (prior to study drug dose), 1-hour post-drug, and 4 hours post-drug and on final study day or day of discharge.

We hypothesize that TRV734 will be superior to placebo in therapeutic effects and will have fewer adverse effects than oxycodone.

TRV734 will be supplied to the NIDA IRP pharmacy by Trevena, in the form of TRV734 fumarate powder in bags. The NIDA IRP pharmacy will encapsulate the powder into hard gelatin capsules, using inert packing to formulate different dosages (including a placebo dosage that can be administered double-blind. The NIDA IRP pharmacy will develop and maintain the randomization code. No other members of the study team will have access to the randomization code, which can be broken by the PI, MAI, or designee in an emergency upon request. In addition, the NIDA IRP pharmacy maintains emergency and p.r.n. medication boxes available to all clinicians to address emergency scenarios in the care of all research participants; these boxes are stored in both the BRC and CRU locations.

6B. Recruitment

Recruitment strategy: Consistent with the other clinical protocols in the NIDA IRP, recruitment efforts will take place directly through the approved NIDA screening protocol, as study-specific recruitment materials will be utilized. Participants will be recruited through referrals from the NIDA Recruitment and Outreach team NIH Volunteer Office, NIH clinicians and from the NIH Office of Patient Recruitment as well as through ResearchMatch.org (facilitated through OPR). Participants will be recruited by word of mouth and through local pre-approved advertisements created by the NIDA IRP Recruitment and Outreach team. Advertisement language will be used as flyers with tear-off tabs, posted on the NIDA and Johns Hopkins campuses and universities, colleges, local business establishments and medical institutions in the greater Baltimore Maryland metro area and in the DC area. Only IRB-approved recruitment materials will be used in this study. Special outreach efforts are made toward women and minorities. Additionally, advertisements will be placed on billboards of public places and public transportation services in the greater Baltimore metro area. Advertisements will also be posted on the radio, in electronic and printed local media, including newsletters, websites, and local newspapers in the greater Baltimore area (for example, the ‘Baltimore Examiner’). Multiple social-media platforms will be key to the dissemination of approved materials, as well as in NIH and other local email distribution lists, that are moderated, and following approval from the managers of these lists. ‘ClinicalTrials.gov’ may also represent a source of recruitment. Finally, participants will also be recruited via the NIDA Screening Protocol, as this protocol serves as the screening protocol not only for this study but also for other protocols at the NIDA IRP.

6C. Screening methods

Participants will be screened under the NIDA screening protocol.

As with most of our protocols for human research at NIDA IRP, we have written a study “Fact Sheet” for study candidates to read on their first day of screening, when many of them are being screened for multiple studies. Unlike a consent form, the fact sheets are specifically geared toward informing candidates about aspects of the study that they might find too unpalatable to agree to. (For this protocol, those aspects are the long stay on a restrictive residential unit, the skipped methadone doses, and some of the session procedures.) The fact sheet does not ask the candidate to agree to anything; it has no space for initials or a signature. It is just an early opportunity to say no. We have found that the timely provision of these fact sheets helps people self-select out of consideration for a study as soon as they wish, rather than having to do it during a separate visit on the day of consent.

6D. Follow-up / termination procedures

There are no follow-up visits for this study. Section 8B (below) describes specific termination criteria and procedures. Note: methadone treatment will continue per the dosing agreement with the participant’s OTP.

6E. Research Blood collection

At the start of each session, nursing staff will place an intravenous catheter into one of the participant’s arms. Blood samples (2 mL) for pharmacokinetic analysis will be taken at the following times: 0 (within 30 minutes prior to dosing), 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 10 hours post-dose. Actual sampling times will be recorded in the eCRF. Samples will be centrifuged and the plasma collected as outlined in the Study Procedures manual. Samples should be taken approximately ± 10 minutes of the scheduled time. If other assessments need to be performed at the same time as a scheduled PK sample, the PK sample will be taken last. If the catheter fails during the session, we will perform up to three individual blood draws if the participant agrees to them.

6F. Plasma drug analysis and assay methodology

Plasma concentrations of TRV734 will be determined using a validated LC-MS/MS assay. Currently, the validated range of the assay is 5-5000 ng/ml.

6G. Pharmacokinetics Analysis

Plasma samples will be sent, without personal identifiers, to an independent contract

laboratory for quantification of TRV734.

Plasma concentration-time data for TRV734 will be analyzed by non-compartmental methods using PKPlus version 2.0 or higher. Actual sampling times will be used for the calculation of all parameters.

The following parameters will be determined, as appropriate:

- C_{max}
- T_{max}
- AUC(0-t)
- AUC (0-∞), as appropriate
- Half-life (t_{1/2}), as appropriate

6H. Other procedural issues

Some participants may need to reschedule their experimental sessions due to unforeseen issues in their personal lives. Depending on the reasons and the participant's status, we may re-admit them to the study later after reassessing their eligibility. Because circumstances vary greatly across participants, we have chosen not to adopt a rigid cutoff for the maximum time a patient's participation can be delayed in this way.

6H1. Research vs. Clinical Care

Methadone is delivered in a manner consistent with standard clinical care, except 1-2 days before each session day, when it is necessary to skip a dose of methadone to study withdrawal.

6H2. The IND sponsor is NIDA.

6H3. No radiation is used in this protocol

6H4. The relationship of this study to other protocols

Screening for this study is conducted under the NIDA screening protocol. Participants are not otherwise required to have participated in any other protocol in order to be eligible for the current protocol. Data collected for the current protocol under the screening protocol will be analyzed and reported for participants who enroll in the current protocol.

