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CLINICAL STUDY PROTOCOL

Title	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Phase to Determine the Efficacy and Safety of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End-of-Dose "Wearing-Off" (TOZ-PD)
Protocol Number	TOZ-CL05 (FINAL, 13 October 2017)
Phase	3
IND Number	78,230
EudraCT Number	2014-005630-60
Date of Amendment 3	**13 October 2017**
Date of Amendment 2	10 June 2015
Date of Amendment 1	19 May 2015
Original Date of Issue	30 March 2015
Sponsor	Biotie Therapies (a wholly owned subsidiary of Acorda Therapeutics Inc.) 701 Gateway Boulevard, Suite 350 South San Francisco, CA 94080 USA
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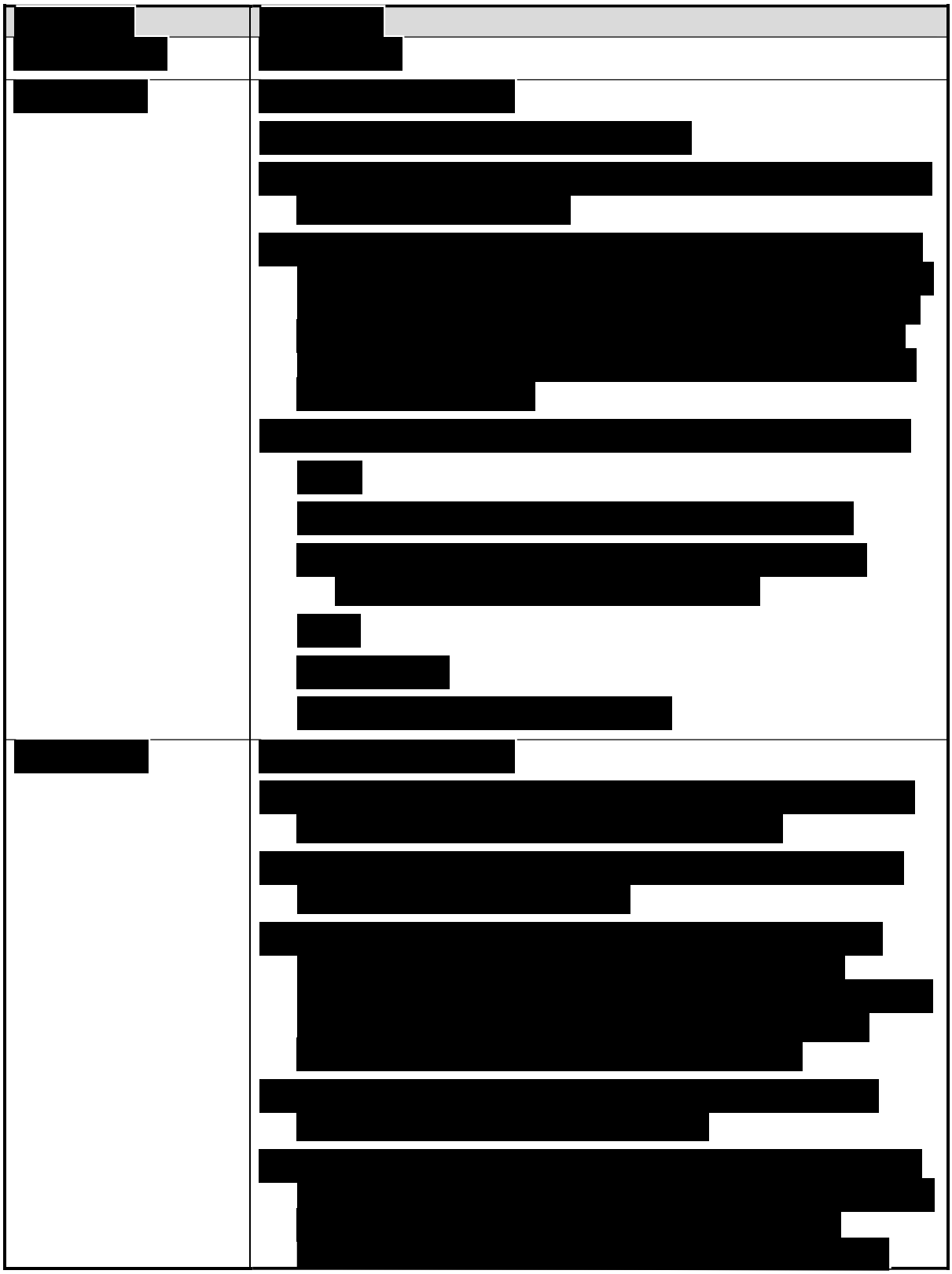

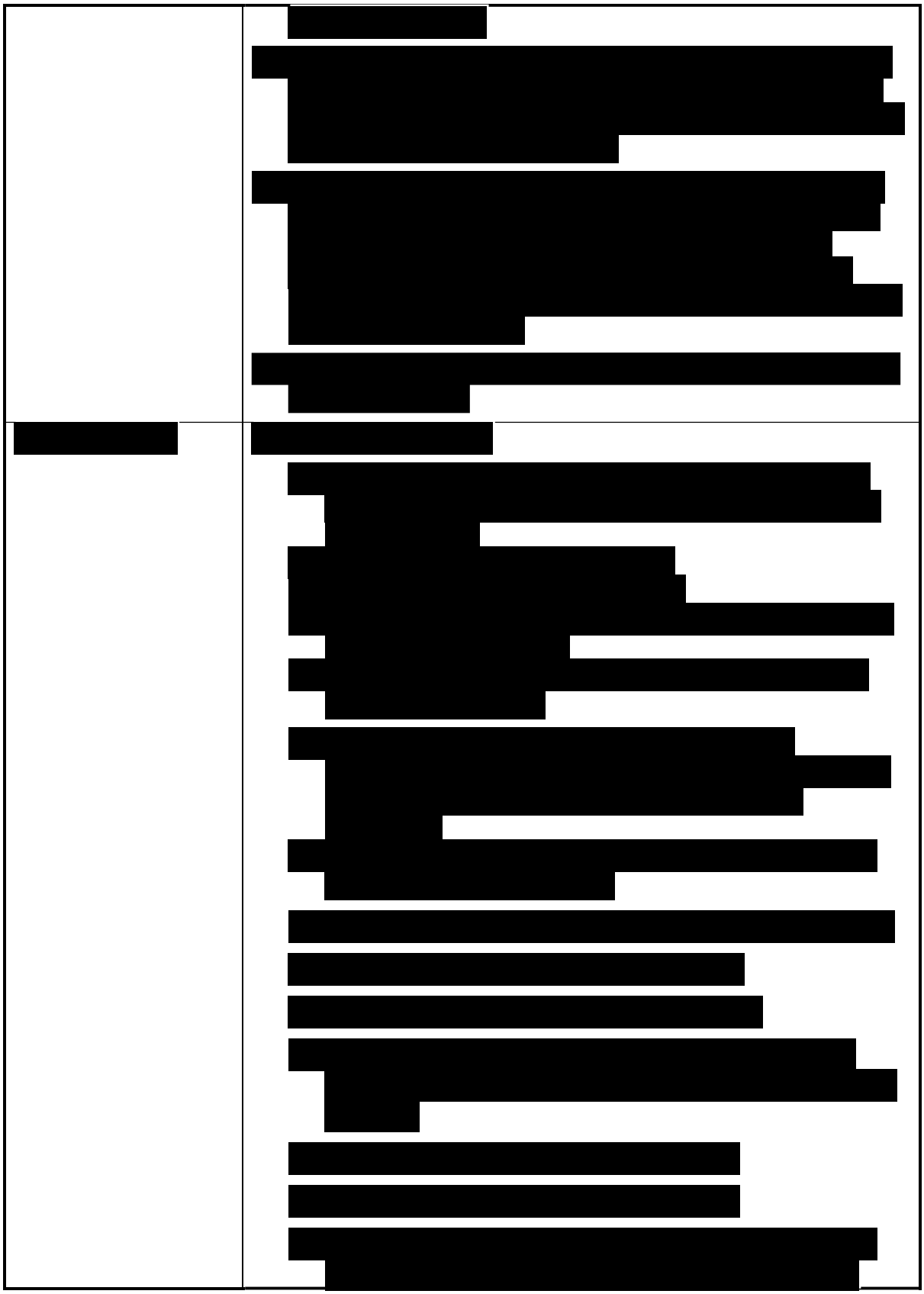

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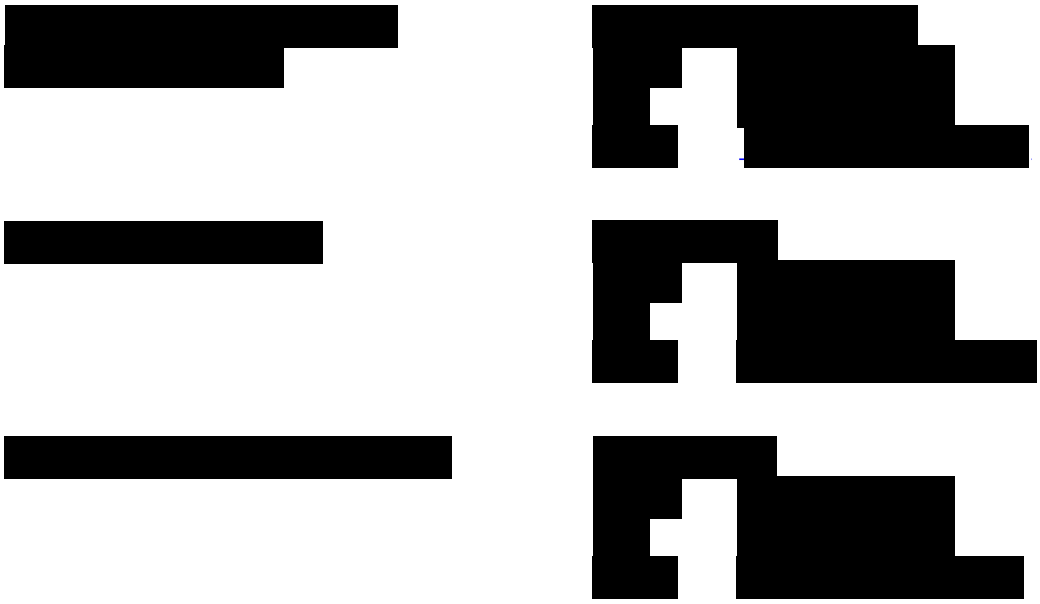
STUDY CONTACT INFORMATION

Biotie Therapies – Sponsor



REPORTING OF SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

1. Results in death.
2. Is life-threatening, i.e., places the patient, in the view of the investigator, at immediate risk of death at the time of the event.

   Note: Life-threatening does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity, i.e., results in a substantial disruption of a person's ability to conduct normal life functions.
5. Is a congenital anomaly or birth defect, i.e., an adverse event (AE) that occurs in the child or fetus of a patient exposed to a study drug prior to conception or during pregnancy.
6. Is an important medical event, i.e., an event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other serious outcomes listed above.

   Examples of important medical events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions. Interruption, discontinuation, or adjustment of dose level of study drug alone will not be considered an intervention that satisfies the definition of important medical event.

Although fulfilling the above listed criteria, the following events are not regarded as being serious for this study:

Hospitalizations for:

- Facilitation of assessments specific to this protocol not associated with any deterioration in condition (e.g., when travel time between a patient's home and the study site would otherwise preclude adequate evaluation).
- Elective or preplanned assessment or treatment for a preexisting condition that has not worsened since initiation of study drug administration.

Any SAE meeting above criteria that occurs during the study or within 4 weeks after the last dose of study drug must be reported within 24 hours (1 working day) by email and/or fax and by completing the AE electronic case report form (eCRF) and the SAE Report Form. Once the AE eCRF is completed designating an AE as serious, an email will be generated to notify [redacted] and [redacted] that an SAE has occurred and the information will be transmitted to the designated parties for review.

[redacted]

Refer to additional SAE reporting instructions in **Section 9.2**.

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

The undersigned have reviewed the format and content of this protocol and have approved Clinical Study Protocol TOZ-CL05 entitled **A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Phase to Determine the Efficacy and Safety of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End-of-Dose "Wearing-Off" (TOZ-PD)**, Amendment No. 3. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the investigator and must be documented in writing.

Sponsor: Biotie Therapies (a wholly owned subsidiary of Acorda Therapeutics Inc.)

Protocol Number: TOZ-CL05, Amendment No. 3

Date of Issue: 13 October 2017

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INVESTIGATOR'S STUDY ACKNOWLEDGMENT/DISCLOSURE

By my signature, I confirm that my staff and I understand that the protocol and Investigator's Brochure are the confidential and proprietary property of Biotie Therapies. Further, I/we have carefully read and understand this protocol and agree to comply with the conduct and terms of the study specified therein. In particular, I/we have agreed to:

1. Abide by all obligations per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines and applicable country regulations.
2. Conduct the study according to the protocol, its amendments and study procedure manuals and study guides.
3. Assure that written and dated approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the protocol, any amendments to the protocol, written informed consent form (ICF), any ICF updates, and Investigator's Brochure is available prior to initiation of any study-related procedure, and assure periodic review by the IRB/IEC as required per local and country regulations.
4. Obtain witnessed, written informed consent from each study participant or his/her legal representative.
5. Report all serious adverse events (SAEs) to Biotie Therapies or its agents and to the IRB/IEC, as required by the protocol, country and IRB/IEC regulations.
6. Assure access by study monitors to original source documents.
7. Cooperate fully with any study-related Good Clinical Practice (GCP) audit as performed by Biotie Therapies or its agents, the US Food and Drug Administration (FDA) and/or the Regulatory Health Authorities of the participating countries.
8. Maintain confidentiality and assure security of confidential documents such as the protocol, informed consent, case report forms, Investigator's Brochure, final study reports, study data, study procedure manuals, study guides, manuscript, and/or unpublished data and correspondence.
9. Maintain confidentiality of any supplemental information that may be added to this document.

Protocol Number: TOZ-CL05, Amendment No. 3

Date of Issue: 13 October 2017

Principal Investigator's Signature Date

Principal Investigator's Name
(printed first and last name)

LIST OF ABBREVIATIONS

6-OHDA	6-hydroxydopamine
A2a	Adenosine receptor subtype 2a
ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (alanine aminotransferase)
AM	Ante meridiem (before noon)
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of covariance
AST	Aspartate transaminase (aspartate aminotransferase)
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CK	Creatine phosphokinase
COMT	Catechol-O-methyltransferase
CPMP	Committee for Medicinal Products for Human Use
CRA	Clinical Research Associate
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
d	Day(s)
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMEA	European Medicines Agency
EQ-5D-5L	EuroQol 5D-5L Health Questionnaire
ESS	Epworth Sleepiness Scale
ET	Early Termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	US Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase (gamma-glutamyl transferase)
GMP	Good Manufacturing Practice

h	Hour(s)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD	Impulse control disorder
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IU/L	International units per liter
IUD	Intrauterine device
IXRS	Interactive Response System
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MAO-B	Monoamine oxidase type B
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat set
mMIDI	Modified Minnesota Impulse Disorders Interview
MMSE	Mini-Mental State Exam
MMRM	Mixed model repeated measures
msec	Millisecond
NMDA	N-methyl-D-aspartate
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Quality of Life Questionnaire
PGI-I	Patient's Global Impression of Improvement
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Interval from onset of P wave to start of QRS complex in ECG
PRN	As needed
PT	Preferred term
SCOPA-cog	Scales for Outcomes in Parkinson's Disease–cognition
QA	Quality assurance
QD	Once a day
QRS	Interval from onset of Q wave to end of S wave in ECG, representing time for ventricular depolarization
QT	Interval between Q and T waves in ECG

QTcF	Heart rate-corrected interval between Q and T waves in ECG calculated using Fridericia's correction formula
RR	Interval between successive peaks of R wave in ECG
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SS	Safety set
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
TSQM-9	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
ULN	Upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
US/USA	United States of America
V	Visit
VAS	Visual Analogue Scale
W	Week
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SYNOPSIS	
Title	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Phase to Determine the Efficacy and Safety of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End-of-Dose "Wearing-Off" (TOZ-PD)
Protocol Number	TOZ-CL05
Phase	3
Number of Sites/ Location	Approximately 80 sites in North America and Europe will participate.
Test Product, Dose and Mode of Administration	Test Product: Tozadenant tablet [redacted] Test Product Doses: 60 mg twice daily (BID), 120 mg BID. Comparator: Matching placebo tablet (double-blind phase [Part A] only). Mode of Administration: Oral.
Indication	Parkinson's disease (PD)
Study Objectives	Primary Efficacy Objective (Part A): To demonstrate the efficacy of the A2a receptor antagonist tozadenant in the treatment of levodopa-treated PD patients experiencing end-of-dose "wearing-off", based on the change from Baseline to Week 24 in the number of hours per day spent in the OFF state. Key Secondary Efficacy Objectives (Part A): 1. To evaluate the effect of tozadenant on good ON time (defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia). 2. To evaluate the effect of tozadenant on Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (Activities of Daily Living [ADL] subscale) + III (motor subscale) total scores. Other Secondary Efficacy Objectives (Part A): 1. To evaluate the effect of tozadenant on investigator global impressions of improvement (Clinical Global Impression of Improvement [CGI-I]). 2. To evaluate the effect of tozadenant on patient global impressions of improvement (Patient Global Impression of Improvement

PROTOCOL SYNOPSIS	
	[PGI-I]). 3. To evaluate the effect of tozadenant on UPDRS Part III (motor subscale) scores in the ON state. 4. To evaluate the effect of tozadenant on investigator global impressions of severity of illness (Clinical Global Impression of Severity [CGI-S]). 5. To evaluate the effect of tozadenant on UPDRS Part II (ADL subscale) scores. 6. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia). 7. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state without dyskinesia. 8. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome). 9. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state with non-troublesome dyskinesia. 10. To evaluate the effect of tozadenant on PD-related quality of life as measured by Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (total score and individual domain scores). 11. To evaluate the effect of tozadenant on UPDRS Part IV. 12. To evaluate the effect of tozadenant on UPDRS Part I. <u>Safety Objectives (Parts A and B)</u>: 1. To evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing end-of-dose "wearing-off", based on assessment of adverse events (AEs), vital signs, electrocardiograms (ECGs), physical and neurological exams, and clinical laboratory tests. 2. To evaluate the effects of tozadenant on the occurrence of daytime drowsiness (including episodes of sudden onset of sleep), impulsive behavior, and suicidality.
Study Population	Male or female patients, aged 30–80 years (inclusive), with a diagnosis of idiopathic PD who are receiving levodopa treatment and at least one other concomitant anti-PD medication and experiencing end-of-dose "wearing-off" (see inclusion and exclusion criteria).

PROTOCOL SYNOPSIS	
Study Design	Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm safety and efficacy study (Part A) with an open-label phase (Part B).
Number of Patients to be Screened/ Randomized	Part A: Approximately 645 patients will be screened, assuming a 30% screen failure rate, to randomize 450 patients. Part B: It is anticipated 80% of the randomized patients (i.e., approximately 360 patients) will complete Part A and continue into the open-label phase.
Study Duration	During Part A, each patient will participate for up to 30 weeks, which includes a Screening Period of 1 to ≤ 6 weeks, followed by a Baseline Visit and 24 weeks of double-blind treatment: • Screening Period: 1 – 6 weeks. • Double-Blind Treatment Period: 24 weeks. After completion of Part A, patients will continue in Part B for an additional 56 weeks: • Open-Label Treatment Period: 52 weeks. • Post-Treatment Safety Follow-Up: 4 weeks. The total anticipated study duration for an individual patient not prematurely terminated from the study will be a minimum of 81 weeks and a maximum of 86 weeks. The end of the study is defined as the date of the last visit of the last patient in the study.
Randomization	At the Baseline Visit (Part A), patients will be randomly allocated in equal proportion (1:1:1) to 1 of 3 double-blind treatment groups: 1. Group A: tozadenant 60 mg BID (one 60 mg active tozadenant tablet plus one placebo tablet, BID) 2. Group B: tozadenant 120 mg BID (two 60 mg active tozadenant tablets, BID) 3. Group C: placebo BID (two placebo tablets, BID)

PROTOCOL SYNOPSIS	
Dose Regimen	During Part A, randomized patients will be instructed to take two (2) tablets of the dispensed blinded investigational medicinal product (IMP) by mouth BID, in the morning and in the evening preferably at the same time each day, for a total of four (4) tablets per day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing. During Part A, the fixed study drug dosage may not be changed. Patients experiencing AEs considered to be study drug related and not tolerated by the patient will be discontinued from the study. Upon completion of Part A, all patients will begin dosing with open-label tozadenant IMP in Part B. Initially, patients will receive 120 mg (i.e., 60 mg × 2 tablets) by mouth BID, taken in the morning and in the evening preferably at the same time each day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses 1 hour before or 2 hours after a meal and to refrain from eating for 1 hour after dosing. Adjustments to the open-label tozadenant dose are allowed starting at Week 26 and at subsequent study visits. Doses of 60 or 120 mg BID are permitted; the investigator may adjust a patient's dose to either level as clinically indicated. Patients experiencing AEs considered to be study drug-related and not tolerated by the patient, despite dose reduction, will be discontinued from the study.
Concomitant Anti-PD Medications	To be eligible for randomization, patients are required to be on a stable regimen of permitted anti-PD medications for at least 4 weeks prior to Screening (see inclusion and exclusion criteria). The stable anti-PD medication regimen must include at least four doses of a levodopa-containing medication per day and at least one other concomitant anti-PD medication (dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone). All efforts should be made to maintain patients on the same stable dose and frequency of their anti-PD medications throughout Part A. After randomization, 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 patient's anti-PD medication(s) are not permitted. A PRN (as needed) dose of levodopa or other anti-PD medication would be considered a change in frequency as it is not a regular part

PROTOCOL SYNOPSIS	
	of the daily regimen. However, at the investigator's discretion, a decrease in the total daily dosage of concomitant anti-PD medication because of medication-related AEs is permitted: • A decrease in total daily dosage should be done by lowering the number or strength of tablets taken and must not be done by changing (lowering) the frequency (# of times per day the dose is taken). • Following a decrease in total daily dosage, the dose may be increased again but cannot exceed the total daily dosage at randomization. During Part B, patients' concomitant anti-PD medications (i.e., levodopa-containing medication, dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone) may be adjusted as needed under the investigator's supervision. The optimal dose of open-label tozadenant for each patient will be defined following discussion between the patient and the investigator, taking into account the potential for improvement of disease symptoms and the tolerability profile. Throughout Parts A and B, all medications taken by a patient and the reason for their use will be recorded in the source documents and electronic case report form (eCRF). Patients will use their own supply of anti-PD medication throughout the study.
Non-Pharmacologic Treatments for PD	Patients will be instructed that all non-pharmacologic treatments used to manage or control their PD symptoms should remain consistent throughout the double-blind portion (Part A) of the study. Such non-pharmacologic treatments may include, but are not limited to exercise, yoga, tai chi, martial arts, boxing, physical therapy, dance, music therapy, acupuncture, acupressure, and massage.
Efficacy Endpoints	<u>Primary Efficacy Endpoint (Part A)</u>: The primary efficacy endpoint will be the change from Baseline to Week 24 in the number of hours per day spent in the OFF state, as assessed by patient-completed PD diaries and averaged over 3 consecutive days. <u>Key Secondary Efficacy Endpoints (Part A)</u>: 1. Change from Baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia. 2. Change from Baseline to Week 24 on UPDRS Parts II

PROTOCOL SYNOPSIS	
	(ADL subscale) + III (motor subscale) total scores. Other Secondary Efficacy Endpoints (Part A): The other secondary efficacy endpoints include the change from Baseline to Week 24 (where applicable), for the following: 1. CGI-I at Week 24. 2. PGI-I at Week 24. 3. UPDRS Part III (motor subscale) score in the ON state. 4. CGI-S. 5. UPDRS Part II (ADL subscale) score. 6. Number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia). 7. Number of hours per day spent in the ON state without dyskinesia. 8. Number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome). 9. Number of hours per day spent in the ON state with non-troublesome dyskinesia. 10. PDQ-39 (total score and individual domain scores). 11. UPDRS Part IV score. 12. UPDRS Part I score. Exploratory Endpoints (Part A): The exploratory endpoints in Part A include the change from Baseline to Week 24 (where applicable), for the following: 1. Number of hours per day spent in the asleep state. 2. Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV. 3. Falls as measured by question 13 on UPDRS Part II. 4. Responder analysis of number (%) of patients with ≥ 1.0 h improvement in OFF time (evaluated at Week 24). 5. Responder analysis of number (%) of patients with ≥ 2.0 h improvement in OFF time (evaluated at Week 24). 6. Percent change in total levodopa equivalent dose. 7. Percent change in the number of hours per day spent in OFF state. 8. Percent change in the number of hours per day spent in ON state without troublesome dyskinesia. 9. Percent change in the number of hours per day spent in ON

PROTOCOL SYNOPSIS	
	state with troublesome dyskinesia. 10. Scales for Outcomes in Parkinson's Disease–cognition (SCOPA-cog) score. 11. Fall questionnaire score. 12. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and only one additional concomitant anti-PD medication. 13. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and two additional concomitant anti-PD medications. 14. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and three additional concomitant anti-PD medications. 15. EuroQol 5D-5L Health Questionnaire (EQ-5D-5L). 16. Treatment Satisfaction Questionnaire for Medication (TSQM-9) (evaluated at Weeks 6 and 24).
	Exploratory Endpoints (Part B): The exploratory endpoints in Part B include the following: 1. Change from Baseline in UPDRS Part II (ADL subscale) + Part III (motor subscale) total score. 2. Change from Baseline in UPDRS Part II (ADL subscale) score. 3. Change from Baseline in UPDRS Part III (motor subscale) score in the ON state. 4. Change from Baseline in UPDRS Part I total score. 5. Change from Baseline in UPDRS Part IV total score. 6. Change from Baseline in dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV. 7. Change from Baseline in SCOPA-cog score. 8. Change from Baseline in Fall questionnaire score. 9. Percent change from Baseline to the end of open-label treatment in total levodopa equivalent dose. 10. Exploratory endpoints to evaluate potential disease modification (see **Section 11.4.6**). 11. EQ-5D-5L. 12. TSQM-9 (evaluated at Week 76).

PROTOCOL SYNOPSIS	
Safety Endpoints	The safety and tolerability of tozadenant will be evaluated in this study using the following measures: 1. Treatment-emergent adverse events (TEAEs). 2. Physical and neurological examination. 3. Supine and standing pulse and blood pressure (BP). 4. Standard 12-lead ECG: RR, PR, QRS, QT and QTcF. 5. Laboratory parameters: hematology, chemistry, thyroid function (thyroid stimulating hormone [TSH], free T3, and free T4), and urinalysis. 6. Columbia-Suicide Severity Rating Scale (C-SSRS). 7. Daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), including assessment of episodes of sudden onset of sleep. 8. Modified Minnesota Impulse Disorders Interview (mMIDI).
Inclusion Criteria	Patients must fulfill all of the following inclusion criteria in order to be randomized: 1. Patient is 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. 2. Patient is considered reliable and capable of adhering to the protocol (e.g., able to understand and complete diaries), visit schedule, and medication administration instructions according to the judgment of the investigator. 3. Patient has a documented history of idiopathic Parkinson's disease consistent with the UK Parkinson's Disease Society Brain Bank Diagnostic criteria prior to the Screening Visit. 4. Patient has a PD duration of at least 3 years from diagnosis. 5. Patient is male or female and 30–80 years old (inclusive) at Screening. 6. Patient has a modified Hoehn and Yahr stage 2–4 when in OFF state (estimated) and ≤ 3 in ON state. 7. Patient must have a good response to levodopa in the opinion of the investigator, be taking at least four doses of a levodopa-containing medication per day, and at least one other concomitant anti-PD medication (dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone). 8. Patient is maintained on a regimen of permitted anti-PD

PROTOCOL SYNOPSIS	
	medications that has been stable for at least 4 weeks prior to Screening. 9. Patients must have been taking a levodopa-containing anti-PD medication continuously for at least the previous 12 months and must be currently experiencing end-of-dose "wearing-off" with at least 2.5 hours of OFF time per day as confirmed by a 3-day Baseline diary. 10. Patient must have achieved the following results for PD diary training, practice diary collection, and Baseline diary recordings: a. During a diary concordance session with an approved PD diary trainer/rater (minimum 2.5 hours), patient achieved at least 80% overall diary concordance including at least 1 OFF interval. b. Returned a valid 3-day (i.e., 3 consecutive 24-hour periods) practice diary. c. Returned valid diary recordings for each of the 3 consecutive days preceding the Baseline Visit that indicated at least 2.5 hours of OFF time on each of the 3 days. Note: A valid diary record will not have more than 4 invalid entries (double or missed entries) over a given 24-hour period (defined as starting at 6 AM). An invalid diary entry is defined as more than one entry recorded in a given half-hour interval, an unreadable entry, or the absence of an entry in a given half-hour interval. Patients will be required to view the PD diary training video. Caregivers may assist patients in completion of the PD diary. If a caregiver participates in completion of the PD diary, he or she is required to participate in the PD diary training session, in addition to viewing the PD diary training video. Patients who do not meet the criteria for proper practice diary completion may be retrained within the 6-week window of the Screening Period, if the patients are otherwise eligible for the study. 11. Contraception: a. Women of childbearing potential must use an acceptable method* of contraception starting 4 weeks prior to study drug administration and for a minimum of 1 month after study completion. Otherwise, women must be postmenopausal (at least 1 year absence of vaginal bleeding

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	or spotting) as confirmed by FSH ≥ 40 mIU/mL (or ≥ 40 IU/L) or be surgically sterile. b. Men with a potentially fertile partner must have had a vasectomy or be willing to use an acceptable method* of contraception for the duration of the study and for 3 months after study drug discontinuation. *For men and women: Acceptable methods of contraception include use of a condom with spermicide; oral, implantable or injectable contraceptives; IUD; diaphragm with spermicide; or, diaphragm with condom.
Exclusion Criteria	Patients with any of the following characteristics will be excluded from being randomized: 1. Patient previously participated in any study with tozadenant. 2. Patient is currently participating in or has participated in another study of an IMP or medical device in the last 3 months or within 5 half-lives of the IMP (whichever is longer). 3. Patient has any form of secondary or atypical parkinsonism (e.g., drug-induced, post stroke). 4. Severe obesity defined as a BMI greater than 35. 5. Patient has a QTcF interval of ≥ 500 msec at Screening (Visit 1) or the patient has an average QTcF interval ≥ 450 msec for males or ≥ 470 msec for females at Baseline (Visit 2). The average at Baseline will be taken from 3 serial ECGs done several minutes apart. (Fridericia's correction [QTcF] must be used for correction of the QT interval.) 6. Known diagnosis of malignant melanoma. 7. History of neurosurgical intervention for PD. 8. Patient with grade 2 hypertension (supine systolic BP ≥ 160 or diastolic BP ≥ 100 mmHg), treated or untreated, at Screening or at Baseline confirmed by at least 1 of 2 further measurements. Patients may be rescreened once if excluded due to this exclusion criterion, following appropriate treatment. 9. Patient with a history of hypertensive crisis unless the underlying cause has been removed. 10. Patient has a history of chronic alcohol or drug abuse within the last 2 years. 11. Patient is taking apomorphine, budipine, istradefylline, tolcapone, or [redacted] within 4 weeks prior to Screening or is

