PRODUCT: XADAGO (Safinamide)
PROTOCOL NUMBER / AMENDMENT: USWM-SA1-4001 / 02

SPONSOR:
MDD US Operations, LLC, a subsidiary of Supernus Pharmaceuticals, Inc.
9715 Key West Avenue
Rockville, Maryland 20850

TITLE:

A Prospective, Observational Study to Evaluate Changes in Non-Motor Symptoms and other Clinical Outcome Assessments of Parkinson's Disease Patients Treated with XADAGO (safinamide) Tablets

DOCUMENT DATE: 12OCT2018
IND NUMBER: N/A
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CLINICAL STUDY PROTOCOL

A Prospective, Observational Study to Evaluate Changes in Non-Motor Symptoms and other Clinical Outcome Assessments of Parkinson's Disease Patients Treated with XADAGO (safinamide) Tablets

Protocol Number:	USWM-SA1-4001
Product:	XADAGO (safinamide) tablets
Development Phase of Study:	Phase IV
Sponsor Contact:	
Contract Research Organization:	N/A
Sponsor:	US WorldMeds, LLC 4441 Springdale Road Louisville, KY 40241
Protocol Date:	12 October 2018 (Amendment 2; Final) 01 November 2017 (Amendment 1; Final) 28 August 2017 (Final)

PROTOCOL AMENDMENTS

Amendment 1 dated 01 November 2017:

- Added this Protocol Amendments section to summarize revisions.
- Updated Sponsor Contact / Scientific Lead on the Title Page, Signature Page (Section 1) and Procedures in Case of Emergency (Section 2) from
- Updated Protocol Date and Version from 28 August 2017 (Original) to 01 November 2017 (Amendment 1).
- Updated Appendix C to replace PDQ-39 with the version provided by license holder.

Refreshed Table of Contents (Section 4).

Amendment 2 dated 12 October 2018:

- Updated Protocol Amendments section to summarize revisions.
- Refreshed Table of Contents and List of Tables (Section 4).
- Updated List of Abbreviations and Specialist Terms (Section 5) and Reference List (Section 15).
- Updated Clinical Project Manager in Table 1: Emergency Contact Information from
- Updated Medical Monitor / Safety Physician in Table 1:Emergency Contact Information from
- Updated SAE reporting instructions in Table 1: Emergency Contact Information.
- Updated Protocol Date and Version from 01 November 2017 (Amendment 1) to October 2018 (Amendment 2).
- Updated Signature Page for an observational non-registration study and identified responsibility for ensuring regulatory requirements are met.
- Changed the planned date for last patient completed from November 2019 to April 2020.
- Modified language to refer to Patients rather than Subjects, and to identify study timepoints by Study Day rather than Week for clarity.
- Removed the separate statements of primary and secondary objectives, and restated them in one Study Objective: “gathering observational data from the following assessments in individuals in the US with Parkinson’s disease during XADAGO treatment: MDS-UPDRS, PDQ-39, MoCA, TSQM-9, CGI-C, and PGI-C.”
- Deleted the secondary objective of evaluating the Care Partner’s assessment of the patient’s non-motor symptoms and overall health.

- Removed the assessments NMSS, GRID-HAMD-17, LARS, LARSi, PFS-16, SCOPA-SLEEP, SCOPA-COG and mCGI-C from the study.
- Added the assessments MoCA and MDS-UPDRS Parts I, II, and IV to the study.
- Modified the Primary Outcome Analysis to an examination of changes in MDS-UPDRS, PDQ-39, and MoCA from the Baseline Assessment Visit to the Primary Endpoint (Study Day 60).
- Changed the Main Study duration from 6 months to 2 months/3 Study Visits; changed the optional extension study duration from 6 months to 4 months/3 Study Visits.
- Modified the Study Visits/Schedule of Assessments, and updated the list of Study Assessments in Section 8.1:
  - Clarified that Screening and Baseline Assessments may occur at the same clinic visit.
  - Changed Visit 2 to a Telephone Follow-up on Study Day 30
  - Changed Visit 3 to the Primary Endpoint Visit on Study Day 60
  - Changed Visit 4 to a Follow-up Clinic Visit on Study Day 90
  - Changed Visit 5 to include a PRO Assessment only on Study Day 120
  - Changed Visit 6 to a Follow-up Clinic Visit on Study Day 180 (there is no End-of-Study Visit)
  - Added MoCA to Study Visits 1, 3, and 6
- Increased number of planned enrolled patients to up to 540.
- Clarified Inclusion Criterion 3, stating that patient age requirement applies to age at initial screening assessment.
- Removed Inclusion Criterion 5, which required patients to be on XADAGO for less than 2 weeks; patient must be newly prescribed XADAGO at entry into this study.
- Removed Inclusion Criterion 8, which described optional Care Partner participation in the study. A Care Partner may still assist patient with visits and procedures as necessary.
- Modified the 2 study cohorts in Amendment 1 to the 3 cohorts below:

  Cohort A – Patients that have switched to XADAGO from a dopamine agonist

  Cohort B – Patients that have switched to XADAGO from a monoamine oxidase-B (MAO-B) inhibitor

  Cohort C – Patients that are MAO-B inhibitor naïve
- Clarified that Health Care Professional taking part in the study must be certified.
- Clarified that interim data analyses will be performed periodically to provide study updates and to support potential presentation of interim results.

- Removed eSAE forms from procedures; only paper SAE forms will be used.
- Clarified the method by which study drug XADAGO will be made available to patients for treatment, XADAGO labeling and storage conditions, and accountability procedures.
- Removed 1 Per-Protocol Population and renamed the other as the "Evaluable Population", redefined to include patients in the safety population who complete at least the MDS-UPDRS assessment at the Study Day 60 visit. The previous definition specified completion of any 1 assessment.
- Deleted Adjustment for Multiplicity section.

1. SIGNATURE PAGE

Protocol Approval: By signing below, US WorldMeds, LLC indicates approval of this protocol as well as assurance that this study will be conducted according to the procedures described in the protocol, Good Clinical Practices as applicable for an observational non-registration study, with Sponsor oversight ensuring all applicable regulatory requirements.

Signature: _____ Date: 15-Oct-2018

Name (print): _____

Principal Investigator Agreement: I have read and understand the prescribing information in the XADAGO (safinamide) Package Insert and have also read the protocol and agree to conduct the study as outlined herein which includes ensuring all applicable regulatory requirements are met.

