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

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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)

Study code: PL101-LID201

Phase 2B study (Modified Post-COVID-19 to a Phase 2 PoC Study)

STATISTICAL ANALYSIS PLAN, VERSION 1.0

23 July 2020

Signature Page

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Contents

1 Abbreviations

Term	Description
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BP	Blood Pressure
CGI-C	Clinical Global Impression of Change
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
ET	Early Termination
ITT	Intention-To-Treat
LID	Levodopa-Induced Dyskinesia
LS	Least Square
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intention-To-Treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini–Mental State Examination
NMSS	Non-Motor Symptom Scale
PD	Parkinson's Disease
PDQ-39	39-item Parkinson's Disease Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic

PT	Preferred Term
QD	Once daily
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-DD	World Health Organization Drug Dictionary

2 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analysis, shortly after the decision to terminate the study due to coronavirus disease 2019 (COVID-19) pandemic and other reasons. The SAP will serve as a complement to the study protocol and supersedes it in case of differences. The study is still ongoing, and this SAP is being finalized prior to locking the database and unblinding the study.

3 Study Objectives

The objectives of the study as indicated in the protocol are described below. Since the study is being terminated early, there may not be a sufficient number of subjects within each treatment arm. Therefore, the objectives may also include evaluation of only pridopidine 100 mg BID dose at the end of titration at Week 3/5 (Visit 3), the pooled active doses (pridopidine 100 mg BID and 150 mg BID) at Week 8/10 (Visit 5) and potentially comparing results with placebo data from historical data.
Study weeks are further explained in Section **Error! Reference source not found.**.

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of 2 dosages of pridopidine administered twice daily (BID), 100 mg BID and 150 mg BID (individually and combined) vs placebo BID for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's disease (PD) at Week 8/10 (Visit 5).

The primary objective will also evaluate subjects on 100 mg BID as compared to placebo at Week 3/5(Visit 3), since both 100 mg BID and 150 mg BID groups are on 100 mg BID at the end of titration.

3.2 Secondary Objectives

1. To determine if the effect of pridopidine (100 mg BID, 150 mg BID and pooled 100+150 mg BID) vs placebo is associated with changes (worsening or improvement) in parkinsonian features at Weeks 3/5 and 8/10 (Visits 3 and 5).

2. To evaluate the effect of pridopidine (100 mg BID, 150 mg BID and pooled 100+150 mg BID) vs placebo on measures of global improvement, activities of daily living, and quality of life in subjects with PD LID at Weeks 3/5 and 8/10 (Visits 3 and 5).

3.3 Safety Objective

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.

3.4 Pharmacokinetic (PK) Objectives:

1. To evaluate the PK of pridopidine and its main metabolite TV-45065 in subjects with PD-LID

2. To explore the relationship between pridopidine exposure and dyskinesia

4 Design and Type of the Study

The study was originally designed as a 16-week study with a 2 week titration phase (January 24th, 2019 original protocol, v1.1) and was modified on 15th October 2019 (Amendment 1) via Safety Urgent Measures letter to increase the titration period from 2 to 4 weeks. This change along with other changes were implemented in Amendment 1 (19th November 2019, v2.0). The duration of the study was thus increased from 16 to 18 weeks.

The study was designed as a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel-group 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.

Due to COVID-19 the study was terminated early and is now considered a Phase 2 proof of concept (PoC) study. The study will evaluate efficacy and safety of the two doses of pridopidine vs placebo as well as the pooled active doses vs. placebo.

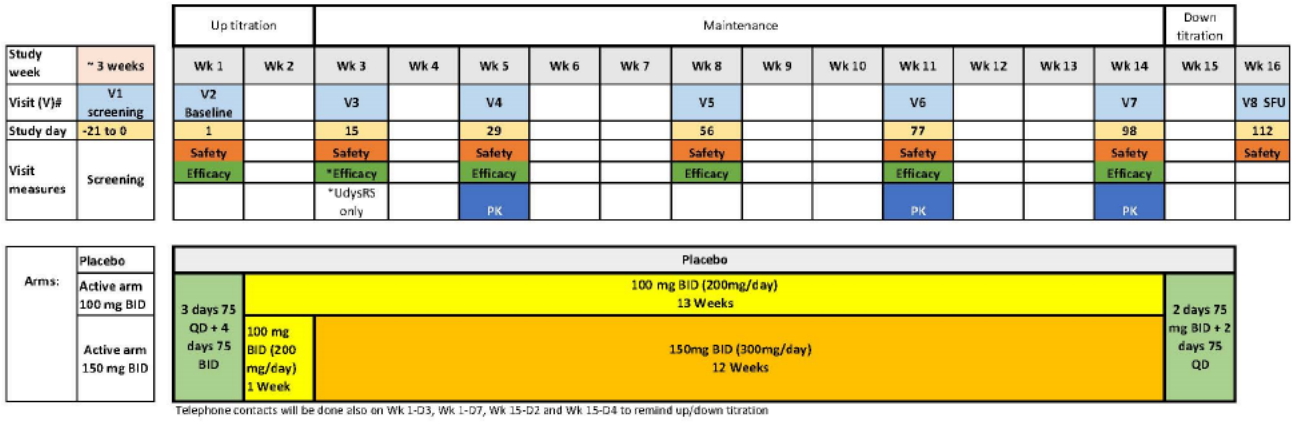
4.1 Visit Structure

Study visits in the original and Amendment 1 (amended as per the Oct 15th Safety letter) are as below:

Prilenia Therapeutics — Pridopidine

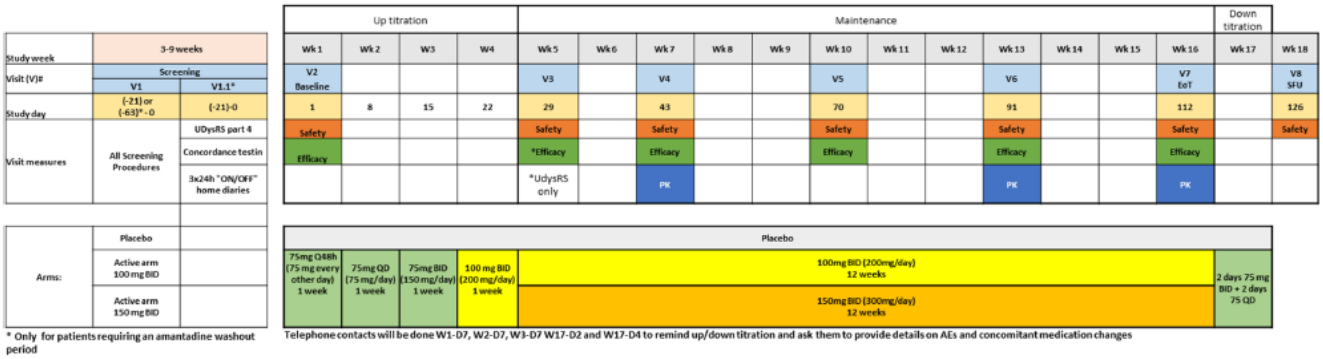
Protocol: PL101-LID201 Final/1.1 — 24 Jan 2019

S-Figure 1 Study Design



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

Figure 1 **Study Design**



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

4.2 Study Treatment

Subjects who met eligibility criteria were randomly assigned at Baseline (Visit 2) to receive pridopidine 100 mg BID, 150 mg BID or placebo using a 1:1:1 randomization. No stratification factors were used in the randomization. During the 14/16-week active treatment period, two oral capsules were taken in the morning (at 7:00 AM ±1 hour) and 2 oral capsules in the afternoon (at 1:00 PM ±1 hour). The time difference between the 2 administrations was 6-8 hours apart.

Subjects in the active treatment arms underwent either a 2-week (original amendment) or a 4-week (Amendment 1) dosage titration period as described below:

- Original protocol: Subjects who underwent a 2-week titration period were treated for 3 days with pridopidine 75 mg QD (once daily), 4 days of pridopidine 75 mg BID, and 1 week with pridopidine 100 mg BID.
- Amendment 1: Subjects who underwent a 4-week titration period were treated with pridopidine 75 mg on alternate days (Q48h) during one week, 75 mg QD during 1 week ,75 mg BID during 1 week , and 100 mg BID during one week.

Under both protocol versions, maintenance treatment with pridopidine 100 mg BID or 150 mg BID was then continued for an additional 12 weeks.

Subjects randomly assigned to the placebo arm received matching placebo throughout the treatment period in a double-blind fashion at the same dosing schedule as subjects assigned to the active treatments.

At the end of the maintenance period or at early termination (ET), all subjects underwent a down-titration period in which they received 1 capsule of pridopidine 75 mg (or the matching placebo) and 1 capsule of

placebo BID on Days 1 to 2 followed by one capsule of pridopidine 75 mg (or the matching placebo) and one capsule of placebo QD on Days 3 to 4 of Week 17.

4.3 Study Population

PD subjects with a documentation of mild to moderate LID (subjects with severe LID were included after Amendment 1) by the investigator and by home diary were enrolled in the study. The full list of inclusion criteria can be found in Section 4.1.1 of the study protocol and exclusion criteria in Section 4.1.2 of the study protocol.

5 Analysis Populations

The following analysis populations (analysis sets) will be used for the analysis of the disposition, demographic, efficacy, safety and PK data.

Subjects will be grouped according to the actual treatment received if there were inaccuracies in study drug taken compared to what treatment subjects were randomized to.

5.1 Efficacy Evaluable (EE) Population

The Efficacy Evaluable 1 (EE1) population includes all subjects that were randomized, received at least 80% of their dose of study drug and were on treatment at Visit 3 (Week 3/5) and have a post-randomization assessment of the primary endpoint.

The Efficacy Evaluable 2 (EE2) population includes all subjects who were on treatment at Visit 5 (Week 8/10), have at least 80% compliance to study drug and have a valid assessment of the primary endpoint.

5.2 Safety Population

The Safety Population will include all subjects receiving at least one dose of study treatment. The subjects will be grouped according to the highest treatment regimen actually reached.. Anyone with mean total daily dose > 0 and ≤ 100 mg BID will be included in the 100 mg BID group, anyone with mean total daily dose > 100 mg BID will be included in the 150 mg BID group. The Safety Population will be used for the safety analyses.

5.3 PK Population

The PK Population will include all subjects in the safety population with at least one pridopidine concentration sample result reported. The PK population will be used for the PK analyses. The PK analyses may or may not be performed based on outcome of other analyses and availability of PK data.

