PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Treatment of Restless Legs Symptoms with Pramipexole to Improve the Outcomes of Protracted Opioid Withdrawal in OUD: A Pilot Double-blind, Randomized Clinical Trial

I. BACKGROUND AND SIGNIFICANCE

The current national opioid crisis includes over 10 million Americans misusing opioids, 2 million with opioid use disorder (OUD) and nearly 50,000 killed per year due to opioid overdose (Centers for Disease Control and Prevention, 2019). The US national life expectancy has dropped as a result of opioid deaths. Beyond this, the financial cost of opioid misuse was recently estimated at 504 billion dollars annually (Council of Economic Advisers, 2017). Chronic use of opioids is associated with tolerance to their analgesic effects and withdrawal upon discontinuation. Such opioid withdrawal symptoms are very distressing, produce multiple (primarily CNS, gastrointestinal and autonomic) systemic effects and strongly motivate a return to opioid use (Blanco & Volkow, 2019). In one recent study at McLean Hospital, over 50% of those initially prescribed opioids for pain relief reported that avoidance of opioid withdrawal symptoms was the primary reason they continued to use opioids (Weiss et al., 2015). Improvements in treatment of opioid withdrawal symptoms have the potential to reduce the burden of OUD and enhance transition into longer-term treatment.

Restless Legs Syndrome (RLS) is a movement disorder characterized by a powerful urge to move the legs, usually accompanied by unpleasant dysesthesias, that is precipitated by rest, relieved by movement, and most pronounced in the evening or at night (Trenkwalder et al., 2018). These symptoms contribute to the primary morbidity of RLS which is severe sleep disturbance, interfering with both falling and staying asleep as well as overall sleep quality due to RLS sensory-motor symptoms and the presence of periodic limb movements of sleep (PLMS) (Winkelman et al., 2009; Fulda, 2015). The severe restlessness and sleep disturbance produce substantial acute psychological distress. Both idiopathic and secondary RLS are independently associated with substantial long-term detrimental effects on health, cognition, quality of life, psychiatric morbidity and all-cause mortality (Winkelman et al., 2009, Li et al., 2013, 2018, Kendzerska et al., 2017; Zhuang et al., 2019).

Secondary RLS is common in multiple medical conditions, including end-stage renal disease, iron deficiency, and pregnancy (Trenkwalder et al., 2018). We have recently confirmed anecdotal reports (e.g., Freye et al., 2004, Ghosh & Basu, 2014) that RLS is also common among patients with OUD experiencing opioid withdrawal. Our original investigation (Mackie et al., 2016), using a self-administered questionnaire, found that 50% of 124 patients met criteria for RLS during a 3-day detox admission at McLean Hospital. In a confirmatory study from India, 53% of patients in an opioid detox setting developed RLS symptoms (Gupta et al., 2018). In those affected patients, RLS initially appeared after a mean of 1.7 days of abstinence and was characterized as a crawling, creeping sensation in the muscles, most commonly limited to their legs. We have recently established, using face-to-face interviews in the Gavin Foundation opioid detox step-down

stabilization unit (where this study will be conducted), that RLS symptoms were present for at least 2 weeks beyond initial withdrawal in 45% of OUD patients (Winkelman, Wilens et al., preliminary data). Similarly, in the Gupta study described above, RLS symptoms persisted in 70% of those affected during acute withdrawal and was still present on discharge from the acute detox.