Signature: _____ Date: _____

Name (print): _____

2. PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Project Manager		US WorldMeds, LLC 4441 Springdale Road Louisville, KY 40241
Sponsor Contact / Scientific Lead		US WorldMeds, LLC 4441 Springdale Road Louisville, KY 40241
Medical Monitor / Safety Physician		US WorldMeds, LLC 4441 Springdale Road Louisville, KY 40241
SAE Reporting		

3. SYNOPSIS

Name of Sponsor/Company:

US WorldMeds, LLC

4441 Springdale Road
Louisville, KY 40241

Name of Marketed Drug Product:

XADAGO® (safinamide) tablets

Name of Active Ingredient:

Safinamide mesylate

Title of Study:

A Prospective, Observational Study to Evaluate Changes in Non-Motor Symptoms and other Clinical Outcome Assessments of Parkinson's Disease Patients Treated with XADAGO (safinamide) Tablets

Study Sites:

Approximately 50 investigative sites; US only

Study Duration:	**Phase of Development:**
Planned date first patient enrolled to planned date last patient completed: November 2017 – April 2020	Phase IV (Prospective, Observational)

Study Objective:

The objective of this prospective observational study is to gather real-world observational data from the following assessments in individuals in the United States (US) with Parkinson's disease (PD) during XADAGO treatment: the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Parkinson's Disease Questionnaire (PDQ-39), the Montreal Cognitive Assessment (MoCA), the Treatment Satisfaction Questionnaire for Medication (TSQM-9), the Clinical Global Impression of Change (CGI-C), and the Patient Global Impression of Change (PGI-C).

Methodology:

This is a multisite, prospective, observational study to evaluate clinician-reported outcomes (ClinRO) and patient-reported outcomes (PRO) related to motor and non-motor symptoms, health status/QoL, and treatment satisfaction in PD patients who have been newly prescribed XADAGO according to Package Insert indication (Appendix A). Eligible study participants will be consented, enrolled, and prospectively followed for 2 months, with potential to participate in a 4-month study extension. ClinRO measures will be completed by the Principal Investigator (PI) or certified health care professional (HCP) designee (i.e., MD, DO, PA, NP, or RN), depending on the specific assessment scale. Investigative sites will be

provided secure access to a 21 CFR Part 11-compliant electronic Case Report Form (eCRF) and electronic Clinical Outcome Assessment (eCOA) system for collecting all patient data.

As shown in Table 3: Schedule of Assessments, the Main Study will include:

- Baseline Assessment Visit at the PI's clinic, including electronic completion of ClinRO measures by the PI/certified HCP designee and PRO measures by the patient (by use of a smartphone, tablet, or desktop, based on site and patient electronic capabilities) (Study Day 1)
- Telephone follow-up with the patient by the PI/certified HCP designee (Study Day 30)
- Primary Endpoint Assessment Study Visit at the PI's clinic including electronic completion of ClinROs by the PI/ certified HCP designee and PROs by the patient (Study Day 60)

Eligible patients who compliantly complete the Main Study may participate in the 4-month Extension Study (Table 3:Schedule of Assessments), which will include:

- Two follow-up Study Visits at the PI's clinic, including electronic completion of ClinROs by the PI/certified HCP designee and PROs by the patient (Study Days 90 and 180)
- One scheduled PRO assessment to be completed electronically by the patient on Study Day 120

If an enrolled patient discontinues XADAGO treatment for any reason at any point in the study (i.e., prior to Study Day 60 for the Main Study or Study Day 180 for the Extension Study), the patient is permitted to remain on study and complete the full schedule of assessments per protocol, as long as the patient is otherwise eligible and is able and willing to continue participation and complete the Main Study (through Study Day 60) or the Extension Study (through Study Day 180).

Number of Patients (planned):

Up to 540 patients enrolled

Inclusion Criteria:

1. Patient (and Care Partner, if required per Inclusion Criterion 7) is able to understand and provide signed informed consent and HIPAA authorization in English
2. Patient with diagnosis of idiopathic PD (all stages)
3. Male or female, 30 to 80 years of age, inclusive, at initial screening assessment
4. Independent of the study, clinician's and patient's choice of treatment is XADAGO in accordance with the Package Insert indication (Appendix A)
5. Patient is willing and able to participate in the study and complete study-related assessments for 2 months and, if eligible, continue for a 4-month study extension
6. Patient has access to an electronic device for the interim completion of PROs

7. Patient has an available Care Partner who is able and willing to assist with clinic attendance and completion of study assessments (e.g., PROs, health outcomes, etc.), if in the PI's opinion, assistance is needed to comply with all study visits and procedures

Exclusion Criteria:

1. Any of the warnings, precautions, or contraindications listed in the Package Insert (Appendix A) that in the opinion of the PI would prevent appropriate treatment with XADAGO or impair study participation (e.g., pregnancy, lactation, severe hepatic impairment, etc.)
2. Participation in any other clinical trial of an investigational drug or device within 4 weeks prior to the Baseline Visit or at any time during the study
3. Patient is currently receiving chemotherapy or radiation for any form of cancer (if history of cancer, must be in clinical remission at study entry) or currently receiving immunotherapy
4. Patients with conditions that are likely to prevent them from accurately and reliably completing study assessments, including evidence of moderate or severe dementia as determined by the clinician (not to include mild cognitive impairment [MCI]); major psychiatric illness (specifically diagnosis of schizophrenia, bipolar disorder or a history of attempted suicide); and/or severe and progressive medical illness (including terminal cancer, end-stage renal disease +/- undergoing dialysis)
5. Severe or unpredictable dyskinesia at the time of the Baseline Visit
6. Previous participation in this study; a patient may not re-enroll after prior discontinuation or completion

Medicinal Product, Dosage and Mode of Administration:

XADAGO (safinamide) tablets, 50 mg and 100 mg, oral.

Duration of Patient Participation:

Planned patient participation will be 2 months for patients in the Main Study, including Baseline Assessment and Primary Endpoint Visits at the PI's clinic, and a telephone Follow-up Visit. A window of ± 7 days is allowed for the Baseline Assessment Visit.

Eligible patients participating in the Extension Study (if applicable) will be in the study for a total of 6 months. A window of ± 14 days is allowed for the Clinic Visit on Study Day 180.

Criteria for Evaluation:

The assessments listed below will be performed at the Baseline Assessment Visit and at subsequent visits according to the Schedule of Assessments (Table 3). If patient is unable to self-complete the assessments, the Care Partner may record patient-directed responses to the questions in the assessments. The Care Partner may not answer the questions in the assessments from the Care Partner perspective.

- MDS-UPDRS (Movement Disorders Society – Unified Parkinson's Disease Rating Scale) (Appendix D) administered by the PI/certified HCP designee
- PDQ-39 (Parkinson's Disease Questionnaire; health status/quality of life) (Appendix B) to be completed by the patient
- MoCA (Montreal Cognitive Assessment) (Appendix C) administered by the PI/certified HCP designee
- TSQM-9 (Treatment Satisfaction Questionnaire for Medication) (Appendix E) to be completed by the patient
- CGI-C (Clinical Global Impression of Change in health) (Appendix F) administered by the PI/certified HCP designee
- PGI-C (Patient Global Impression of Change in health) (Appendix G) to be completed by the patient

Safety Management:

The use of XADAGO in this study is not experimental, study procedures (questionnaires) are not associated with greater than minimal risk, and safety is not the principal objective of this protocol. However, in keeping with the Sponsor's requirement to review and report all information relevant to the safety of the marketed drug XADAGO, about which the Sponsor becomes aware through notification by the investigator and study patients, all adverse events (AEs) spontaneously reported by the patient and/or in response to an open question from the site personnel or revealed by observation will be recorded at the investigational site and in the CRF for each study patient during active participation in the study.