6 Endpoints

The following endpoints are pre-defined for this study.

6.1 Primary Endpoint: Sum of Parts 1, 3, and 4 of UDysRS

The primary endpoint is the mean change and % change from Baseline (Visit 2) to Week 3/5 (Visit 3) and Week 8/10 (Visit 5) in the sum of Parts 1, 3, and 4 of the Unified Dyskinesia Rating Scale (UDysRS) while the patient is in the peak "ON" state and experiencing maximal peak dose dyskinesia.

The sum of Parts 1, 3, and 4 of the UDysRS will be calculated as the sum of Part 1 (historical disability of ON-dyskinesia impact), Part 3 (objective impairment) and Part 4 (objective disability). The sum scores will be calculated as follows:

- Part 1: sum of UDysRS items 1-11; 0-44 points
- Part 3: sum of UDysRS items 16-22; 0-28 points
- Part 4: sum of UDysRS items 23-26; 0-16 points.

For the sum scores of Parts 1, 3 and 4, the following imputation rules will be used in case of incomplete data:

- Part 1: Part 1 is sum of Part 1A (item 1) and Part 1B (items 2-11)
  - If Part 1A (item 1) is missing, the Part 1 sum score will be set as missing.
  - If there is one missing item in Part 1B (items 2-11), the missing item will be replaced by the average of the non-missing items 2-11 from the same subject.
  - If there is more than one missing item in Part 1B (items 2-11), the Part 1 sum score will be set as missing.
- Part 3:
  - If there is one missing item in Part 3 (items 16-22), the missing item will be replaced by the average of the non-missing items 16-22 from the same subject.
  - If there is more than one missing item in Part 3 (items 16-22), the Part 3 sum score will be set as missing.
- Part 4:
  - If there is one missing item in Part 4 (items 23-26), the missing item will be replaced by the average of the non-missing items 23-26 from the same subject.
  - If there is more than one missing item in Part 4 (items 23-26), the Part 4 sum score will be set as missing.
- Sum of Parts 1, 3 and 4:
  - The sum of Parts 1, 3 and 4 will be calculated only if sum of Part 1, sum of Part 3 and sum of Part 4 are all non-missing, after applying the imputation rules presented above. Otherwise, the sum of Parts 1, 3 and 4 will be set as missing.

6.2 Secondary Endpoints

Secondary endpoints are defined as below:

6.2.1 ON time without troublesome dyskinesia and other endpoints based on "ON/OFF" home diary

Mean actual value and mean change from Baseline (Visit 2) to all post-baseline visits in ON time without troublesome dyskinesia based on "ON/OFF" home diary completed by the subjects during 3 consecutive 24 hour intervals will be evaluated as a secondary endpoint. The daily ON time without troublesome dyskinesia is defined as the sum of daily ON time without dyskinesia and daily ON time with non-troublesome dyskinesia.

This endpoint will be presented both as daily ON time without troublesome dyskinesia during waking hours and as total number of hours with ON time without troublesome dyskinesia, normalized to a 16-hour waking day.

The Baseline is defined as the home diary obtained on 3 consecutive days prior to the Baseline visit (Visit 2). The diaries collected during the Maintenance Period, on 3 consecutive days prior to Visit 4 (Week 5/7), Visit 5 (Week 8/10), Visit 6 (Week 11/13) and Visit 7 (Week 14/16) will be used as response variables. In case of missing or non-valid diary days during the 3 consecutive days prior to the visits during the Maintenance Period, the last 3 recorded days between Visits 3-4 (for Visit 4), 4-5 (for Visit 5), 5-6 (for Visit 6) and 6-7 (for Visit 7), but no more than 7 days before the visit with non-missing and valid diary data will be used instead. In case of missing or non-valid diary days before Baseline, the 3 last non-missing and valid diary days prior to the first dose of study drug will be used regardless of time between the day when the diary was completed and the Baseline visit.

The validity of the diary entries will be checked prior to including a diary day in the summary calculations. Only valid diary days will be included in the diary summarizations. The diary endpoints will be derived as defined below.

- A day will be considered as being valid if at least 44 of the 48 half hour periods during the day have been completed per instructions. That is, for each half hour period, only one entry among the responses (Asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, or ON with troublesome dyskinesia) has been checked. The entry will not be used if no responses are checked or more than one response is checked. If there are duplicate entries (i.e., multiple entries recorded with same date and time interval), the worst entry will be used for the date and time interval in question. The worst entry will be defined in the following order: OFF, ON with troublesome dyskinesia, ON with non-troublesome dyskinesia, ON without dyskinesia, Asleep. On without troublesome dyskinesia

- The diary data expressed as hours will be normalized to 16 waking hours per day. The daily ON time without troublesome dyskinesia will be extrapolated to a 16-hour period by determining the percentage of ON time without troublesome dyskinesia among accurately recorded entries, excluding Asleep time and missing/non-valid recordings, and by multiplying this percentage by 16 hours.

- The mean daily ON time without troublesome dyskinesia prior to each visit will be calculated as mean value of the valid days documented in the subject's diary prior to that visit. In case there are gaps within the 3 days preceding the visit, the last 3 recorded days before the visit will be used regardless of the gaps (as defined above). If there are more than 3 valid days, only the last 3 days will be used. If

there are only 2 valid days, the average of these days will be used. In case there is only 1 valid day, the visit will be considered missing.

