PROTOCOL NEP-PD-201

PHASE 2A, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF BTRX-246040 IN PARKINSON'S DISEASE SUBJECTS WITH MOTOR FLUCTUATIONS

Sponsor: BlackThorn Therapeutics, Inc.

780 Brannan Street

San Francisco, CA 94103

Date: 05 March 2019

1 SYNOPSIS

Name of Investigational Study Product:
BTRX-246040

Title of Study: Phase 2a, Double-blind, Placebo-Controlled Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Efficacy of BTRX-246040 in Parkinson's Disease Subjects with Motor Fluctuations

Approximate Number of Planned Subjects:	**Phase of Development:**
24 subjects or 3 cohorts of 8 subjects each	2a

Length of Study: Treatment Duration is 1 day and total duration of the study is up to 36 days including the 28-day screening period

Study Objective:

The purpose of this study is to assess the safety, tolerability, pharmacokinetics and efficacy of BTRX-246040 in subjects with PD who have motor fluctuations and predictable early morning off periods.

Safety Objectives

- To evaluate the safety of single ascending doses of BTRX-246040 in PD subjects with motor fluctuations and predictable early morning off periods

Tolerability Objectives

- To assess the tolerability of BTRX-246040 in PD subjects with motor fluctuations and predictable early morning off periods

[redacted]

Efficacy Objectives:

- To evaluate the effect of single ascending doses of BTRX-246040 on the clinical features of Parkinson's disease in levodopa-treated PD subjects with motor fluctuations and predictable early morning off periods

Study Population:

Levodopa-responsive Parkinson's disease subjects with motor fluctuations and predictable morning OFF periods.

Study Design:

The study will consist of 3 sequential, single ascending dose cohorts of 8 subjects each with a 6:2 randomization to BTRX-246040 or placebo. The planned dosing for each cohort will be 40, 80, and 120 mg. After enrollment of the first cohort has been completed, doses for subsequent cohorts may be modified based on a review of the available data (safety, tolerability, efficacy, and PK) by an unblinded Dosing Review Committee (DRC). A similar review and determination of dosing for the subsequent cohort will be performed after completion of each cohort and based on all data available from previous cohorts.

Following signing of IRB-approved informed consent, screening, and acceptance by an Enrollment Authorization Committee, subjects in each cohort who meet entry criteria will present to the clinic on the morning of Day 1 in the practically defined OFF state (having withheld anti-parkinsonian medications after 10:00 PM the evening prior). Prior to dosing on Day 1, Subjects will be randomized to either placebo or BTRX-246040. Subjects will then be dosed with study drug and UPDRS Part III motor response, dyskinesia rating and ON/OFF status will be assessed pre-dose and every 30 minutes for 4 hours and then hourly for 4 additional hours (i.e., 8 hours total post-dose). Subjects who turn ON following study drug administration, and remain ON after 8 hours, should be called the next morning to record the time they turned OFF and took their first regularly scheduled anti-parkinsonian medications after study drug, to a maximum of 24 hours.

On Day 1 subjects will come to clinic in a fasted state and will be administered a standard low protein breakfast. [redacted]
Subjects who reach and remain in the ON state for 8 hours will resume their regularly scheduled anti-parkinsonian medications 8 hours post-dosing. Subjects should remain on study drug until they experience an OFF episode after a full ON for 8 hours. However, if after 4 hours post study drug dosing, a subject's motor symptoms are severe and not responsive to study drug, the subject's regularly scheduled levodopa dose and other anti-parkinsonian medications may be administered, if deemed necessary based on the judgment of the investigator. All subjects, whether they are administered their regularly scheduled anti-parkinsonian medication or not will continue with study procedures until the end of the observation period of 8 hours. Orthostatic vital signs will be assessed pre-dose and 2, 4, 6, and 8 hours after dosing.

Subjects will return to the clinic 7 days later (Day 8) for a follow-up safety visit.

Following completion of cohorts 1 and 2, a Dosing Review Committee (DRC) meeting will take place to review available unblinded safety, tolerability, efficacy and, if available, PK data and determine if it is safe to go up to the next higher dosage for the next cohort. At any point, the DRC can request that a dosage be repeated for safety or tolerability rather than increased.

Inclusion Criteria

1. Diagnosed with Parkinson`s disease (consistent with the UK PD Society Brain Bank Criteria for the Diagnosis of PD)
2. Men or women ≥ 30 years old and ≤ 76 years old
3. Female subjects must be either surgically sterilized or 2 years post menopausal at screening
4. Modified Hoehn and Yahr scale ≤ 3 in the ON state
5. Montreal Cognitive Assessment (MoCA) Score ≥ 26
6. Currently has a clear and decisive response to levodopa, and receiving a stable dose of levodopa (at least 4 doses per day of levodopa or ≥ 3 doses per day of RytaryTM (Carbidopa and levodopa Extended-Release Capsules) for at least four weeks prior to screening)
7. Experiencing motor fluctuations during waking hours with at least 2 hours of OFF periods each day, including predictable early morning OFF periods, based on subject assessment
8. Able to participate in the study in the practically defined OFF state
9. All anti-parkinsonian medications maintained at a stable dose for at least 4 weeks prior to the initial Screening Visit with the exception of MAO-B inhibitors, which must be maintained at a stable level for at least 8 weeks prior to the screening visit
10. Approved by a central Enrollment Authorization Committee as meeting entry criteria and being a suitable candidate for the study
11. Male subjects agree to use a reliable method of birth control during the study and for at least 90 days following the last dose of BTRX-246040 or placebo.
12. Informed and given ample time and opportunity to think about his/her participation in this study and has given his/her written informed consent on an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved consent form
13. Judged to be reliable and able to keep all appointments for clinic visits, tests, and procedures, including venipuncture, and examinations required by the protocol.

Exclusion Criteria

1. Diagnosis of secondary or an atypical Parkinsonian syndrome
2. Severe disabling dyskinesia
3. Clinically significant psychosis or hallucinations or history of psychosis in past 6 months
4. History of previous neurosurgery for PD
5. Currently or previously on Duopa/Duodopa
6. Currently taking apomorphine
7. Has a diagnosis or history of a substance related disorder per DSM-V criteria (including alcohol but excluding nicotine and caffeine), during the 12 months prior to the Screening Visit
8. Medical or recreational use of marijuana in the 6 months prior to the Screening Visit
9. Has tested positive at the Screening Visit for drugs of abuse (opiates, cannabinoids, methadone, cocaine, and amphetamines [including ecstasy])

10. Active suicidal ideation within one year prior to the Screening Visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 1 year
11. Current major depressive episode or a Beck Depression Inventory-II (BDI-II) score of > 19. Subjects receiving treatment for depression with antidepressants may be enrolled if they have been on a stable daily dose for at least 8 weeks before the Screening Visit and are clinically stable in the opinion of the PI
12. Currently or within 8 weeks of screening receiving bupropion
13. Exposure to neuroleptics (antipsychotic drugs) for more than 1 month within the past 2 years, or any exposure within the past year
14. Any malignancy in the 5 years prior to randomization (excluding successfully treated basal cell carcinoma of the skin or cervical carcinoma in situ)
15. Current or previous diagnosis of malignant melanoma or the presence of any suspicious skin lesion based on physical exam findings.
16. Any other clinically significant medical condition or circumstance prior to randomization that, in the opinion of the Investigator, could affect subject safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study (e.g., uncontrolled diabetes mellitus, renal or hepatic impairment, coronary artery disease, evidence of significant active cardiac, respiratory, or hematologic disease, cancer with < 5 year remission (excluding successfully treated basal cell carcinoma of the skin or cervical carcinoma in situ), chronic pain, fibromyalgia or gastric bypass).
17. Prior seizures (other than childhood febrile seizure) or other condition that would place the subject at increased risk of seizures or is taking anticonvulsants for seizure control.
18. History of serious head injury (e.g., skull fracture, cerebral contusion, or trauma resulting in prolonged unconsciousness), intracranial neoplasm or hemorrhage.
19. Orthostatic hypotension that is symptomatic or requires medication
20. Participation in another study of an IMP or medical device currently or in the last 30 days or within 5 half-lives of the IMP (whichever is longer) prior to Screening
21. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 2x upper limit of normal (ULN) or glomerular filtration rate ≤ 60 mL/min at Visit 1 (screening)
22. Nephritic syndrome, end-stage renal disease (and using renal replacement therapy such as hemodialysis or peritoneal dialysis), or a serum creatinine ≥ 2 mg/dL (≥ 172 µmol/L) at the Screening Visit
23. Any other clinically significant abnormalities (i.e., laboratory deviations requiring acute medical intervention or further medical evaluation) in laboratory results at screening including clinical chemistries, hematology, and urinalysis, that, in the judgment of the Investigator, should preclude a subject's participation at study entry.
24. ECG abnormalities at Visit 1 (screening) or Visit 2 that, in the judgment of the Investigator, are clinically significant related to the subject's participation
25. Using the following concomitant medications (contact the Sponsor-designated medical monitor to determine eligibility when in doubt):
    a) proton pump inhibitors within 5 half-lives of Screening
    b) fluoxetine and irreversible monoamine oxidase inhibitors within 4 weeks of Screening

26. Currently taking or have taken, within 5 half-lives of Screening, any medications or supplements that are strong inhibitors or inducers of CYP3A4.
27. A known hypersensitivity to gelatin capsules.
28. Investigator site personnel directly affiliated with this study, and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
29. Employees of the Sponsor or of any third-party organizations (TPOs) involved in study who require exclusion of their employees.
30. Have participated in a clinical trial or any other type of medical research judged by the Investigator to be scientifically or medically incompatible with this study within 30 days prior to Visit 1 (screening). Contact the Sponsor-designated medical monitor to determine eligibility when in doubt.
31. Previous completion or withdrawal from this study or any other study investigating BTRX-246040 (previously called LY2940094).

