Official Title: A Double-Blind, Randomized, Three-Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine Versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients With Parkinson's Disease (gLIDe)

NCT Numbers: NCT03922711

Document Date: 19 Nov 2019

CLINICAL STUDY PROTOCOL

IND NUMBER: 141222

A Double-Blind, Randomized, Three-Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)

PL101-LID201

Sponsor:	Prilenia Therapeutics
Sponsor Contact:	[redacted] Head of Clinical Operations
Medical Monitor:	[redacted]
Version of Protocol:	2.0 (Protocol Amendment 1)
Date of Protocol:	19 Nov 2019
Previous Versions and Dates:	Original (1.0), 14 Jan 2019 Final (1.1), 24 Jan 2019

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A Double-Blind, Randomized, Three Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)
Protocol Number	PL101-LID201
Protocol Date	19 Nov 2019

Protocol accepted and approved by:

Head of Clinical Operations (for Sponsor)

[redacted]

Prilenia Therapeutics
Head of Clinical Operations

[redacted]

Signature

19 Nov 2019

Date

Protocol Approval – Sponsor Signatory

Study Title	A Double-Blind, Randomized, Three Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)
Protocol Number	PL101-LID201
Protocol Date	19 Nov 2019

Protocol accepted and approved by:

Chief Medical Officer (for Sponsor)

[redacted]
Prilenia Therapeutics

[redacted]

19 Nov 2019
Date

Protocol Approval – Lead Statistician

Study Title A Double-Blind, Randomized, Three Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)

Protocol Number PL101-LID201

Protocol Date 19 Nov 2019

Protocol accepted and approved by:

Lead Statistician (for Sponsor)

[redacted]

Signature

19 NOV 2019

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Double-Blind, Randomized, Three Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 2.0, dated 19 Nov 2019, the International Council for Harmonisation harmonized tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Prilenia Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Prilenia Therapeutics.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Summary of Changes

Protocol Amendment History and Reasons for Amendment

Version	Date	Reason for Amendment
Version 1.0	14 Jan 2019	Original Protocol
Version 1.1	24 Jan 2019	• Administrative updates were made to the cover page, signatory pages, synopsis, Section 5.7 (Blinding), Section 6.5.1.6 (Suspected Unexpected Serious Adverse Reactions and Nonserious Adverse Events of Special Interest), Section 9.1, (Independent Ethics Committee or Institutional Review Board), and Section 11.3 (Study Termination) • A summary of changes was added • Exclusion criterion 20 was updated to prohibit the use of cannabis within 3 months (instead of 6 months) prior to baseline. • Creatinine clearance stopping rules were added • It was added that patients with CrCL <50 mL/min/1.73 m^2 at any time point after Baseline (Visit 2) will be requested to return to the clinic for an unscheduled visit 1 week later to repeat the CrCL test. If the repeated CrCL value is confirmed to be <50 mL/min/1.73 m^2, the patient will be discontinued from the study treatment. Any decrease in CrCL that is judged by the investigator as a clinically significant change (worsening) from Baseline (Visit 2) result will be considered an AE.
Version 2.0	19 Nov 2019	• Significant updates were made to the cover page, signatory pages, synopsis, Section 1.1.3 (Current Available Pharmaceutical Options for the Treatment of LID), Section 2 (Study Objectives), Section 3 (Investigational Plan), Section 4.1.1 (Inclusion Criteria), Section 4.1.2 (Exclusion Criteria), Section 4.2.1 (Reasons for Withdrawal/Discontinuation, Section 5.2 (Treatments Administered), Section 5.3 (Dose Modifications – new section), Section 5.4.1 (Study Treatment Packaging, Storage, and Dispensing), Section 5.4.3 (Study Treatment Accountability), Section 5.10 (Prior and Concomitant Therapy), Section 6, Table 4 (Schedule of Assessments), Section 6.2 (Efficacy Assessments), Section 6.5.1.6 (Suspected Unexpected Serious Adverse Reactions and Nonserious Adverse Events of Special Interest, 6.5.2 (ECG: QTc Parameters), 7.2 (Secondary Efficacy Endpoints), 7.4 (Exploratory Endpoints), 7.10.3 (Analyses of Exploratory Endpoint), 8.1 (Data Management), Appendix 13.1 (Visit Assessments and Procedures Flow – Baseline [Visit 2]), Appendix 13.2 (Visit Assessments and Procedures Flow – Visit 3-Visit 7) • The protocol title was updated • The summary of changes was updated • Inclusion criterion 4 was updated to include patients with Hoehn and Yahr stage 4 or less, such that the patient can complete the study assessment • Inclusion criterion 5 was modified to remove the specification of mild

Version	Date	Reason for Amendment
		to moderate LID • Inclusion criterion 6 was modified to remove the use of the Abnormal Involuntary Movement Scale during the screening (visit 1) and replace it with the Unified Dyskinesia Rating Scale, Part 4 – Disability Scale • Inclusion criterion 8 was updated to reflect that patients must experience all motor states during concordance testing • Inclusion criterion 9 was added to note that patients who are stable on a daily dose of ≤200 mg amantadine must be off this treatment at least for weeks prior to certain screening assessments • Inclusion criterion 10 was updated to reflect multiple anti-Parkinson's disease treatments and specify stability during the 12-week maintenance period • Exclusion criterion 3, requiring documentation of severe dyskinesia by the investigator, was removed • Exclusion criterion 5 was updated to specify arterial hypotension as an orthostasis symptom • Exclusion criterion 11, excluding the use of amantadine products within 6 weeks prior to Screening, was removed • Exclusion criterion 13 was modified to require a Mini-Mental State Examination (MMSE) score of <24 (not including dementia) • Exclusion criterion 20 was updated to prohibit the use of all oral cannabinoids, with the exception of topical formulations of cannabidiol, within 28 days prior to Baseline • Exclusion criterion 23 was updated to reflect the use of body surface area adjustment for creatinine clearance • Study design and duration was updated to reflect a minimum 3-week and up to 9-week screening period, a 4-week up-titration period, a 12-week maintenance treatment period, and a 4-day down-titration period • The study design was updated to reflect the requirement for patients to complete dosing diaries to record their study treatment intake during the 16-week active treatment period • The 39-item Parkinson's Disease questionnaire, Parkinson's Disease Sleep Scale, and Non-Motor Symptom Scale and all associated endpoints and analyses were removed • The study treatment, dosage, and packaging sections were updated to reflect amended study periods (4-week up-titration period, 12-week maintenance treatment period, and 4-day down-titration period)

For details of Protocol Amendments 1 and 2, see Section 13.3.

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[redacted]

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Protocol Synopsis

Protocol Number:	PL101-LID201
Title:	A Double-Blind, Randomized, Three Arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine versus Placebo for the Treatment of Levodopa-Induced Dyskinesia in Patients with Parkinson's Disease (gLIDe)
Sponsor:	Prilenia Therapeutics [redacted]
Study Phase:	2B
Study Sites:	Approximately 42 sites in the United States
Indication:	Levodopa-induced dyskinesia in patients with Parkinson's disease (PD-LID)
Rationale:	The most widely used and effective therapy for the treatment of Parkinson's disease (PD) is a 3,4-dihydroxyphenylalanine (L-DOPA). Over time, however, chronic L-DOPA therapy is complicated by the development of levodopa-induced dyskinesia (LID), which can severely impact function and quality of life. The first and only drug approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy is amantadine (Gocovri™ extended-release capsules). However, Gocovri™ is associated with significant side-effects including hallucinations, narcolepsy, psychosis, impulse control/compulsive behavioral disturbances as well as withdrawal-emergent hyperpyrexia and confusion. There remains a significant need for effective, safe, and tolerable treatment options for patients with PD who suffer from LID. Preclinical studies using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) macaque model suggest pridopidine can effectively reduce PD-LID in a dose-dependent manner [redacted] Furthermore, this benefit is not associated with any worsening of Parkinsonian features. In previous clinical trials in Huntington Disease (HD), pridopidine at doses up to 112.5 mg BID was established to be safe and tolerable. Taken together, these preclinical and clinical data justify testing pridopidine for PD-LID in a clinical study.
Objectives:	**Primary Objective:** 1. To evaluate the efficacy of 2 dosages of pridopidine (100 mg BID and 150 mg BID) vs placebo for the treatment of PD-LID **Secondary Objectives:** 1. To determine if any effects of 2 dosages of pridopidine (100 mg BID and 150 mg BID) on the reduction of LID are associated with changes (worsening or improvement) of Parkinsonian features

2. To evaluate the effect of 2 dosages of pridopidine (100 mg BID and 150 mg BID) vs placebo on global improvement, and activities of daily living in patients with PD-LID

Safety Objective:

1. To evaluate the safety and tolerability of 2 dosages of pridopidine (100 mg BID and 150 mg BID) vs placebo in patients with PD-LID

Pharmacokinetic (PK) Objectives:

1. To evaluate the PK of pridopidine in patients with PD-LID
2. To explore the relationship between pridopidine exposure and dyskinesia

Study Population: **Inclusion Criteria:**

Patients may be included in the study only if they meet all of the following criteria:

1. Male or female patients between 30 and 85 years of age, inclusive
2. Signed an institutional review board (IRB)-approved informed consent form
3. Diagnosis of PD consistent with the UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria
4. Hoehn and Yahr Stage 4 or less in the "ON" state such that the patient can complete the study assessments
5. Documentation of LID by the investigator
6. A Score of 3 on 2 elements of the Unified Dyskinesia Rating Scale (UDysRS) part 4 – Disability Scale
7. Using the three consecutive 24-hour "ON/OFF" home diaries completed prior to Baseline (Visit 2), at least two half-hour time periods between 8:00 AM and 5:00 PM of each 24-hour period are indicated as "ON with dyskinesia"
8. Patient and/or study partner must demonstrate during the screening period an ability to keep accurate home diary entries of PD symptoms ("ON, OFF, and dyskinesia") with <75% concordance with the study rater. During the 4-hour concordance testing, patient must experience all motor states: "ON", "OFF", and at least one period of "ON with dyskinesia"
9. Patients who are stable on a total daily dose of ≤200 mg amantadine must be off this treatment at least 4 weeks prior to the assessment of UDysRS part 4, the concordance testing and the completion of the three consecutive 24-hour "ON/OFF" home diaries which are performed during screening

10. All anti-PD treatments are **stable** for at least 28 days prior to Baseline (Visit 2), including a levodopa preparation administered no less than three times daily, with the same dosing regimen during the 12-week maintenance study treatment period
11. If taking allowed antidepressant or antipsychotic medication, must be on a stable dose for at least 28 days prior to Baseline (Visit 2) and must be kept constant during the study
12. Any other routine and allowed prescription/nonprescription medications and/or nutritional supplements taken regularly must be at stable dosages for at least 28 days prior to Baseline (Visit 2) and remain during study participation
13. Willing and able to comply with study requirements
14. Approval for entry into the study by an independent Enrollment Authorization Committee (EAC)

Exclusion Criteria:

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

1. Diagnosis of atypical Parkinsonism
2. History of exclusively diphasic, "OFF" state, myoclonic, or dystonic dyskinesia without peak-dose choreiform dyskinesia
3. Treatment with dopamine blocking drugs (e.g., neuroleptics, Reglan® [metoclopramide])
4. History of surgical intervention related to PD (e.g., deep brain stimulation, carbidopa-levodopa intra-enteral suspension [CLES; Duopa™]).
5. Presence of clinically significant orthostasis symptoms, e.g., arterial hypotension
6. Clinically significant medical, surgical, psychiatric, or laboratory abnormality in the judgment of the investigator
7. Any physical impairment that by the judgment of the investigator impairs the ability of the patient to complete study assessments
8. History of severe depression, psychosis or hallucinations within 6 months prior to Screening (Visit 1)
9. History of active suicidal ideation as assessed by the investigator or measured by a score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS) within 6 months prior to Screening (Visit 1), or suicidal attempt within 5 years prior to Screening (Visit 1)
10. History of cancer within 5 years prior to Screening (Visit 1), with the following exceptions if adequately treated: non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer

11. Presence of cognitive impairment, as evidenced by a Mini Mental State Examination (MMSE) score of <24 not including dementia during Screening (Visit 1)
12. A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at Screening (Visit 1)
13. Clinically significant heart disease at Screening (Visit 1), defined as follows:
    (i) significant cardiac event within 12 weeks prior to Baseline (Visit 2) (e.g., admission for myocardial infarction, unstable angina, or decompensated heart failure), angina pectoris or episode of congestive heart failure with symptoms > grade 2 New York Heart Association classification, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia
    (ii) history of complex arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (Common Terminology Criteria for Adverse Events grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia
    (iii) symptomatic bradycardia, sick sinus syndrome or atrioventricular block greater than first degree in the absence of a functioning pacemaker
    (iv) unexplained syncope
    (v) Brugada syndrome
    (vi) hypertrophic cardiomyopathy
14. History of congenital long QT syndrome or a first degree relative with this condition
15. History of epilepsy or of seizures within 5 years prior to Baseline (Visit 2)
16. History of clinically significant deficit from stroke or transient ischemic attack within 6 months prior to Screening (Visit 1)
17. Serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at Screening (Visit 1) and considered clinically significantly abnormal by the investigator. Repeat testing is allowed (up to a maximum of three tests) if required to establish whether values are within normal range or not clinically significant
18. Use of all oral cannabinoids (including all preparations containing any cannabinoids, prescribed oral medical marijuana and oral cannabidiol) with the exception of topical formulations of cannabidiol, within 28 days prior to Baseline (Visit 2)
19. Use of medications (within the last 6 weeks prior to Baseline [Visit 2]) that have been demonstrated to prolong the QT interval, or any patients who may require such medications during the course of the study such as but not limited to prohibited antipsychotic medications, tricyclic

antidepressants and/or Class I antiarrhythmic (see Table 3 and Section 5.10.1)

20. Treatment with apomorphine during the 28 days prior to Screening (Visit 1)
21. Body surface area (BSA)-adjusted creatinine clearance <50 mL/min/1.73 m^2 at Screening (Visit 1), calculated using the Cockcroft-Gault equation: [(140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL) × BSA (m^2)/1.73]. Repeat testing is allowed once, if clinically appropriate
22. Alcohol and/or drug abuse within 6 months prior to Screening (Visit 1), as defined by Diagnostic and Statistical Manual – Fifth Edition Text Revision Criteria for Substance Abuse
23. Female patients who are pregnant or breastfeeding
24. Sexually active female patients, who are not surgically sterile or at least 2 years postmenopausal prior to Screening (Visit 1), and do not agree to utilize a highly effective hormonal method of contraception (an intrauterine device or vasectomized male partner is also acceptable), in combination with a barrier method, from Screening (Visit 1) through at least 4 weeks after the completion of study treatment
25. Male patients not using highly effective contraception or not agreeing to continue highly effective contraception through at least 90 days after the completion of study treatment
26. Known allergy to any ingredients of the study treatment or placebo (pridopidine, silicified microcrystalline cellulose, magnesium stearate)
27. Treatment with any investigational product within 30 days of Screening (Visit 1) or patients planning to participate in another clinical study assessing any investigational product during the study
28. Planned elective surgery during study participation

Study Design: Following a minimum of a 3-week and up to 9-week screening period, patients will be randomized in a 1:1:1 ratio into one of the three treatment arms: pridopidine 100 mg BID, pridopidine 150 mg BID or matching placebo. Patients randomly assigned to the active treatment arms will undergo a dosage regimen titration period during which they will be treated with pridopidine 75 mg once every other day (Q48h) for 1 week, followed by pridopidine 75 mg once daily (QD) for 1 week, pridopidine 75 mg twice daily (BID) for the following week, and 100 mg BID for the final fourth week of titration. Maintenance treatment with pridopidine 100 mg BID or 150 mg BID will then continue for an additional 12 weeks. Patients randomly assigned to the placebo arm will receive matching placebo for the duration of the 16-week active treatment period. During the 16-week active treatment period, patients will be requested to complete "Dosing diaries" to record their study treatment intake. Upon completion of the 16-week active treatment period, patients will undergo a 4-day down titration phase, which will be followed by a safety follow-up visit at Visit 8 (2 weeks after completion of the 16-week active treatment period). During the 4-week titration period, for patients who suffer from symptoms indicating worsening of PD, the levodopa regimen may be adjusted until the regimen is optimal according to the

Investigator's judgment. This optimal regimen must be obtained within the 4 weeks titration period and cannot be lower than the levodopa regimen at the time of screening.

The study duration (from first patient randomized to last patient last visit) will be approximately 12 months.

Estimated Study Duration:

The total study duration will be 21 to 27 weeks and will consist of a minimum of a 3-week and up to 9-week screening period; a 16-week active treatment period, consisting of 4-week up-titration period and a 12-week maintenance period; a 4-day down titration period, and a safety follow-up visit (2 weeks after completion of the 16-week active treatment period). Study visits will be conducted at Screening (Visit 1), Baseline (Visit 2), at the **beginning of** Week 5 (Visit 3) and Week 7 (Visit 4), and **at the end of** Week 10 (Visit 5), Week 13 (Visit 6), and Week 16/early termination (ET) (Visit 7) to assess efficacy, PK, and safety. Telephone contacts will be conducted during the titration period on Days 7 of Weeks 1-4 to remind patients to up-titrate their dosage and record any tolerability/safety reports from the patient , and on Days 2 and 4 of Week 17 to remind patients to down-titrate and discontinue the dosing. A safety follow-up visit will be performed at Week 18 (Visit 8). In-clinic unscheduled visits can be performed for safety concerns at any time.

The study duration (from first patient randomized to last patient last visit) will be approximately 12 months.

Efficacy Endpoints:

Primary and all secondary endpoints will be assessed for both the 100 mg BID and the 150 mg BID pridopidine dosages vs placebo in a hierarchical manner.

Primary Endpoint / Outcome Measure:

The primary endpoint is the mean change from Baseline (Visit 2) to Visit 7/ET in the sum of Parts 1, 3, and 4 of the Unified Dyskinesia Rating Scale (UDysRS) while the patient is the peak in "ON" state and judged to be experiencing peak dose dyskinesia.