As above the following will also be summarized:

- ON time without any dyskinesia
- OFF time

6.2.2 The above analysis will be generated for the EE1 and EE2 populations. Total UDysRS score - Sum of Parts 1 to 4

Mean change and % change from Baseline (Visit 2) to Week 3/5 (Visit 3) and Week 8/10 (Visit 5) in the total UDysRS score (Parts 1 to 4) will be evaluated as a secondary endpoint. The total UDysRS score will be calculated as the sum of Part 1 (historical disability of ON-dyskinesia impact), Part 2 (historical disability of OFF-dyskinesia impact), Part 3 (objective impairment) and Part 4 (objective disability).

The sum scores for Parts 1, 3 and 4 will be calculated similarly as for the primary endpoint. The sum score of Part 2 will be calculated as follows:

- Part 2: sum of UDysRS items 12-15; 0-16 points

For the sum scores of Parts 1, 2, 3 and 4, the following imputation rules will be used in case of incomplete data:

- Part 1: see definition of the primary endpoint
- Part 2: Part 2 is sum of Part 2A (item 12) and Part 2B (items 13-15)
  - If Part 2A (item 12) is missing, the Part 2 sum score will be set as missing.
  - If there is one missing item in Part 2B (items 13-15), the missing item will be replaced by the average of the non-missing items 13-15.
  - If there is more than one missing item in Part 2B (items 13-15), the Part 2 sum score will be set as missing.
- Part 3: see definition of the primary endpoint
- Part 4: see definition of the primary endpoint
- The total UDysRS score
  - The total UDysRS score, i.e. the sum of Parts 1, 2, 3 and 4 will be calculated only if sum of Part 1, sum of Part 2, sum of Part 3 and sum of Part 4 are all non-missing, after applying the imputation rules presented above. Otherwise, the total UDysRS score will be set as missing.

The above analyses will be presented for the EE1 and EE2 populations.

6.2.3 Unified Parkinson's Disease Rating Scale (UPDRS) Part 2

Mean change and % change from Baseline (Visit 2) to each post baseline assessment in the score of Unified Parkinson's Disease Rating Scale (UPDRS) Part 2 will be evaluated as a secondary endpoint. The

UPDRS Part 2 sum score will be calculated as the sum of UPDRS items 5-17 (range 0-52 points). The Part 2 sum score will only be calculated if all 13 items have been completed. In case of at least 1 missing item, the whole score will be set as missing.

The above will be summarized for the EE1 and EE2 population.

6.2.4 Proportion of Responders

Proportion of responders (with improvement in dyskinesia and improvement in dyskinesia with no worsening in parkinsonian motor function separately) at Visits 3 and 5 will be evaluated as a secondary endpoint. 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 motor function is defined as ≤30 minutes increase in OFF time from Baseline (Visit 2).

In addition, proportion of responders with improvements of ≥ 35%, ≥ 25% and ≥ 20% will also be summarized.

A Fisher's exact test will be used to compare differences between each of the active treatment group vs placebo.

The UDysRS score (Parts 1, 3, and 4) will be derived as defined in Section 6.1 and the OFF time as defined in Section 6.2.8, represented as hours normalized to a 16-hour waking day. The percentual change in the UDysRS score from baseline will be calculated as the absolute change divided by the baseline value. A decrease in the UDysRS score indicates improvement.

The visits with missing data in either the UDysRS score (Parts 1, 3, and 4) or in OFF time will be set as missing. However, a sensitivity analysis will be conducted by considering missing data as non-improvements.

The above will be summarized for the EE1 and EE2 population.

6.2.5 UPDRS Part 3 as Measured Immediately Prior to the In-clinic L-DOPA Dose

Mean change and % change Baseline (Visit 2) to each post baseline visit in the UPDRS Part 3 as measured immediately prior to the in-clinic L-DOPA dose will be evaluated as a secondary endpoint. The UPDRS Part 3 sum score will be calculated as the sum of UPDRS items 18-31 (range 0-108 points). The Part 3 sum score will only be calculated if all 27 items have been completed. In case of at least 1 missing item, the whole score will be set as missing.

The above will be summarized for the EE1 and EE2 population.

6.2.6 Patient Global Impression of Change (PGI-C) and Clinician Global Impression of Change (CGI-C)

The proportion of subjects improving based on the Patient Global Impression of Change (PGI-C) and Clinician Global Impression of Change (CGI-C) will be evaluated as secondary endpoints. The PGI-C and CGI-C will be analyzed by categorizing the non-missing assessments as improvements (very much improved, much improved, minimally improved) or non-improvements (no change, minimally worse, much worse, very much worse). The visits with missing assessments will be set as missing.

A Fisher's exact test will be used to compare differences between each of the active treatment group vs placebo.

PGI-C and CGI-C will be summarized for the EE1 population for each post baseline assessment.

6.2.7 Parkinson's Disease Questionnaire -39 (PDQ-39)

Since PDQ-39 was removed per the amendment any available data will be included in listings and no analyses will be performed.

6.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be presented in listings and may be analyzed post-hoc.