Statistical Methods:

A Statistical Analysis Plan (SAP) describing all analyses will be developed for this study.

Eligible, consented, and enrolled study participants will be analyzed for the following subgroups:

Cohort A – Patients that have switched to XADAGO from a dopamine agonist

Cohort B – Patients that have switched to XADAGO from a monoamine oxidase-B (MAO-B) inhibitor

Cohort C – Patients that are MAO-B inhibitor naïve

4. TABLE OF CONTENTS AND LIST OF TABLES

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5. ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
ClinRO	Clinician-Reported Outcome
COMT	Catechol-O-methyl transferase
DO	Doctor of Osteopathic Medicine
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Forms
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MAO-B	Monoamine oxidase B
MCI	Mild Cognitive Impairment
MD	Doctor of Medicine
MDS-UPDRS	Movement Disorders Society - Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
NMS	Non-Motor Symptoms
NP	Nurse Practitioner
PA	Physician Assistant
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire; health status/quality of life

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PGI-C	Patient Global Impression of Change
PI	Principal Investigator The investigator who leads the study conduct at an individual study site. Every study site has a Principal Investigator.
PRO	Patient-Reported Outcome
QoL	Quality of Life
RN	Registered Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
TSQM-9	Treatment Satisfaction Questionnaire for Medication
US	United States
USWM	US WorldMeds, LLC

6. INTRODUCTION

6.1. Parkinson's Disease

Parkinson's disease (PD), a chronic neurodegenerative disorder, affects approximately 1-2% of people over the age of 60 years, and approximately 4% of patients older than 80 years (Dorsey, 2007). PD is second only to Alzheimer's disease in frequency. With the aging of the population, the number of PD patients is expected to increase dramatically (de Lau, 2006; Olanow, 2009). The symptoms of PD can be highly variable at disease onset, as well as throughout the progression of disease. As a result of the heterogeneity of PD, and the variation in response to treatment, each patient requires individualized care and a personalized treatment plan.

For decades, PD treatment has focused on management of motor symptoms. The progressive loss of nigrostriatal dopaminergic neurons leads to the well-known set of PD motor symptoms characteristic of the disease. Although PD is generally considered to be a movement disorder, there is a growing recognition of the non-motor symptoms, which have a major impact on the quality of life of patients and their families (Olanow, 2009; Weintraub, 2008). Non-motor symptoms are frequently observed in PD prior to the occurrence of any motor symptoms, a finding that implicates not only dysregulation of the dopaminergic system but also other neurotransmitter involvement in different areas of the brain (Chaudhuri, 2009; Barone, 2010).

The understanding that PD is a syndrome of dopamine deficiency led to the introduction of the clinical use of levodopa, a precursor of dopamine that crosses the blood brain barrier, in addition to the use of other dopaminergic agents, including selective inhibitors of monoamine oxidase B (MAO-B), the major dopamine-metabolizing enzyme in humans.

Levodopa remains the most effective single pharmacotherapy for PD. Unfortunately, oral levodopa use is often limited by the development of incapacitating motor complications, related in part to the daily dosage used (Obeso, 2000; Olanow, 2013). Approximately 40% of PD patients develop motor fluctuations after 4 to 6 years of levodopa treatment (Ahlskog, 2001). These effects can be managed by modifying the dose or frequency of oral levodopa administration, changing the formulation of levodopa, or using add-on therapy, but such strategies may increase the risk of dyskinesia (Ferreira, 2013). Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement or delay the use of established dopaminergic therapies (Fox, 2008).

6.2. XADAGO®

XADAGO (safinamide) is one of the newest treatments recently approved by the Food and Drug Administration (FDA) in the United States (US) as an add-on therapy to levodopa/carbidopa in patients with PD experiencing *off* episodes as described in the XADAGO Package Insert, May 2017 (Appendix A). XADAGO is an orally active, water-soluble, α-aminoamide derivative. It is a potent, selective, and reversible MAO-B inhibitor. In addition, the molecule safinamide has been shown in animal studies to exhibit state-dependent blockade of voltage-gated sodium channels, modulation of calcium channels, and subsequent inhibition of stimulated release of glutamate (Caccia, 2006; Caccia, 2007; Chazot, 2007; Pevarello, 1998; Stocchi, 2006) which may be implicated in the development of dyskinesia (Chase, 2003; Gregoire, 2013). The clinical implication of the activity is not known.

XADAGO was evaluated in two double-blind, placebo-controlled, multinational, 24-week studies. In both studies, change in *on* time without dyskinesia plus *on* time with non-troublesome dyskinesia, as determined by patient diary, was the primary endpoint. Secondary endpoints included change in *off* time and clinician-rated change in Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores. The trials were conducted in patients with PD who had at least 1.5 hours of daily *off* time, despite optimized treatment regimens of levodopa/carbidopa. Patients could also be taking dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, anticholinergics, and amantadine. In Study 1, patients were randomized to placebo, 50 mg/day or 100 mg/day of XADAGO. In Study 2, patients were randomized to placebo or a treatment group in which all patients were started on 50 mg/day for 2 weeks, then increased to 100 mg/day thereafter (Borgohain, 2014a; Schapira, 2017). Both studies showed significant improvements in *on* time without troublesome dyskinesia as compared to placebo, as well as significant decreases in *off* time and improvement in UPDRS Part III scores (Borgohain, 2014a; Schapira, 2017). The improvements in *on* time and *off* time seen at 6 months were maintained out to 2 years in an 18-month extension of Study 1 (Borgohain, 2014b). Both the 50 mg/day and 100 mg/day doses of XADAGO were well tolerated by patients and had safety profiles similar to that of placebo. The most commonly reported adverse event (AE) was dyskinesia, which was significantly higher in the treatment groups versus placebo. Of the patients who discontinued due to an AE, 1% of patients in the treatment group discontinued due to dyskinesia and 0% in the placebo group. In addition to the clinical benefits seen in motor function, there were also improvements noted in measures of activities of daily living, depressive symptoms, patients' clinical status, and aspects of quality of life such as emotional well-being, communication, and bodily discomfort (Borgohain, 2014a; Borgohain, 2014b; Schapira, 2017). These improvements in non-motor symptoms were seen for the 100 mg/day group in secondary measures, specifically the Parkinson's Disease Questionnaire; health status/quality of life (PDQ-39) and the Clinical Global Impression of Change in health (CGI-C) outcomes.

6.3. Study Rationale

The objective of this prospective, observational, post-marketing study is to obtain further data on the effect of XADAGO on motor and non-motor symptoms in patients newly prescribed XADAGO. Although the cardinal symptoms of PD are motor, there is increasing appreciation of the non-motor symptoms, which at times may be a greater burden to the patient than the motor symptoms (Olanow, 2009; Weintraub, 2008). Along with the greater recognition, there is also an evolving science into the etiology of non-motor symptoms in PD. XADAGO as a treatment option is unique in that the molecule has a dual mechanism of action: 1) MAO-B inhibition improves motor symptoms, and 2) the second mechanism of action, sodium channel inhibition and subsequent modulation of glutamate, may have a role in improving non-motor symptoms. Secondary and post-hoc analyses of XADAGO clinical trial data described above find signals for improvement with endpoints in pain, quality of life, and mood that suggest possible clinical effects of the drug through this second mechanism of action.