Investigational Study Product, Dose and Mode of Administration:

BTRX-246040 will be administered orally as follows:

- 40 mg ([redacted] in Cohort 1
- 80 mg ([redacted] in Cohort 2
- 120 mg ([redacted] in Cohort 3

Reference Therapy, Dose and Mode of Administration:

Placebo will be administered orally at the same number of capsules as active drug at each Cohort. Placebo capsules will consist of inactive ingredients and look identical to BTRX-246040.

Planned Duration of Treatment:

Study drug will be administered once on Day 1

Criteria for Evaluation:

Safety: Will be assessed descriptively by adverse events reporting which will include AEs, SAEs, vital signs, laboratory values, physical and neurological exams, C-SSRS, and ECGs.

Tolerability: Will be assessed by percent who complete protocol

Pharmacokinetics: Descriptive review of Pharmacokinetic (PK) [redacted]

Efficacy: Will be assessed descriptively for the following endpoints.

Primary Endpoint:

- Maximal change in UPDRS Part III from pre-dose to post-dose on Day 1

Secondary Endpoints:

- Duration of ON time on Day 1
- Percentage of subjects that turn ON on Day 1
- Time to ON on Day 1

• Area under the curve for UPDRS Part III during the 8 hours of assessment on Day 1 • Change from pre-dose dyskinesia rating (from the UPDRS Part III motor response and dyskinesia assessment)
Statistical Methods: All data will be assessed descriptively as presented in the SAP, and no formal statistical comparisons will be performed.
Sample Size Calculation: Formal sample size calculation will not occur. A sample size of 8 subjects per group is deemed sufficient to evaluate the preliminary safety, tolerability, and efficacy of the different dose levels.

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[redacted] March 5th 2019

Date

Responsible Medical Officer
BlackThorn Therapeutics, Inc.

Principal Investigator Declaration:

I have read and understood the requirements and conditions of the study protocol. I am aware of my responsibilities as an Investigator under the guidelines of the Internal Conference on Harmonization Good Clinical Practice (ICH GCP) standards, the Declaration of Helsinki, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the study team assigned to me who will be involved in the study.

I agree to use the study material, including investigational treatment medication, only as specified in the protocol.

I understand that the protocol must be approved by the Ethics Committee and Regulatory Authorities prior to its implementation. I confirm that if I or any of my staff are members of the ethical review board, we will abstain from deliberation and voting on this protocol.

I understand that non-compliance with the study protocol may lead to early termination of the study.

Principal Investigator Signature **Date**

Principal Investigator Name (printed)

3 ABBREVIATIONS

Ab	Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Curve
AUD	Alcohol Use Disorder
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Change
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Plasma Drug Concentration
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-reactive protein
C-SSRS	Columbia Suicidality Severity Rating Scale
DRC	Dosing Review Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
EAC	Enrollment Authorization Committee
EAF	Enrollment Authorization Form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
HAV-Ab [IgM]	Hepatitis A Virus Antibody

HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IFNγ	interferon gamma
IL-1ß, IL-2, IL-6, IL-10	interleukin 1 beta, 2, 6 and 10
IgM	Immunoglobulin M
IND	US Investigational New Drug Application
INR	International Normalized Ratio
IRB	Investigational Review Board
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LS Means	Least-square means
MDD	Major Depressive Disorder
Noc/OFQ	Nociceptin/Orphanin FQ
MoCA	Montreal Cognitive Assessment
MOS	Margin of Safety
NOAEL	No-Observed- Adverse-Effect-Level
NONREM	Nonlinear Mixed Effect Modeling
NOPR	Nociceptin Receptor
PK	Pharmacokinetic
POC	Proof-of-concept
QD	Once Daily
QTcF	Fridericia's correction method for QT Interval
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
RO	Receptor Occupancy

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment-emergent Adverse Event
TNFα	Tumor necrosis factor alpha
TPO	Third-party Organization
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WHODD	World Health Organization Drug Dictionary

4 INTRODUCTION

Parkinson's Disease (PD) is a progressive neurodegenerative motor disorder caused by the loss of dopamine-producing cells in the brain. The primary motor symptoms of PD are tremor, rigidity, bradykinesia and postural instability. Disabling non-motor symptoms of PD include depression, cognitive dysfunction, sleep disturbances, hallucinations, impulse control disorder and constipation. The pathogenesis of idiopathic PD is marked by the abnormal presence of Lewy bodies in the brain and the loss of dopamine neurons in the substantia nigra pars compacta (SNpc). Additional dysfunction in glutamate, GABA and acetylcholinergic signaling in corticothalamic motor circuits contribute to motor and non-motor symptoms in PD (DeLau & Breteler, 2006), (Galvan & Wichmann, 2008), (Moustafa & Poletti, 2013), (Tysnes & Storstein, 2017).

The standard of care for PD patients invariably centers on dopamine replacement pharmacotherapy, including L-DOPA, dopamine receptor agonists and modulators of dopamine synthesis and metabolism. Drugs that attenuate acetylcholinergic neurotransmission or that block the glutamate NMDA receptor are also approved for the treatment of PD motor symptoms. Medications for PD motor symptoms are frequently used in strategic combinations to exploit additive or synergistic therapeutic effects and to better manage motor symptom complications, e.g., L-DOPA-induced dyskinesias. Patients with poorly managed motor complications may be candidates for deep brain stimulation therapy (Delong & Wichmann, 2015).

Nociceptin/orphanin-FQ (N/OFQ) is an endogenous neuropeptide that selectively activates the nociceptin receptor (NOPR). N/OFQ levels in cerebrospinal fluid are elevated in PD patients and, in post-mortem brains from PD patients, increased in the SN and decreased in dopamine-depleted striatum samples. In rodents, N/OFQ increases glutamate release from SN pars reticulata neurons but inhibits activity and dopamine release from SNpc neurons and behavioral motor activity. In contrast, pharmacological blockade of NOPR, which are expressed in brain regions underlying locomotor behavior and reward processing, attenuates Parkinsonian-like disability in rodent and non-human primate models of PD (Viaro, et al., 2008), (Visanji, et al., 2008), (Marti, et al., 2013). Moreover, NOPR antagonists reduce neurodegeneration of dopamine neurons and stimulate dopamine release in the substantia nigra, suggesting potential disease-modifying mechanisms of action for anti-Parkinsonian therapeutic efficacy (Marti, et al., 2004), (Marti, et al., 2005).

BTRX-246040 is a novel, potent and selective antagonist of human NOPR. [redacted]

[redacted]

In addition, BTRX-246040 has antidepressant properties in humans and rodent models and reduces impulsivity-related behaviors, suggesting the potential to treat important non-motor symptoms in PD patients (Lambert, 2008), (Witkin, et al., 2014), (Post, et al., 2015), (Rorick-Kehn, et al., 2016), (Statnick, et al., 2016), (Zaveri, 2016). It is hypothesized that blocking NOPR with BTRX-246040 will modulate aberrant circuits underlying motor and non-motor symptoms of PD and thereby improve quality of life for patients.

[redacted]

Study NEP-MDD-201 evaluated the efficacy and safety of BTRX-246040 in subjects with major depressive disorder (MDD). This randomized, double-blind, placebo-controlled, parallel-group study compared single-daily dosing of BTRX-246040 vs. placebo administered over 8 weeks. After screening, eligible subjects were randomized to either 40 mg of BTRX-246040 or placebo. After one week the BTRX-246040 dose was increased to 80 mg and allowed to be down-titrated to 40 mg at the next visit for tolerability. At the end of the treatment period investigational product is abruptly discontinued. One subject assigned to the placebo group had an SAE (Preferred Term: rhabdomyolysis). No deaths were reported.

More information about the known and expected benefits, risks and reasonably anticipated AEs may be found in the Investigator's Brochure (IB).

5 OBJECTIVES

5.1 PRIMARY OBJECTIVE

Safety Objective:

- To evaluate the safety of increasing doses of BTRX-246040 in levodopa-treated PD subjects with motor fluctuations and predictable early morning off periods

Tolerability Objective:

- To assess the tolerability of BTRX-246040 in PD subjects with motor fluctuations and predictable early morning off periods

[redacted]

Efficacy Objective:

- To evaluate the effect of increasing doses of BTRX-246040 on Parkinson's disease motor features of Parkinson's disease in levodopa-treated PD subjects with motor fluctuations and predictable early morning off periods

6 INVESTIGATIONAL PLAN

6.1 SUMMARY OF STUDY DESIGN

The study will consist of 3 sequential, ascending dose cohorts of 8 subjects each with a 6:2 randomization to BTRX-246040 or placebo. The planned dosing for each cohort will be 40, 80, and 120 mg. After enrollment of the first cohort has been completed, doses for subsequent cohorts may be modified based on review of the available data (safety, tolerability, efficacy, and PK) by an unblinded Dosing Review Committee (DRC). A similar review and determination of dosing for the subsequent cohort will be performed after completion of cohorts 1 and 2 and based on all data available from previous cohorts.

