CLINICAL STUDY PROTOCOL

Protocol Title:	A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End of Dose "Wearing-Off"
Protocol Number:	TOZ-CL06
Development Phase:	3
US IND Number:	078230
EudraCT Number:	2016-003961-25
Protocol Version:	3.0
Version Date:	09 October 2017
Original Date of Issue	30 September 2016
Sponsor	Biotie Therapies (a wholly owned subsidiary of Acorda Therapeutics Inc.) 701 Gateway Boulevard, Suite 350 South San Francisco, CA 94080 USA [redacted]

STUDY CONTACT INFORMATION

Study Director	[redacted]
Chief Medical Officer	[redacted]
VP Clinical Development and Study Physician	[redacted]
VP Clinical Operations	[redacted]
Sr. Director, Clinical Operations	[redacted]

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 by email and/or fax and by completing the AE electronic case report form (eCRF) and the SAE Report Form. The SAE Report Form must be sent to North America – [redacted]

E-mail: [redacted].

Europe – [redacted]:

E-mail: [redacted]

Australia – [redacted]

E-mail: [redacted]

The email address and fax number used for SAE reporting is also provided on the SAE/ Pregnancy Reporting Form Cover Page.

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-CL06 entitled **A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End of Dose "Wearing-Off"**.

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-CL06

Protocol Version: Amendment No. 2, Version 3.0

Date of Issue: 09 October 2017

[redacted]

[redacted]

[redacted]

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-CL06, Amendment No.2, Version 3.0
Date of Issue: 09 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)
ANC	Absolute Neutrophil Count
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
CK	Creatine phosphokinase
CMV	Cytomegalovirus
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
EBV	Epstein Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol 5D-5L Health Questionnaire
ESS	Epworth Sleepiness Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EU	European Union
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
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IU/L	International units per liter
IUD	Intrauterine device
IXRS	Interactive Response System
LDH	Lactate dehydrogenase
MAO-B	Monoamine oxidase type B
MedDRA	Medical Dictionary for Regulatory Activities
mMIDI	Modified Minnesota Impulse Disorders Interview
MMSE	Mini-Mental State Examination
msec	Millisecond
PD	Parkinson's disease
PDF	Portable document file
PDQ-39	Parkinson's Disease Quality of Life Questionnaire 39-Item
PGI-I	Patient's Global Impression of Improvement
PK	Pharmacokinetic
PR	Interval from onset of P wave to start of QRS complex in ECG
PRN	As needed
PT	Preferred term
QA	Quality assurance

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
UK	United Kingdom
ULN	Upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
US/USA	United States of America
VAS	Visual Analogue Scale
WBC	White Blood Cells
WHO	World Health Organization

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Title	A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End of Dose "Wearing-Off"
Protocol Number	TOZ-CL06
Phase	3
Number of Sites/ Location	Approximately 120 sites in North America, Europe and Asia/Pacific countries will participate.
Test Product, Dose and Mode of Administration	Test Product: Tozadenant tablets [redacted] Test Product Doses: 60 mg twice daily (BID; one 60 mg tablet); 120 mg BID (two 60 mg tablets or one 120 mg tablet) Comparator: N/A Mode of Administration: Oral
Indication	Parkinson's disease (PD)
Study Objectives	Primary Objective: • To evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing motor fluctuations, based on assessment of treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), and clinical laboratory tests. Secondary Objectives: • To evaluate the effects of tozadenant on the occurrence of daytime drowsiness, impulsive behavior, and suicidality.
Study Population	Male or female patients with idiopathic PD who are receiving levodopa treatment and experiencing end-of-dose 'wearing-off' (see inclusion and exclusion criteria).
Study Design	Phase 3, international, multicenter, open-label safety study.
Number of Patients to be Enrolled	Approximately 450 patients will be enrolled.
Dose Regimen	Eligible patients will begin dosing with investigational medicinal product (IMP) at a dose of 120 mg (i.e., two 60 mg tablets or one 120 mg tablet) 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 each dose at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing. At Week 2 or thereafter, the investigator may adjust the

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	patient's IMP dose as clinically indicated; doses of 60 mg BID and 120 mg BID will be permitted.
Concomitant Anti-PD Medications	Investigators can adjust concomitant anti-PD medications during this study as needed. The optimal dose of IMP 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. All anti-PD medications taken by a patient during the course of the study and the reason for their use will be recorded in the source documents and electronic case report form (eCRF). Patients are to use their own supplies of concomitant anti-PD medications.
Study Duration	Each patient will participate for up to 62 weeks, which includes a Screening Period of 1 to ≤ 6 weeks, followed by a Baseline Visit, 52 weeks of open-label treatment, and a Safety Follow-Up Visit 4 weeks after completion of investigational treatment: • Screening Period: 1 to ≤ 6 weeks. • Open-Label Treatment Period: 52 weeks. • Post-Treatment Safety Follow-Up: 4 weeks. The end of the study is defined as the date of the last visit of the last patient in the study.
Enrollment Period	Approximately 14 months.
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 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. Daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), including assessment of episodes of sudden onset of sleep. 7. Modified Minnesota Impulse Disorders Interview (mMIDI). 8. Columbia-Suicide Severity Rating Scale (C-SSRS).

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Other Endpoints	The following measures will be assessed to characterize PD status during open-label tozadenant treatment: 1. Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activity of Daily Living [ADL] subscale) + Part III (motor subscale) total score. 2. UPDRS Part II (ADL subscale) score. 3. UPDRS Part III (motor subscale) score in the ON state. 4. UPDRS Part I total score. 5. UPDRS Part IV, including dyskinesia as measured by questions 32, 33 and 34 and motor fluctuations as measured by question 39. 6. Clinical Global Impression of Improvement (CGI-I). 7. Patient's Global Impression of Improvement (PGI-I). 8. Parkinson's Disease Quality of Life Questionnaire (PDQ-39; total score and individual domain scores). 9. Non-motor Symptom Assessment Scale. 10. EuroQol 5D-5L Health Questionnaire (EQ-5D-5L). 11. Patient-completed diaries (Change from Baseline in the number of hours per day spent as follows: OFF time, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time). 12. Healthcare Resource Utilization. 13. Fall questionnaire.
Inclusion Criteria	Patients must fulfill all of the following inclusion criteria in order to be included in the study: 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 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 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 has a modified Hoehn and Yahr stage 2–4 when in OFF state (estimated) and ≤ 3 in ON state. 6. Patient is male or female and 30–80 years old (inclusive) at Screening. 7. Patient must have a good response to levodopa in the opinion of the

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	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 1year absence of vaginal bleeding or spotting, and confirmed by follicle stimulating hormone

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	[FSH] ≥ 40 mIU/mL [or ≥ 40 IU/L] if less than 2 years postmenopausal) 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; intrauterine device (IUD); diaphragm with spermicide; or, diaphragm with condom. (Note: In Germany, the Czech Republic and other approved local regions, acceptable methods of contraception include complete abstinence; single barrier [diaphragm or condom] combined with use of IUD or contraceptive [oral, implantable or injectable]; or double barrier [diaphragm with condom]).
Exclusion Criteria	Patients with any of the following characteristics will be excluded from the study: 1. Patient previously participated in any study with tozadenant. 2. Patient is currently participating in or has participated in another study and received an IMP (active or placebo) within 5 half-lives of the IMP. 3. Patient has any form of secondary or atypical parkinsonism (e.g., drug-induced, post stroke). 4. Severe obesity defined as a body mass index (BMI) greater than 40. 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, except for the placement of deep brain stimulator electrodes at least 12 months or greater prior to screening; subjects with deep brain stimulation must not be experiencing any clinically meaningful side effects related to the procedure, the device, or stimulation. 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 or treatment adjustments resulting in resolution of the patient's grade 2 hypertension. 9. Patient with a history of hypertensive crisis unless the underlying cause

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	has been removed (e.g. stenting for renal artery stenosis). 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 and pimavanserin are 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. Patient has taken digoxin within 4 weeks prior to Screening or is likely to require digoxin during the study. 14. 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. 15. 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. 16. 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. 17. 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. 18. 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 C-SSRS performed at the Screening or Baseline Visit. 19. 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. 20. Patient is currently lactating or pregnant or planning to become

