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The Tolerability of Buspirone for the Treatment of Anxiety in Parkinson's Disease

Principal Investigator – Irene Richard, MD
Co-Principal Investigator – Ruth Schneider, MD

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PROTOCOL SYNOPSIS

FULL STUDY TITLE	The Tolerability of Buspirone for Treatment of Anxiety in Parkinson's Disease
CLINICAL PHASE	Phase II
INVESTIGATORS/ STUDY GROUP	Irene Richard, MD (PI), Ruth Schneider, MD (Co-PI)
STUDY OBJECTIVE	The primary objective of this study is to determine the tolerability of buspirone for the treatment of anxiety in PD.
STUDY RATIONALE	Anxiety is highly prevalent in Parkinson's disease (PD) and negatively impacts quality of life yet it frequently remains untreated and there have been no clinical trials dedicated to evaluating the pharmacological treatment of anxiety in PD. Buspirone, which primarily acts as a 5HT1A receptor partial agonist, is effective for the treatment of generalized anxiety disorder in the general and elderly population. It is not known if it is effective for the treatment of anxiety in the PD population where there is a more heterogeneous phenomenology of anxiety. Buspirone also may diminish levodopa-induced dyskinesias. However, concerns have been raised about its potential to worsen motor function. A tolerability assessment is necessary prior to proceeding with a phase III efficacy trial.
STUDY SITES	University of Rochester
STUDY PERIOD	3 years
STUDY POPULATION AND NUMBER OF SUBJECTS	35 participants with idiopathic PD and clinically significant anxiety as defined by a score of ≥ 14 on the self-rated Parkinson Anxiety Scale.
STUDY DESIGN	This is a single-center, placebo-controlled, double-blind design with participants randomized with a 4:1 allocation ratio to flexible dosage buspirone (maximum dosage 30 mg twice daily) or placebo for 12 weeks.
MAIN INCLUSION/ EXCLUSION CRITERIA	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Diagnosis of idiopathic PD (UK PD Society Brain Bank Diagnostic Criteria) 2. Significant anxiety Parkinson Anxiety Scale (≥ 14) 3. Able to provide written informed consent 4. At least 18 years of age <p><i>Main Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Diagnosis of atypical or secondary parkinsonism 2. Concomitant treatment with an MAO inhibitor 3. Significant renal or hepatic impairment 4. Significant cognitive impairment (MOCA score < 23) 5. Depression with suicidal or homicidal ideation and concern for patient safety based on clinical determination by the investigator
DOSAGE: ROUTE AND FORM	Over-encapsulated buspirone tablets or matching placebo administered twice daily by mouth.
DOSAGE: JUSTIFICATION	Participants will initiate treatment with either buspirone 7.5 mg or placebo twice daily. Dosage adjustments will be made at the discretion of the investigators at two-week intervals following pre-specified parameters until the optimal dosage has been obtained. The optimal dosage is one that is associated with optimal anxiolytic benefit without intolerable

	adverse events. Investigators will be allowed to decrease or not escalate the dosage in the presence of adverse events. The selected dosage range of 7.5 mg twice daily up to 30 mg twice daily is consistent with current prescribing guidelines.
DURATION OF TREATMENT	12 weeks
PRIMARY OUTCOME MEASURE(S)	The primary outcome measure is the proportion of participants who fail to complete the 12-week study on study drug.
SECONDARY OUTCOME MEASURE(S)	<p>Safety and Tolerability:</p> <ul style="list-style-type: none"> (1) Number and type of adverse events (2) Number and type of serious adverse events (3) Mean change in MDS-UPDRS motor from baseline to 12 weeks (4) Mean change in calculated levodopa-equivalent dose from baseline to 12 weeks <p>Anxiety:</p> <ul style="list-style-type: none"> (1) Mean change in Hamilton Anxiety Rating Scale (HAM-A) from baseline to 12 weeks (2) Proportion of responders (>50% reduction from baseline or reduction to ≤7 on HAM-A) at 12 weeks (3) Proportion “much improved” or “very much improved” on Clinical Global Impressions-Improvement (CGI-I) and Patient Global Impressions-Improvement (PGI-I) at 12 weeks (4) Mean change in Hospital Anxiety and Depression Scale (HADS) from baseline to 12 weeks <p>Levodopa-Induced Dyskinesias:</p> <ul style="list-style-type: none"> (1) Mean change in Unified Dyskinesia Rating Scale (UDysRS) from baseline to 12 weeks <p>Parkinson Anxiety Scale:</p> <ul style="list-style-type: none"> (1) Correlation of change with CGI-I and PGI-I
SAFETY CONSIDERATIONS	Bupirone is FDA-approved for treatment of generalized anxiety disorder. According to the package insert, in premarketing clinical efficacy trials, 10% of 2200 participants discontinued treatment secondary to an adverse event and in pooled analysis of placebo-controlled clinical trials the most common adverse events included dizziness (12%), drowsiness (10%), nausea (8%), headache (6%), nervousness (5%), fatigue (4%), insomnia (3%), lightheadedness (3%), and dry mouth (3%).
SAMPLE SIZE CONSIDERATIONS	A sample size of 21 will provide 80% power to reject the null hypothesis of tolerability (observed intolerability rate of ≤20%) in favor of the alternative hypothesis of intolerability (observed intolerability rate of >20%) if the true intolerability rate is greater than 40%, using a binomial test and a one-tailed significance level of 10%. With the introduction of a placebo arm for blinding and relying on a 4:1 allocation ratio, the sample size increases to 27. The use of a futility design provides a higher probability of correctly failing to reject the null hypothesis of tolerability at the cost of a decreased chance of correctly rejecting the null hypothesis of tolerability. We are willing to accept a higher chance that we declare an intolerable drug tolerable as the expected intolerabilities (headache, nausea, drowsiness, dizziness, and worsening of PD motor function) are not expected to be severe, may be experienced by only a portion of subjects, and could be confirmed in larger studies.

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

Anxiety is common in patients with Parkinson's disease (PD) and negatively impacts quality of life. Despite this, anxiety is under-treated and there have been no clinical trials specifically examining the pharmacological treatment of anxiety in PD. Buspirone may be effective for the treatment of anxiety in PD. While it has the additional potential benefit of reducing levodopa-induced dyskinesias there have also been concerns that it may worsen PD motor function. The primary objective of this study is to determine the tolerability of buspirone for the treatment of anxiety in Parkinson's disease (PD).

Primary Objective:

To determine the tolerability of buspirone in PD as defined by the proportion of participants who complete the 12-week study on study drug.

Secondary Objectives:

- a. To explore the preliminary efficacy of buspirone in reducing symptoms of anxiety.
- b. To explore the preliminary efficacy of buspirone in reducing levodopa-induced dyskinesias.
- c. To pilot the Parkinson Anxiety Scale (PAS) for assessing change in symptoms of anxiety over time.

1.2. Background

The prevalence of anxiety disorders in Parkinson's disease (PD) is 25%-43%^{1,2,3,4,5} and anxiety as a symptom is reported by 56% of PD patients.⁶ Anxiety negatively impacts quality of life^{7,8} and may be a more important determinant than depression or apathy.⁹ Yet anxiety disorders are untreated in up to 50% of patients with PD.¹⁰ The current state of treatment may reflect the heterogeneous phenomenology of anxiety in PD,^{1,3-5} the lack to date of an appropriate scale to detect anxiety in PD,^{2,11,12} the absence of guidelines regarding the treatment of anxiety in PD or a combination of these factors.

The National Institute of Neurological Disorders and Stroke (NINDS) 2014 PD Research Recommendations highlighted the treatment of non-motor symptoms as an area of importance.¹³ There is emerging interest in the treatment of anxiety specifically, including a recent pilot study examining the feasibility of cognitive behavioral therapy¹⁴. However, there have been no clinical trials designed to evaluate the optimal pharmacological treatment of anxiety in PD. With no evidence upon which to base treatment decisions for this common and disabling condition in patients with PD, clinicians most commonly prescribe selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines.¹⁰ However, in the multicenter Study of Antidepressants in Parkinson's Disease (SAD-PD) trial both paroxetine (an SSRI) and venlafaxine XR (a serotonin norepinephrine reuptake inhibitor or SNRI) were more effective than placebo for the treatment of depressive symptoms but neither demonstrated any effect on a secondary anxiety measure.¹⁵ In fact, higher baseline anxiety levels predicted poorer response to treatment of depressive symptoms.¹⁶ A second randomized placebo-controlled trial comparing nortriptyline and paroxetine for the treatment of

depression in PD also demonstrated no effect for paroxetine on a secondary anxiety measure.¹⁷ Although neither of these studies was powered to detect changes in anxiety, they highlight the need to further evaluate treatment approaches for anxiety in PD. Benzodiazepine therapy is not ideal given a side effect profile including sedation, delirium, and balance impairment associated with an increased risk of falls. Benzodiazepines are also associated with high abuse potential and there is a possible increased risk of Alzheimer's dementia associated with long-term use.¹⁸