Following screening and acceptance by an Enrollment Authorization Committee, subjects in each cohort who meet entry criteria and sign an IRB approved informed consent, will present to the clinic on the morning of Day 1 in the practically defined OFF state (having withheld anti-parkinsonian medications after 10:00 PM the evening prior). Prior to dosing on Day 1, subjects will be randomized to either placebo or BTRX-246040. Subjects will then be dosed with study drug and UPDRS Part III motor response, dyskinesia and ON/OFF status will be assessed pre-dose and every 30 minutes for 4 hours and then hourly for 4 additional hours (i.e., 8 hours total post-dose). Subjects who turn ON following study drug administration and remain ON after 8 hours, should be called the next morning to record the time they turned OFF and the time they took their first regularly scheduled anti-parkinsonian medications after study drug, to a maximum of 24 hours. Subjects who turn ON following study drug administration and subsequently turn OFF may be administered their regularly scheduled levodopa dose and other anti-parkinsonian medications.

[redacted] Subjects who reach and remain in the ON state for 8 hours may resume their regularly scheduled anti-parkinsonian medications 8 hours post-dosing. Subjects should remain on study drug until they experience an OFF episode after a full ON for 8 hours. However, if after 4 hours post study drug dosing, a subject's motor symptoms are severe and not responsive to study drug, the subject's regularly scheduled levodopa dose and other anti-parkinsonian medications may be administered, if deemed necessary based on the judgment of the investigator. All subjects, whether they are administered their regularly scheduled anti-parkinson medication or not will continue with study procedures until the end of the observation period of 8 hours.

Subjects will come to clinic in a fasted state and will be administered a standard low protein breakfast.

Orthostatic vital signs will be assessed pre-dose and 2, 4, 6, and 8 hours after dosing.

Subjects will return to the clinic 7 days later (Day 8) for a follow-up safety visit.

Following completion of cohorts 1 and 2, a Dosing Review Committee (DRC) meeting will take place to review available unblinded safety, tolerability, efficacy and, if available, PK data and determine if it is safe to go up to the next higher dosage for the next cohort. At any point the DRC can request that a dosage be repeated.

6.2 Study Design and Control

The initial screening period is designed to ensure subjects meet the required inclusion and exclusion criteria, including diagnosis and stability of depressive symptoms and absence of psychiatric and medical conditions that would preclude study participation.

The randomization, investigational product blinding, and placebo controls will serve to minimize the chance of bias in the implementation and execution of the study. Randomization to treatment assignment reduces the likelihood that results will reflect selection bias. Having both Investigators and subjects blinded to treatment assignment (double-blind) controls for expectation bias relative to any particular treatment condition. A placebo arm is included to control the subject and Investigator expectations of improvement during the study that could confound interpretation of pharmacological effects of treatment.

7 STUDY POPULATION

Subjects who meet all Inclusion Criteria and are subsequently not excluded by the Exclusion Criteria will be eligible for participation in the study.

7.1 INCLUSION CRITERIA

Subjects are eligible to be included in the study only if they meet **all** the following criteria:

1. Diagnosed with Parkinson`s disease (consistent with the UK PD Society Brain Bank Criteria for the Diagnosis of PD)
2. Men or women ≥ 30 years old and ≤ 76 years old
3. Female subjects must be either surgically sterilized or 2 years post menopausal at screening
4. Modified Hoehn and Yahr scale ≤ 3 in the ON state
5. Montreal Cognitive Assessment (MoCA) Score ≥ 26
6. Currently has a clear and decisive response to levodopa, and receiving a stable dose of levodopa (at least 4 doses per day of levodopa or ≥ 3 doses per day of RytaryTM (Carbidopa and levodopa Extended-Release Capsules) for at least four weeks prior to screening)
7. Experiencing motor fluctuations during waking hours with at least 2 hours of OFF periods each day, including predictable early morning OFF periods, based on subject assessment
8. Able to participate in the study in the practically defined OFF state
9. All anti-parkinsonian medications maintained at a stable dose for at least 4 weeks prior to the initial Screening Visit with the exception of MAO-B inhibitors, which must be maintained at a stable level for at least 8 weeks prior to the screening visit
10. Approved by a central Enrollment Authorization Committee as meeting entry criteria and being a suitable candidate for the study
11. Male subjects agree to use a reliable method of birth control during the study and for at least 90 days following the last dose of BTRX-246040 or placebo.
12. Informed and given ample time and opportunity to think about his/her participation in this study and has given his/her written informed consent on an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved consent form
13. Judged to be reliable and able to keep all appointments for clinic visits, tests, and procedures, including venipuncture, and examinations required by the protocol.

7.2 EXCLUSION CRITERIA

Subjects will be excluded from participation in the study if they meet **any** of the following criteria:

1. Diagnosis of secondary or an atypical Parkinsonian syndrome
2. Severe disabling dyskinesia
3. Clinically significant psychosis or hallucinations or history of psychosis in past 6 months
4. History of previous neurosurgery for PD
5. Currently or previously on Duopa/Duodopa
6. Currently taking apomorphine
7. Has a diagnosis or history of a substance related disorder per DSM-V criteria (including alcohol but excluding nicotine and caffeine), during the 12 months prior to the Screening Visit
8. Medical or recreational use of marijuana in the 6 months prior to the Screening Visit
9. Has tested positive at the Screening Visit for drugs of abuse (opiates, cannabinoids, methadone, cocaine, and amphetamines [including ecstasy])
10. Active suicidal ideation within one year prior to the Screening Visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 1 year
11. Current major depressive episode or a Beck Depression Inventory-II (BDI-II) score of > 19. Subjects receiving treatment for depression with antidepressants may be enrolled if they have been on a stable daily dose for at least 8 weeks before the Screening Visit and are clinically stable in the opinion of the PI
12. Currently or within 8 weeks of screening receiving bupropion
13. Exposure to neuroleptics (antipsychotic drugs) for more than 1 month within the past 2 years, or any exposure within the past year
14. Any malignancy in the 5 years prior to randomization (excluding successfully treated basal cell carcinoma of the skin or cervical carcinoma in situ)
15. Current or previous diagnosis of malignant melanoma or the presence of any suspicious skin lesion based on physical exam findings.
16. Any other clinically significant medical condition or circumstance prior to randomization that, in the opinion of the Investigator, could affect subject safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study (e.g., uncontrolled diabetes mellitus, renal or hepatic impairment, coronary artery disease, evidence of significant active cardiac, respiratory, or hematologic disease, cancer with < 5 year remission (excluding successfully treated basal cell carcinoma of the skin or cervical carcinoma in situ), chronic pain, fibromyalgia or gastric bypass).

17. Prior seizures (other than childhood febrile seizure) or other condition that would place the subject at increased risk of seizures or is taking anticonvulsants for seizure control.
18. History of serious head injury (e.g., skull fracture, cerebral contusion, or trauma resulting in prolonged unconsciousness), intracranial neoplasm or hemorrhage.
19. Orthostatic hypotension that is symptomatic or requires medication
20. Participation in another study of an IMP or medical device currently or in the last 30 days or within 5 half-lives of the IMP (whichever is longer) prior to Screening
21. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 2x upper limit of normal (ULN) or glomerular filtration rate ≤ 60 mL/min at Visit 1 (screening)
22. Nephritic syndrome, end-stage renal disease (and using renal replacement therapy such as hemodialysis or peritoneal dialysis), or a serum creatinine ≥ 2 mg/dL (≥ 172 μmol/L) at the Screening Visit
23. Any other clinically significant abnormalities (i.e., laboratory deviations requiring acute medical intervention or further medical evaluation) in laboratory results at screening including clinical chemistries, hematology, and urinalysis, that, in the judgment of the Investigator, should preclude a subject's participation at study entry.
24. ECG abnormalities at Visit 1 (screening) or Visit 2 that, in the judgment of the Investigator, are clinically significant related to the subject's participation
25. Using the following concomitant medications (contact the Sponsor-designated medical monitor to determine eligibility when in doubt):
    a) proton pump inhibitors within 5 half-lives of Screening
    b) fluoxetine and irreversible monoamine oxidase inhibitors within 4 weeks of Screening
26. Currently taking or have taken, within 5 half-lives of Screening, any medications or supplements that are strong inhibitors or inducers of CYP3A4.
27. A known hypersensitivity to gelatin capsules.
28. Investigator site personnel directly affiliated with this study, and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
29. Employees of the Sponsor or of any third-party organizations (TPOs) involved in study who require exclusion of their employees.
30. Have participated in a clinical trial or any other type of medical research judged by the Investigator to be scientifically or medically incompatible with this study within 30 days prior to Visit 1 (screening). Contact the Sponsor-designated medical monitor to determine eligibility when in doubt.
31. Previous completion or withdrawal from this study or any other study investigating BTRX-246040 (previously called LY2940094).

7.2.1 Rationale for Exclusion of Certain Subjects

The exclusion criteria in section 7.2 are intended to ensure that subjects with conditions that could be exacerbated by participation in the study are excluded, and that subjects with conditions that could confound the interpretation of efficacy or safety results are excluded. No subject is to be excluded on the basis of race, ethnicity, or gender.