6H5. Storage of Data and Specimens: Future use and disposition

Electronic data are stored on the NIDA IRP secure, password-protected electronic medical records system (Clinical Data Warehouse; CDW). Paper records are stored in our clinic under double lock that authorized only research and clinical staff have access (BRC building; room number 01B605). E-CRF's and Regulatory binders may be found on password protected

files on NIDAFILESTORE. NIDA FILESTORE is a server on the NIH network used to store research data that are physically secured, encrypted, behind NIH firewall, operated at NIDA IRP, managed by The Biomedical Informatics Section (BIS) in compliance with all relevant federal laws, regulations, and policies. They shall have undergone a Security Assessment and Authorization (SA&A) process with associated memorandums that designate the systems as fully accredited and have an Authority to Operate (ATO). After the study is completed and data have been analyzed, the paper records will be stored at an NIH-approved commercial facility for the storage of sensitive data until approval for their disposal has been given.

Stored biological specimens will be kept in a secure -80 C freezer in the NIDA IRP freezer room until they are analyzed.

6H6. Data-sharing description

To advance science, it is helpful for researchers to share information. We share information with researchers outside the NIH in two ways. Most commonly, we have specific partnerships with other researchers. Also, we may put data into one or more scientific databases, where it is stored along with information from other studies. Researchers can then study the information combined from many studies to learn even more about health and disease.

We will share some protocol data with our scientific research partners inside or outside the NIH. Research partners outside the NIH sign an agreement with the NIH to share data. This agreement indicates the type of data that can be shared and what can be done with those data.

Some health information collected under this protocol may be placed into one or more scientific databases after it has been stripped of identifiers such as name, so that it may be used for future research on any topic and shared broadly for research purposes. A researcher who wants to study the information must apply to the database and be approved. Researchers with an approved study may be able to see and use the data from this protocol, along with that from many other studies. We do not expect any direct benefits for participants resulting from the use of protocol data and information, though new discoveries that may help other people could occur. The Principal Investigator is open to answering any participant questions about how these data may be used.

Participants may stop participating in this study at any time. They may subsequently decide to withdraw permission for the use of their individual data, specimens and health information for additional or future research at any time. If they choose, we will destroy their

data. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

7. Risks and Discomforts

7A. Description of Risks

Risks associated with TRV734. Safety and AE data for TRV734, taken from the Investigator's Brochure (IB), are summarized in a separately uploaded document (along with data on TRV734's pharmacokinetics and pharmacodynamics). The human data in the IB are based on three Phase 1 studies in which 129 adults who received TRV734 in single doses ranging from 2 mg to 250 mg and multiple doses ranging from 60 mg to 175 mg. The IB states: "Generally, the adverse events reported with TRV734 have been mild to moderate in severity, dose-related, and consistent with the opioid class. The most commonly reported adverse events included somnolence, nausea, and dizziness. There were no severe treatment-emergent adverse events (TEAEs) in any of the three studies."

In three instances, AEs led to discontinuation of the participant; each occurred with a dose of 175 mg. One AE was mild vomiting (judged probably related); the other two AEs were vomiting accompanied by nausea (vomiting considered moderate and probably related for both participants; nausea considered moderate and probably related for one, mild and possibly related for the other).

Apart from somnolence, nausea, and dizziness, other expected risks of single doses of TRV734 are similar to risks associated with traditional mu-opioids agonists: respiratory depression, hypotension, bradycardia, syncope and pruritis. Because participants in the proposed study will be highly tolerant to opioids, the likelihood of all these mu-typical responses may be lower than in the nontolerant participants enrolled in the three Phase 1 studies.

Recent data have suggested that TRV734 may be a partial rather than a full agonist at MORs. If so, there is a small theoretical risk that TRV734 could induce precipitated withdrawal (sudden, severe opioid withdrawal symptoms) when administered to someone who still has active circulating levels of a full agonist (such as fentanyl or methadone). Cases of precipitated withdrawal have been reported to occur in OUD patients who initiate treatment with the partial agonist buprenorphine after stopping methadone or fentanyl use, and even if the patient is already in subjective and objective withdrawal at the time of buprenorphine initiation. The risk of precipitated withdrawal is greatest if buprenorphine is given soon (within a few hours) after

stopping the full agonist, especially if done before the patient is experiencing significant withdrawal symptoms. We believe this risk is low in our protocol because TRV734 will not be administered until after the patient has spent several days on a closed residential unit; we are excluding patients with a history of intolerably severe opioid withdrawal (including precipitated withdrawal) from our study; and we will not administer the study drug before the emergence of moderate to moderately severe opioid withdrawal symptoms after abstaining from methadone for 2-3 days. However, it is theoretically possible that precipitated withdrawal could still occur given that our patients will have been taking methadone, which is a long-acting full agonist that is thought to be less potent at MORs than TRV734. If precipitated withdrawal were to occur, we would administer a short-acting, high-efficacy opioid (such as intravenous hydromorphone) as a rescue agent, and the study physician make take additional medical actions, on a case-by-case basis, as the clinical situation may dictate.

Risks associated with opioid withdrawal. A major goal of this protocol is to assess the effectiveness of biased agonists for suppressing opioid withdrawal. Therefore, it will be necessary to produce “spontaneous” withdrawal by skipping the participant's usual dose of methadone before each test session, which starts about 52-76 hours after the last dose of methadone. Withdrawal from methadone can produce lacrimation, rhinorrhea, sneezing, nausea, vomiting, fever, chills, tremor and tachycardia. To relieve any withdrawal symptoms that might occur as a result of the missed methadone dose, and also to re-establish a baseline before the next test session, participants will be given their usual methadone dose after each test session.

Possible opioid-withdrawal discomfort will be minimized with the use of adjunct medications to address the signs and symptoms of opioid withdrawal. Medications for symptomatic relief of opiate withdrawal will be administered as needed. These medications may include but are not limited to: ibuprofen, acetaminophen, hydroxyzine, dicyclomine, and magnesium hydroxide. There are no known contraindications between these medications and the study drugs. Adjunct medications will be discontinued at midnight before each test session unless the MAI determines otherwise.