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	likely to require any of these drugs during the study. 12. Current treatment with antipsychotics; however, quetiapine administered at doses of ≤ 100 mg per day is permitted if the patient has been on a stable daily dose for at least 4 weeks before Screening. PRN (as needed) dosing is not permitted. 13. Exposure to neuroleptics (antipsychotic drugs) for more than 1 month within the past 2 years, or any exposure within the past year (except for quetiapine). 14. Patient has taken digoxin within 4 weeks prior to Screening or is likely to require digoxin during the study. 15. Hyperthyroidism or hypothyroidism, unless all of the following conditions are met: a. Patient has received a stable dose of thyroid medication for at least 3 months before the Baseline Visit. b. TSH concentrations are in the normal range (± 10% as a window either side of the normal range). c. Patient is clinically euthyroid. 16. Orthostatic hypotension requiring medication. 17. Any out-of-range laboratory values at Screening that have not been reviewed and documented as not clinically significant by the investigator. Any questionable safety lab results may be repeated for confirmation. 18. A score of < 26 on the Mini-Mental State Examination, Second Edition (MMSE-II) at the Screening Visit. If the MMSE-II is not validated in the requisite language, the MMSE (Original) may be used. 19. Patients with a current episode of major depression. Patients receiving treatment for depression with antidepressants may be enrolled if they have been on a stable daily dose of the antidepressant for at least 8 weeks before the Baseline Visit. 20. Patient has a recent history of suicide attempt (defined as an active, interrupted or aborted attempt within the past 5 years), or reports suicidal ideation in the past 6 months as indicated by a positive response ('Yes') to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) performed at the Screening Visit. 21. Patient has evidence of an impulse control disorder (ICD) (i.e., one or more positive modules) according to the Modified

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	Minnesota Impulse Disorders Interview (mMIDI) unless a structured clinical interview performed during Screening confirms that the patient does not have an ICD. 22. Patient is currently lactating or pregnant or planning to become pregnant during the duration of the study. 23. Patient has a known hypersensitivity to any components of the IMP or excipients. 24. Any other condition or clinically significant abnormal findings on the physical or neurological examination, psychiatric and medical history, at Screening or at Baseline that, in the opinion of the investigator, would make the patient unsuitable for the study or put the patient at additional risk or prejudice evaluation of safety and efficacy of the IMP. 25. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) ≥3x upper limit of normal (ULN), or total bilirubin ≥1.5x ULN, at Screening. 26. Patients with a history of hepatic dysfunction secondary to viral infection (hepatitis B or C; Epstein Barr virus [EBV]; or cytomegalovirus [CMV]), or a history of diagnosed drug- or alcohol-induced hepatic toxicity or frank hepatitis. 27. Patients with moderate to severe hepatic or renal impairment. 28. [redacted] 29. Patients with pacemakers or implantable cardioverter defibrillators.
Overview of Study Procedures	**Part A:** Consented patients will be asked to view the study-provided video ("What to expect during this clinical trial") and screened for eligibility. The purpose of the video is to advise patients not to expect therapeutic benefit from investigational treatment or participation in the study, and to understand how an investigator/study participant relationship differs from the typical doctor/patient relationship. During the Screening Period, the patient (and any caregiver that will assist the patient to complete PD diaries during the study) will complete PD diary training and a diary concordance session with the site's diary trainer/rater. The patient (and caregiver, as applicable) will review the PD diary training video

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	and receive instruction on how to complete the PD diary, including the definitions of ON and OFF. The definitions of ON and OFF will be reviewed, including ON time according to dyskinesia categories "without dyskinesia", "with non-troublesome dyskinesia" or "with troublesome dyskinesia", with emphasis on the need for the patient to be consistent in their use of the definitions when rating their status in the PD diary during the study. When instructions appear to have been understood by the patient (and caregiver, as applicable), a diary concordance session will be initiated during which the patient and the diary trainer/rater will concurrently complete separate training diaries for at least 5 consecutive half-hour intervals (minimum 2.5 hours). During the diary concordance session, the patient must experience both ON and OFF. The 2.5 hour session may be extended, as needed, so that the patient experiences OFF. If the patient is OFF at the beginning of the diary concordance session, they may be administered their next dose of levodopa-containing medication in order to experience ON. When the session is completed, the diary trainer/rater will review and assess the patient's diary concordance with the trainer/rater. The patient is required to reach at least 80% overall diary concordance with the trainer/rater including at least 1 OFF interval. If the concordance criteria are not achieved, the trainer/rater will schedule a second PD diary training and diary concordance session within the 6-week Screening Period, unless the patient declines further participation. Following successful completion of the PD diary training and diary concordance session, patients/caregivers will be required to complete practice PD diaries on 3 consecutive prespecified days (24-hour periods starting at 6 AM each day). The trainer/rater will telephone the patient to remind them to start keeping the PD diary prior to the start date, to review the ON and OFF definitions, and to answer any questions the patient may have regarding completion instructions. Practice PD diaries will be returned to the trainer/rater and reviewed with patients/caregivers over the telephone or in person to ensure PD diary completion instructions are fully understood. Patients with invalid practice diaries will be asked by the trainer/rater either to complete a second PD diary training and diary concordance session followed by a repeat 3-day practice diary, or else asked to repeat the 3-day practice diary, depending on the patient's understanding of the diary instructions. Patients who do not satisfy diary concordance criteria during a second PD diary training and/or who return a second

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	set of practice diaries that are invalid, will be considered screen failures. Patients who return valid practice PD diaries and who the investigator considers eligible for the study will have their screening data reviewed by the Sponsor/Sponsor's designee and, if confirmed to be eligible, will have the Baseline Visit scheduled within 6 weeks from the Screening Visit. They will be instructed to complete the Baseline PD diary on the 3 consecutive days directly preceding the scheduled Baseline Visit. The trainer/rater will telephone the patient prior to the start date to remind them to start keeping the PD diary, to review the ON and OFF definitions, and to answer any questions the patients or caregiver may have regarding completion instructions. The patients will be requested to bring the Baseline PD diary to the Baseline Visit, at which the PD diary will be assessed for validity and to confirm the patient's eligibility. Patients not meeting the criteria for valid Baseline PD diary completion may be retrained, as described above, and may return for another Baseline assessment within the 6-week Screening Period. Eligible patients who meet all the entry criteria at Baseline will be randomized to receive double-blind IMP for 24 weeks. The first dose of IMP will be taken at home after the Baseline Visit. Patients will be evaluated at scheduled study visits on Weeks 2, 6, 12, 18 and 24 and will be asked to complete a PD diary on the 3 consecutive days directly preceding these visits. Prior to each 3-day PD diary completion period, patients will be telephoned to be reminded to comply with the PD diary instructions. Patients will be requested to bring their PD diary to the scheduled visits, to return the IMP kit (including all used and unused blister cards) dispensed at the previous visit, to take their IMP in the morning before the visit, and to bring their other medications to the visit. Patients will be instructed to have already taken their normally scheduled dose of levodopa and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in the ON state (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in OFF will not be evaluated. Safety evaluations will be performed at each study visit. Patients will also be scheduled for a laboratory draw (hematology only) at Weeks 4, 8, 10, 16 and 22. In the event of Early Termination during Part A, patients will be asked to complete an Early Termination Visit as soon as possible and to return for a Safety Follow-Up Visit 28 ± 3 days after their last dose of IMP. Efficacy-

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	related measures (e.g., PD diary, UPDRS, CGI-I, PGI-I, and CGI-S) will not be completed at an Early Termination Visit if the subject stopped taking study drug more than 24 hours prior to the Early Termination Visit. If a patient decides to withdraw from study at Week 24, their Week 24 visit will be an Early Termination Visit and they will be asked to return for a Safety Follow-Up Visit within 28 ± 3 days. **Part B:** Upon completion of Part A, patients will enter Part B and receive open-label tozadenant IMP for 52 weeks. Patients will attend scheduled study visits at Weeks 26, 30, 36, 48, 60, 76, and at Week 80 (Safety Follow-Up Visit). At each Part B visit, patients will be asked to return unopened and opened IMP bottles and to bring their other medications to the study site. Patients will be instructed to have already taken their normally scheduled doses of levodopa prior to arriving at the study site. At the Week 26 and Week 30 visits, patients will be asked to have a morning tozadenant PK sample drawn and then will take their morning dose of IMP in the office (i.e., patients will be instructed not to take the morning dose of IMP at home on those days). For all subsequent visits, patients in Part B will be instructed to take their morning IMP dose at home prior to arriving at the study site. Safety evaluations will be performed at each study visit. Patients will also be scheduled for a laboratory draw (hematology only) at Weeks 28, 32, 34, 40, 44 and 68. For all patients completing the study, a postdose Safety Follow-Up Visit will occur 28 ± 3 days after completion of the 52-week open-label phase. In the event of Early Termination during Part B, patients will be asked to complete an Early Termination Visit as soon as possible and to return for a Safety Follow-Up Visit 28 ± 3 days after their last dose of IMP. Efficacy-related measures (e.g., UPDRS) will not be completed at an Early Termination Visit if the subject stopped taking study drug more than 24 hours prior to the Early Termination Visit. Please refer to the Schedule of Events/Evaluations in **Table 1**, **Table 1.1 Table 2** and **Table 2.1** specific timing of assessments.
Criteria for Patient Discontinuation from Study	Patients are free to withdraw from the study at any time, without prejudice to their continued care. Patients may be discontinued from the study at any time if clinically significant out-of-range laboratory values, clinically significant abnormal findings on physical examination, or intolerable AEs put the patient at additional risk, as judged by the investigator. Patients

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	must be discontinued from the study if the absolute neutrophil count is less than 1000/mm^3 (or 1.0 x 10E9/L). During Part A, patients will also be discontinued from the study if their PD symptoms worsen to the extent that, in the judgment of the investigator, they require the addition of new anti-PD medication or an increase in the frequency or dose of their concomitant anti-PD medication. A complete list of reasons for patient discontinuation is located in **Section 4.3**. The Study Sponsor (Biotie Therapies) has the right to terminate the study at any time. All patients who discontinue prematurely from the study will be requested to return to the study site as soon as possible to complete the safety and efficacy evaluations outlined for an Early Termination Visit in **Table 1** and **Table 2**, Schedule of Events/Evaluations. The Early Termination Visit should be done while the patient is taking IMP, if possible. After Early Termination, the patient will also be asked to return for a Safety Follow-Up Visit to be scheduled 28 days after the last dose of IMP, unless the Early Termination Visit itself occurred 28 or more days after the last dose of IMP. All treatment-emergent AEs will be followed until resolution, return to Baseline level, or stabilization.
Sampling for Tozadenant Plasma Drug Concentrations	During Part A, PK blood samples for determination of plasma tozadenant concentrations will be collected at Baseline, at Weeks 2, 6, 12, 18, and 24 (End of Dosing), and at an Early Termination Visit unless the patient's last dose of IMP was taken more than 7 days before the Early Termination Visit. For Unscheduled Visits, PK sample collection is at the investigator's discretion (e.g., in the event of AEs thought to be study drug related). Two (2) PK blood samples will be collected at the study visits at Weeks 2 and 24. For Weeks 6, 12 and 18 (and if collected during an Unscheduled Visit), one (1) PK blood sample will be taken at the most convenient time during the visit. For an Early Termination Visit, one (1) PK blood sample will be taken at the most convenient time during the visit, provided that the patient's last dose of IMP was not taken more than 7 days before the visit. For each PK collection, the times of sampling and of the most recent IMP dosing prior to sampling will be recorded. When two (2) PK samples are to be collected, the first sample will be taken on arrival

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	and the second sample taken on departure. The time between the two PK blood draws should be approximately 45 minutes or longer, and dosing with study drug must not occur between the first and second draws. During Part B, at Weeks 26 and 30, PK blood samples for plasma tozadenant will be collected from patients who have a study visit in the morning (before 10:00 AM) and who have not yet taken their morning IMP dose. For each collection, one (1) PK blood sample will be taken prior to receiving the morning dose of IMP at the study site. The times of sampling and of the most recent IMP dosing prior to sampling will be recorded.
Sampling for Pramipexole Plasma Concentrations	For Patients Who Are Concomitantly Taking Pramipexole Only: During Part A, PK blood samples collected for tozadenant (see above) will also be analyzed for plasma pramipexole concentration at Baseline, at Week 2 (both samples), Week 24 (both samples), and at an Early Termination Visit in those patients who are concomitantly taking pramipexole. In addition, a second PK blood sample will be taken at the Baseline Visit and analyzed for plasma pramipexole. In the event of AEs thought to be pramipexole-related (e.g., dyskinesia, hallucinations, delusions, hypotension, somnolence, nausea, vomiting) noted at the time of a scheduled study visit, PK blood samples collected for tozadenant (see above) will also be analyzed for plasma pramipexole concentration. If noted at the time of an Unscheduled Visit, a PK sample for plasma pramipexole concentration will be collected unless a PK blood sample for tozadenant is collected, in which case that sample will also be analyzed for plasma pramipexole collection. During Part B, no analysis for plasma pramipexole is planned for the scheduled visits. A plasma pramipexole concentration will be determined during Part B in the event of AEs thought to be pramipexole-related, whether noted at the time of a scheduled study visit or an Unscheduled Visit. If a PK blood sample is not being collected for tozadenant then collect a plasma pramipexole concentration as applicable. For each pramipexole PK collection, the time of sampling and patient-reported date and approximate time of the most recent pramipexole dose taken prior to sampling must be recorded.
Sample Size Justification	For Part A, the primary efficacy endpoint is the change from Baseline to Week 24 in the number of hours per day spent in the OFF

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	state. A sample size of 150 in each group will provide 85% power to detect a difference in mean response of 0.9 hours between tozadenant and placebo assuming the common standard deviation is 2.6 hours and using a two group t-test with a 0.050 two-sided significance level. Across the 3 treatment groups, the total number of patients to be randomized is 450. For Part B, no formal sample size determination will be performed. It is anticipated 80% of the patients randomized into Part A (i.e., approximately 360 patients) will continue into Part B.
Data and Safety Monitoring	Concurrent safety data monitoring is planned for this study, for which responsibility will be assigned to an independent Data and Safety Monitoring Board (DSMB). The DSMB will oversee the safety of the study by reviewing relevant data on a regular basis. The DSMB will consist of members who are independent from Biotie Therapies. Study enrollment will not be halted during planned DSMB reviews of safety data. The objectives and procedures for the DSMB will be detailed in the DSMB charter.
Statistical Analysis	<u>Analysis of the Primary Efficacy Variable</u> The primary efficacy variable will be the change from Baseline to Week 24 in the number of hours per day spent in the OFF state, as assessed by patient-completed PD diaries and averaged over 3 consecutive days. Descriptive statistics will be used to summarize results for the observed OFF time and the change from Baseline in OFF time by treatment group and visit. The primary analysis of the primary variable will be based on the mITT set and a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, country, the baseline number of hours of OFF time, and the interaction between treatment group and week. The model will define patient as a random effect and utilize an unstructured covariance pattern. The "country" term in the model may be redefined in the Statistical Analysis Plan (SAP) to geographical region (countries grouped together) if some countries do not contribute an adequate number of patients. Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis, however for the Per Protocol Set (PPS). A further analysis will utilize the Last Observation Carried Forward (LOCF) approach; missing values will be replaced by the last observed post-baseline

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	value of the variable and the analysis will be performed on the resulting dataset. Finally a multiple imputation method **(Rubin, 1987**; **Little and Rubin, 1987)** will be applied. In addition, for each imputation method, a univariate ANCOVA will be performed at Week 24 which includes the model terms: country/region, treatment group and baseline value. Key Secondary Efficacy Analyses All continuous secondary efficacy variables will be summarized descriptively by treatment group and week. Descriptive statistics will be generated for the observed and the change from Baseline. For categorical variables, frequency and percentages will be produced. The key secondary efficacy variables will be analyzed using the model defined in the primary analysis of OFF time in the mITT. Sensitivity analyses, including analysis in the PPS, LOCF and multiple imputation will also be performed. Multiplicity Adjustment for Primary and Key Secondary Endpoints All analyses of the primary and two key secondary endpoints will focus on the comparison of tozadenant 120 mg BID vs. placebo, followed by tozadenant 60 mg BID vs. placebo. The following six comparisons will be conducted using sequential testing with a fixed sequence, which controls the family-wise error for multiple comparisons at an alpha level of 0.05 (two-tailed): 1. Comparison of tozadenant 120 mg BID vs. placebo using the primary endpoint (Change from baseline to Week 24 in the number of hours per day spent in OFF state). 2. Comparison of tozadenant 120 mg BID vs. placebo using the first key secondary endpoint (Change from baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia). 3. Comparison of tozadenant 120 mg BID vs. placebo using the second key secondary endpoint (Change from baseline to Week 24 in UPDRS Parts II + III total score). 4. Comparison of tozadenant 60 mg BID vs. placebo using the primary endpoint (Change from baseline to Week 24 in the number of hours per day spent in OFF state). 5. Comparison of tozadenant 60 mg BID vs. placebo using the first key secondary endpoint (Change from baseline to Week 24 in the number of hours per day spent in good ON time, defined as the

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	sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia). 6. Comparison of tozadenant 60 mg BID vs. placebo using the second key secondary endpoint (Change from baseline to Week 24 in UPDRS Parts II + III total score). Testing will begin with tozadenant 120 mg BID vs. placebo for change from baseline to Week 24 in the number of hours per day spent in OFF state. If the p-value is less than or equal to an $\alpha = 0.05$, then the result is considered statistically significant and testing will proceed to the next comparison, and so forth. Testing will stop with the first adjusted p-value > 0.05 and that comparison, as well as any comparison later in the sequence will be considered not statistically significant. P-values from the analyses of all other efficacy outcomes will be reported as nominal, with no adjustment for multiplicity. <u>Other Efficacy Analyses</u> All other efficacy analyses will be performed in the mITT only with no adjustment for multiplicity. In addition, no sensitivity analyses are planned for other efficacy analyses. <u>Safety Analysis</u> Safety data, including AEs, vital signs, ECGs, ESS, physical and neurological examination, and clinical laboratory test results will be summarized descriptively for each treatment group and for the entire tozadenant group, where appropriate. The descriptive statistics will be provided for the observed data and for the change from Baseline at each measured time point. Tables will summarize AE data as appropriate by dose group. Note that counting will be by patient, not event and patients are only counted once within each system organ class or preferred term. Laboratory test results will be classified as below the lower limit of normal, within normal limits and above the upper limit of normal. Shift tables will be used to summarize changes from Baseline to each visit by treatment group. Clinically significant physical or neurological examination findings and any clinically significant out-of-range laboratory tests are recorded as AEs and will be documented in the AE summaries. Analyses will be performed for the Safety Set as randomized.

Table 1: Part A – Schedule of Events/Evaluations

TOZ-CL05 PART A: DOUBLE-BLIND PHASE										
Study Period	**Screening** [a]	**Baseline Predose**	**Double-Blind Treatment (24 weeks)**					**Early Termination** [x]	**Safety Follow-Up for ET**	**Unscheduled**
Study Week	**−6 to −1**	**BL**	**2 (±3 d)**	**6 (±3 d)**	**12 (±3 d)**	**18 (±3 d)**	**24 (±7 d)**		**28 (±3) d after last dose of IMP**	
Assessments / Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**A98**	**A99**	**A97**
Written informed consent	X									
Patient to view study-provided video ("What to expect during this clinical trial")	X				X					
Demographic data, medical history, including neurological and PD history	X									
Recording of concomitant and anti-PD medications	X	X	X	X	X	X	X	X	X	X
BP [b], pulse [b]	X [c]	X [c]	X	X	X	X	X	X	X	X [d]
Weight (include height at Screening)	X						X	X		
Physical and neurological examination	X						X	X	X	X [d]
Caffeine Intake Questionnaire		X								
PD diary training and diary concordance session	X									
12-lead ECG [e]	X	X	X	X	X	X	X	X	X	X [d]
Modified Hoehn and Yahr staging (observed ON; OFF estimated per history)	X									
UPDRS Parts I, II, III, and IV (in ON state) [f]	X	X	X	X	X	X	X	X [x]		
MMSE-II (in ON state)	X									
mMIDI [g]	X			X	X	X	X	X	X	X [d]
C-SSRS	X	X	X	X	X	X	X	X	X	X [d]
Sponsor eligibility review	X									
PD diary collection (phone call prior to start of 3 consecutive 24-hour diary completion periods)	X [h]	X [h]	X [i]	X [i]	X [i]	X [i]	X [i]	X [j, x]		

Table 1: Part A – Schedule of Events/Evaluations (continued)

TOZ-CL05 PART A: DOUBLE-BLIND PHASE										
Study Period	**Screening** [a]	**Baseline Predose**	**Double-Blind Treatment (24 weeks)**					**Early Termination** [x]	**Safety Follow-Up for ET**	**Unscheduled**
Study Week	**−6 to −1**	**BL**	**2 (±3 d)**	**6 (±3 d)**	**12 (±3 d)**	**18 (±3 d)**	**24 (±7 d)**		**28 (±3) d after last dose of IMP**	
Assessments / Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**A98**	**A99**	**A97**
PD diary review	X	X	X	X	X	X	X	X [j]		
Final verification of inclusion and exclusion criteria		X								
Patient randomization		X								
CGI-I [k]			X	X	X	X	X	X [x]		
PGI-I [k]			X	X	X	X	X	X [x]		
CGI-S [k]		X	X	X	X	X	X	X [x]		
SCOPA-cog [k]		X					X	X		
PDQ-39 [k]		X			X	X	X	X		
EQ-5D-5L [k]		X					X	X		
TSQM-9 [k]				X			X	X		
Sudden onset of sleep		X	X	X	X	X	X	X	X	
ESS [k]		X	X	X	X	X	X	X	X	
Fall questionnaire		X					X	X		
Healthcare Resource Utilization			X	X	X	X	X	X		
IMP dispensing and return [l]		X	X	X	X	X	X	X		X
Recording of AEs	X [m]	X [m]	X	X	X	X	X	X	X	X
Anti-PD medications		Patients continue stable dose of levodopa and other allowed anti-PD medications throughout Part A.								
FSH test, females who are postmenopausal for < 2 years	X									
Thyroperoxidase antibody	X									
Laboratory tests: hematology [n], chemistry [o] (including thyroid [p])	X	X	X	X	X	X	X	X	X	X [d]
Urine pregnancy test, females of childbearing potential [q]	X	X	X	X	X	X	X	X	X	X [d]
Urinalysis [r]	X	X	X	X	X	X	X	X	X	X [d]
Tozadenant blood sampling [s]		X	X [t]	X	X	X	X [t]	X [t]		X [d]
Pramipexole blood sampling (applicable patients only)		X [u]	X [v]	X	X	X	X [v]	X [v]		X [w]
eCRF completion	X	X	X	X	X	X	X	X	X	X

Table 1: Part A – Schedule of Events/Evaluations (continued)

TOZ-CL05 PART A: DOUBLE-BLIND PHASE

AE, adverse event; BP, blood pressure; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinician Global Impression of Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day(s); ECG, electrocardiogram; eCRF, electronic case report form; EQ-5D-5L, EuroQol 5D-5L Health Questionnaire; ESS, Epworth Sleepiness Scale; ET, Early Termination; FSH, follicle stimulating hormone; IMP, investigational medicinal product; mMIDI, Modified Minnesota Impulse Disorders Interview; MMSE-II, Mini-Mental State Exam−Second Edition (MMSE-II); P, pulse (beats per minute); PD, Parkinson's disease; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; PGI-I, Patient Global Impression of Improvement; SCOPA-cog, Scales for Outcomes in Parkinson's Disease - cognition; TSQM-9, Treatment Satisfaction Questionnaire for Medication; UPDRS, Unified Parkinson's Disease Rating Scale; V, Visit.

Part A - Footnotes:

[a] Screening Period may not exceed 6 weeks.

[b] Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 minute and 3 minutes.

[c] At Screening and at Baseline (before dosing), obtain and record serial BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes, on 3 occasions approximately 10 minutes apart.

[d] Optional assessments that may be performed for evaluation of AEs, at the investigator's discretion.

[e] Resting supine 12-lead ECGs will be collected after the patient has been in a supine position for a minimum of 5 minutes. ECGs should be collected at a time during visit when the patient is not experiencing dyskinesia that would interfere with an adequate recording. At Baseline, obtain triplicate 12-lead ECGs (3 serial readings performed several minutes apart).

[f] UPDRS to be measured in ON state approximately 1 to 3 hours after patients have taken a scheduled dose of levodopa (preferably their morning dose of levodopa). Patients will be instructed to have already taken their normally scheduled dose of levodopa (and their IMP for visits following randomization) before arriving at the study site in order to have their UPDRS Part III evaluated in the ON state. UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in the patient's "best" ON.

[g] At Screening, send patient for structured clinical interview if one or more positive mMIDI modules. If the structured clinical interview confirms that the subject does not have an ICD, he/she will not be considered ineligible on that basis. After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.

[h] The 3-day practice diary during the Screening Period and the 3-day Baseline diary must both be valid in order to randomize a patient. The trainer/rater will call the patient before the scheduled start of the diary completion periods to remind him or her to keep the PD diary and to review completion instructions. The patient will also be reminded to send the completed practice diary to the trainer/rater and to bring their Baseline diary to the Baseline Visit. If the practice or Baseline diary is invalid, the patient may be retrained and complete another practice or Baseline diary within the 6-week window of the Screening Period, if the patient is otherwise eligible for the study.

[i] PD diary collected over the 3 consecutive 24-hour periods before the day of the scheduled study visits on Week 2, 6, 12, 18 and 24. The PD diary trainer/rater will call the patient before the scheduled start of the 3-day PD diary completion period (at the latest, on the last working day before the scheduled start of the PD diary completion) and review completion instructions. The patient will also be reminded to bring their PD diary to the visit. The trainer/rater will instruct the patient if the PD diary contains missing and/or invalid entries to reinforce instructions for appropriate completion.

[j] Done only if the ET date coincides with the scheduled diary collection return date.

[k] To be collected during patient's ON state.

[l] Patients will be instructed to take two (2) tablets of the dispensed blinded IMP by mouth twice daily (BID), in the morning and in the evening preferably at the same time each day, for a total of four (4) tablets per day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing.

[m] Pretreatment AEs.

Table 1: Part A – Schedule of Events/Evaluations (continued)

TOZ-CL05 PART A: DOUBLE-BLIND PHASE

[n] Hematology tests: Hemoglobin concentration, hematocrit, red blood cell count, total and differential white blood cell, thrombocyte (platelet) count.

[o] Blood chemistry (including liver function) tests: Aspartate amino transferase (AST), alanine amino transferase, (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (conjugated and unconjugated), albumin, creatinine, urea/blood urea nitrogen (BUN), bicarbonate, uric acid, total protein, sodium, chloride, potassium, calcium, phosphate, glucose, cholesterol, creatine phosphokinase (CK). Regarding liver function tests at Screening, refer to Exclusion Criterion #25 (**Section 4.2**).

[p] TSH, free T3, and free T4.

[q] Document method of contraception at Screening and verify continuation of (or any change to) contraceptive method at each visit. For female of childbearing potential, perform a urine pregnancy test.

[r] Urinalysis: Specific gravity, pH, ketones, blood, protein, glucose. If urine dipstick is positive for leukocytes, protein, or erythrocytes, a microscopic evaluation and culture will be performed.

[s] PK blood samples will be collected for determination of tozadenant concentration levels at Baseline before dosing, at Weeks 2, 6, 12, 18, and 24 (End of Dosing), and in the event of an Early Termination Visit unless the patient's last dose of IMP was taken more than 7 days before the visit. For Weeks 6, 12, and 18, and at Early Termination, one (1) PK blood sample will be taken at the most convenient time at each visit. For Unscheduled Visits, one (1) PK blood sample may be collected at the investigator's discretion (e.g., for AEs thought to be study drug related). For each collection, the time of sampling and patient-reported date and approximate time of the most recent IMP dosing prior to sampling will be recorded. See **Section 8.1**.

[t] Collection of two (2) tozadenant PK blood samples at Weeks 2 and 24 is required. The first sample will be taken on arrival and the second sample taken on departure, with the time between the blood samples being at least 45 minutes or longer and no IMP dosing between the two blood draws. (For an Early Termination Visit, PK blood samples are not required if the patient's last dose of IMP was taken more than 7 days before the Early Termination Visit.) See **Section 8.1**.

[u] Only for patients concomitantly taking pramipexole: PK blood sample collected for tozadenant will also be analyzed for plasma pramipexole at Baseline (Visit 2, predose). A second PK blood sample for plasma pramipexole concentration will be taken at Baseline at least 45 minutes after the first PK sample is collected.

[v] Only for patients concomitantly taking pramipexole: PK blood samples collected for tozadenant will also be analyzed for plasma pramipexole concentration including both samples collected at Weeks 2 (Visit 3) and 24 (Visit 7) and Early Termination Visit during Part A. If a tozadenant sample is not being collected at the Early Termination Visit (patient's last dose of IMP was taken more than 7 days before the visit) a PK sample for plasma pramipexole concentration will be collected.

[w] Only for patients with potential pramipexole-related AEs: During Part A, in the event of AEs thought to be pramipexole-related (e.g., dyskinesia, hallucinations, delusions, hypotension, somnolence, nausea, vomiting), either noted at the time of a scheduled study visit or an Unscheduled Visit, PK blood sample collected for tozadenant will also be analyzed for plasma pramipexole, i.e., at Week 6 (Visit 4), Week 12 (Visit 5) or Week 18 (Visit 6). If a tozadenant sample is not being collected at an Unscheduled Visit a PK sample for plasma pramipexole concentration will be collected. See **Section 8.2**.

[x] If patient has discontinued IMP, perform the Early Termination Visit as soon as possible after the last dose of IMP. Efficacy-related measures (e.g., PD diary, UPDRS, CGI-I, PGI-I, and CGI-S) will not be completed at an Early Termination Visit if patient stopped taking study drug more than 24 hours prior to the assessment of the measures during the Early Termination Visit. If patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Post-Early Termination Safety Follow-Up Visit **(Section 6.2.35)** is not required.

Table 1.1: Part A – Schedule of Events/ Evaluations for Hematology Monitoring

TOZ-CLO5 PART A: DOUBLE-BLIND PHASE						
Study Period	**Double-Blind Treatment (24 weeks)**					**Weekly monitoring [b] (if required)**
Study Week	**4 (±3 d)**	**8 (±3 d)**	**10 (±3 d)**	**16 (±3 d)**	**22 (±3 d)**	
Assessments / Study Visit	**V3.5**	**V4.3**	**V4.8**	**V5.5**	**V6.5**	**A97**
Laboratory test: hematology [a]	X	X	X	X	X	X
Recording of AEs						X
Recording of concomitant and Anti-PD medications						X
eCRF completion	X	X	X	X	X	X

[a] Hematology tests: Hemoglobin concentration, hematocrit, red blood cell count, neutrophils, total and differential white blood cell, thrombocyte (platelet) count.
[b] Only for patients that require weekly hematology monitoring per section 4.3.2. To be captured as an unscheduled visit in EDC/RAVE.