Every effort should be made to encourage subjects who discontinue from the study early to complete all of the Day 8 visit procedures.

7.3 Discontinuations

7.3.1 Early Discontinuation

Every effort should be made to encourage subjects who discontinue from the study early to complete all of the Day 8 visit procedures.

If early discontinuation occurs, all appropriate reasons will be reported on the study completion CRF. Reasons for early disconuation are listed below.

1. Physician Decision
    a. The Investigator/physician decides that the subject should be withdrawn from the study for any reason.
2. Withdrawal by Subject
    a. The subject requests to be withdrawn from the study for any reason. If the reason to request withdrawal is an adverse event, this should be documented as the primary reason for discontinuation.
3. Study Terminated by Sponsor
    a. The Sponsor stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and good clinical practice (GCP).
4. Adverse Event
    a. Discontinuation should be considered by the Investigator after consultation with the Sponsor or its Medical Monitor designee when a subject has the following abnormal liver tests:
        i. ALT or AST > 8 x ULN
        ii. ALT or AST > 3 x ULN and total bilirubin level > 2 x ULN
        iii. ALT or AST > 3 x ULN and prothrombin time > 1.5 x ULN
        iv. ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

b. If the subject is thought to be at risk of harm to him/herself or others at any time during the study, a further psychiatric assessment by the Investigator must be conducted. Subjects must be discontinued from study participation if they:

   i. are assessed as homicidal

   ii. are actively suicidal (any suicidal ideation with intent or specific plan or any suicide attempt)

   iii. are at serious suicidal risk as assessed by the C-SSRS (score of "YES" on item 4 or 5)

   The Investigator must assure that these subjects receive the appropriate psychiatric care and follow-up.

c. Any subject who is discontinued from investigational product due to AEs or clinically significant laboratory abnormalities will be followed until resolution or clinical stabilization.

d. The Investigator remains responsible for following, through an appropriate healthcare option, AEs that caused the subject to discontinue study drug.

5. Lost to Follow-Up

   a. For subjects who are lost to follow-up, all steps performed to contact them (dates of telephone calls, registered letters, etc.) will be reported in the source documents. The Investigators are required to make at least two attempts to contact the subject for a follow-up safety visit.

6. Other

   a. Any reason other than Physician Decision, Withdrawal by Subject, Study Terminated by Sponsor, Adverse Event, or Lost to Follow-up.

7.3.2 Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8 STUDY PROCEDURES

8.1 VISIT 1: SCREENING

The total time for the screening period will be 28 days. Screening procedures may require more than one visit to complete.

Before any screening procedure is performed, subject informed consent must be obtained. After obtaining the subject's informed consent, the following procedures will be conducted - see schedule of Assessments (Appendix 1). The following order of procedures is recommended to prioritize eligibility and safety assessments:

The Investigator (or his or her designee) will conduct/administer the following assessments:

1. Collection of demographic data
2. Collection of medical history, including PD history
3. Physical and neurological examination
4. Collection of concomitant medications
5. Vital signs (BP and pulse both supine and standing, respiratory rate, temperature), height and weight
6. Columbia-Suicide Severity Rating Scale (C-SSRS) – Baseline/Screening version
7. Montreal Cognitive Assessment (MoCA)
8. Beck Depression Inventory-II (BDI-II)
9. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease -Rating Scale (QUIP-RS) Screening version
10. UPDRS Part III and dyskinesia rating in the ON state, including Modified Hoehn and Yahr scale in the ON state
11. UPDRS Part III and dyskinesia rating in the OFF state
12. 12 lead ECG
13. Urine Drug Screen
14. Review of Inclusion/Exclusion criteria
15. Safety laboratory collection (including clinical chemistry panel, hematology, coagulation [including PT, aPTT, INR] parameters and urinalysis)
16. Enter subject information in interactive web-response system (IWRS)

17. Complete the Enrollment Authorization Form (EAF) if the PI determines that the subject is eligible for randomization. There is no need to complete the EAF if the subject is a known screen failure.

The investigator will review results from all screening procedures to consider whether a subject has met all of the inclusion criteria and none of the exclusion criteria. The investigator will complete the Enrollment Authorization Form (EAF) for submission to the EAC for subjects who the investigator deems potentially eligible. Upon receipt of the EAF, the EAC will review the provided information and the investigator will be notified of the EAC's eligibility decision. If the EAC rejects the inclusion of a subject, the reason for exclusion will be provided to the investigator. Only after receiving confirmation from the EAC that the subject meets eligibility criteria may the investigator plan to enroll the subject.

8.2 Visit 2: Treatment Period (Day 1)

For each cohort, subjects approved by the EAC for further participation in the study will return to the clinic within 28 days of the screening visit on the morning of Day 1, in the practically defined OFF state (having not taken any anti-PD medications since 10 PM the evening before).

Subjects will come to clinic in a fasted state and will be administered a standard low protein breakfast. Subjects will be randomized to either BTRX-246040 or placebo.

In the clinic, subjects determined to be in the OFF state by the Investigator will be dosed with study drug and UPDRS Part III motor response and dyskinesia rating, and ON/OFF status will be assessed pre-dose and every 30 minutes post-dose for 4 hours, and then hourly for an additional 4 hours (i.e., 8 hours total post-dose). Time to ON and duration of ON, if applicable, will also be recorded.

[redacted]

Subjects who reach and remain in the ON state for 8 hours may resume their regularly scheduled anti-parkinsonian medications 8 hours post-dosing. Subjects should remain on study drug until they experience an OFF episode after a full ON for 8 hours. However, if after 4 hours post study drug dosing, a subject's motor symptoms are severe and not responsive to study drug, the subject's regularly scheduled levodopa dose and other anti-parkinsonian medications may be administered, if deemed necessary based on the judgment of the investigator. All subjects whether they are administered their regularly scheduled anti-parkinsonian medications or not, will continue with study procedures unil the end of the observation period of 8 hours.

The following assessments will be completed on Day 1 - see the Schedule of Assessments (Appendix 1) for details:

1. Collection of concomitant medications

2. Vital Signs: (BP and pulse both supine and standing, respiratory rate, temperature) and weight. Three sets each of supine and standing BP and pulse rate will be measured at least 15-20 minutes apart at pre-dose and will be measured once at 2, 4, 6, and 8 hours after dosing
3. C-SSRS – since last visit version
4. QUIP-RS – since last visit version
5. 12-lead ECG pre-dose and 1 hour after study drug administration.
6. Randomization via IWRS
7. UPDRS Part III and dyskinesia rating in the OFF state pre-dose and every 30 minutes for 4 hours and then hourly for another 4 hours (i.e., 8 hours following study drug administration). If the subject remains ON after 8 hours, they should be called the next morning to record the time they turned OFF, and the time they took their first regularly scheduled anti-parkinsonian medications after study drug, to a maximum of 24 hours.
8. Administration of Study drug
9. Time to ON and duration of ON following study drug administration.

[redacted]

11. Drug accountability.
12. Collection of AEs.

Subjects will be discharged from the clinic and instructed to return to the clinic 7 days later (Day 8 ±1).

8.3 VISIT 3: SAFETY FOLLOW-UP (DAY 8 ±1)

All randomized subjects will return to the clinic for a final safety visit approximately 7 days after the last dose of study drug.

The following assessments will be performed at the follow-up visit (see Schedule of Assessments [Appendix 1] for details):

1. Collection of concomitant medications.
2. Vital signs (BP and pulse both supine and standing, respiratory rate, temperature), and weight
3. C-SSRS – since last visit version
4. QUIP-RS since last visit version
5. Physical and neurological examinations
6. 12-lead ECG
7. Safety laboratory assessment (including clinical chemistry panel, hematology, coagulation [including PT, aPTT, INR] parameters and urinalysis)

8. Collection of AEs.

8.4 Early Termination Visit

If the participant is willing, all of the procedures scheduled to be performed on the Day 8 visit should be conducted at the early termination visit (see Schedule of Assessments [Appendix 1]).

9 TREATMENT

9.1 TREATMENTS ADMINISTERED

This study involves a comparison of BTRX-246040 versus placebo taken orally as a single dose in 3 sequential ascending dose cohorts of 8 subjects each with a 6:2 randomization to BTRX-246040 or placebo. The planned dosing for each cohort will be as noted in Table 1. Following completion of the first cohort, unblinded safety, tolerability, efficacy and, if available, PK data will be reviewed by an unblinded Dosing Review Committee (DRC) to determine if it is safe to proceed to the next higher dose level (see section 9.7). Similar dosing review and determination of dosing for each subsequent cohort will be performed based on all data available from previous cohorts. At any point, the DRC may request that a dosage be repeated rather than increased.