It is not surprising that opioid withdrawal commonly produces RLS symptoms since opioids are an established effective treatment for RLS, both medically for patients with refractory symptoms (e.g., controlled release oxycodone-naloxone is approved for RLS in Europe)(Silber et al., 2018; Mackie & Winkelman, 2017; Trenkwalder et al., 2013; Trenkwalder et al., 2017) and, anecdotally, self-administered to address RLS restlessness related to acute and protracted opioid withdrawal (Winkelman et al., preliminary data). "Restlessness" and "aching" dysesthesias are two of the core items assessed by both patient-reported subjective (SOWS) (Handelsman et al., 1987) and clinician-administered (COWS) (Wesson & Ling, 2003) withdrawal scales; SOWS and COWS are the primary tools used to assess the severity of opioid withdrawal. These symptoms are usually viewed by clinicians narrowly as features of opioid withdrawal and not recognized in that context as, in fact, potentially secondary RLS. On the other hand, patient-oriented websites commonly discuss RLS in the context of opioid withdrawal. This clinical mischaracterization of restlessness as simply opioid withdrawal rather than RLS precludes efficacious treatment of this symptom with established non-opioid approaches to RLS and may thus prevent patients from entering detox or result in relapse to opioid use by those in detox. Thus, appropriate RLS treatment may be an effective approach to relieve the restlessness and aching dysesthesias of protracted opioid withdrawal, as well as the resulting sleep disturbance, and may thus constitute a previously unrecognized modifiable risk factor for increasing initiation, engagement, and retention in treatment. All of these improve the probability of successful transition into longer-term treatment (Fleury et al., 2016).

Dopamine agonists such as pramipexole are efficacious and first-line FDA-approved treatments in low doses for primary (i.e., idiopathic) RLS (Winkelman et al., 2006, 2016). Dopamine agonists are also efficacious for secondary RLS associated with end-stage renal disease (Pellecchia et al., 2004), peripheral neuropathy (Bastia et al., 2015) and pregnancy (Dostal et al., 2013). A few published case reports suggest that dopamine agonists are also effective in opioid withdrawal-related RLS (Ghosh & Basu, 2014; Park et al., 2010, 2014), and it is not uncommon for opioid detoxification units to have dopamine agonists (e.g., ropinirole, pramipexole) on formulary to address RLS. FDA-approved dopamine agonists not only dramatically reduce core RLS symptoms of leg restlessness and dysesthesia but by this mechanism produce substantial improvements in sleep disturbance in both primary and secondary RLS (Winkelman et al., 2016). As opioid withdrawal is prominently characterized by sleeplessness (Oyefeso et al., 1997), which is thought to independently confer risk for relapse to opioid use (Beswick et al., 2003), treatment of protracted opioid withdrawal related RLS may also improve sleep in this cohort.

We hypothesize that effective treatment of RLS symptoms with pramipexole is an effective treatment for RLS symptoms in OUD patients during post-detox clinical stabilization. Further, we

hypothesize that treatment of RLS in this context will also improve overall symptoms of opioid withdrawal as assessed by the SOWS. As exploratory aims, we also hypothesize that treatment of RLS symptoms will (i) improve subjective sleep quality and duration and reduce self-reported sleep disruption, and (ii) contribute to longer stays in the inpatient OUD step-down stabilization treatment facility. Retention in treatment – longer stays in the facility with its multi-dimensional treatment strategy options - is highly correlated with success in OUD outcomes. (Fleury et al., 2016).

II. SPECIFIC AIMS

Primary Aim:

- To determine whether pramipexole will have significantly greater effect than placebo in reducing RLS symptoms in OUD patients immediately following acute opioid withdrawal during post-detox clinical stabilization

Secondary Aim:

- To determine whether pramipexole will have significantly greater effect than placebo in reducing self-reported opioid withdrawal symptoms in OUD patients immediately following acute opioid withdrawal during post-detox clinical stabilization.

Exploratory Aims:

- To determine whether pramipexole will have significantly greater effect than placebo for self-reported sleep metrics (e.g., quality, disturbance, sleep latency and duration) in OUD patients immediately following acute opioid withdrawal during post-detox clinical stabilization.
- To determine whether OUD patients on pramipexole will stay in the post-detox clinical stabilization unit longer than those on placebo. This will enable a higher rate of successful referral to after-care than those on placebo.

III. SUBJECT SELECTION

The following lists the inclusion/exclusion criteria for prospective participants.