Table 2: Part B – Schedule of Events/Evaluations

TOZ-CL05 PART B: OPEN-LABEL PHASE										
	Study Period	**Start of Part B**	**Open-Label Treatment (52 weeks)**						**Early Termination [p]**	**Safety Follow-Up**	**Unscheduled**
	Study Week [a]	**24 (±7 d)**	**26 (±3 d)**	**30 (±3 d)**	**36 (±3 d)**	**48 (±7 d)**	**60 (±7 d)**	**76 (16 weeks) (±14 d)**		**80 (±3 d)**	
Assessments	**Study Visit**	**(V7)**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**B98**	**V14**	**B97**
Recording of concomitant and anti-PD medications		See **Table 1**: Part A – for Visit 7 (Week 24 ± 7 d)	X	X	X	X	X	X	X	X	X
BP [b], pulse [b]			X	X	X	X	X	X	X	X	X [c]
Weight					X	X		X	X	X	
Physical and neurological examination					X	X	X	X	X	X	X [c]
12-lead ECG [d]			X	X	X	X	X	X	X	X	X [c]
UPDRS Parts I, II, III and IV (in on state) [e]			X	X	X	X	X	X	X [p]		
mMIDI [f]				X	X	X	X	X	X	X	X [c]
C-SSRS			X	X	X	X	X	X	X	X	X [c]
ESS [g]					X	X		X	X	X	
PDQ-39 [g]								X	X		
SCOPA-cog [g]						X		X	X		
Fall questionnaire						X		X	X		
TSQM-9 [g]								X	X		
EQ-5D 5L [g]								X	X		
Healthcare Resource Utilization			X	X	X	X	X	X	X		
Recording of AEs			X	X	X	X	X	X	X	X	X
Laboratory tests: hematology [h], chemistry [i] (including thyroid function [j])			X	X	X	X	X	X	X	X	X [c]
Urine pregnancy test, females of childbearing potential [k]			X	X	X	X	X	X	X	X	X [c]
Urinalysis [l]			X	X	X	X	X	X	X	X	X [c]
IMP dispensing and/or return [m]		X	X	X	X	X	X	X	X		X
Tozadenant blood sampling			X [n]	X [n]							X [c]
Pramipexole blood sampling (applicable patients only)			X [o]	X [o]	X [o]	X [o]	X [o]	X [o]	X [o]		X [o]
eCRF completion		X	X	X	X	X	X	X	X	X	X

Table 2: Part B – Schedule of Events/Evaluations (continued)

TOZ-CL05 PART B: OPEN-LABEL PHASE

AE, adverse event; BP, blood pressure; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day(s); ECG, electrocardiogram; eCRF, electronic case report form; EQ-5D-5L, EuroQol 5D-5L Health Questionnaire; ESS, Epworth Sleepiness Scale; ET, Early Termination; IMP, investigational medicinal product; mMIDI, Modified Minnesota Impulse Disorders Interview; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; SCOPA-cog, Scales for Outcomes in Parkinson's Disease - cognition; TSQM-9, Treatment Satisfaction Questionnaire for Medication; UPDRS, Unified Parkinson's Disease Rating Scale; V, Visit.

Part B - Footnotes:

[a] Visit windows provided are in relation to Visit 7 (Week 24).

[b] Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 minute and 3 minutes.

[c] Optional assessments that may be performed for evaluation of AEs at the investigator's discretion.

[d] Resting supine 12-lead ECGs will be collected after the patient has been in a supine position for a minimum of 5 minutes. ECGs should be collected at a time during visit when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[e] UPDRS to be measured in ON state approximately 1 to 3 hours after patients have taken a scheduled dose of levodopa (preferably their morning dose of levodopa). Patients will be instructed to have already taken their normally scheduled dose of levodopa and their IMP before arriving at the study site in order to have their UPDRS Part III evaluated in the ON state. UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in the patient's "best" ON.

[f] If patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.

[g] To be collected during patient's ON state.

[h] Hematology tests: Hemoglobin concentration, hematocrit, red blood cell count, total and differential white blood cell, thrombocyte (platelet) count.

[i] Blood chemistry (including liver function) tests: Aspartate amino transferase (AST), alanine amino transferase, (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (conjugated and unconjugated), albumin, creatinine, urea/BUN, bicarbonate, uric acid, total protein, sodium, chloride, potassium, calcium, phosphate, glucose, cholesterol, creatine phosphokinase (CK).

[j] TSH, free T_3, and free T_4.

[k] Document method of contraception at Screening and verify continuation of (or any change to) contraceptive method at each visit. For female of childbearing potential, perform a urine pregnancy test.

[l] Urinalysis: Specific gravity, pH, ketones, blood, protein, glucose. If urine dipstick is positive for leukocytes, protein, or erythrocytes, a microscopic evaluation and culture will be performed.

[m] Patients will be instructed to take the assigned dose of open-label tozadenant by mouth BID, in the morning and in the evening preferably at the same time each day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing.

[n] PK blood samples for plasma tozadenant concentrations will be obtained for patients having a visit in the morning (before 10:00 AM) who, as instructed, have not yet taken their morning IMP dose on the day of the visit. (No PK sample will be taken for patients who have taken their morning IMP dose before the visit.)

[o] Only for patients concomitantly taking pramipexole: During Part B, in the event of AEs thought to be pramipexole-related (e.g., dyskinesia, hallucinations, delusions, hypotension, somnolence, nausea, vomiting), either noted at the time of a scheduled study visit or an Unscheduled Visit: If a PK blood sample is collected for tozadenant it will also be analyzed for plasma pramipexole; if a tozadenant sample is not being collected, a PK sample for plasma pramipexole concentration will be collected. See **Section 8.2**.

[p] If patient has discontinued IMP, perform Early Termination Visit as soon as possible after the last dose of IMP. Efficacy-related measures (e.g., UPDRS) will not be completed at an Early Termination Visit if patient stopped taking study drug more than 24 hours prior to the Early Termination Visit. If patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Post-Early Termination Safety Follow-Up Visit (**Section 6.2.35**) is not required.

Table 2.1: Part B – Schedule of Events/ Evaluations for Hematology Monitoring

TOZ-CLO5 PART B: OPEN LABEL PHASE							
Study Period	**Open Label Treatment (52 weeks)**						**Weekly monitoring (if required)** [b]
Study Week	**28 (±3 d)**	**32 (±3 d)**	**34 (±3 d)**	**40 (±3 d)**	**44 (±3 d)**	**68 (±14 d)**	
Assessments / Study Visit	**V8.5**	**V9.3**	**V9.8**	**V10.3**	**V10.8**	**V12.5**	**B97**
Laboratory test: hematology [a]	X	X	X	X	X	X	X
Recording of AEs							X
Recording of concomitant and anti-PD medications							X
eCRF completion	X	X	X	X	X	X	X

[a] Hematology tests: Hemoglobin concentration, hematocrit, red blood cell count, neutrophils, total and differential white blood cell, thrombocyte (platelet) count.
[b] Only for patients that require weekly hematology monitoring per section 4.3.2. To be captured as an unscheduled visit in EDC/RAVE

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1.0 BACKGROUND AND RATIONALE

1.1 Background

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative movement disorder characterized clinically by resting tremor, rigidity, bradykinesia and gait disturbance with postural instability. Other features can include masked faces, micrographia, and non-motor features including hyposmia, autonomic dysfunction, mood disturbances, and cognitive dysfunction. Estimates of the incidence and prevalence of PD vary considerably among studies due to differences in study populations, case ascertainment and diagnostic criteria. However, it is recognized that the incidence and prevalence of PD increase with age; and it is estimated that 1−2% of the population aged over 65 years are affected **(Von Campenhausen et al, 2005)**.

The characteristic pathological findings in the brains of patients with PD are loss of dopaminergic neurons of the substantia nigra pars compacta coupled with the presence of intracytoplasmic inclusions (Lewy bodies). It is now appreciated that neurodegeneration also involves the olfactory system, the cerebral hemispheres, the lower brain stem, the spinal cord, and the peripheral autonomic nervous system. Current therapy is primarily based on a dopamine "replacement" strategy using the dopamine precursor levodopa. Levodopa has revolutionized the therapy of PD, but chronic treatment is associated with the development of motor complications ("wearing-off" and dyskinesia) in the majority of patients. Other available pharmacologic treatments include dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, and catechol-*O*-methyl transferase (COMT) inhibitors. These have not been shown to be superior to levodopa, but have been shown to either delay the need for levodopa or reduce OFF time in levodopa-treated patients. Each of these agents is thought to act directly on the dopaminergic system. Each has shown benefit, but there remains a need for agents that can treat and prevent motor complications **(Olanow et al, 2009)**.

Adenosine A2a receptor antagonists have emerged as a potentially attractive new class of drugs for the treatment of PD **(Pinna, 2009)**. A2a receptors are highly localized in the basal ganglia, specifically within the indirect output pathway which is important in the control of voluntary movement. Alterations in firing patterns in these neurons are also thought to be involved in the development of motor complications induced by levodopa. A2a receptor antagonists modulate gamma-aminobutyric acid and glutamate release in the basal ganglia along with other key neurotransmitters that modulate motor activity. In both rodent and primate models of PD, A2a receptor antagonists have been shown to produce alterations in motor behavior when administered alone or in combination with dopaminergic drugs, suggesting that they might be effective in the symptomatic treatment of PD **(Bibbiani et al, 2003**; **Yu et al, 2006**; **Jenner et al, 2009)**. Because of the potential of A2a antagonists to inhibit abnormal firing of overactive D2-bearing neurons in the indirect striato-nigral pathway, they have the potential to improve OFF time in patients with PD. A2a inhibition may also slow neurodegeneration **(Schwarzschild et al, 2003)**.

[redacted]

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Efficacy Objective (Part A)

The primary efficacy objective of this study is to demonstrate the efficacy of the A2a receptor antagonist tozadenant in the treatment of levodopa-treated PD patients experiencing end-of-dose "wearing-off", based on the change from Baseline to Week 24 in the number of hours per day spent in the OFF state.

2.1.2 Key Secondary Efficacy Objectives (Part A)

The key secondary efficacy objectives of this study are:

1. To evaluate the effect of tozadenant on good ON time (defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia).
2. To evaluate the effect of tozadenant on UPDRS Parts II (Activities of Daily Living [ADL] subscale) + III (motor subscale) total scores.

2.1.3 Other Secondary Efficacy Objectives (Part A)

Other secondary efficacy objectives of this study are:

1. To evaluate the effect of tozadenant on investigator global impressions of improvement (Clinical Global Impression of Improvement [CGI-I]).
2. To evaluate the effect of tozadenant on patient global impressions of improvement (Patient Global Impression of Improvement [PGI-I]).
3. To evaluate the effect of tozadenant on UPDRS Part III (motor subscale) scores in the ON state.
4. To evaluate the effect of tozadenant on investigator global impressions of severity of illness (Clinical Global Impression of Severity [CGI-S]).
5. To evaluate the effect of tozadenant on UPDRS Part II (ADL subscale) scores.
6. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia).
7. To evaluate the effect of tozadenant on the number of hours per day spent in the ON state without dyskinesia.

8. To evaluate the effect of tozadenant in the number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome).
9. To evaluate the effect of tozadenant in the number of hours per day spent in the ON state with non-troublesome dyskinesia.
10. To evaluate the effect of tozadenant on PD-related quality of life as measured by Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (total score and individual domain scores).
11. To evaluate the effect of tozadenant on UPDRS Part IV.
12. To evaluate the effect of tozadenant on UPDRS Part I.

2.1.4 Safety Objectives (Parts A and B)

The safety objectives of this study are:

1. To evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients with end-of-dose "wearing-off", based on assessment of AEs, vital signs, electrocardiograms (ECGs), physical and neurological exams, and clinical laboratory tests.
2. To evaluate the effects of tozadenant on the occurrence of daytime drowsiness (including episodes of sudden onset of sleep), impulsive behavior, and suicidality.

2.2 Efficacy Endpoints

2.2.1 Primary Efficacy Endpoint (Part A)

The primary efficacy endpoint will be the change from Baseline to Week 24 in the number of hours per day spent in the OFF state, as assessed by patient-completed PD diaries and averaged over 3 consecutive days.

2.2.2 Key Secondary Efficacy Endpoints (Part A)

The key secondary efficacy endpoints, to be analyzed according to a prespecified hierarchy of hypotheses, include:

1. Change from Baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia.
2. Change from Baseline to Week 24 on UPDRS Parts II (ADL subscale) + III (motor subscale) total scores.

2.2.3 Other Secondary Efficacy Endpoints (Part A)

The other secondary efficacy endpoints include the change from Baseline to Week 24 (where applicable), for the following:

1. CGI-I at Week 24.

2. PGI-I at Week 24.
3. UPDRS Part III (motor subscale) score in the ON state.
4. Investigator global impressions of severity of illness (CGI-S).
5. UPDRS Part II (ADL subscale) score.
6. Number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia).
7. Number of hours per day spent in the ON state without dyskinesia.
8. Number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome).
9. Number of hours per day spent in the ON state with non-troublesome dyskinesia.
10. PDQ-39 (total score and individual domain scores).
11. UPDRS Part IV.
12. UPDRS Part I.

2.2.4 Exploratory Endpoints (Part A)

The exploratory endpoints in Part A include the change from Baseline to Week 24 (where applicable), for the following:

1. Number of hours per day spent in the asleep state.
2. Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
3. Falls as measured by question 13 on UPDRS Part II.
4. Responder analysis of number (%) of patients with ≥ 1.0 h improvement in OFF time (evaluated at Week 24).
5. Responder analysis of number (%) of patients with ≥ 2.0 h improvement in OFF time (evaluated at Week 24).
6. Percent change in total levodopa equivalent dose.
7. Percent change in the number of hours per day spent in OFF state.
8. Percent change in the number of hours per day spent in ON state without troublesome dyskinesia.
9. Percent change in the number of hours per day spent in ON state with troublesome dyskinesia.
10. Scales for Outcomes in Parkinson's Disease–cognition (SCOPA-cog) score.
11. Fall questionnaire score.

12. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and only one additional concomitant anti-PD medication.
13. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and two additional concomitant anti-PD medications.
14. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and three additional concomitant anti-PD medications.
15. EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
16. Treatment Satisfaction Questionnaire for Medication (TSQM-9) (evaluated at Weeks 6 and 24).

2.2.5 Exploratory Endpoints (Part B)

The exploratory endpoints in Part B include the following:

1. Change from Baseline in UPDRS Part II (ADL subscale) + Part III (motor subscale) total score.
2. Change from Baseline in UPDRS Part II (ADL subscale) score.
3. Change from Baseline in UPDRS Part III (motor subscale) score in the ON state.
4. Change from Baseline in UPDRS Part I total score.
5. Change from Baseline in UPDRS Part IV total score.
6. Change from Baseline in dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
7. Change from Baseline in SCOPA-cog score.
8. Change from Baseline in Fall questionnaire score.
9. Percent change from Baseline to the end of open-label treatment in total levodopa equivalent dose.
10. Exploratory endpoints to evaluate potential disease modification (see **Section 11.4.6**).
11. EQ-5D-5L.
12. TSQM-9 (evaluated at Week 76).

2.2.6 Safety Endpoints

The safety and tolerability of tozadenant will be evaluated in this study using the following measures:

1. TEAEs.
2. Physical and neurological examination.
3. Supine and standing pulse and BP.
4. Standard 12-lead ECG: RR, PR, QRS, QT and QTcF.

5. Laboratory parameters: hematology, chemistry, thyroid function (thyroid stimulating hormone [TSH], free T3, and free T4), and urinalysis.
6. Columbia-Suicide Severity Rating Scale (C-SSRS).
7. Daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), including assessment of episodes of sudden onset of sleep.
8. Modified Minnesota Impulse Disorders Interview (mMIDI).

3.0 STUDY DESIGN

3.1 Study Description

This is a Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm study with an open-label phase in levodopa-treated patients with PD experiencing end-of-dose "wearing-off". This study includes a Screening Period of up to 6 weeks that starts with a Screening Visit, a 24-week Double-Blind Treatment Period, a 52-week Open-Label Treatment Period, and a Safety Follow-Up Visit 4-weeks post-treatment. After providing written informed consent, patients will undergo screening evaluations. Patients must meet all inclusion criteria and none of the exclusion criteria, and they must successfully complete the diary training and achieve 80% overall diary concordance with the PD diary trainer/rater including at least 1 OFF interval to be considered for randomization. If preliminary eligibility is confirmed by the investigator and the Sponsor/Sponsor's designee, patients will then be scheduled for a Baseline Visit and will be required to return a valid set of Baseline diaries. Final eligibility will be determined at the Baseline Visit.

Eligible patients will be randomized in Part A to receive 1 of 2 tozadenant doses (60 mg BID or 120 mg BID) or placebo in a ratio of 1:1:1. Blinded IMP will be dispensed to patients at each study visit and will be taken BID (approximately 12 hours apart) for 24 consecutive weeks. Patients will return to the study site for evaluation at Weeks 2, 6, 12, 18, and 24. Patients will be contacted by telephone before the start of each 3-day PD diary completion period to be reminded to complete the diary for 3 consecutive days prior to their next scheduled visit. Patients will also be scheduled for a laboratory draw (hematology only) at Weeks 4, 8, 10, 16 and 22. Unscheduled Visits can be arranged as considered necessary by the investigator (see **Section 6.2.34**). In the event of Early Termination during Part A, patients will be asked to complete an Early Termination Visit as soon as possible (see **Section 6.2.32**) and then return 28 ± 3 days after their last dose of IMP for a Post-Early Termination Safety Follow-Up Visit (**Section 6.2.35**). Blinded safety data from the double-blind phase (Part A) will be provided to the Data and Safety Monitoring Board (DSMB), at a frequency specified by the DSMB charter, for ongoing monitoring of safety and detection of any trends. If requested by the DSMB, the DSMB statistician will provide unblinded safety data to the DSMB on a per needed basis, to enable a fully informed review.

During Part B, scheduled study visits for evaluations will take place at Weeks 26, 30, 36, 48, 60, and 76, and at Week 80 (Safety Follow-Up Visit). Patients will also be scheduled for a laboratory

draw (hematology only) at Weeks 28, 32, 34, 40, 44 and 68. The Safety Follow-Up Visit will occur 28 ± 3 days after the patient's last open-label dose of tozadenant. Patients who received tozadenant during Part A will continue on open-label tozadenant and those who received placebo will initiate open-label tozadenant. Neither the patient nor the investigator will be unblinded to the treatment received during Part A unless required for safety purposes as determined by the investigator and agreed to by the Sponsor. Upon starting Part B, patients will receive open-label tozadenant at a dose of 120 mg BID. Adjustments to the open-label tozadenant dose are allowed starting at Week 26 and at subsequent visits. Doses of 60 or 120 mg BID are permitted; the investigator may adjust a patient's dose to either level as clinically indicated. Because the information entered in the Interactive Response System (IXRS) will be used to manage the tozadenant inventory at each study site, timely entries into the IXRS will be important.

During Part B, patients' concomitant anti-PD medications may be adjusted as needed under the investigator's supervision (see **Section 5.9.1**). The optimal dose of open-label tozadenant for each patient will be defined following discussion between the patient and the investigator, taking into account the potential for improvement of disease symptoms and the tolerability profile.

During Part B, Unscheduled Visits can be arranged as considered necessary by the investigator (see **Section 6.2.34**). In the event of Early Termination during Part B, patients will be asked to complete an Early Termination Visit as soon as possible (see **Section 6.2.33**) and then return 28 ± 3 days after their last dose of IMP for a Post-Early Termination Safety Follow-Up Visit (**Section 6.2.35**). Safety data from Part B will be provided to the DSMB, at a frequency specified by its charter, for ongoing monitoring of safety and detection of any trends.

3.1.1 Study Duration Per Patient

During Part A, each patient will participate for up to 30 weeks, which includes a Screening Period of 1 to ≤ 6 weeks, followed by a Baseline Visit and 24 weeks of double-blind treatment:

- Screening Period: 1 to ≤ 6 weeks.
- Double-Blind Treatment Period: 24 weeks.

After completion of Part A, patients will continue in Part B for an additional 52 weeks:

- Open-Label Treatment Period: 52 weeks.
- Post-Treatment Safety Follow-Up: 4 weeks.

The total anticipated study duration for an individual patient will be a minimum of 81 weeks and a maximum of 86 weeks. The end of the study is defined as the date of the last visit of the last patient in the study.

3.1.2 Planned Number of Patients and Sites

Part A: Approximately 645 patients will be screened, assuming a 30% screen failure rate, to randomize 450 patients.

Part B: It is anticipated that 80% of the randomized patients (i.e., approximately 360 patients) will complete Part A and continue into the open-label phase.

Approximately 80 sites will participate in the study.

3.1.3 Anticipated Regions and Countries

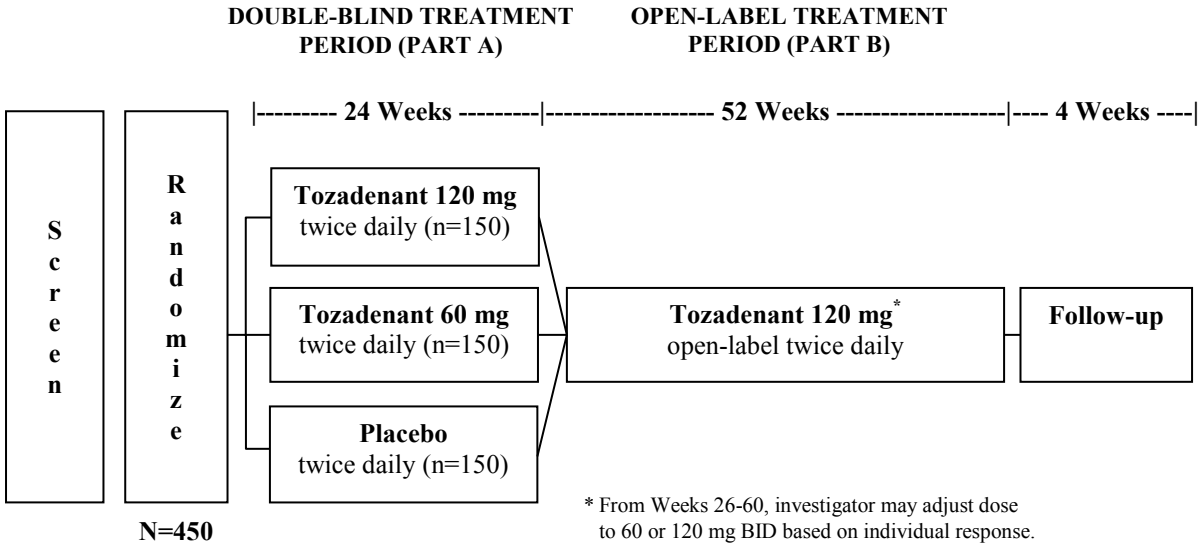
This international study will be conducted in North America and Europe.

3.2 Schedule of Events/Evaluations

The Schedule of Events/Evaluations is shown in **Table 1, Table 1.1, Table 2 and Table 2.1**.

3.3 Schematic Diagram

Figure 1: Schematic Diagram of Study Design



3.4 Rationale for Dose Selection and Placebo Control

[redacted]

4.0 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria in order to be randomized:

1. Patient is 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.
2. Patient is considered reliable and capable of adhering to the protocol (e.g., able to understand and complete diaries), visit schedule, and medication administration instructions according to the judgment of the investigator.
3. Patient has a documented history of idiopathic Parkinson's disease consistent with the UK Parkinson's Disease Society Brain Bank Diagnostic criteria prior to the Screening Visit.
4. Patient has a PD duration of at least 3 years from diagnosis.
5. Patient is male or female and 30–80 years old (inclusive) at Screening.
6. Patient has a modified Hoehn and Yahr stage 2–4 when in OFF state (estimated) and ≤ 3 in ON state.
7. Patient must have a good response to levodopa in the opinion of the investigator, be taking at least four doses of a levodopa-containing medication per day, and at least one other

concomitant anti-PD medication (dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone).

8. Patient is maintained on a regimen of permitted anti-PD medications that has been stable for at least 4 weeks prior to Screening.
9. Patients must have been taking a levodopa-containing anti-PD medication continuously for at least the previous 12 months and must be currently experiencing end-of-dose "wearing-off" with at least 2.5 hours of OFF time per day as confirmed by a 3-day Baseline diary.
10. Patient must have achieved the following results for PD diary training, practice diary collection, and Baseline diary recordings:
    a. During a diary concordance session with an approved PD diary trainer/rater (minimum 2.5 hours), patient achieved at least 80% overall diary concordance including at least 1 OFF interval.
    b. Returned a valid 3-day (i.e., 3 consecutive 24-hour periods) practice diary.
    c. Returned valid diary recordings for each of the 3 consecutive days preceding the Baseline Visit that indicated at least 2.5 hours of OFF time on each of the 3 days.

    Note: A valid diary record will not have more than 4 invalid entries (double or missed entries) over a given 24-hour period (defined as starting at 6 AM). An invalid diary entry is defined as more than one entry recorded in a given half-hour interval, an unreadable entry, or the absence of an entry in a given half-hour interval.

    Patients will be required to view the PD diary training video. Caregivers may assist patients in completion of the PD diary. If a caregiver participates in completion of the PD diary, he or she is required to participate in the PD diary training session, in addition to viewing the PD diary training video.

    Patients who do not meet the criteria for proper practice diary completion may be retrained within the 6-week window of the Screening Period, if the patients are otherwise eligible for the study.
11. Contraception:
    a. Women of childbearing potential must use an acceptable method* of contraception starting 4 weeks prior to study drug administration and for a minimum of 1 month after study completion. Otherwise, women must be postmenopausal (at least 1 year absence of vaginal bleeding or spotting) as confirmed by FSH $\geq$ 40 mIU/mL (or $\geq$ 40 IU/L) or be surgically sterile.
    b. Men with a potentially fertile partner must have had a vasectomy or be willing to use an acceptable method* of contraception for the duration of the study and for 3 months after study drug discontinuation.

*For men and women: Acceptable methods of contraception include use of a condom with spermicide; oral, implantable or injectable contraceptives; IUD; diaphragm with spermicide; or, diaphragm with condom.

4.2 Exclusion Criteria

Patients with any of the following characteristics will be excluded from being randomized:

1. Patient previously participated in any study with tozadenant.
2. Patient is currently participating in or has participated in another study of an IMP or medical device in the last 3 months or within 5 half-lives of the IMP (whichever is longer).
3. Patient has any form of secondary or atypical parkinsonism (e.g., drug-induced, post stroke).
4. Severe obesity defined as a BMI greater than 35.
5. Patient has a QTcF interval of ≥ 500 msec at Screening (Visit 1) or the patient has an average QTcF interval ≥ 450 msec for males or ≥ 470 msec for females at Baseline (Visit 2). The average at Baseline will be taken from 3 serial ECGs done several minutes apart. (Fridericia's correction [QTcF] must be used for correction of the QT interval.)
6. Known diagnosis of malignant melanoma.
7. History of neurosurgical intervention for PD.
8. Patient with grade 2 hypertension (supine systolic BP ≥ 160 or diastolic BP ≥ 100 mmHg), treated or untreated, at Screening or at Baseline confirmed by at least 1 of 2 further measurements. Patients may be rescreened once if excluded due to this exclusion criterion, following appropriate treatment.
9. Patient with a history of hypertensive crisis unless the underlying cause has been removed.
10. Patient has a history of chronic alcohol or drug abuse within the last 2 years.
11. Patient is taking apomorphine, budipine, istradefylline, tolcapone, or [redacted] within 4 weeks prior to Screening or is likely to require any of these drugs during the study.
12. Current treatment with antipsychotics; however, quetiapine administered at doses of ≤100 mg per day is permitted if the patient has been on a stable daily dose for at least 4 weeks before Screening. PRN (as needed) dosing is not permitted.
13. Exposure to neuroleptics (antipsychotic drugs) for more than 1 month within the past 2 years, or any exposure within the past year (except for quetiapine).
14. Patient has taken digoxin within 4 weeks prior to Screening or is likely to require digoxin during the study.
15. Hyperthyroidism or hypothyroidism, unless all of the following conditions are met:
    a. Patient has received a stable dose of thyroid medication for at least 3 months before the Baseline Visit.
    b. TSH concentrations are in the normal range (± 10% as a window either side of the normal range).
    c. Patient is clinically euthyroid.

16. Orthostatic hypotension requiring medication.
17. Any out-of-range laboratory values at Screening that have not been reviewed and documented as not clinically significant by the investigator. Any questionable safety lab results may be repeated for confirmation.
18. A score of <26 on the Mini-Mental State Examination, Second Edition (MMSE-II) at the Screening Visit. If the MMSE-II is not validated in the requisite language, the MMSE (Original) may be used.
19. Patients with a current episode of major depression. Patients receiving treatment for depression with antidepressants may be enrolled if they have been on a stable daily dose of the antidepressant for at least 8 weeks before the Baseline Visit.
20. Patient has a recent history of suicide attempt (defined as an active, interrupted or aborted attempt within the past 5 years), or reports suicidal ideation in the past 6 months as indicated by a positive response ('Yes') to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) performed at the Screening Visit.
21. Patient has evidence of an impulse control disorder (ICD) (i.e., one or more positive modules) according to the Modified Minnesota Impulse Disorders Interview (mMIDI) unless a structured clinical interview performed during Screening confirms that the patient does not have an ICD.
22. Patient is currently lactating or pregnant or planning to become pregnant during the duration of the study.
23. Patient has a known hypersensitivity to any components of the IMP or excipients.
24. Any other condition or clinically significant abnormal findings on the physical or neurological examination, psychiatric and medical history, at Screening or at Baseline that, in the opinion of the investigator, would make the patient unsuitable for the study or put the patient at additional risk or prejudice evaluation of safety and efficacy of the IMP.
25. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) ≥3x upper limit of normal (ULN), or total bilirubin ≥1.5x ULN, at Screening.
26. Patients with a history of hepatic dysfunction secondary to viral infection (hepatitis B or C; Epstein Barr virus [EBV]; or cytomegalovirus [CMV]), or a history of diagnosed drug- or alcohol-induced hepatic toxicity or frank hepatitis.
27. Patients with moderate to severe hepatic or renal impairment.
28. [redacted]
29. Patients with pacemakers or implantable cardioverter defibrillators.

4.3 Criteria for Withdrawal from Study

Patients are free to withdraw from the study at any time, without prejudice to their continued care.

4.3.1 Potential Criteria for Withdrawal from Study

Investigators should contact the Medical Monitor in advance, whenever possible, to discuss the potential discontinuation of a patient from the study. Investigators must contact the Medical Monitor to discuss any of the following events that may lead to the patient being discontinued from the study:

1. Patient is noncompliant with the study procedures or medications.
2. Patient takes prohibited concomitant medications as defined in this protocol or receives prohibited neurosurgical intervention for PD.
3. Patient has one or more clinically significant out-of-range laboratory values or clinically significant abnormal findings on physical examination, or AEs that are intolerable (as determined by the patient) or that put the patient at additional risk as judged by the investigator.
4. Double-blind phase (Part A), only: Patient's PD symptoms worsen to the extent that, in the judgment of the investigator, they require the addition of one or more new anti-PD medications and/or an increase in the frequency or dose of existing concomitant anti-PD medication.

4.3.2 Definite Criteria for Withdrawal from Study

Patients must be discontinued from the study if any of the following events occur:

1. Patient develops an illness that would interfere with his or her continued participation.
2. Patient withdraws his or her consent.
3. Confirmation of patient pregnancy during the study, as evidenced by a positive pregnancy test.
4. The Sponsor/Sponsor's designee or a regulatory agency requests withdrawal of the patient.
5. The Sponsor or a regulatory agency terminates the study.
6. Patient has active suicidality since last visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS, or reports any suicidal behavior since their last C-SSRS assessment. The patient should be referred immediately to a Mental Healthcare Professional.
7. The patient has a QTcF interval consistently $\geq$ 500 msec and/or a QTcF interval consistently increased by $\geq$ 60 msec compared to the average baseline QTcF interval. The average baseline QTcF interval is defined as the average of the three QTcF interval values obtained at Visit 2. Fridericia's method must be used for correction of QT intervals.
8. Investigators must follow guidelines provided related to monitoring hepatic parameters in relation to investigation guidelines and stopping rules. The following necessitate immediate cessation of dosing with IMP:

a. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) >8x ULN.

b. Patients with ALT or AST ≥3x ULN and co-existing total bilirubin ≥2x ULN*.

c. Patients with ALT or AST ≥3x ULN who exhibit a temporally associated fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (without clear alternative cause), rash or eosinophilia (>5%).

*Patients with significant elevation of ALP (ALP >2x ULN) indicating biliary obstruction to be discussed with the Medical Monitor.

9. Patients noted to have an elevated BP post-baseline, with a systolic BP ≥ 160 mmHg and/or a diastolic BP ≥ 100 mmHg that is present at 2 consecutive post-baseline study visits.