- Parkinson's Disease Sleep Scale (PDSS-2) overall score

  The PDSS-2 overall score will be calculated as the sum of responses to the 15 questions, each scored from 0 to 4 (Never = 0, Occasionally = 1, Sometimes = 2, Often = 3, Very often =4). In case of at least 1 missing item, the overall PDSS-2 score will be set as missing.

- Total Non-motor Symptom Scale (NMSS) score

  The NMSS includes 30 items on 9 different domains. For each item, the severity is rated on a scale from 0 to 3 and frequency from 1 to 4. These two ratings are multiplied to derive a final item score, ranging from 0 to 12. A domain score is calculated for each of the 9 domains as the sum of the item scores within that domain. The NMSS total score is the sum of all 30 item scores (ranging from 0 to 360).

6.4 Safety and tolerability endpoints

Following safety and tolerability endpoints will be evaluated. For more details, see section 15 (Analysis of safety and tolerability data).

- Safety
  - Adverse events (AEs) occurring throughout the study.

- QTc parameters: absolute QTcF of >450 msec, >480 msec and ≤500 msec, and >500 msec, mean QTcF, changes in QTcF>30 msec and ≤60 msec, and changes in QTcF>60 msec throughout the study.
- Clinical safety laboratory (Only Creatinine Clearance, Serum Creatinine, Potassium and Magnesium), vital signs (including assessment of orthostatic hypotension), physical and neurological examination, concomitant medications throughout the study.
- Columbia-Suicide Severity Rating Scale (C-SSRS)- At baseline and Since last visit throughout the study.
- Change from Baseline (Visit 2) in impulse control disorder as evaluated by the Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) throughout the study.

- Tolerability
  - The number (%) of subjects who complete the study drug
  - The number (%) of subjects who fail to complete the study drug due to AEs
  - The number (%) of subjects who fail to complete the study drug due to QTcF and QT stopping rules, seizure or convulsions.

6.5 PK Endpoints

Plasma concentrations of pridopidine and its metabolite TV-45065.

7 Sample Size Considerations

The sample size calculations for the study were based on 38 randomized subjects in each treatment group (114 randomized subjects overall) providing 80% power to detect a between-group difference of 8.5 points in the UDysRS score with standard deviation of 13 points using two sided significance level of 0.05. Assuming a drop-out rate of 15%, a total of 135 subjects were to 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.

Due to COVID-19 the study was terminated early.

8 Statistical Hypotheses

Each primary and secondary endpoint includes the comparison of each of the two dosages of pridopidine vs placebo as well as the two Pridopidine doses combined vs. placebo.

9 General Statistical Considerations

All data from all subjects entered into the database will be included in subject data listings. The listings will be generally sorted by study drug, center and subject number (and by visit, if applicable). In addition to the data collected on the case report form, all other study data, including data collected electronically outside of the case report form and all protocol violations will be listed.

All applicable data will be summarized by treatment group (pridopidine 150 mg BID, pridopidine 100 mg BID, pridopidine 150 mg BID and 100 mg BID pooled active or placebo). Where appropriate, data will be summarized by visit in addition to the treatment group.

Unless otherwise indicated unscheduled or repeat assessments will not be included in summary tables, but will be included in listings. For safety analyses which summarize the total number of abnormal values over the whole study or period, the unscheduled or repeat assessments will be used for these totals, but not for the visit-specific analyses. For assessments done at the ET visit, these assessments will be used as data for the scheduled visit closest to the ET time point, in case the corresponding data are missing from this closest visit.

Unless specific otherwise, baseline is defined as the last non-missing assessment prior to the first dose of the study drug.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum, and maximum. Standard error of the mean (SEM) will also be provided for summaries of efficacy data, if relevant.

Descriptive statistics for categorical data will include frequency counts and percentages. The total number of subjects in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise. Missing categories will be included as appropriate.

Significance testing will be 2-sided using $\alpha = 0.05$, unless otherwise specified.

All statistical analyses and summaries will be produced using SAS version 9.4 or higher. Deviations from the statistical plan will be reported in the clinical study report, including the rationale for the deviation.

9.1 Adjustment for Covariates

For the analysis of efficacy endpoints, the baseline value of the endpoint in question will be included as a baseline covariate (for continuous endpoints) or as a stratification factor (for categorical endpoints), if available. As a general rule, the last assessment before the first dose of study drug at the Baseline visit (Visit 2) will be used as the baseline covariate.

As no stratification factors were used in the randomization, the primary analyses will not include any additional covariates.

9.2 Handling of Drop-Outs or Missing Data

In this study, missing or incomplete efficacy data are managed in two steps. In the first step, imputation methods are defined to derive endpoints from questionnaires or diaries with incomplete data within a visit or time point. In the second step, statistical methods are defined for analysis of incomplete longitudinal datasets in case data are still missing after the first step.

9.2.1 Imputation of Incomplete Data within a Visit or Timepoint

- The imputation rules for the incomplete UDysRS ratings are provided in Sections 6.1 and 6.2, in order to derive the endpoints based on UDysRS.

- The imputation rules for the incomplete "ON/OFF" home diaries (i.e., diaries for days with less or more than 24 recorded hours per day) are provided in Section 6.2.1, in order to derive the relevant endpoints based on the "ON/OFF" home diaries.

- The imputation rules for the other continuous efficacy endpoints derived from questionnaires (UPDRS sum scores, PDQ-39 summary index and dimension scores, PDSS-2 and NMSS scores) are provided in Sections 6.2 and 6.3.