Risks associated with blood sampling. Peripheral venous blood sampling may cause pain, tenderness, bruising, or bleeding at the needle puncture site. Some subjects may feel transient lightheadedness or dizziness, or lose consciousness (syncope), because of anxiety and vasovagal reaction. This risk is minimized by performing venipuncture while subjects are

seated and having them remain under staff observation until it is clear that there are no acute adverse effects from the procedure. The risk of infection is negligible because standard sterile technique is used. Placement of indwelling venous catheters poses a risk of infection or thrombophlebitis, which increases with duration of placement. This risk is minimized by use of careful sterile technique with prompt removal if there are clinically significant signs or symptoms such as tenderness, swelling, or redness. The risk of anemia is negligible because the total amount of blood to be collected (approximately 535 mL over 11 days) is about the amount collected during a routine blood donation.

7B. Minimization of risks

Participants are carefully screened medically and psychologically to exclude individuals who may be at increased risk for adverse events. Participants are carefully monitored by trained staff as described below. Ample opportunity to take breaks will minimize the risk of restlessness. Any significant change from baseline, adverse event, or observation of concern will be promptly evaluated by the MAI or designee.

To minimize the risks described above, participants will be closely monitored by NIDA staff during the study sessions and by Johns Hopkins CRU staff on the inpatient unit. Any unusual behavior or participant complaint will be relayed to the nurses and to the MAI or designee.

Before dispensing each methadone dose, nurses will query the participants on their clinical state. If there is a suspicion of intoxication, the study physician will meet with the participant to try to determine what drug (i.e., methadone, other opioids, cocaine, alcohol, or sedatives) has caused the intoxication. Participants are queried about outside medications—OTC, herbal, and prescription. After the start of the study, use of new substances will be minimized with the inpatient study design. If use of new substances is discovered or reported the MAI or designee will review each new outside medication and make a decision about its safety and the ability of the participant to continue in the study.

ECGs will be done in screening, on the first day of the protocol and on each test day (see Fig. 1). For pilot participants only, ECG will be monitored continuous through each session. In the main study, on each test day, ECGs will be done at baseline (prior to study drug dose), 1 hour post-drug, and 4 hours post-drug, and on final study day or day of discharge.

The investigators, NIDA/IRP counselors, and medical staff will address psychological or

medical issues that may arise during the study. Supervisory sessions and case conferences will be used to review clinical issues. NIDA/IRP clinicians are available 24 hours a day in the event of a medical problem. If immediate medical assessment or intervention beyond the capabilities of the NIDA IRP is required, the participant will be escorted to an appropriate medical facility. NIDA/IRP medical policies will be followed.

8. Subject monitoring

8A. Parameters monitored

Participants will be monitored by the medical, nursing, and research staff for any untoward effects, and the study session will be terminated for the participant if major or unexpected adverse events make termination advisable. Oxygen saturation and heart rate will be monitored continuously throughout the experimental session. Respiratory rate and blood pressure will be monitored every 15-30 minutes.

Participants will be assessed at the end of each experimental session and will not be returned to the inpatient unit until they exhibit stable vital signs, an alert and oriented demeanor, and a normal pupil response to light, and have received clearance from the Medical Advisory Investigator (MAI) or designee. Any impairment in locomotor coordination or judgment will be monitored by the nursing and research staff.

8B. Criteria for individual participant withdrawal/termination

Nonmedical criteria for termination. Participants will be discontinued from the study if they: 1) are found to be using unapproved drugs during the study; 2) fail to comply with data collection; 3) are rude and/or disruptive to the staff or to other patients; 4) try to buy or sell drugs on clinic or hospital property; 5) deface or damage clinic or hospital property; 6) try to tamper with a urine sample (for instance, by using someone else's urine, or by adding something to the urine); 7) violate any of the inpatient CRU rules; (8) cannot have the first experimental session because they do not meet criteria for methadone withdrawal in the allotted time frame (3 missed doses over a 3-day period).

Medical Criteria for Termination. Participants will be discontinued from the study if they develop a psychiatric or medical comorbidity that precludes safe participation in the protocol, as judged by the MAI. Significant increases in the QTc interval, as observed in ECG monitoring via the QTcF method, will be a medical criterion for discontinuation. Specifically, (a) QTcF > 500msec; (b) QTcF change > delta 60 msec from baseline AND >450 msec for men or >

470 msec for woman. (Both criteria in (b) must be met.)

Participants will also be discontinued if they cannot tolerate the study drug, if they develop severe or intolerable opioid withdrawal symptoms, or if they experience precipitated withdrawal after administration of TRV734. Women who become pregnant during the study will be discontinued and referred to follow-up care.

Participants may also, at any time, choose to discontinue participation for any reason.

9. Outcome measures

9A. Primary outcome measure

- a. Suppression of withdrawal symptoms:
SOWS (Subjective Opioid Withdrawal Scale)

9B. Secondary outcome measures

- 1. Suppression of withdrawal signs:
 - a. COWS (Clinical Opioid Withdrawal Scale)
 - b. Pupil diameter
- 2. Psychomotor performance
 - a. The Four-Choice Reaction-Time Task
 - b. The Number-Vigilance Test
- 3. Tolerability and acceptability
 - a. Scales for adverse effects
 - b. Differential dropout across sessions

10. Statistical Analysis

10A. Analyses

The design is entirely within-subjects. The general plan for analysis is to assess each outcome with an omnibus repeated-measures mixed regression, because the maximum-likelihood methods used in such models permits F tests like those that would be obtained in repeated-measures ANOVAs or ANCOVAs without requiring listwise deletion of data from participants whose data are incomplete. These models can also account for order effects and can accommodate a variety of within-subject error structures, and, by using random intercept terms, can appropriately deal with between-subject heterogeneity. Our specific hypothesis tests will rely on planned contrasts between conditions (placebo, oxycodone, and two doses of TRV734); these contrasts derive from the same models as the omnibus F tests, but use Tukey HSD tests,

which do not require that the omnibus F be significant (Myers & Well, 1995; Hancock & Klockars, 1996; Ware et al., 2013).

