Statistical Analysis Plan

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF K0706 IN SUBJECTS WITH EARLY PARKINSON'S DISEASE

Statistical Analysis Plan: Final

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Sponsor: Sun Pharma Advanced Research Company Limited (SPARC)

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

[redacted]

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
[redacted]	
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BM	Biomarker
BUN	Blood Urea Nitrogen
[redacted]	
CI	Confidence Interval
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CV	Coefficient of Variation
[redacted]	
DaT SPECT	Dopamine Transporter Single Photon Emission Computed Tomography
DB	Double-blinded
[redacted]	
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOT	End of Treatment
EQ-5D-5L	European Quality of Life Questionnaire 5 level
FDA	Food and Drug Administration
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
[redacted]	
[redacted]	
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
LDL	Low Density Lipoprotein
[redacted]	
LS	Least Squares
MAOB	Monoamine Oxidase B
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
[redacted]	
MNAR	Missing Not At Random
MRI	Magnetic Resonance Imaging
NC	Not Calculated
[redacted]	
PD	Parkinson's disease
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PPS	Per-Protocol Set

Abbreviation	Term
PT	Preferred Term
QTcF	Fridericia corrected QT interval
SAP	Statistical Analysis Plan
[redacted]	
SCOPA-AUT	Scales for Outcome in PD-Autonomic
SD	Standard Deviation
SE	Standard Error
[redacted]	
SOC	System Organ Class
TFL	Tables, Figures and Listings
TEAE	Treatment Emergent AEs
US	United States
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization

[redacted]

2.0 PROTOCOL SYNOPSIS

2.1 Overall Study Design

This study consists of 2 parts. Part 1 is a double-blind, placebo-controlled, [redacted] study to evaluate the efficacy, safety, and tolerability of 2 dose levels of K0706 compared to placebo in subjects with early Parkinson's disease (PD) who are not receiving symptomatic therapy. Part 2 is an optional long-term extension study for subjects who have completed the End of Treatment (EOT) visit of Part 1 (Visit 11/Week 40) and who have chosen to participate in Part 2 of the study, according to the schedule of assessments (Appendix 3).

2.1.1 Part 1 (Day 1 to Week 40/[redacted]

This part is a randomized, multicenter, double-blind, [redacted], parallel-group study, to evaluate the efficacy, safety and tolerability of 2 dose levels of K0706 compared to placebo in subjects with early PD who are not receiving symptomatic therapy. [redacted]

The study population includes subjects aged ≥ 50 years in whom an initial diagnosis of PD had been made within 3 years of the Screening visit, who scored on a modified Hoehn and Yahr stage ≤ 2, and who are not on any symptomatic treatment other than Monoamine Oxidase B (MAOB) inhibitors.

Subjects will be equally randomized (1:1:1) to receive K0706 low dose [redacted], or high dose [redacted] or matching placebo, and randomization will be [redacted]

Subjects will take the study drug (K0706 or placebo) orally, once daily, for 40 weeks in Part 1. The Week 40 visit (Visit 11) is the EOT visit of Part 1, and the Week 44 visit (Visit 12) is the follow-up visit for subjects having completed Part 1 but not participating in Part 2. Early discontinued subjects will also attend a follow-up visit about 4 weeks after the last dose of the study drug.

In earlier versions of the protocol (Amendments 01 and 02), subjects were dosed with [redacted] containing [redacted] (low dose) or [redacted] (high dose) of K0706 or matching placebo. The study continued with that formulation and doses until the [redacted] formulation was available, at which point newly enrolled subjects were randomized to [redacted] containing [redacted] (low dose) or [redacted] (high dose) of K0706 or placebo [redacted] Subjects who started the study on [redacted] formulation were switched to the [redacted] dose for their corresponding dose group (placebo stays on placebo, [redacted]). Subjects who had a [redacted] dose reduction to

[redacted] or to placebo (from placebo) remained on the same dose level of the powder formulation. Subjects who had a dose reduction from [redacted] were discontinued from the study [redacted]. See Table 1 for an overview of the currently available [redacted] formulations. An alternate formulation under development may further displace the current [redacted] formulation. Transitions occur in a blinded manner via the Interactive Web Response System (IWRS) and occur at the subject's subsequent visit.

[redacted]

Treatment assignments will remain masked to subjects, Investigators, site staff not directly provisioning kits on behalf of the Sponsor, and unless specified otherwise, the Sponsor will remain masked to treatment assignments until the last subject completes the Week 40 assessments for efficacy and the clinical database is locked for the final analysis of Part 1. Sponsor and affiliates may be unblinded to perform the final analysis of Part 1 (Week 40) data and report those results at that time.

2.1.2 Part 2 (Week 40 to Week 80)

Subjects who complete the EOT visit of Part 1 (Visit 11/Week 40) and who consent to participate in Part 2 of the study will be screened according to Part 2 eligibility criteria. Subjects randomized to placebo dosing in Part 1 will be rolled over to a high dose [redacted] at Week 40 or their first dosing opportunity in Part 2. This will enable the collection of additional safety data for the high dose level. Subjects randomized to K0706 (either dose level) in Part 1 of the study will remain on the same dosing regimen in Part 2. All Part 2 subjects will continue taking the study drug (K0706) orally, once daily, for an additional 36 weeks. The Week 76 visit (Visit 19) is the EOT visit of Part 2. The Week 80 visit (Visit 20) is the follow-up visit of Part 2 to collect safety outcomes.