Table 1 Treatment Regimens

Treatment Group	Regimen*
BTRX-246040	• Cohort 1 - 40 mg ([redacted]) • Cohort 2 - 80 mg ([redacted]) • Cohort 3 - 120 mg ([redacted])
Placebo	• Cohort 1 - ([redacted]) • Cohort 2 - ([redacted]) • Cohort 3 - ([redacted])

9.2 MATERIALS AND SUPPLIES

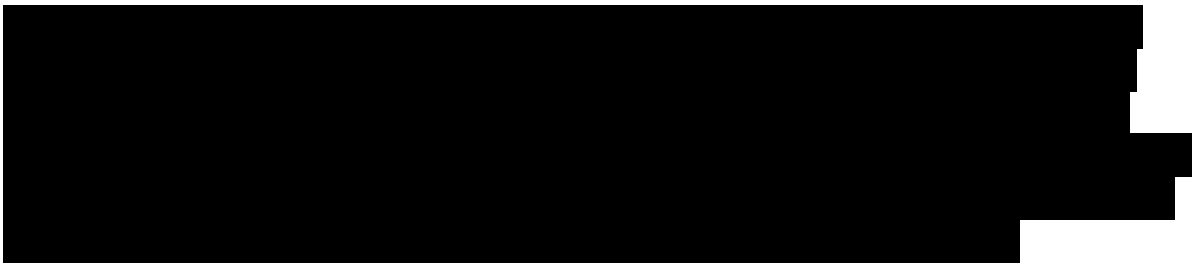
BTRX-246040 and placebo capsules and packaging will be identical to maintain Investigator and subject blinding. Subjects should be instructed to swallow capsules whole and not crush or chew and store the capsules in their original packaging at the temperature listed on the package label. Clinical trial materials will be labeled according to the regulatory requirements.

9.3 METHOD OF ASSIGNMENT TO TREATMENT

Subjects who meet all inclusion criteria and are subsequently not excluded by the exclusion criteria will be randomized to double-blind treatment at Visit 2 using an IWRS. Subjects will be randomized in a 6:2 ratio to one of two treatment arms (BTRX-246040 or placebo).

9.4 RATIONALE FOR SELECTION OF DOSES IN THE STUDY

The starting dose for cohort 1 will be 40 mg. A[redacted]



Another Phase 2 study, NEP-MDD-201, compared single-daily dosing of BTRX-246040 vs. placebo administered over 8 weeks in a double-blind, placebo-controlled, parallel-group study. After screening, eligible subjects were randomized to either 40 mg of BTRX-246040 or placebo and after one week the dose was increased to 80 mg and allowed to be down-titrated to 40 mg at the next visit for tolerability. BTRX-246040 and placebo had a similar rate of dose reduction (3/53 [5.7%] vs. 2/51 [3.9%]). The most common TEAEs that occurred more frequently with BTRX-246040 than placebo were nausea (5/53 [9.4%] vs. 3/51 [5.9%]), upper respiratory tract infection (3/53 [5.7%] vs. 2/51 [3.9%]), gastroenteritis, urinary tract infection, anxiety, and irritability (all 3/53 [5.7%] vs. 1/51 [2.0%]). One subject assigned to the placebo group had an SAE (Preferred Term: rhabdomyolysis). No deaths were reported.

In all three Phase 2 studies, most TEAEs were mild or moderate in severity. There were no notable treatment-related clinical laboratory findings or abnormal ECGs. Vital signs were generally within normal ranges, with no notable treatment-related changes reported following 40 mg and following 80 mg QD BTRX-246040. In all studies, no increase in suicidal ideation or behavior relative to placebo was detected following BTRX-246040 administration, as assessed by the C-SSRS.

As BTRX-246040 has not previously been tested in PD, three dosing cohorts (40, 80, and 120 mg) of 8 subjects with a 6:2 randomization to BTRX-246040 or placebo are planned in order to explore the effective dose range.

9.5 Selection and Timing of Doses

BTRX-246040 has only been dosed with a light breakfast in clinical pharmacology studies to date; there are currently no PK data available for BTRX-246040 when dosed in the fasted state.

Therefore, in the current study, subjects will take the investigational study drug orally in the morning with a light breakfast.

9.6 BLINDING

This is a double-blind study. Subjects, site personnel, and the Sponsor will be blinded to treatment.

The Investigator should make every effort to contact the medical monitor prior to unblinding a subject's treatment assignment. If an Investigator, site personnel performing the assessments, or subject is unblinded, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the Investigator must obtain specific approval from the Sponsor-designated Medical Monitor for the subject to continue in the study.

9.7 DOSING REVIEW COMMITTEE

Safety will be evaluated by the DRC, which will be comprised of the Principal Investigator, Medical Monitor and Pharmacovigilance to assess safety, tolerability, and efficacy of BTRX-246040. The DRC may make the following decisions based on its review of the available data:

- escalation to the next higher dose level
- escalation of the dose level is not warranted because of dose-related toxicity
- escalation is warranted to a lower dose than originally planned
- escalation should be postponed pending collection of additional data from currently-enrolled subjects
- additional subjects should be added to a cohort to better understand safety at that level.

After enrollment of the first cohort has been completed, doses for subsequent cohorts may be modified as above based on review of the available data (safety, tolerability, efficacy, and PK) by an unblinded Dosing Review Committee (DRC). A similar review and determination of dosing for the subsequent cohort will be performed after completion of cohorts 1 and 2 and based on all data available from previous cohorts.

9.8 CONCOMITANT THERAPIES

In general, stable doses of concomitant medications will be allowed during the study if stable dosing occurred during the 1 month prior to the screening visit. Subjects may receive antidepressant medications if the doses have been stable for at least 8 Weeks prior to the screening visit. The Investigator should instruct subjects to notify the study site about any new medications he/she takes and about any significant non-pharmacological therapies administered after the start of the study drug (e.g. acupuncture, hypnosis etc.). All medications, including over the counter medications and supplements, and also significant non-pharmacological therapies, administered after the subjects start treatment with study drug must be listed on the corresponding CRFs.

9.8.1 ANTI-PD MEDICATIONS

Subjects are required to be on a stable regimen of permitted anti-PD medications for at least 4 weeks (with the exception of MAO-B inhibitors, which must be stable for 8 weeks) prior to Screening (see inclusion and exclusion criteria Section 7.1 and 7.2). All efforts should be made to maintain subjects on the same stable dose and frequency of their anti PD medications throughout their participation. The addition of any new anti-PD medications or an increase in the dose of any anti-PD medications is not permitted. Likewise, changes to the frequency (number of doses taken per day) or to the intervals between doses (duration of time between doses on a given day) of a subject's anti-PD medication(s) are not permitted. An as needed dose of levodopa or other anti-PD medication would be considered a change in frequency as it is not a regular part of the daily regimen.

9.8.2 PROHIBITED MEDICATIONS/TREATMENTS

The following concomitant medications are prohibited:

- Current or previous use of Duopa/Dupdopa
- Current use of Apomorphine
- All anti-psychotic medications for more than 1 month within the past 2 years, or any exposure within the past year
- Use of proton pump inhibitors within 5 half-lives of Visit 2
- Fluoxetine and irreversible monoamine oxidase inhibitors within 4 weeks of Visit 2
- Bupropion within 8 weeks of the screening visit
- Current use or use within 5 half-lives of Screening of any medications or supplements that are strong inhibitors or inducers of CYP3A4. Examples are provided below. A further listing of strong CYP3A4 inhibitors and inducers can be found in Appendix 2.
    - Strong CYP3A4 inhibitors include:
        - Antifungal azoles
        - Macrolide antibiotics
        - Human immunodeficiency virus protease inhibitors
        - Boceprevir
        - Nefazodone
        - Conivaptan
    - Strong CYP3A4 inducers include:
        - Rifampin
        - Phenytoin
        - Carbamazepine
        - Enzalutamide
    - St. John's wort

10 SAFETY, EFFICACY EVALUATIONS, BLOOD SAMPLE COLLECTION AND TESTING, AND SAFETY MEASUREMENTS

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 1) All scales and tasks will be completed and/or administered by qualified and trained site raters who meet the training requirements and qualifications of the scale or task standards set by the Sponsor and training vendors.

10.1 EFFICACY MEASURES

10.1.1 UNIFIED PARKINSON'S DISEASE RATING SCALE

The UPDRS is well-established and the most widely used assessment to quantify the signs and symptoms of PD (Fahn, Elton, & Committee, 1987). The total UPDRS consists of 4 parts which assess the following:

1. Mentation, behavior and mood
2. Activities of Daily Living (ADL)
3. Motor function
4. Complications of therapy

Only Part III will be utilized in this trial. The UPDRS Part III is a 14-item rating scale, which consists of the motor examination. Each item is scored from 0 (Normal) to 4 (Most severe). The UPDRS Part III scale should only be administered by a rater who has adequate experience with subjects with PD and should be a trained neurologist or other trained research staff with experience in conducting the UPDRS. All attempts should be made to ensure that the same trained research staff member performs the UPDRS part III for a given subject.

An additional single item to rate dyskinesia is added to the scale and is rated from 0 (No dyskinesia) to 4 (Severe dyskinesia: maximal amplitude and present during most of the exam).

The UPDRS and dyskinesia rating will be conducted as indicated in the Schedule of Assessments (Appendix 1).

10.2 SAFETY MEASURES

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The Investigator is responsible for the appropriate medical care of subjects during the study.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

10.2.1 Adverse Events

An AE is any sign, symptom, illness, clinically significant abnormal laboratory value or ECG finding, or other untoward medical occurrence associated with the use of an investigational product that appears or worsens in a subject during a clinical study. This definition does not imply a causal relationship between the AE and the investigational product.