For the primary outcome measure, the SOWS, each participant's post-capsule scores for each of the four conditions will be expressed as an area under the curve (AUC). This will be the dependent variable in a multilevel model. The independent variables will be drug (placebo, oxycodone, TRV734 lower dose, and TRV734 higher dose) and pre-capsule score on the SOWS from that session, such that the model will functionally be an ANCOVA controlling for baseline. The likely nonindependence of adjacent observations from each participant can be accounted for in the error structure for the model (e.g., first-order autoregressive, spatial power, or unstructured); the choice of error structure will be guided by model convergence with the lowest AIC and BIC. We will test whether results differ with inclusion of possibly relevant between-person predictors such as sex or sequence of drug conditions, and retain those predictors if appropriate. The Tukey HSD contrasts for which we have directional hypotheses are: placebo > TRV734-PooledDoses (i.e., worse withdrawal symptoms after placebo than after a pooled condition combining the two dose levels of TRV734), placebo > TRV734-HigherDose (i.e., an effect of the higher dose of TRV734), TRV734-LowerDose > TRV734-HigherDose (i.e., a dose-dependent effect of TRV734), and placebo > oxycodone. We will also perform these Tukey HSD contrasts, for which we do not have directional hypotheses: placebo vs.

TRV734-LowerDose; oxycodone vs. TRV734-PooledDose (we expect the two to be roughly equal in suppressing withdrawal symptoms).

For secondary outcome measures related to suppression of withdrawal *signs* (COWS, pupil diameter), analyses will follow the same plan, with the same hypotheses. This will also apply to VAS items assessing relief from withdrawal.

For performance on the psychomotor tests, our general aim is to determine whether the withdrawal-suppressing effects of TRV734 are relatively free of the subtle decrements in psychomotor/cognitive function that can accompany withdrawal suppression by traditional mu agonists. We cannot test this directly, because, without a long-term, drug-free control condition, we cannot directly demonstrate that our traditional mu agonist (oxycodone) is producing a decrement. More likely, task performance under both oxycodone and TRV734 will be superior to task performance under placebo, because performance under placebo will be impaired by acute withdrawal symptoms. In other words, task performance will simultaneously

be driven upward by withdrawal relief and downward by acute opioid effects. We will try to dissect this as follows. The four post-capsule scores to be obtained in each session will be dependent variables in omnibus multilevel models comparing all four drug conditions, similar to the analyses specified above for the SOWS (e.g., pre-capsule baseline from that session will be included as a covariate). However, we will include SOWS scores as an additional covariate.

Controlling for SOWS will ask, in effect: Does TRV734 produce less psychomotor impairment than oxycodone *at a given level of withdrawal-symptom relief*? The Tukey HSD contrasts for which we have directional hypotheses are: TRV734-PooledDoses > oxycodone (i.e., better performance after a pooled condition combining the two dose levels of TRV734 than after oxycodone), TRV734-HigherDose > oxycodone (i.e., even the higher dose of TRV734 will not disrupt performance as much as oxycodone does). In other Tukey HSD contrasts, we will test the directional hypothesis that performance under each of active drug condition will be superior to performance under placebo. Finally, for descriptive purposes, we will report the results in terms of published norms; we predict that performance will be within the normal range at all timepoints when withdrawal has been effectively suppressed by either oxycodone or TRV734.

For adverse-effects measures, and the VAS item assessing ratings of “bad effects from the study pills,” the analysis will follow a similar plan as for the psychomotor tests, with the same directional hypotheses favoring TRV734.

To test for differential dropout across sessions, we will code dropout as a dichotomous dependent variable, either present or absent after each session for each participant. The working assumption is that dropout may indicate that the preceding test session was not well tolerated. (The reality will often be more complex; we assume only that there will be some association.)

If a participant drops out with several sessions remaining, dropout will be coded as *present* for the immediately preceding session, then *missing* for the remaining sessions. This will be analyzed in a generalized linear mixed model. Generalized linear mixed models are an extension of mixed models; they handle nonnormally distributed (e.g., dichotomous) outcomes, and functionally, can be used like repeated-measures logistic regressions. The independent variable will be drug condition (placebo, oxycodone, TRV734-HigherDose, TRV734- LowerDose), a time-varying covariate. Tukey HSD pairwise comparisons will be used to test which, if any, drug conditions differed from others in their propensity to be followed

by dropout.

Pharmacokinetic measures will be presented descriptively, and their associations with subjective and physiological responses will be assessed as secondary outcomes, using correlation and multiple regression.

10B. Criteria for significance

We will report both the p value and the Bayes factor (Dienes, 2014; Beard et al., 2016) for each pairwise comparison. If the results favor the alternative hypothesis (Bayes factor > 3) or p -value < 0.05 , we will conclude that TRV734 was superior. If the p value and Bayes factor lead to different interpretations, we will conclude that further research is necessary.

We will also analyze results separately across the two psychomotor tasks, but we will use FDR correction for the p values. If TRV734 appears superior on only one task, we will not present that result without mentioning the findings from the other task, and we will conclude that replication and follow-up are necessary.