Buspirone is FDA approved for the treatment of generalized anxiety disorder. It may be possible to reposition buspirone for the treatment of anxiety in PD however it has not yet been evaluated in this population, where the pathophysiology of anxiety might be different, and it is necessary to ensure that it does not worsen PD motor function. Buspirone is primarily a 5HT1A receptor partial agonist with weak dopamine D2 and 5HT2 receptor activity.¹⁹ Buspirone is effective for the treatment of generalized anxiety disorder,^{20,21,22} is well-tolerated in the elderly population,^{23,24} and can be used as an adjunctive agent for the treatment of depression.²⁵ Through its action on the 5HT1A receptor, buspirone may have the added benefit of diminishing levodopa-induced dyskinesias^{26,27,28} an effect corroborated by early clinical studies.^{29,30} This is a particularly compelling indication given the relationship between anxiety, motor fluctuations,^{31,32,33,34} and freezing of gait.³⁵ However, this effect has not been conclusively demonstrated having only been shown in two very small trials and buspirone, through its effects on the dopaminergic system and weak affinity for D2 receptors, could potentially be associated with worsening of PD motor function. The potential motor impact of buspirone in PD makes a preliminary tolerability study the first logical step prior to embarking on a larger efficacy trial.

The underlying pathophysiology of anxiety in PD has not been fully elucidated and may differ from that of anxiety in the general population. Anxiety symptoms in PD can respond to treatment with dopamine agonists^{36,37} and, among fluctuators, anxiety may improve acutely with levodopa infusions;³⁸ however, in general, anxiety does not respond well to dopaminergic treatment³⁹ supporting the notion that dopamine dysregulation is not the sole pathophysiologic mechanism. Serotonergic dysfunction contributes to the pathophysiology of anxiety in the general population⁴⁰ and 5HT1A receptors have been specifically implicated.⁴¹ 5HT1A receptors modify serotonergic, glutaminergic, and dopaminergic transmission and in PD, 5HT1A receptor levels are altered.⁴² In rats with anxiety-like behavior induced by 6-hydroxydopamine lesions of the medial forebrain bundle, injection of a 5-HT1A receptor agonist, 8-OD-DPAT, into the prelimbic region or medial subdivision of the central nucleus of the amygdala has an anxiolytic effect.^{43,44} Thus, buspirone, which is primarily a 5HT1A receptor partial agonist, is a promising therapeutic for anxiety in PD.

The phenomenology of anxiety in PD is heterogeneous. Recent studies report variable prevalence rates for anxiety subtypes in PD: generalized anxiety disorder 3-20.6%, agoraphobia without panic 1.6-15.5%, panic disorder 3.9-30%, social phobia 7.9-13%, obsessive compulsive disorder 0.8-5.5%, and anxiety disorder not otherwise specified 11.4-25%.^{1,3-5} Commonly used anxiety scales, including the Beck Anxiety Inventory, Hamilton Anxiety Rating Scale, and Hospital Anxiety and Depression Scale were developed for use in the general population and do not have ideal psychometric properties for use in PD.^{2,11,45} A new scale, the Parkinson Anxiety Scale, was developed specifically for use in the PD population and has thus far demonstrated

validity and reliability^{46,47} but its sensitivity to change has not yet been demonstrated. This clinical trial will pilot the use of the Parkinson Anxiety Scale for detecting change over time and determine the feasibility of using it in larger phase III trials.

1.3 Supporting Data

Pharmacokinetics: Buspirone is administered two to three times daily. Buspirone is rapidly absorbed and metabolized via CYP3A4 to several metabolites, including 1-pyrimidinylpiperazine (1-pp), which is an active metabolite. The half-life is approximately 2-3 hours and time to peak concentration is 40-90 minutes. It is excreted in urine (29-63%) and feces (18-38%). There are no significant differences in AUC and C max between elderly and younger patients or between male and female subjects (label).

General Population: Buspirone is FDA-approved for treatment of generalized anxiety disorder. In premarketing clinical efficacy trials, 10% of 2200 participants discontinued treatment secondary to an adverse event. In pooled analysis of placebo-controlled clinical trials of buspirone the most common adverse events included dizziness (12%), drowsiness (10%), nausea (8%), headache (6%), nervousness (5%), fatigue (4%), insomnia (3%), lightheadedness (3%), and dry mouth (3%). Hypertensive crisis has been reported with concomitant MAO inhibitor use. Possible serotonin syndrome has been reported with concomitant SSRI use. Complete package insert information for buspirone can be found at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-190_BuSpar_Prntlbl.pdf.⁴⁸

Parkinson's Disease Population: There have been four small human studies of buspirone in PD. None of the trials was designed to evaluate the efficacy of buspirone for the treatment of anxiety and none of the trials selected participants for the presence of anxiety at baseline. In the two small trials that found no effect of buspirone on anxiety, baseline anxiety levels were low, suggesting a possible floor effect.^{29,49} Three of these studies suggest that, at dosages up to 60 mg per day, buspirone does not worsen PD motor function,^{29,49,50} however one study demonstrated worsening of PD motor function at lower dosages.³⁰

Table 1: Studies of buspirone in Parkinson's disease.

Study	N	Design	Anxiety	Dyskinesias	Parkinsonism
Ludwig ⁴⁹	16	RCT; targeting PD	No change at ≤60 mg/day	No change at ≤60 mg/day	Worsened at >60 mg/day
Hammerstad ⁵⁰	11	Open-label; targeting PD	Not reported	Not reported	Worsened at >60 mg/day
Bonifati ²⁹	10	RCT; targeting dyskinesias	No change	Improved	No change
Kleedorfer ³⁰	5	Open-label; targeting dyskinesias	"heightened degree of relaxation and tranquility"	Improved	Worsened at ≤60 mg/day

Buspirone is FDA-approved for treatment of generalized anxiety disorder in the general population. Given the heterogeneous phenomenology of anxiety in PD, this study will not be limited to those with generalized anxiety disorder. As there is no intention to use the results of the proposed study to support a new indication, change

in labeling, or change in advertisement for buspirone, the proposed route of administration and dosage are consistent with current prescribing guidelines, and any special safety concerns relate only to potential worsening of PD motor function it is our determination that the proposed study is exempt from the investigational new drug requirements.

2. STUDY DESIGN

2.1. Overview

This is a single-center, placebo-controlled, double-blind, futility study with participants with PD and anxiety randomized in a 4:1 allocation to flexible dosage buspirone or placebo for 12 weeks. The initial dose will be 7.5 mg twice daily and investigators will increase the dosage as necessary and tolerated up to 30 mg twice daily to achieve the optimal dosage (the dosage with optimal balance of anxiolytic effect and adverse events). Investigators will be encouraged to increase the dosage at two-week intervals until Hamilton Anxiety Scale (HAM-A) is ≤ 7 or there has been a 50% reduction in baseline score. The investigator will be allowed to not escalate or decrease the dosage if the participant has significant adverse events. Adverse events, severity of anxiety, presence of dyskinesias, and PD motor function will be assessed at baseline, week 2, 4, 8, and 12. There will be interim telephone visits to assess efficacy and tolerability at week 6 and 10. The primary outcome is the proportion of participants who fail to complete the 12-week study on study drug (any dosage). Secondary analysis of efficacy will focus on the change in outcome variables from baseline to 12 weeks.

2.2. Rationale for Study Design

The primary objective of this study is to determine the tolerability of buspirone in PD. The primary outcome is the proportion of participants who fail to complete the 12-week study on study drug. We hypothesize that $> 20\%$ of participants will fail to complete the study on study drug. As the primary tolerability concern with buspirone that is specific to the PD population is worsening of motor function, we considered selecting mean MDS-UPDRS motor scale change from baseline to 12 weeks as the primary outcome for tolerability. This approach was rejected as it would not capture alternative reasons for intolerability (such as nausea, headache, or dizziness). The 12-week duration should provide adequate time for response to treatment and to assess any effect on PD motor function.

From the standpoint of sample size calculations and statistical analysis this is a single-arm futility design; a placebo arm is introduced to allow for blinding and calibration. The use of a futility design over a traditional design allows for higher sensitivity at the cost of lower specificity.⁵¹ In other words, the futility design increases the probability of declaring a truly tolerable drug tolerable (correctly failing to reject the null hypothesis of tolerability) at the cost of a decreased probability of declaring a truly intolerable drug intolerable (correctly rejecting the null hypothesis of tolerability). Given the importance of moving a therapeutic for anxiety through and as the expected intolerabilities (headache, nausea, drowsiness, dizziness, and worsening of PD motor function) are either not expected to be serious or expected to be reversible, and could be confirmed in larger studies, this is a favorable scenario.