Adverse events beginning with the initial dose of investigational product or during the subsequent duration of their enrollment in the study will be considered treatment-emergent AEs (TEAE). TEAEs will be recorded on the AE CRF to include the event, date of onset, severity, frequency, seriousness, date of resolution, action taken with respect to the AE (e.g., concomitant medication, non-pharmacological treatment, etc.), outcome, and relationship to the investigational product. All TEAEs related to study drug will be followed through resolution or 30 days after the subject terminates from the study, whichever occurs first.

Medical conditions present or AEs occurring prior to the first dose of investigational product will be captured as medical history in the CRF. Any AE occurring during the study that is related to a pre-existing condition or event that worsens in intensity or frequency after the first dose of investigational product will be recorded as a TEAE.

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

10.2.2 Classification of an Adverse Event

10.2.2.1 Severity of Event

Each AE will be assessed by the Investigator with regard to the categories discussed in the sections below. The Investigator will assess all AEs for severity in accordance with the following standard ratings.

MILD = of little concern to the subject and/or of no clinical significance; is not expected to have any effect on the subject's health or well-being;

MODERATE = discomfort enough to cause interference with or change in usual activities; is likely to require medical intervention and/or close follow-up;

SEVERE = incapacitating or unable to work or participate in many or all usual activities, is of concern to the subject and/or poses substantial risk to the subject's health or well-being; is likely to require medical intervention and/or close follow-up.

For an AE that begins and ends on the same day and severity worsens over that day, one AE will be recorded and will be assessed with the highest level of severity for that day. For an AE that continues over multiple days (past the initial day of onset), if an increase in severity level occurs, only the maximum level of severity will be documented. For a non-TEAE in which the duration continues beyond administration of the first dose of study drug, if the AE increases in severity or frequency after study drug administration, then the initial AE will be closed and a new TEAE

will be opened documenting the new higher level of severity (at the maximum severity level for the remaining duration of the AE). An AE characterized as intermittent requires documentation of onset and duration of each episode.

10.2.2.2 Relationship to Study Drug

The Investigator will assess the causality/relationship between study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions below and all contributing factors:

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to study drug administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the study drug should be clinically plausible.
Probably Related	A clinical event, including laboratory test abnormality, is a known effect of drug with a reasonable time sequence to administration of the drug, and which cannot be reasonably explained by the known characteristics of the participant's clinical state.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Not Related	A clinical event, including laboratory test abnormality, with little or no temporal relationship with study drug administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals)

10.2.3 Overdose

In the event of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the Sponsor-designated Medical Monitor, or designee. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug. Such documentation may include, but not be limited to the Investigator's Brochure. As the study drug will only be administered by study staff while the subject is in the clinic, the likelihood of an overdose occurring in this study is considered unlikely.

10.2.4 Pregnancy

Any pregnancy that occurs from baseline after study drug exposure until study completion must be reported to the Sponsor-designated Medical Monitor on a Pregnancy Notification Form within 24 hours of learning of its occurrence.

Each pregnancy must be reported as well to the Sponsor-designated Medical Monitor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

10.2.5 Serious Adverse Events

A serious adverse event (SAE) is any AE that results in one of the following outcomes, regardless of the Investigator's opinion of causation:

1. death
2. initial or prolonged in-subject hospitalization
    a. Surgeries planned prior to signing the ICF will not be considered SAEs. However, worsening of the underlying medical condition during the study will be considered an AE and must be captured as serious if any SAE-defining outcomes occur as a result.
3. a life-threatening experience (that is, immediate risk of dying)
4. persistent or significant disability/incapacity
5. congenital anomaly/birth defect
6. other medically important serious event as determined by the Investigator (for example, an AE that jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition). If a subject experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will be captured as medical history in the CRF and not submitted as reportable-event unless the Investigator feels the event may have been caused by a protocol procedure.

SAEs reported after a subject has taken a dose of investigational product will be collected in the pharmacovigilance system for 30 days after the last dose of investigational product. Thereafter, only SAEs that the Investigator feels were related to the investigational product or a protocol procedure must be reported.

All SAEs must be captured on a study-specific SAE form in addition to the AE CRF. Study site personnel must alert the Sponsor-designated Medical Monitor of the SAE and must submit the completed study-specific SAE form to the Sponsor-designated Medical Monitor within 24 hours of the site's awareness of the SAE.

The Investigator and supporting personnel responsible for subject care should discuss with the Sponsor-designated Medical Monitor or designee any need for supplemental investigations of

SAEs. The results of these additional assessments conducted must be reported to the Sponsor-designated Medical Monitor. If a subject death occurs during participation in the study and a post-mortem examination is performed and a copy of the autopsy report is available, it should be submitted to the Sponsor-designated Medical Monitor.

The Investigator is responsible for safety reporting in compliance with their Institutional Review Board (IRB).

10.2.6 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure.

The Sponsor is responsible for IND safety reporting as per 21 CFR 312.32.

10.3 Measures to be performed only at Screening

10.3.1 Modified Hoehn and Yahr Scale

The Modified Hoehn and Yahr PD Staging is a scale expressing the severity of the symptoms of PD (Hoehn & Yahr, 1967). It provides a practical classification of 5 stages of ever increasing severity. The stages are defined as:

- Stage 0 = No signs of disease.
- Stage 1 = Unilateral disease.
- Stage 1.5 = Unilateral plus axial involvement.
- Stage 2 = Bilateral disease, without impairment of balance.
- Stage 2.5 = Mild bilateral disease, with recovery on pull test.
- Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
- Stage 4 = Severe disability; still able to walk or stand unassisted
- Stage 5 = Wheelchair bound or bedridden unless aided.

Modified Hoehn and Yahr scale will be assessed in the ON state at Screening.

10.3.2 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is a widely used screening assessment for detecting cognitive impairment (Nasreddine, et al., 2005). It was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points; a score of 26 or above is considered normal.

10.3.3 Beck Depression Inventory-II

The BDI-II is a 21 question, multiple choice self-report inventory used to measure the severity of depression (Beck, Steer, & Brown, 1996). In its current version, the BDI-II is designed for individuals aged 13 and over and is composed of items relating to symptoms of depression, such as hopelessness and irritability; cognitions, such as guilt or feelings of being punished; and physical symptoms, such as fatigue, weight loss, and lack of interest in sex. Each question is scored on a scale value of 0 to 3, with higher total scores indicating more severe depressive symptoms.

10.4 Laboratory Procedures/Evaluations

10.4.1 Safety Laboratory Evaluations

Clinical laboratory evaluations (including clinical chemistry panel, hematology, coagulation [including PT, aPTT, INR] parameters and urinalysis) will be collected as indicated in the Schedule of Assessments (Appendix 1).

A urine drug screen for selected drugs of abuse will be performed at Screening.

Investigators must document their review of each safety laboratory report.

Clinical laboratory assessments will be performed by a central laboratory. Detailed processing, storage, and shipping instructions for the clinical samples will be provided in a separate Laboratory Manual.

Additional clinical laboratory evaluations may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggest a more detailed assessment of clinical laboratory safety evaluations is required. Any changes to the scheduled times of clinical laboratory determination will be agreed to with the Sponsor and documented in the study master file.

Table 2 Clinical Laboratory Tests

The following laboratory variables will be determined:

Hematology:	**Clinical Chemistry:** Serum concentrations of:
Hemoglobin	Sodium
coagulation [including PT, aPTT, INR] parameters	Potassium
Hematocrit	Sodium bicarbonate
Erythrocyte count (red blood cell [RBC])	Chloride
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (white blood cell [WBC])	Alkaline phosphatase
Neutrophils, segmented	

Absolute Neutrophil Count (ANC) Lymphocytes Monocytes Eosinophils Basophils Platelets **Urinalysis:** Specific gravity pH Protein Glucose Ketones Blood Urine leukocyte esterase	Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) Gamma-glutamyl transferase (GGT) Blood urea nitrogen (BUN) Creatinine Uric acid Phosphorous Calcium Glucose (random) Albumin Total cholesterol Creatine kinase (CK)[a]
Urine Drug Screen[b] Amphetamines Barbiturates Benzodiazepine Cannabinoids Cocaine Ethyl alcohol Opiates Phencyclidine Propoxyphene Methadone	**Viral Serology:** Hepatitis B Surface Antigen (HBs Ag) Hepatitis B Core Antibody (HBc Ab) Hepatitis C Antibody (HC Ab) Hepatitis A Antibody (HAV-Ab [IgM]) HIV

[a] Creatine kinase muscle-brain isoenzyme (CK-MB) is to be assayed if CK results >1000 IU/L.
[b] Performed at screening and at the Investigator's discretion throughout the study.

10.4.2 URINE DRUG SCREEN

A urine drug screen for drug abuse will include: amphetamines, barbiturates, benzodiazepine, cannabinoids, cocaine, ethyl alcohol, opiates, phencyclidine, propoxyphene, and methadone. No retest is allowed for a positive result with a drug of abuse (e.g., cocaine, cannabinoids, phencyclidine, and methadone).

The site must contact the Sponsor-designated Medical Monitor or designee for pre-approval before a retest of other drugs that presented as positive as long as the subject has a valid prescription and there is no evidence of a Substance Use Disorder. In the case of Alcohol (Ethyl Alcohol) as long as there is clear justification for the finding and no history nor lab pattern

consistent with Alcohol Use Disorder. If the results from an allowed repeat urine drug screen are negative, the subject may be included. If the repeat results are positive, the subject must be excluded from the study. A second retest is not admissible.