Inclusion Criteria:

1. Men or women of any ethnic origin.
2. Written informed consent is obtained
3. Speaks and writes in English
4. A willingness and ability to comply with study procedures.
5. Age 18–75 years

6. Patients with diagnosed OUD who have undergone primary detoxification for their OUD in any detox facility, have been transferred to the Gavin Clinical Stabilization Service (CSS), and have some persistent opioid withdrawal as indicated by a SOWS>1 on Day 1
7. Diagnosis of RLS from the Hening Telephone Diagnostic Interview (HTDI) with subsequent confirmation by clinical interview conducted by a study physician (e.g., Dr. Winkelman, Wilens)
8. International Restless Legs Syndrome Severity Scale (IRLS) Symptoms subscale score of >11 for three consecutive days prior to randomization. Participants who miss one day of questionnaires prior to randomization may be included if the IRLS subscale score is >11 for each day questionnaires are completed.

Exclusion Criteria:

1. Pregnant. Gavin Foundation staff perform pregnancy tests upon admission to the CSS.
2. Participants with active or unstable major psychiatric disorder other than OUD, who, in the investigators' judgement, require further treatment
3. Neurological disorder or cardiovascular disease raising safety concerns about use of pramipexole and/or judged to interfere with ability to assess efficacy of the treatment
4. Medical instability considered to interfere with study procedures
5. Stage 3, 4, or 5 renal insufficiency
6. Participation in this study on a previous admission to the CSS

IV. SUBJECT RECRUITMENT AND ENROLLMENT

Methods of recruitment and procedures for informed consent:

The target enrollment for this study is N = 160 men and women with OUD experiencing withdrawal symptoms and RLS. Recruitment will occur directly at the Gavin Foundation site. Participants will be notified that participation is voluntary and that not participating will not affect their ability to receive standard care at the Gavin Foundation.

All patients admitted to the Gavin Clinical Stabilization Service (CSS) from the Gavin Acute Treatment Service (ATS) will be eligible. The CSS provides clinical stabilization, initiation into longer term remission, case management and coordination for outpatient care and living arrangements; induction onto longer term medication-assisted treatments as requested. Upon admission to the CSS, potential participations will be notified about the study through an information sheet provided by nurses and flyers posted around the facility. Interested patients who satisfy a preliminary RLS screening (which is part of the standard clinical care at Gavin) will be instructed to call the study coordinator for a pre-screening. Those patients who meet basic inclusion and exclusion criteria and report symptoms of RLS (detailed below) will be asked to participate in the study. If they agree, they will be contacted by Dr. Winkelman, Dr. Wilens, Dr.

Klerman or their designate; (s)he will provide more information about the study and will obtain informed consent. Details of consent are described elsewhere.

Our recruitment procedures provide all applicants with an equal opportunity to participate in our studies regardless of race, color, creed, or national origin. We expect all populations to be represented in our protocol, but we do not have the statistical power to find differences among the groups.

Study Design and projected enrollment:

This is a parallel, two-arm, double-blind, randomized placebo-controlled 10-day trial investigating the effects of pramipexole 0.25–0.5 mg on RLS symptoms in patients suffering from opioid withdrawal. This parallel design consists of two treatment groups: one receiving 0.25-0.5 mg pramipexole (one or two 0.25 mg tablets), and the other receiving placebo (one or two identical tablets).

All study procedures will be conducted virtually by study staff over Partners-approved channels of communication. We expect to consent and evaluate for eligibility up to 160 inpatients at the Gavin CSS in order to achieve our projected randomized sample size of 88 patients with OUD to have 68 participants complete the 10-day trial. Participants will be randomized in a 1:1 ratio to pramipexole 0.25–0.5 mg or equivalent placebo for 10 days.

Eligible patients will be randomized to 10 days of pramipexole or placebo after an initial 3-day screening period to ensure the stability of RLS and opioid withdrawal symptoms. Participants will complete 5 study visits mainly over video or phone: initial screening visit (V1), consent/screening visit (V2), randomization visit (V3), Day 3 interim visit (V4), and an end-of-treatment visit (V5).

Pramipexole will be started at 0.25 mg nightly or identical placebo for the first 3 days. If this dose is well tolerated but not effective after 3 days of treatment, as determined by the day 3 visit, two tablets per night will be given. Note that this means some patients will receive two doses of placebo tablets per night.