The secondary exploratory objectives examining the efficacy of buspirone in reducing symptoms of anxiety and in reducing levodopa-induced dyskinesias were included to provide the opportunity to detect a signal of efficacy regarding potential therapeutic uses of buspirone in PD.

This clinical trial will also pilot the use of the recently developed and validated Parkinson Anxiety Scale, which adequately captures the full phenomenological spectrum of anxiety in PD, for detecting change over time and determine the feasibility of using it in larger phase III trials. We selected a cut-off of ≥ 14 on the Parkinson Anxiety Scale as necessary for study eligibility, consistent with the data from the initial validation study.⁴⁶ We considered the use of a more traditional scale, such as the Hamilton Anxiety Scale or Hospital Anxiety and Depression Scale for use in the inclusion criteria, however concluded that these scales would not capture all of the subtypes of anxiety that are seen in PD and would result in the exclusion of appropriate participants.

2.3. Rationale for Dosage

A flexible dosage design was selected to reflect clinical practice, render more generalizable results, and remain consistent with general prescribing guidelines. As such, this study assesses the tolerability of buspirone rather than the tolerability of a specific dosage of buspirone. To minimize the risk for investigator bias influencing dosage adjustments we will employ specific parameters for dosage adjustment. Participants will receive 7.5 mg of buspirone or placebo twice daily for the first two weeks. Increases can be made at two-week intervals if a dosage is without significant adverse events and optimal anxiolytic effect (defined as Hamilton Anxiety Scale score $<50\%$ of baseline score or ≤ 7) has not been attained. These are traditional parameters used to define treatment efficacy in studies of anxiolytic medications. Pre-specified dosage levels of 7.5 mg twice daily, 10 mg twice daily, 15 mg twice daily (with 3 preceding days of 12.5 mg twice daily), 20 mg twice daily (with 3 preceding days of 17.5 mg twice daily), 25 mg twice daily (with 3 preceding days of 22.5 mg twice daily), and 30 mg twice daily (with 3 preceding days of 27.5 mg twice daily) will be imposed to minimize dosage variation and maintain consistency with prescribing guidelines. This is detailed in section 5.1.2. We anticipate that future phase III efficacy trials would employ a similar design.

2.4 Rationale for Placebo Arm

The introduction of a placebo arm enables the blinding of participants and investigators to treatment. The introduction of some uncertainty regarding treatment assignment for both the participants and investigators will allow for more rigorous assessment of the tolerability of the study drug by reducing bias. The use of a placebo arm will also allow for calibration, to verify assumptions about the background rate of intolerability. The assumed intolerability rate of placebo is zero and the incorporation of a small placebo group allows for verification of this assumption. The study will not be powered for direct between group comparisons. A similar approach has been used in prior PD research studies; in these studies, a placebo group was introduced to verify historical data regarding the anticipated progression of PD (as measured by the Unified Parkinson's Disease Rating Scale), which was used for sample size calculations.^{52,53}

In both cases, the rate of progression in the placebo group did not align with historical data and the researchers were able to perform additional analyses based on an updated rate of progression.

We recognize the potential for anxiety to not improve or worsen, particularly among those participants in the placebo arm, and that this may have a negative effect on their quality of life. However, we believe that the benefits of including a placebo arm for blinding and to allow for calibration of baseline assumptions regarding intolerability outweigh the potential risks. We will institute measures to ensure the safety of all participants. Of note, participants will not be asked to discontinue any pre-existing anxiolytics or antidepressants (with the exception of MAO inhibitors which pose a potential safety concern) or discontinue psychotherapy to participate in the study. Participants will only be asked not to increase the dosage of pre-existing anxiolytics or antidepressants, start new anxiolytics or antidepressants, or initiate psychotherapy for the duration of the study. Investigators will exclude from participation any patients where there is a concern for patient safety. If a participant's anxiety symptoms worsen significantly during the course of the study or if he/she develops suicidal ideation, which is deemed severe enough to reflect a significant suicidal risk, we will terminate the participant from the study and we will immediately refer the patient to a mental health provider for treatment. The investigator will determine the most appropriate referral, which may be referral to an outpatient mental health provider or referral to the Comprehensive Psychiatric Emergency Program. Participants and their caregivers will be encouraged to contact the investigators at any time if there is concern about worsening anxiety or adverse experiences.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

- a) **Number of Subjects:** 300. This number reflects the use of identified data during the screening process to identify potential participants. The total anticipated number of enrolled participants is 35, which includes screen failures.
- b) **Gender and Age of Subjects:** There will be no gender based enrollment restrictions. Participants will need to be at least 18 years of age. Based on the known demographics of PD, we anticipate that approximately 55-60% of the participants will be male and that the majority of participants will be over 50.
- c) **Racial and Ethnic Origin:** There will be no enrollment restrictions based upon race or ethnic origin. Based on the known demographics of PD and our patient population, we anticipate that the majority of the participants will be Caucasian.
- d) **Vulnerable Subjects:** PD is a disease that increases in prevalence with age and as such we expect a number of participants to be elderly. Participants will be able to withdraw from the study at any time.

3.2. Inclusion and Exclusion Criteria

- a) **Inclusion Criteria:**
 - Diagnosis of idiopathic PD by UK Parkinson's Disease Society Brain Bank

Clinical Diagnostic Criteria

- Significant anxiety as determined by the self-rated Parkinson Anxiety Scale (score ≥ 14)
- Able to provide written informed consent
- At least 18 years of age

b) **Exclusion Criteria:**

- Diagnosis of atypical or secondary parkinsonism
- Concomitant treatment with an MAO inhibitor within the 14 days prior to screening visit
- Significant renal or hepatic impairment
- Significant cognitive impairment defined as MOCA score < 23
- On-going depression with suicidal or homicidal ideation and concern for patient safety based on clinical determination by the investigator
- Allergy or intolerance to study drug, matching placebo, or their formulations
- History of prior exposure to study drug
- Lactating or pregnant woman
- Concomitant treatment with a disallowed medication (detailed in section 6.2)
- Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements
- Concomitant treatment with an anxiolytic or antidepressant will be allowed however potential participants who had dosage changes in the 30 days prior to the screening visit will be excluded
- Use of an investigational drug within 30 days prior to screening visit
- Any medical or psychiatric comorbidity that, in the opinion of the investigator, would compromise study participation
- Dysphagia defined as a score of ≥ 2 on MDS-UPDRS Item 2.3 *Chewing and Swallowing*

During the Study:

- The addition of new anti-parkinsonian medications or increase in dosage of existing anti-parkinsonian medications will be prohibited for the duration of the trial.
- The addition of a new anxiolytic or antidepressant or increase in dosage of an existing anxiolytic or antidepressant will be prohibited for the duration of the trial.
- Participants will not be allowed to initiate or discontinue psychotherapy following enrollment. If they are participating in it at the time of enrollment, it should be continued for the duration of the study.

3.3. **Discussion of Study Population**

Participants will not be excluded on the basis of Hoehn and Yahr stage, pharmacologic treatment of Parkinson disease (with the exception of MAO inhibitors), or history of deep brain stimulation or stereotactic surgery. Participants will not be excluded due to the presence of comorbid depression or other comorbid psychiatric disorders, unless, in the opinion of the investigator, their study participation would be compromised. While the exclusion of participants with depression would eliminate a potential confounding factor it would also limit recruitment as anxiety and depression are

common comorbid diagnoses. Concomitant treatment with other anti-anxiety medications and/or antidepressants (with the exception of MAO inhibitors) will be allowed assuming stable dosages for 30 days prior to study entry. Our criteria will allow for the most representative patient sample and improve the generalizability of the study results.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method Of Participant Identification And Recruitment

We anticipate recruiting a total of 35 eligible participants at one site over a 24 month period. We will use multiple methods to identify potential participants.

(1) The primary investigator (Dr. Richard) and co-primary investigator (Dr. Schneider) will use i2b2 (Informatics for Integrating Biology and the Bedside), a software for running clinical database queries, to query our electronic medical record (EMR) and identify patients with an ICD-9 diagnosis of 332.0 (parkinsonism) or ICD-10 diagnosis G20 (Parkinson's disease) *and* a diagnosis of an anxiety disorder who are seen by a URMC or URMC affiliated provider. For each identified patient, the primary care provider or neurologist in charge of their care will be contacted and permission to contact the identified patient will be requested.

(2) We will design and distribute informational flyers to local patient advocacy groups and affiliated and non-affiliated neurology, primary care, and psychiatry offices. Area providers will be sent informational letters and reference pocket cards. We will conduct informational presentations for area providers and promote the study at regional symposiums and other events. Additional efforts may be made to promote the study in the local media.

(3) The trial will be posted on appropriate clinical trial registries including Fox Trial Finder, clinicaltrials.gov and Research Match.