The focus of this study will be on measurement of changes in real-world outcomes (motor and non-motor symptoms, health status, and general quality of life) in the near term; therefore, the primary endpoint is set at 2 months, with an optional additional 4 months of treatment.

This study also will gather “real world” data from a PD population in the US regarding their overall experience and degree of satisfaction with the use of XADAGO as an add-on treatment to their L-dopa regimen. Treatment experience will be captured using patient self-rating assessments as well as clinician ratings on assessments.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. Study Objective

The objective of this prospective, observational study is to gather real-world observational data from the following assessments in individuals in the United States (US) with Parkinson's disease (PD) during XADAGO treatment: the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Parkinson's Disease Questionnaire (PDQ-39), the Montreal Cognitive Assessment (MoCA), the Treatment Satisfaction Questionnaire for Medication (TSQM-9), the Clinical Global Impression of Change (CGI-C), and the Patient Global Impression of Change (PGI-C).

7.2. Study Endpoints

Study endpoints are the changes from the Baseline Visit to Visit 3 (Study Day 60, Primary Endpoint) in motor and non-motor symptoms, general health status/quality of life, treatment satisfaction, and global impression (Section 8.1 and Table 3) as measured by MDS-UPDRS, PDQ-39 and MoCA, TSQM-9, and CGI-C/PGI-C, respectively.

7.2.1. Motor Symptoms and Non-Motor Symptoms

MDS-UPDRS (Appendix D) provides an assessment of the effects of PD on multiple aspects of a patient's life. The assessment is administered by the Principal Investigator (PI) or certified Health Care Professional (HCP) designee and consists of 4 parts:

- Part I focuses on non-motor experiences of daily living, such as mood, sleeping habits, pain, and fatigue. In IA, the investigator assesses various behaviors using information from the patient and caregiver; in IB, the assessments are completed by the patient without input from the investigator. Difficulties are rated on a 5-point scale, from 0=no problems to 4=severe problems.
- Part II is an evaluation of motor experiences of daily living, such as speech, eating, hygiene, and movement, and is completed by the patient. Difficulties are rated using the same 5-point scale as Part I.
- Part III assesses the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, and postural instability). It includes 33 scores based on 18 items, and difficulties are rated using the same 5-point scale as Part I.
- Part IV is made up of questions on motor complications, and difficulties are rated using the same 5-point scale as Part I. This section integrates patient-derived information with the investigator's clinical observations and judgments and is completed by the rater (Goetz, 2008). It will be scored by the Investigator.

7.2.2. General Health Status/Quality of Life

PDQ-39 (Parkinson's Disease Questionnaire) (Appendix B) is a disease-specific, health-related quality-of-life assessment. It is a self-completed, patient-reported outcome (PRO) designed to address aspects of functioning and well-being for those affected by PD. Each of the 39 items is rated using a 5-point Likert scale, with 0 for never having difficulties/problems and 4 for always

having difficulties/problems. The sum score of the 39 items will be calculated and used for analysis, with the maximum score of 156 (Peto, 1998).

MoCA (Montreal Cognitive Assessment) (Appendix C) is a validated, 30-point, 1-page test administered by the PI or certified HCP designee and designed to assess several cognitive domains, including visuospatial abilities (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points), and orientation to time and place (6 points).

7.2.3. Treatment Satisfaction

TSQM-9 (Treatment Satisfaction Questionnaire for Medication) (Appendix E) is the abbreviated version of the original questionnaire (TSQM 1.4), a reliable and valid instrument with 14 questions to assess patients' satisfaction with medication. This PRO provides scores on four scales: side effects, effectiveness, convenience, and global satisfaction. Because questions relative to side effects could potentially interfere with patient care in a naturalistic setting, the 9 questions on effectiveness, convenience, and global satisfaction are often used without the 5 on side effects (Bharmal, 2009).

7.2.4. Global Impression

CGI-C (Clinical Global Impression – Change) (Appendix F) is a rating of the patient's overall improvement, based on a 7-point scale, using a range of responses from 1 (very much improved) through to 7 (very much worse) (Guy, 1976). The patient's improvement is rated by the PI/certified HCP designee.

PGI-C (Patient Global Impression – Change) (Appendix G) is a 7-point scale depicting a patient's rating of overall improvement. A patient reports his/her own change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse" (Hurst, 2004).

8. CLINICAL INVESTIGATION PLAN

8.1. Study Design and Schedule of Assessments

This is a multisite, prospective, observational study to evaluate clinician-reported outcomes (ClinROs) and patient-reported outcomes (PROs) related to motor and non-motor symptoms, health status/QoL, and treatment satisfaction in a "real world" PD population in the US newly prescribed XADAGO in accordance with the Package Insert indication (Appendix A). The decision to prescribe XADAGO by clinician and patient must be made before site study staff discuss the study with the patient. If the patient is interested in participating in the study, an informed consent form (ICF) will be provided to the patient for review, contents of the ICF will be discussed, and patient's signature will be obtained. Enrolled patients will be prospectively followed for 2 months, with the potential to participate in a 4-month Extension Study.

The Schedule of Assessments (Table 3) presents all the study activities that will occur at each study interaction with patients during clinic visits, by telephone at protocol-specified time points, and by PRO via the electronic Clinical Outcome Assessment (eCOA) system. Investigative sites will be provided secure access to 21 CFR Part 11-compliant electronic Case Report Forms (eCRF), and sites and patients will have access to the eCOA system(s) for collecting all patient data.

8.1.1. Screening / Baseline Assessments (Visit 1, Study Day 1)

The Screening Visit and the Baseline Assessment Visit may occur on the same day. During the Screening Visit, patients who provide written consent to participate in the study and HIPAA authorization to use their personal health information will be screened for inclusion in the study according to the following procedures:

- Assessment of eligibility criteria (i.e., Inclusion [Section 9.1] and Exclusion [Section 9.2] Criteria)
- Collection of demographics and medical history information, including history of PD and other neurological conditions

For patients determined to be eligible for the study, Baseline Assessments should be conducted at the same visit that Screening occurs. If the patient requires a separate Baseline Assessment Visit, it should occur no more than 7 days after the Screening Visit.

Patients will arrive at the Investigator's clinic in an "on" motor state. The following activities and outcome assessments (Baseline Assessments) will be completed at the clinic Baseline Visit:

- Presentation of study instructions relative to XADAGO administration, concomitant medications, reporting of safety events, patient and Care Partner (if applicable), completion of CROs and PROs, downloading and training on the eCOA system, and documentation of other study data
- Registration and training on the eCOA system (in which the patient will report PRO results)
- Assessment of concomitant medications
- MDS-UPDRS by the PI/certified HCP designee

- PDQ-39 by the patient
- MoCA by the PI/certified HCP designee
- Study Day 1 administration of XADAGO

8.1.2. Telephone Follow-up with Patient by Study Site Staff (Visit 2, Study Day 30)

All patients will be contacted by telephone on Study Day 30. If the patient is scheduled for a routine clinic visit within ±5 days of the Study Day 30 visit, the study assessments may be performed in person with the patient during the routine clinic visit.