Secondary Endpoints / Outcome Measures:

1. Mean change from Baseline (Visit 2) to Visit 7/ET in "ON time without troublesome dyskinesia" based on "ON/OFF" home diary completed by the patients during three consecutive 24-hour intervals
2. Mean change from Baseline (Visit 2) to Visit 7/ET in the total UDysRS score (Parts 1 to 4)
3. Proportion of patients improving based on the Patient Global Impression of Change (PGI-C) at Visit 7/ET
4. Mean change from Baseline (Visit 2) to Visit 7/ET in "ON time without any dyskinesia" based on "ON/OFF" home diary
5. Proportion of patients improving based on CGI-C at Visit 7/ET
6. Mean change from Baseline (Visit 2) to Visit 7/ET in the Unified Parkinson's Disease Rating Scale (UPDRS) Part 2

7. Proportion of responders (improvement in dyskinesia and no worsening in motor function) at Visit 7/ET. The improvement in dyskinesia is defined as ≥30% improvement in UDysRS score (Parts 1, 3, and 4) from Baseline (Visit 2) and no worsening from Baseline (Visit 2) in "OFF" is defined as ≤30 minutes increase in "OFF time" from Baseline (Visit 2) per a 24-hour period
8. Mean change from Baseline (Visit 2) to Visit 7/ET in "OFF time" based on "ON/OFF" home diary
9. Mean change from Baseline (Visit 2) to Visit 7/ET in the UPDRS Part 3 as measured immediately prior to the in-clinic L-DOPA dose

Pharmacokinetic Endpoint:

Plasma concentration of pridopidine and its metabolite TV-45065 before and after in-clinic pridopidine dose.

Pharmacogenetic and Plasma Biomarker Endpoints:

1. To analyze the correlation of potential genetic variations and plasma biomarkers with clinical treatment responses to study drug (e.g., efficacy, PK, tolerability, and safety features)
2. To assess potential genetic variation and plasma biomarkers associated with disease progression and severity

Safety Endpoints:

1. Adverse events (AEs) occurring throughout the study
2. QTc parameters: QTcF of >450 msec, >480 msec, and >500 msec mean QTcF, change in QTcF>30 msec and <60 msec or change in QTcF>60 msec throughout the study
3. Clinical safety laboratory (clinical chemistry, hematology and urinalysis), vital signs (including assessment of orthostatic hypotension), physical and neurological examination, and concomitant medications throughout the study
4. Change from Baseline (Visit 2) in suicidality as evaluated with the C-SSRS throughout the study
5. Change from Baseline (Visit 2) in impulse control disorder (ICD) as evaluated by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) throughout the study

<u>Tolerability</u>:

1. The number (%) of patients who complete the study treatment
2. The number (%) of patients who fail to complete the study treatment due to AEs
3. The number (%) of patients who fail to complete the study treatment due to QTcF and QT stopping rules, seizures, or convulsions

Study Treatment, Dosage, and Route of Administration:

Study treatment: oral capsules containing 75 mg and 100 mg of pridopidine.

Control treatment product: identical placebo capsules matching the pridopidine capsules.

Patients will be randomly assigned at Baseline (Visit 2) to receive pridopidine 100 mg BID, 150 mg BID or placebo using a 1:1:1 allocation ratio. Capsules will be swallowed whole with water.

Study treatments and matching placebo will be administered as oral capsules. During the 16-week active treatment period, the first study treatment daily dose will be taken between 6:00 and 8:00 AM and the second study treatment daily dose will be taken 6 to 10 hours after the first study treatment daily dose administration and not later than 5:00 PM. The second study treatment daily dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). As much as possible, study treatment should be taken at the same time throughout the study. Patients assigned to active treatments will undergo a dosage regimen according to the following schedule (allowances for dose reduction are detailed in Section 5.3):

1. Up-titration period:
    a. Week 1 - Patients will receive 75 mg of pridopidine and placebo Q48h
    b. Week 2 - Patients will receive 75 mg of pridopidine and placebo QD (total daily dose: 75 mg)
    c. Week 3 - Patients will receive 75 mg of pridopidine and placebo BID (total daily dose: 150 mg)
    d. Week 4 - Patients will receive 100 mg of pridopidine and placebo BID (total daily dose: 200 mg)
2. Maintenance period:
    a. Weeks 5-16 - • Patients will receive 100 mg BID of pridopidine (total daily dose: 200 mg) or 150 mg BID (total daily dose: 300 mg), as randomized, for 12 weeks.
3. Down-titration period:
    a. Days 1 to 2 - Patients will receive 75 mg pridopidine and placebo BID (total daily dose: 150 mg)
    b. Days 3 to 4 - Patients will receive 75 mg and placebo QD (total daily dose: 75 mg)

Patients randomly assigned to the placebo arm will receive matching placebo throughout the active treatment period in a double-blind fashion at the same dosing schedule as patients assigned to the active treatments.

Based on the evaluation of the safety and tolerability of the 150 mg BID treatment arm by the Drug Safety Monitoring Board (DSMB), the sponsor reserves the right to allocate, in a random manner, newly enrolled patients and/or switch all patients who are still in the titration period to the 100 mg BID dose level.

Sample Size: A sample size of 38 randomized patients in each treatment group (114 randomized patients overall) will provide 80% power to detect a between-group difference of 8.5 points in the UDysRS score with standard deviation of 13 points using a two-sided significance level of 0.05, using an ordinary least squares model. Assuming a drop-out rate of 15%, a total of 135 patients will be randomized. The sample size was calculated based on two sample t-test assuming equal variances in the two groups, using nQuery Advisor version 7.0.

Statistical Methods: Details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan (SAP), which will be approved before breaking the blind of the study.

Analysis Sets

The efficacy analysis will be based on the modified intention to-treat (mITT) set. The mITT set will include all randomized patients who receive a dose of study treatment and have efficacy assessments both at Baseline (Visit 2) and at least one post-randomization time point. The patients will be grouped as randomized.

Safety and tolerability analyses will be based on the safety set. The safety set will consist of all patients receiving at least one dose of study treatment. The patients will be grouped according to the treatment regimen actually received.

Pharmacokinetic analyses will be based on the PK set. The PK set will consist of all patients in the safety set with at least one pridopidine concentration sample result reported.

Statistical Testing Procedure

Each primary and secondary endpoint includes the comparison of each of the two dosages of pridopidine vs placebo. The overall Type I error rate within the family of each primary and secondary endpoint will be maintained by using the Hochberg's step-up method. Furthermore, the primary and secondary endpoint families will be evaluated in a hierarchical manner as described below and will be described in the SAP. For this purpose, the matched parallel gatekeeping procedure will be used.

Primary Analysis

The primary endpoint is the mean change from Baseline (Visit 2) to Visit 7/ET in the UDysRS sum score of Parts 1, 3, and 4, in the "ON" state, will be analyzed using a Mixed Model for Repeated Measures (MMRM) with no imputation using the mITT population. The Baseline (Visit 2) score will be included as a covariate and the treatment group (pridopidine 100 mg BID, pridopidine 150 mg BID or placebo), visit (Visit 4, Visit 5, Visit 6, or Visit 7/ET) and the interaction between treatment group and visit as fixed factors in the MMRM. The difference between each dosage of pridopidine vs placebo at Visit 7/ET will be estimated from the MMRM.

Secondary Analysis

The continuous secondary endpoints (sum scores derived from UDysRS, UPDRS, and endpoints based on the "ON/OFF" home diaries) will be analyzed with MMRM models similar to those used for analysis of the primary endpoint. The mITT population will be used for these analyses.

The categorical secondary endpoints (proportion of responders and proportion of patients improving based on PGI-C or CGI-C) will be analyzed in the mITT population using a generalized linear mixed model (using the using the GLIMMIX procedure from SAS for binomial data with logit link).

PK Analysis

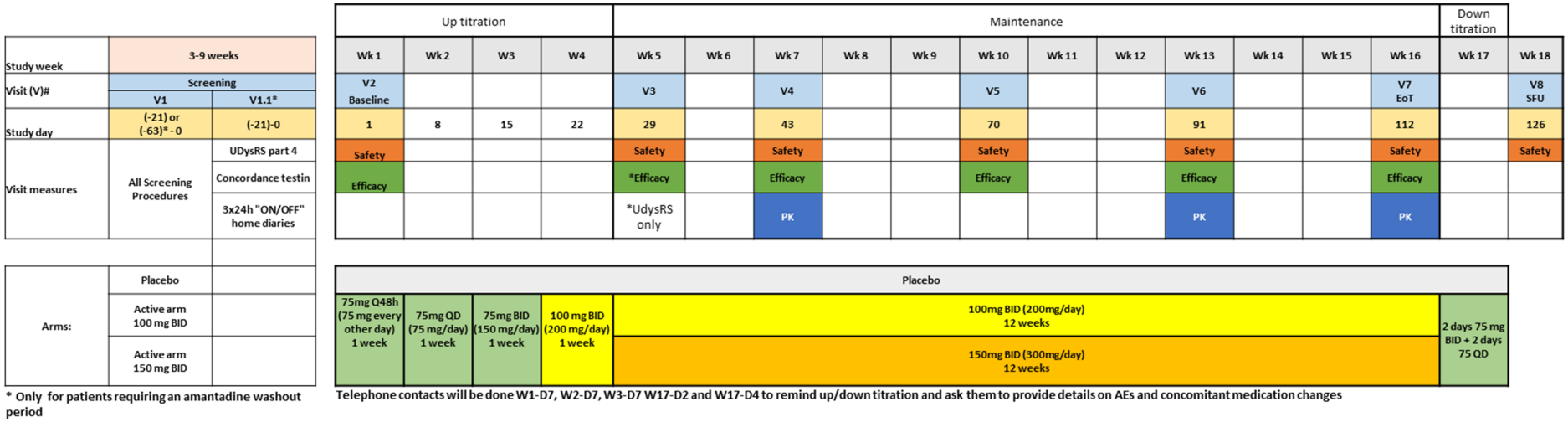
The PK analysis will be conducted on the PK set. Plasma concentrations of pridopidine and its metabolite TV-45065 will be listed and summarized by visit and time point. Descriptive statistics will include the mean, coefficient of variation, geometric mean, minimum, median, and maximum. Relationships between plasma concentrations of pridopidine and TV-45065 at Visit 4, Visit 6, and Visit 7/ET vs key safety and efficacy measures will be explored graphically.

Safety Analysis

The safety analysis will be conducted on the safety set. The treatment-emergent AEs will be coded according to the Medical Dictionary for Regulatory Activities and summarized by treatment group, organ class and preferred term. Further summaries will be done -by seriousness, severity, relationship to study treatment and dose at the time of onset. Other safety endpoints will be summarized with descriptive statistics.

Version and Date of Protocol: 2.0 (Protocol Amendment 1); 19 Nov 2019

S-Figure 1 Study Design



Abbreviations: BID, twice daily; PK, pharmacokinetic; Q48h, once every 48 hours, QD, once daily; SFU, safety follow-up; UDysRS, Unified Dyskinesia Rating Scale; V, visit; Wk, week

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BID	twice daily
BP	blood pressure
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CI	confidence interval
CLES	carbidopa-levodopa enteral suspensions
C_{max}	observed maximum plasma or serum concentration after administration
CrCL	creatinine clearance
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Drug Safety Monitoring Board
EAC	Enrollment Authorization Committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HD	Huntington disease
ICD	impulsive-compulsive disorders
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intention-to-treat
IWRS	interactive web response system
L-DOPA	3,4-dihydroxyphenylalanine
LID	levodopa-induced dyskinesia
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to-treat
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination

Abbreviation	Definition
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NHP	nonhuman primates
OTC	over-the-counter
PD	Parkinson's disease
PD-LID	levodopa-induced dyskinesia in patients with Parkinson-'s disease
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic(s)
Q48H	once every 48 hours
QD	once daily
QTcF	Fridericia-corrected QT
QUIP-RS	Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating-Scale
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale

1 Introduction

1.1 Levodopa-Induced Dyskinesia

1.1.1 Epidemiology

The most widely employed and effective therapy for the treatment of Parkinson's disease (PD) is 3,4-dihydroxyphenylalanine (L-DOPA or levodopa). Over time, however, chronic L-DOPA therapy can be complicated by the development of levodopa-induced dyskinesia (LID), which can severely impact function and quality of life. After 5 years of treatment about 40 to 50% of patients will have developed dyskinesia (Rascol et al 2000), and after 10 years of treatment, the vast majority of patients will have developed dyskinesia depending on the levodopa dose employed (Hauser et al 2007).

Levodopa dosage is one of the main risk factors for the development of dyskinesia. For example, in the ELLDOPA study, 16.5% of patients randomized to a daily dose of 600 mg developed dyskinesia after 9 months of treatment vs 2.3% of patients randomized to a daily dose of 300 mg (Fahn et al 2004). Estimates indicate approximately 40% of patients have dyskinesias after 4 to 6 years of levodopa use (Ahlskog and Muenter 2001). Duration of treatment has also been demonstrated to be an independent risk factor, although this may also reflect disease duration and severity which have been shown to correlate highly with both treatment duration and the rate of dyskinesia. It has also been recognized that LID tend to be more severe and occur more frequently and sooner in patients with a younger age of onset (before the age of 50) (Kumar et al 2005).

1.1.2 Impact on Quality of Life

Dyskinesia can have a major impact on the quality of life of the PD patient. In a public meeting to hear perspectives from PD patients, caretakers and other patient representatives on the most significant effects of their disease, patients commented that despite the benefits of carbidopa-levodopa, they experienced significant side effects. Many patients identified dyskinesia as "more of a problem than the actual symptom [the medication] was treating." Some patients stated that they often questioned whether to continue treatment because of the severity of dyskinesia. Several perspectives were provided on ideal treatments for PD. The top three aspects of ideal treatment desired by commenters included medications with less "off" time (unpredictable exacerbation of symptoms during which medications were less effective), better symptom control, and fewer side effects (FDA 2016).

1.1.3 Currently Available Pharmaceutical Options for the Treatment of LID

The first and only drug approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy is amantadine (Gocovri™ extended-release capsules). In the two clinical studies that formed the basis of US Food and Drug Administration (FDA) approval in August 2017, significant between-group differences in the absolute value changes from

baseline were demonstrated in the mean Unified Dyskinesia Rating Scale (UDysRS) total score (reduction in dyskinesia) at Week 12 in patients treated with Gocovri™ compared with placebo. In Study 301, there was a between-group least-squares means' (LSMEANS) difference in the absolute value changes from baseline between -amantadine and placebo- of -7.9 points (95% confidence interval [CI] = -12.5, -3.3), and in Study 304, there was a least-squares means difference of amantadine versus -placebo of -14.4 points (95% CI = -20.4, -8.3).

However, Gocovri™ is associated with significant side-effects including hallucinations, narcolepsy, psychosis, impulse control/compulsive behavioral disturbances as well as withdrawal-emergent hyperpyrexia and confusion. In controlled studies, the incidence of, e.g., hallucinations was 21% in patients treated with Gocovri™ 274 mg and 3% in placebo-treated patients.

Gocovri™ is also associated with a high incidence of dizziness and orthostatic hypotension - in controlled clinical studies, 16% of Gocovri™-treated patients and 1% of placebo-treated patients reported dizziness, 13% of Gocovri™-treated patients and 1% of placebo-treated patients experienced orthostatic hypotension. Overall 29% of Gocovri™-treated patients and 2% of placebo-treated patients experienced dizziness, syncope, orthostatic hypotension, presyncope, postural dizziness or hypotension.

There is clearly a major unmet need for additional treatment options for levodopa-induced dyskinesia in patients with Parkinson's disease (PD-LID).

1.2 Pridopidine

Pridopidine may fulfill an unmet need in the treatment of dyskinesia based on preclinical studies that support the ability of pridopidine to reduce PD-LID without causing an adverse effect on Parkinsonian features. In addition, clinical studies in patients with Huntington Disease (HD) involving pridopidine at doses up to 112.5 mg twice daily (BID), was established to be safe and tolerable.

1.2.1 Pridopidine in PD-LID

1.2.1.1 Proof of Concept

The gold standard model for the preclinical evaluation of compounds with antidyskinetic potential was used to assess the ability of pridopidine to reduce LID in nonhuman primates. Eight cynomolgus macaques were rendered Parkinsonian by once daily (QD) subcutaneous injection of 0.2 mg/kg 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), administered for 8 to 12 days, until the first appearance of Parkinsonism symptoms. The Parkinsonian syndrome was allowed to stabilize over the next 30 days. Additional administrations of MPTP were given to some animals to titrate to similar degrees of Parkinsonism in individuals across the group. The monkeys were allowed to recover for a minimum of an additional 30 days until

their Parkinsonism was demonstrated as being stable. Animals were then treated with L-DOPA (25 mg/kg) QD for at least 4 months to allow for LID to develop.

Once LID was established, animals were treated with vehicle and three different doses of pridopidine (15, 20, and 30 mg/kg) that were administered via oral-gavage. Treatments were separated by a 1-week washout interval. Following treatment, animal behavior was recorded on HD-video during a 6-hour period. These recordings were used by a movement disorders neurologist blinded to treatment to rate animals for Parkinsonism and dyskinesia.

Doses of 20 and 30 mg/kg demonstrated dose-related anti-LID effects up to 71% at the 30 mg/kg dose. Pridopidine also decreased the duration of ON-time with disabling dyskinesia evoked by L-DOPA by 37% (20 mg/kg dose) and 60% (30 mg/kg dose). On the other hand, pridopidine did not compromise the anti-Parkinsonian benefit of L-DOPA at any of the doses tested.