10. Patients with an absolute neutrophil count less than 1000/mm^3 (or 1.0 x 10E9/L).* Following study drug discontinuation, these patients will require weekly hematology measurements until the WBC and/or ANC returns to 75% of the baseline value (Visit 2). Assess for adverse events and concomitant medication changes and record as an unscheduled visit. Discuss with medical monitor to assure that the patient is discontinued from study drug and that the appropriate follow up safety measures are taken.

* Any patient experiencing a decline in absolute neutrophil count (ANC) and/or white blood cells (WBC) by 50% from baseline (Visit 2) will require a weekly hematology measurement until the WBC and/or ANC returns to 75% of the baseline value. The patient will continue with dosing during the weekly hematology follow-up. Assess for adverse events and concomitant medication changes and record as an unscheduled visit. If the WBC and/or ANC returns to 75% of baseline, the patient should return to routine evaluations as outlined in the Schedule of Events/Evaluations. Discuss with medical monitor.

All patients who discontinue prematurely from the study will be requested to return to the study site as soon as possible to complete the safety and efficacy evaluations outlined for an Early Termination Visit in the Schedule of Events/Evaluations **(Table 1** and **Table 2)** and in **Sections 6.2.32** and **6.2.33**. The Early Termination Visit should be done under IMP treatment, if possible. After Early Termination, the patient will also be asked to return for a Safety Follow-Up Visit to be scheduled 28 (±3) days after their last dose of IMP, unless the Early Termination Visit itself occurred 28 or more days after the last dose of IMP (see **Section 6.2.35**).

All treatment-emergent AEs will be followed until resolution, return to Baseline level, or stabilization. Investigators will attempt to obtain information on patients in the case of study withdrawal or discontinuation. For patients considered lost to follow-up, the investigator should make an effort (at least one phone call and one written message to the patient) and document his or her effort (include the date and summary of the phone call(s) and a copy of the written message(s) in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the patient, must be recorded in the source documents. The electronic case report form (eCRF)

must document the primary reason for study withdrawal or discontinuation. Patients who discontinue prematurely from the study will not be replaced.

5.0 STUDY TREATMENT(S)

5.1 Description of Investigational Medicinal Products

Table 3: Investigational Medicinal Products

	Tozadenant	Placebo for Tozadenant (Part A, only)
Dosage Form:	[redacted]	Tablets (oblong, white to off-white, debossed, film-coated), matched to 60 mg tozadenant tablet
Route of Administration:	Oral	
Batch Number:	Will be assigned according to Good Manufacturing Practice (GMP)	
Retest Date:	Will be assigned according to GMP	

5.2 Treatment(s) to be Administered

Investigational medicinal products are comprised of immediate-release, active and placebo tablets for oral administration, as described above. Placebo tablets to be used in Part A are visually and physically indistinguishable from the active drug product and contain no active ingredient.

5.3 Packaging

The IMP supplies for this study will be packaged according to current GMP guidelines and applicable national laws and regulations. Supplies will be packaged in such a way as to protect the products from deterioration during transport and storage. For Part A, IMP will be packaged in a double-blind fashion and for Part B, IMP will be packaged in an open-label fashion.

For Part A, IMP will be packaged in kits. Each kit consists of multiple blister cards (7 days of dosing per card) and will be labeled with a unique number by which it will be identified and dispensed through the IXRS. Kits will include extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.

For Part B, IMP will be packaged in high-density polyethylene bottles containing one hundred (100) 60 mg tozadenant tablets per bottle.

For Parts A and B, sites will be supplied with an initial stock that will be monitored by the IXRS, and resupply will be organized throughout the duration of the study in order to ensure sufficient double-blind and open-label clinical IMP supplies are available onsite.

5.4 Labeling

Supplies of IMP will be labeled in accordance with current FDA regulations (and as applicable, International Conference on Harmonisation (ICH) guidelines) regarding Good Clinical Practice (GCP) and GMP, and will include any locally required statements. If necessary, labels will be translated into the local language.

5.5 Handling and Storage Requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP supplies at the site in accordance with labeling and written storage instructions. From receipt until final disposition (e.g., return shipment to Sponsor's authorized designee), IMP stored by the investigator is to be kept in a secured area with limited access.

[redacted] ppropriate storage conditions must be ensured and documented by completion of a temperature log in accordance with local requirements on a regular basis, showing minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Sponsor/Sponsor's designee before further use of the IMP. The Sponsor/Sponsor's designee will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Sponsor's Quality Assurance (QA) representative. Based on discussion with the Sponsor's QA representative, the Sponsor/Sponsor's designee will then provide the site with instructions regarding use of the IMP.

The investigator or designee will instruct the patient to store the IMP according to the instructions on the label.

5.6 Dosing Instructions

In Part A, randomized patients will be instructed to take two (2) tablets of the dispensed blinded IMP by mouth BID, in the morning and in the evening preferably at the same time each day, for a total of four (4) tablets per day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing. In the event of a missed dose, patients will be instructed to take their next dose of IMP at the normally scheduled time. During Part A, the fixed study drug dosage may not be changed. Patients experiencing AEs considered to be study drug related and not tolerated by the patient will be discontinued from the study (see **Section 4.3**).

In Part B, patients will be instructed to take the specified number tablets of open-label IMP by mouth BID, in the morning and in the evening preferably at the same time each day.

All patients, upon start of Part B: 2 tablets (2 × 60 mg tablets), BID

If dose reduced at Week 26 or later: 1 tablet (1 × 60 mg tablet), BID

If dose is subsequently increased: 2 tablets (2 × 60 mg tablets), BID

The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing. In the event of a missed dose, patients will be instructed to take their next dose of IMP at the normally scheduled time.

5.7 Drug Accountability

A Drug Accountability Form will be used to record IMP dispensing and return information on a by-patient basis and will serve as source documentation during the study. Details of any IMP lost (due to breakage or wastage) or not used at the study site or returned to the Sponsor's authorized designee must also be recorded on the appropriate forms. All clinical IMP supplies and drug accountability and related pharmacy documentation must be made available throughout the study for the Sponsor/Sponsor's designee to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used clinical IMP supplies (i.e., kits for Part A and bottles for Part B) until they are returned to the Sponsor's authorized designee.

Periodically during the study and upon completion of the clinical phase of the study, all used, unused, and partially used clinical IMP supplies will be reconciled and returned in their original containers (i.e., kits for Part A and bottles for Part B) to the Sponsor's authorized designee.

Clinical IMP supplies intended for this study cannot be used for any other purpose than that described in this protocol. The investigator must ensure that IMP is used only in accordance with this protocol.

5.8 Procedures for Monitoring Patient Compliance

After IMP is dispensed, at each subsequent study visit patients must return all used, unused, and partially used clinical IMP supplies (i.e., kits for Part A and bottles for Part B). Drug accountability must be done in the patient's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability Form. Upon completion of the patient's Visit 13 at Week 76 (or Early Termination Visit, whichever occurs first), the authorized study staff will enter the date of the last dose of IMP taken in the source documents and eCRF to register the end of treatment for that patient.

If a patient is found to be persistently noncompliant (≤ 80 to ≥ 120% of the assigned dose), the Sponsor/Sponsor's designee, in conjunction with the investigator, will make a decision as to whether the patient should be discontinued from the study.

5.9 Concomitant Medications/Treatments

5.9.1 Allowed Anti-PD Medications/Treatments

During Part A, patients are required to be on a stable regimen of permitted anti-PD medications for at least 4 weeks prior to Screening (see inclusion and exclusion criteria). The stable anti-PD medication regimen must include at least four doses of a levodopa-containing medication per day, and at least one other concomitant anti-PD medication (dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone).

All efforts should be made to maintain patients on the same stable dose and frequency of their anti-PD medications throughout Part A. After randomization, 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 patient's anti-PD medication(s) are not permitted. A PRN (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.

However, at the investigator's discretion, a decrease in the total daily dose of concomitant anti-PD medication because of medication-related AEs is permitted:

- A decrease in total daily dose should be done by lowering the number or strength of tablets taken and must not be done by changing (lowering) the frequency (# of times per day the dose is taken).
- Following a decrease in total daily dose, the dose may be increased again but cannot exceed the dosage at randomization.

During Part B, patients' concomitant anti-PD medications (i.e., levodopa-containing medication, dopamine agonists, MAO-B inhibitors, anticholinergic agents, amantadine or entacapone) may be adjusted as needed under the investigator's supervision. The optimal dose of open-label tozadenant for each patient will be defined following discussion between the patient and the investigator, taking into account the potential for improvement of disease symptoms and the tolerability profile.

Throughout Parts A and B, all anti-PD medications taken by a patient during the study and the reason for their use will be recorded in the source documents and eCRF.

Patients will use their own supply of anti-PD medication throughout the study.

5.9.2 Prohibited Concomitant Medications/Treatments

The following concomitant medications and treatments are prohibited throughout the study (Parts A and B):

- Digoxin.
- Neurosurgical intervention for PD, including but not limited to deep brain stimulation.
- [redacted]

The following concomitant medications are prohibited during Part A of the study:

- Apomorphine.
- Tolcapone.
- [redacted] (levodopa/carbidopa enteral suspension).
- Istradefylline.
- Budipine.
- All neuroleptics (antipsychotics) at any dose (typical and atypical), except for quetiapine taken as a daily dose ≤100 mg. Quetiapine taken PRN (as needed) or at doses >100 mg is prohibited.
- Midodrine.
- Fludrocortisone.
- Methyldopa.
- Amphetamines and ephedra.

5.9.3 Other Concomitant Medications/Treatments

During the study, patients are asked to refrain from the use of any concomitant medication without the specific prior approval by the investigator. All medications taken by a patient and the reasons for their use will be recorded in the source documents and eCRF.

1. Restrictions on prestudy use of medications are described in the exclusion criteria in **Section 4.2**, Exclusion Criteria; these prestudy restrictions will continue throughout the double-blind phase of the study (Part A).
2. Patients taking thyroid medication for hypothyroidism or hyperthyroidism must be on a stable dose for at least 3 months prior to the Baseline Visit.
3. Patients will be instructed to keep caffeine intake stable throughout the study.

5.10 Concomitant Non-Pharmacologic Therapies During Part A

Patients will be instructed that all non-pharmacologic treatments used to manage or control their PD symptoms should remain consistent throughout the double-blind portion (Part A) of the study. All non-pharmacologic treatments in use by the patient for PD will be recorded in the source documents and eCRF at Baseline (Visit 1).

Such non-pharmacologic treatments may include, but are not limited to:

- Exercise.
- Yoga.
- Tai chi, martial arts, boxing.

- Physical therapy.
- Dance.
- Music therapy.
- Acupuncture, acupressure.
- Massage.

5.11 Blinding

During Part A, an IXRS will be used for assigning eligible patients to a treatment regimen based on a predetermined production randomization and/or packaging schedule. The randomization schedule will be produced by a biostatistician. The IXRS will generate individual assignments for patient IMP kits according to the visit schedule. The identity of the dosing group assignments will be concealed by identical appearance, packaging, labeling, and schedule of administration. The randomization code will be kept strictly confidential until the time of unblinding and will not be broken without authorization. Blinding will not be compromised for individuals involved with operational aspects of the study including bioanalysis of samples for study drug concentrations, as well as individuals involved with the planning and conduct of the final statistical analyses.

Blinded safety data from the double-blind phase (Part A) will be provided to the DSMB, at a frequency specified by the DSMB charter, for ongoing monitoring of safety and detection of any trends. If requested by the DSMB, the DSMB statistician will provide unblinded safety data to the DSMB, on a per needed basis and in accordance with the DSMB charter, to enable a fully informed review.

The study will be open-label during Part B.

5.11.1 Procedures for Maintaining and Breaking the Treatment Blind

5.11.1.1 Maintenance of Study Treatment Blind

During Part A, all patient treatment details will be allocated and maintained by the IXRS.

5.11.1.2 Breaking the Treatment Blind in an Emergency Situation

In the event of an emergency during Part A, for which knowledge of the IMP received would affect the medical management of the patient, or for a regulatory requirement, it will be possible to determine to which treatment arm and dose the patient has been allocated by contacting the IXRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

All contacts to the IXRS resulting in an unblinding event will be recorded and reported by the IXRS to the Medical Monitor and the Sponsor/Sponsor's designee. If the blind is broken for an

individual patient due to a medical emergency, the date and time of unblinding together with the reason for the unblinding will be recorded in the patient's source records, and all associated AE information will be included. The unblinding event and the date of unblinding will be noted in the eCRF to enable censoring of any data as appropriate.

5.12 Randomization and Numbering of Patients

During Part A, an IXRS will be used for assigning eligible patients to a treatment regimen based on a predetermined randomization schedule. The final randomization schedule will be created and sent to the IXRS provider. The IXRS is responsible for assigning blinded IMP kits to randomized patients, as appropriate, according to the randomization and the visit schedules.

To screen a patient (Visit 1), after the ICF has been signed, the investigator or designee will access the IXRS and provide brief details about the patient to be screened. Each patient will receive a unique patient number assigned by the site staff at Screening which will serve as their identifier throughout the study. The patient number will be required in all communication between the investigator (or designee) and the IXRS regarding a particular patient. Patient numbers and kit numbers will be tracked via the IXRS.

To randomize a patient (Visit 2, Baseline), the investigator (or designee) will access the IXRS and provide required information about the patient to be randomized, including the site number and screening number, which combined will become the unique patient number. The IXRS will allocate a kit number to the patient for each visit at which kitted IMP is dispensed.

During Part B, the IXRS will be used for initiating the dispensing of open-label IMP as well as tracking the progression of patients in the open-label phase and ensuring adequate supply of open-label IMP. The IXRS will also be used to dispense IMP supplies, according to the visit schedule and dose level assigned by the investigator.

6.0 STUDY PROCEDURES BY VISIT

6.1 Overview of Study Procedures

An overview of the conduct of the study, including the timing of study visits and assessments performed, may be found in **Table 1, Table 1.1, Table 2,** and **Table 2.1**. Details of efficacy and safety assessment methods can be found in **Section 7.0** and **Section 9.0**, respectively, and in the applicable appendices. Plasma drug concentration assessments are described in **Section 8.0**. Detailed procedures by visit are provided in **Section 6.2**.

Note: Laboratory supplies that are needed for protocol-specified tests will be provided by the central laboratory.

Consented patients will be asked to view the study-provided video ("What to expect during this clinical trial") and screened for eligibility. The purpose of the video is to advise patients not to expect therapeutic benefit from investigational treatment or participation in the study, and to

understand how an investigator/study participant relationship differs from the typical doctor/patient relationship. During the Screening Period, the patient (and any caregiver that will assist the patient to complete PD diaries during the study) will complete PD diary training and a diary concordance session (see **Section 7.1** and **Appendix 15.3**) with the site's diary trainer/rater. The patient (and caregiver, as applicable) will review the PD diary training video and receive instruction on how to complete the PD diary, including the definitions of ON and OFF. The definitions of ON and OFF will be reviewed, including ON time according to dyskinesia categories "without dyskinesia", "with non-troublesome dyskinesia" or "with troublesome dyskinesia", with emphasis on the need for the patient to be consistent in their use of the definitions when rating their status in the PD diary during the study.

When instructions appear to have been understood by the patient (and caregiver, as applicable), a PD diary concordance session will be initiated during which the patient and diary trainer/rater will concurrently complete separate training diaries for at least 5 consecutive half-hour intervals (minimum 2.5 hours). During the diary concordance session, the patient must experience both ON and OFF. The 2.5 hour session may be extended, as needed, so that the patient experiences OFF. If the patient is OFF at the beginning of the diary concordance session, they may be administered their next dose of levodopa-containing medication in order to experience ON. When the session is completed, the trainer/rater will review and assess diary concordance between the patient and the trainer/rater. The patient is required to reach at least 80% overall concordance with the trainer/rater including at least 1 OFF interval. If the concordance criteria are not achieved, the trainer/rater will schedule a second PD diary training and diary concordance session within the 6-week Screening Period, unless the patient declines further participation.

Following successful completion of the PD diary training and a diary concordance session, patients/caregivers will be required to complete practice PD diaries on 3 consecutive prespecified days (24-hour periods starting at 6 AM each day). The trainer/rater will telephone the patient to remind them to start keeping the PD diary prior to the start date, to review the ON and OFF definitions, and to answer any questions the patient may have regarding completion instructions.

Practice PD diaries will be returned to the trainer/rater and reviewed with patients/caregivers over the telephone or in person to ensure PD diary completion instructions are fully understood. Patients with invalid practice diaries will be asked by the trainer/rater either to complete a second PD diary training and diary concordance session followed by a repeat 3-day practice diary, or else asked to repeat the 3-day practice diary, depending on the patient's understanding of the diary instructions. Patients who do not satisfy diary concordance criteria during a second PD diary training and/or who return a second set of practice diaries that are invalid, will be considered screen failures.

Patients who return valid practice PD diaries and who the investigator considers eligible for the study will complete the Authorization for Baseline Form and enter relevant data using electronic data capture (EDC) for access and review/approval. If confirmed as eligible, the patient's Baseline Visit will be scheduled within 6 weeks from the Screening Visit. The patient will be instructed to complete the Baseline PD diary on the 3 consecutive days directly preceding the

scheduled Baseline Visit. The trainer/rater will contact the patient prior to the start date to remind them to start keeping the PD diary, to review the ON and OFF definitions, and to answer any questions the patients or caregiver may have regarding completion instructions. The patients will be requested to bring the Baseline PD diary to the Baseline Visit, at which the PD diary will be assessed for validity and to confirm the patient's eligibility. Patients not meeting the criteria for valid Baseline PD diary completion may be retrained, as described above, and may return for another Baseline assessment within the 6-week Screening Period.

Eligible patients who meet all the entry criteria at Baseline will be randomized via IXRS and will begin Part A (double-blind phase) for 24 weeks. The first dose of IMP will be taken at home after the Baseline Visit. Patients will be evaluated at scheduled study visits on Weeks 2, 6, 12, 18 and 24 and will be asked to complete a PD diary on the 3 consecutive days directly preceding these visits. Prior to each 3-day PD diary completion period, patients will be telephoned to be reminded to comply with the PD diary instructions. Patients will be requested to bring their PD diary to the scheduled visits, to return the IMP kits (including all used, unused and partially used blister cards) dispensed at the previous visit, to take their IMP in the morning before the visit as applicable, and to bring their other medications to the visit. Patients will be instructed to have already taken their normally scheduled dose of levodopa and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in the ON state (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in OFF will not be evaluated. Safety evaluations will be performed at each study visit. Pharmacokinetic blood samples will be collected for tozadenant (and if applicable, for pramipexole) as outlined in **Table 1** and **Table 2**, Schedule of Events/Evaluations and as described in **Section 6.2**. Patients will also be scheduled for a laboratory draw (hematology only) at Weeks 4, 8, 10, 16 and 22 as outlined in **Table 1.1.** In the event of Early Termination during Part A, patients will be asked to complete an Early Termination Visit as soon as possible and to return for a Safety Follow-Up Visit 28 ± 3 days after their last dose of IMP. If a patient decides to withdraw from study at Week 24, their Week 24 visit will be an Early Termination Visit and they will be asked to return for a Safety Follow-Up Visit within 28 ± 3 days.

Upon completion of Part A, patients will enter Part B and receive open-label tozadenant for 52 weeks. Patients will attend scheduled study visits at Weeks 26, 30, 36, 48, 60, 76, and 80. At each Part B visit, patients will be asked to return unopened and opened IMP bottles and to bring their other medications to the study site. Patients will be instructed to have already taken their normally scheduled doses of levodopa and IMP prior to arriving at the study site except at Weeks 26 and 30. At the Week 26 and Week 30 visits, patients will be asked to take their morning dose of IMP in the office to accommodate a morning tozadenant PK sample prior to dosing. For all subsequent Part B visits, patients will be instructed to take their morning IMP dose at home prior to arriving at the study site. Safety evaluations will be performed at each study visit. **Patients will also be scheduled for a laboratory draw (hematology only) at Weeks 28, 32, 34, 40, 44 and 68 as outlined in Table 2.1.** All patients completing the study will be scheduled for a required postdose Safety Follow-Up Visit 28 ± 3 days after completion of the 52-week open-label phase. In the event of Early Termination during Part B, patients will be

asked to complete an Early Termination Visit as soon as possible and to return for a Safety Follow-Up Visit 28 ± 3 days after their last dose of IMP.

Please refer to the Schedule of Events/Evaluations in **Table 1, Table 1.1 Table 2** and **Table 2.1** for specific timing of assessments and **Section 6.2** for detailed study procedures.

6.2 Detailed Study Procedures

6.2.1 Recruitment and Informed Consent Process

Interested patients will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. If interested in participating, patients will be given an IRB/IEC-approved study-specific informed consent form (ICF) to read and ask questions and share with family members if requested. Prior to a patient's participation in the study, written informed consent will be obtained in accordance with ICH GCP. The written IRB/IEC-approved ICF will be signed and dated by the patient and by the person who conducted the informed consent discussion. In addition, a statement to document the informed consenting process will be recorded in the patient's source documents.

Any patient who has difficulty understanding the ICF will discuss it with a research staff member. Research staff will work closely with patients in an effort to help them understand the requirements of their participation. Patients' questions must be answered fully by trained and qualified staff. Any patient who is unable to demonstrate understanding of the information contained in the ICF will be excluded from study participation.

The ICF and any other information provided to patients will be revised whenever important new information becomes available that is relevant to a patient's consent and continued participation in the study. The revised ICF and information must receive IRB/IEC approval/favorable opinion prior to use, and a copy of the IRB/IEC's approval/favorable opinion will be provided to the Sponsor/Sponsor's designee. The investigator, or a person designated by the investigator, will fully inform all patients of all pertinent aspects of the study and any new information relevant to the patients' willingness to continue participation in the study. This communication with the patient should be documented by the patient signing and dating the revised ICF and by written documentation of this discussion with the patient in the investigator's study files available to Sponsor/Sponsor's designee or regulatory authorities for onsite review.

Patients who consent to participate in the study will receive a copy of the signed ICF and any other information provided to patients prior to the participation in the study. The original signed forms will be maintained at the investigator's site.

After providing and documenting consent on the IRB/IEC-approved written ICF, patients will be assigned their patient screening number and proceed to the Screening Period.

6.2.2 Visit 1 (Week -6 to -1) Screening Period

The following assessments will be obtained during the Screening Period and used to determine whether a patient meets eligibility criteria for the study. Screening data will be reviewed by the

Sponsor or Sponsor's designee using EDC and documented on a completed Authorization for Baseline Form prior to the Baseline Visit. Patients meeting eligibility criteria at Screening must also meet eligibility criteria at the Baseline Visit including the completion of a valid 3-day Baseline PD diary. The PD diary training and evaluation instructions are described in **Section 7.1** and in **Appendix 15.3**.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Screening Visit with the courier (see Central Laboratory Procedures Manual).

6.2.2.1 Screening Assessments

1. Obtain written informed consent (see **Section 6.2.1**), and provide a copy to the patient.
2. Have patient view the study-provided video "What to expect during this clinical trial". The purpose of the video is to advise patients not to expect therapeutic benefit from investigational treatment or participation in the study, and to understand how an investigator/study participant relationship differs from the typical doctor/patient relationship.
3. Obtain demographics and previous medical history including any co-existing pretreatment AEs.
4. Obtain neurological and PD history.
5. Obtain complete medication history including anti-PD medications (current and prior history). Record the date and approximate time of the most recent dose of levodopa taken prior to the Screening assessment.
6. Perform physical and neurological examination.
7. Obtain weight and height.
8. Obtain and record serial BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes, on 3 occasions approximately 10 minutes apart.
9. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.
10. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Modified Hoehn and Yahr stage in the ON state (estimate OFF state per history and document for entry criteria).
    c. Administer the following assessment:
        - MMSE-II. (If the MMSE-II is not validated in the requisite language, the MMSE [Original] may be used.)

11. Administer the following assessments (may be done anytime during visit):
    - mMIDI
    - C-SSRS.
12. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. For females who are postmenopausal for less than 2 years and who are not surgically sterile: obtain a blood sample for FSH.
    b. Document method of contraception.
    b. For females of childbearing potential: urine pregnancy test.
    c. Hematology and chemistry (including liver function tests).
    d. TSH, free T3, free T4, and thyroperoxidase antibody.
    e. Urine sample for urinalysis.
13. Instruct the patient (and any caregiver that will assist the patient to complete PD diaries during the study) on how to complete the PD diary, including the definitions of ON and OFF.
    a. Have patient (and caregiver, as applicable) review the PD diary training video.
    b. Perform patient (and caregiver, as applicable) PD diary training.
    c. Review the definitions of ON and OFF, including ON time according to categories "without dyskinesia", "with non-troublesome dyskinesia" or "with troublesome dyskinesia". Emphasize the need for the patient to be consistent in their use of the definitions when rating their status in the PD diary during the study.
    d. When instructions appear to have been understood by the patient (and caregiver, as applicable), initiate a diary concordance session during which the patient and the diary trainer/rater concurrently complete separate training diaries during at least 5 consecutive half-hour intervals (minimum 2.5 hours).
        - During the diary concordance session, the patient must experience both ON and OFF. The 2.5 hour session may be extended, as needed, so that the patient experiences OFF. If the patient is OFF at the beginning of the session, they may be administered their next dose of levodopa-containing medication in order to experience ON.
        - During this time, other study-related assessments that do not interfere with the half-hourly ratings may take place.
14. When the diary concordance session is completed, the diary trainer/rater will review and assess diary concordance between the patient and the trainer/rater.
    - For the session, the patient is required to reach at least 80% overall diary concordance with the trainer/rater including at least 1 OFF interval.

- If the concordance criteria are not achieved, the trainer/rater will schedule a second PD diary training and diary concordance session within the 6-week Screening Period, unless the patient declines further participation.

15. If the patient does not otherwise meet inclusion and exclusion criteria, e.g., if a laboratory result disqualifies the patient from participating in the study, the patient is considered a screen failure. Record the primary reason for screen failure in the appropriate eCRF module and all applicable eCRFs for a screen failure. For patients who remain eligible, proceed with instructions in **Section 6.2.2.2**.

6.2.2.2 Screening / "Practice" PD Diary

Following successful completion of the PD diary training and a diary concordance session, patients/caregivers will be required to complete practice diaries on 3 consecutive prespecified days (24-hour periods starting at 6 AM each day). The trainer/rater will telephone the patient to remind them to start keeping the practice diary prior to the start date, to review the ON and OFF definitions, and to answer any questions the patient may have regarding completion instructions.

Practice PD diaries will be returned to the diary trainer/rater and reviewed with patients/caregivers, over the telephone or in person, to assess the diaries for validity and completeness and to ensure PD diary completion instructions are fully understood.

Patients with invalid practice diaries will be asked by the diary trainer/rater either to complete a second diary training and diary concordance session followed by a repeat 3-day practice diary, or else asked to repeat the 3-day practice diary, depending on the patient's understanding of the diary completion instructions. Patients who do not satisfy concordance criteria during a second diary training and/or who return a second set of practice diaries that are invalid, will be considered screen failures.

For patients who return a valid 3-day practice diary, proceed with instructions in **Section 6.2.2.3**.

6.2.2.3 Patient Preliminary Review and Acceptance

1. Patients who return a valid practice diary and who the investigator considers eligible for the study will have their screening data reviewed by the Sponsor or Sponsor's designee. Results of preliminary screening assessments of patients who meet all inclusion criteria and none of the exclusion criteria and who complete a valid practice diary will be entered using EDC for review on the Authorization for Baseline Form. This information will include demographics, medical history and neurological history (including Parkinson's disease, UPDRS scores, modified Hoehn and Yahr staging, anti-PD medications history, current treatment and concomitant medications, and specified information from the practice diary).
2. The information will be sent to Sponsor/Sponsor's designee to request confirmation of preliminary eligibility of the patient.

3. Sites will be notified of receipt of preliminary screening information if the patient is acceptable for additional screening by receiving a signed Authorization for Baseline Form within the eCRF.
4. Once preliminary eligibility of the patient has been confirmed by the Sponsor/Sponsor's designee:
   a. The patient will be instructed to complete the Baseline PD diary on 3 consecutive prespecified days prior to the Baseline Visit. The trainer/rater will telephone the patient prior to the start date to remind them to start keeping the PD diary, to review the ON and OFF definitions, and to answer any questions the patients or caregiver may have regarding completion instructions.
   b. The Baseline Visit will be scheduled approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa) to ensure the UPDRS can be collected in the ON state.
   c. Instruct the patient to bring their medications (including anti-PD medications) to the visit so that they are able to maintain their regular treatment schedule.
   d. Schedule the Baseline Visit, which must occur within 6 weeks from the date of the Screening Visit.
5. If the patient is a screen failure, record the primary reason for screen failure in the source documents and appropriate eCRF module and all applicable eCRFs for a screen failure.

6.2.3 Visit 2 Baseline

6.2.3.1 Predosing Baseline Procedures

Randomization will occur at Baseline (Visit 2), after the patient's eligibility for the study has been confirmed and all predosing Baseline procedures have been performed.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Baseline Visit with the courier (see Central Laboratory Procedures Manual).

Note: Patients will continue to take their anti-PD medications and other medications according to their regular treatment schedule.

6.2.3.2 Confirm Patient's Eligibility for Study Participation

1. Review the Baseline PD diary to assess for validity and confirm the patient's eligibility by demonstrating 2.5 hours of OFF time on each of the 3 days.

   Note: Patients not meeting criteria for a valid PD diary at the Baseline Visit may be retrained and can return for another Baseline assessment within the 6-week Screening Period.
2. Review patient's medical history and co-existing pretreatment AEs since the previous assessment and confirm continued eligibility for the study.

a. If appropriate, a physical or neurological examination will be performed in the event of an ongoing pretreatment AE.

3. Record concomitant medication use and confirm that no changes have occurred in the patient's concomitant medications (particularly anti-PD medications) since Screening that would make the patient ineligible for the study.
4. If the patient does not meet the criteria for study participation, the patient is considered a screen failure. Record the primary reason for screen failure in the source documents and appropriate eCRF module.

6.2.3.3 Perform Baseline Assessments

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Baseline Visit with the courier (see Central Laboratory Procedures Manual).

1. Upon arrival, obtain samples for the following laboratory tests and record the date and time of collection:
   a. Verify method of contraception has not changed since Screening. For females of childbearing potential: urine pregnancy test.
   b. Hematology and chemistry (including liver function tests).
   c. TSH, free T3, and free T4.
   d. PK blood sample for plasma tozadenant concentration (predose) and pramipexole, if applicable. Record the date and time of PK sample collection.
      - For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. See **Section 8.2**.
   e. Urine sample for urinalysis.
2. Update medical history and any pretreatment AEs.
3. Obtain and record serial BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes, on 3 occasions approximately 10 minutes apart.
4. Obtain 12-lead ECGs (3 serial readings performed several minutes apart) and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.
5. Record the date and approximate time of the most recent dose of levodopa taken prior to UPDRS assessment.

6. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Administer the following assessments:
        - CGI-S.
        - SCOPA-cog.
    c. Have the patient complete the following self-assessment questionnaires:
        - PDQ-39.
        - EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
        - ESS.
7. Administer the following assessments (may be done anytime during visit):
    - C-SSRS.
    - Assessment for episodes of sudden onset of sleep.
    - Caffeine Intake Questionnaire.
    - Fall questionnaire.
8. If the patient does not meet the criteria for study participation, the patient is considered a screen failure. Record the primary reason for screen failure in the source documents and the appropriate module of the eCRF.
9. For patients concomitantly taking pramipexole, obtain a second PK blood sample (for plasma pramipexole concentration only) approximately 45 minutes or longer after the first PK sample collection for tozadenant and pramipexole. Record the date and time of sample collection and the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to each sampling.