The following assessments will be completed:

- Review of patient information relevant to XADAGO administration and concomitant medication administration
  - Daily record (e.g., electronic diary or log) will be available for the patient to enter information relevant to XADAGO and concomitant medications taken if patient decides to utilize
- PRO assessment:
  - TSQM-9

8.1.3. Primary Endpoint Assessments (Visit 3, Study Day 60)

Patients will come to the study clinic for Primary Endpoint Assessments at Study Day 60.

The following assessments will be completed:

- Review of patient information relevant to XADAGO administration and concomitant medications administration
- Assessment of AEs
- Review of PRO completion compliance
- Clinical outcome assessments administered by the PI/certified HCP designee:
  - MDS-UPDRS
  - MoCA
  - CGI-C
- PRO assessments:
  - PDQ-39
  - TSQM-9
  - PGI-C

8.1.4. Follow-Up Study Assessments (Visit 4 [Study Day 90], Visit 6 [Study Day 180])

Patients will come to the study clinic on Study Days 90 and 180.

The following assessments will be completed:

- Review of patient information relevant to XADAGO administration and concomitant medications administration
- Assessment of AEs
- Review of PRO completion compliance
- Clinical outcome assessments administered by the PI/certified HCP designee:
  - MDS-UPDRS
  - MoCA (Visit 6 only)
  - CGI-C
- PRO assessments:
  - PDQ-39
  - TSQM-9
  - PGI-C

8.1.5. PRO Assessment Timepoints (Visit 5]Study Day 120])

PRO assessment:

- TSQM-9

8.2. Number of Patients

Up to 600 patients are planned for screening. This is expected to result in a final sample size of up to 540 eligible and evaluable enrolled patients, distributed among approximately 50 investigative sites in the US.

Table 3: Schedule of Assessments

Protocol Activity *(Visit Type, Location, and Number; Study Day and Month; Window Allowance)*	**2-Month Main Study**			**4-Month Extension Study**		
	Screening/Baseline Assessment Visit [a]	**Follow-up**	**Primary Endpoint Visit**	**Follow-up**	**PRO Assessment Only**	**Follow-up**
	Clinic	**Telephone**	**Clinic**	**Clinic**		**Clinic**
	Visit 1	***Visit 2***	***Visit 3***	***Visit 4***	***Visit 5***	***Visit 6***
	Day 1	***Day 30***	***Day 60***	***Day 90***	***Day 120***	***Day 180***
	Month 1		***Month 2***	***Month 3***	***Month 4***	***Month 6***
	±7 days	***±2 days***	***±7 days***	***±7 days***	***±7 days***	***±14days***
Informed Consent and HIPAA Authorization	X					
Eligibility: Inclusion/Exclusion Criteria	X					
Medical History and Demographics	X					
Medical History of PD, other Neurological Conditions	X					
Presentation of Study Instructions to Patient	X					
Registration and Training on eCOA System	X					
Concomitant Medications Assessment[b]	X	X	X	X		X
XADAGO Administration Compliance Review[b]		X	X	X		X
PRO Compliance Review[b]			X	X		X
Adverse Events Assessment[b]			X	X		X
MDS-UPDRS[b]	X		X	X		X
PDQ-39[c]	X		X	X		X
MoCA[b]	X		X			X
TSQM-9[c]		X	X	X	X	X
CGI-C[b]			X	X		X
PGI-C[c]			X	X		X

[a] Screening will take place not more than 7 days before the Baseline Visit and may occur at the same time as the Baseline Visit. The first study dose of XADAGO will occur in the clinic on the Baseline Visit day, which will be designated Study Day 1.

[b] Assessments to be administered by the PI/certified or HCP designee.

[c] Assessments to be completed by the patient, with Care Partner assistance, if required.

8.3. Criteria for Study Termination

US WorldMeds, LLC (USWM), the study Sponsor, has the right to terminate this study at any time. The PI will be notified by telephone and/or in writing if the Sponsor decides to suspend or discontinue the study for any reason. The written notice will provide the PI with the reason that the study was suspended or discontinued along with instructions on how the site should proceed to close down the study.

Reasons for terminating the study may include, but are not limited to, the following:

- Discovery (from this or other studies) of an unexpected, serious, or unacceptable health hazard to patients
- A decision on the part of the Sponsor to suspend evaluation or marketing of the product
- Unsatisfactory patient enrollment
- Failure of the PI and/or investigative site to comply with pertinent FDA regulations
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data that threatens the scientific integrity of the study
- Evidence from the data that there are sufficient technical problems with the study to believe with a high degree of certainty that patients are being involved in the study without a realistic expectation of evaluable data

9. SELECTION AND WITHDRAWAL OF PATIENTS

9.1. Inclusion Criteria

1. Patient (and Care Partner if required per Inclusion 7) is able to understand and provide signed informed consent and HIPAA authorization in English
2. Diagnosis of idiopathic PD (all stages)
3. Male or female, 30 to 80 years of age, inclusive, at initial screening assessment
4. Independent of the study, clinician's and patient's choice of treatment is XADAGO in accordance with the Package Insert indication (Appendix A)
5. Patient is willing and able to participate in the study and complete study-related assessments for 2 months and, patients can continue for an optional 4-month study extension
6. Patient has access to an electronic device for the interim completion of PROs
7. Patient has an available Care Partner who is able and willing to assist with clinic attendance and completion of study assessments (e.g., PROs, health outcomes, etc.), if in the PI's opinion, assistance is needed to comply with all study visits and procedures

9.2. Exclusion Criteria

1. Any of the warnings, precautions, or contraindications listed in the Package Insert (Appendix A) that in the opinion of the PI would prevent appropriate treatment with XADAGO or impair study participation (e.g., pregnancy, lactation, severe hepatic impairment, etc.)
2. Participation in any other clinical trial of an investigational drug or device within 4 weeks prior to the Baseline Visit or at any time during this study
3. Patient is currently receiving chemotherapy or radiation for any form of cancer (if history of cancer, must be in clinical remission at study entry) or currently receiving immunotherapy
4. Patients with conditions that are likely to prevent them from accurately and reliably completing study assessments, including evidence of moderate or severe dementia as determined by the clinician (not to include mild cognitive impairment [MCI]); major psychiatric illness (specifically diagnosis of schizophrenia, bipolar disorder or a history of attempted suicide); and/or severe and progressive medical illness (including terminal cancer, end-stage renal disease +/- undergoing dialysis)
5. Severe or unpredictable dyskinesia at the time of the Baseline Visit
6. Previous participation in this study; a patient may not re-enroll after prior discontinuation or completion

9.3. Screening or Enrollment Failures

A screening and enrollment log for all potential study participants who are assessed, and for those patients who have provided written informed consent and HIPAA authorization and

completed Baseline Assessment Visit procedures, will be maintained at the Investigator's site.