10C. Power analysis and accrual-number request:

Each of the main hypotheses tests is a pairwise comparison (derived from an omnibus model that accounts for the larger aspects of the design). Thus, power can be expressed in terms of Cohen's d . A sample size of 30 participants will provide power of .90 to detect a Cohen's d of 0.61 or more at an alpha of .05, two-tailed. For the primary outcome, suppression of withdrawal after withholding of maintenance methadone, this is a highly powered study: even classes of medication that are relatively ineffective at suppressing withdrawal symptoms (Jasinski et al., 1985) can produce large effects (on the order of $d = 2.4$) on the SOWS under these conditions, relative to placebo (FDA, 2018). For secondary outcome measures, such as differences in psychomotor effects, we have no a priori data on which to base an expected effect size.

Some participants might not have appreciable symptoms of withdrawal after one skipped dose of methadone; any instance of this will slightly reduce our power to detect beneficial effects of TRV734, but we will use data from all participants.

11. Human-Subjects Protection

11A. Equitability

Participant selection will be equitable, without regard to nationality, sex, race, religion, or creed. The anticipated racial/ethnic and sex distribution will reflect that of the local

community and drug-using population.

11B. Justification for the exclusion of children under 18

Children under 18 will not be included because the law does not permit them to be maintained on methadone. As a research facility, we could circumvent that regulation, but to do so would reduce the generalizability of our results to community settings.

11C. Justification for the inclusion or exclusion of other vulnerable subjects

Individuals who are cognitively impaired to the extent that they cannot give informed consent, cannot benefit from the substance-abuse treatment offered, or cannot give self-reports appropriately will be excluded. Self-report is a central outcome measure; including participants who cannot do it would invalidate the study. Including participants who cannot give informed consent cannot be justified for this study.

HIV status is not an inclusion or exclusion criterion for this study. During intake, HIV testing will be offered; however, neither the decision to take the test nor the results of the test will affect participation in the study. Participants should be ambulatory and their health status at a level that will not compromise participation in the research study.

11D. Justification of sensitive procedures

HIV testing is conducted as part of subject safety at screening; however, it is optional.

11E. Safeguards for vulnerable subjects

Pregnancy will be an exclusion criterion because the biased agonist we will study has not been previously tested in pregnant women. Our inclusion/exclusion criteria are designed to prevent female participants from becoming pregnant during or soon after the study, and also to prevent the partners of male participants from becoming pregnant during or soon after the study. Urine pregnancy tests will be performed prior to withholding of methadone doses and prior to test sessions. Anyone who becomes pregnant will be excluded from that portion of the study and will be referred for prenatal care and for specialized treatment for pregnant opioid abusers. People with cognitive impairments are excluded. NIH Employees will not be eligible for enrollment so as to avoid possible compromises to the privacy of their OUD status.

12. Assessment of risks and potential benefits

The main risk in this protocol is the discomfort inherent in repeated use of the withdrawal-suppression procedure, in which a daily dose of methadone is withheld to determine whether emergent symptoms of opioid withdrawal are suppressed by a test drug (Lofwall et al.,

2007) (Jicha et al., 2015). We are minimizing the likelihood of severe withdrawal symptoms by informing study candidates exactly how the procedure works and what degree of withdrawal we intend to induce, and more specifically by enrolling only candidates who report that they do not experience intolerable symptoms after missing just 1-2 doses. (Patients on methadone maintenance for OUD usually become highly attuned to their own specific patterns and time courses of response to a missed dose.) Patients who have unexpectedly severe responses to dose omission can leave the study at any time, and we will be fully supportive of their decision to do so. The MAI or designee will assess the participants daily and alert the rest of the study team when an individual seems to be in too much discomfort. The MAI or designee will talk with the participant about whether to continue in the study. The consent form tells participants that we may discharge them if they “develop a medical problem that would make it less safe” for them to remain in the study; although opioid withdrawal is not medically dangerous, we would discharge a participant whose response to a dose omission seemed extreme. The discharge would occur only after the participant had been stabilized on the next daily dose of methadone.

The value of the study is that the results are likely to yield generalizable knowledge about the efficacy of TRV734 in suppressing or reducing opioid withdrawal symptoms. This is a necessary step in what we intend to be a fully translational process, one that leads to real, accessible alternative medications for people with OUD.

13. Consent documents and process

Individuals applying for the study and meeting its eligibility criteria will be asked to give informed consent. Consent will be obtained only by the IRB approved investigators and co-investigators named on this protocol, all of whom have completed NIH's course in human-research ethics and consent training course, and are qualified to answer questions about the study. Any study candidate who has questions or concerns about the study will be offered a chance to speak with the PI or MAI before signing consent. After the consent form is read to or by the study candidate, he/she will take and sign the NIDA Evaluation of Potential Research Participants' Ability to Consent questionnaire for 20-DA-N014 (10-item) to ensure that he/she understands the protocol. A score of 80% and correct response on 2 required questions will be considered passing; if the score is lower than that and/or the participant incorrectly answers a required question, the questionnaire will be re-administered once. If a study candidate does not pass the questionnaire a second time, he or she will not be enrolled in the study. The process will

be documented in the CDW by the investigator who obtains consent. The consent form contains all IRB-required elements.

14. Data and Safety monitoring

a. Data and safety monitor

This is a single-site study with short-term administration of medications, but it will be monitored by the NIDA IRP Data and Safety Monitoring Board (DSMB). The Principal Investigator and Medical Advisory Investigator will also monitor the study.

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

The PI will be responsible for all aspects of the study. Some responsibilities may be delegated to other Associate Investigators. Delegation of responsibilities are documented on a study staff Delegation of Authority Log. The responsibilities shared by the Associate Investigators are documented in the Study Personnel Page.

For this protocol, Clinical Research Quality Management (CRQM) team with the ORSC in the Clinical Center will conduct protocol monitoring. A risk-based approach of source data review and verification will be conducted as described in the Clinical Monitoring Plan. The monitoring reports will be distributed to the PI and the Sponsor.