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

6.2.3.4 Randomization and Dispensing Investigational Medicinal Product

1. For patients meeting all entry criteria, complete the randomization transaction by following the IXRS procedures provided.
    a. Dispense the double-blind IMP kit assigned by the IXRS to the patient for this study visit. Each kit consists of multiple blister cards (7 days of dosing per card) and includes extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.
    b. Record the dates the patient is instructed to take IMP on the blister cards.

c. Record the date IMP was dispensed on front of card(s) and in IMP dispensing records.

d. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP kit (including all used, unused and partially used blister cards) at the next visit.

e. Patients will be instructed to take two (2) tablets of the dispensed blinded IMP by mouth twice daily (BID), in the morning and in the evening preferably at the same time each day, for a total of four (4) tablets per day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses 1 hour before or 2 hours after a meal and to refrain from eating for 1 hour after dosing.

2. Document patient understood dosing instructions and the use of the extra days if visit delayed and/or use of visit window.

   a. Record the following information: patient number, assigned IMP kit number, date and time IMP was dispensed.

   b. Patient to take the first dose of IMP at home after the Baseline Visit.

   c. Schedule the Week 2 visit.

   d. Transcribe the patient number on the paperwork for the laboratory samples that were drawn prior to receipt of IMP.

6.2.4 Telephone Call on Week 2 (to Occur Prior to PD Diary Start Date)

Patients will be telephoned prior to the start of the 3-day PD diary completion period preceding the Week 2 visit.

Note: The telephone call should take into account the window for study visits to ensure the call is made, at the latest, on the last working day prior to the start of the PD diary completion period.

1. Patients will be reminded of the following:

   a. To comply with instructions for taking the IMP.

   b. To complete the PD diary according to the instructions (see **Section 7.1**). The patients will be reminded by the trainer/rater to apply the ON and OFF definitions during PD diary completion on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the scheduled Week 2 visit. Any questions from the patient regarding PD diary completion will be addressed.

   c. To bring the PD diary with them to the visit.

   d. To bring the IMP kit (including all used, unused and partially used blister cards) with them to the visit.

   e. To take the IMP in the morning before the visit.

f. To take all doses of their routine medications (including anti-PD medications) according to their normal schedule on the day of the scheduled visit and to bring their medications to the visit.

6.2.5 Visit 3 (Week 2)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 2 visit with the courier (see Central Laboratory Procedures Manual).

1. Upon arrival, obtain sample for the following laboratory tests and record the date and time of collection:
   a. Obtain first PK blood sample for plasma tozadenant concentration. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of PK sample collection.
      - For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. See **Section 8.2**.
   b. Hematology and chemistry (inclusive of liver function tests).
   c. TSH, free T3, and free T4.
   d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.
   e. Urinalysis.

   Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.
3. Assess AEs by asking open-ended queries and record the assessments.
4. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
6. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.

8. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Administer the following assessments:
        - CGI-I.
        - CGI-S.
    c. Have the patient complete the following self-assessment questionnaires:
        - PGI-I.
        - ESS.
9. Administer the following assessments (may be done anytime during visit):
    - C-SSRS.
    - Assessment for episodes of sudden onset of sleep.
    - Healthcare Resource Utilization.
10. Obtain second PK blood sample for plasma tozadenant concentration, approximately 45 minutes or longer after the first PK sample collection, and record the date and time of the second PK collection.
    - For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling.

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
11. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the Baseline Visit.
12. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    a. Review and reconcile any discrepancies with the patient.
13. Dispense the double-blind IMP kit assigned by the IXRS to the patient for this study visit. Each kit consists of multiple blister cards (7 days of dosing per card) and includes extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.
    a. Record the dates the patient is instructed to take IMP on the blister cards.
    b. Record the date IMP was dispensed on front of card(s) and in IMP dispensing records.

14. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP kit (including all used, unused and partially used blister cards) at Week 6.
15. Document patient understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.
16. Instruct the patient on the completion of the PD diary on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the scheduled Week 6 visit and provide the patient with the PD diary.
17. Schedule the (next lab draw visit (Week 4) and telephone call (Week 6).

6.2.6 Visit 3.5 (Week 4)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 4 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the next study visit and reconfirm the next telephone call (Week 6)

6.2.7 Telephone Call on Week 6 (to Occur Prior to PD Diary Start Date)

Patients will be telephoned prior to the start of the 3-day PD diary completion period preceding the Week 6 visit.

Note: The telephone call should take into account the window for study visits to ensure the call is made, at the latest, on the last working day prior to the start of the PD diary completion period.

1. Patients will be reminded of the following:
   a. To comply with instructions for taking the IMP.
   b. To complete the PD diary according to the instructions (see **Section 7.1**). The patients will be reminded by the trainer/rater to apply the ON and OFF definitions during PD diary completion on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the scheduled Week 6 visit. Any questions from the patient regarding PD diary completion will be addressed.
   c. To bring the PD diary with them to the visit.
   d. To bring the IMP kit (including all used, unused and partially used blister cards) with them to the visit.
   e. To take the IMP in the morning before the visit.

f. To take all doses of their routine medications (including anti-PD medications) according to their normal schedule on the day of the scheduled visit and to bring their medications to the visit.

6.2.8 Visit 4 (Week 6)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 6 visit with the courier (see Central Laboratory Procedures Manual).

1. Review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.
2. Assess AEs by asking open-ended queries and record the assessments.
3. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
4. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
5. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
6. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
7. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Administer the following assessments:
        - CGI-I.
        - CGI-S.
    c. Have the patient complete the following self-assessment questionnaires:
        - PGI-I.
        - ESS.
        - Treatment Satisfaction Questionnaire for Medication (TSQM-9).
8. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)

- C-SSRS.
- Assessment for episodes of sudden onset of sleep.
- Healthcare Resource Utilization.

9. Obtain samples for the following laboratory tests and record the date and time of collection:
   a. Hematology and chemistry (inclusive of liver function tests).
   b. TSH, free T3, and free T4.
   c. PK blood sample for plasma tozadenant concentration. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of PK sample collection.
      - If the patient has an AE considered to be related to pramipexole, indicate the PK blood sample collected for tozadenant is also to be analyzed for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. (See **Section 8.2**.)
   d. Urine sample for urinalysis.
   e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

   Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
10. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the Week 2 visit.
    a. Record the date and approximate time when the patient took the most recent dose of IMP.
    b. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    c. Review and reconcile any discrepancies with the patient.
11. Dispense the double-blind IMP kit assigned by the IXRS to the patient for this study visit. Each kit consists of multiple blister cards (7 days of dosing per card) and includes extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.
    a. Record the dates the patient is instructed to take IMP on the blister cards.
    b. Record the date IMP was dispensed on front of card(s) and in IMP dispensing records.
12. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP kit (including all used, unused and partially used blister cards) at Week 12.
    a. Document patient understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.

13. Instruct the patient to complete the PD diary on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the Week 12 visit. Provide the patient with the PD diary.
14. Schedule the next lab draw visit (Week 8) and telephone call (Week 12).

6.2.9 Visit 4.3 (Week 8)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 8 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the next lab draw visit (Week 10)

6.2.10 Visit 4.8 (Week 10)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 10 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the next study visit and reconfirm the next telephone call (Week 12).

6.2.11 Telephone Call on Week 12 (to Occur Prior to PD Diary Start Date)

Patients will be telephoned prior to the start of the 3-day PD diary completion period preceding the Week 12 visit.

Note: The telephone call should take into account the window for study visits to ensure the call is made, at the latest, on the day prior to the start of the PD diary completion period.

1. Patients will be reminded of the following:
   a. To comply with instructions for taking the IMP.
   b. To complete the PD diary according to the instructions (see **Section 7.1**). The patients will be reminded by the trainer/rater to apply the ON and OFF definitions during PD diary completion on the 3 consecutive days (i.e., 3 consecutive, 24-hour periods) directly preceding the scheduled Week 12 visit. Any questions from the patient regarding PD diary completion will be addressed.
   c. To bring the PD diary with them to the visit.
   d. To bring the IMP kit (including all used, unused and partially used blister cards) with them to the visit.
   e. To take the IMP in the morning before the visit.

f. To take all doses of their routine medications (including anti-PD medications) according to their normal schedule on the day of the scheduled visit and to bring their medications to the visit.

6.2.12 Visit 5 (Week 12)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 12 visit with the courier (see Central Laboratory Procedures Manual).

1. Have patient view the study-provided video "What to expect during this clinical trial".
2. Review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.
3. Assess AEs by asking open-ended queries and record the assessments.
4. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
6. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
7. Perform the following assessments in the ON state (items a, b and c):
   a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
   b. Administer the following assessments:
      - CGI-I.
      - CGI-S.
   c. Have the patient complete the following self-assessment questionnaires:
      - PGI-I.
      - ESS.
      - PDQ-39.
8. Administer the following assessments (may be done anytime during visit):
      - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
      - C-SSRS.
      - Assessment for episodes of sudden onset of sleep.

- Healthcare Resource Utilization.

9. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
10. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. Hematology and chemistry (including liver function tests).
    b. TSH, free T3, and free T4.
    c. PK blood sample for plasma tozadenant concentration. Record the patient-reported date and approximate time when the patient took the last dose of IMP. Record the date and time of PK sample collection.
        - If the patient has an AE considered to be related to pramipexole, indicate the PK blood sample collected for tozadenant is also to be analyzed for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. (See **Section 8.2**.)
    d. Urine sample for urinalysis.
    e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
11. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the Week 6 visit.
    a. Record the date and approximate time when the patient took the last dose of IMP.
    b. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    c. Review and reconcile any discrepancies with the patient.
12. Dispense the double-blind IMP kit assigned by the IXRS to the patient for this study visit. Each kit consists of multiple blister cards (7 days of dosing per card) and includes extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.
    a. Record the dates the patient is instructed to take IMP on the blister cards.
    b. Record the date IMP was dispensed on front of card(s) and in IMP dispensing records.
13. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP kit (including all used, unused and partially used blister cards) at Week 18.
    a. Document patient understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.

14. Instruct the patient to complete the PD diary on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the Week 18 visit. Provide the patient with the PD diary.
15. Schedule the next lab draw visit (Week 16) and telephone call (Week 18).

6.2.13 Visit 5.5 (Week 16)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 16 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the next study visit and reconfirm the next telephone call (Week 18)

6.2.14 Telephone Call on Week 18 (to Occur Prior to PD Diary Start Date)

Patients will be telephoned prior to the start of the 3-day PD diary completion period preceding the Week 18 visit.

Note: The telephone call should take into account the window for study visits to ensure the call is made, at the latest, on the day prior to the start of the PD diary completion period.

1. Patients will be reminded of the following:
   a. To comply with instructions for taking the IMP.
   b. To complete the PD diary according to the instructions (see **Section 7.1**). The patients will be reminded by the trainer/rater to apply the ON and OFF definitions during PD diary completion on the 3 consecutive days (i.e., 3 consecutive, 24-hour periods) directly preceding the scheduled Week 18 visit. Any questions from the patient regarding PD diary completion will be addressed.
   c. To bring the PD diary with them to the visit.
   d. To bring the IMP kit (including all used, unused and partially used blister cards) with them to the visit.
   e. To take the IMP in the morning before the visit.
   f. To take all doses of their routine medications (including anti-PD medications) according to their normal schedule on the day of the scheduled visit and to bring their medications to the visit.

6.2.15 Visit 6 (Week 18)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 18 visit with the courier (see Central Laboratory Procedures Manual).

1. Review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.
2. Assess AEs by asking open-ended queries and record the assessments.
3. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
4. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
5. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
6. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Administer the following assessments:
        - CGI-I.
        - CGI-S.
    c. Have the patient complete the following self-assessment questionnaires:
        - PGI-I.
        - ESS.
        - PDQ-39.
7. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
    - C-SSRS.
    - Assessment for episodes of sudden onset of sleep.
    - Healthcare Resource Utilization.
8. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
9. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. Hematology and chemistry (including liver function tests).
    b. TSH, free T3, and free T4.

c. PK blood sample for plasma tozadenant concentration. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of PK sample collection.

- If the patient has an AE considered to be related to pramipexole, indicate the PK blood sample collected for tozadenant is also to be analyzed for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. (See **Section 8.2**.)

d. Urine sample for urinalysis.

e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

10. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the Week 12 visit.
11. Record the date and approximate time when the patient took the last dose of IMP.
12. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    a. Review and reconcile any discrepancies with the patient.
13. Dispense the double-blind IMP kit assigned by the IXRS to the patient for this study visit. Each kit consists of multiple blister cards (7 days of dosing per card) and includes extra IMP for the patient to use in the event of a delayed visit and/or use of visit window.
    a. Record the dates the patient is instructed to take IMP on the blister cards.
    b. Record the date IMP was dispensed on front of card(s) and in IMP dispensing records.
14. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP kit (including all used, unused and partially used blister cards) at Week 24.
    a. Document patient understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.
15. Instruct the patient to complete the PD diary on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the Week 24 visit. Provide the patient with the PD diary.
16. Schedule the next lab draw visit (Week 22) and telephone call (Week 24).

6.2.16 Visit 6.5 (Week 22)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 22 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the next study visit and reconfirm the next telephone call (Week 24)

6.2.17 Telephone Call on Week 24 (to Occur Prior to PD Diary Start Date)

Patients will be telephoned prior to the start of the 3-day PD diary completion period preceding the Week 24 visit.

Note: The telephone call should take into account the window for study visits to ensure the call is made, at the latest, on the day prior to the start of the PD diary completion period.

1. Patients will be reminded of the following:
   a. To comply with instructions for taking the IMP.
   b. To complete the PD diary according to the instructions (see **Section 7.1**). The patients will be reminded by the trainer/rater to apply the ON and OFF definitions during PD diary completion on the 3 consecutive days (i.e., 3 consecutive, 24-hour periods) directly preceding the scheduled Week 24 visit. Any questions from the patient regarding PD diary completion will be addressed.
   c. To bring the PD diary with them to the visit.
   d. To bring the IMP kit (including all used, unused and partially used blister cards) with them to the visit.
   e. To take the IMP in the morning before the visit.
   f. To take all doses of their routine medications (including anti-PD medications) according to their normal schedule on the day of the scheduled visit and to bring their medications to the visit.

6.2.18 Visit 7 (Week 24) (End of Double-Blind / Start of Open-Label Phase)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 24 visit with the courier (see Central Laboratory Procedures Manual).

Note: If a patient decides to withdraw from study at Week 24, their Week 24 visit will be an Early Termination Visit (see **Section 6.2.32**) and they will be asked to return for a Safety Follow-Up Visit within 28 ± 3 days (see **Section 6.2.35**).

1. Upon arrival, obtain samples for the following laboratory tests and record the date and time of collection:
   a. Obtain first PK blood sample for plasma tozadenant concentration. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of PK sample collection.

- For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. See **Section 8.2**.

b. Hematology and chemistry (including liver function tests).

c. TSH, free T3, and free T4.

d. Urine sample for urinalysis.

e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

2. Review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.
3. Assess AEs by asking open-ended queries and record the assessments.
4. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
6. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
7. Obtain weight.
8. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
9. Perform the following assessments in the ON state (items a, b and c):

a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.

b. Administer the following assessments:

- CGI-I.
- CGI-S.
- SCOPA-cog.

c. Have the patient complete the following self-assessment questionnaires:

- PGI-I.

- ESS.
- PDQ-39.
- EQ-5D-5L.
- TSQM-9.

10. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
    - C-SSRS.
    - Assessment for episodes of sudden onset of sleep.
    - Fall questionnaire.
    - Healthcare Resource Utilization.
11. Obtain second PK blood sample for plasma tozadenant concentration, approximately 45 minutes or longer after the first PK sample collection, and record the date and time of the second PK collection.
    - For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling.

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
12. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
13. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the Week 18 visit.
14. Record the date and approximate time when the patient took the last dose of double-blind IMP.
15. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    a. Review and reconcile any discrepancies with the patient.
16. Dispense open-label IMP (bottles) according to IXRS.
    a. Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.
17. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at the next visit.

a. Patient will begin dosing in the open-label phase (Part B) at the 120 mg dose level (i.e., two [2] tablets of open-label tozadenant 60 mg taken by mouth BID, in the morning and evening preferably at the same time each day, for a total of four (4) tablets per day).

b. Remind the patient that the first dose of open-label IMP will be taken at home in the evening.

c. Ask the patient to refrain from taking their morning dose on the day of their next visit (Week 26).

d. Document patient understood dosing instructions.

18. Schedule the Week 26 Visit in the morning before 10 AM. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.19 Visit 8 (Week 26)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 26 Visit with the courier (see Central Laboratory Procedures Manual).

1. A sample for plasma tozadenant concentration will be collected from patients who have refrained from taking their morning IMP dose prior to the visit, as instructed at the prior visit.

   a. Record patient-reported date and approximate time of the previous (evening) dose of IMP.

   b. Collect blood sample for plasma tozadenant concentration (before 10 AM). Record the date and time of PK sample collection.

   c. Have the patient take their morning dose of IMP and record the date and time of the morning dosing in the clinic.

   d. If the patient has an AE considered to be related to pramipexole, indicate the PK blood sample collected for tozadenant is also to be analyzed for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. (See **Section 8.2**.)

   Note: For collection, processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

2. Obtain samples for the following laboratory tests, and record the date and time of collection:

   a. Hematology and chemistry (including liver function tests).

   b. TSH, free T3, and free T4.

   c. Urine sample for urinalysis.

   d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

   Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

3. Assess AEs by asking open-ended queries and record the assessments.
4. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
6. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
8. Perform the following assessment in the ON state:
    - Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
9. Administer the following assessments (may be done anytime during visit):
    - C-SSRS.
    - Healthcare Resource Utilization.
10. Collect the unopened and opened IMP bottles dispensed at the Week 24 visit.
11. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    a. Review and reconcile any discrepancies with the patient.
12. Dispense open-label IMP (bottles) based on the dosage (60 mg BID or 120 mg BID) as determined by the investigator.
    a. Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.
13. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at Week 30.
    a. Ask the patient to refrain from taking their morning dose of IMP on the day of their Week 30 visit.
    a. Document patient understood dosing instructions.
14. Schedule the Week 28 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.20 Visit 8.5 (Week 28)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 28 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Remind the subject once again to refrain from taking their morning dose of IMP on the day of their next visit (Week 30)
3. Schedule the Week 30 visit in the morning before 10 AM. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient)

6.2.21 Visit 9 (Week 30)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 30 Visit with the courier (see Central Laboratory Procedures Manual).

1. A sample for plasma tozadenant concentration will be collected from patients who have refrained from taking their morning IMP dose prior to the visit, as instructed at the prior visit.
   a. Record patient-reported date and approximate time of the previous (evening) dose of IMP.
   b. Collect blood sample for plasma tozadenant concentration (before 10 AM). Record the date and time of sample collection.
   c. Have the patient take their morning dose of IMP and record the date and time of the morning dosing in the clinic.
   d. If the patient has an AE considered to be related to pramipexole, indicate the PK blood sample collected for tozadenant is also to be analyzed for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. (See **Section 8.2**.)

   Note: For collection, processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Obtain samples for the following laboratory tests, and record the date and time of collection:
   a. Hematology and chemistry (including liver function tests).
   b. TSH, free T3, and free T4.
   c. Urine sample for urinalysis.
   d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

3. Assess AEs by asking open-ended queries and record the assessments.
4. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
6. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
8. Perform the following assessment in the ON state:
    - Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
9. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
    - C-SSRS.
    - Healthcare Resource Utilization.
10. Collect the unopened and opened IMP bottles dispensed at the Week 26 Visit.
11. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    a. Review and reconcile any discrepancies with the patient.
12. Dispense open-label IMP (bottles) based on the dosage (60 mg BID or 120 mg BID) as determined by the investigator.
    a. Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.
13. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at Week 36.
    a. Document patient understood dosing instructions.
14. Schedule the Week 32 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.22 Visit 9.3 (Week 32)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 32 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the Week 34 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.23 Visit 9.8 (Week 34)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 34 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the Week 36 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.24 Visit 10 (Week 36)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 36 Visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
5. Obtain weight.
6. Perform physical and neurological examination and assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
8. Perform the following assessments in the ON state (items a and b):

a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.

b. Have the patient complete the following self-assessment questionnaire:

- ESS.

9. Administer the following assessments (may be done anytime during visit):

- mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
- C-SSRS.
- Healthcare Resource Utilization.

10. Obtain samples for the following laboratory tests, and record the date and time of collection:

a. Hematology and chemistry (including liver function tests).

b. TSH, free T3, and free T4.

c. Urine sample for urinalysis.

d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

11. Collect the unopened and opened IMP bottles dispensed at the Week 30 Visit.

a. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).

b. Review and reconcile any discrepancies with the patient.

12. Dispense open-label IMP (bottles) based on the dosage (60 mg BID or 120 mg BID) as determined by the investigator.

a Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.

13. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at Week 48.

a. Document patient understood dosing instructions.

14. Schedule the Week 40 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.25 Visit 10.3 (Week 40)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 40 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the Week 44 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.26 Visit 10.8 (Week 44)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 44 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the Week 48 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.27 Visit 11 (Week 48)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 48 Visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
5. Obtain weight.
6. Perform physical and neurological examination and assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.

8. Perform the following assessments in the ON state (items a, b and c):
   a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
   b. Administer the following assessment:
      - SCOPA-cog.
   c. Have the patient complete the following self-assessment questionnaire:
      - ESS.
9. Administer the following assessments (may be done anytime during visit):
   - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
   - C-SSRS.
   - Fall questionnaire.
   - Healthcare Resource Utilization.
10. Obtain samples for the following laboratory tests, and record the date and time of collection:
    a. Hematology and chemistry (including liver function tests).
    b. TSH, free T3, and free T4.
    c. Urine sample for urinalysis.
    d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.
    e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
11. Collect the unopened and opened IMP bottles dispensed at the Week 36 Visit.
    a. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    b. Review and reconcile any discrepancies with the patient.
12. Dispense open-label IMP (bottles) based on the dosage (60 mg BID or 120 mg BID) as determined by the investigator.

a. Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.

13. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at the next visit.
    a. Document patient understood dosing instructions.
14. Schedule the Week 60 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.28 Visit 12 (Week 60)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 60 Visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
5. Perform physical and neurological examination and assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
6. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
7. Perform the following assessments in the ON state (item a):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
8. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
    - C-SSRS.
    - Healthcare Resource Utilization.
9. Obtain samples for the following laboratory tests, and record the date and time of collection:
    a. Hematology and chemistry (including liver function tests).

b. TSH, free T3, and free T4.

c. Urine sample for urinalysis.

d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

10. Collect the unopened and opened IMP bottles dispensed at the Week 48 Visit.
    a. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    b. Review and reconcile any discrepancies with the patient.
11. Dispense open-label IMP (bottles) based on the dosage (60 mg BID or 120 mg BID) as determined by the investigator.
    a. Record the date IMP was dispensed on front of bottle(s) and in IMP dispensing records.
12. Review the dosing instructions for open-label IMP with the patient, answer any questions, and remind the patient to return unopened and opened IMP bottles at Week 76.
    a. Document patient understood dosing instructions.
13. Schedule the Week 68 visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.29 Visit 12.5 (Week 68)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 68 visit with the courier (see Central Laboratory Procedures Manual).

1. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.
2. Schedule the Week 76 Visit. If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.30 Visit 13 (Week 76)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 76 Visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
5. Obtain weight.
6. Perform physical and neurological examination and assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
8. Perform the following assessments in the ON state (items a, b and c):
    a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
    b. Administer the following assessment:
        - SCOPA-cog.
    c. Have the patient complete the following self-assessment questionnaires:
        - ESS.
        - PDQ-39.
        - EQ-5D-5L.
        - TSQM-9.
9. Administer the following assessments (may be done anytime during visit):
    - mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
    - C-SSRS.
    - Fall questionnaire.
    - Healthcare Resource Utilization.
10. Obtain samples for the following laboratory tests, and record the date and time of collection:
    a. Hematology and chemistry (including liver function tests).
    b. TSH, free T3, and free T4.

c. Urine sample for urinalysis.

d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

11. Collect the unopened and opened IMP bottles dispensed at the Week 60 Visit.
    a. Assess and document IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).
    b. Review and reconcile any discrepancies with the patient.
12. Schedule the Safety Follow-Up Visit (Week 80). If needed, use the visit window in relation to the date of the Week 24 visit (when Part B began for a given patient).

6.2.31 Visit 14 (Week 80)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Safety Follow-Up Visit (Week 80) with the courier (see Central Laboratory Procedures Manual).

All patients who complete dosing and study evaluations through Week 76 will be scheduled for a required Safety Follow-Up Visit at Week 80.

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
5. Obtain weight.
6. Perform physical and neurological examination and assess any changes from Baseline, defined as the patient's baseline in Part A, for clinical significance.
7. Have the patient complete the following self-assessment questionnaire:
    - ESS.
8. Administer the following assessments (may be done anytime during visit):

- mMIDI.
- C-SSRS.

9. Obtain samples for the following laboratory tests, and record the date and time of collection:
   a. Hematology and chemistry (including liver function tests).
   b. TSH, free T3, and free T4.
   c. Urine sample for urinalysis.
   d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.
   e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

   Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

6.2.32 Early Termination Visit – Part A (Weeks 0–24)

Note: Confirm the arrangement for laboratory sample pick-up on the day of patient's Early Termination Visit with the courier (see Central Laboratory Procedures Manual).

If the patient has discontinued IMP, perform this visit as soon as possible after the last dose of IMP. If the patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Post-Early Termination Safety Follow-Up Visit (**Section 6.2.35**) is not required.

1. If the Early Termination Visit coincides with previously planned scheduled visit for which a PD diary was completed, review the patient's PD diary recordings for the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding this visit, and address any illegible or unclear entries.

   Note: Efficacy-related measures (e.g., PD Diary) will not be completed at an Early Termination Visit during Part A if the subject stopped taking study drug more than 24 hours prior to the assessment of the measure.
2. Assess AEs by asking open-ended queries and record the assessments.
3. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
4. Obtain weight.
5. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

6. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
7. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
8. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
9. Perform the following assessments in the ON state (items a, b and c):

   Note: Efficacy-related measures (e.g., UPDRS, CGI-I, PGI-I, and CGI-S) will not be completed at an Early Termination Visit during Part A if the subject stopped taking study drug more than 24 hours prior to assessment of the measure.

   a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
   b. Administer the following assessments:
      - CGI-I.
      - CGI-S.
      - SCOPA-cog.
   c. Have the patient complete the following self-assessment questionnaires:
      - PGI-I.
      - ESS.
      - PDQ-39.
      - EQ-5D-5L.
      - TSQM-9.
10. Administer the following assessments (may be done anytime during visit):
      - mMIDI.
      - C-SSRS.
      - Assessment for episodes of sudden onset of sleep.
      - Fall questionnaire.
      - Healthcare Resource Utilization.
11. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. Hematology and chemistry (inclusive of liver function tests).

b. TSH, free T3, and free T4.

c. Blood sample for plasma tozadenant concentration, if applicable. (If the last dose was taken more than 7 days before the Early Termination Visit, no sample needs to be taken.) Record the patient-reported date and approximate time when the patient took the last dose of IMP. Record the date and time of PK sample collection.

- For patients concomitantly taking pramipexole, plasma will also be analyzed for pramipexole plasma concentration using the same PK blood sample as drawn for tozadenant PK. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. See **Section 8.2**.

d. Urine sample for urinalysis.

e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

12. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the previous visit from the patient.
13. Obtain and record the date and approximate time when the patient took the last dose of IMP.
14. Assess and document IMP accountability and compliance (document any missed dose[s], lost tablets, and number of tablets taken). In case of discrepancies, review and reconcile them with the patient.

6.2.33 Early Termination Visit – Part B (After Week 24 Visit)

Note: Confirm the arrangement for laboratory sample pick-up on the day of patient's Early Termination Visit with the courier (see Central Laboratory Procedures Manual).

If the patient has discontinued IMP, perform this visit as soon as possible after the last dose of IMP. If the patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Post-Early Termination Safety Follow-Up Visit (**Section 6.2.35**) is not required.

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain weight.
4. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
5. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.

6. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
7. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
8. Perform the following assessments in the ON state (items a, b and c):

   Note: Efficacy-related measures (e.g., UPDRS) will not be completed at an Early Termination Visit during Part B if the subject stopped taking study drug more than 24 hours prior to the Early Termination Visit.

   a. Perform full UPDRS Parts I, II, III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON.
   b. Administer the following assessment:
      - SCOPA-cog.
   c. Have the patient complete the following self-assessment questionnaires:
      - ESS.
      - PDQ-39.
      - EQ-5D-5L.
      - TSQM-9.
9. Administer the following assessments (may be done anytime during visit):
   - mMIDI.
   - C-SSRS.
   - Fall questionnaire.
   - Healthcare Resource Utilization.
10. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. Hematology and chemistry (inclusive of liver function tests).
    b. TSH, free T3, and free T4.
    c. Urine sample for urinalysis.
    d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.
    e. If the patient has an AE considered to be related to pramipexole, collect PK blood sample for plasma pramipexole. Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record date and time of PK sample collection. (See **Section 8.2**.)

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

11. Collect the unopened and opened IMP bottles from the patient.
12. Record the patient-reported date and approximate time when the patient took the last dose of IMP.
13. Assess and document IMP accountability and compliance (document any missed dose[s], lost tablets, and number of tablets taken). In case of discrepancies, review and reconcile them with the patient.

6.2.34 Unscheduled Visit

Note: Confirm the arrangement for laboratory sample pick-up on the day of an Unscheduled Visit with the courier (see Central Laboratory Procedures Manual).

An Unscheduled Visit is defined as any additional visit performed at the investigator's discretion, at any time between Baseline (Visit 2) and the Safety Follow-Up Visit (Week 80).

6.2.34.1 Required Assessments for Unscheduled Visit

The following assessments must be performed:

1. Assess AEs by asking open-ended queries and record the assessments.
2. Collect the IMP kit (including all used, unused and partially used blister cards) dispensed at the previous visit (in Part A) or open-label tozadenant bottles (in Part B) from the patient.
3. Obtain and record the date and approximate time when the patient took the most recent dose of IMP.
4. Assess and document IMP accountability and compliance (document any missed dose[s], lost tablets, and number of tablets taken). In case of discrepancies, review and reconcile them with the patient.
5. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.

If the purpose of the unscheduled visit is to collect a hematology sample (to comply with the weekly hematology monitoring, see Section 4.3.2), then only the following assessments must be performed:

1. **Confirm the arrangement for laboratory sample pick-up with the courier. Obtain hematology sample and record the date and time of collection. For processing, labeling and shipping of sample, follow the instructions provided in the Central Laboratory Procedures Manual.**
2. **Assess AEs by asking open-ended queries and record the assessments.**

3. **Record concomitant medication use; assess and record any changes to anti PD medication dose or regimen.**

6.2.34.2 Additional Assessments at Investigator's Discretion

The following additional assessments may be performed at an Unscheduled Visit for assessment of an AE, at the investigator's discretion depending on the type of AE (e.g., an out-of-range lab value, presence of suicidality, impulsivity, etc.):

1. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
2. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
3. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
4. Administer C-SSRS if suicide risk concern.
5. Administer mMIDI. (Note: After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.)
6. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. PK blood sample for plasma tozadenant concentration, at investigator's discretion (e.g., in the event of an AE thought to be study drug related). Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of PK sample collection.
    b. For patients concomitantly taking pramipexole, if the patient has an AE considered to be related to pramipexole (e.g., dyskinesia, hallucinations, delusions, hypotension, somnolence, nausea, vomiting) and a PK sample is being collected for tozadenant, indicate the PK blood sample for tozadenant is also to be analyzed for plasma pramipexole. Otherwise, obtain a PK sample for pramipexole plasma concentration). Record the patient-reported date and approximate time when the patient took the previous dose of pramipexole prior to sampling. Record the date and time of PK sample collection. See **Section 8.2**.
    b. Hematology and chemistry (inclusive of liver function tests).
    c. TSH, free T3, and free T4.
    d. Urine sample for urinalysis.
    e. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

7. In consultation with the Medical Monitor, discuss any other appropriate diagnostic tests required to evaluate patient's AE.
8. Redispense remaining unused IMP collected from the patient to continue IMP dosing to the next scheduled visit (if applicable).