Potential study participants who fail the study inclusion/exclusion criteria may be re-assessed for inclusion at the PI's discretion at a minimum of 2 weeks later. Re-assessed potential participants must fulfill all study criteria to be considered eligible for enrollment. Per Exclusion Criterion 6, a patient who has completed the study may not enroll a second time.

9.4. Patient Withdrawal Criteria

Any patient not completing the study for any reason will be considered a premature discontinuation and the study site staff must record the reason(s) for withdrawal in the patient's study records. Patients who discontinue or are withdrawn from the study may not re-enter the study.

A patient is free to withdraw consent from the study at any time, regardless of his/her reasons, and without prejudice against further treatment. The patient (and Care Partner, if applicable) will be queried about the reason(s) for the decision to withdraw consent and the reasons(s) must be clearly documented in the patient's study record to ensure the decision was not due to an AE. If withdrawal was due to an AE, including SAE, the AE should be indicated as the reason for discontinuation even if the PI would not have considered discontinuation from the study because of the AE.

The PI or Sponsor may withdraw an individual patient from the study at any time if it is deemed clinically appropriate. Circumstances can include the following:

- Patient's safety may be compromised due to intolerable AEs or a physical or mental condition
- Patient requires a medication that was prohibited on this study
- Patient is non-compliant with required study regimens or procedures specified in this protocol
- Patient is lost to follow-up

Any patient who experiences an SAE or is removed from the study because of an intolerable AE must be followed until the event resolves or stabilizes. If a patient cannot be reached for the telephone follow-up contacts or fails to return for any study visits required by the PI, repeated attempts will be made to reach the patient (or Care Partner, if applicable) (defined as a minimum of 3 telephone calls, followed by sending a certified letter). If repeated attempts are unsuccessful, lost to follow-up will be recorded in the patient's study record. The PI should always inform a patient that he/she has been withdrawn from participation in a study and the reasons for withdrawal.

10. XADAGO AND OTHER MEDICATIONS

10.1. XADAGO

XADAGO is an FDA-approved and marketed product in the US. The Sponsor will initially provide to each qualified and activated site a supply of XADAGO (described in Section 10.1.1) only for use in the study. Kits will be uniquely labeled for tracking kit assignments to each study patient.

When a patient is prescribed XADAGO and the patient agrees to participate in the study, which includes providing informed consent, the patient will be considered an enrolled study patient.

Patients who discontinue XADAGO treatment during the conduct of the study can remain in the study or discontinue early (Section 10.1.4).

10.1.1. XADAGO Study Supplies

Each site will receive a supply of XADAGO to begin the study:

- 3 patient kits, each of which will contain:
  - 1 blister pack of 50-mg tablets
  - 4 blister packs of 100-mg tablets
- 2 extra blister packs of 50-mg tablets
- 3 bags

10.1.2. XADAGO Drug Storage

XADAGO should be stored at 25°C (77°F) with excursions between 15°C to 30°C (59°F to 86°F) permitted per Appendix A (Package Insert).

10.1.3. XADAGO Accountability

10.1.3.1. Site Accountability

Accurate recording of all XADAGO study supplies received by the site and dispensed to patients in a XADAGO Study Kit will be maintained by study site personnel.

At the end of the study, all unused XADAGO supplies or XADAGO Study Kits returned by study participants should be inventoried. If any XADAGO Study Kit is lost or damaged, its disposition should be documented. The Sponsor will provide instructions to return the unused study kits to the Sponsor's designee at the end of the study.

10.1.3.2. Patient/Care Partner Accountability

Patients will take XADAGO as directed by the treating physician. Patients/Care Partners will be responsible for obtaining and storing XADAGO medication taken during the study and informing site study staff of any changes.

10.1.4. XADAGO Discontinuation

If an enrolled patient discontinues XADAGO treatment for any reason at any point in the study, the patient is permitted to remain on study and complete the full schedule of assessments per protocol, as long as the patient is otherwise eligible, and is able and willing to continue study participation through the end of the Main Study or the Extension Study, as appropriate. Refer to Section 9.4 for patients who discontinue XADAGO and wish to discontinue the study.

10.2. Parkinson's Disease Medications and Other Medications

Patients will continue taking all prescribed PD medications (e.g., levodopa / carbidopa) including any other prescribed medication as directed by the treating physician. Any changes to prescribed regimen should be reported to study clinic staff.

11. SAFETY MANAGEMENT

11.1. Safety Assessments

The use of XADAGO in this study is not experimental, study procedures are not greater than minimal risk, and safety is not the principal objective of this protocol. In keeping with the Sponsor's requirement, however, to review and report all information relevant to the safety of the marketed drug, XADAGO, about which the Sponsor becomes aware through notification by the investigator and study patients, all AEs spontaneously reported by the patient and/or in response to an open question from the site study personnel or revealed by observation will be recorded at the investigational site for each study patient during his/her active participation in the study.

Additional information regarding AE reporting is available from the following sections of the CFR from the FDA, as well as from the designated website: CFR: §314.80, http://www.fda.gov/medwatchlindex.html.

Please note that the governing Institutional Review Board (IRB) may impose additional safety reporting requirements with which the investigator's site must comply.

11.2. Definition of Adverse Events

11.2.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered related to the product.

11.2.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening
- Patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above

11.3. Relationship to XADAGO

For each AE, the investigator will assess the attribution of XADAGO to the AE and determine whether the AE is or is not related to XADGAO as defined below. When in doubt, the AE should be considered at least "possibly related" until further evidence becomes available to refute this assessment.

- Definitely Not Related
  - Patient did not receive XADAGO, the temporal sequence of the AE onset relative to administration of XADAGO is not reasonable, or there is another obvious cause of the AE.
- Possibly Related
  - There is evidence of exposure to XADAGO and the temporal sequence of the AE onset relative to administration of XADAGO is reasonable, but the AE could have been due to another equally likely cause.
- Probably Related
  - There is evidence of exposure to XADAGO, the temporal sequence of the AE onset relative to administration of XADAGO is reasonable, and the AE is more likely explained by taking XADAGO than by any other cause.
- Definitely Related
  - There is evidence of exposure to XADAGO, the temporal sequence of the AE onset relative to administration of XADAGO is reasonable, the AE is more likely explained by taking XADAGO than by any other cause, and the AE shows a pattern consistent with previous knowledge in the label of XADAGO or similar drug class.

AEs determined by the investigator to be "possibly" or "probably" related will be documented as related to XADAGO for the purposes of expedited regulatory reporting and clinical reporting.

11.4. Recording Adverse Events

AEs spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.

Information about AEs (and SAEs) will be collected from the time the patient signs the informed consent for this study and takes the first study dose of XADAGO until the patient's last follow-up visit. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset date, resolution date, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.2. An AE of severe intensity may not be considered serious.