Effective doses of 20 and 30 mg/kg were associated with geometric mean observed maximum plasma or serum concentration after administration (C_{max}) values of 1487 and 2676 ng/mL, respectively. It was concluded that in the macaque, a pridopidine minimal dose of 20 mg/kg is needed to produce a significant decrease in LID, with higher doses (30 mg/kg) having stronger effect. Pridopidine was shown not to compromise the anti-Parkinsonian benefit of L-DOPA (Johnston et al 2018). The observed dose-response in the macaque model suggests higher efficacy at higher doses. The correlation of the macaque pharmacokinetic (PK) parameters (C_{max}) at effective doses (20 and 30 mg/kg) with known human pridopidine exposure (Table 2) indicates that the 20 mg/kg macaque dose correlates with the human 90 mg BID dose (C_{max} 1487 ng/mL and 1480 ng/mL, respectively), [redacted] Safety and tolerability of pridopidine in humans has been demonstrated up to 112.5 mg BID (highest dose tested).

1.2.1.2 Potential Mechanism of Action

In vitro binding assays to assess pridopidine's affinity to a range of receptors were conducted. Pridopidine was tested in the range of 10 nM – 100 µM.

Table 1 Pridopidine Binding Profile Ranked in Descending Order

Target	IC_{50} (µM)	K_i (µM)	nH
Sigma-1 (σ_1R)	0.14	0.057	0.87
Adrenergic α_{2C}	3.56	1.58	0.76
Dopamine D_3	4.79	1.63	0.90
Serotonin 5-HT_{1A}	6.36	3.63	0.72
Sigma-2 (σ_2R)	7.16	5.45	0.80
Serotonin 5-HT_{2A}	24.5	7.00	0.81
Serotonin 5-HT_7	14.8	8.51	1.02
Adrenergic α_{2A}	22.0	11.0	0.98
Histamine-H_3	37.6	18.3	0.85
Muscarinic-M_2	58.1	24.4	0.62
Dopamine D_2	88.4	29.5	0.94

Abbreviations: IC_{50}, half maximum inhibitory concentration; Ki, inhibition constant calculated using the equation of Cheng and Prusoff; nH, Hill coefficient, defining the slope of the competitive binding curve, was calculated using MathIQTM.

Pridopidine was found to have the highest affinity for the sigma-1 receptor (σ_1R), with a Ki of 57 nM. Moderate affinity binding in the micromolar-range was also evident for adrenergic α_{2C}, dopamine-D_3 and serotoninergic 5-HT_{1A} receptors, with lower-affinity binding to 5-HT_{2A}, 5-HT_7, α_{2A}, histamine-H_3 and muscarinic-M_2 (Table 1). There was only negligible binding of pridopidine to D_2R (Ki 29.5 µM). Additional targets were tested including the N-methyl-D-aspartate, 5-HT_6 and tachykinin NK1 receptors along with the dopamine, norepinephrine and the serotonin-transporters, all of which exhibited no detectable levels of binding (Johnston et al 2018).

In vivo σ_1R and D_2R occupancies were calculated using (i) known binding-affinities of pridopidine to human and rodent receptors in-vitro; (ii) in vivo positron-emission tomography imaging in humans and monkeys; and (iii) the extensive PK profiling of pridopidine in the different species.

Table 2 [redacted]

[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AUC, area under the curve; BID, twice daily; C_{max}, observed maximum plasma or serum concentration after administration; NHP, nonhuman primate; PET, positron-emission tomography; PO, per os.
C_{max} and AUC values for NHP as a function of oral pridopidine dose measured in the macaque (Johnston et al 2018; DPR-2017-016; DPR-2017-099). Human C_{max} and AUC values for 45 and 90 mg BID are from Pride-HD (Study TV7820-CNS-20002) and simulated for 150 mg BID. Human σ_1R and D_2R occupancy at 45 mg BID derived from human PET study TV7820-IMG-10082 and estimated for higher doses. NHP D_2R occupancy data is based on in vivo PET imaging with pridopidine (subcutaneous) using specific D_2R ligand 11C-raclopride (PHA070005). NHP σ_1R occupancy data extrapolated from in vitro binding investigations with 3H-fluspidine, a specific σ_1R tracer, (Johnston et al 2018, supplementary)
[a] Simulated data using the population pharmacokinetic modeling

From Table 2, it is clear that in the macaques, plasma exposures following the ineffective pridopidine dose (15 mg/kg) are associated with full σ1R (>85%) suggesting σ1R engagement alone is unlikely to account for the antidyskinetic benefits of pridopidine that were observed. Exposures following effective doses (20 to 30 mg/kg), while still providing full σ-1-occupancy, provide only modest D_2R-occupancy (25-40%). On the other hand, effective pridopidine doses clearly engage a range of receptors (including adrenergic-α_2C, dopamine-D3 and serotoninergic-5-HT_{1A} sites) to a greater degree than D2 (Johnston et al 2018).

It is hypothesized that the ability of pridopidine to reduce PD-LID possibly involves- a complex pharmacological profile, associated with high σ_1R occupancy together with multiple nonsigma receptors, including adrenergic α_2C, 5-HT_{1A}, and DA receptors.

2 Study Objectives

Primary Objective:

1. To evaluate the efficacy of 2 dosages of pridopidine (100 mg twice daily [BID] and 150 mg BID) vs placebo for the treatment of PD-LID

Secondary Objectives:

1. To determine if any effects of 2 dosages of pridopidine (100 mg BID and 150 mg BID) on the reduction of LID are associated with changes (worsening or improvement) of Parkinsonian features

2. To evaluate the effect of 2 dosages of pridopidine (100 mg BID and 150 mg BID) vs placebo on global improvement, and activities of daily living in patients with PD-LID

Safety Objective:

1. To evaluate the safety and tolerability of 2 dosages of pridopidine (100 mg BID and 150 mg BID) vs placebo in patients with PD-LID

Pharmacokinetic Objectives:

1. To evaluate the PK of pridopidine in patients with PD-LID

2. To explore the relationship between pridopidine exposure and dyskinesia

3 Investigational Plan

3.1 Study Design

This is a Phase 2B, multicenter, randomized, three-arm, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy, safety, and PK of pridopidine 100 mg BID and 150 mg BID vs placebo for the treatment of PD-LID, experiencing dyskinesia.

Following a minimum of a 3-week and up to 9-week screening period, patients will be randomized in a 1:1:1 ratio into one of the three treatment arms: pridopidine 100 mg BID, pridopidine 150 mg BID or exactly matching placebo. Patients randomly assigned to the active treatment arms will undergo a dosage regimen titration period during which they will be treated with pridopidine 75 mg once every other day (Q48h) for 1 week, followed by pridopidine 75 mg once daily (QD) for 1 week, pridopidine 75 mg BID for 1 week, and finally by 100 mg BID for the fourth and final week of titrations. Maintenance treatment with pridopidine 100 mg BID or 150 mg BID will then continue for an additional 12 weeks. Patients randomly assigned to the placebo arm will receive a matched placebo for the duration of the 16-week active treatment period. Upon completion of the 16-week active treatment period, patients will undergo a 4-day down titration phase, which will be followed by a safety follow-up visit at Visit 8 (2 weeks after completion of the16-week active treatment period).

During the 4-week titration period, for patients who suffer from symptoms indicating worsening of PD, the levodopa regimen may be adjusted until the regimen is optimal according to the Investigator's judgment. This optimal regimen must be obtained within the 4 weeks titration period and cannot be lower than the total daily levodopa dose regimen at the time of screening.

The study duration (from first patient randomized to last patient last visit) will be approximately 12 months.

The study design is presented in Figure 1.

Figure 1 Study Design

			Up titration				Maintenance											Down titration	
Study week	3-9 weeks		Wk 1	Wk 2	W3	W4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18
Visit (V)#	Screening		V2 Baseline				V3		V4			V5			V6			V7 EoT		V8 SFU
	V1	V1.1*																		
Study day	(-21) or (-63)* - 0	(-21)-0	1	8	15	22	29		43			70			91			112		126
Visit measures	All Screening Procedures	UDysRS part 4	Safety				Safety		Safety			Safety			Safety			Safety		Safety
		Concordance testin	Efficacy				*Efficacy		Efficacy			Efficacy			Efficacy			Efficacy		
		3x24h "ON/OFF" home diaries					*UdysRS only		PK						PK			PK		
Arms:	Placebo		Placebo																	
	Active arm 100 mg BID		75mg Q48h (75 mg every other day) 1 week	75mg QD (75 mg/day) 1 week	75mg BID (150 mg/day) 1 week	100 mg BID (200 mg/day) 1 week	100mg BID (200mg/day) 12 weeks											2 days 75 mg BID + 2 days 75 QD		
	Active arm 150 mg BID						150mg BID (300mg/day) 12 weeks													

* Only for patients requiring an amantadine washout period

Telephone contacts will be done W1-D7, W2-D7, W3-D7 W17-D2 and W17-D4 to remind up/down titration and ask them to provide details on AEs and concomitant medication changes

Abbreviations: BID, twice daily; PK, pharmacokinetic; Q48h, once every 48 hours, QD, once a day; SFU, safety follow-up; UDysRS, Unified Dyskinesia Rating Scale; V, visit; Wk, week

Study visits will be conducted at Screening (Visit 1), Baseline (Visit 2), **at the beginning of** Week 5 (Visit 3) and Week 7 (Visit 4), and **at the end of** Week 10 (Visit 5), Week 13 (Visit 6), and Week 16/early termination (ET, Visit 7) to assess efficacy, PK, and safety. Telephone contacts will be conducted on Days 7 of Week 1-4 to remind patients to up-titrate their dosage and record any tolerability/safety reports from the patients. Patients will be contacted by the site team on Days 2 and 4 of Week 17 to remind them to down-titrate and discontinue the dosing. A safety follow-up visit will be performed at Week 18 (Visit 8). In-clinic unscheduled visits can be performed for safety concerns at any time, per the discretion of the investigator.

During the study, an independent Drug Safety Monitoring Board (DSMB) will perform an ongoing review of serious adverse events (SAEs) and periodically review accumulating unblinded safety data. Further details are provided in Section 6.6.

3.1.1 Minimum 3-Week and Up to 9-Week Screening Period

After signing an institutional review board (IRB)-approved informed consent document, screening will be performed within a minimum of 21 (3 weeks) days and up to 63 days (9 weeks) prior to Baseline (Visit 2). A review of screened patients to ensure safety and to confirm eligibility will be performed by an Enrollment Authorization Committee (EAC) prior to randomization (see Section 4.1 and Section 6.10).

For patients requiring an amantadine washout period, two screening visits will be required during the screening period: Visit 1 and Visit 1.1. Visit 1, the first screening visit, will be performed up to 9 weeks/63 days prior to Baseline (Visit 2) and Visit 1.1 will be performed no later than on 3 weeks/ Day -21 days prior to Baseline (Visit 2) as defined in Table 4.

For patients not requiring a washout period for any prohibited medication (see Section 5.10.1), only one screening visit will be required during the screening period: Visit 1. As much as possible, this visit should be performed 3 weeks/ 21 days prior to Baseline (Visit 2) as defined in Table 4.

During the screening period (either during Visit 1 or Visit 1.1 depending on the need for amantadine washout), potential patients and any involved caregivers or study partners will be trained by a rater, a qualified study staff member to recognize the different motor states ("ON without dyskinesia," "ON with no troublesome dyskinesia," "ON with troublesome dyskinesia," and "OFF"), and to complete a corresponding "ON/OFF" home diary.

After training, the study rater and the patient will complete an "ON/OFF" diary at half-hour intervals over a 4-hour period to ensure concordance of >75% between the evaluations (e.g., "ON, OFF and dyskinesia") of the rater and the patient. During this concordance testing, patients must experience each of the motor states and at least one time period rated as "ON with dyskinesia". After assurance of >75% concordance, the patients will complete the "ON/OFF home diary" at home during three consecutive 24-hour periods (72 hours total). The patients will send the completed diaries to the site (e.g., via fax, email) up to 1 week before

end of the screening period because these diaries will serve as the baseline motor home diary and for eligibility to participate in the study. Training may be repeated during the screening period to ensure concordance with the rater.

Patients' existing anti-PD medication regimen, including, but not limited to, levodopa oral preparations, must be maintained at a stable dose for at least 28 days prior to Baseline (Visit 2) and for the entire duration of the maintenance treatment duration period. Allowed antidepressant or antipsychotic medication and any other routine allowed prescription/over-the-counter medications and/or nutritional supplements taken regularly, must also maintained at a stable dose for at least 28 days prior to Baseline (Visit 2) and for the entire duration of the treatment duration period.

Details of all assessments performed at the Screening period (Visit 1 and Visit 1.1) are provided in Section 6, Table 4.

3.1.2 16-week Active Treatment Period (Up-titration and Maintenance) and Down-titration Period

IRB-consented- patients who meet eligibility criteria will be randomly assigned at Baseline (Visit 2) to receive pridopidine 100 mg BID, 150 mg BID or placebo using a 1:1:1 allocation ratio. Study treatment and matching placebo will be administered as oral capsules. During the 16-week active treatment period, the first study treatment daily dose will be taken between 6:00 and 8:00 AM and the second study treatment daily dose will be taken 6 to 10 hours after the first study treatment dose administration and not later than 5:00 PM. The second study treatment daily dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). As much as possible, study treatment should be taken at the same time throughout the study. If a patient misses the morning study treatment dose on an in-clinic day, the visit should be rescheduled.

Patients in the active treatment arms will undergo a 4-week dosage regimen titration period during which they will be treated with pridopidine 75 mg Q48h for 1 week, followed by pridopidine 75 mg QD for 1 week, followed by pridopidine 75 mg BID for 1 week, followed by 100 mg BID for 1 week. Telephone contacts will be conducted on Days 3 and 7 of Weeks 1 through 4 to remind patients to up-titrate their dosage and ask them to provide details on AEs and concomitant medication changes. A **one-time** dose reduction for up to 7 days, to the prior dosing level will be permitted, at the Investigator's discretion. Further details of the dosing schedule are provided in Section 5.2.

See Figure 1 for up-titration. The up-titration is the same for both groups to maintain the blind and effectively the 100 mg BID group is in maintenance at the end of the Week 1.

During the 4-week titration period, for patients who suffer from symptoms indicating worsening of PD, the levodopa regimen may be adjusted until the regimen is optimal according

to the Investigator's judgment. This optimal regimen must be obtained within the 4-week titration period and cannot be lower than the levodopa regimen at the time of screening.

Maintenance treatment with pridopidine 100 mg BID or 150 mg BID will then be continued for an additional 12 weeks. During the maintenance period, patients unable to tolerate the study treatment will be allowed a 3-day reduction from BID to QD dosing. This down titration is not permitted in the 7 days before the patient's next site visit and on the day of the site visit itself. Patients will be discontinued if they cannot tolerate the study treatment after the 3-day down-titration during maintenance phase. Further details of the dosing schedule are provided in Section 5.2.

At the end of the maintenance period or at ET, active-treatment patients will undergo a down-titration period during which they will receive one capsule of pridopidine 75 mg and one capsule of placebo BID on Days 1 and 2 followed by one capsule of pridopidine 75 mg and one capsule of placebo QD on Days 3 and 4 of Week 17. Telephone contacts will be conducted on Days 2 and 4 of Week 17 to remind patients to down-titrate, discontinue the dosing, and ask them to provide details on AEs and concomitant medication changes

Patients randomly assigned to the placebo arm will receive matching placebo throughout the treatment period in a double-blind fashion at the same dosing schedule as patients assigned to the active treatments. Details of all assessments performed at during the 16-week active treatment period are provided in Section 6, Table 4.

Based on the evaluation of the safety and tolerability of the 150 mg BID treatment arm by the DSMB, the sponsor reserves the right to allocate, in a random manner, newly enrolled patients to the 100 mg BID dose level and placebo. Patients randomly assigned to the 150 mg BID arm who are still in the titration period could also be switched to the 100 mg BID arm.

3.1.3 Safety Follow-up Visit

A safety follow-up visit will be performed 2 weeks after Visit 7/ET.

3.1.4 Efficacy

Onsite/in-clinic assessments will be scheduled around the second (PM) study daily treatment dose from 11:00 AM through 5:00 PM at time points consistent with each patient's usual levodopa dosing. The "scheduled levodopa dose" is defined as the afternoon levodopa dose prior to which the UPDRS assessment is performed and after which the UDysRS Parts 3+4 assessment is performed. The second study treatment dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). A consistent effort will be made to ensure that all study visits for an individual patient will occur at approximately the same time of the day. The same in-clinic procedural timing will be kept as best as possible for all visits for each patient. Every effort should be made to ensure that, for a given efficacy assessment, all measurements are performed by the same rater for each individual patient for all visits.

An in-clinic assessment of dyskinesia according to UDysRS will be conducted by the study rater at the time points noted in the schedule of assessments (Table 4). At Baseline (Visit 2), all UDysRS parts (Parts 1 to 4) must be assessed before the initial study treatment dose (refer to Appendix 13.1). For the rest of the time points, UDysRS must be assessed as per the in-clinic visit procedural flow in Appendix 13.2. The historical parts of the UDysRS (Parts 1 and 2) will be performed at any time during the visit (at Baseline [Visit 2], at any time before the initial study treatment dose). The objective score (Parts 3 and 4) will be performed at least 30 minutes following the patient's in-clinic dose of levodopa (the "scheduled levodopa dose"), at a time when the patients are normally in an "ON" state and experiencing their peak dose dyskinesia.

Patients will complete an "ON/OFF" home diary for 3 consecutive days before the in-clinic visit at the time points noted in the schedule of assessments (Table 4). The patients will record their motor state ("OFF", "ON with no dyskinesia", "ON with no troublesome dyskinesia", "ON with troublesome dyskinesia", and "asleep") every 30 minutes during the 24-hour period. During this period, patients will also record their anti-PD and study treatment doses. A phone call will be made 4 days before each of these in-clinic visits to remind patients to complete their "ON/OFF" home diaries and bring them to the clinic.