6.2.35 Post-Early Termination Safety Follow-Up Visit

After Early Termination, the patient will also be asked to return for a Safety Follow-Up Visit to be scheduled 28 days after the last dose of IMP. If an Early Termination Visit took place 28 or more days after the last dose of IMP, this visit will not be conducted.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
4. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
    - Part B only: Obtain weight.
5. Have the patient complete the following self-assessment questionnaire:
    - Parts A and B: ESS.
6. Administer the following assessments (may be done anytime during visit):
    - Parts A and B: mMIDI.
    - Parts A and B: C-SSRS.
    - Part A only: Assessment for episodes of sudden onset of sleep.
7. Obtain samples for the following laboratory tests and record the date and time of collection:
    a. Hematology and chemistry (inclusive of liver function tests).
    b. TSH, free T3, and free T4.
    c. Urine sample for urinalysis.
    d. Verify method of contraception has not changed since the previous visit. For females of childbearing potential: urine pregnancy test.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

8. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.

7.0 ASSESSMENT OF EFFICACY

7.1 Hauser Parkinson's Disease Home Diary

During Screening and through Part A of the study, the Hauser Parkinson's Disease Home Diary will be completed on specified days directly preceding the scheduled study visits/assessments as outlined in the study procedures. Motor activity will be recorded as OFF, ON (mobility improved), or asleep time. Patients will be asked to record ON time according to dyskinesia categories "without dyskinesia", "with non-troublesome dyskinesia" or "with troublesome dyskinesia" **(Hauser et al, 2000)**.

During Screening, patients (and/or caregivers) will be trained to complete a PD diary to record their status at half-hourly intervals as OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, or asleep. The PD diary trainer/rater will emphasize the need for the patient to be consistent in their use of the definitions when rating their status in the PD diary during the study.

When instructions appear to have been understood by the patient (and caregiver, as applicable), a PD diary concordance session will be initiated during which the patient and trainer/rater will concurrently complete separate training diaries for at least 5 consecutive half-hour intervals (minimum 2.5 hours). During the diary concordance session, the patient must experience both ON and OFF. The 2.5 hour session may be extended, as needed, so that the patient experiences OFF. If the patient is OFF at the beginning of the diary concordance session, they may be administered their next dose of levodopa-containing medication in order to experience ON. When the session is completed, the trainer/rater will review and assess diary concordance between the patient and the trainer/rater. For the session, the patient is required to reach at least 80% overall diary concordance with the trainer/rater including at least 1 OFF interval. If the concordance criteria are not achieved, the trainer/rater will schedule a second PD diary training and diary concordance session within the 6-week Screening Period, unless the patient declines further participation.

Following successful completion of the PD diary training and a diary concordance session, patients/caregivers will be required to complete practice PD diaries on 3 consecutive prespecified days (24-hour periods starting at 6 AM each day). The patient will be telephoned and reminded to start keeping the PD diary prior to the start date, to review the ON and OFF definitions, and to answer any questions the patient may have regarding completion instructions.

Practice PD diaries will be returned to the diary trainer/rater and reviewed with patients/ caregivers over the telephone or in person to ensure PD diary completion instructions are fully

understood. Patients with invalid practice diaries will be asked by the trainer/rater either to complete a second PD diary training and diary concordance session followed by a repeat 3-day practice diary, or else asked to repeat the 3-day practice diary, depending on the patient's understanding of the diary instructions. Patients who do not satisfy diary concordance criteria during a second PD diary training and/or who return a second set of practice diaries that are invalid, will be considered screen failures.

Patients who return valid practice PD diaries and who the investigator considers eligible for the study will have their screening data reviewed by the Sponsor or Sponsor's designee and, if confirmed to be eligible, will have the Baseline Visit scheduled within 6 weeks from the Screening Visit. They will be instructed to complete the Baseline PD diary on the 3 consecutive days directly preceding the scheduled Baseline Visit. Patients will be telephoned prior to the start of the Baseline PD diary session. During the call the trainer/rater will:

1. Remind about the date when patient should start to complete the Baseline PD diary.
2. Remind to complete the Baseline PD diary starting at 6:00 AM on the required date and to continue recording until 6:00 AM of the day of the visit.
3. Review completion instructions including the ON and OFF definitions and address any questions from the patient.
4. Patients will be requested to bring the Baseline PD diary to the Baseline Visit at which the PD diary will be assessed for validity and to confirm the patient's eligibility.

Those not meeting the criteria for valid Baseline PD diary completion may be retrained, as described above, and may return for another Baseline assessment within the 6-week Screening Period.

After randomization, patients will be telephoned prior to the start of each subsequent PD diary session. The purpose of these calls is to:

1. Remind about the date when patient should start to complete the PD diary.
2. Remind to complete the PD diary starting at 6:00 AM on the required date and to continue recording until 6:00 AM of the day of the visit.
3. Review completion instructions including the ON and OFF definitions and address any questions from the patient.
4. Ask patient to bring their PD diaries when scheduled for a visit during Part A (Weeks 2, 6, 12, 18 and 24).

The PD diary trainer/rater will evaluate PD diaries after receiving them and discuss with the patient if invalid entries are noted to remind them of correct procedures.

In order to achieve a high standard of PD diary completion across the patient population, a Central Review process will be used to alert investigators to incomplete or inconsistent PD diary entries. Sites will be required to forward completed diaries for Central Review during Part A of the study, from Screening through Week 24 (Visit 7).

Only Sponsor/Sponsor's designee-approved trainers/raters may administer the PD diary training and concordance session in accordance with the requirements for background, experience and training as documented on the Certificate of Rater Approval.

An example of the diary and instructions are provided in **Appendices 15.2** and **15.3**.

7.2 Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is a scale that was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment **(Fahn et al, 1987)**.

The scale itself has four components, largely derived from preexisting scales that were reviewed and modified by a consortium of movement disorders specialists (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor Examination; Part IV, Complications of Therapy). One of the core advantages of the UPDRS is that it was developed as a compound scale to capture multiple aspects of PD. It assesses both motor disability (Part II: Activities of Daily Living) and motor impairment (Part III: Motor Examination). In addition, Part I addresses mental dysfunction and mood, and Part IV assesses treatment-related motor and non-motor complications. Of all available clinical scales for the assessment of Parkinsonian motor impairment and disability, the UPDRS is currently the most commonly used.

Only Sponsor/Sponsor's designee-accepted raters may administer the UPDRS subscales in accordance with the requirements for background, experience in a research setting and training as documented on the Certificate of Rater Approval.

Patients will be instructed to have already taken their normally scheduled dose of levodopa and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in the ON state (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in "best" ON. UPDRS Part III in OFF will be not be evaluated.

An example of the scale is provided in **Appendix 15.1**.

7.3 Clinical/Patient Global Impression Scales (CGI-S, CGI-I and PGI-I)

Clinical Global Impression of Severity (CGI-S):

For the CGI-S, the investigator or rater is asked, considering his or her total clinical experience with the PD population, to rate the severity of the patient's disease at that time, based on a 1-7 point weighted scale ranging from "normal, not at all ill" (1) to "among the most extremely ill patients" (7). A zero score is assigned if the score is not assessed.

Clinical Global Impression of Improvement (CGI-I):

For the CGI-I, the investigator or rater is asked to rate the patient's total improvement, whether or not in his or her judgment it is due entirely to drug treatment, based on a 1-7 point weighted

scale ranging from "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed.

Patient Global Impression of Improvement (PGI-I):

For the PGI-I, the patient is asked to rate the total improvement of their PD, whether or not in the patient's judgment it is due entirely to drug treatment, based on a 1-7 point weighted scale ranging from "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed.

Examples of the CGI-S, CGI-I, and PGI-I scales are provided in **Appendix 15.4**.

7.4 Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

The PDQ-39 is a copyrighted instrument to assess symptoms of PD with 39 questions relating to mobility, activities of daily living, emotional well-being, social support, cognition, communication and bodily discomfort. The questionnaire asks a patient to rate each question regarding their PD symptoms over the past month.

An example of the PDQ-39 is provided in **Appendix 15.10**.

7.5 Scales for Outcomes in Parkinson's Disease–Cognition (SCOPA-cog)

The SCOPA-cog is a validated 10-item instrument that has shown sensitivity to the specific cognitive deficits in PD **(Marinus et al, 2003)**. The SCOPA-cog has been used to measure change in cognitive functioning over time in interventional research in PD patients. Domains assessed and included in the total sum score include memory and learning (including delayed recall), attention, executive functions, and visuo-spatial functions.

An example of the SCOPA-cog is provided in **Appendix 15.11**.

7.6 Fall Questionnaire

A Fall questionnaire will be utilized to solicit information about patient falls, defined as coming to rest on the ground inadvertently from a standing position, during this study. The questionnaire will be administered at Baseline (Visit 2), at Week 24 (Visit 7), Week 48 (Visit 11) and Week 76 (Visit 13) and in the event of an Early Termination Visit (during Part A or B). The assessment will ask if a patient has been experiencing falls over the past 3 months, and if so, approximately how many falls have occurred during that interval.

An example of the Fall questionnaire is provided in **Appendix 15.13**.

7.7 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a 9-item validated questionnaire that assesses patients' satisfaction with medication and captures information on treatment effectiveness, convenience, and global satisfaction **(Bharmal, 2009**; **Atkinson et al, 2004**; **Atkinson et al, 2005)**. The TSQM-9

provides 4 domain scores: effectiveness, convenience, and global satisfaction ranging from 0 to 100 with higher scores representing higher satisfaction on that domain.

7.8 EQ-5D-5L

The EQ-5D-5L™ is a standardized, patient-reported, generic instrument for measuring health outcome **(EuroQol Group, 1990**; **Herdman et al, 2011)**. It provides a simple descriptive profile and a single index value for health status. The instrument consists of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale (EQ VAS). The descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with 5 levels of severity within each particular EQ-5D dimension. The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine". This information can be used as a quantitative measure of health as judged by the individual respondents.

7.9 Healthcare Resource Utilization

Information about hospitalizations (i.e., inpatient admissions) and emergency room visits will be collected using the Healthcare Resource Utilization Questionnaire **(Appendix 15.14)** and captured in the eCRF according to the schedule shown in **Table 1** and **Table 2**. In addition to hospital admission and discharge dates, and emergency room visit dates, the reason for the hospital admission or emergency room visit and whether or not it was Parkinson's disease-related will be recorded.

An example of the Healthcare Resource Utilization Questionnaire is provided in **Appendix 15.14**.

8.0 ASSESSMENT OF PLASMA DRUG CONCENTRATIONS

Specific procedures for PK blood sample collection and processing, storage, shipping, and analysis will be provided in the Central Laboratory Procedures Manual.

All samples for bioanalysis will be destroyed upon authorization by the Sponsor or Sponsor's designee, after finalization of the clinical study report.

8.1 Tozadenant Plasma Concentrations

During Part A, PK blood samples for determination of plasma tozadenant concentrations will be collected at Baseline, at Weeks 2, 6, 12, 18, and 24 (end of double-blind dosing), and at an Early Termination Visit unless the patient's last dose of IMP was taken more than 7 days before the Early Termination Visit. For Unscheduled Visits, PK sample collection is at the investigator's discretion (e.g., in the event of AEs thought to be study drug related).

1. Two (2) PK blood samples will be collected at the study visits at Weeks 2 and 24. When two (2) PK samples are to be collected, the first sample will be taken on arrival and the second sample taken on departure. The time between the two blood draws should be approximately 45 minutes or longer, and dosing with study drug must not occur between the first and second draws.
2. For Weeks 6, 12, and 18 (and if PK sample is to be collected during an Unscheduled Visit), one (1) PK blood sample will be collected at the most convenient time during the visit.
3. For an Early Termination Visit, one (1) PK blood sample will be collected at the most convenient time during the visit, provided that the patient's last dose of IMP was not taken more than 7 days before the visit.
4. For each collection, the dates and times of sampling and the patient-reported date and approximate time of the most recent IMP dosing prior to sampling will be recorded.

During Part B, at Weeks 26 and 30, PK blood samples for plasma tozadenant will be collected from patients who have a visit in the morning (before 10:00 AM) and who have not yet taken their morning IMP dose. For each collection, one (1) PK blood sample will be taken. The patient-reported date and approximate time of the previous (evening) dose of IMP will be recorded, the blood sample collected, and the date and time of sample collection recorded. The morning dose of tozadenant will then be administered.

8.2 Pramipexole Plasma Concentrations

For Patients Concomitantly Taking Pramipexole Only:

During Part A, for those patients concomitantly taking pramipexole, a subset of PK blood samples collected for tozadenant (see **Section 8.1**) will also be analyzed for plasma pramipexole concentration. These samples include the sample collected at Baseline (Visit 2, predose) and both samples collected at Weeks 2 (Visit 3) and 24 (Visit 7). In addition, a second PK sample for plasma pramipexole concentration will be taken at Baseline (Visit 2) at least 45 minutes after the first PK sample is collected. Refer to the Central Laboratory Procedures Manual for specific instructions.

In the event of an Early Termination Visit in patients concomitantly taking pramipexole at any time during the study (Part A or B), a PK sample for plasma pramipexole concentration will be collected. If a PK sample for tozadenant is also indicated (Early Termination during Part A), the tozadenant sample is to be indicated for determination of pramipexole levels without the requirement of an additional pramipexole sample.

During Part A, in the event of AEs thought to be pramipexole-related (e.g., dyskinesia, hallucinations, delusions, hypotension, somnolence, nausea, vomiting), either noted at the time of a scheduled study visit or an Unscheduled Visit, PK blood sample collected for tozadenant will also be analyzed for plasma pramipexole, i.e., at Week 6 (Visit 4), Week 12 (Visit 5) or Week 18 (Visit 6). If a tozadenant sample is not being collected at an Unscheduled Visit a PK sample for plasma pramipexole concentration will be collected.

A PK sample for plasma pramipexole concentration will only be collected during Part B in the event of AEs thought to be pramipexole-related, whether noted at the time of a scheduled study visit or an Unscheduled Visit. If a PK sample for tozadenant is also indicated at Week 26 or Week 30, the tozadenant sample(s) are to be indicated for determination of pramipexole levels without the requirement of an additional pramipexole sample(s).

For each pramipexole PK collection, the date and time of sampling and patient-reported date and approximate time of the most recent pramipexole dosing prior to PK sampling will be recorded.

9.0 ASSESSMENT OF SAFETY

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (i.e., after the signing of the ICF), including any pretreatment and post-treatment periods required by the protocol, must be recorded in source documents and the eCRF even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial Screening Visit and all AEs that recurred or worsened after the initial Screening Visit. Events that occur prior to dosing are captured as medical history and pretreatment AEs. Events that occur after Baseline and prior to dosing are captured as AEs.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the patient's history or during the baseline period.

9.1.2 Procedures for Reporting and Recording Adverse Events

The patient will be given the opportunity to report AEs spontaneously. An open-ended, non-leading prompt will also be given at each study visit to detect AEs. For example:

"*Did you notice anything unusual about your health (since your last visit)?*"

In addition, the investigator should review self-assessment procedures employed in the study.

9.1.3 Description of Adverse Events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, whenever possible, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the patient's own words on his/her own records and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF (including judgment of relationship to IMP and assessment of intensity) are described in the eCRF Completion Guidelines.

9.1.4 Follow Up of Adverse Events

An AE will be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

If an AE is still ongoing at the end of the study for a patient, follow up will be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the patient is lost to follow up. If no follow up is provided, the investigator must provide a justification. Follow up will usually be continued for 30 days after the patient has discontinued his/her IMP.

9.1.5 Rule for Repetition of an Adverse Event

An increase in the intensity of pretreatment AE / medical history should lead to the repetition of the event being reported with:

- The outcome of "worsening" and the outcome or end date of the pretreatment AE / medical history event that is not related to the natural course of the disease being the same as the start date of the AE.
- The AE verbatim term being the same for the pretreatment AE / medical history, so that the repeated AE can be easily identified as the worsening of the first one.

9.1.6 Pregnancy

In the event a patient becomes pregnant after the first intake of any IMP, the Sponsor's drug safety representative should be informed immediately. The patient should be withdrawn from the study as soon as pregnancy is known, and the following should be completed:

1. The patient should return for an Early Termination Visit as soon as possible.
2. The patient should immediately stop the intake of the IMP.
3. A Safety Follow-Up Visit should be scheduled 28 ± 3 days after the patient has discontinued IMP.
4. The investigator must inform the patient of information currently known about potential risks and about available treatment alternatives.

In cases where the partner of a male patient enrolled in a clinical study becomes pregnant, Sponsor will ask the investigator or designee to contact the patient and his partner to request consent via the Partner Pregnancy Consent Form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome Form will be forwarded to the patient's partner for completion.

The pregnancy will be documented on the Pregnancy Report and Outcome Form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report and Outcome Form in which the investigator has to report on the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

In certain circumstances, Sponsor may request that follow up is continued for a period longer than 30 days after birth.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Sponsor-provided SAE Report Form.

9.1.7 Overdose of Investigational Medicinal Product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in source documents and in the Drug Accountability module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (e.g., suicide attempt).

9.1.8 Safety Signal Detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that the DSMB, investigators, clinical study patients, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Medical Monitor or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Sponsor's drug safety representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at the Sponsor may identify additional safety measures (e.g., AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the study. The DSMB will be informed as defined in the DSMB charter.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Event

Once it is determined that a patient experienced an AE, the seriousness of the AE must be determined. An SAE must meet one or more of the following criteria:

1. Results in death.
2. Life-threatening.

   Note: Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
3. Significant or persistent disability/incapacity.
4. Congenital anomaly/birth defect (including that occurring in a fetus).
5. Important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious.

   Note: Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
6. Initial inpatient hospitalization or prolongation of hospitalization.

   Note: A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for one of the other criteria in the definition of serious (e.g., life-threatening adverse experience, important medical event).

   Hospitalizations for reasons not associated with the occurrence of an AE (e.g., preplanned surgery or elective surgery for a preexisting condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. For example, if a patient has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the preexisting condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

Note: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat

to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2.2 Procedures for Reporting Serious Adverse Events

If an SAE is reported, the Sponsor must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). An SAE Report Form will be provided to the investigator. The SAE Report Form must be completed in English.

The investigator must forward to the Sponsor (or its representative) a duly completed SAE Report Form provided by the Sponsor, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

It is important for the investigator, when completing the SAE Report Form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for the Sponsor to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (e.g., autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the SAE Report Form.

The investigator is specifically requested to collect and report to the Sponsor (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP) up to 4 weeks from the date of last IMP for each patient, and to also inform participating patients of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to the Sponsor regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report Form, the Sponsor will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the current IB.

9.2.3 Follow Up of Serious Adverse Events

An SAE will be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the global safety database without limitation of time.

9.3 Immediate Reporting of Adverse Events

The following AEs must be reported immediately:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality.
- Suspected transmission of an infectious agent via a medicinal product.

9.4 Laboratory Measurements

The laboratory tests listed below **(Table 4)** are to be performed and analyzed as outlined in the Schedule of Events/Evaluations **(Table 1** and **Table 2)**.

Sample collection kits and the laboratory procedures manual with detailed sample processing and shipping instruction will be provided by the accredited central laboratory.

All laboratory samples will be destroyed upon authorization by the Sponsor or Sponsor's designee, at the finalization of the clinical study report.

The following laboratory parameters will be measured:

Table 4: Laboratory Measurements

Hematology	Chemistry	Thyroid	Urinalysis [b]
Basophils	AST	TSH	Protein
Eosinophils	ALT	Free T_3	Glucose
Hematocrit	ALP	Free T_4	pH
Hemoglobin	Albumin	Thyroperoxidase antibody (screening only)	Blood
Lymphocytes	Bicarbonate		Ketones
Monocytes	Calcium		Specific gravity
Neutrophils	Chloride		Urine pregnancy test (females of childbearing potential, only)
Platelet count	Creatine phosphokinase with automatic Troponin-I and CK-MB if value > 2 x the ULN		
RBC count	Creatinine		
WBC count	Glucose		
	GGT		
	LDH		
	Phosphate		
	Potassium		
	Sodium		
	Total bilirubin [a]		
	Total cholesterol		
	Total protein		
	Urea/BUN		
	Uric acid		
	Follicle stimulating hormone (females postmenopausal <2 years, only)		

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CK-MB, creatine phosphokinase-MB; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; pH, reverse logarithmic representation of relative hydrogen proton (H+) concentration; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ULN, upper limit of normal; WBC, white blood cell.

[a] Conjugated and unconjugated.

[b] If urine dipstick is positive for leukocytes, protein, or erythrocytes, a microscopic evaluation and culture will be performed.

9.5 Other Safety Measurements

9.5.1 Blood Pressure and Pulse Measurements

Blood pressure and pulse rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. A full set of measurements will include BP and pulse obtained after at least 5 minutes supine rest, followed by BP and pulse obtained after the patient has been standing for approximately 1 and 3 minutes. At Screening and Baseline (Visit 2), the full set of BP and pulse measurements will be collected on 3 occasions approximately 10 minutes apart. If repeats are performed for either supine or standing BP, the

full set (BP and pulse) should be repeated after 5 minutes supine rest (i.e., supine followed by standing measurements). The measurements will be obtained throughout the study using an appropriate cuff size from the patient's non-dominant arm. If possible, all measurements for a given patient will be obtained from the same arm using the same cuff. The cuff should be placed on the designated arm at least 5 minutes prior to collection. If available, an automatic BP cuff (sphygmomanometer) with a digital readout will be used.

Supine and standing systolic and diastolic BP and pulse rate will be recorded at the nominal time points specified in the Schedule of Events/Evaluations **(Table 1** and **Table 2)**. If, for any reason, an accurate reading cannot be obtained (e.g., dyskinesia), collect the measurement as close to the nominal time point as feasible and record the date and time of collection.

Patients noted to have an elevated BP post-baseline, with a systolic BP $\geq$ 160 mmHg and/or a diastolic BP $\geq$ 100 mmHg that is present at 2 consecutive post-baseline study visits, will be discontinued from study (see **Section 4.3.2)**.

9.5.2 Twelve-lead Electrocardiogram (ECG)

A resting supine 12-lead ECG will be collected at the time points specified in the Schedule of Events/Evaluations **(Table 1** and **Table 2)** after the patient has been in a supine position for a minimum of 5 minutes.

The 12-lead ECG includes standard PR, QRS, QT and QTc (heart rate-corrected QT) intervals as read by the ECG machine provided by the cardiac core lab. Fridericia's correction (QTcF) must be used for correction of the QT interval.

A central ECG core lab will overread all ECGs and provide the final interpretation. At Screening the results will be available within 72 hours of the visit. At Baseline, the overread of the 3 serial ECGs will be available within 24 hours. The investigator should use the ECG-recorded QTcF interval to meet eligibility requirements.

9.5.3 Epworth Sleepiness Scale (ESS)

The ESS is a copyrighted short self-administered assessment that measures daytime sleepiness. The instrument asks patients to rate the probability of dozing in eight different day-to-day scenarios. The ratings are as follows:

0 = no chance of dozing

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

The scores for the eight situations are then added to one total score. A score within the range 0−9 is considered to be normal while a score within the range of 10−24 would indicate medical help should be solicited.

An example of the form is provided in **Appendix 15.5**.

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

Suicidality will be assessed by trained study personnel using the C-SSRS **(Posner et al, 2011)**. The C-SSRS is a copyrighted standardized suicidality rating system conducted by a certified rater. The interview measures presence of suicidality and consists of 4 categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual/potential lethality. This scale will be used for screening as well as to assess for the occurrence of any suicidal ideation and/or behavior during the study.

9.5.5 Assessment for Episodes of Sudden Onset of Sleep

To assess the potential development of episodes of sudden onset of sleep**,** patients will be asked if they experienced any abrupt episodes of unplanned sleep during or while engaged in some activity where they are not expected to occur (e.g., eating/drinking, speaking, or driving), which may or may not have been preceded by somnolence or sedation. Any positive response should be further evaluated to determine whether the patient's continued participation in the study puts them at risk and whether they should be discontinued from the study **(**see **Appendix 15.6)**.

9.5.6 Modified Minnesota Impulse Disorders Interview (mMIDI)

The Minnesota Impulse Disorders Interview has been previously used in Parkinson's subjects to monitor for development of impulse control disorders (ICDs). The Modified Minnesota Impulse Disorders Interview (mMIDI) is applicable for both initial identification of a potential ICD and for monitoring ICDs during a clinical trial. The mMIDI focuses on the five most common ICDs which may be associated with dopamine agonist use: compulsive buying, compulsive gambling, compulsive eating, hypersexuality and punding. The mMIDI will be considered positive if a subject gives a positive answer to any question after the gateway question in a specific module. If during screening a subject has evidence of an ICD (i.e., one or more positive modules on the mMIDI), the subject will be considered ineligible for the study unless a structured clinical interview confirms that the subject does not have an ICD. After Baseline, if a patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.

An example of the mMIDI is provided in **Appendix 15.7**.

10.0 STUDY MANAGEMENT AND ADMINISTRATION

10.1 Adherence to Protocol

The investigator should not deviate from the protocol. In medical emergencies, the investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

10.2 Monitoring

The Sponsor/Sponsor's designee will monitor the study to meet ICH GCP guidelines and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by the Sponsor/Sponsor's designee to a contract research organization (CRO) or a contract monitor.

The investigator and his/her staff are expected to cooperate with the Sponsor/Sponsor's designee and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow the Sponsor/Sponsor's designee to periodically review all eCRFs and corresponding source documents (e.g., hospital and laboratory records for each study participant). Monitoring visits will provide the Sponsor/Sponsor's designee with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

10.2.1 Definition of Source Data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

None of the data will be recorded directly in the eCRF and therefore all source documentation will appear in a source document as defined above.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (e.g., ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the patient's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as ECG tracings/reports or electroencephalogram records, must be saved and stored as instructed by the Sponsor/Sponsor's designee.

10.2.2 Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. All data reported on the eCRF should be supported by source documents, unless otherwise specified in **Section 10.2.1**.

The patient's consent and enrollment in the study must be recorded in the patient's medical record. These data should identify the study and document the dates of the patient's participation.

During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable based on source documents (including, but not limited to, consent forms, patient files, recordings from automated instruments, tracings [ECG], x-ray films, and laboratory notes).

10.3 Data Handling

10.3.1 Case Report Form Completion

The study will be performed using EDC. The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/ electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

In accordance with the applicable regulatory requirements, the confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules.

The investigator will maintain a Site Delegation Personnel Log to document signatures and initials of all persons qualified and authorized by the investigator to make entries and/or corrections to the source documents. Any corrections to non-electronic source documents are made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed, and explained (if necessary) by the person making the correction and must not obscure the original entry.

For source documents such as automated pharmacy records, the investigator will review during Screening and prior to randomization any pharmacy records in the medical chart and other physician medical notes and review the information with the patient and clarify with a note in the chart any items that are inconsistent or medications that may have been prescribed but the patient is not currently taking and have been discontinued.

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.3.2 Database Entry and Reconciliation

Electronic case report forms will be available for review by the Clinical Research Associate (CRA), Sponsor and Sponsor's designee after completion by the site. The eCRFs will be monitored remotely and onsite by the CRO after documented training and in accordance with the monitoring plan. The CRA will review the eCRF data on a regular basis and post any queries for the site to complete prior to the scheduled onsite monitoring visits. Only those individuals who are qualified and authorized by the investigator to complete eCRFs will be trained and receive passwords allowing eCRF completion.

The completed eCRF must be electronically reviewed, signed, and dated by a qualified physician who is designated as Principal or Sub-investigator for the study. The investigator must retain the original source documents. A final portable document format (PDF) copy of the eCRFs will be provided to the study site by the CRO or designee at the end of the study for archival purposes.

If a patient is a screen failure, the primary reason for screen failure will be recorded in the eCRF.

An electronic audit trail system will be maintained within the eCRF to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

10.3.3 Patient Identification Code List

The investigator will keep a Patient Identification Code list. This list remains with the investigator and is used for unambiguous identification of each patient.

10.4 Termination of the Study

Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, Sponsor (or its representative) will inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirements. The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the investigator/institution, as specified by the applicable regulatory requirements. In addition, arrangements will be made for the return of all unused IMP and other material in accordance with Sponsor procedures for the study.

10.5 Archiving and Data Retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, informed consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with Sponsor **(CPMP/ICH/135/95, 2002** [Section 4.9.5]). The investigator will contact Sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify Sponsor should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

10.6 Audit and Inspection

The investigator will permit study-related audits and inspections mandated by domestic or foreign regulatory authorities or study-related audits mandated by the Sponsor's Clinical QA or designee, after reasonable notice.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, that enrolled patients (i.e., those signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC standard operating procedures (SOPs), ICH GCP, and applicable regulatory requirements. The investigator will work with the Sponsor to resolve any audit observations and implement corrective and preventative actions as appropriate.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform the Sponsor/Sponsor's designee.

10.7 Good Clinical Practice

Noncompliance with the protocol, ICH Guidelines and GCP regulations, or local regulatory requirements by the investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by the Sponsor/Sponsor's designee to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

11.0 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

11.1 Definition of Analysis Sets

Intent-to-Treat Set (ITT): The ITT according to the intention-to-treat principle will consist of all randomized subjects. Patients will be accounted for in the treatment group to which they were originally randomized.

Safety Set (SS): The SS will consist of all randomized patients who received at least one dose of IMP. Patients will be accounted for in the treatment group based on IMP actually received at first dose.

Modified Intent-to-Treat Set (mITT): The mITT will consist of all randomized patients who took at least 1 dose of study drug and had valid diaries at baseline and had valid diaries on at least 1 post-baseline visit. Patients will be accounted for in the treatment group to which they were originally randomized.

Per Protocol Set (PPS): The PPS will consist of all randomized patients who have an efficacy evaluation (number of hours per day spent in the OFF state while awake) at Week 24 and have no major protocol deviations/violations. In addition, subjects randomized to tozadenant must have measurable plasma concentrations at each post-baseline visit for the subject to be considered in the PPS (i.e., not have a below-the-limit-of-quantitation result from the bioanalysis at any post-baseline visit). This will not exclude subjects who had missing samples or values, for any reason, from the analysis. (For example, instances where the analytical lab was unable to obtain a result from a sample they received, or no sample was received, or the bioanalytical results were considered invalid.)

Patients will be accounted for in the treatment group to which they were originally randomized.

11.2 Study Variables

11.2.1 Efficacy Variables

11.2.1.1 Primary Efficacy Variable (Part A)

The primary efficacy variable is the change from Baseline to Week 24 in the number of hours per day spent in the OFF state.

11.2.1.2 Key Secondary Efficacy Variables (Part A)

The key secondary efficacy variables include the following:

1. Change from baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia.

2. Change from baseline to Week 24 in UPDRS Parts II (ADL subscale) + III (motor subscale) total scores.

11.2.1.3 Other Secondary Efficacy Variables (Part A)

The other secondary efficacy variables include the change from Baseline to Week 24 (where applicable), for the following:

1. CGI-I at Week 24.
2. PGI-I at Week 24.
3. UPDRS Part III (motor subscale) score in the ON state.
4. CGI-S.
5. UPDRS Part II (ADL subscale) score.
6. Number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia).
7. Number of hours per day spent in the ON state without dyskinesia.
8. Number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome).
9. Number of hours per day spent in the ON state with non-troublesome dyskinesia.
10. PD-related quality of life as measured by PDQ-39 (total score and individual domain scores).
11. UPDRS Part IV score.
12. UPDRS Part I score.