11.4.1. Non-Serious Adverse Event (AE)

If a non-serious AE occurs for any patient after signing an informed consent for this study and having taken XADAGO, the site should record the AE in the patient's source medical record and eCRF in as real time as possible, but no later than 5 business days of observation or notification that such an event has occurred. The patient's medical record and eCRF should be completed with as much information as is available at that time and the Sponsor will contact the site if additional information is required regarding the non-serious AE. Additional instruction for entering non-serious AE data in the eCRF is provided in the investigator site file (study binder).

11.4.2. Serious Adverse Event (SAE)

All SAEs (related and unrelated) that occur for any patient after signing an informed consent for this study and having taken XADAGO must be recorded by the investigator and reported. The site should record the SAE in the patient's source medical record within 24 hours of observation or notification that such an event has occurred. The patient's medical record should be completed with as much information as is available at that time with the knowledge that full clinical details may not be immediately available. The Sponsor will contact the site if additional information is required regarding the SAE. In addition, an SAE form located in the ISF binder must be completed and submitted to (see Table 1 for details).

All SAEs must be followed until they resolve or stabilize (i.e., a new baseline has been established). The PI must provide the Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the experience and judgment regarding the relationship to XADAGO. Patients who discontinue because of an SAE before study completion will be contacted 7 days (±3 days) after discontinuation to determine if the SAE has resolved, continues unabated, or has reached a new baseline.

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Reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.4.3. Pregnancy and Lactation

Pregnancy is not considered an AE. According to the XADAGO Package Insert, XADAGO is classified as Pregnancy Category C. There are no adequate and well-controlled studies of XADAGO in pregnant women. XADAGO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from safinamide, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

12. STATISTICAL METHODS

12.1. General Statistical Considerations

All assessments will be summarized at specified time points. Continuous variables will be summarized using the number of patients, mean, standard deviation (SD), and minimum, median, and maximum values. Categorical variables will be summarized using the number and percentage. All data will be summarized according to cohort and overall.

Endpoints are defined at Study Day 60 (primary endpoint). Descriptive statistics will be provided for all data collected. All tests of significance, unless otherwise stated, will be performed using a two-sided alpha at 0.05.

All analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

12.2. Analysis Populations

The 2 analysis populations are defined in the study's Statistical Analysis Plan (SAP) as follows:

- Safety Population: All patients who sign informed consent for the study, complete baseline assessments, and receive at least 1 dose of XADAGO.
- Evaluable Population: All patients in the safety population who complete at least the MDS-UPDRS assessment at the Study Day 60 visit.

The principal analysis of the primary endpoint will be conducted for the evaluable population. Sensitivity analysis of the primary endpoint will be carried out for the safety population. Safety summaries will be provided for the safety population.

Eligible, consented, and enrolled study participants will be analyzed based on concomitant PD medication regimen change at Baseline:

Cohort A – Patients that have switched to XADAGO from a Dopamine Agonist

Cohort B – Patients that have switched to XADAGO from an MAO-B inhibitor

Cohort C – Patients that are MAO-B inhibitor naïve

12.3. Sample Size and Decision Rules

This is an observational study that will not assign treatment to patients. Patients will be analyzed collectively and in one of 3 cohorts based on the study entry criteria. A sample size of up to 540 patients was selected to ensure a meaningful representation in each of the 3 cohorts.

12.4. Handling of Missing Values

PROs will handle missing values per the recommended process for that instrument. In general, missing item values for PRO instruments will not be imputed. Missing values will usually result in non-computational item scores for the patient.

Missing visit information will usually be handled by analyzing using last-observation-carried-forward (LOCF) imputations.

12.5. Subgroups and Covariate Adjustment

Age, sex, and disease duration will be included in any subgrouping and/or covariate modeling. When variables are used in modeling, the inclusion in model will only stay if the p-value < 0.10 for those situations.

12.6. Interim Analysis

Interim data analyses will be performed periodically to provide study updates and to support potential presentation of interim results via posters, publications, and other data dissemination vehicles. Since this study is observational only and treatments are not assigned to specific patient/treatment groups, these interim analyses will have no statistical implications.

12.7. Population and Patient Disposition

Frequency of patients enrolled, safety population, and evaluable patients will be displayed. Populations will be reported by cohort, site.

Patient disposition will be summarized in each cohort along with reason of discontinuation. Frequency and percentages of patients completing and discontinuing the study prior to the primary endpoint (Study Day 60) and prior to the last study visit (Study Day 180) will be analyzed.

12.8. Demographic and Baseline Characteristics

Demographic and baseline characteristics will include age, sex, weight, height, body mass index (BMI), race, and vital signs. Baseline characteristics will be detailed for all PROs and will be analyzed descriptively.

12.9. Analysis

12.9.1. Primary Outcome Analysis (Observational Assessments)

The change in MDS-UPDRS, PDQ-39, and MoCA from the Baseline Assessment Visit to the Primary Endpoint (Study Day 60) will be analyzed and described in detail in the SAP.

For the endpoints of CGI-C and PGI-C, the data will be dichotomized to have two categories, with ‘very much improved’ and ‘much improved’ into one category and the remaining levels into the other.

12.9.2. Safety Analysis

Serious and non-serious AEs will be collected as part of this study and reported for each cohort and overall.

13. STUDY MONITORING AND QUALITY CONTROL

13.1. Study Monitoring

The Sponsor is responsible for monitoring the progress of this study and overseeing data quality.

13.2. Inspection of Records

The Sponsor, designated representatives, the IRB, and any applicable regulatory agency will be provided with direct access to all information in original source documents and/or certified copies of original records of clinical findings, observations, or other activities in the clinical study necessary for the reconstruction and evaluation of the study.

13.3. Site Audits

It may be necessary for the Sponsor, designated representatives, and/or a regulatory agency to audit an investigative site. The purpose of an audit is to assess the accuracy, adequacy, and consistency of the study records and patient data, as well as to assess the site's adherence to the procedures described in the study protocol. Direct access must be provided to all information in original source documents (if applicable) and/or certified copies of original records of clinical findings, observations, or other activities in the clinical study necessary for the reconstruction and evaluation of the study.

13.4. Quality Control

14. ETHICS

This study will be conducted according to US CFRs dealing with Protection of Human Subjects (US 21 CFR Part 50) and IRBs (US 21 CFR Part 56); the Nuremberg Code; and the Declaration of Helsinki, revised version of Fortaleza, Brazil, October 2013 (in compliance with FDA guidance).

14.1. Ethics Review

The US FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to regulations and guidance issued by the FDA and are included in the following parts of the US CFR and guideline document:

- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 314.80 - Post-marketing reporting of adverse drug experiences

Copies of these materials can be downloaded from the FDA's website at www.fda/gov.

The purpose of these regulations, legal obligations, and guidelines is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

14.2. Ethical Conduct of the Study and Institutional Review Board (IRB) Approval

The Sponsor of this study is responsible for selecting qualified investigators, providing investigators with the information needed to properly conduct a study, properly monitoring the study, and ensuring that the FDA and all participating investigators are properly informed of significant new information regarding post-marketing adverse drug experiences or risks associated with the marketed drug XADAGO.