The Unified Parkinson's Disease Rating Scale (UPDRS) Parts 2 and 3 and Patient Global Impression of Change (PGI-C) will be conducted at the time points noted in the schedule of assessments (Table 4). At Baseline (Visit 2), UPDRS Parts 2 and 3 must be assessed before the initial study treatment dose (refer to Appendix 13.1). For the rest of the time points, UPDRS Part 2 and Part 3 must be assessed as per the in-clinic visit procedural flow in Appendix 13.2. UPDRS Part 3 will be measured before the in-clinic levodopa dose (the "scheduled levodopa dose"). Part 2 can be measured at any time during the visit (at Baseline [Visit 2], at any time before the initial study treatment dose).

Additional assessments to be performed include the Clinical Global Impression of Change (CGI-C) and the Patient Global Impression of Change (PGI-C). These additional scales will be assessed at the time points noted in the schedule of assessments (Table 4) and can be measured at any hour during the visit. Details of all efficacy assessments performed during the study are provided in Section 6, Table 4.

3.1.5 Safety

Concomitant medications, laboratory tests, and safety assessments including adverse events (AEs), Columbia-Suicide Severity Rating Scale (C-SSRS), Questionnaire for -Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS), and vital signs (including orthostatic assessment) will be performed at all visits. A 12-lead electrocardiogram (ECG) will be conducted at Screening (Visit 1) and then at Baseline (Visit 2) and every visit thereafter; three consecutive 12-lead electrocardiogram (ECG) evaluations will be conducted before and 1 to 2 hours after the study treatment dose administered at the clinic (approximate C_{max}).

All AEs and concomitant medications will be recorded from Screening (Visit 1) until the last study visit. During all telephone contacts, patients will be asked to provide details on AEs and concomitant medication changes.

Details of all safety assessments performed during the study are provided in Section 6, Table 4.

3.1.6 Pharmacokinetics

PK sampling for levels of pridopidine and its metabolite TV-45065 will be performed at the time points noted in the schedule of assessments (Table 4) (approximately 1 hour before and 1 to 2 hours after the PM pridopidine dose). When coincident with ECG monitoring, PK samples will be collected within 30 minutes after the ECG recording.

Details of all PK assessments performed during the study are provided in Section 6, Table 4.

3.1.7 Pharmacogenetic and Plasma Biomarker Substudy

Patients will sign a separate informed consent form (ICF) for pharmacogenetic and plasma biomarker assessments before any are performed. Participation in this assessment is voluntary and patients can opt out at any time.

Sampling analyses for DNA extraction will be performed only once during the study at Screening (Visit 1) or Baseline (Visit 2). Plasma samples for potential biomarkers research will be collected at the time points noted in the schedule of assessments (Table 4).

3.1.8 Rationale of Study Design

A randomized, double-blind, placebo-controlled, three-arm, parallel-group study design was chosen for this Phase 2B study to allow comparison of safety, tolerability, efficacy, and PK for 2 dosages of the study treatment versus the placebo control arm.

The starting dose was chosen based on prior clinical experience demonstrating that the initiation of treatment with a pridopidine dose of 67.5 mg BID in healthy volunteers (135 mg/day, multiple-ascending dose study) was well tolerated, and that a dose of 45 mg BID (90 mg/day) has a safety profile similar to that of placebo as seen in HD patients.

Pridopidine has the potential to fulfill an unmet need in the treatment of dyskinesia based on preclinical studies that support the ability of pridopidine to reduce LID without causing an adverse effect on Parkinsonian symptoms and in clinical studies of patients with HD involving pridopidine at doses up to 112.5 mg BID, that demonstrate an overall good safety and tolerability profile.

The variables used for assessing PK, safety and efficacy are standard measures in clinical study in PD patients.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 135 patients will be enrolled at 42 sites in the US (45 randomized patients in each treatment group). Patients will be assigned to study treatment only if they meet all the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

1. Male or female patients between 30 and 85 years of age, inclusive

2. Signed an IRB-approved ICF

3. Diagnosis of PD consistent with the UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria

4. Hoehn and Yahr Stage 4 or less in the "ON" state such that the patient can complete the study assessments

5. Documentation of LID by the investigator

6. A score of 3 on 2 elements of the Unified Dyskinesia Rating Scale (UDysRS) part 4 – Disability Scale

7. Using the three consecutive 24-hour "ON/OFF" home diaries completed prior to Baseline (Visit 2), at least two half-hour time periods one between 8:00 AM and 5:00 PM of each 24-hour period are indicated as "ON with dyskinesia"

8. Patient and/or study partner must demonstrate during the screening period an ability to keep accurate home diary entries of PD symptoms ("ON, OFF, and dyskinesia") with >75% concordance with the study rater. During the 4-hour concordance testing, patient must experience all motor states: "ON", "OFF" and at least one period of "ON with dyskinesia"

9. Patients who are stable on a total daily dose of ≤200 mg amantadine must be off this treatment at least 4 weeks prior to the assessment of UDysRS part 4, the concordance testing and the completion of the three consecutive 24-hour "ON/OFF" home diaries which are performed during screening

10. All anti-PD treatments are stable for at least 28 days prior to Baseline (Visit 2), including a levodopa preparation administered no less than three times daily, with the same dosing regimen during the 12-week maintenance study treatment period

11. If taking allowed antidepressant or antipsychotic medication, must be on a stable dose for at least 28 days prior to Baseline (Visit 2) and must be kept constant during the study

12. Any other routine and allowed prescription/nonprescription medications and/or nutritional supplements taken regularly must be at stable dosages for at least 28 days prior to Baseline (Visit 2) and remain during study participation

13. Willing and able to comply with study requirements

14. Approval for entry into the study by an independent EAC (see Section 6.10)

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Diagnosis of atypical Parkinsonism

2. History of exclusively diphasic, "OFF" state, myoclonic, or dystonic dyskinesia without peak-dose choreiform dyskinesia

3. Treatment with dopamine blocking drugs (e.g., neuroleptics, Reglan® [metoclopramide])

4. History of surgical intervention related to PD (e.g., deep brain stimulation, carbidopa-levodopa intra-enteral suspension [CLES; Duopa™])

5. Presence of clinically significant orthostasis symptoms, e.g., arterial hypotension

6. Clinically significant medical, surgical, psychiatric, or laboratory abnormality in the judgment of the investigator

7. Any physical impairment that by the judgment of the investigator impairs the ability of the patient to complete study assessments

8. History of severe depression, psychosis or hallucinations within 6 months prior to Screening (Visit 1)

9. History of active suicidal ideation as assessed by the investigator or measured by a score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS) within 6 months prior to Screening (Visit 1), or suicidal attempt within 5 years prior to Screening (Visit 1)

10. History of cancer within 5 years prior to Screening (Visit 1), with the following exceptions if adequately treated: non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer

11. Presence of cognitive impairment, as evidenced by a Mini Mental State Examination (MMSE) score of <24 not including dementia at Screening (Visit 1)

12. A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at Screening (Visit 1)

13. Clinically significant heart disease at Screening (Visit 1), defined as follows:
    (i) significant cardiac event within 12 weeks prior to Baseline (Visit 2) (e.g., admission for myocardial infarction, unstable angina, or decompensated heart failure), angina pectoris or episode of congestive heart failure with symptoms > grade 2 New York Heart Association classification, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia
    (ii) history of complex arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (Common Terminology Criteria for Adverse Events grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia
    (iii) symptomatic bradycardia, sick sinus syndrome or atrioventricular block greater than first degree in the absence of a functioning pacemaker
    (iv) unexplained syncope
    (v) Brugada syndrome
    (vi) hypertrophic cardiomyopathy

14. History of congenital long QT syndrome or a first degree relative with this condition

15. History of epilepsy or of seizures within 5 years prior to Baseline (Visit 2)

16. History of clinically significant deficit from stroke or transient ischemic attack within 6 months prior to Screening (Visit 1)

17. Serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at Screening (Visit 1) visit and considered clinically significant by the investigator. Repeat testing is allowed (up to a maximum of three tests) if required to establish whether values are within normal range or not clinically significant

18. Use of all oral cannabinoids (including all preparations containing any cannabinoids, prescribed oral medical marijuana and oral cannabidiol) with the exception of topical formulations of cannabidiol, within 28 days prior to Baseline (Visit 2)

19. Use of medications (within the last 6 weeks prior to Baseline [Visit 2]) that have been demonstrated to prolong the QT interval, or any patients who may require such medications during the course of the study such as but not limited to prohibited antipsychotic medications, tricyclic antidepressants and/or Class I antiarrhythmic (see Table 3 and Section 5.10.1)

20. Treatment with apomorphine during the 28 days prior to Screening (Visit 1)

21. Body surface area (BSA)-adjusted creatinine clearance <50 mL/min/1.73 m^2 at Screening (Visit 1), calculated using the Cockcroft-Gault equation: [(140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL) × BSA (m^2)/1.73]. Repeat testing is allowed once, if clinically appropriate

22. Alcohol and/or drug abuse within 6 months prior to Screening (Visit 1), as defined by Diagnostic and Statistical Manual – Fifth Edition Text Revision Criteria for Substance Abuse

23. Females who are pregnant or breastfeeding

24. Sexually active female patients, who are not surgically sterile or at least 2 years postmenopausal prior to Screening (Visit 1), and do not agree to utilize a highly effective hormonal method of contraception (an intrauterine device or vasectomized male partner is also acceptable), in combination with a barrier method, from Screening (Visit 1) through at least 4 weeks after the completion of study treatment

25. Male patients not using highly effective contraception or not agreeing to continue highly effective contraception through at least 90 days after the completion of study treatment

26. Known allergy to any ingredients of the study treatment or placebo (pridopidine, silicified microcrystalline cellulose, magnesium stearate)

27. Treatment with any investigational product within 30 days of Screening (Visit 1) or patients planning to participate in another clinical study assessing any investigational product during the study

28. Planned elective surgery during study participation

4.2 Withdrawal of Patients from Study Treatment and/or the Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through the last safety follow-up visit at Visit 8. If a patient discontinues treatment, they will be encouraged to remain in the study and continue study visits and procedures for the full course of the study without receiving study treatment. Patients who withdraw from the

study before the Visit 7/ET visit and are not willing to continue study visits and procedures for the full course of the study will be asked, to undergo an ET visit that will include all evaluations that were intended to be performed at the final visit.

4.2.1 Reasons for Withdrawal/Discontinuation

Patients are free to withdraw from the study at any time and for any reason without prejudice. The investigator also has the right to withdraw a patient from the study if an intercurrent illness or AE occurred, if the patient did not cooperate, or for any reason concerning the health or well-being of the patient. The reasons for patients not completing the study will be recorded.

Among other reasons, a patient may be discontinued from the study treatment or the study if they meet any of the following stopping rules:

QTcF stopping rules

- QTcF >500 msec (based on the mean value from the triplicate ECG measurements)
- QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from Baseline (Visit 2)
- Patients with QTcF >480 msec or with an increase of QTcF >60 msec from Baseline (Visit 2) will return to the clinic within 48 to 72 hours for repeat evaluation of electrolyte levels and repeat triplicate ECGs to demonstrate reversibility of the effect on QTcF. Decision on discontinuation will be determined by EAC

Creatinine clearance stopping rule

Patients with an adjusted CrCL <50 mL/min/1.73 m^2 calculated by CrCL * BSA/1.73, where CrCL is calculated using the Cockcroft-Gault equation [(140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)] at any time point after Baseline (Visit 2) will be requested to return to the clinic for an unscheduled visit 1 week later to repeat the CrCL test one more time for confirmation. If the repeated CrCL value is confirmed to be <50 mL/min/1.73 m^2, the patient will be discontinued from the study treatment.

The investigator will also withdraw a patient if Prilenia Therapeutics or regulatory authorities terminate the study. If a patient is discontinued because of an AE, the event will be followed until it has resolved.

4.2.2 Handling of Withdrawals

The reason(s) for withdrawal will be documented in the patient's electronic case report form (eCRF). Patients withdrawing from the study will be encouraged to complete the same final evaluations as patients completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who completed the study. Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts

must be documented in the patient's file. The sponsor has the right to terminate the study at any time in case of serious AEs (SAEs) or if special circumstances concerning the study treatment or the company itself occur, making further treatment of patients impossible. In this event, the investigator(s) will be informed of the reason for study termination.

4.2.3 Replacements

Patients who withdraw, are withdrawn by the investigator, or are lost to follow-up after randomization will not be replaced.

5 Study Treatments

The study treatment will be oral capsules containing 75 mg and 100 mg of pridopidine and matching placebo capsules (as the control treatment product) identical in appearance.

Pridopidine capsules contain the active ingredient pridopidine (75 mg or 100 mg) and inactive excipients. The excipients are [redacted].

The investigational product will be produced and packed in 60 count bottles provided by [redacted]

The secondary packaging and labeling of study treatment will be performed by [redacted] All packaging and labeling operations for study treatment will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bottles containing the investigational product or placebo capsules will be packed in kits. Each medication kit will contain two distinct labeled bottles in accordance with the associated treatment arm. Both outer pack and bottles will be labeled with a unique pack number.

Four types of kit will be prepared for use in this study:

- Kit type 1: One bottle of 75 mg pridopidine and one bottle of placebo
- Kit type 2: One bottle of 100 mg pridopidine and one bottle of placebo
- Kit type 3: Two bottles of 75 mg pridopidine
- Kit type 4: Two bottles of placebo

5.1 Method of Assigning Patients to Treatment Groups

Patients will be randomly assigned at Baseline (Visit 2) to receive pridopidine 100 mg BID, 150 mg BID or placebo using a 1:1:1 allocation ratio.

An interactive web response system (IWRS) will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential patient randomization numbers to treatment codes.

5.2 Treatments Administered

Study treatments and matching placebo will be administered as oral capsules. During the 16-week active treatment period, the first study treatment daily dose will be taken between 6:00 and 8:00 AM and the second study treatment daily dose will be taken 6 to 10 hours after

the first study treatment dose administration and not later than 5:00 PM. The second study treatment daily dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). As much as possible, study treatment should be taken at the same time throughout the study.

Capsules will be swallowed whole with water. Study treatment can be taken irrespective of meals.

If a patient misses a study treatment dose(s) on a non-clinic day, the following guidelines should be followed:

- If the first study daily treatment dose is missed, it can be taken up to 11:00 AM that day. If it is not taken by 11:00 AM, the first study daily treatment dose should be skipped, and the patient continues to the normal dosing schedule
- If the second study daily treatment dose is missed, it can be taken up to 5:00 PM that day. If it is not taken by 5:00 PM, the second study daily treatment dose should be skipped, and the patient continues to the normal dosing schedule the following day

If a patient misses the morning study treatment dose on an in-clinic day, the visit should be re-scheduled.

Patients randomized to each of the active treatment arms, **pridopidine 100 mg BID or 150 mg BID** will receive the following during these designated periods in the study (as per the schedule detailed in Section 5.4.1):

1. Up-titration-period (Weeks 1 through 4)

    a. Week 1-3: One kit type 1 (one bottle of 75 mg pridopidine capsules and one bottle of placebo capsules in a blinded fashion):

        i. Week 1 (Days 1-7) - patients will receive one capsule of study medication from each of the 2 bottles, every other day (Q48h) (either AM or PM).

        ii. Week 2 (Days 8-14) - patients will receive one capsule of study medication from each of the 2 bottles, once per day (QD) (either AM or PM). The total daily dose will be 75 mg pridopidine.

        iii. Week 3 (Days 15-21)- patients will receive one capsule of study medication from each of the 2 bottles, twice per day (BID). The total daily dose will be 150 mg pridopidine.

    b. Week 4: One kit type 2 (one bottle of 100 mg pridopidine and one bottle of placebo in a blinded fashion):

i. Week 4 (Days 22-28) - patients will receive one capsule of study medication from each of the 2 bottles, BID. The total daily dose will be 200 mg pridopidine.

2. Maintenance period (Weeks 5 to 16) –

   a. **100 mg BID arm**, patients will receive 3 kits type 2 (each comprises one bottle of 100 mg pridopidine capsules and one bottle of placebo capsules in a blinded fashion), in total 3 kits for 12 weeks.

      i. Weeks 5 -16 (Days 29 to 112) - patients will receive one capsule of 100 mg pridopidine and one capsule of placebo, one capsule from each of the 2 bottles, BID (total daily dose of 200 mg pridopidine). On Day 1 of Week 5 (Day 29), the first daily dose patients will take before coming to Visit 3 is from the up-titration kit they used during Week 4.

   b. **150 mg BID arm**, patients will receive 3 kits type 3 (each comprises 2 bottles of 75 mg pridopidine capsules in a blinded fashion), in total 3 kits for 12 weeks.

      i. Weeks 5-16 (Days 29 to 112) - patients will receive 2 capsules of 75 mg pridopidine, one capsule from each of the 2 bottles, BID (total daily dose of 300 mg pridopidine).

3. Down-titration period (Week 17)-

   a. Patients will receive one kit type 1 (one bottle of 75 mg pridopidine capsules and one bottle of placebo capsules in blinded fashion):

      i. Week 17 (Days 1 to 2) - patients will receive one capsule of study medication from each of the 2 bottles, BID. The total daily dose will be 150 mg pridopidine.

      ii. Week 17 (Days 3 to 4) - patients will receive one capsule of study medication from each of the 2 bottles, QD (either AM or PM). The total daily dose will be 75 mg pridopidine.