Independent audits will not be conducted by CRQM to ensure monitoring practices are performed consistently across all participating sites.

Monitoring Reports

After monitoring is performed, the final monitoring report will be sent to ORSC at REGSupportORSC@nih.gov within 7 days of PI receipt.

Regulatory Binders

The PI will be responsible for maintaining the Investigator's Regulatory Binder for the protocol. The ORSC RSS will maintain the Sponsor's Regulatory Binder. The PI and study team will forward all relevant documents to the ORSC RSS contact or to REGSupportORSC@nih.gov.

b. Data and safety monitoring plan

Data to be monitored

- Participant accrual
- Safety data

Adverse events; serious, nonserious, expected, and unexpected

Study dropout, including the reason(s) for dropout (adverse event, treatment failure, etc.)

Materials submitted to the DSMB

In addition to the materials identified above that will be sent to the DSMB for regularly scheduled reviews, we will report protocol-related serious, unexpected adverse events to the DSMB at the same time that we report them to the IRB, the Clinical Director, and other NIH officials. Additionally, we will notify the DSMB promptly of any protocol amendments.

Interim Analyses

No interim analyses are planned because the study is small.

DSMB Reports

The DSMB will make findings and interpret the data, then report to the PI, IRB, and Clinical Director about continuation, modification, suspension, or termination of the protocol based on observed beneficial or adverse effects of the experimental treatment under study. The Clinical Director and investigators will act promptly on any findings indicating the need for an amendment to the protocol or affecting the continuation of the protocol.

Review Schedule

The DSMB met with us in February 2021 and approved initiation of the pilot portion of the study. Their memo, dated March 17, 2021, states:

Upon completion of the three pilot subjects, investigators should review the pilot-phase and the level of withdrawal experienced by the three initial pilot participants (utilizing SOWS Scores) as well as the associated data. This should be utilized to determine if effect sizes meet appropriate criteria levels before further subjects are enrolled.

An ongoing protocol review should take place after the first (non-pilot) subjects have completed the protocol.

We will adhere to the DSMB's recommendations. The DSMB can, at its discretion, examine either dose-coded or fully unblinded data.

- i. Advanced plans for interim/futility analyses: We are not planning interim or futility

analyses for this study.

- ii. Information to be monitored: The information monitored will fall into three groups.
 - 1. *Participant Safety*: While we continually monitor adverse events for serious situations, and report all AEs to the IRB at the time of Continuing Review and to the FDA as part of the Annual report. As participants can receive methadone treatment, we will monitor the literature for any health concerns associated with that treatment. Should a question arise out of the literature we will conduct an analysis of adverse event data to protect our participants.
 - 2. *Study Demographics*: We will monitor recruiting and enrollment data to assure the consistency of our efforts with enrolling a diverse population representative of Baltimore.
 - 3. *Data Quality*: At the time of each continuing review, we will download and examine a random set of 15% participants from the last year and check their data integrity as it relates to the primary outcome measures.
- iii. Communication: The MAI, LAI and/or other members of the research and clinical teams will bring safety and data integrity concerns to the PI. Safety and data integrity concerns will be immediately brought to the attention of the IRB and the Clinical Director via Reportable events Form submissions when appropriate.
- iv. Transfer of data to collaborators: We will remove personal identifiers from data before transfer to an outside collaborator. As an extra layer of security, we will use NIH's Secure E-mail & File Transfer Service (SEFT) <<https://secureemail.nih.gov/>> to transfer any raw data, even after removal of identifiers. This service allows NIH users to send and receive email and large files on a connection encrypted by secure socket layer (SSL). SEFT complies with the Federal Information and Security Management Act (FISMA), helping ensure the protection of personally identifiable information (PII). SEFT also offers a level of nonrepudiation (i.e., it ensures that data are received unmodified from the authentic sender) and tracks correspondence history.

15. Adverse Events and Serious Adverse Events

15A. Definition of Adverse Event (AE)

Consistent with the Common Terminology Criteria for Adverse Events (CTCAE V 5.0), an adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or

procedure that may or may not be considered related to the medical treatment or procedure.

15B. Definition of Serious Adverse Event (SAE)

An AE is considered “serious” if, in the view of either the investigators or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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, or the development of drug dependency or drug abuse.

15C. Classification of an AE

Severity of each recorded AE (grading) will be determined consistent with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Severity will be described using the following guidelines:

- Mild – Requiring minimal or no treatment not interfering with the participant’s daily activities.
- Moderate – Resulting in a low level of inconvenience or concern with the therapeutic measures. May cause some interference with functioning.
- Severe – Interrupting a participant’s usual daily activity, and possibly requiring systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious.”

Relationship to study intervention: All recorded AEs will have their relationship to the study intervention assessed by the investigator who examines and evaluates the participant, based on temporal relationship and clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and

other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related,” as appropriate.
- **Unlikely to be related** – The event's temporal relationship to the study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention), and other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The event is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness will be determined by the MAI. An AE will be considered unexpected if its nature, severity, or frequency is not consistent with the risk information previously described

for the study intervention.

15D. Time period and frequency for event assessment and follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during interactions with the participant or upon later review of data.

All recorded AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured in the NIDA IRP's secure, password-protected system of electronic medical record system. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent will be documented in terms of onset and duration of each episode.

The MAI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

15E. AE recording

In this protocol, we are purposefully eliciting mild-to-moderate opioid withdrawal symptoms by withholding doses of methadone in methadone-dependent participants for specified durations. These elicited withdrawal symptoms indicate that the experimental procedures are working as intended; thus, we will not record them as AEs unless their severity, nature, or time course exceeds what would reasonably be expected to result from that withholding. Examples of mild-to-moderate opioid withdrawal signs and symptoms include but are not limited to anxiety, irritability, yawning, perspiration, eye tearing, rhinorrhea, goosebumps, muscle tremor or twitching, hot and cold flushes, muscle and joint aches, restlessness, nausea, loose stool, stomach cramps, and craving for opioids.