[redacted]

10.4.4 Specimen Preparation, Handling and Storage

Blood and urine samples for clinical laboratory evaluation will be prepared, handled, and stored per details provided in the Central Laboratory Manual. [redacted]

Blood samples for analysis of BTRX-246040 levels will be collected via direct venipuncture or cannulation. The volume of blood to be collected for clinical [redacted] analysis is included in Table 3.

Table 3: Schedule and volume of Blood Sampling

Study Periods	SCRN	Treatment Period	F/U or ET
Visit no.	**1**	**2**	**3**
Study Day	**-28 to 0**	**1**	**8 (±1)**
Laboratory Evaluation	**mL**	**mL**	**mL**
Serum biochemistry	10	--	10
Hematology	4	--	4
[redacted]	--	18	--
Maximum Total	**14**	**18**	**14**

Abbreviations: SCRN=Screening Visit; FU=Follow-up, ET=Early Termination Visit
[redacted]

10.5 Other Safety Measures

10.5.1 Vital Sign Measurements

Vital signs (respiratory rate, oral temperature, orthostatic blood pressure, and pulse) will be measured at each visit as specified in the Schedule of Assessments (Appendix 1).

Orthostatic vital signs will be measured after subjects remain supine for at least 5 minutes prior to obtaining a single measurement of blood pressure and pulse. Subjects will then stand, and blood pressure and pulse will be taken approximately 2 minutes after standing. Three sets of supine and standing vital signs will be measured at least 15-20 minutes apart prior to dosing and will be measured once approximately 2, 4, 6, and 8 hours after dosing with study drug as indicated in the Schedule of Assessments (Appendix 1). When vital signs are scheduled at the same time as blood draws, the vital signs will be obtained prior to blood collection. Blood will be collected as close to the scheduled time as possible.

10.5.2 Height and Weight

Height and weight will be measured during the study as indicated in the Schedule of Assessments (Appendix 1). Height should be measured only once at screening with no shoes for correct measurement. The BMI will be calculated based on height and weight measured at screening.

10.5.3 Physical Examination

A routine physical examination of general appearance, skin (sufficient to detect any suspicious lesions, particularly any lesions potentially suggestive of melanoma), head, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, lymph nodes, and extremities will be performed at the time points specified in the Schedule of Assessments (Appendix 1).

10.5.4 Neurological Examination

Neurological examination of cranial nerves, motor system, sensory, and reflexes will be conducted at screening and all subsequent study visits. Complete neurological examination including mental status, cranial nerves, motor systems, deep tendon reflexes, cerebellar function (balance and coordination), gait, and sensory systems will be performed by a qualified physician in the ON state whenever possible, at the time points specified in the Schedule of Assessments (Appendix 1).

10.5.5 Collection of Electrocardiograms

For each subject, single 12-lead digital ECGs will be collected as indicated in the Schedule of Assessments after resting for 5 min.

The ECGs will initially be interpreted by a qualified physician (the Investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the Fridericia's correction method for the QT (QTcF) interval from baseline (e.g. QTcF $\geq$ 500 msec and/or QTcF increased $\geq$ 60 msec) or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the Investigator for symptoms (e.g., palpitations, near syncope, syncope) and to determine whether the subject can continue investigational product. The Investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation for each time point.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full over-read. A report based on data from this over-read will be issued to the investigative site. All data from the over-reads will

be placed in the Sponsor database for analytical and study report purposes. Any clinically significant finding that was present on the fully over-read ECG will be reported to the Investigator and to the Sponsor.

When there are differences in ECG interpretation between the Investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the Investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The Investigator (or qualified designee) must document his/her review of ECGs printed at the time of collection, the final over-read ECG report issued by the central ECG laboratory, and any alert reports.

10.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be used to assess suicidal tendency ("C-SSRS for Research", 2016). The Baseline/Screening version of the C-SSRS will be used at the Screening visit. This version assesses suicidality in a subject's lifetime and during the past specified months. The Since Last Visit version of the C-SSRS will be used at all other visits. This version assesses suicidality since the subject's last visit. Efforts must be made to ensure that the same trained team member completes this questionnaire for each subject.

If a suicide-related event is identified at any time during the study, a thorough evaluation should be performed by a study physician and appropriate medical care should be provided. In some subjects taking antidepressants, worsening of depression, suicidal events (suicidal thinking and/or behavior), or unusual changes in behavior have been reported, especially at the beginning of the drug therapy. It is important that subjects are instructed to notify their doctor immediately if they have any distressing thoughts or feelings at any time related to harm to either self or others. Subjects who answered YES to questions 4 or 5 in the C-SSRS questionnaire at Screening are excluded and should be referred to a mental health professional.

10.5.7 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale (QUIP-RS)

The QUIP-RS is an instrument used to measure the extent of impulsive and compulsive behaviors in PD patients (Weintraub, et al., 2012). The Screening version of the QUIP-RS will be used at the Screening visit. This version assesses compulsive behaviors in PD patients over the last four weeks. THE QUIP-RS Since Last visit version will be used at all other visits. The QUIP-RS is The QUIP-RS consists of 4 questions which have to be answered for each disorder (gambling, sex, buying, eating, hobbyism, punding, and PD medication use) on a 5-point Likert scale. The scoring range for each scale (ie, disorder) is 0–16. The QUIP-RS will be completed as indicated in the Schedule of Assessments (Appendix 1).

10.5.8 Safety Monitoring

The Sponsor-designated Medical Monitor and the study team will monitor blinded safety data throughout the course of the study. This will include review of AEs, SAEs, any AEs of special interest, ECG findings, neurological exams, laboratory results, vital signs, and other safety data.

The unblinded Dosing Review Committee (DRC) will convene to review unblinded safety and tolerability data at the completion of cohorts 1 and 2 to determine if it is safe to proceed with the next higher dose, repeat the same dose or stop the study.

10.5.8.1 Complaint Handling

The Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Subjects will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

For blinded studies, all product complaints associated with material packaged, labeled, and released by the Sponsor or its delegate will be reported.

The Investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

1. recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
2. submitting the completed product complaint form within 24 hours to the Sponsor or its designee.

[redacted]

10.7 Appropriateness of Measurements

Efficacy and safety assessments used in the study are generally regarded as reliable, accurate, and relevant in this subject population.

11 DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

1. provide instructional material to the study sites, as appropriate
2. provide start-up training to instruct the Investigators and study site personnel. This training will give instruction on the protocol, the completion of the eCRFs, study procedures, and on handling and administering the study drug
3. make periodic visits to the study site
4. be available for consultation and stay in contact with the study site personnel by email and telephone
5. review and evaluate eCRF data and standard computer edits to detect errors in data collection
6. conduct a quality review of the database.

In addition, the Sponsor or its representatives may periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the Sponsor, its representatives, and/or applicable regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRBs with direct access to original source documents.

11.1 DATA CAPTURE SYSTEM

The Sponsor will select a 21-CFR compliant electronic data capture system (EDC) and provide appropriately trained site personnel user permissions to enter information on the electronic CRFs (Case Report Forms). The site will maintain a separate source for the data entered onto CRFs. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appears inconsistent, incomplete, or inaccurate.

Electronic data collected on other devices will be transferred to the Sponsor's selected EDC, as applicable.

An identification code assigned via the use of the randomization envelopes to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting study-related data.

12 SAMPLE SIZE AND STATISTICAL METHODS

12.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation is being calculated. A sample size of 8 subjects per cohort is deemed sufficient to evaluate the preliminary safety, tolerability, and efficacy of the different dose levels.

12.2 STATISTICAL AND ANALYTICAL PLANS

12.2.1 GENERAL CONSIDERATIONS

Data collected from eCRFs, ECG, or clinical laboratory evaluations will be listed by treatment group and subject identification.

Generally, if not specified, continuous data will be summarized by descriptive statistics, including number of subjects with data, mean, standard deviation, median, and range. Categorical data will be summarized by the number and percentage of subjects for each category or classification.

A detailed statistical analysis plan (SAP) will be developed by the Sponsor or its designee and will be finalized before locking the study database.

12.2.2 ANALYSIS POPULATIONS

12.2.2.1 MODIFIED INTENTION TO TREAT POPULATION

The modified Intention-to-Treat (mITT) Population will include all randomized subjects who received at least one dose of study drug and have at least 1 post-baseline scoring of motor activity. In accordance with the intent-to-treat principle, all subjects will be kept in their randomized treatment group. The mITT Population will serve as the primary population for efficacy evaluation.

12.2.2.2 SAFETY POPULATION

The Safety Population will include all subjects who received study drug. All subjects will be evaluated according to actual treatment type received.

12.2.3 SUBJECT DISPOSITION

Subject disposition will be presented for the mITT and Safety Populations

12.2.4 BASELINE SUBJECT CHARACTERISTICS

Summary tables of demographics and other baseline characteristics will be presented for the mITT and Safety Populations to assess the comparability of the treatment groups at study start. For continuous variables, descriptive statistics (n, mean, SD, standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary.