11.2.1.4 Exploratory Variables (Part A)

The exploratory variables in Part A include the change from Baseline to Week 24 (where applicable), for the following:

1. Number of hours per day spent in the asleep state.
2. Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
3. Falls as measured by question 13 on UPDRS Part II.
4. Responder analysis of number (%) of patients with ≥ 1.0 h improvement in OFF time (evaluated at Week 24).
5. Responder analysis of number (%) of patients with ≥ 2.0 h improvement in OFF time (evaluated at Week 24).
6. Percent change in total levodopa equivalent dose.
7. Percent change in the number of hours per day spent in OFF state.

8. Percent change in the number of hours per day spent in ON state without troublesome dyskinesia.
9. Percent change in the number of hours per day spent in ON state with troublesome dyskinesia.
10. Scales for Outcomes in Parkinson's Disease–cognition (SCOPA-cog) score.
11. Fall questionnaire score.
12. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and only one additional concomitant anti-PD medication.
13. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and two additional concomitant anti-PD medications.
14. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and three additional concomitant anti-PD medications.

11.2.1.5 Exploratory Variables (Part B)

The exploratory variables in Part B include the following:

1. Change from Baseline in UPDRS Part II (ADL subscale) + Part III (motor subscale) total score.
2. Change from Baseline in UPDRS Part II (ADL subscale) score.
3. Change from Baseline in UPDRS Part III (motor subscale) score in the ON state.
4. Change from Baseline in UPDRS Part I total score.
5. Change from Baseline in UPDRS Part IV total score.
6. Change from Baseline in dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
7. Change from Baseline in SCOPA-cog score.
8. Change from Baseline in Fall questionnaire score.
9. Percent change from Baseline to the end of open-label treatment in total levodopa equivalent dose.
10. Exploratory endpoints to evaluate potential disease modification (see **Section 11.4.6**).

11.2.2 Safety Variables

Safety variables include the following:

1. TEAEs.
2. Physical and neurological examination.
3. Supine and standing pulse and BP.

4. Standard 12-lead ECG: RR, PR, QRS, QT and QTcF.
5. Laboratory parameters: hematology, chemistry, thyroid function (TSH, free T3, and free T4), and urinalysis.
6. C-SSRS.
7. Daytime sleepiness as measured by the ESS, including assessment of episodes of sudden onset of sleep.
8. mMIDI.

11.2.3 Pharmacokinetic Variables

1. Tozadenant concentrations and time point of IMP intake and blood sampling.
2. Tozadenant concentrations at Weeks 26 and 30 (Part B).
3. Pramipexole concentrations and time point of pramipexole intake and blood sampling (in applicable patients only) at Baseline, Week 2, and Week 24 (Part A), and in the event of AEs thought to be pramipexole-related (Parts A and B).

11.3 General Statistical Considerations

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purpose of analysis. For continuous variables, descriptive statistics will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

In general, Baseline values for efficacy and safety variables will be determined from the last non-missing data collected prior to the first dose of study medication.

11.4 Planned Efficacy Analyses

All analyses of the primary and two key secondary endpoints will focus on the comparison of tozadenant 120 mg BID vs. placebo followed by a comparison of tozadenant 60 mg BID vs. placebo. Adjustment for multiplicity for p-values from the analyses of the primary and two key secondary endpoints will be performed per **Section 11.4.3**. All other p-values derived from analyses of the remaining efficacy endpoints will be reported as nominal without adjustment for multiplicity.

To explore treatment differences by geographical location, a country/region term will be included in the analysis model. If there are insufficient number of patients represented in a country, patients by be pooled using a specific criterion that will be determined prior to database lock.

11.4.1 Analysis of the Primary Efficacy Variable

The primary efficacy variable will be the change from Baseline to Week 24 in the number of hours per day spent in the OFF state, as assessed by patient-completed PD diaries and averaged over 3 consecutive days. Descriptive statistics will be used to summarize results for the observed OFF time and the change from Baseline in OFF time by treatment group and visit. The primary analysis of the primary variable will be performed on the mITT and based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, country, the baseline number of hours of OFF time, and the interaction between treatment group and week. The model will define patient as a random effect and utilize an unstructured covariance pattern. The "country" term in the model may be redefined in the SAP to geographical region (countries grouped together) if some countries do not contribute an adequate number of patients.

Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis, however for the PPS. A further analysis will utilize the Last Observation Carried Forward (LOCF) approach; missing values will be replaced by the last observed post-baseline value of the variable and the analysis will be performed on the resulting dataset. Finally a multiple imputation method **(Rubin, 1987; Little and Rubin, 1987)** will be applied. In addition, for each imputation method, a univariate ANCOVA will be performed at Week 24 which includes the model terms: country/region, treatment group and baseline value.

11.4.2 Analysis of Key Secondary Efficacy Variables

All continuous secondary efficacy variables will be summarized descriptively by treatment group and week. Descriptive statistics will be generated for the observed and the change from Baseline. For categorical variables, frequency and percentages will be produced.

The key secondary efficacy variables will be analyzed using the model defined in the primary analysis of OFF time in the mITT.

Adjustment for multiplicity for p-values from the analyses of the two key secondary endpoints will be performed per **Section 11.4.3**.

Sensitivity analyses, including analysis in the PPS, LOCF and multiple imputation will also be performed.

11.4.3 Multiplicity Adjustment for Primary and Key Secondary Endpoints

All analyses of the primary and two key secondary endpoints will focus on the comparison of tozadenant 120 mg BID vs. placebo followed by tozadenant 60 mg BID vs. placebo. The following six comparisons will be conducted using sequential testing with a fixed sequence, which controls the family-wise error for multiple comparisons at an alpha level of 0.05 (two-tailed):

1. Comparison of tozadenant 120 mg BID vs. placebo using the primary endpoint (Change from baseline to Week 24 in the number of hours per day spent in OFF state).
2. Comparison of tozadenant 120 mg BID vs. placebo using the first key secondary endpoint (Change from baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia).
3. Comparison of tozadenant 120 mg BID vs. placebo using the second key secondary endpoint (Change from baseline to Week 24 in UPDRS Parts II + III total score).
4. Comparison of tozadenant 60 mg BID vs. placebo using the primary endpoint (Change from baseline to Week 24 in the number of hours per day spent in OFF state).
5. Comparison of tozadenant 60 mg BID vs. placebo using the first key secondary endpoint (Change from baseline to Week 24 in the number of hours per day spent in good ON time, defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia).
6. Comparison of tozadenant 60 mg BID vs. placebo using the second key secondary endpoint (Change from baseline to Week 24 in UPDRS Parts II + III total score).

Testing will begin with tozadenant 120 mg BID vs. placebo for change from baseline to Week 24 in the number of hours per day spent in OFF state. If the p-value is less than or equal to an $\alpha = 0.05$, then the result is considered statistically significant and testing will proceed to the next comparison, and so forth. Testing will stop with the first adjusted p-value >0.05 and that comparison, as well as any comparison later in the sequence will be considered not statistically significant.

The adjusted p-values $\acute{p}_i$ for i = 1 to 6 will be calculated by taking the maximum of the raw p-value (p_i) from the statistical test and the adjusted p-value ($\acute{p}_{i-1}$) from the prior test, as shown below:

$$\acute{p}_1 = p_1$$

$$\acute{p}_2 = \max(\acute{p}_1, p_2)$$

$$\acute{p}_3 = \max(\acute{p}_2, p_3)$$

…

$$\acute{p}_6 = \max(\acute{p}_9, p_6)$$

P-values from the analyses of all other efficacy outcomes will be reported as nominal, with no adjustment for multiplicity.

11.4.4 Other Secondary Efficacy Analyses

The other secondary efficacy analyses include the change from Baseline to Week 24 (where applicable), for the following:

1. CGI-I.
2. PGI-I.
3. UPDRS Part III (motor subscale) score in the ON state.
4. Investigator global impressions of severity of illness (CGI-S).
5. UPDRS Part II (ADL subscale) score.
6. Number of hours per day spent in the ON state (without dyskinesia, with non-troublesome dyskinesia, or with troublesome dyskinesia).
7. Number of hours per day spent in the ON state without dyskinesia.
8. Number of hours per day spent in the ON state with any dyskinesia (troublesome or non-troublesome).
9. Number of hours per day spent in the ON state with non-troublesome dyskinesia.
10. PDQ-39 (total score and individual domain scores).
11. UPDRS Part IV.
12. UPDRS Part I.

All continuous other secondary efficacy variables will be analyzed using the model defined in the primary analysis of OFF time (**Section 11.4.1**) and the mITT. Sensitivity analyses of the other secondary efficacy variables are not planned.

All other variables will be analyzed using adequate statistical methods.

11.4.5 Exploratory Analyses (Part A)

The exploratory analyses in Part A include the change from Baseline to Week 24, for the following:

1. Number of hours per day spent in the asleep state.
2. Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
3. Falls as measured by question 13 on UPDRS Part II.
4. Responder analysis of number (%) of patients with ≥ 1.0 h improvement in OFF time (evaluated at Week 24).
5. Responder analysis of number (%) of patients with ≥ 2.0 h improvement in OFF time (evaluated at Week 24).
6. Percent change in total levodopa equivalent dose.

7. Percent change in the number of hours per day spent in OFF state.
8. Percent change in the number of hours per day spent in ON state without troublesome dyskinesia.
9. Percent change in the number of hours per day spent in ON state with troublesome dyskinesia.
10. Scales for Outcomes in Parkinson's Disease–cognition (SCOPA-cog) score.
11. Fall questionnaire score.
12. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and only one additional concomitant anti-PD medication.
13. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and two additional concomitant anti-PD medications.
14. Number of hours per day spent in the OFF state in the sub-population of subjects taking levodopa and three additional concomitant anti-PD medications.
15. EQ-5D-5L.
16. TSQM-9 (evaluated at Weeks 6 and 24).

These analyses will be documented by descriptive statistics by treatment group in the mITT. No statistical analyses are planned.

11.4.6 Exploratory Analyses (Part B)

The exploratory analyses in Part B include the following:

1. Change from Baseline in UPDRS Part II (ADL subscale) + Part III (motor subscale) total score.
2. Change from Baseline in UPDRS Part II (ADL subscale) score.
3. Change from Baseline in UPDRS Part III (motor subscale) score in the ON state.
4. Change from Baseline in UPDRS Part I total score.
5. Change from Baseline in UPDRS Part IV total score.
6. Change from Baseline in dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
7. Change from Baseline in SCOPA-cog score.
8. Change from Baseline in Fall questionnaire score.
9. Percent change from Baseline to the end of open-label treatment in total levodopa equivalent dose.

10. Exploratory Endpoints to Evaluate Potential Disease Modification:

    10.1 Compare the estimate of change from Baseline to Week 76 in UPDRS I-III score between patients who were randomized to tozadenant in Part A (early-start) and those who were randomized to placebo in Part A (late start) for each dose (60 mg and 120 mg BID).

    10.2 Test the noninferiority of the slope estimates from the UPDRS I-III score of the early-start and delayed-start tozadenant groups (60 mg and 120 mg BID) during Part B (Weeks 36–76).

    10.3 Compare the estimate of change from Baseline to Week 76 in the SCOPA-cog score between patients who were randomized to tozadenant in Part A (early-start) and those who were randomized to placebo in Part A (late start) for each dose (60 mg and 120 mg BID).

    10.4 Test the noninferiority of the slope estimates from the SCOPA-cog score of the early-start and delayed-start tozadenant groups (60 mg and 120 mg BID) during Part B (Weeks 36–76).

    10.5 Compare the estimate of change from Baseline to Week 76 in Fall questionnaire score between patients who were randomized to tozadenant in Part A (early-start) and those who were randomized to placebo in Part A (late start) for each dose (60 mg and 120 mg BID).

    10.6 Test the noninferiority of the slope estimates from the Fall questionnaire score of the early-start and delayed-start tozadenant groups (60 mg and 120 mg BID) during Part B (Weeks 36–76).

    10.7 Compare the estimate of change from Baseline to Week 76 in total daily levodopa equivalents between patients who were randomized to tozadenant in Part A (early start) and those who were randomized to placebo in Part A (late start) for each dose (60 mg and 120 mg BID).

    10.8 Test the noninferiority of the slope estimates from total daily levodopa equivalents of the early-start and delayed-start tozadenant groups (60 mg and 120 mg BID) during Part B (Weeks 36–76).

11. EQ-5D-5L.

12. TSQM-9 (evaluated at Week 76).

All continuous other secondary efficacy variables will be analyzed using the model defined in the primary analysis of OFF time (**Section 11.4.1**) and the mITT. Sensitivity analyses of the other secondary efficacy variables are not planned.

All other variables will be analyzed using adequate statistical methods.

11.5 Planned Safety and Other Analyses

11.5.1 Safety Analyses

The primary safety variables will be the occurrence of TEAEs including nonserious and serious TEAEs, and TEAEs leading to permanent withdrawal of study medication during the study.

All AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, high level term and preferred term. The data will be displayed as number of patients experiencing the AEs, percentage of patients and number of AEs.

Safety data, including AEs, vital signs, ECGs, ESS including assessment of episodes of sudden onset of sleep, C-SSRS, mMIDI, physical and neurological examination, clinical laboratory test results, and concomitant medications will be summarized descriptively for each treatment group and for the entire tozadenant group, where appropriate. The descriptive statistics will be provided for the observed data and for the change from Baseline at each measured time point. Tables will summarize AE data as appropriate by dose group. Note that counting will be by patient, not event and patients are only counted once within each MedDRA system organ class (SOC) or preferred term (PT).

Clinical laboratory tests results, vital signs, ECGs, dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV, ESS, weight, physical and neurological examination results, and UPDRS will be summarized descriptively. Descriptive statistics will be presented for continuous variables utilizing the observed data and the change from baseline (at each measured time point). Frequencies and percentages will be presented for categorical variables. Laboratory test results will be classified as below the lower limit of normal, within normal limits and above the ULN. Shift tables will be used to summarize changes from Baseline to each visit by treatment group. Clinically significant physical or neurological examination findings and any clinically significant out-of-range laboratory tests are recorded as adverse events and will be documented in the AE summaries.

Analyses will be performed for the SS as randomized.

11.5.2 Other Analyses

Patient Disposition

The number of patients who were screened, randomized, completed scheduled follow up, and prematurely withdrew study participation will be summarized overall and by treatment group. Reasons for non-participation and for withdrawal from study will also be presented.

Exposure to IMP/Compliance

The number of days of exposure to IMP will be summarized by treatment group. Compliance with IMP will be calculated as the number of doses taken divided by the scheduled number of doses taken, expressed as a percentage. Compliance will be summarized overall and by week for each treatment group.

Prior and Concomitant Medication Use

All prior and concomitant medications taken during the study period will be listed for each patient, including dosage and indication. Medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced and classified as past medication (last dose taken prior to the first dose of IMP), concomitant medication ongoing at Baseline, or concomitant medication initiated after Baseline. The percentage of patients taking each medication (or class of medications) will be summarized overall and by treatment group.

Plasma Drug Concentrations

Results of the assays of tozadenant (and of pramipexole, in patients concomitantly taking pramipexole during the study) will be descriptively analyzed and reported in the clinical study report. Separate population analysis on the data from this study alone or combined with data from other studies as deemed appropriate will be performed and reported separately.

11.6 Unblinding Upon Completion of Part A

Immediately after Part A (double-blind phase) of the study completes and the database is cleaned and locked, the responsible CRO(s) will follow their SOPs to unblind Part A. A blinded data review will be performed (per ICH E9) before the database is locked and before the study groups are unblinded. Primary and secondary efficacy analyses are final and will not be modified. Exploratory analyses that do not involve the primary or secondary efficacy analyses are subject to modification.

11.7 Handling of Protocol Deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary efficacy or safety. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined prior to unblinding. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all patients.

11.8 Handling of Dropouts or Missing Data

A valid diary will not have more than 2 hours (4 invalid entries) over a given 24-hour period. An invalid diary entry is defined as more than one entry recorded in a given half-hour interval, an unreadable entry, or the absence of an entry in a given half-hour interval. The average diary information from 3 valid diaries (if available) for each visit will be used to calculate diary-based efficacy endpoints. If there are only 2 valid diaries for a visit then the average information from the 2 valid diaries will be used. If only one diary is valid, information from the single valid diary

will be used. If no valid diaries are available for a patient visit then the diary information is considered missing.

For patients that prematurely withdrew from study, data collected during the Early Termination Visit will be used to impute 'OFF' time at the next visit. If the first diary day for a premature withdrawal visit was recorded more than one day after the last dose was administered, then the visit will not be used. The primary analysis of the primary efficacy variable will be based on an MMRM approach, hence visits beyond the Early Termination Visit will not to be imputed.

The total time 'OFF' will be determined by using the mean of the 3-day diary data immediately before each visit. A diary day will be regarded to be valid if at least 22 hours of the 24 hour clock are filled in. The missing hours will be imputed according to the proportions of being "on without dyskinesia", "on with troublesome dyskinesia", "on with non-troublesome dyskinesia", "off" and asleep. The visit data will be regarded to be valid if at least 2 days out of 3 are valid.

11.9 Planned Safety Data Monitoring

Concurrent safety data monitoring is planned for this study, for which responsibility will be assigned to an independent DSMB. The DSMB will oversee the safety of the study by reviewing relevant data on a regular basis. The DSMB will consist of members who are independent from Biotie Therapies. Study enrollment will not be halted during planned DSMB reviews of safety data. The objectives and procedures for the DSMB will be detailed in the DSMB charter.

11.10 Determination of Sample Size

The primary efficacy endpoint is the change from Baseline to Week 24 in the number of hours per day spent in the OFF state. A sample size of 150 in each group will provide 85% power to detect a difference in mean response of 0.9 hours between tozadenant and placebo assuming the common SD is 2.6 hours and using a two group t-test with a 0.050 two-sided significance level. Across the 3 treatment groups, the total number of patients to be randomized is 450.

Although the sample size calculation is based on the primary endpoint, OFF time, for this study the total sample size of 450 patients is anticipated to yield power to detect treatment differences in the [redacted]

Approximately 645 patients will be screened, assuming a 30% screen failure rate, to randomize 450 patients.

12.0 ETHICS AND REGULATORY REQUIREMENTS

12.1 Informed Consent

Patient's informed consent must be obtained and documented in accordance with local regulations, ICH GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the investigator (or designee). Each patient will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the written ICF will be signed and personally dated by the patient, and by the person who conducted the informed consent discussion (investigator or designee). The patient must receive a copy of the signed and dated ICF. As part of the consent process, each patient must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended ICF.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act (HIPAA) authorization form.

The patient may withdraw his/her consent to participate in the study at any time. A patient is considered to be in the study once they have signed the ICF. An eCRF must not be started, nor may any study-specific procedure be performed for a given patient, without having obtained the patient's written consent to participate in the study.

12.2 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator and CRO will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator or if a central IRB/IEC is used, the Sponsor/Sponsor's designee will forward copies of the protocol, ICF, IB, investigator's curriculum vitae (if

applicable), advertisement (if applicable), and all other patient-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human patients or others, and any protocol deviations, to eliminate immediate hazards to patients.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the patients. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of patient risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

Sponsor (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

12.3 Patient Privacy

Sponsor staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to the Sponsor/Sponsor's designee will be identified only by the patient number and/or site identifier (ID) and patient screening number.

The investigator agrees that representatives of Sponsor, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the patient's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports for deaths occurring during the study).

12.4 Protocol Amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by the Sponsor, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

13.0 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and institution clinical trial agreements with the Sponsor/CRO, as applicable.

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15.0 APPENDICES

15.1 Unified Parkinson's Disease Rating Scale (UPDRS)

UNIFIED PARKINSON'S DISEASE RATING SCALE

Part I MENTATION, BEHAVIOR AND MOOD (RATE ITEMS 1 TO 4 BY INTERVIEW)
When completing this section, indicate the patient's level of function during the past week.

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (DUE TO DEMENTIA OR DRUG INTOXICATION)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression
0 = Not present.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

Part II. ACTIVITIES OF DAILY LIVING (RATE ITEMS 5 TO 17 BY INTERVIEW)
When completing this section, indicate the patient's level of function during the past week.

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have start-hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

Part III. MOTOR EXAMINATION (Acceptable responses are 0, 1, 2, 3, 4)
Instructions: All efforts should be made to conduct the motor exam while the patient is in a stable state (e.g., "On" for the entire exam or "Off" for the entire exam). If unstable, re-examine the patient in a stable state, if possible.

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

20a. Face, lips + chin: _____
20b. Right Hand: _____
20c. Left Hand:_____
20d: Right Foot:_____
20e: Left Foot: _____

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.
21a. Right Hand:_____
21b. Left Hand: ___

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.
22a. Neck
22b. RUE
22c. LUE
22d. RLE
22e. LLE

23. Finger Taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task
23a. Right Hand:_____
23b. Left Hand: ___

24. Hand Movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
24a. Right Hand:_____
24b. Left Hand: ___

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
25a. Right Hand:_____
25b. Left Hand: ___

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be about 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
26a. Right Leg:_____
26b. Left Leg ___

27. Arising from Chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient is erect, with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Indicate the patient's PD state during the examination:
1. "On" during exam
2. Fluctuated during the exam
3. "Off" during exam

Part IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are any "off" periods **predictable as to timing after a dose of medication?**
0 = No
1 = Yes

37. Are any "off" periods **unpredictable as to timing after a dose of medication?**
0 = No
1 = Yes

38. Do any of the "off" periods **come on suddenly, e.g., over a few seconds?**
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
0 = No
1 = Yes

Fahn S, Elton RL, Members of the UPDRS Development Committee (1987). Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. *Recent developments in Parkinson's disease*. Florham Park, NJ: MacMillan Health Care Information, pp. 153-63, 293-304.

15.2 Hauser Parkinson's Disease Home Diary

PARKINSON'S DISEASE DIARY

Instructions: For each half-hour time period place one X mark to indicate your predominant status during most of that half-hour period.
ON = Time when medication is providing benefit with regard to mobility, slowness, and stiffness.
OFF = Time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness
Dyskinesia = Involuntary twisting, turning movements. These movements are an effect of medication and occur during ON time.
Non-troublesome dyskinesia does not interfere with function or cause meaningful discomfort.
Troublesome dyskinesia interferes with function or causes meaningful discomfort.
Tremor is shaking back and forth and is not considered dyskinesia.

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00-6:30 AM					
6:30-7:00 AM					
7:00-7:30 AM					
7:30-8:00 AM					
8:00-8:30 AM					
8:30-9:00 AM					
9:00-9:30 AM					
9:30-10:00 AM					
10:00-10:30 AM					
10:30-11:00 AM					
11:00-11:30 AM					
11:30-12:00 PM					
12:00-12:30 PM					
12:30-1:00 PM					
1:00-1:30 PM					
1:30-2:00 PM					
2:00-2:30 PM					
2:30-3:00 PM					
3:00-3:30 PM					
3:30-4:00 PM					
4:00-4:30 PM					
4:30-5:00 PM					
5:00-5:30 PM					
5:30-6:00 PM					

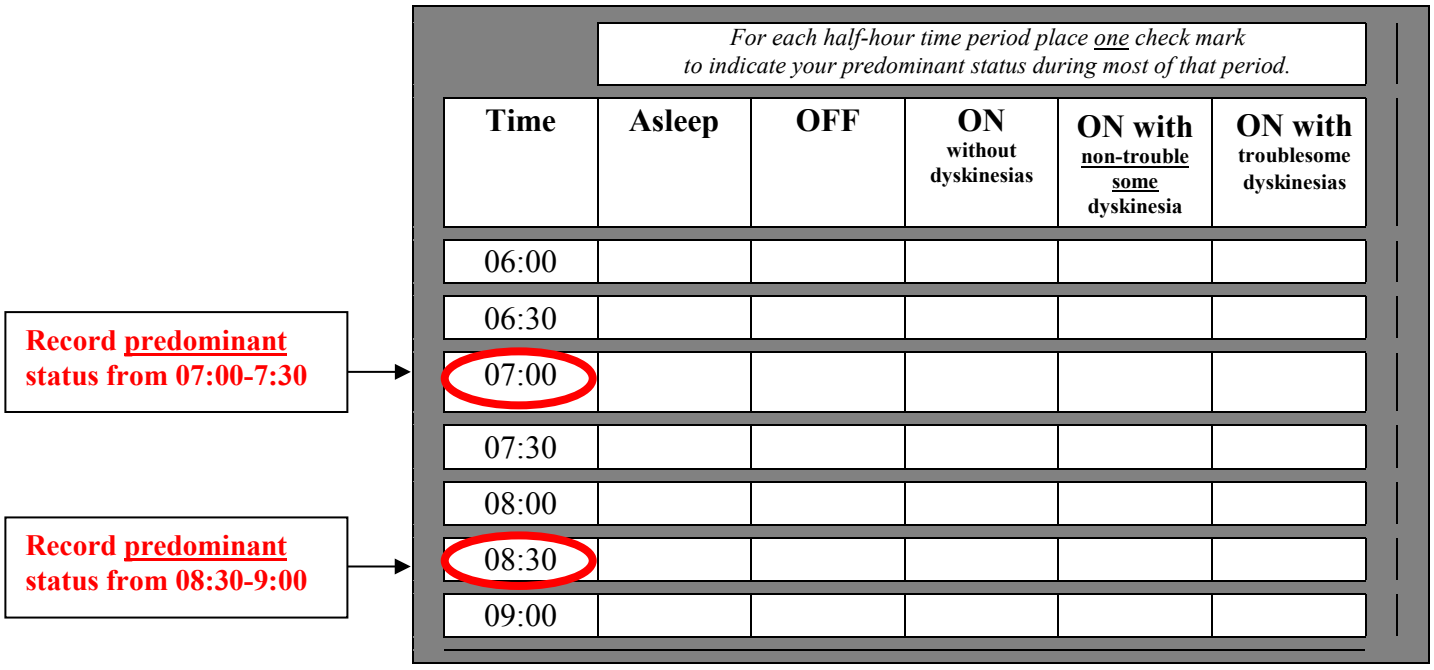
time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00-6:30 PM					
6:30-7:00 PM					
7:00-7:30 PM					
7:30-8:00 PM					
8:00-8:30 PM					
8:30-9:00 PM					
9:00-9:30 PM					
9:30-10:00 PM					
10:00-10:30 PM					
10:30-11:00 PM					
11:00-11:30 PM					
11:30-12:00 AM					
12:00-12:30 AM					
12:30-1:00 AM					
1:00-1:30 AM					
1:30-2:00 AM					
2:00-2:30 AM					
2:30-3:00 AM					
3:00 -3:30 AM					
3:30-4:00 AM					
4:00-4:30 AM					
4:30-5:00 AM					
5:00-5:30 AM					
5:30-6:00 AM					

 Hauser et al. J Clin Neurophar 2000; 23:75-81.

15.3 PD Home Diary Training, Concordance, Validation

Parkinson's Diary Completion Basics:

- Patient records motor state for half-hour intervals over a 24-hour period
- What counts is the predominant state during a given 30-minute interval
- Patients rate their ON and OFF status every 30 minutes while awake and immediately record their rating
- On waking in the morning, patients will record the 30-minute intervals that they were asleep
- Diary Completion is performed during the Screening Period and on the 3 consecutive days directly preceding scheduled visits
  - Screening/Practice Diary (Weeks −6 to −1)
  - before Baseline Visit (Week −1)
  - before Week 2 Visit
  - before Week 6 Visit
  - before Week 12 Visit
  - before Week 18 Visit
  - before Week 24 Visit
- Recording time starts at 6 AM and ends 72 hours later at 6 AM.



For each half-hour time period place one check mark to indicate your predominant status during most of that period.

Time	Asleep	OFF	ON without dyskinesias	ON with non-troublesome dyskinesia	ON with troublesome dyskinesias
06:00					
06:30					
07:00					
07:30					
08:00					
08:30					
09:00					

Parkinson's Diary Patient Training:

During the Screening Period, patients and Sponsor accepted trainers will view the Hauser PD diary training video and instructions on completion of the diary will be clarified. The patient and trainer/rater will then concurrently complete separate training diaries during at least 5 half-hour intervals (minimum 2.5 hours). The patient should experience both ON and OFF during this time, and the diary concordance session may be extended to allow the patient to experience OFF. If the patient is OFF at the beginning of the diary concordance session, they may be administered their next dose of levodopa-containing medication in order to experience ON.

Note:

- Definitions of ON and OFF will be reviewed with the patient during the training session in accordance with the provided definitions.
- Predominant state at the end of every 30-minute interval is reported as:
  - Off
  - On without dyskinesias
  - On with non-troublesome dyskinesias
  - On with troublesome dyskinesias (only the Patient can define what troublesome means to them)
  - Asleep (Note: This state will not occur during training. Instruction to record the asleep time when they awake in the morning must be provided verbally to the patient during this session)
- Patient cannot change the definitions for ON and OFF.

Trainer/Rater and Patient Diary Concordance Assessment:

- The diary trainer/rater and the patient view the Hauser PD diary training video and discuss how the patient would define the triggers for their own ON and OFF state.
- When the patient appears to understand instructions for diary completion, the minimum 2.5 hour concordance session begins.
  - Trainer/rater completes a diary by observing the patient each 30-minute period and rates the patient as OFF or "ON with dyskinesia" or "ON without dyskinesia" using the definitions of ON and OFF.
  - Patient completes a diary each 30-minute period in the presence of the trainer/rater and at the same time the trainer/rater records their observation. The patient rates OFF or "ON without dyskinesia", "ON with non-troublesome dyskinesia", or "ON with troublesome dyskinesia" using the definitions of ON and OFF.
- Distinction between non-troublesome or troublesome dyskinesias is the decision of the patient and not to be rated by the trainer/rater.

- Concordance (√) has to be at least 80%, e.g., at least 4 of 5 half-hour intervals rated in the same way by the diary trainer/rater and the patient during a minimum period of 2.5 hours **including at least 1 OFF interval**. For an ON rating to be considered concordant, there must be agreement between the patient and the trainer/rater on the presence (or absence) of dyskinesia. The trainer/rater will only rate the presence or absence of dyskinesia, whereas the patient will be asked to record dyskinesia using the categories "without dyskinesia", "with non-troublesome dyskinesia", or "with troublesome dyskinesia".
- Review valid and invalid entries with the patient.
- If sufficient concordance is not reached during the first diary concordance session, the trainer/rater will schedule a second PD diary training and concordance session, unless the patient refuses further study participation.

Trainer/Rater rates	Patient rates	Concordance reached
OFF	OFF	Yes
ON without dyskinesias	ON without dyskinesias	Yes
On with dyskinesias	On with non-troublesome dyskinesias OR On with troublesome dyskinesias	Yes (only patient can determine if dyskinesias are troublesome)
ON with dyskinesia	OFF	No (confusion with OFF vs. dyskinetic state)
OFF	On with dyskinesias	No (confusion with OFF vs. dyskinetic state)
OFF	On with troublesome dyskinesias	No (confusion with OFF vs. dyskinetic state)
ON without dyskinesia	On with troublesome dyskinesia OR On with non-troublesome dyskinesia	No (patient may be rating dyskinesia not seen by trainer)

AFTER CONCORDANCE IS REACHED:

- Provide the patient with a copy of their screening training diary (trainer/rater keeps both originals at site).
- Provide the patient with a practice diary which they are required to complete on 3 prespecified days (i.e., 3 consecutive 24-hour periods agreed to by the patient and the trainer) and return to the trainer/rater for review.
- If a valid practice diary is returned by the patient, request Sponsor or Sponsor's designee to approve preliminary eligibility of the patient for the study.
- If the patient is not confirmed to be eligible by the Sponsor/Sponsor's designee, inform the patient they are not considered eligible and cancel Baseline Visit.
- If preliminary eligibility of the patient is confirmed by the Sponsor/Sponsor's designee, send a Baseline diary to the patient and schedule the Baseline Visit.
- Instruct the patient to complete the Baseline diary on the 3 prespecified days (i.e., 3 consecutive 24-hour periods) directly preceding the Baseline Visit.
- Telephone the patient prior to the scheduled Baseline diary completion. The patient will be reminded by the trainer/rater to apply the ON and OFF definitions discussed during PD diary completion. Any questions from the patient regarding PD diary completion will be addressed.