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	pregnant during the duration of the study. 21. Patient has a known hypersensitivity to any components of the IMP or excipients. 22. 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. 23. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) ≥3x upper limit of normal (ULN), or total bilirubin ≥1.5x ULN, at Screening. 24. 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. 25. Patients with moderate to severe hepatic or renal impairment. 26. [redacted] **27. Patients with absolute neutrophil count less than 2000/mm^3 (or 2.0 x 10E9/L) at screening.**
Overview of Study Procedures	Consenting patients will be screened for eligibility. 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 and receive instruction on how to complete the PD diary. 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

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	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 6week 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 pre-specified 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 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 enrolled

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	and receive open-label IMP for 52 weeks. Patients will be assessed for safety and tolerability regularly throughout the study and 4 weeks after their last dose of IMP. Blood pressure and pulse (supine and standing) will be taken at each outpatient visit. For scheduled study visits at Weeks 2, 6, 12, 24, 36, and 52, 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 ON (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in OFF will not be evaluated. Patients will be asked to complete a PD diary on the 3 consecutive days directly preceding visits at Weeks 12, 24 and 52. 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. Please refer to the Schedule of Events/Evaluations (Table 1) for 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 TEAEs put the patient at additional risk, as judged by the investigator. Patients experiencing TEAEs considered to be study drug-related and not tolerated by the patient will be discontinued from the study. **Patients must be discontinued from the study if the absolute neutrophil count is less than 1000/mm^3 (or 1.0 x 10E9/L).** A complete list of reasons for patient discontinuation is located in Section 4.3 of the protocol. The Study Sponsor (Biotie Therapies, Inc.) 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 the Schedule of Events/Evaluations (Table 1). 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 TEAEs will be followed until resolution, return to Baseline level, or stabilization.

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Sampling for Tozadenant Plasma Drug Concentrations	Pharmacokinetic (PK) blood samples for determination of plasma tozadenant concentration will be collected at the Week 2 study visit. [redacted] blood sample will be collected at the most convenient time during the visit ("Sparse PK Sampling"). [redacted] PK blood samples may be collected ("Expanded PK Sampling" - additional details are provided in Appendix 15.9). On the morning of the Week 2 visit, participating subjects will refrain from taking their 120 mg IMP dose until after collection of a predose/trough PK sample. [redacted]
Sample Size Justification	Approximately 645 patients will be screened, assuming a 30% screen failure rate, to enroll 450 patients.
Data and Safety Monitoring	Concurrent safety monitoring is planned for this study. Responsibility for safety monitoring will be assigned to the independent Data and Safety Monitoring Board (DSMB) of study TOZ-CL05, which will also oversee the safety of TOZ-CL06 by reviewing relevant data on a regular basis. The DSMB will consist of members who are independent from Biotie Therapies, Inc. Study enrollment will not be halted during planned DSMB reviews of safety data. The objectives and procedures for the DSMB are detailed in the DSMB charter.
Statistical Analysis	Safety data, including TEAEs, vital signs, ECGs, ESS, physical examination, and clinical laboratory test results will be summarized descriptively. The descriptive statistics will be provided for the observed data and for the change from Baseline at each measured time point, where appropriate. Tables will summarize TEAE data as appropriate. Note that counting will be by patient, not event and patients will only be 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 ULN. Shift tables will be used to summarize changes from Baseline to each visit by treatment group. Clinically significant physical or neurological exam findings and any clinically significant out-of-range laboratory tests that are TEAE will be recorded as TEAEs and documented in the TEAE summaries. Other variables will be summarized descriptively. Descriptive statistics will be generated for the observed and the change from Baseline. For categorical variables, frequency and percentages will be produced.

Table 1: Schedule of Events/Evaluations

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [w]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) *[16 weeks]*	56 (28 ± 3 d after last dose of IMP)		
Assessments Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9		
Written Informed Consent	X										
Demographics and 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	X
BP [c], pulse [c]	X [d]	X [d]	X	X	X	X	X	X	X	X	X [e]
12-lead ECG [f]	X	X [g]	X	X	X	X	X	X	X	X	X [e]
Weight (include height at Screening)	X				X	X		X	X	X	X [e]
Physical and neurological examination	X				X	X	X	X	X	X	X [e]
PD diary training and diary concordance session	X										
Modified Hoehn and Yahr staging (observed ON; OFF estimated per history) [h]	X										
UPDRS Parts I, II, III and IV [i]	X	X	X	X	X	X	X	X		X	
MMSE-II (in ON state)	X										
mMIDI [j]	X		X	X	X	X	X	X	X	X	X [e]
ESS [h]		X	X	X	X	X	X	X	X	X	
PD diary collection (phone call prior to start of 3 consecutive 24 hour diary completion periods)	X [k]	X [k]			X [l]	X [l]		X [l]		X [m]	
PD diary review	X	X			X	X		X [m]		X [m]	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X [e]
CGI-I [h]			X	X	X	X	X	X		X	
PGI-I [h]			X	X	X	X	X	X		X	
PDQ-39 [h]		X				X		X		X	
Sudden onset of sleep	X	X	X	X	X	X	X	X	X	X	
Fall questionnaire		X				X		X		X	
Healthcare Resource Utilization			X	X	X	X	X	X		X	
Non-motor Symptom Assessment Scale [h]		X				X		X		X	
EQ-5D-5L [h]		X				X		X		X	
Recording of AEs	X [n]	X [n]	X	X	X	X	X	X	X	X	X

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [w]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) *[16 weeks]*	56 (28 ± 3 d after last dose of IMP)		
Assessments Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9		
Laboratory tests: hematology [o], chemistry [p] (including thyroid function [q])	X	X	X	X	X	X	X	X	X	X	X [e]
FSH test, females who are postmenopausal for < 2 years	X										
Method of contraception [r]	X	X	X	X	X	X	X	X	X	X	X [e]
Urine pregnancy test, females of childbearing potential [s]	X	X	X	X	X	X	X	X	X	X	X [e]
Urinalysis [t]	X	X	X	X	X	X	X	X	X	X	X [e]
Review of inclusion/exclusion criteria	X										
Final verification of eligibility		X									
Tozadenant blood sampling			X [u]								
IMP dispensing and/or return [v]		X	X	X	X	X	X	X		X	X [e]
eCRF completion	X	X	X	X	X	X	X	X	X	X	X

AE, adverse event; BP, blood pressure; CGI-I, Clinical Global Impression of Improvement; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day; ECG, electrocardiogram; eCRF, electronic case report form; 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); PD, Parkinson's disease; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; PGI-I, Patient's Global Impression of Improvement; UPDRS, Unified Parkinson's Disease Rating Scale; V, Visit.

Footnotes

[a] Screening period may not exceed 6 weeks.

[b] Visit windows for scheduled visits after Baseline (V2) are in relation to the date of the Baseline Visit (V2).

[c] 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.

[d] At Screening and 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. Repeat these BP and pulse measurements 2 more times approximately 10 minutes apart.

[e] Optional activities (e.g., additional assessments for evaluation of AEs) that may be performed at the investigator's discretion.

[f] A resting supine 12-lead ECG will be collected after the patient has been in a supine position for a minimum of 5 minutes. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[g] At Baseline, obtain three 12-lead ECGs (i.e., 3 serial readings, performed several minutes apart). Ensure the ECGs are collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

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

[i] UPDRS to be measured in ON state. UPDRS Part III should be measured 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.

Table 1: Schedule of Events/Evaluations (continued)

[j] 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.

[k] The 3-day practice diary during the Screening Period and the 3-day Baseline diary must both be valid in order to enroll 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.

[l] PD diary collected over the 3 consecutive 24-hour periods before the day of the scheduled study visits on Weeks 12, 24 and 52. 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.

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

[n] Pretreatment AEs.

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

[p] 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).

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

[r] For applicable patients: At Screening, document method of contraception used by patient. At subsequent visits, verify continuation of (or any change to) contraceptive method.

[s] For females of childbearing potential: urine pregnancy test.

[t] 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.