(4) We will reach out to local patient advocacy groups to increase awareness and engage potential participants.

A screening log will be maintained. The screening log will document how potential participants learned about the trial, where they were referred from, reasons for ineligibility, and reasons for nonparticipation of eligible participants. This information will be reviewed monthly to identify any problems and develop strategies to enhance recruitment.

4.2. Process of Consent

Interested participants will be contacted by a study coordinator to assess their willingness to participate. Potential participants will be scheduled for a screening visit at which time eligibility will be assessed and written informed consent will be obtained. Written informed consent will be obtained using an IRB approved consent form. The study coordinator obtaining consent will be trained in human subject's protection according to University of Rochester IRB procedures.

Capacity to consent to the study will be determined by the study coordinator during the consent process. As delineated in the consent form, capacity will be determined based on the potential participant's understanding of why the study is being done, what will happen during the study, possible risks and benefits, alternatives to participation in the study, how personal information will be protected, and what to do if there is a problem or question.

Investigators and study team members will ensure that prospective participants have sufficient knowledge and understanding of the details of the study to allow them to make an informed decision whether or not to participate. Prospective participants will be provided with an opportunity to ask questions. Every effort will be made to provide potential participants with a copy of the consent form prior to the screening visit. Prospective participants will also be asked to consent to future contact to update their contact information and inform them about future studies. Participants may decline to consent to this aspect and still participate in the study.

Documentation of consent will be stored in a secure filing cabinet in a division office and consent acknowledgment will be electronically recorded in REDCap. A copy of the consent form will be provided to the participant upon obtainment of consent. If an individual is unable or unwilling to consent, the individual will be excluded from the study but their routine clinical care will not be affected.

5. METHODS AND STUDY PROCEDURES

SCHEDULE OF ACTIVITIES

	Screening	Baseline (within 0- 14 days)	Entry	2 Week (+/- 3 days)	4 Week (+/- 3 days)	6 Week Phone (+/- 3 days)	8 Week (+/- 3 days)	10 Week Phone (+/- 3 days)	12 Week (+/- 3 days)	Adverse Event Visit	Premature Termination Visit
Informed Consent	X										
Demographics		X									
Neurological Exam	X									X*	
General Medical Exam	X									X	
Past Medical History	X										
Health Update		X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X
Labs	X*									X*	X*
Urine Pregnancy Test	X^										
UK Brain Bank Criteria	X										
NINDS CDE PD Med History		X									
MOCA	X										
Adverse Events				X	X	X	X	X	X	X	X
UKU				X	X	X	X	X	X	X	X
MDS-UPDRS		X									
MDS-UPDRS motor				X	X		X		X	X	X
MDS-UPDRS Item 2.3	X										
Vital Signs	X	X		X	X		X		X	X	X
Unified Dyskinesia Rating Scale		X		X	X		X		X		X
Parkinson Anxiety Scale	X	X			X		X		X		X
CGI-Improvement				X	X		X		X		X
PGI-Improvement				X	X		X		X		X
Hamilton Anxiety Rating Scale		X		X	X	X	X	X	X		X
Hospital Anxiety and Depression Scale		X		X	X		X		X		X
Dosage Assessment				X	X	X	X	X	X	X	
Adherence Assessment				X	X		X		X	X	X

*If required as determined by investigator

^For women of child-bearing potential

5.1. Treatment Dosage and Administration

5.1.1. Overview

Participants will initially receive buspirone or placebo 7.5 mg twice daily administered orally. Investigators will evaluate the participants at two-week intervals and make dosage adjustments as necessary and tolerated up to a maximum of 30 mg twice daily to achieve an optimal dosage that balances efficacy with tolerability. Treatment duration is 12 weeks.

5.1.2. Dosage Adjustments

Study investigators and study team members, with the exception of the study team member managing drug dispensation, will be blinded to treatment assignment. To minimize the risk for investigator bias influencing dosage adjustments we will employ specific parameters for dosage adjustment. If a dosage is tolerable, the investigator will increase the dosage if optimal anxiolytic effect (defined as Hamilton Anxiety Scale score <50% of baseline score or ≤ 7) has not been attained. Participants will not be blinded to dosage adjustments but will remain blinded to treatment assignment. Pre-specified dosage levels of 7.5 mg twice daily, 10 mg twice daily, 15 mg twice daily (with 3 preceding days of 12.5 mg twice daily), 20 mg twice daily (with 3 preceding days of 17.5 mg twice daily), 25 mg twice daily (with 3 preceding days of 22.5 mg twice daily), and 30 mg twice daily (with 3 preceding days of 27.5 mg twice daily) will be imposed as detailed in the following table. The investigator will be allowed to decrease the dosage or not escalate the dosage if there are adverse events.

REGIMEN DESCRIPTION				
Agent	Precautions	Dose	Route	Schedule
Buspirone	Take consistently either with or without food.	7.5 mg twice daily	Oral	Week 1-2
Placebo	Take consistently either with or without food.	7.5 mg twice daily	Oral	Week 1-2

DOSAGE ADJUSTMENTS					
Agent	Precautions	Prior Dose	New Dose	Route	Schedule
Buspirone	Take consistently either with or without food.	7.5 mg twice daily	10 mg twice daily	Oral	Week 1-2
		10 mg twice daily	15 mg twice daily	Oral	Day 1-3: 12.5 mg twice daily Day 4-14: 15 mg twice daily
		15 mg twice daily	20 mg twice daily	Oral	Day 1-3: 17.5 mg twice daily Day 4-14: 20 mg twice daily
		20 mg twice daily	25 mg twice daily	Oral	Day 1-3: 22.5 mg twice daily Day 4-14: 25 mg twice daily
		25 mg twice daily	30 mg twice daily	Oral	Day 1-3: 27.5 mg twice daily Day 4-14: 30 mg twice daily
Placebo	Take consistently either with or without food. Avoid grapefruit.	7.5 mg twice daily	10 mg twice daily	Oral	Week 1-2
		10 mg twice daily	15 mg twice daily	Oral	Day 1-3: 12.5 mg twice daily Day 4-14: 15 mg twice daily
		15 mg twice daily	20 mg twice daily	Oral	Day 1-3: 17.5 mg twice daily Day 4-14: 20 mg twice daily
		20 mg twice daily	25 mg twice daily	Oral	Day 1-3: 22.5 mg twice daily Day 4-14: 25 mg twice daily
		25 mg twice daily	30 mg twice daily	Oral	Day 1-3: 27.5 mg twice daily Day 4-14: 30 mg twice daily

5.1.3. *Study Drug/Placebo*

The absorption of buspirone may be decreased by taking it with food and participants will be instructed to take the study drug either consistently with food or consistently without food.

5.2 **Timing of Visits**

5.2.1 *Screening Visit*

The screening visit will occur within 0-14 days of the baseline visit. Prior to completing any study activities, written informed consent will be obtained. Participants will be assigned a confidential participant identification number. The study coordinator and investigator will assess potential participants for study eligibility. All of the inclusion criteria and none of the exclusion criteria must be met. If a participant is being withdrawn from a medication to qualify for the study, the consent form must be signed prior to the initiation of the withdrawal.

Evaluations:

- Informed Consent
- Neurological Examination
- General Medical Examination
- Past Medical History
- Concomitant Medications
- Labs (if required as determined by investigator)
- Verification of Parkinson's disease diagnosis (UK Brain Bank Criteria)
- MOCA
- Vital Signs
- Parkinson Anxiety Scale
- MDS-UPDRS Item 2.3
- Urine pregnancy test for women of child-bearing potential

5.2.2 *Baseline Visit*

The baseline visit will occur within 0-14 days of the screening visit. If laboratory studies are obtained at the screening visit, results must be reviewed prior to the baseline visit. Participants will be randomized to one of two treatment groups. Participants will be randomized to group according to a computer-generated randomization scheme. Based on this randomization, study personnel will be informed which drug bottles to supply the participant. The first dose of study drug or placebo should be taken the following morning.

Evaluations:

- Demographics
- Health Update
- Concomitant Medications
- NINDS Common Data Elements PD Medical History
- MDS-UPDRS
- Vital Signs
- Unified Dyskinesia Rating Scale
- Parkinson Anxiety Scale
- Hamilton Anxiety Scale

- Hospital Anxiety and Depression Scale

5.2.3 *Visit 01 (Day 14 +/- 3 days), Visit 02 (Day 28 +/- 3 days), Visit 03 (Day 56 +/- 3 days), and Visit 04 (Day 84 +/- 3 days)*

Visit 01, Visit 02, Visit 03, and Visit 04 should occur within 3 days of the target date. Previously dispensed study drug bottles will be collected and new study drug bottles dispensed at each visit.