OVERVIEW OF INVALID ENTRIES

- Invalid entries are missing or double entries.
- No more than 4 invalid entries for each 24 h period.
- Patient with more than 4 invalid entries at Baseline may be retrained within the 6-week screening window.

Correct	**Wrong**
"X" marks the predominant state for each 30-minute interval, therefore total time in a given state is X times 30 minutes.	**"X" marks start or end time of a given state.**
Each "X" is entered immediately at the end of each given 30-minute interval while awake. When asleep, an "X" in the respective "asleep" box is entered immediately after waking up. If patient awakens at night they should record status for each 30-minute interval awake during the night.	**"Awake" is interpreted as "daytime" and periods with "on" or "off" occurring during the night are not marked. If they awaken in the night, the patient forgets to mark their status.**
Recording time starts at 6 AM and ends at 6 AM after the 3-day period, i.e., ends at 6 AM on the day of scheduled visits.	**Recording time during Days -3 and -2, thus ending on the day before scheduled visits.**
Any 30-minute interval is to be rated and counts for calculation, whether during the day or night.	**Early morning "off" time is not included in calculation of total daily "off" time.**

Please Refer to the Parkinson's Diary Training Video for Examples and Further Instructions for Valid and Invalid Entries.

HAUSER PD HOME DIARY VALIDATION AND CALCULATIONS

In the example below, the patient has indicated that he/she is OFF for most of the time in 5 of the 30-minute intervals or 2.5 hours (5 x 0.5 hours = 2.5 hours, and not 2 hours from 7:00 to 9:00). Each X therefore represents the predominant status for that 30-minute time interval.

Time	Asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
7:00-7:30 AM		X			
7:30-8:00 AM		X			
8:00-8:30 AM		X			
8:30-9:00 AM		X			
9:00-9:30 AM		X			

In the diary example on first 24-hour patient diary, the total OFF time is 5 hours and in the second 24-hour patient diary, the total OFF time is 7 hours.

First 24 hour period: (10 x 0.5 hours) = 5 hours OFF time					
time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00-6:30 AM	X				
6:30-7:00 AM	X				
7:00-7:30 AM	X				
7:30-8:00 AM	X				
8:00-8:30 AM	X				
8:30-9:00 AM		**X**			
9:00-9:30 AM		**X**			
9:30-10:00 AM		**X**			
10:00-10:30 AM		**X**			
10:30-11:00 AM				X	
11:00-11:30 AM				X	
11:30-12:00 PM					X
12:00-12:30 PM					X
12:30-1:00 PM			X		
1:00-1:30 PM			X		
1:30-2:00 PM			X		
2:00-2:30 PM			X		
2:30-3:00 PM			X		
3:00 -3:30 PM			X		
3:30-4:00 PM			X		
4:00-4:30 PM			X		
4:30-5:00 PM			X		
5:00-5:30 PM			X		
5:30-6:00 PM			X		
6:00-6:30 PM			X		
6:30-7:00 PM		**X**			
7:00-7:30 PM		**X**			
7:30-8:00 PM		**X**			
8:00-8:30 PM		**X**			
8:30-9:00 PM		**X**			
9:00-9:30 PM		**X**			
9:30-10:00 PM			X		
10:00-10:30 PM			X		
10:30-11:00 PM			X		
11:00-11:30 PM	X				
11:30-12:00 AM	X				
12:00-12:30 AM	X				
12:30-1:00 AM	X				
1:00-1:30 AM	X				
1:30-2:00 AM	X				
2:00-2:30 AM	X				
2:30-3:00 AM	X				
3:00-3:30 AM	X				
3:30-4:00 AM	X				
4:00-4:30 AM	X				
4:30-5:00 AM	X				
5:00-5:30 AM	X				
5:30-6:00 AM	X				

Second 24 hour period: (14 x 0.5 hours) = 7 hours OFF time					
time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00-6:30 AM	X				
6:30-7:00 AM	X				
7:00-7:30 AM	X				
7:30-8:00 AM	X				
8:00-8:30 AM	X				
8:30-9:00 AM		**X**			
9:00-9:30 AM		**X**			
9:30-10:00 AM		**X**			
10:00-10:30 AM		**X**			
10:30-11:00 AM				X	
11:00-11:30 AM		**X**			
11:30-12:00 PM					X
12:00-12:30 PM					X
12:30-1:00 PM		**X**			
1:00-1:30 PM			X		
1:30-2:00 PM			X		
2:00-2:30 PM			X		
2:30-3:00 PM			X		
3:00 -3:30 PM			X		
3:30-4:00 PM			X		
4:00-4:30 PM		**X**			
4:30-5:00 PM			X		
5:00-5:30 PM			X		
5:30-6:00 PM			X		
6:00-6:30 PM			X		
6:30-7:00 PM		**X**			
7:00-7:30 PM		**X**			
7:30-8:00 PM		**X**			
8:00-8:30 PM		**X**			
8:30-9:00 PM		**X**			
9:00-9:30 PM		**X**			
9:30-10:00 PM		**X**			
10:00-10:30 PM			X		
10:30-11:00 PM			X		
11:00-11:30 PM	X				
11:30-12:00 AM	X				
12:00-12:30 AM	X				
12:30-1:00 AM	X				
1:00-1:30 AM	X				
1:30-2:00 AM	X				
2:00-2:30 AM	X				
2:30-3:00 AM	X				
3:00-3:30 AM	X				
3:30-4:00 AM	X				
4:00-4:30 AM	X				
4:30-5:00 AM	X				
5:00-5:30 AM	X				
5:30-6:00 AM	X				

15.4 Clinical/Patient Global Impression Scales (CGI-S, CGI-I and PGI-I)

Clinical Global Impression of Improvement (CGI-I)

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at admission to the study, how much has he/she changed?

- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

Clinical Global Impression of Severity (CGI-S)

Considering your total clinical experience with this particular population, how severe is the subject's Parkinson's disease at this time?

- ☐ 1 = Normal, not at all ill
- ☐ 2 = Borderline ill
- ☐ 3 = Mildly ill
- ☐ 4 = Moderately ill
- ☐ 5 = Markedly ill
- ☐ 6 = Severely ill
- ☐ 7 = Among the most extremely ill patients

Patient Global Impression of Improvement (PGI-I)

Rate total improvement of your Parkinson's disease, whether or not in your judgment it is due entirely to drug treatment. Compared to your condition at admission to the study, how much have you changed? Place an X in one of the boxes below best describing your impression.

- ☐ 1. Very much improved.
- ☐ 2. Much improved.
- ☐ 3. Minimally improved.
- ☐ 4. No change.
- ☐ 5. Minimally worse.
- ☐ 6. Much worse.
- ☐ 7. Very much worse.

15.5 Epworth Sleepiness Scale

Epworth Sleepiness Scale (ESS)

Name: _____ Today's date: _____

Your age (Yrs.): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you have not done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

- 0 = no chance of dozing
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

It is important that you answer each item as best you can.

Situation	**Chance Of Dozing**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car or bus, while stopped for a few minutes in traffic	

THANK YOU FOR YOUR COOPERATION

15.6 Assessment for Episodes of Sudden Onset of Sleep

Assessment for Episodes of Sudden Onset of Sleep

Definition of sudden onset of sleep: Abrupt episodes of unplanned sleep during activities of daily living where they are not expected to occur. These events may or may not be preceded by somnolence or sedation.

Instructions for the Baseline Visit:

Did the subject experience any sudden onset of sleep in the last 6 weeks? (Check only 1 box)

☐ Yes, but the subject felt sleepy before (This is an indication of a possible sudden onset of sleep).

☐ Yes, subject fell asleep completely unexpected without prior sleepiness (This is an indication of a possible sudden onset of sleep).

☐ Yes, sometimes with, sometimes without prior sleepiness (This is an indication of a possible sudden onset of sleep).

☐ No

If the subject responds "Yes" to any of the above, the investigator should record the applicable response into the subject's Medical History. (e.g., "possible sudden onset of sleep")

Instructions for Visits <u>After</u> Baseline:

Did the subject experience any sudden onset of sleep since the last visit? (Check only 1 box)

☐ Yes, but the subject felt sleepy before (This is an indication of a possible sudden onset of sleep).

☐ Yes, subject fell asleep completely unexpected without prior sleepiness (This is an indication of a possible sudden onset of sleep).

☐ Yes, sometimes with, sometimes without prior sleepiness (This is an indication of a possible sudden onset of sleep).

☐ No

If the subject responds "Yes" to any of the above (indicating a possible sudden onset of sleep), the investigator should evaluate if this is a change from Baseline and if so report as an Adverse Event and determine whether the subject's continued participation in the study puts them at risk and whether they should be discontinued from the study.

15.7 Modified Minnesota Impulse Disorders Interview (mMIDI)

Modified Minnesota Impulse Disorders Interview (mMIDI)

Module 1: Buying Disorder Screen

Gateway Question:

Do you or others think that you have a problem with buying things too often or with spending too much money?

0	1
No	Yes

If NO, go to the next module. If Yes, proceed with the following questions:

1. Do you ever experience an irresistible urge or uncontrollable need to buy things or mounting tension that can only be relieved by buying?

☐0	☐1	☐2	☐3
No	Rarely	Occasionally	Frequently

2. Has problem buying led to social, marital, family, financial or work problems or caused you to experience significant distress?

☐0	☐1	☐2	☐3
No	Rarely	Occasionally	Frequently

Module 1 score: _____ (add up all numbers, including gateway question**)**

Module 2: Compulsive Gambling Screen

Gateway Question:

Do you gamble?

☐0 No ☐1 Yes

If NO, go to the next module. If Yes, proceed with the following questions:

1. Do you or others think that you have ever had a problem with gambling?

   ☐0 No ☐1 Rarely ☐2 Occasionally ☐3 Frequently

2. Have you ever felt guilty about the way you gamble or what happens when you gamble?

   ☐0 No ☐1 Rarely ☐2 Occasionally ☐3 Frequently

3. Have you been preoccupied with gambling or obtaining money to gamble?

   ☐0 No ☐1 Rarely ☐2 Occasionally ☐3 Frequently

4. Have you gambled larger amounts of money or over longer periods of time than you intended to?

   ☐0 No ☐1 Rarely ☐2 Occasionally ☐3 Frequently

Module 2 score: _____ (add up all numbers, including gateway question**)**

Module 3: Compulsive Sexual Behavior Screen

Gateway Question:

Do you or others that you know think that you have a problem with being overly preoccupied with some aspect of your sexuality or being overly sexually active?

☐0 ☐1

No Yes

If NO, go to the next module. If Yes, proceed with the following questions:

1. Do you have repetitive sexual fantasies which you feel are out of your control or cause you distress?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

2. Do you have repetitive sexual urges which you feel are out of your control or cause you distress?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

3. Do you engage in repetitive sexual behavior which you feel is out of control or causes you distress?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

Module 3 score: _____ (add up all numbers, including gateway question**)**

Module 4: Compulsive Eating Module

Gateway Question:

Do you or others that you know think that you have a problem with being overly preoccupied with food or actively overeating?

☐0 ☐1
No Yes

If NO, go to the next module. **If Yes, proceed with the following questions:**

1. Do you have repetitive fantasies about eating which are out of your control or cause you distress?

   ☐0 ☐1 ☐2 ☐3
   No Rarely Occasionally Frequently

2. Do you have repetitive urges to eat which you feel are out of your control or cause you distress?

   ☐0 ☐1 ☐2 ☐3
   No Rarely Occasionally Frequently

3. Do you engage in constant or overly frequent eating which you feel is out of control or causes you distress?

   ☐0 ☐1 ☐2 ☐3
   No Rarely Occasionally Frequently

Module 4 score: _____ (add up all numbers, including gateway question**)**

Module 5: Punding Behavior Screen

Gateway Question:
Do you find yourself fascinated with or performing repetitive and/or mechanical tasks such as taking apart and putting back together simple mechanical objects, or picking at oneself, or sorting and arranging common objects?

☐0 ☐1

No Yes

If NO, end the module. If Yes, proceed with the following questions:

1. Do you collect things such as rocks, coins or books, and line them up together?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

2. Do you disassemble mechanical things such as doorknobs, watches, radios or other objects, and then re-assemble them?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

3. Do you find performing such repetitive tasks comforting?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

4. Do you get frustrated if you are unable to perform such repetitive tasks?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

5. Have you ever taken amphetamines?

   ☐0 ☐1 ☐2 ☐3

   No Rarely Occasionally Frequently

Module 5 score: _____ (add up all numbers, including gateway question**)**

SCORING:

The mMIDI consists of 5 modules: compulsive buying, compulsive gambling, compulsive eating, hypersexuality and punding.

Positive Answer:
Any answer other than "no" on any question is considered a "yes"/positive answer.

Negative Module:
A module is considered negative if the patient's answer to a gateway (initial) question is "no" **or** if a patient answers "yes" to a gateway question and "no" to **all** of the remaining answers after the gateway question in that module.

Positive Module:
A module is considered positive if a patient gives a positive answer (rarely = 1, occasionally = 2, frequently = 3) to any question after the gateway (initial) question in one or more of the 5 modules.

During screening, if a subject has evidence of an impulse control disorder (ICD) (i.e., one or more positive modules on the mMIDI) the subject is ineligible for the study unless a structured clinical interview confirms that the subject does not have an ICD.

After administration of study drug, if a subject has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.

Total Score (add up all module scores):_____

Modules (Circle One Answer for Each Module: Positive or Negative**)**:

Module 1: Buying Disorder:	☐Positive	☐Negative
Module 2: Compulsive Gambling:	☐Positive	☐Negative
Module 3: Compulsive Sexual Behavior:	☐Positive	☐Negative
Module 4: Compulsive Eating:	☐Positive	☐Negative
Module 5: Punding Behavior:	☐Positive	☐Negative

15.8 UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Step 1: Diagnosis of Parkinsonian syndrome
-Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
-At least one of the following:
  -Muscular rigidity
  -4-6 Hz rest tremor
  -Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2: Exclusion criteria for Parkinson's disease
-History of repeated strokes with stepwise progression of Parkinsonian features
-History of repeated head injury
-History of definite encephalitis
-Oculogyric crises
-Neuroleptic treatment at onset of symptoms
-More than one affected relative
-Sustained remission
-Strictly unilateral features after 3 years
-Supranuclear gaze palsy
-Cerebellar signs
-Early severe autonomic involvement
-Early severe dementia with disturbances of memory, language, and praxis
-Babinski sign
-Presence of cerebral tumor or communicating hydrocephalus on CT scan
-Negative response to large doses of levodopa (if malabsorption excluded)
-MPTP exposure

Step 3: Supportive prospective positive criteria for Parkinson's disease
(Three or more required for diagnosis of definite Parkinson's disease)

-Unilateral onset
-Rest tremor present
-Progressive disorder
-Persistent asymmetry affecting side of onset most
-Excellent response (70-100%) to levodopa
-Severe levodopa-induced chorea
-Levodopa response for 5 years or more
-Clinical course of 10 years or more

15.9 Assessment of Caffeine Intake

Caffeine Exposure Questionnaire

This questionnaire concerns your use of major dietary sources of caffeine (that is, coffee, tea, soft drinks that contain caffeine, energy drinks, chocolate, and caffeine-containing medicines).

1. On a typical week, how frequently do you consume some caffeinated product?

   _____# of days per week (number 0 – 7)

2. On a typical day (for example, yesterday or the day before), list the number(s) and type(s) of caffeinated products that you consumed. Do not include caffeinated products that you sometimes consume but did not consume on this "typical" day. Do not include decaffeinated products. Also record your typical serving size and the typical brand name that you use.

   Guide for estimating serving size:

   Shot = 2 fluid ounces (oz) or 60 milliliters (mL)
   Tea cup = 5 oz or 148 mL
   Regular cup or small mug = 8 oz or 237 mL
   Large mug = 12 oz or 355 mL
   Can = 12 oz or 355 mL
   Bottle = 16 oz or 1/2 liter (500 mL)
   Large bottle = 32 oz or 1 liter (1000 mL)

Type	# Servings	Serving Size	Brand Name
Coffee (roasted or ground)		□ oz □ mL	
Coffee (instant)		□ oz □ mL	
Espresso (single shot)		□ oz □ mL	
Espresso (double shot)		□ oz □ mL	
Black or Green Tea (bag or leaf)		□ oz □ mL	
Tea (instant)		□ oz □ mL	
Caffeinated Soft Drinks		□ oz □ mL	
Energy Drinks		□ oz □ mL	
Hot chocolate or chocolate milk		□ oz □ mL	
Dark Chocolate (semisweet)		□ oz □ g	

Caffeine-containing medicines*		□ tab or cap □ oz	
Other (specify) or check □ if not applicable		□ _____	
oz = ounces; mL = milliliters; tab = tablet; cap = capsule. ** To be recorded on Concomitant Medication source and CRF.*			

15.10 Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Due to having Parkinson's disease,
how often <u>during the last month</u> have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	had difficulty doing the leisure activities you would like to do?	☐	☐	☐	☐	☐
2.	had difficulty looking after your home, for example, housework, cooking or yardwork?	☐	☐	☐	☐	☐
3.	had difficulty carrying grocery bags?	☐	☐	☐	☐	☐
4.	had problems walking half a mile?	☐	☐	☐	☐	☐
5.	had problems walking 100 yards (approximately 1 block)?	☐	☐	☐	☐	☐
6.	had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	had difficulty getting around in public places?	☐	☐	☐	☐	☐
8.	needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please verify that you have ***<u>checked one box for each question</u>***
before going on to the next page**.**

Page 1 of 5

Due to having Parkinson's disease,
how often <u>during the last month</u> have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
9.	felt frightened or worried about falling in public?	☐	☐	☐	☐	☐
10.	been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	had difficulty showering and bathing?	☐	☐	☐	☐	☐
12.	had difficulty dressing?	☐	☐	☐	☐	☐
13.	had difficulty with buttons or shoelaces?	☐	☐	☐	☐	☐
14.	had problems writing clearly?	☐	☐	☐	☐	☐
15.	had difficulty cutting up your food?	☐	☐	☐	☐	☐
16.	had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17.	felt depressed?	☐	☐	☐	☐	☐
18.	felt isolated and lonely?	☐	☐	☐	☐	☐

Please verify that you have ***<u>checked one box for each question</u>***
before going on to the next page.

Due to having Parkinson's disease,
how often <u>during the last month</u> have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
19.	felt weepy or tearful?	☐	☐	☐	☐	☐
20.	felt angry or bitter?	☐	☐	☐	☐	☐
21.	felt anxious?	☐	☐	☐	☐	☐
22.	felt worried about your future?	☐	☐	☐	☐	☐
23.	felt you had to hide your Parkinson's from people?	☐	☐	☐	☐	☐
24.	avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25.	felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26.	felt worried about other people's reaction to you?	☐	☐	☐	☐	☐
27.	had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please verify that you have ***<u>checked one box for each question</u>***
before going on to the next page**.**

Due to having Parkinson's disease,
how often <u>during the last month</u> have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
28.	lacked the support you needed from your spouse or partner? *If you do not have a spouse or Partner, please check here* ☐	☐	☐	☐	☐	☐
29.	lacked the support you needed from your family or close friends?	☐	☐	☐	☐	☐
30.	unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	had problems with your concentration, for example when reading or watching TV?	☐	☐	☐	☐	☐
32.	felt your memory was failing?	☐	☐	☐	☐	☐
33.	had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	had difficulty speaking?	☐	☐	☐	☐	☐
35.	felt unable to communicate effectively?	☐	☐	☐	☐	☐
36.	felt ignored by people?	☐	☐	☐	☐	☐

Please verify that you have ***<u>checked one box for each question</u>***
before going on to the next page**.**

Due to having Parkinson's disease,
how often <u>during the last month</u> have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
37.	had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38.	had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39.	felt uncomfortably hot or cold?	☐	☐	☐	☐	☐

Please verify that you have ***<u>checked one box for each question</u>.***

Thank you for completing the questionnaire.

15.11 Scales for Outcomes in Parkinson's Disease–Cognition (SCOPA-cog)

SCOPA-cog

MEMORY AND LEARNING

1. *Verbal recall*

Ten words are repeatedly shown for at least 4 seconds, get the patient to read them out loud, the time allowed for recall is unlimited. Underline each word that has been named. When words are named that were not shown, no penalty is given. When a false answer is changed (e.g., king into queen), it is correct.

Instruction: "Read the following 10 words aloud and try to remember as many as possible. After reading them all, name as many words as possible, the order of the words is not important."

10 words: Butter arm shore letter queen cabin pole ticket grass engine

(10 correct = 5, 8-9 correct = 4, 6-7 correct = 3, 5 correct = 2, 4 correct = 1, ≤ 3 correct= 0)

score ……../5

2. *Digit span backward*

Ask the patient to repeat a series of numbers backwards; the numbers are read out separately, 1 second per number; if incorrectly repeated, the alternative in the second column is presented. Continue until both the first and the alternative series are repeated incorrectly. Make sure the time interval between numbers stays the same. Read the numbers calmly and make sure the time between numbers is equal. Record the highest series that is repeated correctly at least once; Give an example: "If I say 2-7-3, then you say (3-7-2)."

backwards		score:
2-4	5-8	= 1
6-2-9	4-1-5	= 2
3-2-7-9	4-9-6-8	= 3
1-5-2-8-6	6-1-8-4-3	= 4
5-3-9-4-1-8	7-2-4-8-5-6	= 5
8-1-2-9-3-6-5	4-7-3-9-1-2-8	= 6
9-4-3-7-6-2-5-8	7-2-8-1-9-6-5-3	= 7

score ……../7

3. *Indicate cubes*

Point to the cubes in the order given below; the patient should copy this; do this slowly; the patient decides for himself with which hand he/she prefers. Indicate the cubes in the order as indicated. Observe carefully if the patient copies the order correctly. When a patient wants to correct a mistake, let him/her do the complete order again. This is not counted as a mistake. However, if the patient forgets the order and would like to see the order a second time, the researcher does not repeat the order again but starts with the next order.

1 2 3 4

a. 1-2-4-2

b. 1-2-3-4-3

c. 3-4-2-1-4

d. 1-4-2-3-4-1

e. 1-4-2-3

score ……../5

ATTENTION

4. *Counting backwards (30 to 0)*

Instruction: "Would you subtract three from 30, and subtract three again from the result and continue till zero?"

Mistakes can be: the order, missing or not knowing a number, or not finishing off the series. Record the order of numbers named by the patient. If the patient asks where to start or how much to subtract, the researcher repeats the instructions but counts that as one mistake. If the patient makes a mistake but continues from that point to subtract three, it is only one mistake. If the patient stops the order and starts all over again, it is one mistake.

(0 mistakes = 2, 1 mistake = 1, ≥ 2 mistakes = 0)

score ……../2

5. *Months backwards*

Instruction: "Name the months of the year in reverse order, starting with the last month of the year."

Mistakes are: the order, missing or not knowing the next month, or not finishing off the series. Underline the months that are named correctly. When a month is passed over, this is a mistake, even if the patient corrects it later on. If the patient stops the order and starts all over again, it is one mistake. If the patient starts naming the month forward, repeat the instructions and count it as one mistake.

Dec- Nov-Oct-Sept-Aug-July-June-May-April-March-Feb-Jan.

(0 mistakes = 2, 1 mistake = 1, ≥ 2 mistakes = 0)

score ……../2

EXECUTIVE FUNCTIONS

6. *Fist-edge-palm*

1. fist with ulnar side down, 2. stretched fingers with ulnar side down, 3. stretched fingers with palm down; Practice 5 times together with the patient, the patient chooses which hand he/she prefers. Do it slowly and tell the patient to watch carefully and repeat what you are doing. Practice first 5 rounds, with verbal help, e.g., FIST- STRETCH- PALM. Then tell the patient to make the movements alone.

Instructions: "Now it is your turn to make the three movements, fist-stretch-palm, 10 times in a row. You don't have to count, I will tell you when to stop."

Note the number of correct trios from a total of 10; Count carefully but not out loud. Every time a patient makes a wrong movement, count it as a mistake, even when the patient corrects it halfway.

(10 correct = 3, 9 correct = 2, 8 correct = 1, ≤ 7 correct = 0)

score ……../3

7. *Semantic fluency*

Tell the patient to name as many animal as he/she knows in one minute. Note all answers that are given by the patient. No repetition or variations of words, such as lion- lioness, tiger-tigress; categories are allowed, bird and pigeon are both correct. Count the number of animals correctly named. The purpose is that the patient generates the animals actively, therefore no clues are allowed. When the patient asks whether, for instance, naming different types of birds is allowed, this may be confirmed. When the patient almost immediately says he/she does not know any more animals, try to stimulate the patient by saying "there is still a lot of time left", but do not give clues. When the patient starts naming other

things than animals, do not correct the patient. Naming other things besides animals is not counted as an additional mistake.

Write down all animals named:

(≥25 correct = 6, 20-24 = 5, 15-19 = 4, 10-14 = 3, 5-9 = 2, 1-4 = 1 0=0)

number of animals correct: …….

score ……../6

8. *Dice*

Use 2 cards, one with YES = EVEN, NO = ODD; one with YES = HIGHER, NO = LOWER. Put the correct card face up next to the explanation of the test and make sure that the other, irrelevant card is out of sight. The first round (situation 1) is not scored, and the patient is corrected if necessary.

SITUATION 1: YES = EVEN

Put the card "YES=EVEN, NO=ODD" on the table and leave it there during the test.

Instruction: "Say YES for an even number on a dice and NO for an odd number, when you see a picture of a dice with an EVEN number of pips, I would like you to say YES, and NO when the number of pips is ODD."

Show the first two examples (3 even and 3 odd dices) and ask the patient "If you see one of these dice, do you say yes or no?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why. It is important that the patient says YES or NO and not EVEN or ODD. Show the next two examples (with only one dice) and ask the patient "if you see this dice, do you say yes or no?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why.

Then show the patient the following 10 dices. Correct the patient if the answer is wrong.

SITUATION 2: YES = HIGHER

With the card "example 1" (dice with 3 pips) the next condition starts. Put the card "YES=HIGHER, NO=LOWER" on the table and remove the former card.

Instruction: "Now, we change the test a little. When you see a picture of a dice that is higher than the dice on the page before, you say YES. When the dice is lower, you say NO."

Tell the patient you have an example (example 1). "Try to remember this dice" (turn the page) "Is this YES or NO?" Tell the patient whether the answer is correct or not. If the answer is not correct, explain why. Continue with example 2 and say "now remember this dice" (turn the page) "Is this YES or NO?" Tell the patient if the answer is correct or not. If the answer is not correct, explain why.

Then start the test and show all 10 dices one after another. The first response counts and corrections are not allowed. Do NOT correct when a wrong answer is given. If a patient corrects a wrong answer, it is still counted as a mistake. If the patient asks for the instruction, the researcher explains but that is counted as one mistake.

(10 correct = 3, 9 correct = 2, 8 correct =1, ≤ 7 correct = 0)

number correct: …./10

score ……../3

VISUO-SPATIAL FUNCTIONS

9. *Assembling patterns*

The patient is shown 5 incomplete patterns and has to choose 2 or 3 shapes out of 4 to 6 possible alternatives in order to complete the pattern. First practice 2 figures.

Show the patient example A and give the instruction to choose the shapes that form the pattern. Tell the patient if the answer is correct or not. If the answer is not correct, explain why and give the correct solution. Repeat this with example B. Then show the 5 patterns. Do not tell the patient whether the answer is correct or not. There is no time limit. If the patient corrects a wrong answer, this is not counted as a mistake.

a. b. c. d. e.

score ……../5

MEMORY

10. *Delayed recall*

Instruction: "Can you name as many as possible of the 10 words that you learned during the first test?"

Underline each word that has been named. When words are named that were not shown, no penalty is given. When a false answer is changed (e.g., king into queen), it is correct.

10 words: butter arm shore letter queen cabin pole ticket grass engine

(10 correct = 5, 8-9 correct = 4, 6-7 correct = 3, 5 correct = 2, 4 correct = 1, ≤ 3 correct = 0)

number of correct words: …. /10

score ……../5

Total COG score: ……../43

Marinus J, Visser M, Verwey NA, Verhey FRJ, Middelkoop HAM, Stiggelbout AM, et al. (2003). Assessment of cognition in Parkinson's disease. *Neurology.* **61**:1222-8.

15.12 Modified Hoehn and Yahr

Modified Hoehn and Yahr PD Staging

The Modified Hoehn and Yahr PD Staging is a scale expressing the severity of the symptoms of PD. 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.

Hoehn MM, Yahr MD (1967). Parkinsonism: onset, progression and mortality. *Neurology*. **17**(5):427-42.

15.13 Fall Questionnaire

Fall Questionnaire

Baseline (Visit 2):

Have you been experiencing falls over the past 3 months? Yes/No

If yes, approximately how many falls have occurred in the past 3 months?_____

At Week 24 (Visit 7), Week 48 (Visit 11) and Week 76 (Visit 13):

Have you been experiencing falls over the past 3 months? Yes/No

If yes, approximately how many falls have occurred in the past 3 months?_____

In the event of an Early Termination Visit (Part A or B):

Have you been experiencing falls over the past 3 months? Yes/No

If yes, approximately how many falls have occurred in the past 3 months?_____

15.14 Healthcare Resource Utilization Questionnaire

Healthcare Resource Utilization Questionnaire

INPATIENT ADMISSIONS

Instructions: Please record in the table below all inpatient admissions **since the subject's last scheduled clinic visit. Do not include inpatient admissions for the facilitation of assessments specific to this protocol not associated with any deterioration in condition.**

- If the subject had no inpatient admissions since the last scheduled clinic visit, please check the appropriate box below.
- If the patient was hospitalized since the last scheduled clinic visit, please record the admission and discharge dates of each hospitalization. Also indicate if the type of each admission was Parkinson's disease (PD)-related or Non-PD related along with the reason for each admission, e.g. pneumonia, which should be consistent with source documentation and eCRF entries.

☐ No inpatient admissions **since the subject's last scheduled clinic visit**

	Admission Date (dd / mmm / yyyy)	**Discharge Date** (dd / mmm / yyyy)	**Type of Admission**	**Reason for Admission**
1.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	
2.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	
3.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	

EMERGENCY ROOM (ER) VISITS

Instructions: Please indicate how many times the subject visited an Emergency Room **since the last scheduled clinic visit** for PD-related and non-PD related reasons**.**

- If the subject had no emergency room visits since the last scheduled clinic visit, please check the appropriate box below.
- If the subject visited the emergency room since the last scheduled clinic visit, please record the date of each visit. Also indicate if the visit was PD-related or Non-PD related along with the reason for each visit, e.g. pneumonia, which should be consistent with source documentation and eCRF entries.
- If an Emergency Room visit resulted in an inpatient admission, please record that event above as an inpatient admission only and **do not** record here.

☐ No emergency room visits **since the subject's last scheduled clinic visit**

	ER Visit Date (dd / mmm / yyyy)	**Type of ER Visit**	**Reason for ER Visit**
1.	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	
2.	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	
3.	_ _ / _ _ _ / _ _ _ _	☐ PD-related ☐ Non-PD related	

[redacted]