[u] A PK blood sample should be collected at the most convenient time during the Week 2 visit. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of the PK sample collection. See Section 8.0 of the protocol. (Note: sites participating in Expanded PK Sampling should refer to Appendix 15.9).

[v] 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.

[w] If patient has discontinued IMP, perform Early Termination Visit as soon as possible after the last dose of IMP. If patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Safety Follow-Up Visit (Section 6.2.19) is not required.

Table 1.1: Schedule of Events/ Evaluations for Hematology Monitoring

Assessments	Study Period	Open-Label Treatment (52 weeks)						Weekly monitoring [b] (if required)
	Study Week	4 (±3 d)	8 (±3 d)	10 (±3 d)	16 (±3 d)	20 (±3 d)	44 (±7 d)	
	Study Visit	V3.5	V4.3	V4.8	V5.3	V5.8	V7.5	
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]

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nt

[redacted]

[redacted]

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing motor fluctuations, based on assessment of TEAEs, vital signs, electrocardiograms (ECGs), and clinical laboratory tests.

2.1.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effects of tozadenant on the occurrence of daytime drowsiness, impulsive behavior, and suicidality.

2.2 Endpoints

2.2.1 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 triiodothyronine [T3], and free thyroxine [T4]), and urinalysis.
6. Daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), including assessment of episodes of sudden onset of sleep.
7. Modified Minnesota Impulse Disorders Interview (mMIDI).
8. Columbia-Suicide Severity Rating Scale (C-SSRS).

2.2.2 Other Endpoints

The following measures will be assessed to characterize PD status during open-label tozadenant treatment:

- UPDRS Part II (Activity of Daily Living [ADL] subscale) + Part III (motor subscale) total score.

- UPDRS Part II (ADL subscale) score.
- UPDRS Part III (motor subscale) score in the ON state.
- UPDRS Part I total score.
- UPDRS Part IV, including dyskinesia as measured by questions 32, 33 and 34 and motor fluctuations as measured by question 39.
- Clinical Global Impression of Improvement (CGI-I).
- Patient's Global Impression of Improvement (PGI-I).
- Parkinson's Disease Quality of Life Questionnaire 39-Item (PDQ-39; total score and individual domain scores).
- Non-motor Symptom Assessment Scale.
- EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
- Patient-completed diaries (Change from Baseline in the number of hours per day spent as follows: OFF time, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time).
- Healthcare Resource Utilization.
- Fall Questionnaire.

3.0 STUDY DESIGN

3.1 Study Description

This is a Phase 3, international, multicenter, open-label study 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, followed by a 52-week Open-Label Treatment Period and a Safety Follow-Up Visit 4 weeks after completion of investigational 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, 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.

Patients will return to the study site for evaluation at scheduled visits at Weeks 2, 6, 12, 24, 36 and 52. Patients will be contacted by telephone before the start of each 3-day PD diary completion period to be reminded to complete the diary. **Patients will also be scheduled for a laboratory draw (hematology measurement only) at Weeks 4, 8, 10, 16, 20 and 44.** A final Safety Follow-Up Visit (Week 56) will occur 28 ± 3 days after the patient's last open-label dose of tozadenant. Upon starting study treatment, patients will receive open-label tozadenant at a dose of 120 mg BID. Adjustments to the open-label tozadenant dose are allowed to be made by the investigator starting at Week 2 and at any of the 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. The Interactive Response System (IXRS) will be used to assign, track and manage the tozadenant inventory at each study site.

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.

Unscheduled Visits may be arranged as considered necessary by the investigator (see Section 6.2.21). In the event of Early Termination, patients will be asked to complete an Early Termination Visit as soon as possible (see Section 6.2.20) and then return 28 ± 3 days after their last dose of IMP for a Safety Follow-Up Visit (Section 6.2.19).

Safety data 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.

3.1.1 Study Duration Per Patient

Each patient will participate for up to 62 weeks, which includes a Screening Period of 1 to ≤ 6 weeks, followed by a Baseline Visit, 52 weeks of open-label treatment, and a Safety Follow-Up Visit 4 weeks after completion of investigational treatment:

- Screening Period: 1 to ≤ 6 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 57 weeks and a maximum of 62 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

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

Approximately 120 sites will participate in the study.

3.1.3 Anticipated Regions and Countries

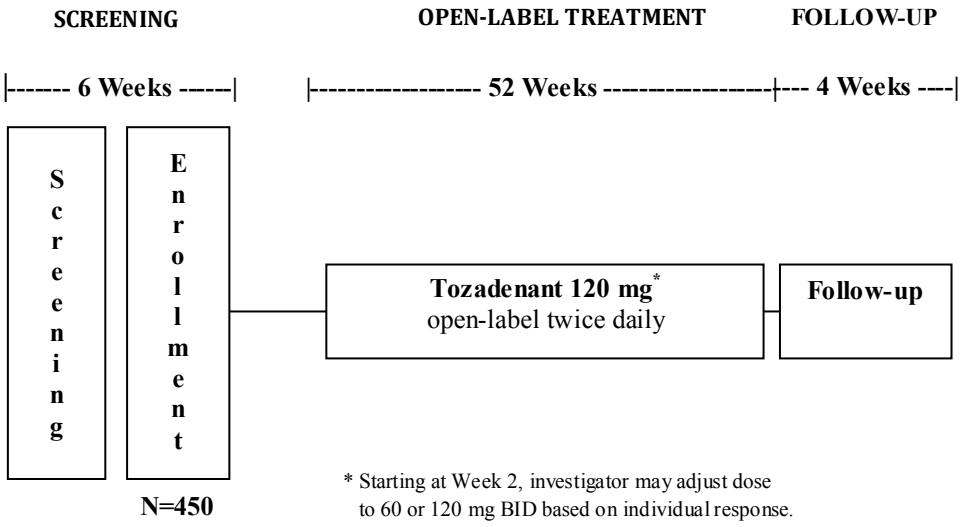
This international study will be conducted in North America, Europe, and Asia/Pacific countries.

3.2 Schedule of Events/Evaluations

The Schedule of Events/Evaluations is shown in Table 1 and Table 1.1.

3.3 Schematic Diagram

Figure 1: Schematic Diagram of Study Design



3.4 Rationale for Dose Selection

[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 included in the study:

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 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 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 has a modified Hoehn and Yahr stage 2–4 when in OFF state (estimated) and ≤ 3 in ON state.
6. Patient is male or female and 30–80 years old (inclusive) at Screening.
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, and confirmed by follicle stimulating hormone [FSH] $\geq$ 40 mIU/mL [or $\geq$ 40 IU/L] if less than 2 years postmenopausal) 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; intrauterine device (IUD); diaphragm with spermicide; or, diaphragm with condom. (Note: In Germany, the Czech Republic, and other approved local regions, acceptable methods of contraception include complete abstinence; single barrier [diaphragm or condom] combined with use of IUD or contraceptive [oral, implantable or injectable]; or double barrier [diaphragm with condom]).

4.2 Exclusion Criteria

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

1. Patient previously participated in any study with tozadenant.

2. Patient is currently participating in or has participated in another study and received an IMP (active or placebo) or medical device treatment within 5 half-lives of the IMP .
3. Patient has any form of secondary or atypical parkinsonism (e.g., drug-induced, post stroke).
4. Severe obesity defined as a body mass index (BMI) greater than 40.
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, except for the placement of deep brain stimulator electrodes at least 12 months or greater prior to screening; subjects with deep brain stimulation must not be experiencing any clinically meaningful side effects related to the procedure, the device, or stimulation.
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 or treatment adjustment resulting in the resolution of the patient's grade 2 hypertension.
9. Patient with a history of hypertensive crisis unless the underlying cause has been removed (e.g. stenting for renal artery stenosis).
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 and pimavanserin are 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. Patient has taken digoxin within 4 weeks prior to Screening or is likely to require digoxin during the study.
14. 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.
15. 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.