All of the participants in this trial are diagnosed with OUD, a condition that may be associated with increased risk of COVID-19-related complications. Thus, considering the safety and psychological wellbeing of our participants, most interactions between participants and study staff will occur remotely. Some visits may take place in person at the Gavin Foundation if virtual visits are considered to be an excess burden to participants or study staff. Necessary precautions, in accordance with MGH policy, will be in place. For the remote visits, research staff will follow the Partners Healthcare requirements for using the appropriate virtual tools: visits will occur via video (Microsoft Teams or other Partners-approved programs) or telephone. A study physician will remain on call in case there any emergent medical or psychiatric issues.

The Gavin Foundation CSS will be provided with a computer that will be used for questionnaires and study visits. This computer will meet all MGB security standards. The Gavin Foundation staff

has agreed to place this computer in a location where participants can complete questionnaires and meet with MGH study staff privately.

V. OVERVIEW OF STUDY PROCEDURES

PRE-SCREEN (VISIT 1):

Interested patients will provide verbal consent at the time of the pre-screening visit, at which time they will be informed that their data will be used in this study. Verbally consented participants will be assigned a unique identifier that will be used to link screening questionnaire data to the participant's record. The initial screen will be conducted over the phone or video, and consist of a brief clinical history for inclusion and exclusion criteria. If preliminary eligibility appears adequate and the individual expresses interest, the Hening Telephone Diagnostic Interview (HTDI) will be used to assess the presence of probable or definite RLS (Hening et al., 2008). The International Restless Legs Syndrome Severity Scale (IRLS) Symptoms subscale will then be administered to assess RLS severity for those with probable or definite RLS (Walters et al., 2003). Those who meet all of the eligibility criteria and have an IRLS subscale score >11 will be asked to participate in the study. Note that IRLS subscale score >11 for the next two days will be required for continuing in the study at the randomization visit (participants may still be included if one day of questionnaires is missed, given that the score of each completed IRLS subscale is >11). If the participant agrees, a screening visit with a study physician will be scheduled for later that day or as soon as possible.

SCREENING VISIT (VISIT 2):

Verbally consented participants will be given written informed consent electronically by the study doctor for the remaining screening procedures and all treatment-related procedures via the REDCap e-consent framework. Risks and benefits associated with use of pramipexole and study procedures will be described. At that time, further eligibility will be assessed with a clinical interview conducted by a study physician to ensure that eligibility criteria are met.

A study physician will confirm a diagnosis of OUD using the Structured Clinical Interview for DSM 5 (American Psychiatric Association, 2013) with the SCID subsection for opioids and identify other problematic or substance use disorders with alcohol, cocaine, and stimulants with the Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) tool (McNeely et al., 2016). The HTDI will be repeated to confirm the presence of RLS.

Screening Run-In (3 days): The participant will receive daily email links to an online sleep diary and three questionnaires: the IRLS subscale, SOWS, and an opioid craving visual analog scale. Baseline subjective sleep measures will be determined from this 3-day period.

RANDOMIZATION VISIT (VISIT 3) AND TREATMENT PERIOD:

A more thorough medical history will be collected at the Randomization Visit, along with demographic information. At this visit, the 3-day sleep diary and questionnaire results will be reviewed for final eligibility before the participant is randomized to treatment.

Eligible participants will be randomized in a 1:1 ratio to 10 days of placebo or pramipexole. Pramipexole will be started at 0.25 mg nightly for the first 3 days. On day 3, a study physician will call the participant over the phone or on video to inquire about efficacy and adverse events (Visit 4). Visit 4 may occur on day 4 or 5 if the study physician is unable to meet on day 3. If the 0.25-mg dose is well tolerated but not effective, the dose can be increased to 0.5 mg.

Participants will receive medication from the Gavin Foundation staff and will complete the online sleep diary and questionnaires every day (see the Table of Procedures below for the exact schedule). Gavin Foundation staff will direct participants to the secure computer on which they can complete the sleep diary and questionnaires.