Evaluations:

- Health Update
- Concomitant Medications
- Adverse Events
- UKU Side Effect Rating Scale
- MDS-UPDRS Motor Component
- Vital Signs
- Unified Dyskinesia Rating Scale
- Parkinson Anxiety Scale (except at Visit 01)
- CGI-Improvement
- PGI-Improvement
- Hamilton Anxiety Rating Scale
- Hospital Anxiety and Depression Scale
- Dosage Assessment
- Adherence Assessment

5.2.4 *Telephone Visit T01 (Day 42 +/- 3 days) and Telephone Visit T02 (Day 70 +/- 3 days)*

Visit 03 and Visit 05 will occur via telephone and should occur within 3 days of the target date. If scheduling requires two separate phone calls for each telephone visit, one with the study coordinator and one with the investigator, this will be allowed so long as they occur within the specified target period. Participants will be required to return previously dispensed study drug bottles and pick up new study drug bottles following each telephone visit within the same designated timeframe (Day 42 +/- 3 days or Day 70 +/- 3 days).

Evaluations:

- Health Update
- Concomitant Medications
- Adverse Events
- UKU Side Effect Rating Scale
- Hamilton Anxiety Rating Scale
- Dosage Assessment

5.2.5 *Unscheduled Visits*

An unscheduled visit may be performed at any time during the study at the participant's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded.

Evaluations:

- Neurological Exam (if deemed necessary by investigator)

- General Medical Exam
- Health Update
- Concomitant Medications
- Laboratory Studies (if deemed necessary by investigator)
- Adverse Events
- UKU Side Effect Rating Scale
- MDS-UPDRS Motor Component
- Vital Signs
- Dosage Assessment
- Adherence Assessment

5.2.6 *Premature Termination Visit*

Participants may withdraw from the study at any time. In the event of premature study withdrawal (either participant or investigator initiated), a premature termination visit should occur. Reasons for premature withdrawal will be documented. At the time of the visit, participants will be instructed to discontinue their study drug, if they have not done so already. The study drug may be discontinued without a taper.

Evaluations:

- Health Update
- Concomitant Medications
- Laboratory Studies (if deemed necessary by investigator)
- Adverse Events
- UKU Side Effect Rating Scale
- MDS-UPDRS Motor Component
- Vital Signs
- Unified Dyskinesia Rating Scale
- Parkinson Anxiety Scale
- CGI-Improvement
- PGI-Improvement
- Hamilton Anxiety Rating Scale
- Hospital Anxiety and Depression Scale
- Dosage Assessment
- Adherence Assessment

5.3 **Efficacy Assessments**

5.3.1 *Parkinson Anxiety Scale (PAS)*

The heterogeneous appearance of anxiety in Parkinson's disease presents difficulties in diagnosing and monitoring anxiety. The PAS was developed specifically for use in the PD population and has demonstrated validity.^{46,47} Commonly used anxiety scales, such as the Hamilton Anxiety Rating Scale and Hospital Anxiety and Depression Scale, do not have ideal psychometric properties for use in PD.^{2,11,45} The self-rated PAS was selected as a screening tool because it was felt to best capture the full phenomenological spectrum of anxiety in PD. A score of ≥ 14 will be required in order to be eligible to participate in this study. A cut-off score of ≥ 14 was selected in accordance with the original study of this scale by Leentjens et al.⁴⁶ The self-rated PAS will be completed at screening, baseline, and each subsequent in-person study visit. It

was not selected as an outcome measure for the secondary anxiety endpoint because its ability to detect change over time has not yet been validated. This trial will pilot the use of the PAS for detecting change over time by correlating change with the Clinical Global Impression-Improvement and Patient Global Impression-Improvement scales. Participants will be trained to complete this scale by the study coordinator at the screening visit and the study coordinator will review the scale for completion.

5.3.2 Clinical Global Impression-Improvement (CGI-I)

The widely-used CGI-I was selected for the ability to obtain clinician impressions of improvement in overall functioning. The CGI-I will be administered by an investigator at the 2 week, 4 week, 8 week, and 12 week visits. Secondary outcome measures will include the proportion “much improved” or “very much improved” on CGI-I at 12 weeks.

5.3.3 Patient Global Impression-Improvement (PGI-I)

The PGI-I was selected for the ability to obtain patient impressions of improvement in overall functioning. The PGI-I will be completed at the 2 week, 4 week, 8 week, and 12 week visits. Secondary outcome measures will include the proportion “much improved” or “very much improved” on PGI-I at 12 weeks. Participants will be trained to complete this scale by the study coordinator at the screening visit and the study coordinator will review the scale for completion.

5.3.4 Hamilton Anxiety Rating Scale (HAM-A)

Despite concerns about construct validity and predictive validity, the 14-item HAM-A was selected because it is a widely used clinician-rated measure and has demonstrated sensitivity to change. The HAM-A will be administered by an investigator at baseline and each subsequent telephone and in-person study visit. There is precedent for administering the HAM-A by telephone and it was done in a study of telephone-based cognitive behavioral therapy for depression in PD.⁵⁴ Secondary outcome measures will include the mean change in HAM-A from baseline to 12 weeks and proportion of responders (>50% reduction from baseline or reduction to ≤ 7 in HAM-A).

5.3.5 Hospital Anxiety and Depression Scale (HADS)

Although there are some concerns regarding validity in the PD population, the HADS was selected because it is a self-rated measure with anxiety and depression subscales and multiple studies have shown acceptable psychometric properties in the PD population.^{55,56} This 14-item self-rated scale does not include somatic symptom questions, which could potentially overlap with PD symptoms. It will be completed at baseline and each subsequent in-person study visit. Secondary outcome measures will include mean change in HADS from baseline to 12 weeks. Participants will be trained to complete this scale by the study coordinator at the screening visit and the study coordinator will review the scale for completion.

5.3.6 Unified Dyskinesia Rating Scale (UDysRS)

The UDysRS was selected as it is a comprehensive, PD-specific tool that incorporates both historical and objective data. It has been shown to be superior to multiple other dyskinesia rating scales.⁵⁷ It will be administered by an investigator at baseline and each subsequent in-person study visit. Investigators will have completed the certification course to ensure adequate inter-rater reliability. In order to minimize

differences in scores attributable to the timing of Parkinson's disease medications, investigators will always attempt to administer the UDysRS during the ON state (generally about 1 hour after levodopa administration). Secondary outcome measures will include mean change in UDysRS from baseline to 12 weeks.

5.4 Safety Assessments

5.4.1 Medical Assessment

A general medical examination will be performed by an investigator at the screening visit. The need for liver function tests, BUN and creatinine to determine the presence of significant renal or liver impairment at screening or to evaluate an adverse event will be left to the discretion of the investigator. The investigator may decide such testing is indicated based on the reporting of a history of certain medical conditions or surgeries, the presence of symptoms that may indicate renal or liver impairment, or examination findings that are concerning for renal or liver impairment. A serum pregnancy test will be obtained at screening for all women of child-bearing potential. All blood and urine tests will be obtained on-site and sent to URM Labs for processing. A complete list of concomitant medications will be obtained at screening, baseline, and all subsequent telephone and in-person study visits by a study coordinator. A medical health update will be obtained by a study coordinator at baseline and all subsequent telephone and in-person study visits.

5.4.2 Confirmation of Diagnosis of Parkinson's Disease

The diagnosis of PD will be confirmed by an investigator following a complete neurological examination using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria at the screening visit. The NINDS Common Data Elements Parkinson's Disease Medical History form will be completed by an investigator to better characterize the participants Parkinson's disease at the baseline visit.

5.4.3 Montreal Cognitive Assessment (MOCA)

The MOCA is a reliable and valid instrument in Parkinson's disease⁵⁸ and is felt to be a better screening instrument in Parkinson's disease than the commonly used Mini-Mental State Exam (MMSE).⁵⁹ It will be administered by an investigator at the screening visit and significant cognitive impairment will be defined as a score < 23.

5.4.5 Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS has been previously validated,⁶⁰ is increasingly being used in Parkinson's disease clinical trials, and is preferable over the UPDRS due to its ability to more finely discriminate degree of impairment. The minimally clinically important difference for improvement (-3.25) and worsening (4.63) on the MDS-UPDRS Motor was recently established.⁶¹ Investigators will be required to provide verification of their completion of the MDS-UPDRS certification course to ensure adequate inter-rater reliability. In order to minimize differences in scores attributable to the timing of Parkinson's disease medications, for participants who are on levodopa investigators will always attempt to administer the MDS-UPDRS Motor during the ON state (generally about 1 hour after levodopa administration). MDS-UPDRS Item 2.3 *Chewing and Swallowing* will be completed by the participant at the screening visit to screen for dysphagia that may result in difficulty swallowing the study drug and would preclude safe participation in the study. A score of ≥ 2 ("I need to have my pills cut or

my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week”) will exclude the participant from the study. The full MDS-UPDRS, including Part 1: Non-Motor Aspects of Experiences of Daily Living, Part II: Motor Aspects of Experiences of Daily Living, Part III: Motor Examination, and Part IV: Motor Complications, will be administered by an investigator at the baseline visit and the participant will complete those aspects of the MDS-UPDRS covered in the patient questionnaire (items 1.7-1.13 and 2.1-2.13). The MDS-UPDRS Motor will be administered by an investigator at each subsequent in-person study visit.