16. 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.
17. 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.
18. 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 C-SSRS performed at the Screening or Baseline Visit.
19. 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.
20. Patient is currently lactating or pregnant or planning to become pregnant during the duration of the study.
21. Patient has a known hypersensitivity to any components of the IMP or excipients.
22. 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.
23. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) ≥3x upper limit of normal (ULN), or total bilirubin ≥1.5x ULN, at Screening.
24. 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.
25. Patients with moderate to severe hepatic or renal impairment.
26. [redacted]
27. **Patients with absolute neutrophil count less than 2000/mm^3 (or 2.0 x 10E9/L) at screening.**

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.
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.

4.3.2 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 ≥ 500 msec and/or a QTcF interval consistently increased by ≥ 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 ALT or 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 alkaline phosphatase (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 supine systolic BP ≥ 160 mmHg and/or a diastolic BP ≥ 100 mmHg that is present at 2 consecutive post-baseline study visits.
10. Patients have concomitant surgical intervention for PD, including but not limited to deep brain stimulation.
11. **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 measurement 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 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 in Section 6.2.20. 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 6.2.19**)**.

All TEAEs 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 Product

Table 2: Investigational Medicinal Product

	Tozadenant
Dosage Form:	[redacted]
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 product is comprised of immediate-release, active tozadenant tablets for oral administration, as described above.

5.3 Packaging

The IMP supplies for this study will be packaged according to current Good Manufacturing Practice (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 this study, IMP will be packaged in an open-label fashion in high-density polyethylene bottles containing one hundred (100) 60 mg tozadenant tablets per bottle or fifty (50) 120 mg tozadenant tablets per bottle.

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 open-label clinical IMP supplies are available onsite.

5.4 Labeling

Supplies of IMP will be labeled in accordance with current FDA and local 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 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] Appropriate 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

Eligible 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 study:	2 tablets (2 × 60 mg tablets), BID **OR** 1 tablet (1 × 120 mg tablet), BID
If dose reduced at Week 2 or later:	1 tablet (1 × 60 mg tablet), BID
If dose is subsequently increased:	2 tablets (2 × 60 mg tablets), BID **OR** 1 tablet (1 × 120 mg tablet), 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 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., bottles) 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. 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 8 at Week 52 (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 $\geq 120\%$ 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 this study, 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 the study, 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:

- Digoxin.
- Surgical intervention for PD during the study.
- [redacted]

- Apomorphine, budipine, istradefylline, tolcapone, or [redacted]
- Antipsychotics except quetiapine administered at doses of ≤100 mg per day and pimavanserin
- Metoclopramide
- 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.

Patients taking thyroid medication for hypothyroidism or hyperthyroidism must be on a stable dose for at least 3 months prior to the Baseline Visit.

5.10 Blinding

This study will be open-label.

5.11 Enrollment and Numbering of Patients

During the study, 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 an 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 and Table 1.1. Details of disease activity 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 screened for eligibility. 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 15.13) 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 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.

Patients who meet all the entry criteria at Baseline will be assigned IMP using the IXRS and will begin open-label treatment for 52 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, 4, 6, 8, 10, 12, 16, 20, 24, 36, 44, 52, and 56; and will be asked to complete a PD diary on the 3 consecutive days directly preceding visits on Weeks 12, 24 and 52. 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. Safety evaluations will be performed at each study visit. At specified visits, patients will be asked to return their IMP dispensed at the previous visit (including all unopened and opened IMP bottles) 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. Pharmacokinetic (PK) blood samples will be collected for tozadenant at Week 2 as outlined in Table 1**,** Schedule of Events/Evaluations. **Patients will also be scheduled for a laboratory draw (hematology measurement only) at Weeks 4, 8, 10, 16, 20 and 44 as outlined in Table 1.1.** 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 treatment period. In the event of Early Termination, 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, unless the Early Termination Visit itself occurred 28 or more days after the last dose of IMP.

Please refer to the Schedule of Events/Evaluations in Table 1 and Table 1.1 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 subject´s source documents 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. Patients meeting eligibility criteria at Screening must also meet eligibility criteria at 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 Appendix 15.13.

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. Obtain demographics and previous medical history, including any co-existing pretreatment AEs.
3. Obtain neurological and PD history.
4. 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.
5. Perform physical and neurological examination.
6. Obtain weight, height and calculate BMI.
7. 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. Repeat these BP and pulse measurements 2 more times approximately 10 minutes apart.
8. Obtain 12-lead ECG. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.
9. Perform the following assessments in the ON state:
    a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.)

10. Administer the following assessments (may be done anytime during visit):
    a. C-SSRS.
    b. Assessment for episodes of sudden onset of sleep.
    c. 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).
11. For all applicable patients: Document method of contraception.
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. 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 source documents, 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.
16. If the investigator determines the patient meets the inclusion and exclusion criteria:
    a. Schedule the Baseline visit to occur within 6 weeks from the date of the Screening Visit and at a time 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.
    b. Instruct the patient to bring their medications (including anti-PD medications) to the Baseline visit so that they are able to maintain their regular treatment schedule.

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 pre-specified 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 [redacted]

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. Once a patient returns a valid practice diary and is considered eligible for the study by the investigator:
   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.
2. 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

Assignment of IMP to the patient using the IXRS will occur at Baseline (Visit 2), after the patient's eligibility for study participation has been confirmed (see Section 6.2.3.3) and all predosing Baseline procedures have been performed (see Section 6.2.3.2).

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 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. For all applicable patients: Determine contraceptive method used by patient and document.
2. Obtain samples for the following laboratory tests and record the date and time of collection:
   a. For females of childbearing potential: urine pregnancy test.
   b. Hematology and chemistry (including liver function tests).
   c. TSH, free T3, and free T4.
   d. Urine sample for urinalysis.

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. Repeat these BP and pulse measurements 2 more times approximately 10 minutes apart.
4. Obtain three 12-lead ECGs (3 serial readings, performed several minutes apart). Ensure the ECGs are collected 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:
   a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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:
      - PDQ-39.
      - EQ-5D-5L.
      - Non-motor Symptom Assessment Scale.
   c. Have the patient complete the following self-assessment questionnaires:
      - ESS.
7. Administer the following assessments (may be done anytime during visit):
   a. C-SSRS.
   b. Fall questionnaire.
   c. Assessment for episodes of sudden onset of sleep.
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 appropriate eCRF module.

6.2.3.3 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. The Baseline PD Diary will also be sent to [redacted] by the trainer/rater or designee for an additional review. The Baseline Diary can be sent for [redacted] review either by fax or e-mail:

   [redacted]

   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 Screening Visit 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.

6.2.3.4 Assignment and Dispensing of Investigational Medicinal Product

Note: Sites participating in Expanded PK Sampling should refer to Appendix 15.9.1 for Assignment and Dispensing of IMP instructions.

1. For patients meeting all entry criteria, complete the IMP assignment transaction using the IXRS by following the procedures provided.
    a. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 50 tablets of 120 mg tozadenant or 100 tablets of 60 mg tozadenant.
    b. Record the date IMP was dispensed in IMP dispensing records including patient number, assigned IMP bottle number(s), and date and time IMP was dispensed.
    c. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP (including all used, unused and partially used bottles) at the next visit.
    d. Patients will be instructed to take either two (2) 60 mg tablets or one (1) 120 mg tablet of the dispensed IMP by mouth BID, in the morning and in the evening preferably at the same time each day, for a total of either two (2) 120 mg tablets or four (4) 60 mg 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. Patients should take the first dose of IMP at home after the Baseline Visit.
2. Instruct the patient to take the first dose of IMP at home on the evening of dispensation.
3. Ensure that the patient understood the dosing instructions and the use of the extra doses included in the bottle if visit delayed and/or use of visit window.
4. Schedule the Week 2 visit. If needed, use the visit window in relation to the date of the Baseline visit.

6.2.4 Visit 3 (Week 2)

Note: Sites participating in Expanded PK Sampling should refer to Appendix 15.9.2 for Week 2 assessments.

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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since Screening and document.
2. Obtain sample for the following laboratory tests and record the date and time of collection:
   a. PK blood sample(s) for plasma tozadenant concentration.
      i. Sparse PK Sampling: Collect one (1) PK blood sample at the most convenient time during the visit. 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.
      ii. Expanded PK Sampling **(Select Sites Only)**: Sites participating in Expanded PK Sampling should refer to Appendix 15.9.2.

      Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
   b. Hematology and chemistry (inclusive of liver function tests).
   c. TSH, free T3, and free T4.
   d. 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.
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. Ensure the ECG is collected 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:
   a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
      - PGI-I.

c. Have the patient complete the following self-assessment questionnaire:
   - ESS.

9. Administer the following assessments (may be done anytime during visit):
   a. C-SSRS.
   b. 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. Assessment for episodes of sudden onset of sleep.
   d. Healthcare Resource Utilization.
10. Collect the IMP (including all used, unused and partially used bottles) dispensed at the Baseline 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.
11. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.
    a. Record the date IMP was dispensed 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 (including all used, unused and partially used bottles) at the next visit.
13. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.
14. Schedule the next study visit (Week 4). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.5 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 (Week 6). If needed, use the visit window in relation to the date of the Baseline visit.**

6.2.6 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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
2. 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. 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. Ensure the ECG is collected 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. 8. Perform the following assessments in the ON state:
   a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
      - PGI-I.
   c. Have the patient complete the following self-assessment questionnaire:
      - ESS.
9. Administer the following assessments (may be done anytime during visit):
   a. 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.)
   b. C-SSRS.
   c. Assessment for episodes of sudden onset of sleep.
   d. Healthcare Resource Utilization.
10. Collect the IMP (including all used, unused and partially used bottles) 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 open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.
    a. Record the date IMP was dispensed 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 (including all used, unused and partially used bottles) at the next visit.
13. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.
14. Schedule the next study visit (Week 8). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.7 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 study visit (Week 10). If needed, use the visit window in relation to the date of the Baseline visit.**

6.2.8 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. **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.**
3. **Schedule the next study visit (Week 12). If needed, use the visit window in relation to the date of the Baseline visit.**

6.2.9 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 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.

6.2.10 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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
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. 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. 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.
4. Assess AEs by asking open-ended queries and record the assessments.
5. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
6. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

7. Obtain 12-lead ECG. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
8. Obtain weight.
9. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
10. Perform the following assessments in the ON state:
    a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
        - PGI-I.
    c. Have the patient complete the following self-assessment questionnaire:
        - ESS.
11. Administer the following assessments (may be done anytime during visit):
    a. 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.)
    b. C-SSRS.
    c. Assessment for episodes of sudden onset of sleep.
    d. Healthcare Resource Utilization.
12. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
13. Collect the IMP (including all used, unused and partially used bottles) 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.
14. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.
    a. Record the date IMP was dispensed in IMP dispensing records.
15. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP (including all used, unused and partially used bottles) at the next visit.
16. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.

17. Schedule the next study visit (Week 16). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.11 Visit 5.3 (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 (Week 20). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.12 Visit 5.8 (Week 20)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 20 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. 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.
3. Schedule the next study visit (Week 24). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.13 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 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.

6.2.14 Visit 6 (Week 24)

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).

1. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
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. 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. 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.
4. Assess AEs by asking open-ended queries and record the assessments.
5. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
6. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
7. Obtain 12-lead ECG. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
8. Obtain weight.
9. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
10. Perform the following assessments in the ON state:
    a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
       - PGI-I.
       - PDQ-39.

- EQ-5D-5L.
- Non-motor Symptom Assessment Scale.

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

- ESS.

11. Administer the following assessments (may be done anytime during visit):
    a. 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.)
    b. C-SSRS.
    c. Fall questionnaire.
    d. Assessment for episodes of sudden onset of sleep.
    e. Healthcare Resource Utilization.
12. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
13. Collect the IMP (including all used, unused and partially used bottles) dispensed at the Week 12 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.
14. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.
    a. Record the date IMP was dispensed in IMP dispensing records.
15. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP (including all used, unused and partially used bottles) at the next visit.
16. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.
17. Schedule the Week 36 Visit. If needed, use the visit window in relation to the date of the Baseline visit.

6.2.15 Visit 7 (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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
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. 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. Ensure the ECG is collected 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:
   a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
      - PGI-I.
   c. Have the patient complete the following self-assessment questionnaire:
      - ESS.
9. Administer the following assessments (may be done anytime during visit):
   a. 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.)
   b. C-SSRS.
   c. Assessment for episodes of sudden onset of sleep.
   d. Healthcare Resource Utilization.
10. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
11. Collect the unopened and opened IMP bottles dispensed at the Week 24 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 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 in IMP dispensing records.
14. 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. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.
15. Schedule the Week 44 Visit. If needed, use the visit window in relation to the date of the Baseline visit.

6.2.16 Visit 7.5 (Week 44)

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. 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. Instruct the patient to complete the PD diary on the 3 consecutive days (i.e., 3 consecutive 24-hour periods) directly preceding the Week 52 visit. Provide the patient with the PD diary.
3. Schedule the next study visit (Week 52). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.17 Telephone Call on Week 52 (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 52 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 52 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 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 8 (Week 52)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 52 Visit with the courier (see Central Laboratory Procedures Manual).

1. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
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. 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. 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.
4. Assess AEs by asking open-ended queries and record the assessments.
5. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
6. Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.
7. Obtain 12-lead ECG. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
8. Obtain weight.
9. Record the date and approximate time of the most recent dose of levodopa taken prior to the UPDRS assessment.
10. Perform the following assessments in the ON state:
    a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
       - PGI-I.
       - PDQ-39.

- EQ-5D-5L.
- Non-motor Symptom Assessment Scale.

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

- ESS.

11. Administer the following assessments (may be done anytime during visit):
    a. 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.)
    b. C-SSRS.
    c. Fall questionnaire.
    d. Assessment for episodes of sudden onset of sleep.
    e. Healthcare Resource Utilization.
12. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
13. Collect the unopened and opened IMP bottles dispensed at the Week 36 Visit.
14. 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.
15. Schedule the Safety Follow-Up Visit (Week 56). If needed, use the visit window in relation to the date of the Baseline visit.

6.2.19 Safety Follow-Up Visit (Visit 9, Week 56)

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Safety Follow-Up Visit (Week 56) with the courier (see Central Laboratory Procedures Manual).

All patients who complete dosing and study evaluations through Week 52 will be scheduled for a required Safety Follow-Up Visit at Week 56. If a patient took the last dose of IMP less than 28 days prior to the Early Termination Visit, a Safety Follow-Up Visit is required.

1. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
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. 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. Ensure the ECG is collected 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. Perform physical and neurological examination and assess any changes from Baseline for clinical significance.
9. Have the patient complete the following self-assessment questionnaire (to be collected during patient's ON state):
    a. ESS.
10. Administer the following assessments (may be done anytime during visit):
    a. mMIDI.
    b. C-SSRS.
    c. Assessment for episodes of sudden onset of sleep.

6.2.20 Early Termination 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 Safety Follow-Up Visit (Section 6.2.19) is not required. If a patient took the last dose of IMP less than 28 days prior to the Early Termination Visit, a Safety Follow-Up Visit (Section 6.2.19) is required.

1. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
2. 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. 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. 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 if the subject stopped taking study drug more than 24 hours prior to the assessment of the measure.

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

    Note: 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.

    a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
        - PGI-I.
        - PDQ-39.
        - EQ-5D-5L.
        - Non-motor Symptom Assessment Scale.
    c. Have the patient complete the following self-assessment questionnaire:
        - ESS.
12. Administer the following assessments (may be done anytime during visit):
    a. mMIDI.
    b. C-SSRS.
    c. Fall questionnaire.

d. Assessment for episodes of sudden onset of sleep.
e. Healthcare Resource Utilization.

13. Collect the unopened and opened IMP bottles from the patient.
14. Record the patient-reported date and approximate time when the patient took the last dose of IMP.
15. 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.

6.2.21 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 56).

6.2.21.1 Required Assessments for Unscheduled Visit

The following assessments must be performed:

1. Assess AEs by asking open-ended queries and record the assessments.
2. Record concomitant medication use; assess and record any changes to anti-PD medication dose or regimen.
3. Collect the unopened and opened IMP bottles dispensed at the most recent study visit (if applicable).
4. Obtain and record the date and approximate time when the patient took the most recent dose of IMP.
5. 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.