Patients randomized to the **placebo treatment arm** will receive the following during these designated periods in the study (as per schedule detailed in Section 5.4.1):

1. Up- titration period (Weeks 1 through 4)
    a. Weeks 1 – 3: One kit type 4 (two bottles of placebo in blinded fashion):
        i) Week 1 (Days 1-7) - patients will receive 2 capsules of placebo (one capsule from each of the 2 bottles), every other day (Q48h) (either AM or PM).
        ii) Week 2 (Days 8-14) - patients will receive 2 capsules of placebo (one capsule from each of the 2 bottles), once per day (QD) (either AM or PM).
        iii) Week 3 (Days 15-21) - patients will receive 2 capsules of placebo (one capsule from each of the 2 bottles), twice per day (BID).
    b. Week 4: One kit type 4 (two bottles of placebo in blinded fashion):
        i) Week 4 (Days 22-28) - patients will receive 2 capsules of placebo (one capsule from each of the 2 bottles), twice per day (BID).
2. Maintenance period (Weeks 5 to 16) –
    a. Patients will receive 3 kits type 4 (each comprises 2 bottles of placebo) , in total 3 kits for 12 weeks.
        i) Week 5-16 (Days 29 to 112) - patients will receive 2 capsules of placebo (one capsule from each of the 2 bottles), BID. On Day 1 of Week 5 (Day 29), the first daily dose patients will take before coming to Visit 3 is from the up-titration kit they used during Week 4.
3. Down-titration period (Week 17):
    a. Patients will receive one kit type 4 (two bottles of placebo in blinded fashion):
        i. Week 17 (Days 1 to 2) - patients will receive two capsules of placebo (one capsule from each of the two bottles), BID.
        ii. Week 17 (Days 3 to 4) - patients will receive 2 capsules of study medication (one capsule from each of the 2 bottles), QD (either AM or PM).

5.3 Dose Modification

5.3.1 Up-titration Period

During the 4-week titration, a one-time dose reduction, for up to 7 days, to the prior dosing level will be permitted, at the Investigator's discretion. After this down-titration, the normal up-titration schedule must be resumed, and patients who still do not tolerate study treatment will be discontinued.

- If the dose reduction occurs during Weeks 1 through 3, the Investigator should instruct the patient to continue to use the same kit

- If the dose reduction occurs in the fourth week of the up-titration period (Week 4), the Investigator should instruct the patient to dose from the kit used during Weeks 1 through 3.

5.3.2 Maintenance Period

During the maintenance period, patients unable to tolerate the study treatment will be allowed a 3-day reduction from BID to QD dosing. This down titration is not permitted in the 7 days before the patient's next site visit and on the day of the site visit itself. Patients will be discontinued if they cannot tolerate the study treatment after the 3-day down-titration during maintenance phase.

5.4 Management of Clinical Supplies

5.4.1 Study Treatment Packaging, Storage, and Dispensing

Pridopidine and matching placebo will be prepared in bottle packs and shipped by [redacted]. Each patient will receive a total of 6 different kits during the following periods of the study:

At Baseline (Visit 2) – 2 kits for the up-titration- (Weeks 1 to 4)

Maintenance period of 12 weeks – Visits 3, 5, 6, and 7

1. At Visit 3 (Week 5) – patients will return the 2 kits used during up-titration (Visit 2) and 2 new kits will be dispensed for a period of 8 weeks (Weeks 5-12).
2. At Visit 5 (Week 10)– patients will return the 2 kits dispensed at Visit 3 for accountability. Bottle with unused capsules will be returned to the patient to continue using during Weeks 11 and 12, and a new kit will be dispensed to use during Weeks 13, 14, 15, and 16. The patient will be sent home with 2 kits; a used kit that was originally dispensed at Visit 3, and a new dispensed kit.

1. At Visit 6 (Week 13) – patients will return the two kits provided to them from Visit 5 for accountability. Unused bottles will be re-dispensed to the patients following the accountability to use during Weeks 14, 15, and 16. The patient will be sent home with one kit that was dispensed at Visit 5.

At Visit 7/ET– Patients will return the one kit from Visit 6. An additional kit will be dispensed for the down-titration- period (Week 17, Days 1 to 4)

5.4.2 Storage Conditions for Study Treatment and Security

All medication supplied in connection with this study (pridopidine and placebo) must be used only for this study and no other purpose.

At each investigational site, the study treatments will be kept at 15 to 25 ºC in a secure, limited-access, controlled storage area. Only authorized personnel will have access to the study treatments. The study personnel at each site will be responsible for the correct storage and handling of the study treatments.

Study treatment is packed in drug kits. Patients will be provided with sufficient drug supplies to cover the period until their next study visit. Each drug kit for maintenance period will contain drug capsules sufficient for 28 + 2 days to accommodate the flexible visit windows.

Each drug kit will be labelled with the protocol number, storage information, warning language (i.e., as required by local legislation for investigational drug products), dosing and storage instructions.

The Investigator is responsible for recording the receipt and use of all drugs supplied, and for ensuring the supervision of the storage and allocation of these supplies. Full accountability will be performed for all used and unused study treatment.

5.4.3 Study Treatment Accountability

During the 16-week active treatment period, patients will be requested to complete “Dosing diaries” to record their study treatment intake. The diaries will be dispensed at Visits 2, 3, 4, 5, 6, and 7. Diaries will be returned at each subsequent visit.

The investigator will maintain accurate records of receipt of all study treatment, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study treatment will be reconciled and retained or destroyed according to applicable regulations.

5.4.4 Other Supplies

Study sites will be supplied with the home diaries and all scales.

5.5 Overdose Management

The determination of an overdose will be left to the discretion of the investigator, based on the quantity of overdose, emergence of any clinical signs and symptoms suggestive of toxic administration, as well as his/her own clinical judgment as it applies to each individual case. Discovery of overdose within 1 hour may warrant induction of emesis, followed by supportive care and observation in a controlled medical setting.

Any overdose, with or without associated AEs, must be promptly reported to the Sponsor [redacted] in an expedited manner using the SAE Report form and following the procedure described in Section 6.5.1.5.

5.5.1 Medication Errors

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures.

In the event of medication error, appropriate therapy for the patient's symptoms and clinical status should be provided.

5.5.2 Treatment of Medication Errors

Not applicable.

5.6 Misuse for Illegal Purposes

Not applicable.

5.7 Off-Label Use

Not applicable.

5.8 Blinding

This is a double-blind study. Patients, investigators, the treating physician who will view clinical laboratory reports and assess AEs, and safety information and an independent evaluating physician, responsible for performing efficacy assessments, and anyone else involved in the study, with the exception of the individuals responsible for sample bioanalysis and PK analysis, will all be blinded. The prolactin should be blinded to all the clinical staff, Prilenia Therapeutics and/or its designee. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members supporting the unblinded data review by the DSMB will know who received study treatment and who received placebo during the study. The DSMB will review the data in an unblinded fashion**.**

The PK scientist will not have access to randomization codes. Unblinding can be performed upon request for reasons related to safety as described in Section 5.8.1.

5.8.1 Breaking the Blind

If a patient is unblinded they will not receive further study treatment but will be encouraged to continue in the study until their final visit.

The study blind may be broken for an individual patient using the IWRS only in the case of an emergency when knowledge of the study treatment is essential for the clinical management of the patient. The Investigator must make every effort to contact the [redacted] prior to breaking the study blind. The breaking of the blind shall be based solely on the Investigator's medical judgment. In the case of unblinding, the Investigator must inform [redacted] immediately without revealing to [redacted] personnel the result of the code break. The Investigator must record in the patient's eCRF and source documents the date of the code break and reason for requiring a code break, in the event of a medical emergency, as soon as possible. It may be discussed with the [redacted] Medical Monitor and the Sponsor if needed, but the final decision is the Investigator's.

If a suspected unexpected serious adverse reaction (SUSAR) or SAE is reported, the [redacted] may unblind the treatment assignment for the individual patient. In such cases, access to the code will only be permitted by authorized drug safety representatives.

5.9 Treatment Compliance

Patients will be instructed to bring with them the used and unused drug kits at Visit 3, Visit 5, Visit 6, Visit 7/ET, and at Visit 8, in which treatment compliance will be evaluated.

Treatment compliance at the Visit 3, Visit 5, Visit 6, Visit 7/ET, and Visit 8 and overall for the 16-week active treatment period will be calculated using the following formula:

> Compliance (%) = [Total number of administered doses/Total number of scheduled doses] × 100

The total number of scheduled doses will be calculated based on the extent (days) of exposure of each patient. A range between 80% to 120% will be taken as reference limits for a satisfactory level of compliance. In addition, compliance will be assessed by tablet count.

During the in-clinic days, the levodopa doses will be recorded and tracked during the "ON/OFF" diary completion days.

5.10 Prior and Concomitant Therapy

To be eligible for entering this study, patients must have dyskinesia and be taking at least three doses/day of oral levodopa. This treatment has to be stable for at least 28 days prior to Baseline

(Visit 2). Patients must be stable on their anti-PD medications and dosage regimens for at least 28 days prior to Baseline (Visit 2) and continue anti-PD medications without change throughout the treatment period.

During the 4-week titration period, for patients who suffer from symptoms indicating worsening of PD, the levodopa regimen may be adjusted until the regimen is optimal according to the Investigator's judgment. This optimal regimen must be obtained within the 4 weeks titration period and cannot be lower than the levodopa regimen at the time of screening.

Use of all prior medications 28 days prior to Baseline (Visit 2) and concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter (OTC) medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Non-emergent levodopa rescue is not permitted during the screening and maintenance periods. In cases of medical emergency, levodopa rescue may be used (based on investigator decision) but not on the days of clinic visits or "ON-OFF" diary completion as much as possible. Use of levodopa must be reported and recorded.

5.10.1 Prohibited Medications and Substitution Alternatives

The medications in the excluded medications column of Table 3 are not allowed within 6 weeks before Baseline (Visit 2) or during the study. By-class substitution alternatives (if available) are also provided in Table 3.

Enrolled patients must be provided with all contact information in order to allow any prescriber to discuss medication changes with the clinical investigator team/medical monitor before making therapeutic decisions and prescribing new medications during the study.

Table 3 Prohibited Medications and Substitution Alternatives

Medication Class	Excluded medications	Substitution Alternatives
Anti PD/ PD-LID	apomorphine, *mucuna pruriens*, topiramate, amantadine, levodopa injection/infusion	Not applicable

Medication Class	Excluded medications	Substitution Alternatives
Antipsychotics	ziprasidone, clozapine, haloperidol, mesoridazine, thioridazine, pimozide, zuclopenthixol, chlorpromazine, paliperidone, iloperidone, fluphenazine, prochlorperazine, trifluoperazine/trifluroperazine, flupentixol, benperidol, amisulpride, and sulpiride	aripiprazole, risperidone, olanzapine, quetiapine, thiothixene, acetophenazine, triflupromazine, loxapine, tiapride, chlorprothixene, bromperidol
Antidepressants	Any tricyclic/tetracyclic antidepressant (e.g., amitriptyline, nortriptyline, imipramine, desipramine, doxepin, clomipramine, protriptyline, and amoxapine), Escitalopram, citalopram, trazodone >100 mg/day All triple reuptake inhibitors lithium (mood stabilizer)	SSRI/SNRIs: venlafaxine, paroxetine, duloxetine, sertraline, omipramol (opipramol), moclobemide, tranylcypromine, buspiron, reboxetine, dibenzepin, fluvoxamine Bupropion: special caution re: seizure risk, maximum 3 × 150 mg/day
Antiarrhythmics	disopyramide, procainamide, quinidine, flecainide, propafenone, amiodarone, dofetilide, ibutilide, sotalol	mexiletine, tocainide
Dopamine antagonists	All dopamine antagonists are prohibited (e.g., Reglan [metoclopramide])	Not applicable
Other[a]	astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, codeine, sevoflurane, tamoxifen, anagrelide, budipine, cotrimoxazole, fluconazole, levofloxacin, lidoflazine, loratadine, ondansetron, probucol, sertindole, terodiline, vandetanib	Clinician's choice and decision on a specific base-basis.

Abbreviations: PD, Parkinson's disease; PD-LID, levodopa-induced dyskinesia in patients with Parkinson's disease; SNRI, serotonin-noepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor;

[a] Due to either QT prolongation effects or metabolism by CYP2D6 into active metabolites

** Fluoxetine is allowed as it carries a conditional risk only for patients with congenital Long QT, hypokalemia or metabolic inhibitors.

Other:

- Use of all oral cannabinoids (including all preparations containing any cannabinoids, including cannabidiol, as well as prescribed oral medical marijuana and oral cannabidiol) with only an exception for topical formulations of cannabidiol, are prohibited within 28 days prior to Baseline (Visit 2) and during the study
- Amantadine is not allowed within 4 weeks prior to the UDyRS Part 4 assessment for eligibility, concordance testing, and completion of the 3 consecutive 24 hour "ON/OFF" home diaries during the screening period
- Apomorphine is not allowed within 28 days prior to screening and during the study

6 Study Assessments and Procedures

Before performing any study procedures, all potential patients will sign an IRB-approved- ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

On-site (in-clinic) visits should be scheduled around the second (PM) study treatment daily dose within the time window of 11:00 AM through 5:00 PM and at consistent time points. Attempts will be made to schedule all study visits for an individual patient at approximately the same time of the day. The same in-clinic procedural timing will be kept for each of the in-clinic- visits for each patient. The in--clinic procedural flow for Baseline (Visit 2) is presented in Appendix 13.1. The in-clinic procedural flow for Visits 3 to 7 is presented Appendix 13.2. The second (PM) study treatment daily dose (at clinic) should be taken 6-10 hours after the first (AM) study treatment daily dose, which is taken at home, and not later than 5:00 PM.

A detailed schedule of study procedures/assessments is provided in Table 4.

Table 4 Schedule of Assessments

Study Period[a]	**Screening**		**Treatment Period**						**Down-titration**	**Safety Follow-Up**
			Up-titration	**Maintenance**						
Study Week			**Week 1**[b]	**Week 5**	**Week 7**	**Week 10**	**Week 13**	**Week 16/ET**[c]	**Week 17**[d]	**Week 18**
Visit #	**Visit 1**	**Visit 1.1**[gg]	**Visit 2**[e]	**Visit 3**[ee]	**Visit 4**[ee]	**Visit 5**[ee]	**Visit 6**[ee]	**Visit 7**[ee]	**TC**	**Visit 8**
Study Visit Day (window)	**-63 days**[ff]	**-21 days (none)**	**1 (none)**	**29 (±1 day)**	**43 (±1 day)**	**70 (±1 day)**	**91 (±1 day)**	**112 (±1 day)**	**119 (none)**	**126 (±1 day)**
Study Phone Call Day			**7, 14, 21,** [f]	**25**[g]	**52**[g]	**73**[g]	**94**[g]		**114, 116**[h]	
Visit Descriptor	**SCR**	**SCR**	**BSL**	**Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety PK**	**Phone call**	**Final Safety Follow-up**
Informed consent	X									
Randomization to treatment groups			X							
Inclusion/ Exclusion criteria	X		X							
MMSE	X									
Demographic data	X									
Psychiatric history	X									
Medication history[j]	X									
Alcohol/ illicit drug use inquiry	X									
Hoehn and Yahr scale	X									
Training on recognizing motor sates and diary documentation[k]	X[hh]	X								
Motor state concordance testing[l]	X[hh]	X								
"ON/OFF" Home diaries dispensing	X[hh]	X		X	X	X	X			

Study Period[a]	**Screening**		**Treatment Period**						**Down-titration**	**Safety Follow-Up**
			Up-titration	**Maintenance**						
Study Week			**Week 1**[b]	**Week 5**	**Week 7**	**Week 10**	**Week 13**	**Week 16/ET**[c]	**Week 17**[d]	**Week 18**
Visit #	**Visit 1**	**Visit 1.1**[gg]	**Visit 2**[e]	**Visit 3**[ee]	**Visit 4**[ee]	**Visit 5**[ee]	**Visit 6**[ee]	**Visit 7**[ee]	**TC**	**Visit 8**
Study Visit Day (window)	**-63 days**[ff]	**-21 days (none)**	**1 (none)**	**29 (±1 day)**	**43 (±1 day)**	**70 (±1 day)**	**91 (±1 day)**	**112 (±1 day)**	**119 (none)**	**126 (±1 day)**
Study Phone Call Day			**7, 14, 21,**[f]	**25**[g]	**52**[g]	**73**[g]	**94**[g]		**114, 116**[h]	
Visit Descriptor	**SCR**	**SCR**	**BSL**	**Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety PK**	**Phone call**	**Final Safety Follow-up**
"ON/OFF" Home diaries assessments			X[m]		X[g]	X[g]	X[g]	X[g]		
Prior and concomitant medications review[n]	X		X	X	X	X	X	X	X	X
Physical examination	X		X[o]					X[p]		X[p]
Vital signs[q]	X		X	X	X	X	X	X		X
Neurological examination	X[hh]	X	X[o]					X[p]		X[p]
Body weight and height[r]	X		X	X	X	X	X	X		X
Clinical laboratory tests (Serum haematology and biochemistry)[s]	X		X	X	X	X	X	X		X
Urinalysis (dip stick)	X		X	X	X	X	X	X		X
Serum pregnancy test (if applicable)[t]	X									
Urine pregnancy test (if applicable)[u]			X	X	X	X	X	X		X
ECG (12-lead) Consecutive triplicate of 10 seconds[v]	X		X	X	X	X	X	X		X
C-SSRS	X[hh]	X	X	X	X	X	X	X		X
QUIP-RS	X[hh]	X	X	X	X	X	X	X		X