12.2.5 Concomitant Therapies

Previous and concomitant drug therapy will be coded to Anatomical, Therapeutic, or Chemical (ATC) level and preferred drug name according to the World Health Organization Drug Dictionary (WHODD). These medications will be summarized by treatment group, ATC classification, and preferred drug name. This analysis will be conducted on the Safety Population.

12.2.6 Multiplicity Issue

Not applicable.

12.2.7 Efficacy Analysis

All efficacy endpoints will be summarized by visit, including change from baseline information.

12.2.7.1 Primary Efficacy Analysis

The maximal change from predose in UPDRS Part III scores will be summarized by data listings, descriptive statistics, and graphical displays. This analysis will use the mITT Population.

12.2.7.2 Sensitivity Analysis of the Primary Efficacy Endpoint

No sensitivity analyses will be performed on the primary efficacy endpoint.

12.2.7.3 Secondary Efficacy Analyses

The secondary endpoints consist of the following:

- Duration of ON time on Day 1
- Percentage of subjects that turn ON on Day 1
- Time to ON on Day 1
- Area under the curve for UPDRS Part III during the 8 hours of assessment on Day 1
- Change from pre-dose dyskinesia rating (from the UPDRS Part III motor response and dyskinesia assessment)

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, subject counts and percentages will be provided. Summaries will be presented by treatment group. Graphical displays will be created as appropriate, including for the UPDRS by time point.

12.2.8 Safety Analyses

Safety analysis will use the Safety Population. The overall safety and tolerability of BTRX-246040 treatment will be assessed by evaluating the safety and tolerability measures listed below.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical

variables, subject counts and percentages will be provided. Summaries will be presented by treatment group.

12.2.8.1 ADVERSE EVENTS

Adverse events will be recorded from the time when a subject has signed the ICF through the Follow-Up period. The MedDRA dictionary will be used to standardize the terms used by the Investigator to describe the AEs. Adverse event analyses will include TEAEs, defined as AEs which start after the first dose of the study medication. The TEAEs will be summarized as subject and event counts, complemented by percentages calculated for the subject count, unless specified otherwise. At least the following analyses of TEAEs will be provided.

- Breakdown of TEAEs by System Organ Class (SOC) and preferred term, according to MedDRA dictionary.
- Breakdown of TEAEs by SOC, preferred term, and severity (event count only, percentages calculated out of the total number of TEAEs)
- Breakdown of TEAEs by SOC, preferred term, and relationship to the study medication (event count only, percentages calculated out of the total number of TEAEs)
- Breakdown of TEAEs leading to death by SOC and preferred term
- Breakdown of Serious TEAEs other than deaths by SOC and preferred term
- Breakdown of AEs leading to premature discontinuation by SOC and preferred term
- Listings of non-TEAEs will also be provided.

In case the number of TEAEs in the tabulations above is low, the tabulations will be replaced by data listings.

12.2.8.2 SAFETY LABORATORY TESTS

Summary statistics of laboratory data will be presented for each visit by treatment group. Actual values and changes from baseline will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from Baseline will be summarized as well.

12.2.8.3 VITAL SIGNS

Summary statistics for vital signs will be presented for each visit by treatment group. Actual values and changes from baseline will be summarized using descriptive statistics.

12.2.8.4 ELECTROCARDIOGRAMS

Summary statistics for ECGs will be presented for each visit by treatment group. Actual values and changes from baseline will be summarized using descriptive statistics.

12.2.8.5 PHYSICAL EXAMINATION

Summary data of physical examination results will be provided by study visit by treatment.

12.2.8.6 Orthostatic Blood Pressure

The first blood pressure will be after the subject lies down for at least 5 minutes; the second blood pressure will be recorded after the subject stands for approximately 2 minutes. This will be repeated for a total of 3 times, approximately 15-20 minutes apart. The average of the three BP and pulse measurements will be used for comparison to all post-treatment measurements to minimize the impact of biological variability and to serve as a more reliable baseline orthostatic vital sign measurement. A drop in systolic blood pressure of $\geq$ 20 mmHg, or in diastolic blood pressure of $\geq$ 10 mmHg upon standing will be considered abnormal.

Orthostatic blood pressure will be summarized by time point with descriptive statistics. Change from baseline will be summarized by post-baseline time point, both with descriptive statistics and categorically.

12.2.8.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. All C-SSRS data will be listed.

12.2.8.8 Impulsive Compulsive Disorders in Parkinson's Disease-Rating Scale

The frequency and percentage of subjects with positive response ("rarely" or higher) for each disorder will be summarized by treatment group and visit. Furthermore, the total Impulsive Control Disorder score and the total QUIP-RS score will be summarized with descriptive statistics by treatment group and visit (both absolute values and changes from baseline).

[redacted]

13 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

13.1 INFORMED CONSENT

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each subject. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

13.2 ETHICAL REVIEW

The Sponsor or its representatives must approve all ICFs before they are submitted to the IRB and are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site(s). The IRB(s) will review the protocol as required.

Any member of the IRB who is directly affiliated with this study as an Investigator or as site personnel must abstain from the IRB's vote on the approval of the protocol.

13.3 REGULATORY CONSIDERATIONS

This study will be conducted in accordance with:

1. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. the ICH GCP Guideline [E6]
3. applicable laws and regulations.

The Sponsor certifies that this study is being conducted under an active US Investigational New Drug (IND) application.

Some of the obligations of the Sponsor will be assigned to a CRO.

13.3.1 Investigator Information

Physicians with a specialty in neurology or physicians with experience or with medical site staff with experience in treating PD will participate as Investigators in this clinical trial.

13.3.2 Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal Investigator will sign the protocol signature page and provide a copy of the signed page to a Sponsor representative.

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15 APPENDICES

Appendix 1 Schedule of Assessments

Study Periods	SCRN	Treatment Period	Follow-up or Early Termination	Unscheduled visits[1]
Visit no.	**1**	**2**	**3**	
Study Day	**-28 to 0**	**1**	**8 (±1)**	
Informed consent Form	X			
Demographic Data	X			
Medical History, including PD history	X			
Vital signs[2]	X	X	X	X
Height and weight[3]	X	X	X	X
Physical Exam	X		X	X
Neurological Exam	X		X	
Concomitant Medications	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)-Baseline/Screening version	X			
Columbia Suicide Severity Rating Scale (C-SSRS)-Since last visit version		X	X	X
Montreal Cognitive Assessment (MoCA)	X			
Beck Depression Inventory-II	X			
QUIP-RS - Screening version	X			
QUIP-RS - Since last visit version		X	X	X
UPDRS Part III and dyskinesia rating in the OFF state	X[4]	X[5]		
UPDRS Part III and dyskinesia rating in the ON state	X[4]	X[5]		
Modified Hoehn and Yahr scale in the ON state	X			
12 lead ECG	X	X	X	X
Inclusion/exclusion criteria	X			

[1] Unscheduled visits may be conducted at any time for safety reasons and/or for any other reason.
[2] Vital signs include supine (at least 5 min) and standing (after approximately 2 min) BP and pulse rate, body temperature and body weight.
At Day 1, 3 sets each of supine and standing BP and pulse rate will be measured at least 15-20 minutes apart at pre-dose and will be measured once at 2, 4, 6, and 8 hours after dosing.
[3] Height will be measured only once, at Screening. Body weight will be measured once per visit.
[4] At screening, UPDRS Part III and dyskinesia rating should be done in the OFF and the ON state. This can be done in either the practically defined OFF state or after a subject wears OFF following a levodopa dose.
[5] At Day 1, UPDRS Part III and dyskinesia rating will be conducted in the OFF state Pre-dose and every 30 minutes for 4 hours and then hourly for another 4 hours (or until subject turns OFF) following study drug administration. If the subject remains ON after 8 hours, they should be called the next morning to record the time they turned OFF, and the time they took their first regularly scheduled anti-parkinsonian medications after study drug, to a maximum of 24 hours.

Laboratory Evaluation	X		X	X
Urine drug screen	X			
Approval via Enrollment Authorization Committee (EAC)	X			
Randomization		X		
Study Drug administered		X		
Adverse Events		X	X	X
[redacted]		[redacted]		
Time to ON and duration of ON recorded		X		
Drug accountability		X		

[redacted]

Appendix 2 Examples of Inhibitors and Inducers of CYP3A4

Per exclusion criteria: Are currently taking or have taken within 5 half-lives of Screening any medications or supplements that are strong inhibitors or inducers of CYP3A4. The listed moderate inhibitors/inducers below are not exhaustive. See also:

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Table 1.a Inhibitors of CYP3A4

Strong inhibitors [a]	Moderate inhibitors [b]
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
erythromycin	ciprofloxacin
grapefruit juice	darunavir
indinavir	diltiazem
itraconazole	erythromycin
ketoconazole	fluconazole
lopinavir	fosamprenavir
mibefradil	imatinib
nefazodone	verapamil
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

[a] Increases the area under the curve (AUC) of the substrate by ≥ 5-fold.
[b] Increases the AUC of the substrate by 2- to 5-fold.

Table 1.b Inducers of CYP3A4

Strong inducers [a]	**Moderate inducers [b]**
avasimibe	bosentan
carbamazepine	efavirenz
enzalutamide	etravirine
phenytoin	modafinil
rifampin	nafcillin
St John's wort	

[a] Decreases the AUC of the substrate by ≥ 80%.

[b] Decreases the AUC of the substrate by 50–80%.