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.**

6.2.21.2 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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since previous visit and document.
2. 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. 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. 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. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.
5. Obtain weight.
6. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.
7. Administer C-SSRS if suicide risk concern.
8. 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.)
9. n consultation with the Medical Monitor, discuss any other appropriate diagnostic tests required to evaluate patient's AE.
10. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.

7.0 ASSESSMENT OF DISEASE ACTIVITY

7.1 Hauser Parkinson's Disease Home Diary

The Hauser Parkinson's Disease Home Diary will be completed throughout the study 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 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 (Weeks 12, 24 and 52).

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.

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

An example of the diary and instructions are provided in Appendices 15.13 and 15.14.

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 [ADL]; 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: ADL) 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 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 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 15.8.

7.4 Clinical/Patient Global Impression Scales (CGI-I and PGI-I)

Clinical Global Impression of Improvement (CGI-I):

For the CGI-I, the investigator or designee 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-I and PGI-I scales are provided in Appendix 15.10.

7.5 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 15.11.

7.6 Non-Motor Symptom Assessment Scale

The Non-motor Symptoms Questionnaire is an established questionnaire with 30 qualitative questions covering all important non-motor symptoms of PD.

An example of the Non-Motor Symptom Assessment Scale is provided in Appendix 15.12.

7.7 EuroQol 5D-5L Health Questionnaire (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.

7.8 Healthcare Resource Utilization

Information about hospitalizations (i.e., inpatient admissions) and emergency room visits will be collected using the Healthcare Resource Utilization Questionnaire (Section 15.15) and captured in the eCRF according to the schedule shown in Table 1. 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 15.15.

8.0 ASSESSMENT OF PLASMA DRUG CONCENTRATION

Pharmacokinetic blood samples for determination of plasma tozadenant concentration will be collected at the Week 2 study visit. [redacted] will be collected at the most convenient time during the visit ("Sparse PK Sampling"). [redacted] be done ("Expanded PK Sampling").

For Sparse PK Sampling, the patient-reported date and approximate time of the most recent IMP dosing prior to the sampling will be recorded.

Sites participating in Expanded PK Sampling should refer to Appendix 15.9 for additional details.

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

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

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 immediately stop the intake of the IMP.
2. The patient should return for an Early Termination Visit as soon as possible.
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 Pregnant Partner Information Release 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, 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. Significant or persistent disability/incapacity, i.e., results in a substantial disruption of a person's ability to conduct normal life functions.
4. Congenital anomaly/birth defect, i.e., an AE that occurs in the child or fetus of a patient exposed to a study drug prior to conception or during pregnancy.
5. 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 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. 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.

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. The SAE Report Form must be sent to:

The email address, fax and telephone number used for SAE reporting is also provided on the SAE/ Pregnancy Reporting Form Cover Page, along with Sponsor contact information. 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.

9.2.4 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.

9.3 Laboratory Measurements

The laboratory tests listed below (Table 3) are to be performed and analyzed as outlined in the Schedule of Events/Evaluations (Table 1).

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 3: 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.

9.4 Other Safety Measurements

9.4.1 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). 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 supine 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).

9.4.2 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) 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 original ECG-provided printout showing QTcF interval to meet eligibility requirements at Baseline rather than the overread QTcF interval that will arrive after the Baseline visit.

9.4.3 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 ESS is provided in Appendix 15.2.

9.4.4 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 15.3).

9.4.5 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.

9.4.6 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 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. 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 15.4.

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 electronic data capture (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 or designee will review during Screening and prior to assignment of IMP using the IXRS 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.

10.3.4 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 are detailed in the DSMB charter.

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

Safety Set (SS): The SS will consist of all enrolled patients who received at least one dose of IMP.

Other analysis sets will be defined in statistical analysis plan as needed.

11.2 Study Variables

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

11.2.2 Pharmacokinetic Variables

- Tozadenant PK concentrations and PK parameters at Week 2.

11.2.3 Other Variables

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activity of Daily Living [ADL] subscale) + Part III (motor subscale) total score.
- UPDRS Part II (ADL subscale) score.
- UPDRS Part III (motor subscale) score in the ON state.
- UPDRS Part I total score.
- UPDRS Part IV, including dyskinesia as measured by questions 32, 33 and 34 and motor fluctuations as measured by question 39.
- Clinical Global Impression of Improvement (CGI-I).
- Patient's Global Impression of Improvement (PGI-I).
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39; total score and individual domain scores).
- Non-motor Symptom Questionnaire.
- EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
- Patient-completed diaries (Change from Baseline in the number of hours per day spent as follows: OFF, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time)

- Healthcare Resource Utilization.
- Fall Questionnaire.

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 available for the purpose of analysis. For continuous variables, descriptive statistics will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

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 unless otherwise specified.

11.4 Planned Efficacy Analyses

Not applicable.

11.5 Planned 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 (SOC), high level term and preferred term (PT). The data will be displayed as the number of patients experiencing the AEs, percentage of patients, and number of AEs. Note that counting will be by patient, and event and patients are only counted once within each MedDRA SOC or PT.

Laboratory test results, vital signs, ECGs, ESS, C-SSRS, mMIDI will be summarized descriptively. The descriptive statistics will be provided for the observed data and for the change from Baseline at each measured time point as appropriate. In addition, 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. Clinically significant physical or neurological examination findings and any clinically significant out of range laboratory tests will be recorded as adverse events and will also be documented in the AE summaries.

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) where appropriate. Frequencies and percentages will be presented for categorical variables.

All safety analyses will be based on the SS population.

11.6 Other Analyses

Patient Disposition

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

Exposure to IMP/Compliance

Exposure to IMP/compliance will be summarized and details will be specified in the SAP.

Prior and Concomitant Medication Use

All prior and concomitant medications taken during the study period will be summarized and 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.

Plasma Drug Concentrations

Results of the assays of tozadenant will be descriptively analyzed and reported.

Exploratory Analyses

Change from baseline to will be evaluated for the following:

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activity of Daily Living [ADL] subscale) + Part III (motor subscale) total score.
- UPDRS Part II (ADL subscale) score.
- UPDRS Part III (motor subscale) score in the ON state.
- UPDRS Part I total score.
- UPDRS Part IV, including dyskinesia as measured by questions 32, 33 and 34 and motor fluctuations as measured by question 39.
- Clinical Global Impression of Improvement (CGI-I).
- Patient's Global Impression of Improvement (PGI-I).
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39; total score and individual domain scores).
- Non-motor Symptom Assessment Scale.
- EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
- Patient-completed diaries (Change from Baseline in the number of hours per day spent as follows: OFF, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time)
- Healthcare Resource Utilization.

- Fall questionnaire.

These analyses will be documented by descriptive statistics.

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 conclusion. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined prior to data analysis. 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.

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 Determination of Sample Size

Approximately 645 patients will be screened, assuming a 30% screen failure rate, to enroll 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 abide by the Health Insurance Portability and Accountability Act (HIPAA).

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. Sponsor staff (or designee) will affirm that the patient's date of birth and initials will not be collected in the European Union (EU) or other regions where it is not permitted. 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 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

15.3 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 Screening 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> Screening:

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 Screening 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.

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

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

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

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

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

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

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

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

☐0 No ☐1 Rarely ☐2 Occasionally ☐3 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

15.5 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

15.6 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.

15.7 [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

15.8 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 6) and Week 52 (Visit 8):

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:

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?_____

15.9 Expanded Pharmacokinetic Sampling Procedures – Applicable to Select Sites Only

For those subjects who have consented to participate in the expanded tozadenant PK sampling, Sections 15.9.1 and 15.9.2 should be referred to instead of Sections 6.2.3.4 (Baseline Assignment and Dispensing and Investigational Medicinal Product) and 6.2.4 (Visit 3/Week 2), respectively.

Pharmacokinetic blood samples for determination of plasma tozadenant concentration will be collected at the Week 2 study visit at select sites only. The Schedule of Events for subjects participating in Expanded PK Sampling is provided in Table 4.