Study Period[a]	**Screening**		**Treatment Period**						**Down-titration**	**Safety Follow-Up**
			Up-titration	**Maintenance**						
Study Week			**Week 1**[b]	**Week 5**	**Week 7**	**Week 10**	**Week 13**	**Week 16/ET**[c]	**Week 17**[d]	**Week 18**
Visit #	**Visit 1**	**Visit 1.1**[gg]	**Visit 2**[e]	**Visit 3**[ee]	**Visit 4**[ee]	**Visit 5**[ee]	**Visit 6**[ee]	**Visit 7**[ee]	**TC**	**Visit 8**
Study Visit Day (window)	**-63 days**[ff]	**-21 days (none)**	**1 (none)**	**29 (±1 day)**	**43 (±1 day)**	**70 (±1 day)**	**91 (±1 day)**	**112 (±1 day)**	**119 (none)**	**126 (±1 day)**
Study Phone Call Day			**7, 14, 21,**[f]	**25**[g]	**52**[g]	**73**[g]	**94**[g]		**114, 116**[h]	
Visit Descriptor	**SCR**	**SCR**	**BSL**	**Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety**	**Efficacy**[i] **Safety PK**	**Efficacy**[i] **Safety PK**	**Phone call**	**Final Safety Follow-up**
UDysRS (Part 4 for eligibility)	X[hh]	X								
UDysRS (Parts 1, 2, 3, 4)[w]			X	X	X	X	X	X		
UPDRS (Parts 2 and 3)[x]			X		X	X	X	X		
PGI-C					X	X	X	X		
CGI-C			X[y]			X		X		
Treatment initiation[z]			X							
Assign and dispense study treatment (bottles and kits)			X	X		X		X		
Collect returned kits and bottles and assess compliance[aa]				X		X	X	X		X
Dispense and/or return dosing diaries			X	X	X	X	X	X		
PK sampling (two samples)[bb]					X		X	X		
Pharmacogenetic sample[cc]	X		X							
Plasma Biomarker sampling[dd]	X		X			X		X		
Safety including AEs	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, Adverse events; BID, twice daily; BSL, baseline; CGI-C, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PGI-C, Patient Global Impression of Change; PK, pharmacokinetics; QD, once daily; QUIP-RS, Questionnaire for Impulsive / -Compulsive Disorders in Parkinson's Disease- Rating Scale; SCR, screening; TC, telephone contact; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

a. In-clinic unscheduled visits can be performed for safety concerns at any time per the discretion of the investigator.
b. Four-week up-titration period. Patients randomly assigned to active treatment will receive 75 mg of pridopidine every other day (Q48h) for one week either AM or PM; then 75 mg of pridopidine once daily (QD) either AM or PM for 1 week; then 75 mg of pridopidine twice daily (BID) for one week; then 100 mg of pridopidine for one week in a blinded fashion. Patients randomly assigned to the placebo arm will receive matching placebo at the same dosing schedule as patients assigned to the active treatments. Refer to Section 5.2.
c. An early termination (ET) visit should be performed for patients who discontinue prematurely within 1 week of ET.
d. Down-titration period. At the end of the maintenance period or at ET, active treatment patients will undergo a down-titration- period in which they will receive pridopidine 75 mg BID on Days 1 to 2 followed by pridopidine 75 mg QD on Days 3 to 4 of Week 17. Patients randomly assigned to the placebo arm will receive matching placebo at the same dosing schedule as patients assigned to the active treatments. Refer to Section 5.2.
e. All efficacy and safety measures, except the ECG after the second study treatment dose must be assessed before the first study treatment dose. Refer to the in-visit procedural flow for Baseline (Visit 2) in Appendix 13.1.
f. Telephone contacts will be conducted on Day 1 of Week 1-4 (up-titration period) to remind patients to up-titrate their dosage and ask them to provide details on AEs and concomitant medication changes.
g. Patients will be called 4 days before each of the relevant visits to remind them to complete the "ON/OFF" home diary every 30 minutes during the 3 consecutive days before the visit and to bring them to the clinic.
h. Telephone contacts will be conducted on Days 2 and 4 of Week 17 to remind patients to down-titrate and discontinue the dosing.
i. Onsite/in-clinic assessments will be scheduled around the second (PM) study daily treatment dose from 11:00 AM through 5:00 PM and will use time points consistent with each patient's usual levodopa dosing. On clinic visit days, the "scheduled levodopa dose" is defined as the in-clinic afternoon levodopa dose prior to which the UPDRS assessment is performed and after which the UDysRS parts 3+4 assessment is performed. The study treatment afternoon dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). As much as possible, all study visits for an individual patient will occur at approximately the same time of the day. The same in-clinic procedural timing will be kept for all visits for each patient.
j. Patients' existing anti-PD medication regimens, including, but not limited to, levodopa oral preparations, must be maintained at a stable dose for at least 28 days prior to Baseline (Visit 2) and for the entire duration of the treatment duration period. During the 4-week titration period, for patients who suffer from symptoms indicating worsening of PD, the levodopa regimen may be adjusted until the regimen is optimal according to the Investigator's judgement. This optimal regimen must be obtained within the 4-week titration period and cannot be lower than the levodopa regimen at the time of screening. Allowed antidepressant or antipsychotic medication and any other routine allowed prescription/nonprescription medications and/or nutritional supplements taken regularly, must also maintained at stable dose for at least 28 days prior to Baseline (Visit 2) for the entire duration of the maintenance treatment duration period.
k. Training of patients and study partners on recognition of motor state and "ON/OFF" home diary documentation to ensure concordance with the investigator rating may be repeated as many times as needed throughout the screening period.

l. After motor state recognition training, the patient will be invited to the clinic, and both the study rater and the patient will complete an "ON/OFF" home diary, at half hour intervals over a 4-hour period, to obtain concordance of >75% between the evaluations (e.g., "ON, OFF and "dyskinesia") of the rater and the patient.
m. After assurance of >75% concordance between the rater and patient, the patients will complete at their homes the "ON/OFF" home diary during three consecutive 24-hour periods (72 hours total) and send the completed diaries to the site (e.g., via fax, email). The patients will send the completed diaries to the site (e.g., via fax, email) up to one week before the end of the screening period because these diaries will serve as the baseline motor home diary and for eligibility to participate in the study.
n. Prior and concomitant medication during 28 days prior to Baseline (Visit 2).
o. The purpose of the assessment at Visit 2 is to confirm that there are no changes since Screening (Visit 1).
p. The assessment will be performed at Visit 7/ET or at Visit 8.
q. Vital signs include supine (after resting for at least 5 minutes), supine, and standing BP, pulse rate, and body weight.
r. Height will be recorded at Screening (Visit 1) only.
s. Prolactin will be assessed at Baseline (Visit 2) and Visit 7/ET only.
t. Human chorionic gonadotropin (HCG) serum test will be performed for all women not surgically sterile or at least two years postmenopausal at Screening (Visit 1). An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and discussed with the medical monitor if persistently indeterminant; no study treatment will be administered until this is resolved.
u. A dipstick urine pregnancy test will be performed for all female patients who are not surgically sterile or who are not at least two years postmenopausal.
v. Three consecutive 12-lead ECG evaluations will be assessed before, and 1 to 2 hours after the study treatment dose administered at the clinic (approximate C_{max}). A single ECG may be used for screening purposes if the QTcF is normal.
w. An in-clinic assessment of dyskinesia according to UDysRS will be conducted by the study rater. At Screening, only Part 4 will be assessed in order to determine eligibility. At Baseline (Visit 2), all UDysRS parts (Parts 1 to 4) must be assessed before the initial study treatment dose (refer to Appendix 13.1). For the rest of the time points, UDysRS must be assessed as per the in-clinic visit procedural flow in Appendix 13.2. The historical parts of the UDysRS (Parts 1 and 2) will be performed at any time during the visit (at Baseline [Visit 2] at any time before the initial study treatment dose). The objective score (Parts 3 and 4) will be performed at least 30 minutes following the patient's in-clinic dose of levodopa (the "scheduled levodopa dose"), at a time when the patients are normally in an "ON" state and experiencing their peak dose dyskinesia. Every effort will be made to ensure that all assessments of UDysRS are performed by the same rater for each individual patient.
x. At Baseline (Visit 2), UPDRS Part 2 and 3 must be assessed before the initial study treatment dose (refer to Appendix 13.1). For the rest of the time points, UPDRS Part 2 and 3 must be assessed as per the in-clinic visit procedural flow in Appendix 13.2. UPDRS Part 3 will be measured before the in-clinic levodopa dose (the "scheduled levodopa dose"); Part 2 can be measured at any time during the visit (at Baseline [Visit 2] at any time before the initial study treatment dose).
y. Investigators must complete a detailed case note at Visit 2 to document the patient's condition before starting study drug. This will be the baseline in which to compare changes in the patients' global condition after receiving study drug for rating the CGI-C.
z. During the 16-week active treatment period, the first study treatment daily dose will be taken between 6:00 and 8:00 AM and the second study treatment daily dose will be taken 6 to 10 hours after the first study treatment dose administration and not later than 5:00 PM. The second study treatment daily dose should be taken 0 to 120 minutes BEFORE the "scheduled levodopa dose" (NOT after). As much as possible, study treatment should be taken at the same

time throughout the study. Capsules will be swallowed whole with water. Study treatment can be taken irrespective of meals. If a patient misses the morning study treatment dose on an in-clinic day, the visit should be rescheduled.

aa. Study treatment kit for down-titration purposes. At the end of the maintenance period or at ET, active treatment patients will undergo a down-titration period in which they will receive one capsule of pridopidine 75 mg and one capsule of placebo BID on Days 1 to 2 followed by one capsule of pridopidine 75 mg and one capsule of placebo QD on Days 3 to 4 of Week 15.Patients receiving placebo will receive matching placebo at the same dosing schedule as patients assigned to the active treatments.

bb. Pharmacokinetic sampling will be performed at Visit 4, Visit 6, and Visit 7/ET approximately 1 hour before and 1 to 2 hours after the PM study treatment dose. When concomitant with ECG recording, PK samples will be collected within 30 minutes after the ECG recording. The timing of UDysRS and UDPRS should be prioritized before PK sampling.

cc. Sampling analyses for DNA extraction will be performed only once during the study at the Screening (Visit 1) or at Baseline (Visit 2).

dd. Sampling analyses will be performed at Screening (Visit 1) or Visit 2, Visit 5, and Visit 7/ET.

ee. If a patient misses the morning study treatment dose on an in-clinic day, the visit should be rescheduled.

ff. For patients requiring an amantadine washout period, two screening visits will be required during the screening period: Visit 1 and Visit 1.1. Visit 1, the first screening visit, will be performed up to 9 weeks/63 days prior to Baseline (Visit 2) and Visit 1.1 will be performed no later than 3 weeks/ 21 days prior to Baseline. For patients not requiring an amantadine washout period, only one screening visit will be required during the screening period: Visit 1. As much as possible, this visit should be performed 3 weeks/ 21 days prior to Baseline.

gg. Additional visit only required for patients requiring an amantadine washout period.

hh. If Visit 1.1 is required due to necessity for amantadine washout, this assessment shall only be performed at Visit 1.1 and not at Visit 1.

6.1 Study Visits

The schedule of assessments by study visit is presented in Table 4. Detailed instructions for the conduct of study assessments and procedures will be provided in the study manual provided to investigators.

6.2 Efficacy Assessments

Every effort should be made to ensure that, for a given efficacy assessment, all measurements are performed by the same rater for each individual patient for all visits.

6.2.1 UDysRS

The UDysRS is designed to evaluate involuntary movements often associated with treated PD. The scale comprises two primary sections:

- Historical [Part 1 (ON-Dyskinesia) and Part 2 (OFF-Dystonia)]
- Objective [Part 3 (Impairment) and Part 4 (Disability)]

ON-Dyskinesia refers to the choreic and dystonic movements described to the patient as "jerking or twisting movements that occur when your medicine is working." OFF-Dystonia should be described to the patient as "spasms or cramps that can be painful and occur when your Parkinson's disease medications are not taken or are not working". The assessments will be carried out at the time points noted in the schedule of assessments (Table 4). Every effort should be made to ensure that all UDysRS assessments are performed by the same rater for each individual patient.

6.2.2 UPDRS

The UPDRS scale is divided into 4 parts. Part 1 is designed to rate mentation, behavior and mood (questions 1 to 4). It is to be collected as historical information without direct relevance to "ON" or "OFF" periods experienced by the patient. Part 2 (questions 5 to 17) is designed to rate activities of daily living for both "ON" and "OFF" periods. Part 3 (questions 18 to 31) is done as a motor examination at the time of a visit. Part 4 (questions 32 to 42) is historical information designed to rate complications of therapy. The various items to be rated are scored using a 5-point system (i.e., 0 is normal and 4 indicates a severe abnormality). UPDRS Part 2 and Part 3 will be measured at the time points noted in the schedule of assessments (Table 4).

6.2.3 "ON/OFF" Home Diary Assessments

The "ON/OFF" home diary assessments are assessed during three consecutive 24-hour periods. During the screening period, potential patients and any involved caregivers or study partners if applicable will be trained to recognize the different motor states ("ON without dyskinesia," "ON with no troublesome dyskinesia," "ON with troublesome dyskinesia," and "OFF"), and to complete a corresponding "ON/OFF" home diary. Training will be conducted by a well-

trained rater. After training, the patients will be invited to the clinic; the study rater and the patients will complete an "ON/OFF" diary at half-hour intervals over a 4-hour period to ensure concordance of >75% between the evaluations (e.g., "ON, OFF and dyskinesia") of the rater and the patient. After assurance of >75% concordance between the rater and patient, the patients will complete at their homes the "ON/OFF Home Diary" during three consecutive 24-hour periods (72 hours total). The patients will send the completed diaries to the site (e.g., via fax, email) during the first two weeks of the screening period because these diaries will serve as the baseline motor home diary and for eligibility to participate in the study. Training may be repeated during the screening period to ensure concordance with investigator ratings. The assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

6.2.4 Patient Global Impression of Change (PGI-C)

Global improvement will be rated by the patient using the PGI-C. Whenever feasible, assessments should be made by the same assessor in an individual patient. The assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

6.2.5 Clinical Global Impression (CGI-C)

Global improvement will also be rated by the investigator or designee separately using the CGI-C. Whenever feasible, assessments should be made by the same assessor in an individual patient. The assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

6.2.6 Mini-Mental State Examination (MMSE)

The MMSE is a scale for eligibility. It comprises a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus, making it an effective way to document an individual's response to treatment. The assessments will be carried out at Screening.

6.3 Pharmacokinetics Assessments

The PK measure will be the determination of plasma concentration of pridopidine and its metabolite TV-45065 using a validated liquid chromatography–mass spectrometry method.

Details on PK sample collection are detailed in Section 6.9.

6.4 Pharmacogenetic and Plasma Biomarker Assessments

Details on pharmacogenetic and plasma biomarker sample collection are detailed in Section 6.9.

6.4.1 Pharmacogenetic Assessments

Pharmacogenetic assessments may include the analysis of DNA variations (e.g., known polymorphism in the σ_1R gene and the catechol-O-methyltransferase [COMT] gene) with a potential relationship with clinical responses to study drug (e.g., efficacy, PK, tolerability, safety features or disease susceptibility, and severity features). The final list of genes that might be investigated will be selected at a later stage before the analysis to allow updating with new scientific information. Genetic analysis could also include sequencing of the whole genome if required. The genetic sample analysis will be performed if and when required. Since new techniques continue to be developed, the method and laboratory that will be used for the genetic analysis cannot be defined at present. The bioanalytical laboratory will be identified at a later stage.

6.4.2 Plasma Biomarker Assessment

The following biomarker candidate assessments will be evaluated: neurofilament light chain protein (NFL), α-synuclein, and DJ-1. Other blood biomarkers may be evaluated for future exploratory purposes upon new scientific knowledge.

6.5 Safety Assessments

Safety assessments include AEs, concomitant medications, laboratory tests (clinical chemistry, haematology, and urinalysis), C-SSRS, 12-lead ECG, QUIP-RS, vital signs (including assessment of orthostatic hypotension), and physical and neurological examination. The assessments will be carried out at the time points noted in the schedule of assessments (Table 4). Every effort should be made to ensure that, for a given safety assessment, all measurements are performed by the same rater for each individual patient for all visits.

6.5.1 Adverse Events

6.5.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, from the signing of the IRB-approved ICF to the last study visit or until satisfactory resolution, regardless of their relationship to study treatment or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment. Patients will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.

6.5.1.2 Serious Adverse Events

An SAE is defined as any event that:

- results in death
- is immediately life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.5.1.3 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to visit of the safety follow-up period (Visit 8).

Serious AEs that occur more than 30 days after the reporting period need not be reported unless the investigator considers them related to study treatment.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being. Patients will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to patient observations, any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital sign measurements), including those that worsen from Visit 2, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. In addition, AEs identified from review of other documents (e.g., patient diaries) that are relevant to patient safety will be documented on the AE page in the eCRF.

6.5.1.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- drug treatment
- dose
- event term
- time of onset
- investigator-specified assessment of severity and relationship to study treatment
- time of resolution of the event
- seriousness
- any required treatment or evaluations
- outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to appropriate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE. Pharmacodynamic symptoms of the treatment are not considered as an AE. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF (Section 5.5).

6.5.1.5 Reporting Serious Adverse Events, Pregnancy, and Overdose

Any AEs reported or observed during the study from informed consent that meets SAE criteria (Section 6.5.1.2) must be reported to the [redacted] immediately (i.e., within 24 hours) after the time site personnel first learn about the event. Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE, i.e., within 24 hours of first knowledge using a pregnancy report form. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and after delivery, the status of mother and child will be reported to the sponsor after delivery. Full details will be recorded on the withdrawal page of the eCRF.

Any overdose, with or without associated AEs, must be promptly reported to the Sponsor [redacted] in an expedited manner using the SAE Report Form, and following the procedure described in this section and from [redacted]. The patient may be hospitalized for observation and appropriate supportive treatment administered. Any concerning overdose (i.e., with an associated AEs or any lab abnormalities) will be reported

via [redacted]. Any AE/SAEs or any lab abnormalities considered related to the overdose should be reported as appropriate.

The determination of an overdose will be left to the discretion of the investigator, based on the quantity of overdose, emergence of any clinical signs and symptoms suggestive of toxic administration, as well as his/her own clinical judgment as it applies to each individual case.

Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

The following contact information is to be used for SAE reporting:

[redacted]

Investigators must report SAEs and follow-up information to their responsible IRB or independent ethics committee (IEC) as applicable per institutional policy.

The sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal investigators with clinical safety updates/reports according to local requirements.

6.5.1.6 Suspected Unexpected Serious Adverse Reactions and Nonserious Adverse Events of Special Interest

The sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the study treatment investigator's brochure.

Prilenia Therapeutics will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed. All AEs will be evaluated with equal interest.

Events of discontinuation due to meeting the QTcF stopping rules (defined in Section 4.2.1) will be considered AEs of special interest.

6.5.1.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.