All events that exceed expected moderate grade (CTCAE Grade 2) opioid withdrawal symptoms will be classified and recorded as AEs. Specifically, events related to opioid withdrawal will be recorded as AEs if they are graded from 3-5 in the Common Terminology Criteria for Adverse Events v.5.0 (CTCAE v.5.0). All withdrawal symptoms, whether or not classified as AEs, will also be monitored and recorded via a daily symptom checklist in the participant's electronic medical records. In addition, all non-withdrawal-related events of any CTCAE grade from 1-5 will be recorded as AEs.

15F AE reporting

All recorded AEs will be aggregated and reported to the IRB at the time of CR; all will be reviewed by the MAI for physician signoff on judgments of expectedness, relatedness, and seriousness. Individual and aggregate reports will also be reviewed by the DSMB on at least a yearly basis and to the sponsor as stated in section **15K. Reporting to the Sponsor**.

In evaluating the expectedness of AEs, the MAI will consider disease-related events (DREs) that are common in people maintained on methadone for OUD. These include both opioid side effects (e.g., constipation and sedation) and symptoms of withdrawal that emerge when a dose is missed (e.g., runny nose, nausea, and vomiting). All these events will be monitored; if their timing or severity is atypical, they will be reported as unexpected and tracked and coded in accordance with the CTCAE v.5.0.

15G. SAE reporting

The investigators will immediately report to the sponsor any SAE as stated in section **15K. Reporting to the Sponsor** and to the NIH IRB as per [Policy 801](#) when appropriate.

15H. Events of special interest

Not applicable.

15I. Reporting of pregnancy

If a female participant contacts us after discharge to report pregnancy that occurs within 90 days after the last dose of TRV734, we will note the reporting of the pregnancy in the medical record, and we will request the participant's permission to follow up at later timepoints. The event will be reported to the MAI and PI within 24 hours. The PI will inform the IRB and the sponsor within another 24 hours. If the participant allows the study team to contact her healthcare provider, we will inform the healthcare provider about the research protocol and give information related to TRV734. If not, we will give the information to the participant and

encourage her to give it to her provider.

If a male participant contacts us after discharge to report a partner's pregnancy that occurs within 90 days after the last dose of TRV734, we will note the reporting of the pregnancy in the medical record, and we will ask the participant to have his partner contact us for follow-up at later timepoints. The event will be reported to the MAI and PI within 24 hours. The PI will inform the IRB and the sponsor within another 24 hours. If the pregnant woman does not contact us, we will give information about TRV734 to the participant and ask him to give that information to her, with a request that she inform her health provider. If she does contact us and allows us to contact her provider, we will give the information to her and to her provider. If not, we will give the information to her and encourage her to give it to her provider.

15J. Reporting of protocol deviations and unanticipated problems

All reportable events will be tracked and reported in compliance with NIH policy 801.

15K. Reporting to the Sponsor

The PI and the Sponsor will be responsible for ensuring the safety of those on the clinical trial. The PI will track adverse events during the study and provide the recorded adverse events to the Sponsor at regular intervals per request. These may be requested quarterly and will be requested no less than once a year at the time of IND annual report to the FDA. All AEs that are collected, as determined by this written protocol, will be tracked in the ORSC RSS' template AE Tracker or similar document. If the Sponsor determines that adverse events are occurring more frequently or more severely than the written protocol had expected and/or anticipated, this will be submitted in an IND Safety Report, as described below. In addition, the PI will be responsible for updating the Sponsor about known risks from the drug, as discovered from literature searches or other means.

In accordance with the requirements of 21 CFR 312.32, the PI or designee will report to the Sponsor all SAEs, whether or not they are considered related to TRV734 or the study intervention that occur throughout the study to the Sponsor, including those events listed in the protocol or Investigator's Brochure as anticipated to occur, as follows:

Deaths: Within 24 hours of the awareness of the investigator or anyone on the study team.

All other SAEs: Within 48 hours of the awareness of the investigator or anyone on the study team.

All AEs will be sent to the Sponsor quarterly, unless requested more or less frequently, for submission to the FDA in the IND Annual Report.

The PI will immediately report all deaths and SAEs to the Sponsor by disclosing all event-related information in a completed MedWatch Form 3500A. This form will include the IND number, protocol number, PI name, and an assessment on the reasonable possibility of a relationship between the event and the study drug or intervention. ARC numbers and other PII will *not* be included on this form. The completed MedWatch Form 3500A will be sent encrypted to the Clinical Director/CEO and/or designated medical monitor with a copy to the NIH Office of Research Support & Compliance (ORSC) Regulatory Support Section.

The Clinical Director and/or designated medical monitor will be responsible for determining whether the event is reportable to the FDA as an IND Safety Report if it is a serious, unexpected, and suspected adverse reaction (SUSAR). If the Sponsor determines that the SAE is an SUSAR, the ORSC will submit an Initial IND Safety Report to the FDA no later than 15 calendar days after the PI's notification of the event to the Sponsor. Deaths or life-threatening events will be reported to the FDA no later than 7 calendar days after the PI's notification of the event to the Sponsor. The Sponsor will submit any relevant additional information in a Follow-up IND Safety Report no later than 15 calendar days after receiving the information. All SAEs will be monitored until satisfactory resolution. All recorded AEs and SAEs will be documented on appropriate study records.

16. Alternatives to participation or alternative therapies

All participants will already be receiving agonist treatment for OUD prior to entering this study. The alternative is to continue receiving this treatment without participating in the study.