15.9.1 Baseline (Visit 2) Assignment and Dispensing and Investigational Medicinal Product for Subjects Participating in Expanded PK Sampling (Replacement Section for Section 6.2.3.4)

1. For patients meeting all entry criteria, complete the IMP assignment transaction using the IXRS by following the procedures provided.
   a. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 50 tablets of 120 mg tozadenant or 100 tablets of 60 mg tozadenant.
   b. Record the date IMP was dispensed in IMP dispensing records including patient number, assigned IMP bottle number(s), and date and time IMP was dispensed.
   c. Review the dosing instructions for the IMP with the patient, answer any questions, and remind the patient to return the IMP (including all used, unused and partially used bottles) at the next visit.
   d. Patients will be instructed to take either two (2) 60 mg tablets or one (1) 120 mg tablet of the dispensed IMP by mouth twice daily (BID), in the morning and in the evening preferably at the same time each day, for a total of either two (2) 120 mg tablets or four (4) 60 mg 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. Patients should take the first dose of IMP at home after the Baseline Visit.
2. Instruct the patient to take the first dose of IMP at home on the evening of dispensation.
3. Ensure that the patient understood the dosing instructions and the use of the extra doses included in the bottle if visit delayed and/or use of visit window.
4. **Subjects participating in the expanded tozadenant PK sampling will be advised to refrain from taking their 120 mg IMP dose on the day of the Week 2 visit, prior to the visit.**
5. Schedule the Week 2 visit. If needed, use the visit window in relation to the date of the Baseline visit.

15.9.2 Visit 3 (Week 2) for Subjects Participating in Expanded PK Sampling (Replacement Section for Section 6.2.5)

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. For all applicable patients: Verify continuation of (or any change to) contraceptive method since Screening and document.
2. **Obtain sample for the following laboratory tests and record the date and time of collection:**
   - **a. Expanded PK blood sample(s) for plasma tozadenant concentration.**
     - **i. Collect one (1) pre-dose/trough PK blood sample before the administration of IMP. Record the date and time of PK sample collection. Document the date and time of the previous IMP dosing.**
     - **ii. Administer the 120mg dose during the visit from the IMP bottle previously dispensed at Baseline visit. Record the date and time when the patient took the 120mg dose of IMP.**
     - **iii.** [redacted]

     Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.
   - b. Hematology and chemistry (inclusive of liver function tests).
   - c. TSH, free T3, and free T4.
   - d. 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.
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. Ensure the ECG is collected 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:
   a. Perform full UPDRS Parts I, II, III (motor) and IV. UPDRS Part III should be performed 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.
      - PGI-I.
   c. Have the patient complete the following self-assessment questionnaire:
      - ESS.
9. Administer the following assessments (may be done anytime during visit):
   a. C-SSRS.
   b. 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. Assessment for episodes of sudden onset of sleep.
   d.. Healthcare Resource Utilization.
10. Collect the IMP (including all used, unused and partially used bottles) dispensed at the Baseline 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.
11. Dispense the open-label IMP bottle(s) assigned by the IXRS to the patient for this study visit. Each bottle consists of either 100 × 60 mg tablets or 50 × 120 mg tablets.
   a. Record the date IMP was dispensed 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 (including all used, unused and partially used bottles) at the next visit.
13. Ensure that the patient understood the dosing instructions and the use of extra doses included in the bottle if visit delayed and/or use of visit window.
14. Schedule the next study visit (Week 4). If needed, use the visit window in relation to the date of the Baseline visit.

Table 4: Schedule of Events/Evaluations for Subjects Participating in Expanded PK Sampling

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [x]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) *[16 weeks]*	56 (28 ± 3 d after last dose of IMP)		
Assessments **Study Visit**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**B98**	**B97**
Written Informed Consent	X										
Demographics and 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	X
BP [c], pulse [c]	X [d]	X [d]	X	X	X	X	X	X	X	X	X [e]
12-lead ECG [f]	X	X [g]	X	X	X	X	X	X	X	X	X [e]
Weight (include height at Screening)	X				X	X		X	X	X	X [e]
Physical and neurological examination	X				X	X	X	X	X	X	X [e]
PD diary training and diary concordance session	X										
Modified Hoehn and Yahr staging (observed ON; OFF estimated per history) [h]	X										
UPDRS Parts I, II, III and IV [i]	X	X	X	X	X	X	X	X		X	
MMSE-II (in ON state)	X										
mMIDI [j]	X		X	X	X	X	X	X	X	X	X [e]
ESS [h]		X	X	X	X	X	X	X	X	X	
PD diary collection (phone call prior to start of 3 consecutive 24 hour diary completion periods)	X [k]	X [k]			X [l]	X [l]		X [l]		X [m]	
PD diary review	X	X			X	X		X [m]		X [m]	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X [e]
CGI-I [h]			X	X	X	X	X	X		X	
PGI-I [h]			X	X	X	X	X	X		X	
PDQ-39 [h]		X				X		X		X	
Sudden onset of sleep	X	X	X	X	X	X	X	X	X	X	
Fall questionnaire		X				X		X		X	
Healthcare Resource Utillization			X	X	X	X	X	X		X	
Non-motor Symptom Questionnaire[h]		X				X		X		X	
EQ-5D-5L [h]		X				X		X		X	
Recording of AEs	X [n]	X [n]	X	X	X	X	X	X	X	X	X

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [x]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) *[16 weeks]*	56 (28 ± 3 d after last dose of IMP)		
Assessments Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	B98	B97
Laboratory tests: hematology [o], chemistry [p] (including thyroid function [q])	X	X	X	X	X	X	X	X	X	X	X [e]
FSH test, females who are postmenopausal for < 2 years	X										
Method of contraception [r]	X	X	X	X	X	X	X	X	X	X	X [e]
Urine pregnancy test, females of childbearing potential [s]	X	X	X	X	X	X	X	X	X	X	X [e]
Urinalysis [t]	X	X	X	X	X	X	X	X	X	X	X [e]
Review of inclusion/exclusion criteria	X										
Final verification of eligibility		X									
Tozadenant blood sampling			[redacted]								
IMP dispensing and/or return [v]		**X [w]**	X	X	X	X	X	X		X	X [e]
eCRF completion	X	X	X	X	X	X	X	X	X	X	X

AE, adverse event; BP, blood pressure; CGI-I, Clinical Global Impression of Improvement; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day; ECG, electrocardiogram; eCRF, electronic case report form; 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); PD, Parkinson's disease; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; PGI-I, Patient's Global Impression of Improvement; UPDRS, Unified Parkinson's Disease Rating Scale; V, Visit.

Footnotes

[a] Screening period may not exceed 6 weeks.

[b] Visit windows for scheduled visits after Baseline (V2) are in relation to the date of the Baseline Visit (V2).

[c] 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.

[d] At Screening and 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. Repeat these BP and pulse measurements 2 more times approximately 10 minutes apart.

[e] Optional activities (e.g., additional assessments for evaluation of AEs) that may be performed at the investigator's discretion.

[f] A resting supine 12-lead ECG will be collected after the patient has been in a supine position for a minimum of 5 minutes. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[g] At Baseline, obtain three 12-lead ECGs (i.e., 3 serial readings, performed several minutes apart). Ensure the ECGs are collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

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

[i] UPDRS to be measured in ON state. UPDRS Part III should be measured 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.

Table 4: Schedule of Events/Evaluations for Subjects Participating in Expanded PK Sampling (continued)

[j] 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.

[k] The 3-day practice diary during the Screening Period and the 3-day Baseline diary must both be valid in order to enroll 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.

[l] PD diary collected over the 3 consecutive 24-hour periods before the day of the scheduled study visits on Weeks 12, 24 and 52. 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.

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

[n] Pretreatment AEs.

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

[p] 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).

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

[r] For applicable patients: At Screening, document method of contraception used by patient. At subsequent visits, verify continuation of (or any change to) contraceptive method.

[s] For females of childbearing potential: urine pregnancy test.

[t] 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.

[u] [redacted]

[v] 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.

[w] **Patients will be instructed to refrain from taking their 120 mg IMP dose on the day of the Week 2 visit, prior to the visit.**

[x] If patient has discontinued IMP, perform Early Termination Visit as soon as possible after the last dose of IMP. If patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Safety Follow-Up Visit (Section 6.2.19) is not required.