9.2.2 Handling of Missing Longitudinal Data

The following methods will be used to manage longitudinal incomplete data after the data within each visit has been imputed as described above.

- For the primary efficacy analysis, likelihood-based modeling approach will be used to handle incomplete data. For this purpose, Mixed Model for Repeated Measures (MMRM) will be applied, see Section 14.1.
- Sensitivity analyses for the primary endpoint data will be conducted using the Multiple Imputation (MI) approach. For the MI approach, each missing value will be replaced with a set of plausible values that represent the uncertainty about the right value to impute, see Section 14.1. Imputation will only be done under the assumption of Missing At Random (MAR).

Safety data will not be subject to any imputation and will be summarized on an observed case basis.

9.3 Interim Analyses and Data Monitoring

No interim analyses were planned.

Since the study was terminated prematurely before 30 subjects were enrolled no formal Drug Safety Monitoring Board (DSMB) meeting was conducted.

9.4 Multiple Comparison/Multiplicity

Since the study was terminated early and the sample size is small no adjustment for multiplicity will be performed. Statistical testing and p-values will be evaluated based on totality of information in assessing efficacy and provided primarily for descriptive purposes.

10 Subjects Disposition, Demographic and Other Baseline Characteristics

The following will be summarized in the Subject Disposition table.

- A summary of the number of subjects in each of the analysis populations.
- The number and percentage of subjects who were randomized but not treated.
- The count and percentage of subjects who completed or discontinued from the study or treatment. For those who discontinued from the study or treatment, the primary reason for discontinuation from the study or treatment will be presented.

Demographics and baseline characteristics will be summarized descriptively for the Safety Population, by treatment group and overall. For categorical endpoints, categories for missing data will be presented.

The following variables will be summarized:

- Demographics: age (continuous, calculated as date of informed consent minus date of birth, divided by 365.25), age categorized as <65 years versus ≥65 years, gender, ethnicity, race, height, weight, BMI (calculated as weight [kg] divided by squared height [m^2]) and country. In case of missing day of birth, the day will be imputed as 15. In case of missing month of birth, the month will be imputed as 6.
- PD history: time since diagnosis of PD, time since start of levodopa treatment and time since onset of levodopa-induced dyskinesia, all measured in years at time of informed consent
- Report of direct observation of ON-time with dyskinesia during half-hour periods of the screening visit
- Baseline dyskinesia status: total score on UDysRS part 4 disability scale.
- Cognitive status: Mini–Mental State Examination (MMSE) total score (as categorical, % of subjects with a score of 30, 29, 28, 27, 26 or <26)
- Distribution of Modified Hoehn and Yahr stages
- Total daily levodopa dose (mg) and distribution of dosing frequency at Screening.

11 Prior and Concomitant Medications

Prior and Concomitant medications data are coded using WHODD Global-B3-Sep 2018 and will be presented in listings with no summary tables.

12 Medical History

Medical History data will be presented in listings with no summary tables.

13 Protocol Deviations

Protocol Deviations data will be presented in listings with no summary tables.

14 Analysis of Efficacy

Each primary and secondary endpoint of this study includes the comparison of each of the two dosages of pridopidine vs placebo and the two pooled active doses vs placebo.

14.1 Primary Endpoint

The primary endpoint of this study is the mean change from Baseline (Visit 2) to Visit 3 and Visit 5 in the sum of Parts 1, 3, and 4 of the UDysRS. The difference in the primary endpoint between the groups (pridopidine 150 mg BID versus placebo, pridopidine 100 mg BID versus placebo) will be estimated using a MMRM using the EE1 and EE2 populations after imputing missing data under assumption of MAR. The model will include the observed changes from Baseline using Visits 3, 4, 5, 6 and 7 as the response values. The treatment difference at each visit will be estimated using contrasts. The MMRM will include the treatment group (pridopidine 150 mg BID, pridopidine 100 mg BID or placebo), visit (3, 4, 5, 6 or 7) and the interaction between the treatment group and visit as fixed factors. The baseline value will be used as a covariate in the model.

A separate analysis will compare pooled active vs placebo under same assumptions as above.

An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, heterogeneous Toeplitz structure (TOEPH), Autoregressive with heterogeneity (ARH (1)), Heterogeneous variances with Compound Symmetry (CSH), Toeplitz (TOEP), Autoregressive(1) (AR(1)) or Compound Symmetry without heterogeneous variances (CS) covariance structure will be used instead in this order. The denominator degrees of freedom will be computed using the Kenward-Roger method.

The least square (LS) means, standard errors and LS mean differences between pridopidine 150 mg BID versus placebo and pridopidine 100 mg BID versus placebo at each visit along with the 95% confidence intervals (CIs) will be provided. The nominal p-values for the hypothesis testing will also be provided. Treatment difference will be assessed with a 2-sided alpha level of 0.05.

The EE1 and EE2 populations will be used for the primary efficacy analysis.