5.4.6 *Vital Signs*

Pulse, temperature, weight, and blood pressure will be obtained at every in-person study visit.

5.4.7 *Adverse Events*

Soliciting of adverse events will be non-specific and participants will be asked the question, “Do you feel different in any way since starting the new treatment?” All adverse events occurring after the baseline visit will be reported. All subsequent adverse events will be reported regardless of relationship to drug.

At each in-person and telephone visit, a study coordinator will solicit adverse events. Adverse events not previously documented in the study will be recorded in the adverse event section in the case report form. The nature of each individual event, date and time of onset, duration, severity, and relationship to treatment will be established by the investigator. Likely alternative etiologies should be recorded for events considered unrelated to study drug. Details of change to the dosing schedule, any corrective treatment, or prescription of a concomitant medication, must be recorded on the appropriate pages of the case report form. We will use the UKU Side Effects Rating Scale, developed by the Committee on Clinical Investigations (Udvalg for kliniske undersøgelser, UKU), which is a standing committee under the Scandinavian Society of Psychopharmacology.⁶² Items in the UKU are sub-grouped into psychic, neurological, autonomic, and other categories. The cardinal PD symptoms of tremor, rigidity, and hypokinesia are included.

Adverse events already documented in the CRF, at a previous visit, and designated as ‘continuing’ should be reviewed at each visit. If an adverse event is resolved, the documentation in the CRF must be completed to that effect. If an adverse event changes in frequency or severity during a study period, a NEW record of that event will be initiated. A record of all adverse events will be reviewed periodically by the study investigators. The documentation and classification of adverse events is further reviewed in section 9.

5.5 **Assessment of Participant Compliance**

In order to determine adherence, participants will be asked to complete an adherence questionnaire in conjunction with the study coordinator and will be instructed to bring previously dispensed study drug bottles to each in-person visit and following telephone visits for pill counts. Pill counts will be performed by the study coordinator and the results recorded on a standard data form to monitor participant adherence. At the end of the study, all returned study medication will be counted and compared to the data

form. Any discrepancies will be resolved and the data form will be updated as necessary.

5.6 Dosage Assessment

At each visit, the investigator will consider the need for dosage adjustment. If a dosage is tolerable, the investigator will increase the dosage if optimal anxiolytic effect (defined as Hamilton Anxiety Scale score <50% of baseline score or ≤ 7) has not been attained. This is further detailed in section 5.1.2.

5.7 Costs to the Participant

Neither the participant nor the participant's insurance will incur any costs as a result of participation in this study.

5.8 Payment for Participation

Participants will not be paid. Participants will be reimbursed at a rate of \$0.54/mile for travel by car. Participants will be reimbursed up to \$50 per study visit for travel expenses.

5.9 Return of Individual Research Results

Research results will not be provided to the participant. The exception will be results of laboratory studies, which may be obtained at the discretion of an investigator. Incidental findings that might have health consequences for the participant will be communicated to the participant and his/her primary care provider.

5.10 Pregnancy and Nursing

Female participants of childbearing potential will be advised to use adequate birth control as there is insufficient data regarding the effects of buspirone on the fetus. Adequate birth control methods include surgical sterilization, a partner who has had a vasectomy, oral contraceptives, condom plus spermicidal cream/jelly, cervical cap plus spermicidal cream/jelly, diaphragm plus spermicidal cream/jelly, intrauterine device (in place for at least 3 months) plus spermicidal cream/jelly, or contraceptive implant or injection. Abstinence is considered an acceptable contraceptive regimen.

If a participant becomes pregnant during the study, it is important that they notify a study team member immediately. In such an event, the study drug must be tapered immediately. The participant may continue in the study off of study drug. All attempts will be made to follow the participant until delivery.

6.0 CONCOMITANT AND DISALLOWED MEDICATIONS

6.1 Allowed Concomitant Medications

Enrolling participants may be on PD medications, with the exception of monoamine oxidase inhibitors. The dosage must be stable for 30 days prior to the baseline visit.

No new PD medications may be initiated for the duration of the study and no increases in the dosages of current PD medications will be allowed.

Enrolling participants may be on antidepressants (with the exception of monoamine oxidase inhibitors), antipsychotics, and/or anxiolytics. The dosage must be stable for 30 days prior to the baseline visit and for the duration of the study. The initiation of one of these medications will be prohibited for the duration of the study.

Strong CYP3A4 inhibitors (atazanavir, boceprevir, ceritinib, clarithromycin, cobicistat and cobicistat containing formulations, darunavir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ombitasvir-paritaprevir-ritonavir, ombitasvir-paritaprevir-ritonavir plus dasabuvir, posaconazole, ritonavir and ritonavir containing formulations, saquinavir, telaprevir, telithromycin, and voriconazole) will be allowed. Participants will be monitored for potential adverse events related to an increase in the serum study drug concentration.

Strong CYP3A4 Inducers (carbamazepine, enzalutamide, fosphenytoin, lumacaftor, mitotaine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and rifapentine) will be allowed.

Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) and interacting macrolide antibiotics (erythromycin, clarithromycin, and telithromycin) will be allowed. Participants will be monitored for potential adverse events related to an increase in the serum study drug concentration.

6.2 Disallowed Medications and Supplements

The following medications will not be allowed during the study:

- Selective and non-selective MAO inhibitors including those whose primary mechanism of action is not monoamine oxidase inhibition: phenelzine, rasagiline, selegiline, procarbazine, isocarboxazid, tedizolid, tranylcypromine, syrian rue, linezolid, methylene blue, moclobemide
- Initiation of any antidepressants, antipsychotics, or anxiolytics.
- Azelastine
- Conivaptan
- Dapoxetine
- Fusidic Acid
- Idelasib
- Orphenadrine
- Paraldehyde
- Thalidomide
- Grapefruit juice, ginkgo biloba, St. John's wort, and ginseng (which interfere with study drug metabolism).
- Initiation of any new PD medications and increases in the dosage of existing PD medications will be prohibited.
- Participants will also be prohibited from beginning any form of psychotherapy following study entry.

If treatment with a disallowed medication is required, the study drug should be discontinued and the participant should continue in the study off of the study drug. The study drug may be restarted after the disallowed medication is stopped.

7.0 PARTICIPANT WITHDRAWALS

Participants will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Participants may be withdrawn by the investigator/sponsor for:

- (1) Non-compliance with study drug or procedures
- (2) Receipt of disallowed medications that cannot be discontinued
- (3) An adverse event which in the investigator's judgment puts the participant at risk
- (4) Illness that prevents continued trial participation
- (5) Termination of study funding
- (6) Worsening of anxiety that in the investigator's judgment requires prompt treatment with an alternative therapy

In the event of a premature study withdrawal, a premature termination visit should occur. Evaluations are detailed in section 5.2.6. Participants withdrawn from the study will not be replaced.

8.0 STUDY DRUG ADMINISTRATION/ASSIGNMENT

8.1 Study Drug

It is the investigator's determination that this study drug is IND exempt.

- Buspirone is lawfully marketed in the United States and is FDA-approved for the treatment of generalized anxiety disorder in the general population.
- There is no intention to use the results of the proposed study to support a new indication or change in labeling for buspirone.
- There is no intention to use the results of the proposed study to support a change in advertisement for buspirone.
- The proposed route of administration (oral) and dosage (up to 30 mg twice daily) are consistent with current prescribing guidelines. There have been prior human studies of buspirone in the Parkinson disease population. One very small study³⁰ indicated that use of buspirone dosages consistent with current prescribing guidelines might be associated with worsening of PD motor function however three studies showed no worsening of PD motor function at the same dosages. The proposed study is designed to determine the tolerability of buspirone in this population. Adverse events will be closely monitored. Buspirone is generally well tolerated and there is no reason to believe that using the medication for the treatment of anxiety in the PD population would significantly increase the risks associated with use of the drug.
- The study will be conducted only after approval by my institutional IRB and participants will be required to provide informed consent.

The buspirone label is included in RSRB application section 50.1 and can be found at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-190_BuSpar_Prntlbl.pdf.