17. Confidentiality

For medical records and research data –All participants' records generated by the NIDA/IRP staff will be accessible to authorized NIDA/IRP staff only and will be kept in locked files or password-protected electronic files (i.e., NIDA/IRP's Clinical Data Warehouse; CDW, a Microsoft SQL Server database, NIDAFILESTORE). All data forms will be identified by code number. The key that links code numbers with participants' names will be kept by the principal investigator in a locked file.

A. *For stored samples* - Samples and date will be stored using codes that we assign. Data will be kept in password-protected computers. Samples will be kept in locked storage. Only

study investigators will have access to the samples and data.

Biospecimen samples will be stored indefinitely. Samples will be identified only by NIDA ARC number, date collected, and sample type. Other identifiers, such as name or date of birth, are not included with these samples. The data files are also password protected.

18. Conflict of Interest / Technology Transfer

A. NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts of interest to report.

19. Compensation

Volunteers will be compensated for time and research-related inconveniences.

Amount of compensation (hourly rate, inconvenience units and maximum for study)

Transportation will be provided to and from NIDA or remuneration of \$15.00 for travel time per study visit.

Volunteers are compensated for time and research-related inconvenience as indicated in the following tables:

Dose-Finding Pilot

Procedure	Inconvenience Units	Amount/unit	Compensation
Task-practice session (\$20/h for 1.5 h)	not applicable		\$30
Blood collection (5 days with 0.5 inconvenience unit per time point)	38.5	\$10	\$480
5 days with intravenous catheter (\$20/day)	not applicable		\$100
Stay on secure unit (up to 30 days)	not applicable		\$3,200*
Computerized tasks (\$20/hr for 20 h)	not applicable		\$400
<i>Subtotal</i>			\$4,210
Completion incentive (10%)	not applicable		\$421
Total			\$4,631 (i.e., at least \$154/day, if stay requires all 30 days)
			<p>* CRU-stay payment prorated as follows for early d/c:</p> <p>0 sessions: = \$1,000 1 session: = \$1,440 2 sessions: = \$1,880 3 sessions: = \$2,320 4 sessions: = \$2,760</p>

Main Study (*original plan with shorter stay, to be updated after pilot phase is complete*)

Procedure	Inconvenience Units	Amount/unit	Compensation
Training (\$20/h for 1.5 h)	not applicable		\$30
Blood collection (4 days with 0.5 inconvenience unit per time point)	38.5	\$10	\$385
4 days with intravenous catheter (\$20/day)	not applicable		\$80
13-day stay on secure unit (\$120/day)	not applicable		\$1,560
Computerized tasks (\$20/hr for 16 h)	not applicable		\$320
<i>Subtotal</i>			\$2,375
Completion incentive (10%)	not applicable		\$237.50
Total			\$2,612.50 or \$201/day

A participant who completes the entire study receives \$2,612.50 or \$201 per day. Compensation will be prorated if participants do not complete the study. Participants who complete all parts of the study receive a completion incentive of 10% of total earnings. Payments to participants may be in-kind, cash, or check, in accordance with NIDA participant remuneration policy. Compensation may be in cash, maximum \$200 per day; participants who choose cash will need to return on multiple days. Other payment options include: mailing the participant multiple daily checks of \$200 each; paying bills for participants; or paying participants electronically with PayPal.

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21. Abbreviations used in this document

AE: adverse event

ANCOVA: analysis of covariance

ANOVA: analysis of variance

ARC: Addiction Research Center (the forerunner of the NIDA IRP; study participants at the NIDA IRP continue to be coded by “ARC numbers”)

AUC: area under the curve

BRC: Biomedical Research Center (the building in Baltimore that houses the NIDA IRP)

CBC: complete blood count

CDW: Clinical Data Warehouse (the NIDA IRP’s secure system for electronic medical records)

Cmax: maximum concentration

CMP: Comprehensive Metabolic Panel

COWS: Clinical Opiate Withdrawal Scale

CRU: Clinical Research Unit (an inpatient research facility on the same campus as the BRC)

CYP3A4: cytochrome P450 3A4

DBP: diastolic blood pressure

IUD: intrauterine device

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Revision

DSMB: Data and Safety Monitoring Board

ECFMG: Educational Commission for Foreign Medical Graduates

ECG: electrocardiogram

FDA: Food and Drug Administration

FDR: false-discovery rate

FISMA: Federal Information Security Management Act

FSH: follicle-stimulating hormone

HCG: human chorionic gonadotropin

HIV: human immunodeficiency virus

HSD: honestly significant difference
IDE: Investigational Device Exemption
IND: Investigational New Drug
IRB: Institutional Review Board
IRP: Intramural Research Program
IU/L: international units per liter
LAI: Lead Associate Investigator
LC-MS/MS: liquid chromatography with tandem mass spectrometry
MAD: multiple ascending dose
MAI: Medical Advisory Investigator
MOR: mu opioid receptor
NIDA: National Institute on Drug Abuse
NIH: National Institutes of Health
OSD: Office of the Scientific Director
OTC: over-the-counter
OUD: Opioid-Use Disorder
PII: personally identifiable information
PK: pharmacokinetic or pharmacokinetics
QTc: corrected QT interval
QTcF: corrected QT interval by Fridericia method
RAPT: Real-World Assessment, Prediction, and Treatment (part of TAMB)
SAD: single ascending dose
SAE: serious adverse event
SBP: systolic blood pressure
SEFT: Secure Email & File-Transfer Service
SOWS: Subjective Opiate Withdrawal Scale
SQL: Structured Query Language
SSL: Secure Socket Layer
TAMB: Translational Addiction Medicine Branch (part of NIDA IRP)
TEAE: treatment-emergent adverse event
Tmax: time to maximum concentration

VAS: visual analog scale