The above analysis will be conducted after imputation of missing data using multiple imputations (MI) under MAR assumption: This methodology will structure data based on missing data patterns. The method will be based on a missingness pattern having a monotone structure, i.e. if among the observations over time one data value is missing, all other values after this missing value will also be treated as missing. For subjects with intermittent missing values, before performing MI, a monotone missingness pattern will be generated. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. The MI procedure in SAS will be used for this purpose and this first MI step is planned

to be repeated 100 times, creating several different datasets with a monotone missing data structure. Seed value of 1995 will be used in the MI procedure. The imputation is based on the MAR assumption, i.e. the missing data are assumed to follow the same model as the other subjects in their respective treatment arm.

After this, the remaining missing data will be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the created dataset with a monotone missing data pattern, the MI procedure in SAS will used to impute missing values based on a sequential procedure reflecting the monotone missing data pattern. Subjects with the first missing value occurring at Visit 3 will have their missing Visit 3 value replaced by an imputed value from a regression model with treatment group and the baseline value as explanatory variables. In the next step, subjects with their Visit 4 value missing will have their missing Visit 4 value replaced by an imputed value from a regression model with treatment group, baseline value and the Visit 3 value as explanatory variables. In the next step, subjects with their Visit 5 value missing will have their missing Visit 5 value replaced by an imputed value from a regression model with treatment group, baseline value and the Visit 3 and Visit 4 values as explanatory variables. Similar procedure will be used to replace the missing values at Visit 6 and 7.

The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the sensitivity analysis of the primary endpoint. MMRM models similar as described for the primary analysis will thus be run on each of the 100 generated imputed datasets and the difference between the treatment groups at Visit 7 will be estimated. Finally, the MIANALYZE procedure in SAS will be applied to combine the results from these analyses to derive overall estimates of the treatment differences at Visit 7. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated.

14.2 Secondary Endpoints

14.2.1 Continuous Secondary Endpoints

The secondary endpoints that will be treated as continuous (all endpoints derived from “ON/OFF” home diaries, UDysRS questionnaire and UPDRS questionnaire part 2 and 3) will be analyzed with MMRMs similar to the one used for the primary endpoint. The baseline value of the analysis variable in question will be used as the baseline covariate in the MMRM. The analyses will be performed in the EE1 and EE2 set. In addition to Visit 7, data from Visits 3, 4, 5 and 6 will be analyzed as well.

For “ON/OFF” home diaries, in addition to the secondary endpoints, also ON time with troublesome dyskinesia and ON time with ON time with non-troublesome dyskinesia will be analyzed as well.

For UDysRS, all four sum scores (Part 1, Part 2, Part 3 and Part 4), Individual parts.

15 Analysis of Safety and Tolerability

15.1 Extent of Exposure

The following information will be summarized by treatment group and overall using the Safety Population.

The summary include either a tabulation of number (and %) of subjects or descriptive statistics (for durations and total exposure).

The number of subjects exposed to study treatment and summary statistics on duration of exposure (Mean, SD, etc.) by each of the 4 treatment groups (placebo, 100 mg BID, 150 mg BID, pridopidine total) – in titration period (all subjects, subjects with 2 weeks titration, subjects with 4 weeks titration), in maintenance period (all subjects, subjects with 2 weeks titration, subjects with 4 weeks titration)

15.2 Compliance

Subjects 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/FU, in which treatment compliance will be evaluated. Treatment compliance at the Visit 3, Visit 5, Visit 6, Visit 7/ET, and Visit 8/FU and overall for the 14 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 subject. A range between 80% to 120% will be taken as reference limits for a satisfactory level of compliance. The compliance (expressed as %) will be summarized with descriptive statistics by treatment group. In addition, the number (and %) of subjects with compliance between 80% to 120% will be tabulated by treatment group.

15.3 Adverse Events

All AEs will be coded using MedDRA version 21.0. Treatment-emergent adverse events (TEAEs) are defined as all AEs that start or increase in severity after the subject receives the first dose of study drug. Events with a missing start time, but with a start date equal to the date of first dose of study drug will be considered treatment-emergent. If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE:

- If the start date is completely missing, the start date will be equal to the date of the first dose of study drug. However, if the stop date is not missing and is before the date of the first dose of study drug, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.
- If the end date is completely missing, the latest end date of any other adverse event, or the date of last study visit for the same subject will be used, whichever occurs later.
- If the end day is missing, the last day of the month will be used.
- If the end day and month are missing, then the last day of the month of the last study visit for the same subject will be used.

In the AE summaries, data will be presented in four columns (pridopidine 150 mg BID, pridopidine 100 mg BID, pridopidine total, placebo) using the Safety Population.

The following summaries will be provided. If not stated otherwise, the tables will be sorted in alphabetic order by SOC, and within each SOC, in descending order according to the % of subjects reporting each PT in the pridopidine total group.

- An overall summary of the number and percentage of subjects reporting TEAEs and the number of TEAE events, treatment-related TEAEs, severe TEAEs, TEAEs leading to death (if there are any subjects who died), SAEs other than death, TEAEs leading to study drug discontinuation and TEAEs leading to temporary withdrawal

- The incidence (number and % of subjects) and frequency (event count) of TEAEs broken down by System Organ Class (SOC) and PT.

15.4 Laboratory Safety Parameters

Only select clinical laboratory safety parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

As of development of this SAP only Creatinine Clearance and Serum Creatinine will be summarized as below. Any other available data will be included in listings.