The Investigational Drug Service at the University of Rochester will manage the over-encapsulation, packaging, and distribution of the study drug and placebo in conjunction with an un-blinded study team member. 5 mg tablets of the study drug will be purchased in bulk from Teva Pharmaceutical. The study drug will be over-encapsulated and repackaged into labeled bottles. In order to account for the necessary titration step with dosage increases (as described in section 5.1.2) the Investigational Drug Service will dispense bottles containing 6 capsules (to cover the 3-day titration period) and 34 capsules (to cover the maintenance period). In the event of dosage escalation beyond 7.5 mg study drug/placebo, participants will be provided with two bottles, one to cover the titration period and one to cover the maintenance period, at each dispensation and carefully instructed as to which bottle to begin with. Double panel medication labels will be provided by the Investigational Drug Service and labeling will include the study number, dosage, route of administration, quantity, directions for use, storage conditions, and additional space for information to be completed by a study team member (dispensing date, participant number). The unblinded team member will remove the outer panel, which will specify whether the bottle contains study drug or placebo, to reveal the inner panel which will not include this specification.

The drug will be stored at the site in a locked storage area with controlled temperature (59° - 86° F).

At each in-person visit and following each telephone visit, participants will receive a 20 day supply of study drug, which will ensure that participants have an adequate supply of study drug until their next visit.

8.2 Dosage of Study Drug

The study drug will be administered orally. Participants will initially receive buspirone 7.5 mg or matching placebo twice daily. Investigators will evaluate the participants at two-week intervals and make dosage adjustments as necessary and tolerated up to a maximum of 30 mg twice daily to achieve an optimal dosage that balances efficacy with tolerability. The investigator will be allowed to decrease the dosage or not escalate the dosage if there are adverse events. The titration schedule and parameters for dosage adjustment are detailed in section 5.1.

In the event of study drug discontinuation due to treatment with a disallowed medication, the study drug may be re-started following discontinuation of the disallowed medication and the same titration schedule and parameters for dosage adjustment should be followed (as specified in section 5.1.2).

8.3 Participant Enrollment/Randomization

We will use computer-generated randomization with participants randomized in a 4:1 ratio to study drug or placebo. Randomization will be managed by the statistician.

8.4 Accountability of Investigational Supplies

The Investigational Drug Service and on-site personnel will share responsibility for control of the study drug. The Investigational Drug Service will be responsible for

dispensing labeled supplies of study drug to the study site. The study coordinator will be responsible for acknowledging the receipt of study drug within 48 hours. The study coordinator and Investigational Drug Service will maintain accurate records of all supplies dispensed/received. Prior to dispensation to the participant, an un-blinded study team member will remove the outer panel of the double panel label on the drug bottle(s) and place this on the Drug Dispensing/Return Log. The un-blinded study team member will be a study coordinator who will not have any role in data collection. All study drug supplies issued to, used by, and returned by each participant must be recorded on the Drug Dispensing/Return Log. Participants will return all unused study drug, including empty bottles. After reconciliation, all remaining study supplies may be destroyed as per institutional policy.

The Investigational Drug Service and study coordinators will communicate regularly regarding study drug supply.

8.5 Participant Withdrawal of Study Drug

Participants who discontinue study drug and do not withdraw their consent, will continue to be followed in the study.

8.6 Emergency Drug Disclosure

The study team will be provided with individually sealed envelopes for each participant containing the treatment assignment. All sealed envelopes will be returned to the statistician at the conclusion of the study and will be inspected to ensure that they have not been opened. A participant's envelope should be opened only in the event of a medical emergency. Treatment assignment may be revealed if the investigator feels that study drug discontinuation is insufficient and knowledge about treatment assignment and/or dosage is required to ensure the safety of the participant. If a drug disclosure is made, a record must be made by the investigator detailing the purpose, date, and personnel involved. The participant will be withdrawn from further exposure to study medication. In accordance with the intention-to-treat principle, these participants will be encouraged to remain in the study and every attempt will be made to continue to follow them and obtain data.

9 SAFETY AND REPORTABLE EVENTS

Bupirone is FDA-approved for the treatment of generalized anxiety disorder with a well-established side effect profile, with common adverse events (>5%) including dizziness, drowsiness, nausea, and headache. Package insert information for bupirone can be found at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-190_BuSpar_Prntlbl.pdf and is also included in RSRB application section 50.1. There is some data to suggest that bupirone may cause worsening of PD motor function and this will be monitored with the use of the MDS-UPDRS motor scale. Hypertensive crisis has been reported and concomitant MAOI use will be prohibited. There have been case reports of possible serotonin syndrome in patients receiving bupirone and fluoxetine,⁶³ sertraline,⁶⁴ citalopram,⁶⁵ and fluvoxamine.⁶⁶ However, bupirone is commonly co-prescribed with SSRIs and in a study examining bupropion versus bupirone for augmentation of citalopram for treatment of depression, 286 participants were randomized to the bupirone-citalopram arm and there were no reports of serotonin syndrome.²⁵ All

participants will be monitored closely. Safety and tolerability will be closely monitored by study investigators. If an intolerability or adverse event occurs, depending on the severity of the event, investigators will decide whether to decrease study drug dosage or to discontinue the study drug. Participants will be able to withdraw from the study at any time.

9.1 Adverse Event Definition

An adverse event is any symptom, sign, illness, or event which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

9.2 Serious Adverse Event

A serious adverse event is defined as any adverse medical event that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious adverse event

9.3 Recording Adverse Events

At each participant visit the site study staff will assess adverse events by recording all voluntary complaints of the participant and by assessment of clinical features. At each study visit, the participant should be questioned directly regarding the occurrence of any adverse events since his/her last visit. Soliciting of adverse events should be non-specific and participants should be asked the question, "Do you feel different in any way since starting the new treatment?"

All adverse events, whether observed by an investigator, elicited from or volunteered by the participant, should be documented on an Adverse Event CRF. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device. This should also include the investigator's opinion of the possible relationship between the adverse event and the study drug or participation in the study. Likely alternative etiologies should be recorded for events considered unrelated to study drug.

Adverse events already documented at a previous visit and designated as 'continuing' should be reviewed at each visit. The investigator is obliged to follow participants with

adverse events until the event has resolved, the condition is considered medically stable, or the participant is no longer available for follow up. Participants who discontinue the study drug due to adverse events will be treated and followed according to established acceptable medical practice. A follow up telephone call will be made to all participants who have unresolved adverse events 30 days from the date of the final study visit. If an adverse event is resolved, the documentation in the CRF must be completed to that effect. If an adverse event changes in frequency or severity during a study period, a NEW record of that event will be initiated. A record of all adverse events will be reviewed periodically by the study investigators.

The recording of adverse events will begin to occur once the participant signs informed consent and continue until the participant completes the study or withdraws from participation.

9.4 Responsibilities for Reporting Serious Adverse Events

The investigator should record all serious adverse events that occur during the study period on an Adverse Event CRF. Details included will be the same as those documented for adverse events (as detailed above). The investigator or their designee will fill out the MedWatch FDA 3500 form for serious adverse events. This will include: an identification that serious event criteria have been met; a detailed description of the event and other relevant information; the current status of the event; if the subject has died, the date of death and autopsy report, if available; and the investigator's current opinion of the relationship between the event and the study drug/participation in the study.

The recording of adverse events will begin to occur once the participant signs informed consent and continue until the participant completes the study or withdraws from participation.

The investigator will comply with regulations and RSRB policy regarding the reporting of adverse events.

9.5 Assessment of Severity

Clinical adverse events will be graded on a three-point scale (mild, moderate, severe) and reported on the CRF and in the log. The definitions are as follows:

MILD	no limitation of usual activities
MODERATE	some limitation of usual activities
SEVERE	inability to carry out usual activities

9.6 Assessment of Relationship

For each adverse event, the relationship to the study drug will be coded as follows:

DEFINITE	Causal relationship is certain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been
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eliminated and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure, if necessary).

PROBABLE High degree of certainty for causal relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge [re-challenge is not required] and other causes have been eliminated or are unlikely).

POSSIBLE Causal relationship is uncertain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge/re-challenge information is either unknown or equivocal and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable).

UNLIKELY Not reasonably related, although a causal relationship cannot be ruled out (i.e., while the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug).

UNRELATED No possible relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible).

10 RISK/BENEFIT ASSESSMENT

10.1 Potential Risks

Potential risks of participating in the study include side effects of therapy. The most common side effects of buspirone include dizziness, drowsiness, headaches, nausea, and nervousness. 10% of those who participated in premarketing clinical efficacy trials for BuSpar stopped treatment as a result of an adverse event (label). In placebo-controlled clinical trials the most common adverse events were: dizziness (12%), drowsiness (10%), nausea (8%), headache (6%), nervousness (5%), fatigue (4%), insomnia (3%), lightheadedness (3%), dry mouth (3%), weakness (2%), numbness (2%), abdominal/gastric distress (2%), diarrhea (2%), blurred vision (2%), depression (2%), confusion (2%), anger/hostility (2%), excitement (2%), and decreased concentration (2%) (label). Some studies have shown worsening of PD motor function with buspirone treatment. However, in the two largest studies this occurred only with dosages higher than 60 mg/day,^{49,50} which will not be used in this study, and it is only in a small (n=5) open-label study where worsening of PD motor function was reported with lower dosages.³⁰ There are case reports of possible serotonin syndrome occurring with concomitant SSRI use⁶¹⁻⁶⁴, however, in clinical practice buspirone and SSRIs are commonly co-prescribed. All participants will be monitored closely. The participant's anxiety may not improve or may worsen during the course of the study. Participants will be encouraged to contact the investigators at any time if there is concern about worsening anxiety or adverse events.