FINAL STUDY VISIT (VISIT 5):

On Day 10, participants will meet with a study physician. The physician will assess the participant on the Clinical Global Impression-Improvement (CGI-I) scale and will also inquire about any adverse events experienced. If a participant is discharged from the Gavin Foundation CSS before Day 10, study staff will attempt to perform Visit 5 before his or her departure from the facility.

Compensation:

Participants will be remunerated. Any earnings will be loaded onto a debit card, which will be given to the participant when he or she leaves the Gavin Foundation CSS.

Participants will be paid based on completion of sleep diaries and questionnaires after receiving study drug.

The payment schedule is as follows:

- $5/day for filling out diaries and questionnaires on the 10 days on study drug
- $25 for fully completing the study (i.e. spending 10 days on the study drug and completing 10 days of diary entries)

The total possible compensation is $75.

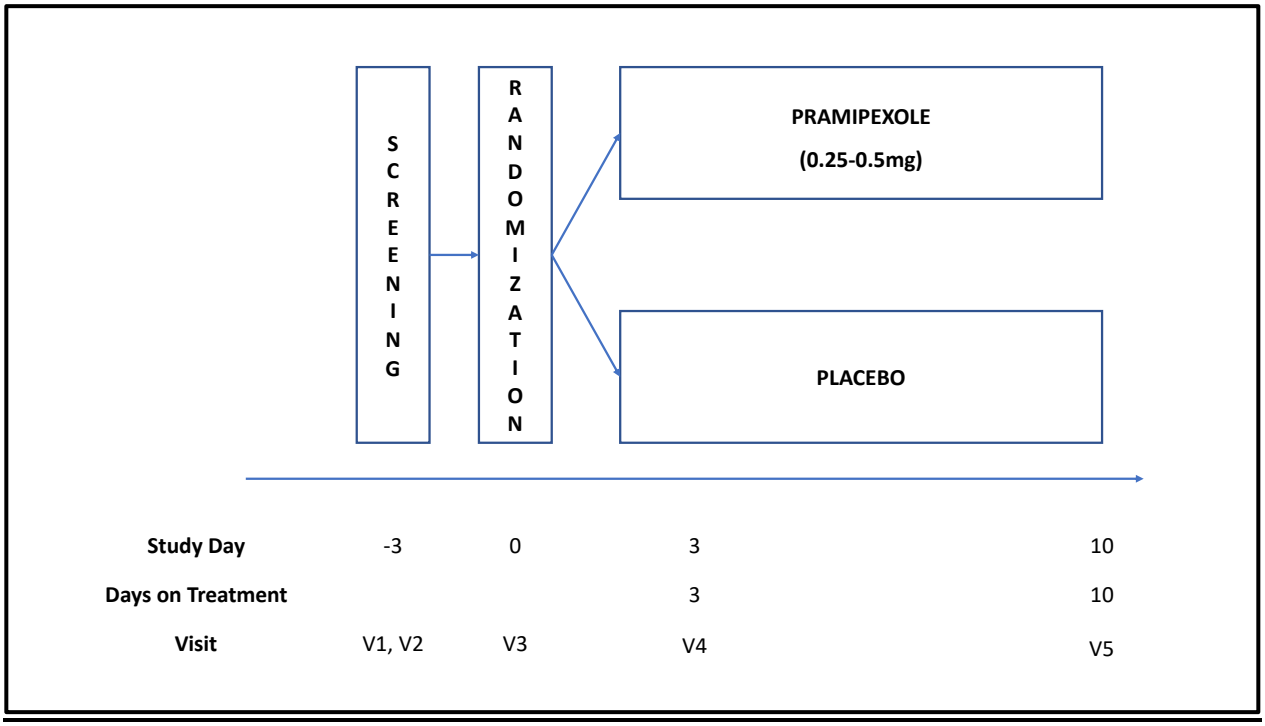
This compensation plan has been discussed with and approved by Gavin Foundation staff.

See below for the **Table of Procedures** and **Study Flowchart**.