The following will be summarized:

- Numeric laboratory parameters: In case the value of a numeric laboratory parameter is below the lower limit of quantification, the lower limit of quantification will be used as the response value for the purpose of calculating the descriptive statistics.
- Laboratory parameters which have an upper and/or lower reference range: Number and percentage of subjects with 6 categories (missing, clinically significant low, not clinically significant low, normal, not clinically significant high, clinically significant high) values at each visit for each parameter will be summarized by treatment group. If a subject has both low and high abnormalities at a given visit, then only the worst value would be displayed in the appropriate category.
- These values will be presented as a shift table, i.e. the distribution of the 6 response categories at each post-baseline visit and the worst post-baseline value across all visits will be classified by the baseline category.

15.5 Vital Signs

Vital sign measurements include pulse rate, systolic and diastolic blood pressure (BP) and body weight. The BPs will be assessed in supine and standing positions and the standing minus supine values will be summarized in addition to the separate summaries of the supine and standing position. The mean of the triplicate values at baseline will be calculated, without rounding the result. These calculated means will constitute the analysis values for baseline.

Potentially clinically significant vital signs will be identified for selected parameters as defined below. These abnormalities will be summarized using at each visit, the last visit and by the worst post baseline values.

- Systolic BP: <90 mmHg, 90-140 mmHg, >140 mmHg – 160 mmHg, >160 mmHg
- Diastolic BP: <50 mmHg, 50-90 mmHg , >90 mmHg – 100 mmHg, >100 mmHg
- Pulse rate: <60 beats per minute (bpm), 60-100bpm, >100 bpm
- Standing minus supine systolic BP ≤-20 mmHg
- Standing minus supine diastolic BP ≤-10 mmHg.

15.6 ECG

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 drug dose administrated at the clinic. The mean of the triplicate ECG values will be calculated, without rounding the result. These calculated means will constitute the analysis values. The original values will be listed only.

The following will be summarized by treatment group and visit:

- Actual values and change from baseline for each ECG parameter will be summarized with descriptive statistics.

The potentially clinically significant ECGs will be identified for selected parameters as defined below. These abnormalities will be summarized using shift tables by visit and the worst value across all visits.

- QTcF: ≤450 msec, >450 – 480 msec, >480 – 500 msec, >500 msec.

In addition to the shift table by visit, the highest post-baseline QTcF value during the study for each subject will be tabulated using the categories listed above.

The potentially clinically significant changes from Baseline in ECGs will be identified for selected parameters as defined below. These abnormalities will be summarized by visit and the worst value across all visits.

- QTcF: change ≤30 msec, change >30 – 60 msec, change >60 msec.

In addition to the summary by visit, the highest post-baseline QTcF change during the study for each subject will be tabulated using the categories listed above.

15.7 Physical and Neurological Examination

Physical exam data will be only listed with no summary tables.

15.8 Other Safety Variables

15.8.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale Screening/Baseline Version (C-SSRS-BL) will be measured at Baseline.

The Columbia-Suicide Severity Rating Scale Since Last Visit Version (C-SSRS-SLV) will be assessed at the post-Baseline visits.

C-SSRS data will only be included in listings and no summary tables created.

15.8.2 Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS)

The QUIP-RS consists of four questions which have to be answered for each disorder (gambling, sex, buying, eating, hobbyism, punding and PD medication use) on a 5-point Likert scale. Scoring range for each scale (i.e. disorder) is 0–16. The total Impulsive Control Disorder (ICD) score and the total QUIP-RS score will be calculated and changes from baseline on these parameters. The individual scores, total scores and changes from baseline in total scores will be presented in listings.

15.9 Tolerability

The evaluation of tolerability is based on the following

- The number (%) of subjects who complete the study drug.
    - This analysis includes all premature discontinuations of the study
- The number (%) of subjects who fail to complete the study drug due to AEs
    - This analysis includes the premature discontinuations of the study, in which the primary reason for the premature discontinuation is defined as an AE or death (as defined on the Study Completion case report form page).

16 Analysis of PK

Plasma concentrations of pridopidine and its metabolite TV-45065 will be summarized with descriptive statistics by visit and timepoint (1 hour before and 1 to 2 hours after the pridopidine dose). The relationship between plasma concentrations of pridopidine and TV-45065 versus the primary endpoint (and the change from baseline in the primary endpoint) may be explored graphically for each visit which include both the PK and primary efficacy assessments. Separate exploration may be conducted for the PK assessments conducted before and 1 to 2 hours after the pridopidine dose.

PK analyses will be performed after the study database is locked, the study unblinded only if they are deemed necessary. Otherwise, PK data will only be included in listings, if there is not much data for analysis.

17 Deviations from the Analyses Planned in the Study Protocol

This analysis plan superseded the analyses planned in the protocol since the study was prematurely terminated.

18 Execution of Statistical Analyses

Statistical analyses will be performed by [redacted] and supervised by the Sponsor.

19 Hardware and Software

Statistical analysis, tables and subject data listings will be performed with SAS® version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

20 References

Clinical Study Protocol: Version 1.1 (24 January, 2019), Company: Prilenia Neurotherapeutics.
Clinical Study Protocol: Version 2 (19 November, 2019), Company: Prilenia Neurotherapeutics.
Johnston G, So Y. Analysis of data from recurring events. In: Proceedings of the twenty-eighth annual SAS users group international conference. Cary: SAS Institute, Inc. Paper 273-28 (2003).