An AE that is sufficiently discomforting to interfere with normal activities.

Severe: These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.5.1.8 Assessment of Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the study treatment. Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment. Causality should be assessed using the categories presented below:

Related: Adverse event judged by the Investigator as having a reasonable suspected causal relationship to the investigational medicinal product

Unrelated: Adverse event judged by the Investigator as NOT having a reasonable suspected causal relationship to the investigational medicinal product

6.5.1.9 Exceptions

In this protocol, symptoms and signs related to PD will not be considered as AEs or captured on the eCRF, however, unexpected worsening of PD should be reported as an AE. The following hospitalization scenarios will not be considered AEs:

- Hospitalization for a preexisting condition, provided that the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease or
  - The patient has not experienced an AE

6.5.1.10 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.5.2 ECG: QTc Parameters

At Baseline (Visit 2) and at every visit thereafter, triplicate 12-lead ECG evaluations will be assessed before, and 1 to 2 hours after the study treatment dose administered at the clinic (approximate C_{max}). A triplicate 12-lead ECG measure is comprised of three 10-second ECG recordings. The time interval between each of the three individual ECG recordings should be approximately 60 seconds. When concomitant with ECG recording, PK samples will be collected within 30 minutes after the ECG recording.

At Screening (Visit 1), a single resting 12-lead ECG will be conducted after at least 5 minutes of supine rest. If there is evidence of a prolonged QTcF interval (defined as a QTcF interval of >450 msec), then the ECG will be repeated twice within 10 minutes of the first ECG recording. The time interval between the two additional ECGs should be approximately 60 seconds. The mean of the three screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study. The decision to repeat an ECG will be made by the investigator and/or the physician assessing the ECG.

At Baseline (Visit 2) and at every clinic visit thereafter, a triplicate 12-lead ECG evaluation (three 10-second recordings) will be conducted before and 1-2 hours after study treatment dose administration. When applicable, PK samples will be collected within 30 minutes after the ECG recording. The QTcF values will be determined by the average of the 12-lead ECG triplicate.

The patient must be in a supine position and resting for at least 5 minutes prior to each ECG measurement. Where applicable, ECG measurements should be taken prior to vital sign measurements and blood being drawn for clinical laboratory or PK evaluations. A qualified physician at the central ECG vendor will be responsible for interpreting the ECG and send results within 24 hours. However, every ECG should be reviewed immediately at site for the purpose of determining any gross abnormality (like new atrial fibrillation or QTcF prolongation) that might affect patient safety and not allow dosing. If the local ECG reading results at the site match any of the discontinuation criteria (see Section 4.2.1), the patient should stop taking study treatment until the central ECG reader's report is received. If the central reader does not report a QTcF interval that would lead to discontinuation according to the above, then the patient should restart study treatment. Any ECG finding that is judged by the investigator or the physician from the central ECG vendor as a clinically significant change (worsening) compared with a Visit 2 value will be considered an AE, recorded on the source documentation and transcribed onto the eCRF and monitored as described in Section 6.5.1.4.

6.5.3 Vital Signs

Vital signs including supine and standing blood pressure (BP), pulse rate, and body weight will be measured at every clinic visit. Height will be measured at Screening (Visit 1) only. Measurements for orthostatic hypotension will be taken at every study visit and at specific time points as described in Table 4. Orthostatic measurements (supine and standing BP and seconds of pulse rate) can be measured manually or using an automated BP machine; the same method of measurement should, however, be used throughout the study for a particular patient. The patient's BP and pulse rate will be measured after the patient has been supine for approximately 5 minutes. The patient will be instructed to rise to a standing position, and a BP measurement will be taken after the patient has been standing for two minutes. Orthostatic hypotension is defined as a reduction of 20 mmHg or more in systolic BP, or a reduction of 10 mmHg or more in diastolic BP, the standing measurement compared to the supine measurement.

At Baseline (Visit 2), three sets of orthostatic vital signs will be collected, at least 25 to 20 minutes apart, to minimize the potential impact of biological variability of a single baseline measurement and use the average of the three orthostatic vital signs measurements for comparison to all post-treatment measurements.

Blood pressure should be measured in seated position after 5 minutes resting (for individual patients, measurements at different visits should be taken in the same position and the same arm). Blood pressure should be repeated in the opposite arm if an abnormal reading is obtained.

6.5.4 Physical and Neurological Examination

The physical and neurological examination of all major body parts (excluding a genitourinary exam) will be carried out by an Investigator (who is a neurologist by medical training) at the time points noted in the schedule of assessments (Table 4). Any clinically significant changes during the treatment period will be recorded on the eCRF.

6.5.5 Concomitant Medications

The concomitant medication assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

6.5.6 Assessment of Suicidal Ideation and Behavior (C-SSRS)

Suicidal ideation and behavior will be assessed using the "Screening" part of the C-SSRS. Each part of the C-SSRS consists of three question groups (suicidal ideation, intensity of ideation, suicidal behavior). It is intended for use by individuals who have been trained in its administration. Ultimately the presence of suicidality depends on clinical judgment.

Throughout the clinical study patients will be monitored for suicidality potential using the C-SSRS scale. Patients who have a C-SSRS suicidal ideation score > 2 will be sent for further evaluation by a mental health care specialist who will assess for imminent risk. The score alone

will not serve as a reason for immediate treatment discontinuation. The assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

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

QUIP-RS is a rating scale designed to measure severity of impulsive-compulsive disorders (ICD) symptoms and support a diagnosis of ICD and related disorders in PD. Four subscales for ICDs (gambling, sexual compulsions, compulsive buying and compulsive eating) have possible scores between 0 and 16 and suggested cut-offs (scores validated as indicative of ICDs via clinical interview) as follows: gambling (≥6); compulsive buying (≥8); sexual compulsions (≥8); compulsive eating (≥7); and combined ICDs (≥10). The QUIP-RS also includes measures for hobbyism (involvement in organized activities like writing or computer use) and punding (repeating activities like cleaning). The assessments will be carried out at the time points noted in the schedule of assessments (Table 4).

6.5.8 Other Assessments

An eligibility review of screened patients to help protect the safety of patients and confirm eligibility will be performed by independent neurologists serving on the EAC (Clintrex) to determine if a patient is correctly diagnosed and to ensure that patient meets the criteria for enrollment in order to avoid unnecessary risks for the patients. Potential patients will be reviewed at least 24 hours before a potential randomization to ensure they meet the criteria for enrollment.

6.6 Data Safety Monitoring Board

During the study, an independent Drug Safety Monitoring Board (DSMB) consisting of a neurologist, a cardiologist and a statistician will periodically review accumulating unblinded safety data. The DSMB will meet when first 30 patients have been enrolled and have completed 2 weeks of maintenance treatment on 150 mg BID, 100 mg BID dose or placebo (Visit 3) Thereafter the DSMB will determine the meeting frequency as they deem necessary. Additionally, DSMB will evaluate all SAEs in real-time.

If a significant safety concern emerges in the high dose treatment, the DSMB will have the authority to discontinue individual patients from the study, discontinue an arm and/or halt the study. In case the 150 mg BID arm is discontinued, all patients who are on maintenance treatment with 150 mg BID arm will immediately be discontinued from the study and will undergo a down-titration period. Patients, randomly assigned to the 150 mg BID arm but still in the titration period, will be switched to the 100 mg BID arm. Newly enrolled patients will be randomized to the 100 mg BID dose or placebo Further details will be provided in the DSMB charter.

6.7 Pregnancy

Human chorionic gonadotropin (HCG) serum test will be performed for all women not surgically sterile or at least two years postmenopausal at Screening (Visit 1). An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and discussed with the medical monitor if persistently indeterminant; no study treatment will be administered until this is resolved. HCG urine tests will be performed for all women not surgically sterile or at least two years postmenopausal as per schedule described in Table 4.

Any patient who becomes pregnant during the study will be withdrawn. Patients will be instructed that known or suspected pregnancy occurring during the study, in female patients or female partners of male patients, should be confirmed and reported to the investigator, who will withdraw a pregnant patient from the study without delay and report the pregnancy within 24 hours of first knowledge using a pregnancy report form. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and after delivery, the status of mother and child will be reported to the sponsor after delivery.

Pregnancy is not regarded as an AE unless there is a suspicion that a study treatment may have interfered with the effectiveness of contraceptive medication. Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE (Section 6.5.1.5).

6.8 Clinical Laboratory Analyses/Evaluations

A laboratory test result that has significantly worsened (according to medical judgment) from Visit 2 result will be recorded on the source documentation, transcribed onto the eCRF as an AE, and monitored as described in Section 6.5.1.4.

Clinical laboratory tests will be performed using a central laboratory, as identified in the Laboratory Procedures Manual provided in the study file documents.

The safety laboratory tests will include:

Haematology: white cell count and differential count, red cell count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count.

Clinical Serum Chemistry: calcium, sodium, potassium, magnesium chloride, bicarbonate or carbon dioxide, glucose, blood urea nitrogen (BUN), creatinine, cholesterol, uric acid, total bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase (GGT), alanine aminotransferase, aspartate aminotransferase, total protein, albumin, lactate dehydrogenase, creatinine phosphokinase (in case of elevated creatinine phosphokinase, the muscle/brain [MB] fraction should be measured), direct bilirubin, indirect bilirubin, prolactin. The prolactin should

be blinded to all the clinical staff, Prilenia Therapeutics and/or its designee. In case of a safety concern, the Investigator will be notified by the central laboratory.

Urinalysis: protein, glucose, ketones, blood (hemoglobin), pH, specific gravity, leukocyte esterase, microscopic (bacteria, red blood cells, white blood cells, casts, crystals). A dipstick urine pregnancy test will be performed as noted in the schedule of assessments (Table 4).

Patients with CrCL <50 mL/min/1.73 m^2 calculated using the Cockcroft-Gault equation [(140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)] at any time point after Baseline (Visit 2) will be requested to return to the clinic for an unscheduled visit 1 week later to repeat the CrCL test one more time for confirmation. If the repeated CrCL value is confirmed to be <50 mL/min/1.73 m^2, the patient will be discontinued from the study treatment.

Any decrease in CrCL that is judged by the investigator as a clinically significant change (worsening) from Baseline (Visit 2) result will be considered an AE, recorded on the source documentation, transcribed onto the eCRF, and monitored as described in Section 6.5.1.4.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are **not** to be reported as AEs or SAEs.

6.9 Sample Collections

Blood samples for the determination of laboratory parameters will be collected as per the schedule of assessments (Table 4) and according to the procedures described in the Laboratory Procedures Manual provided in the study file documents.

Blood samples for the determination of plasma concentrations will be collected at three visits during the study; Visit 4, Visit 6 and Visit 7/ET. Samples will be collected via venipuncture or indwelling catheter in the morning before study treatment administration per the schedule of assessment (Table 4). Plasma concentration of pridopidine will be measured approximately 1 hour before, and approximately 1 to 2 hours after the PM study treatment dose (approximate C_{max}). When concomitant with ECG recording, PK samples will be collected within 30 minutes after the ECG recording. The timing of UDysRS and UPDRS should be prioritized before PK sampling.

The date and time of each PK sample and the dates and times of the last drug administration prior to any collected PK sample will be recorded on the source documentation and transcribed onto the eCRF. Only major deviations (>5%) from the scheduled blood sampling time points will be commented on the respective page of the eCRF.

Samples will be analyzed by [redacted] using an appropriate validated method for pridopidine and its main metabolite TV-45065.

Blood samples for DNA extraction will be collected only once during the study at Screening (Visit 1) or at Baseline (Visit 2). Plasma samples for potential biomarkers research will be collected at the time points noted in the schedule of assessments (Table 4). The details of the sample collection and handling are described in the Laboratory Procedures Manual provided in the study file documents.

6.10 Eligibility Review

An eligibility review will be conducted by the EAC to determine suitability of screened subjects for the study, including review of screening safety data and fulfillment of enrollment criteria. Screened subjects will be reviewed within 48 hours of potential randomization to ensure that they meet the criteria for enrollment.

7 Statistical and Analytical Plan

Details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan (SAP), which will be approved before breaking the blind of the study.

Primary and all secondary endpoints will be assessed for both the 100 mg BID and the 150 mg BID pridopidine dosage vs. placebo in a hierarchical manner.

7.1 Primary Efficacy Endpoint

The primary endpoint is the mean change from Baseline (Visit 2) to Visit 7/ET in the sum of Parts 1, 3, and 4, of the UDysRS while the patient is in the peak "ON" state and judged to be experiencing peak dose dyskinesia.

7.2 Secondary Efficacy Endpoints

The following secondary endpoints will be evaluated:

1. Mean change from Baseline (Visit 2) to Visit 7/ET in "ON time without troublesome dyskinesia" based on "ON/OFF" home diary completed by the patients during three consecutive 24-hour intervals
2. Mean change from Baseline (Visit 2) to the end of Visit 7/ET in the total UDysRS score (Parts 1 to 4)
3. Proportion of patients improving based on PGI-C at Visit 7/ET
4. Mean change from Baseline (Visit 2) to Visit 7/ET in "ON time without any dyskinesia" based on "ON/OFF" home diary
5. Proportion of patients improving based on CGI-C at Visit 7/ET
6. Mean change from Baseline (Visit 2) to Visit 7/ET in the score of UPDRS Part 2
7. Proportion of responders (improvement in dyskinesia and no worsening in motor function) at Visit 7/ET. The improvement in dyskinesia is defined as ≥30% improvement in UDysRS score (Parts 1, 3, and 4) from Baseline (Visit 2) and no worsening from Baseline (Visit 2) in "OFF" which is defined as ≤30 minutes increase in "OFF" time from Baseline (Visit 2) per a 24 hours period
8. Mean change from Baseline (Visit 2) to Visit 7/ET in "OFF time" based on "ON/OFF" home diary
9. Mean change from Baseline (Visit 2) to Visit 7/ET in the UPDRS Part 3 as measured immediately prior to the in-clinic L-DOPA dose

7.3 Safety Endpoints

The following safety and tolerability endpoints will be evaluated:

Safety:

1. AEs occurring throughout the study
2. QTc parameters: absolute QTcF of >450 msec, >480 msec, and >500 msec, mean QTcF, change in QTcF>30 msec and <60 msec, or changes in QTcF>60 msec throughout the study
3. Clinical safety laboratory (clinical chemistry, haematology and urinalysis, vital signs (including assessment of orthostatic hypotension), physical and neurological examination, concomitant medications throughout the study
4. Change from Baseline (Visit 2) in suicidality as evaluated with the C-SSRS throughout the study
5. Change from Baseline (Visit 2) in impulse control disorder (ICD) as evaluated by the QUIP-RS throughout the study

Tolerability:

1. The number (%) of patients who complete the study treatment
2. The number (%) of patients who fail to complete the study treatment due to AEs
3. The number (%) of patients who fail to complete the study treatment due to QTcF and QT stopping rules, seizure or convulsions (Section 4.2.1)

7.4 Pharmacokinetic Endpoints

The PK measure will be the determination of plasma concentration of pridopidine and its metabolite TV-45065 before and after in-clinic pridopidine dose.

7.5 Pharmacogenetic and Plasma Biomarker Endpoints

The following pharmacogenetic and plasma biomarker endpoints may be evaluated:

1. To analyze the correlation of potential genetic variations and plasma biomarkers with clinical treatment responses to study drug (e.g., efficacy, PK, tolerability and safety features).
2. To assess for potential genetic variation and plasma biomarkers associated with disease progression and severity.

7.6 Sample Size Calculations

A sample size of 38 randomized patients in each treatment group (114 randomized patients overall) will provide 80% power to detect a between-group difference of 8.5 points in the UDysRS score with standard deviation of 13 points using a two-sided significance level of 0.05, using an ordinary least squares model. Assuming a drop-out rate of 15%, a total of 135 patients will be randomized. The sample size was calculated based on two sample t-test assuming equal variances in the two groups, using nQuery Advisor version 7.0.

7.7 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat (ITT) Set: The ITT set will include all randomized patients. The patients will be grouped as randomized. Retrieved drop-out data (data captured from the drop-outs after the end-of-study visit when the patient is free of study treatment) will not be included in the ITT set. The ITT set will be used for the sensitivity analysis of the primary endpoint.

Modified Intent-to-Treat (mITT) Set: The mITT set will include all randomized patients who receive a dose of study treatment and have efficacy assessments both at Baseline (Visit 2) and at least one post-randomization time point. The patients will be grouped as randomized. Retrieved drop-out data (data captured from the drop-outs after the end-of-study visit when the patient is free of study treatment) will not be included in the determination of the mITT set. The mITT set will be used for the efficacy analysis.

Completer Set: The completer set is a subset of the mITT set and includes the subsets of patients with efficacy data at Visit 7/ET.

The patients will be grouped as randomized. The completer set will be used for the sensitivity analysis of the primary endpoint.

Safety Set: The safety set will consist of all patients receiving at least one dose of study treatment. The patients will be grouped according to the treatment regimen actually received at Visit 3. The safety set will be used for the safety analyses.

PK Set: The PK set will consist of all patients in the safety set with at least one pridopidine concentration sample result reported. The PK set will be used for the PK analyses.

7.8 Description of Subgroups to be Analyzed

Subgroup analyses may be conducted as deemed necessary and will be defined in the SAP.