Table 4.1: Schedule of Events/ Evaluations for Hematology Monitoring

Study Period	Open-Label Treatment (52 weeks)						Weekly monitoring[b] (if required)
Study Week	4 (±3 d)	8 (±3 d)	10 (±3 d)	16 (±3 d)	20 (±3 d)	44 (±14 d)	
Assessments / Study Visit	V3.5	V4.3	V4.8	V5.3	V5.8	V7.5	
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.

15.10 Clinical/Patient Global Impression Scales (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

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.

15.11 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**.**

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.

15.12 Non-Motor Symptom Assessment Scale for Parkinson's Disease

Patient ID No:_____ **Initials:**_____ **Age:**_____

Symptoms assessed over the last month. Each symptom scored with respect to:

- Severity:
  - 0 – None,
  - 1 – Mild: symptoms present but causes little distress or disturbance to patient,
  - 2 - Moderate: some distress or disturbance to patient;
  - 3 – Severe: major source of distress or disturbance to patient.
- Frequency:
  - 1 – Rarely (< 1/week);
  - 2 – Often (1/week);
  - 3 – Frequent (several times per week);
  - 4 – Very Frequent (daily or all the time)

Domains will be weighed differentially. Yes/No answers are no included in final frequency × severity calculation. (Bracketed text in questions within the scale is included as an explanatory aid).

Domain 1: Cardiovascular including falls		**Severity**	**Frequency**	**Frequency × Severity**
1.	Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?			
2.	Does the patient fall because of fainting or blacking out?			
	SCORE:			

Domain 2: Sleep/fatigue		**Severity**	**Frequency**	**Frequency × Severity**
3.	Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading).			
4.	Does fatigue (tiredness) or lack or energy (not slowness) limit the patient's daytime activities?			
5.	Does the patient have difficulties falling or staying asleep?			
6.	Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?			
	SCORE:			

Domain 3: Mood/cognition		**Severity**	**Frequency**	**Frequency × Severity**
7.	Has the patient lost interest in his/her surroundings?			
8.	Has the patient lost interest in doing things or lack motivation to start new activities?			
9.	Does the patient feel nervous, worried or frightened for no apparent reason?			
10.	Does the patient seem sad or depressed or has he/she reported such feelings?			
11.	Does the patient have flat moods without the normal "highs" and "lows"?			
12.	Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?			
	SCORE:			

Domain 4: Perceptual problems/hallucinations		**Severity**	**Frequency**	**Frequency × Severity**
13.	Does the patient indicate that he/she sees things that are not there?			
14.	Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)			
15.	Does the patient experience double vision? (2 separate real objects and not blurred vision)			
	SCORE:			

Domain 5: Attention/memory		**Severity**	**Frequency**	**Frequency × Severity**
16.	Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)			
17.	Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?			
18.	Does the patient forget to do things? (For example, take tablets or turn off domestic appliances?)			
	SCORE:			

Domain 6: Gastrointestinal tract		**Severity**	**Frequency**	**Frequency × Severity**
19.	Does the patient dribble saliva during the day?			
20.	Does the patient have difficulty swallowing?			
21.	Does the patient suffer from constipation? (Bowel action less than three times weekly)			
	SCORE:			

Domain 7: Urinary		**Severity**	**Frequency**	**Frequency × Severity**
22.	Does the patient have difficulty holding urine? (Urgency)			
23.	Does the patient have to void within 2 hours of last voiding? (Frequency)			
24.	Does the patient have to get up regularly at night to pass urine? (Nocturia)			
	SCORE:			

Domain 8: Sexual function		**Severity**	**Frequency**	**Frequency × Severity**
25.	Does the patient have altered interest in sex? (Very much increased or decreased, please underline)			
26.	Does the patient have problems having sex?			
	SCORE:			

Domain 9: Miscellaneous		**Severity**	**Frequency**	**Frequency × Severity**
27.	Does the patient suffer from pain not explained by other known conditions? (is it related to intake of drugs and is it relieved by anti-parkinson drugs?)			
28.	Does the patient report a change in ability to taste or smell?			
29.	Does the patient report a recent change in weight (not related to dieting)?			
30.	Does the patient experience excessive sweating (not related to hot weather)?			
	SCORE:			

TOTAL SCORE:	

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15.13 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.

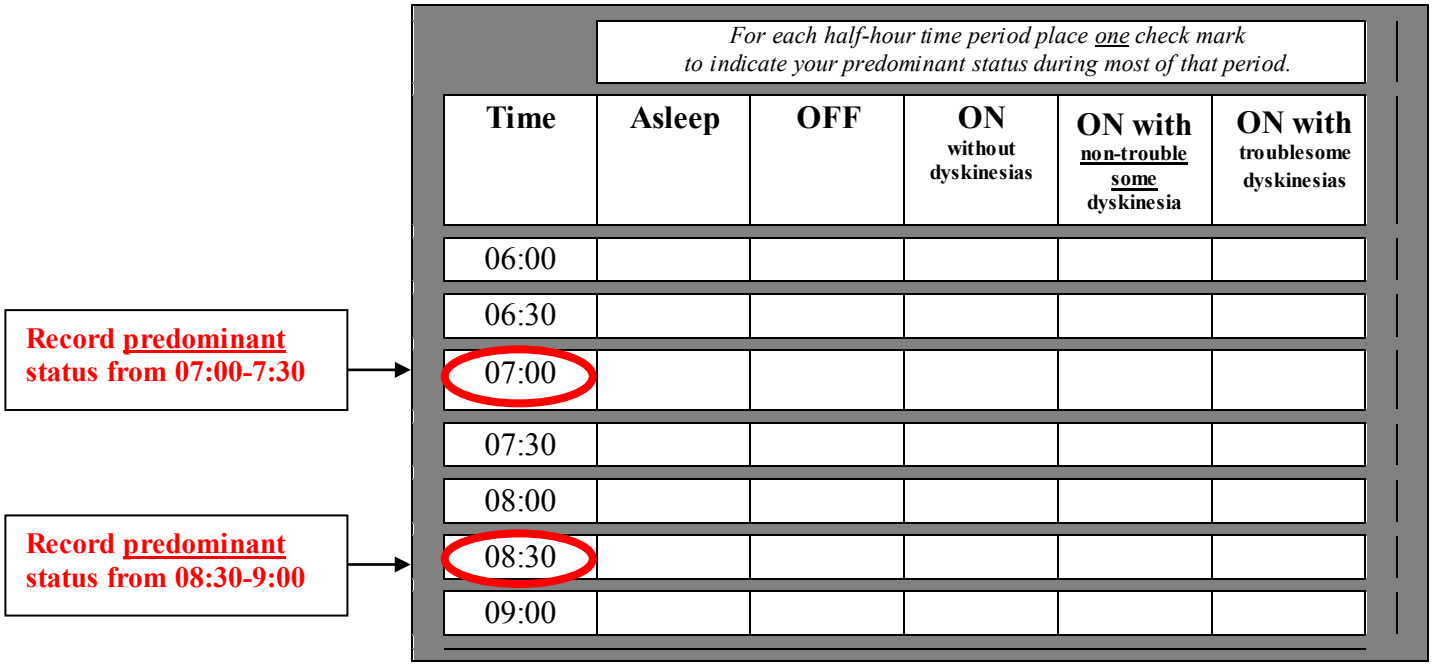
time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00-6:30 AM					
6:30-7:00 AM					
7:00-7:30 AM					
7:30-8:00 AM					
8:00-8:30 AM					
8:30-9:00 AM					
9:00-9:30 AM					
9:30-10:00 AM					
10:00-10:30 AM					
10:30-11:00 AM					
11:00-11:30 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					

15.14 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 12 Visit
  - before Week 24 Visit
  - before Week 52 Visit
- Recording time starts at 6 AM and ends 72 hours later at 6 AM.



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 the patient is not confirmed to be eligible, inform the patient they are not considered eligible and cancel Baseline Visit.
- If preliminary eligibility of the patient is confirmed by the Investigator, 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				

15.15 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	