Table of Procedures:

Visit		Screening Period				Treatment Period									
		V1	V2		V3			V4							V5
Study Day		-4 to -2	-2	-1	0	1	2	3	4	5	6	7	8	9	10
General/ Screening Assessment	Sleep/medical/mental health phone screening and verbal consent	x													
	Written Informed Consent (via REDCap)		x												
	Eligibility Criteria		x												
	Medical History				x										
	Demographic Information				x										
	IRLS	x	x	x	x	x		x		x		x		x	x
	SOWS		x	x	x	x		x		x		x		x	x
	Opioid Craving VAS		x	x	x	x		x		x		x		x	x
	PHQ-9				x					x					x
	GAD-7				x					x					x
	CGI		x												x
Sleep Assessment	Sleep Diaries (administer/review)		x	x	x	x	x	x	x	x	x	x	x	x	x
Medication Dispensing					x			x							
Safety Assessment/ Adverse Event Reporting						x	x	x	x	x	x	x	x	x	x
Medication Adherence						x	x	x	x	x	x	x	x	x	x

Study Flowchart:



VI. STUDY MEDICATION AND SUPPLIES

Study Treatments:

The study medication will consist of one or two 0.25 mg pramipexole tablets, or matching placebo, prepared in identically appearing tablets and distributed by the MGH Clinical Trials Pharmacy to the Gavin Foundation. The medication will be titrated and distributed according to the following schedule:

Dispensing Schedule:

Day	Treatment	Placebo
0-2	One 0.25 mg tablet	One tablet
3-9	One or two 0.25 mg tablets	One or two tablets

Participants will be given the study medication at approximately 6 p.m. each night by Gavin Foundation staff. Participants will be informed during the consent process that they may be receiving drug or placebo during the study.

Study Medication Packaging:

Medication will be prepared and packaged by the MGH Clinical Trials Pharmacy. Bottles will be labeled with the randomization number and the dosing information.

Study Medication Accountability and Compliance:

Starting at the Randomization Visit, study medication will be dispensed to each participant by Gavin Foundation staff. Participants will be asked about medication adherence on each daily sleep diary.

All study medication dispensed by the investigators or designee will be accounted for throughout the study. Information about participant dosing and compliance will be recorded in the participant's clinical records. Participants who are noncompliant with medications (according to clinical records and diaries) may be removed from the study at the discretion of the investigators.

Randomization:

Randomization will be used to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown participant attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

At the initial visit, participants will be assigned a 3-digit participant number, in ascending sequential order beginning with 001. The participant number will be retained by the participant for

the duration of the study. The MGH Clinical Trials Pharmacy will provide and maintain randomization and blinding. Participants will be randomized to receive either pramipexole or placebo in a 1:1 ratio. Participants and investigators will be blinded to treatment assignment. Participants will be randomized sequentially as they qualify for the study.

Blinding:

The randomization code will be maintained by the MGH Clinical Trials Pharmacy and will not be revealed to study participants, investigators or blinded clinical staff until all participants have completed and the database has been finalized.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific treatment would be dictated by knowing the treatment status of the participant. Individual code breaks by the investigators will normally result in withdrawal of the participant from the trial. The date, time and reason for the unblinding must be documented in the study files.

VII. RISKS AND DISCOMFORTS

Medication Side Effects and Adverse Events:

The following adverse events have been reported more frequently during use of pramipexole in restless legs syndrome patients than under placebo: nausea and fatigue. Less common adverse events were constipation, dry mouth, diarrhea, and upper respiratory tract infections. A few rare, but serious adverse events have been linked to pramipexole, including impulse control disorders, confusion, and hallucinations. Note that some of these symptoms overlap with those of opioid withdrawal.

Participants will be assessed for depression and anxiety during the study, using the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder 7-item scale (GAD-7) (Kroenke et al., 2001, Spitzer et al., 2006).

All adverse events that occur between the first study-related procedure and within 30 days of the last dose of study medication will be reported. Adverse events will be reported to the Partners IRB according to guidelines.

Participants will be at Gavin CSS and monitored by Gavin Foundation staff who will report and record symptoms including adverse events.