Participants will also be forgoing the initiation of other potential treatment options, including medications and non-pharmacological therapy, for the duration of the trial. Although there is currently insufficient evidence to guide the choice of therapy in the treatment of anxiety in Parkinson's disease, there is evidence to support the use of a variety of different anxiolytics as well as non-pharmacological therapy options in the general population, and these are often offered as treatment options in clinical practice. Participants may experience a lack of improvement or worsening of anxiety during the trial.

Participants may find it uncomfortable to respond to some of the questions contained in the evaluations. Participants will not be required to answer any questions that make them uncomfortable. Breach of confidentiality is a potential risk. If a breach of confidentiality occurs, the participant(s) will be immediately notified and appropriate steps will be taken to minimize the risk of a future breach of confidentiality occurring.

10.2 Protection Against Risks

To minimize the risk of side effects, we will follow the recommended titration schedule for buspirone. Safety and tolerability will be closely monitored by study investigators. If an intolerability or adverse event occurs, depending on the severity of the event, investigators may decide to decrease the study drug/placebo dosage or to discontinue the study drug/placebo. Participants will be able to withdraw from the study at any time.

Participants in either the study drug or placebo arm may experience worsening of their anxiety. If a participant develops suicidal ideation, which is deemed severe enough by an investigator to reflect a significant suicidal risk, we will terminate the participant from the study and we will immediately refer the patient to a mental health provider for treatment. The investigator will determine the most appropriate referral, which may be referral to an outpatient mental health provider or referral to the Comprehensive Psychiatric Emergency Program. Participants and their caregivers will be encouraged to contact the investigators at any time if there is concern about worsening anxiety. As detailed in section 5.1, investigators will re-evaluate the dosage every two weeks and make dosage adjustments as necessary and tolerated up to a maximum of 30 mg twice daily to achieve an optimal dosage that balances efficacy with tolerability. If, in the opinion of either the participant or the investigator, the level of anxiety is resulting in a degree of emotional distress or impairment considered to be unacceptable, the participant's participation in the study will be terminated and the subject will be referred immediately to a mental health provider for treatment.

Un-blinding of treatment assignment can occur if it is medically required to reveal a participant's actual treatment. This should only occur in consultation with the principal investigator unless there is a medical emergency and the principal investigator cannot be immediately reached. There are very few reasons (eg. medication overdose) that medically require such un-blinding and worsening of baseline anxiety would not in and of itself be considered sufficient cause for un-blinding.

To minimize the risks of breach of confidentiality, study data will be collected using the University of Rochester's REDCap (Research Electronic Data Capture) system, designed specifically for use in research, which restricts access to study data.

REDCap servers are housed in a local data center at the University of Rochester and all web-based information transmission is encrypted. REDCap was developed in a manner consistent with HIPAA security requirements and is recommended to University of Rochester researchers by the URM Research Privacy Officer and Office for Human Subject Protection. All study documents will be reviewed for consistency and completeness when entered into the REDCap database. Each eligible participant will be assigned a unique subject identifier. Data will be collected in a de-identified manner. The log linking subject identifiers to identifying participant information will be destroyed once study data have been fully verified by study investigators. Any paper documents will be stored in locked filing cabinets. The screening log will be destroyed once study recruitment has been completed and study data have been fully verified by study investigators.

All study personnel will be appropriately trained in the administration of study assessments.

10.3 Potential Benefits to Subjects

Participants may experience an improvement in anxiety as a result of participation in this study, however, buspirone is readily available and may be prescribed in the context of routine clinical care.

10.4 Alternatives to Participation

Patients who decline to participate in the study will receive routine clinical care.

11 CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Each participant will be assigned a unique subject identifier. Study data will be collected using the University of Rochester's REDCap system, designed specifically for use in research, which restricts access to study data to individuals granted access. All records pertaining to the study will be kept in a secure location with limited access and destroyed according to institutional guidelines.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, OHSP, the sponsor, or the sponsor's designees. An intentional breach of confidentiality may occur if the investigator feels that the participant represents a risk to him or herself or others as is standard medical practice.

12 RESEARCH INFORMATION IN MEDICAL RECORDS

Information concerning participation in this study will be included in the participant's medical record.

13 DATA ANALYSIS AND MONITORING

13.1 Sample Size Determination

The primary outcome for tolerability is the proportion of participants who fail to complete the 12-week study on study drug (intolerability). This study uses a single-

arm futility design to determine the tolerability of buspirone by comparing the observed intolerability rate (θ_E) against an intolerability rate that would be unacceptably high (θ_O). 20% represents a reasonable value for unacceptably high intolerability (θ_O). Our null hypothesis is that buspirone is tolerable and $\theta_E \leq \theta_O$. Our alternative hypothesis is that buspirone is intolerable and that $\theta_E > \theta_O$. A sample size of 21 will provide 80% power to reject the null hypothesis of tolerability (observed intolerability $\leq 20\%$) in favor of the alternative hypothesis of intolerability (observed intolerability $> 20\%$) if the true intolerability is greater than 40%, using a binomial test and a one-tailed significance level of 10% significance. With the introduction of a placebo arm for blinding and relying on a 4:1 allocation ratio, the desired sample size increases to 27. We are willing to accept a higher chance that we declare an intolerable drug tolerable as the expected intolerabilities (headache, nausea, drowsiness, dizziness, and temporary worsening of PD motor function) are not expected to be serious and could be confirmed in larger studies. We are more concerned about declaring a truly tolerable drug intolerable and not moving forward with larger studies.

13.2 Planned Statistical Analysis

The primary outcome for tolerability is the proportion of participants who fail to complete the 12-week study on study drug, as described in **Sample Size and Accrual**. The number of participants who fail to complete the study on study drug will be determined and if 7 or more participants fail to tolerate the study drug, the null hypothesis will be rejected. Participants who do not complete the study on study drug for any reason will be considered as experiencing intolerability for purposes of the primary analysis.

As a secondary analysis we will calculate the number of participants who fail to complete the study on study drug due to adverse events; separating them from those who fail to complete the study on study drug for alternative reasons. We will also calculate the number of participants who required dosage reductions during the study and use descriptive statistics to describe the average study drug dosage and dosage reductions.

Safety analyses will include tabulating adverse events by treatment group and severity and codifying the relationship to study drug. Serious adverse events attributable to buspirone treatment will be described in detail. Adverse event incidence will be summarized along with the corresponding 95% two-sided confidence interval. The mean change in MDS-UPDRS motor score and from baseline to 12 weeks will be calculated. We will use descriptive statistics to characterize the range and variability of study drug dosages.

Secondary outcomes related to anxiety will include the mean change in HAM-A score from baseline to 12 weeks, mean change in HADS score from baseline to 12 weeks and the proportion of participants "much improved" or "very much improved" on CGI-I, proportion "much improved" or "very much improved" on PGI-I, and proportion of responders ($> 50\%$ reduction from baseline or reduction to ≤ 7 in HAM-A) at 12 weeks. The secondary outcome regarding levodopa-induced dyskinesias will be the mean change in UDysRS score from baseline to 12 weeks. Similar analyses will be done for all outcomes at 2 weeks, 4 weeks, and 8 weeks. For participants lost to follow up, the

last observation carried forward will be used. We will also correlate mean change in the Parkinson Anxiety Scale scores with mean change in the CGI-I and PGI-I scores.

13.3 Data and Safety Monitoring

The principle investigator will be responsible for the overall conduct of this small, phase 2, single-center tolerability study. A neurologist, who is not involved in the conduct of the study, will be appointed to independently monitor the safety of study participants and validity and integrity of the data. If a serious adverse event occurs, a detailed report will be sent to the independent monitor. The independent monitor will periodically review the study; including appropriateness of participant inclusion, protocol adherence, adverse events, and completion of data forms. Following study initiation, a comprehensive review will occur following enrollment of the first 5 participants and then every six months or more frequently if deemed necessary by the independent monitor. Adverse events will be reviewed by the independent monitor every 3 months. The independent monitor will document the results of each review and the RSRB will be notified of all monitoring activity outcomes. As this is a small, single-center study no interim statistical analyses will be conducted.

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