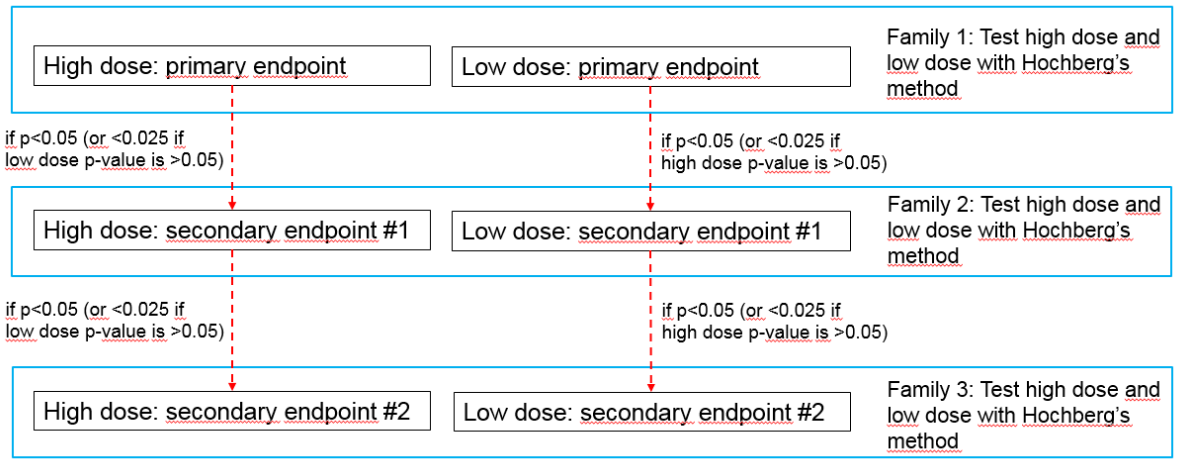
7.9 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.3 or later. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. All collected data will be listed in data listings.

Each primary and secondary endpoint includes the comparison of each of the two dosages of pridopidine vs placebo. The overall Type I error rate within the family of each primary and secondary endpoint will be maintained by using the Hochberg's step-up method. Furthermore, the primary and secondary endpoint families will be evaluated in a hierarchical manner as outlined above. For this purpose, a matched parallel gatekeeping procedure will be used.

The testing strategy is summarized in Figure 2 and detailed below.

Figure 2 Summary of the Statistical Testing Strategy



The primary endpoint family (F1) consists of two null hypotheses H_{11} and H_{12} for comparisons of pridopidine 100 mg BID and pridopidine 150 mg BID, respectively, with placebo in regard to the primary endpoint. That is, $F_1 = \{H_{11}, H_{12}\}$. Similarly, the first secondary endpoint family $F_2 = \{H_{21}, H_{22}\}$ consists of H_{21} and H_{22} for comparisons of pridopidine 100 mg BID and pridopidine 150 mg BID, respectively, with placebo in regard to the secondary endpoint ranked first in the hierarchy. The family F_1 serves as a gatekeeper for F_2 such that F_2 will be examined only when the gatekeeper F_1 has been successfully passed, i.e., at least one of the hypotheses in the F_1 family is rejected. The significance in the secondary endpoint ranked first for a dose level cannot be claimed unless its corresponding primary hypothesis is significant. The same procedure will continue to the next families of secondary endpoints according to the hierarchy defined for the endpoints. The procedure will go on as long as the previous gatekeeper has been successfully passed.

Each family of primary and secondary endpoints includes the comparison of each of the two dosages of pridopidine vs placebo. The overall Type I error rate within the family of each primary and secondary objective with respect to the two active dosages will be maintained by using the Hochberg's step-up method. According to Hochberg's step-up method, the higher of the two p-values will be compared to a two-sided significance level of 0.05. In case the higher p-value is <0.05, both of the two comparisons will be judged as statistically significant. In case the higher p-value is not <0.05, the lower p-value will be compared to a two-sided significance level of 0.025. In case the higher p-value is not <0.05 and the lower p--value is <0.025, only the comparison related to the lower p-value will be judged as statistically significant. The testing will continue if at least one dose level was statistically significant in the previous family. Statistical significance will only be claimed if the dose level in question was statistically significant in the previous family.

In case not all endpoints are compared as a part of the hierarchical testing procedure, the statistical tests will be reported in any case and interpreted in an explorative manner.

7.9.1 Analysis of Primary Endpoint

The primary endpoint will be analyzed using a Mixed Model for Repeated Measures (MMRM with no imputation using the mITT population. The Baseline (Visit 2) score will be included as a covariate and the treatment group (pridopidine 100 mg BID, pridopidine 150 mg BID or placebo), Visit 4, Visit 5, Visit 6 or Visit 7/ET, and the interaction between treatment group and visit as fixed factors in the MMRM. An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure (TOEPH) will be used instead. In case the model will not converge with the heterogeneous Toeplitz structure, heterogeneous compound symmetry will be used. The denominator degrees of freedom will be computed using the Kenward-Roger method. The difference between each dosage of pridopidine vs placebo at Visit 7/ET along with the 95% CIs and associated p-value will be estimated from the MMRM. The differences at Visit 4 and Visit 6 will be estimated as well from the same model.

Sensitivity analyses of the primary endpoint will be conducted in the ITT set with multiple imputation methods, both assuming that data are missing at random and not missing at random. The analysis assuming that data are not missing at random will be conducted with the Copy-Reference approach, i.e., assuming that the patients who have missing data will follow the trajectories of the placebo-treated patients after the first visit with missing data. Further sensitivity analysis will be conducted in the completer set with MMRM. In addition, sensitivity analyses will be conducted by including the retrieved drop-out data (data captured from the drop-outs after the end-of-study visit when the patient is free of study treatment) to the mITT analysis. All efforts will be made to perform scheduled efficacy assessments after patients discontinue.

7.9.2 Analysis of Secondary Endpoint

The continuous secondary endpoints (sum scores derived from UDysRS, UPDRS, and endpoints based on the "ON/OFF" home diaries) will be analyzed with MMRM models similar to those used for analysis of the primary endpoint. The mITT population will be used for these analyses.

The categorical secondary endpoints (proportion of responders and proportion of patients improving based on PGI-C or CGI-C) will be analyzed in the mITT population using the generalized linear mixed model (using the GLIMMIX from SAS for binomial data with logit link). This analysis will model the response data from each postbaseline visit with treatment group (pridopidine 100 mg BID, pridopidine 150 mg BID or placebo), visit (Visit 4, Visit 5, Visit 6 or Visit 7/ET), and interaction between the treatment group and visit. An unstructured covariance structure will be used for the repeated measures model. In case the model will not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure will be used instead. In case the model will not converge with the heterogeneous Toeplitz structure, heterogeneous compound symmetry will be used instead. The odds ratio for the treatment difference, 95% CIs for the odds ratio and p-value will be provided.

7.9.3 Pharmacokinetic Analyses

The PK analysis will be conducted on the PK set. Plasma concentrations of pridopidine and its metabolite TV-45065 will be listed and summarized by visit and time point. Descriptive statistics will include the mean, coefficient of variation, geometric mean, minimum, median, and maximum. Relationships between plasma concentrations of pridopidine and TV-45065 at Visit 4, Visit 6, and Visit 7/ET vs key safety and efficacy measures will be explored graphically. Additional details will be provided in the SAP.

7.9.4 Safety Analyses

The safety analysis will be conducted on the safety set. The AEs will be coded according to the MedDRA and treatment-emergent adverse events (TEAEs) summarized by treatment group, system organ class and preferred term. Further summaries will be done by seriousness, severity, relationship to study treatment and actual dose at the time of onset.

Vital signs, ECG data and laboratory tests at baseline (last non-missing results prior to the first dose of study drug, each postbaseline visit, and changes from baseline to each of the postbaseline visits will be summarized with descriptive statistics. Shift tables for the laboratory tests based on a classification of values as low, normal, or high with respect to the reference range will be summarized.

For vital signs, orthostatic hypotension is defined as a reduction of 20 mmHg or more in systolic blood pressure, or a reduction of 10 mmHg or more in diastolic blood pressure, for the standing measurement compared to the supine measurement. The proportion of patients with orthostatic hypotension will be summarized with shift tables.

For ECG data, absolute QTcF of >450 msec, >480 msec, and >500 msec, changes from baseline in QTcF>30 msec and <60 msec, and changes in QTcF>60 msec throughout the study will be summarized.

All other safety data will be summarized with descriptive methods.

7.9.5 Interim Analyses

No interim analyses are planned for the study.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6 (R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include, but are not limited to, diary cards/laboratory reports/ECG strips/rater scales, etc.

Investigative site personnel will enter patient data into Medidata RAVE. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable Prilenia Therapeutics standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG).

After database lock, each study site will receive a CDROM containing all of their site specific eCRF data as entered into Medidata RAVE for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate CDROM copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/ IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonized tripartite guideline E6 (R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply Prilenia Therapeutics or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Patient Information and Consent

Written informed consent in compliance with regulatory authority regulations shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be patient to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA), or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 Code of Federal Regulations (CFR) 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the patient's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 (R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol

- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae (CV) for the investigator and each subinvestigator listed on Form FDA 1572
- Medical License (ML) for the investigator and each applicable subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least two 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 two years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The administrative structure will include a DSMB and EAC.

11.1 Monitoring

11.1.1 Independent Data Safety Monitoring Board

During the study, an independent DSMB will periodically review accumulating unblinded safety data and SAE/AE in real time. The detailed description is provided in Section 6.6.

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from,

or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Prilenia Therapeutics has every intention of completing the study, Prilenia Therapeutics reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study will be defined as the final date on which data were (or are expected to be) collected.

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study report is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

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Food and Drug Administration. The Voice of the Patient, Parkinson’s Disease. Public Meeting, 22 Sep 2015. Report date Apr 2016 [cited 21 Dec 2018]. Available from: https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm498266.pdf

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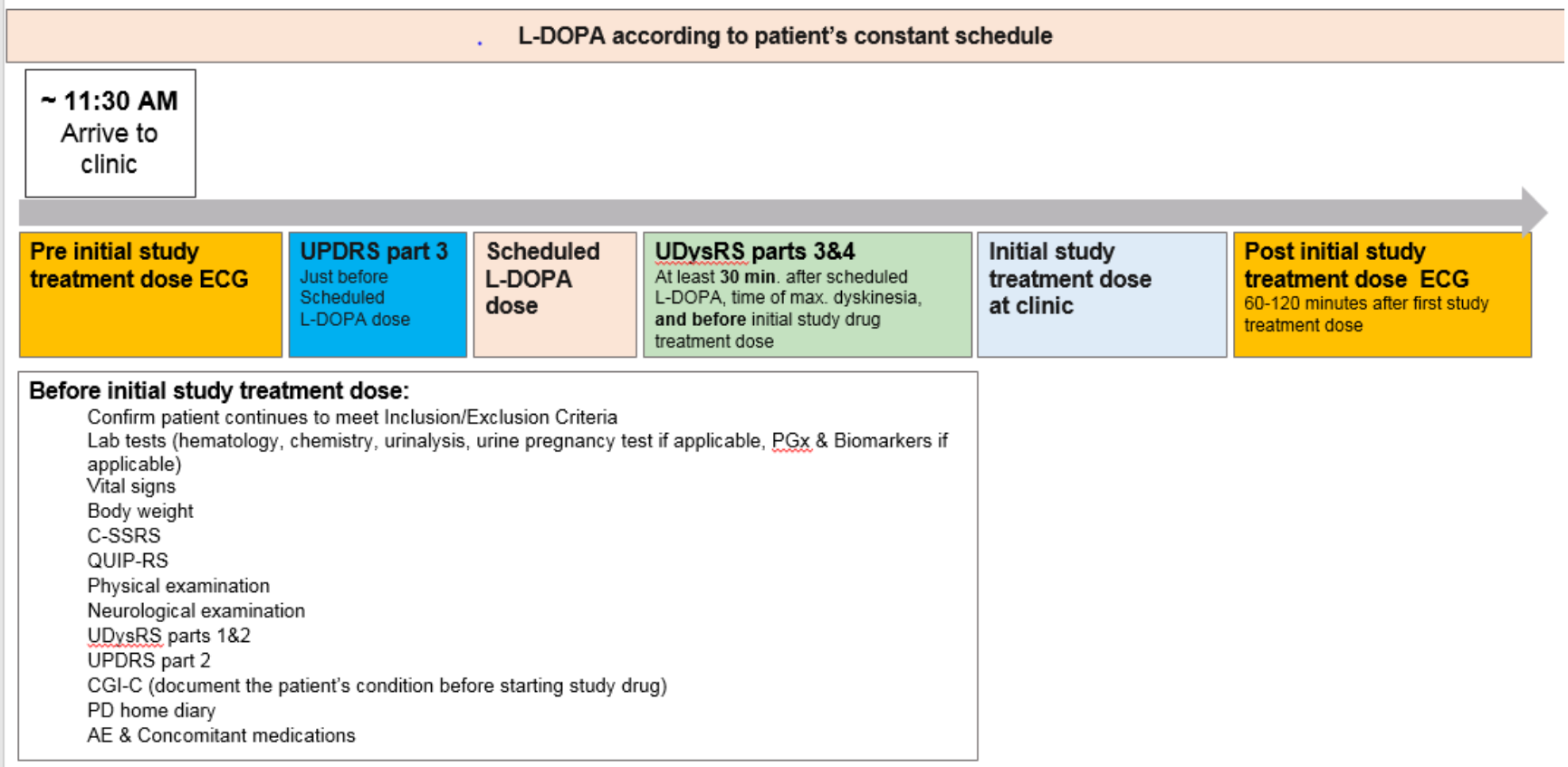
Johnston TH, Geva M, Steiner L, Orbach A, Papapetropoulos S, Savola JM, et al. Pridopidine, a clinic-ready compound, reduces 3,4-dihydroxyphenylalanine-induced dyskinesia in parkinsonian macaques. Mov Disord. Epub 2018 Dec 21.

Kumar N, Van Gerpen JA, Bower JH, Ahlskog JE. Levodopa-dyskinesia incidence by age of Parkinson's disease onset. Mov Disord. 2005;20(3):342-4.

Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med. 2000;342(20):1484-91.

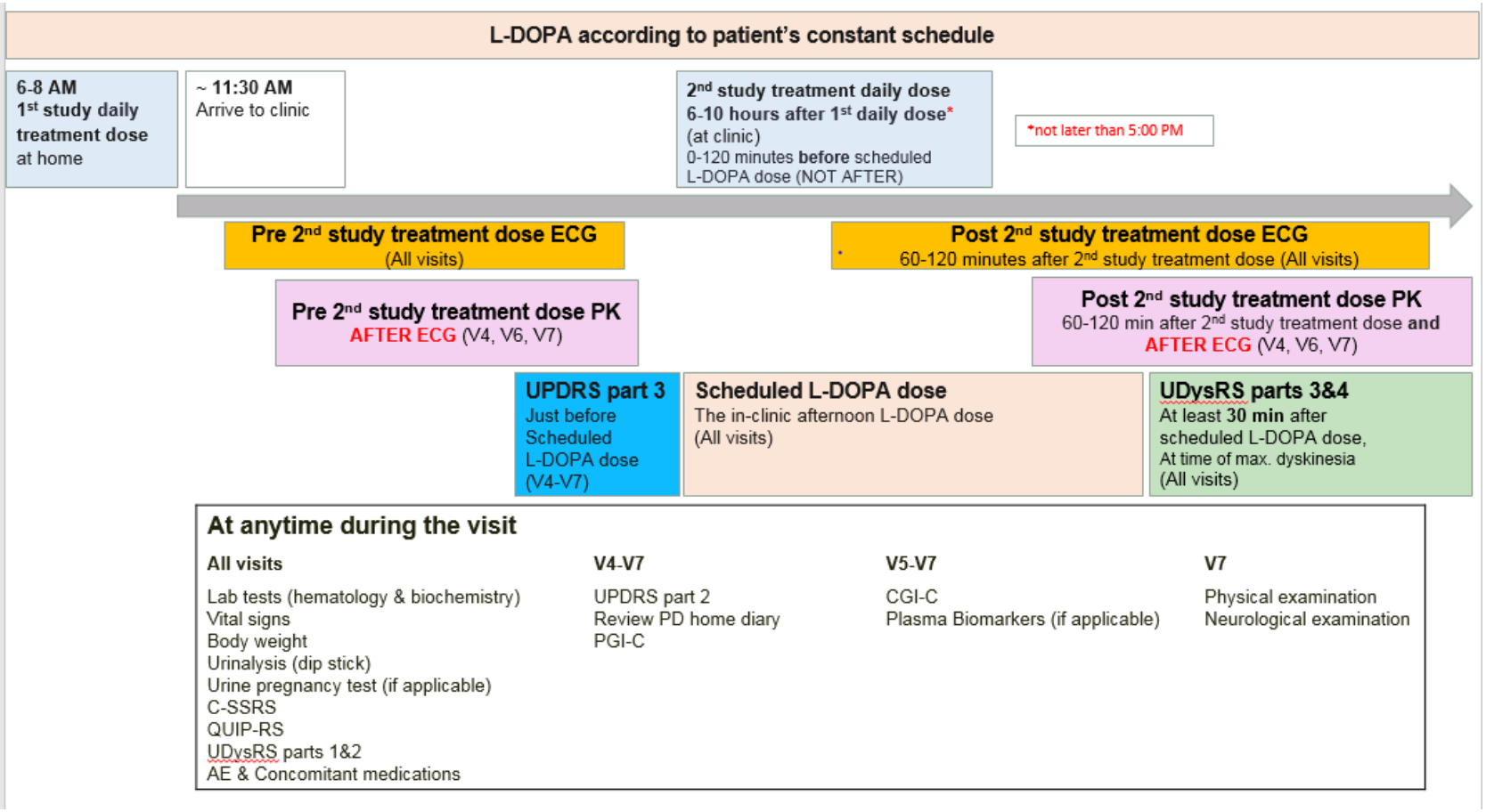
13 Appendices

13.1 Visit Assessments and Procedures Flow – Baseline (Visit 2)



Abbreviations: AE, adverse event; CGI-C, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; L-DOPA, 3,4-dihydroxyphenylalanine; max, maximum; min, minute; PD, Parkinson's disease; QUIP-RS, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

13.2 Visit Assessments and Procedures Flow – Visit 3 – Visit 7



Abbreviations: AE, adverse event; CGI-C, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; L-DOPA, 3,4-dihydroxyphenylalanine; lab, laboratory; max, maximum; min, minute; PD, Parkinson's disease; PGI-C, Patient Global Impression of Change; PK, pharmacokinetic; QUIP-RS, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; V, visit.