Participants will be asked about adverse events each day by Gavin Foundation staff. Participants should report any adverse events voluntarily or in response to general, non-directed questioning (e.g., “How has your health been since the last visit?). Participants will also be asked about adverse events at the Day 3 (Visit 4) call and at the Final Study Visit (Visit 5).

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the participant’s study documents. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper

respiratory infection"). A study physician must document his/her opinion concerning the relationship of the adverse event to the study medication.

VIII. POTENTIAL BENEFITS

Participants may not benefit from taking part in this study. Some participants will receive pramipexole, which may help with their restless legs syndrome symptoms. Participants may benefit from the sleep diaries, review of their symptoms, and discussions with the study doctor. Participants may also be paid for their participation in this study.

This research has potential benefits to society: this study may help other people with OUD and RLS symptoms by adding to the knowledge about this drug, and whether it is a beneficial treatment.

IX. BIOSTATISTICAL ANALYSIS

Analysis of all study data will be conducted by Dr. Winkelman, Dr. Klerman, and Dr. Bettina Hoeppner or another statistician at Partners Healthcare hospitals. All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the hospital Research Pharmacist who generates the randomization code and Dr. Bettina Hoeppner who will conduct the interim analysis will be unblinded to treatment assignment. The final database will not be unblinded to study staff until all study data are complete and a medical and scientific review by Dr. Winkelman is conducted.

Overview of analytic plan:

We will conduct an interim analysis to probe the futility of the study. We will use the data obtained to date to estimate the effect of randomized treatment group on two outcomes (primary outcome: IRLS score; secondary outcome: SOWS). We will then use this estimate to determine the sample size necessary to detect this effect. To protect the blind, a statistician (Dr. Hoeppner) who is not involved in the day-to-day running of the study, will conduct the analyses.

We will perform both intent-to-treat (ITT) analyses (including all patients who received one dose of study medication and complete one assessment post-randomization) and per protocol analyses (including participants with 10 days of evaluable data). Distributions of the outcomes will be examined and data transformation will be applied to satisfy the normality assumptions.

We will analyze data in several ways: comparison of change from randomization to end of Day 5; comparison of change from randomization to end of Day 10; and using all daily values (i.e., longitudinal analyses). The two groups are drug and placebo.

Study endpoints:

The primary outcome (IRLS score) and all secondary and exploratory measures are continuous variables. We will modify the IRLS in two ways: (i) only the symptoms subscale will be employed (only items 1, 2, 4, 6, and 8 will be included); and (ii) the questions will be modified to include symptoms for only the last 24 hours rather than for the previous 7 days. Primary

analyses will focus on the difference in the change in IRLS subscale from randomization to Day 5 and from randomization to Day 10 between the two groups.

The key secondary variables are the difference from randomization to Day 5 and from randomization to Day 10 in SOWS.

Exploratory analyses will similarly focus on the differences from randomization to Day 5 and from randomization to Day 10. These endpoints include:

1. Subjective total sleep time
2. Subjective sleep latency
3. Subjective time awake after sleep onset
4. Depressive (PHQ-9) and anxiety (GAD-7) symptoms
5. Time spent in the Gavin CSS

STATISTICAL METHODS

Interim analysis:

(i) Two-sample t-tests will be applied to estimate the effect of randomized treatment group on IRLS subscale score, for the subjects with post-randomization data to date. Using the estimated treatment effect, we will conduct a power analysis to determine the sample size necessary to detect this effect. (i) Two-sample t-tests will be applied to estimate the effect of randomized treatment group on SOWS, for the subjects with post-randomization data to date. Using the estimated treatment effect, we will conduct a power analysis to determine the sample size necessary to detect this effect.

Primary analysis:

(i) Two-sample t-tests will be applied to compare the change in IRLS subscale from randomization to Day 5 and from randomization to Day 10 between the two groups. (ii) Linear mixed-effects models will also be applied to the longitudinally measured IRLS subscale with entry of covariates that correlate with changes in primary endpoints as required (e.g., age, sex, and at-randomization levels of IRLS severity, and SOWS). Subjective sleep measures from the sleep diary for every night of data collection will also be added as potential covariates to the linear mixed-effects models.