Before the study can be initiated, the PI must obtain written IRB approval from the IRB of the PI's institution and/or a central IRB (whichever is applicable) that complies with the requirements relating to IRBs. The final study protocol and final version of the Informed Consent Form (ICF) must be approved or given a favorable opinion in writing by an IRB as appropriate. The PI must submit written approval to the Sponsor (or designee) before he/she can enroll any patient into the study.

If an amendment(s) to the study protocol becomes necessary, the Sponsor will provide the protocol amendment(s) and the PI will submit the written amendment(s) to his or her IRB for approval before amendment implementation. In addition, the PI's IRB must approve all site-specific advertising used to recruit patients for the study. Re-approval by the IRB must be obtained annually, if the study is more than 1 year in duration.

Progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The PI is also responsible for providing the IRB with reports of all unanticipated problems involving risk to human patients or others, including serious and non-serious AEs.

14.3. Written Informed Consent and HIPAA Authorization

The PI at each research site will ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Attention is directed to the basic elements that are required in the informed consent and process under US CFR for Protection of Human Subjects (21 CFR 50.25 and/or ICH E6 4.8.10). Patients must be told that they may withdraw from the study at any time. The patient should have ample opportunity to ask questions and should be allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before any study procedures are conducted. Patients may require Care Partner support to be considered eligible for the study (e.g., needs help in physically completing assessments or requires assistance with transportation to clinic visits), but must be cognitively capable of communicating and providing responses to questions. Care Partners, if willing, may also need to sign the informed consent form indicating their willingness to assist the patient as necessary. Patients who refuse to participate or who withdraw from the study will be provided care and treated without prejudice.

The PI must maintain the original, signed, and dated ICF. A copy of the fully executed ICF must be given to the patient.

Each patient must also sign a HIPAA Authorization form before his/her participation in the study. A signed copy must be provided to the patient and a signed original shall be maintained in the patient's clinical file.

14.4. Investigator Obligations

The following is a list of key PI responsibilities during the study. A more detailed discussion of investigator obligations may be found in the US 21 CFR Part 50.

- The PI must ensure that the study is conducted according to the protocol as written and must protect the rights, safety, and welfare of study patients in their care. Only the Sponsor may modify the protocol. If a protocol amendment (and perhaps a new ICF) is needed, the Sponsor will prepare the documents and guide all investigators through the amendment process.
- The PI is required to maintain complete and accurate study documentation in compliance with current good documentation standards and make such documentation available as requested in the event of an inspection, review, or audit of the clinical research facility by the Sponsor, its representatives, and/or any appropriate regulatory agencies.
- In accordance with FDA reporting requirements, the PI and site personnel are required to collect, document, and report all SAEs and noteworthy AEs during the study and, under special circumstances, thereafter (as described in Section 9.4 and Section 11.4.2 of this protocol).

15. DATA MANAGEMENT

All data collected in the context of this study will be stored and evaluated in accordance with regulatory requirements and applicable guidance for electronic records.

15.1. Data Capture

Investigative sites will be provided secure access to a 21 CFR Part 11-compliant eCRF and eCOA system(s) for collecting patient data. All information recorded in the eCRF must be supported by source documentation in the patient's medical file unless the electronic entry is the original entry (e.g., assessments completed through electronic device). The patient's source file must include (but is not limited to) the following:

- An entry documenting that the patient signed and dated an ICF and HIPAA authorization form before entry into and participation in the study
- Patient study identification number and protocol number
- Medical diagnosis and entries for all treatment and medications
- Summaries of all clinic visits including those for study purposes
- Documentation of all SAEs and noteworthy AEs

15.2. Retention of Patient and Administrative Records

The Sponsor (or designee) will be allowed to conduct site visits to study facilities for the purpose of monitoring and auditing any aspect of the study. The PI must also allow the IRB and any applicable regulatory agency direct access to all study-related facilities and materials, including original source documents and/or certified copies of original records of clinical findings, observations, or other activities relevant to the study and necessary for the reconstruction and evaluation of study conduct.

The study site must provide the Sponsor with the following essential documents prior to study initiation and retain a copy in its study files:

- Current curriculum vitae for the PI
- Sponsor-approved protocol and protocol amendments signed and dated by the PI
- Written IRB approval of the protocol and protocol amendments
- IRB membership roster or assurance number
- ICF and HIPAA authorization form approved by the IRB and accepted by the Sponsor
- Fully executed Clinical Trial Agreement between the Sponsor and the site

In addition to the documents listed above, the site must also retain the following items:

- All original ICFs/HIPAA authorizations fully signed and dated
- All IRB approvals and correspondence (e.g. informed consent [including any approved revisions], protocol, AEs [including SAEs] advertisements, newsletters)

- Copies of all correspondence (emails, faxes, postal mail) pertaining to the study from the Sponsor and IRB and other relevant parties
- Copies of all safety-related information
- Study personnel signature and delegation of authority log for the site
- A separate file containing the Clinical Trial Agreement and related financial correspondence between the Sponsor and the site

The PI and/or study site must retain copies of all pertinent study information, essential documents, and study data records (e.g., eCRFs, eCOAs, original data, patient identification lists, etc.) for a minimum period of 2 years after the study database lock and closure or until notified, in writing, by the Sponsor that these documents/copies are not needed.

If record retention at the investigative site is no longer possible, or if the investigative site or study records are relocated, the Sponsor must be notified immediately in writing with the address of the new storage location.

16. CONFIDENTIAL INFORMATION

16.1. Confidentiality of Study Data

Confidential information refers to any information provided to your site by the Sponsor or its agents that has not been previously published. This includes, but is not limited to, the study protocol (and protocol amendments, if any), eCRFs (if applicable), assay methods, and basic scientific data. Any data collected at the site during the study are also considered confidential. All confidential information remains the sole property of the Sponsor, may not be disclosed to others without prior written consent from the Sponsor, and may not be used except in the performance of this study. The PI is required to provide the Sponsor with complete test results and all data obtained during this study. At the discretion of the Sponsor, the information from this study may be made available to any applicable regulatory agency and/or other physicians who are conducting similar studies.

16.2. Confidentiality of Patient Records

To maintain patient confidentiality, all laboratory results (if applicable), eCRFs (if applicable), reports, and other records will be coded using patient identification numbers. Only research staff and Sponsor officials will have access to the records. Patient information will not be released without written permission, except as necessary for monitoring by the Sponsor or a regulatory agency.

By participating in this protocol, the PI and research site agree that within local regulatory restrictions and ethical considerations, the Sponsor or any regulatory agency may consult and/or copy study documents to verify eCRF data.

Patient confidentiality will be maintained in any publications or presentations that result from this study.

17. PUBLICATION POLICY

The Sponsor recognizes the importance of communicating medical study data and therefore encourages publication of such data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study are described in the Clinical Trial Agreement between the Sponsor and the PI or his/her institution.

18. REFERENCES

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