Secondary Analysis:

(i) Two-sample t-tests will be applied to compare the change in SOWS from baseline to Day 5 and to Day 10 between the two groups. (ii) Linear mixed-effects models will also be applied to longitudinally measured SOWS with entry of covariates that correlate with changes in primary endpoints as required (e.g., age, sex, and at-randomization levels of IRLS severity, and SOWS).

Subjective sleep measures on every night of data collection will also be added as potential covariates to the linear mixed-effects models.

Exploratory Analyses:

Linear and generalized linear mixed-effects models will be applied to compare changes in the self-reported sleep metrics (e.g., quality, disturbance, sleep latency and duration) across the nights of study and between the groups.

Linear and generalized linear mixed-effects models and survival-based analyses will be applied to compare the number of days patients continue in CSS treatment between the two groups.

Power/Sample Size:

Power calculations are based on Specific Aims 1 and 2 detailed below. There are insufficient published or unpublished data to perform them on exploratory analyses (detailed above). Meta-analyses of RLS clinical trials indicate that placebo effects using the IRLS are strongly related to the duration of these trials (Fulda et al., 2008). Therefore, we are basing our calculations on short-term trials, similar to our study design, for pramipexole in RLS using abbreviated RLS symptom scales (e.g., Oertel et al., 2007; Manconi et al., 2007, 2012)

Aim 1: The primary outcome is the change in IRLS scale from baseline to Day 10. Using the Oertel et al. (2007) data as reference, with n=34 for each group, we will have 80% power to detect a 6.3 points difference in the change of IRLS scale (with a common standard deviation of the change of 9.0) with a two-sided two-sample t-test at alpha=0.05 level. A change of 3 is considered a clinically meaningful difference from placebo (Allen et al., 2013).

Aim 2: The primary outcome is the change in SOWS. Using the Dunn et al. (2017) data as reference, with n=34, we will have 80% power to detect a 4 points difference in the change of SOWS (with a common standard deviation of the change of 6.0) with a two-sided two-sample t-test at alpha=0.05 level.

Therefore, our plan is to enroll 160 people in a 1:1 drug:placebo ratio in order to randomize 88 patients with OUD and have 68 participants complete the 10-day trial. With approximately 16 patients per week admitted to the CSS with opioid use disorder, and an RLS prevalence of 50% in this context, we do not anticipate any difficulty enrolling to our target sample size for the trial within a 20-month enrollment period.

Note: The study has had difficulty enrolling study participants. We originally projected that we would be able to enroll all participants within 24 months. Over the two years since we initiated enrollment, we have enrolled 70 of 160 projected participants, which is 43.7% of our enrollment target. During this period, we have randomized 35 of 68 projected participants, which is 51.5% of our randomization target. Due to this delay, we have added an interim analysis to our study protocol to assess the futility of the study. If the needed sample size is smaller than the originally projected sample size, we will continue the study. If the needed sample size is equal to or larger than the originally projected sample size, we will close the study, as we do not have the resources

to continue the study for another 24 months (i.e., the number of months it would take us to continue to recruit, given our current enrollment rate).

X. MONITORING AND QUALITY ASSURANCE

We will use a Data Safety Monitoring Board (DSMB), meeting every 6 months to review the progress of the study. The Board will comprise two research physicians who are familiar with clinical research, restless legs syndrome, OUD, opioid withdrawal, and pramipexole and its effects, but who are not collaborators or close colleagues of the PI or co-investigators. The Board will also include a biostatistician. The DSMB will review all adverse events and unanticipated problems that arise during the study. Adverse events, including serious adverse events, and unanticipated problems will be managed and reported to the IRB. The data to be monitored for safety include: withdrawal symptoms as assessed by SOWS, drug craving as assessed by craving scales, mood and anxiety scales; clinical staff at Gavin Foundation will also monitor for symptoms of hypomania/mania, impulse control disorders. Dr. Winkelman and/or Dr. Wilens, the PI and Investigator and MDs, will review these data as soon as they are available on each participant and at monthly intervals.

XI. REFERENCES

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