2.2 Study Objectives

2.2.1 Part 1 (Day 1 to Week 40)

2.2.2 Primary Efficacy Objective

To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks, as assessed by the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part-III (motor examination) total score.

2.2.2.1 Secondary Objectives

The secondary objectives of the base study are:

- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients excluding the mild-motor predominant sub-type ([redacted] The rate of progression is assessed by the MDS-UPDRS Part III total score.
- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients with serum NfL value ≥ 13 pg/mL at baseline ([redacted]). The rate of progression is assessed by the MDS-UPDRS Part III total score.
- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks, as assessed by the sum of the MDS-UPDRS Parts II and III total scores.
- To determine if K0706 slows early-stage PD progression by increasing the time to significant worsening of PD on the MDS-UPRDS Parts I, II and III versus placebo.
- [redacted]
- To evaluate efficacy of K0706 compared to placebo in terms of Health Related Quality of Life (HRQoL) as measured by the European Quality of Life Questionnaire 5 level version (EQ-5D-5L).
- To determine if K0706 slows progression of early-stage PD versus placebo over 40 weeks in terms of overall severity of PD as measured by the Clinician Global Impression Severity of (CGIS) scale.
- To evaluate the effect of K0706 versus placebo on autonomic nervous system dysfunction related to PD as measured by the Scales for Outcome in PD-Autonomic (SCOPA-AUT)
- To evaluate the safety and tolerability of K0706.
- To evaluate the [redacted] measures of efficacy and safety.

2.2.2.2 Exploratory Objective(s)

The exploratory objectives of the base study are:

- To evaluate the effect of K0706 on skin pathology markers of PD.
- To evaluate the effect of K0706 on blood and CSF biomarkers linked to PD and target engagement of K0706.
- To investigate genetic and clinical markers that predict the degree of progression of early-stage PD and/or response to K0706.
- To evaluate the effect of K0706 on presynaptic dopamine transporter levels in PD as detected via Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT) brain imaging.
- [redacted]

2.2.3 Part 2 (Week 40 to Week 80)

2.2.3.1 Primary Safety Objective(s)

- To assess the long-term safety/tolerability of K0706 in subjects with early PD.

2.2.3.2 Secondary Objective(s)

- To assess the initial and long-term efficacy of K0706 in subjects with early PD.

2.2.3.3 Exploratory Objective

- To assess the efficacy of K0706 in subjects with delayed treatment initiation relative to those with early treatment initiation.

2.3 Sample Size and Power

The sample size estimate for this study utilizes information from [redacted] subjects in a completed large cohort study (Parkinson's Progression Markers Initiative) who remained off symptomatic medication from study entry to the [redacted]-month visit. In these subjects, the mean change from baseline in the sum of the MDS-UPDRS Parts II and III scores was [redacted] points with a standard deviation (SD) of [redacted] points at the [redacted] assessment. The results from a clinical trial called the ELLDOPA trial [redacted] (The Parkinson Study Group 2004) were also analyzed. In this study, a group of [redacted] early-stage PD subjects receiving a placebo showed a change in the sum of the UPDRS Parts II and III scores (older but similar scale to the MDS-UPDRS) of [redacted] points with an SD of [redacted] points over [redacted] weeks (data for analysis obtained from the National Institute of Neurological Disorders and Stroke, National Institute of Health, United States of America).

[redacted]

[redacted]

[redacted]

Based on the data of Roche's PASADENA trial in the early PD subjects [redacted], the contribution of the MDS-UPDRS Part II to the effect size is expected to be negligible or negative, thus by excluding Part II and using Part III alone as the primary efficacy outcome it is expected to have [redacted] power compared to using the sum of Parts II and III.

[redacted].

The sample size estimate for Part 2 [redacted] consideration but is based on the [redacted] successfully and elect to participate in the extension study.

3.0 ANALYSIS POPULATIONS (SETS)

The following analysis populations (sets) will be used for the analyses.

3.1 All Screened Set

The All Screened Set will include all subjects who signed the informed consent form. This population will be used only for summaries of disposition and the associated listing.

3.2 All Randomized Set, Part 1

All subjects randomized will be included in the All Randomized Set, Part 1. This population will be used for summaries of demographics and baseline characteristics, medical history, and prior and concomitant medications for Part 1 of the study.

3.3 Efficacy Analysis Set

3.3.1 Efficacy Analysis Set, Part 1

The Efficacy Analysis Set, Part 1 will consist of all subjects who were randomized, received at least one dose of the study medication in Part 1 of the study, and had a non-missing baseline and at least one non-missing post-baseline assessment(s) in the primary efficacy variable MDS-UPDRS Part-III total score in Part 1 of the study. This population will be used for all the efficacy analyses for Part 1.

3.3.2 Efficacy Analysis Set, Part 2

The Efficacy Analysis Set, Part 2 will consist of all subjects who received at least one dose of study medication in Part 2 of the study, and who did not start symptomatic PD medications in Part 1, and who had a non-missing baseline and at least one non-missing post-baseline assessment(s) in the primary efficacy variable MDS-UPDRS Part-III total score in Part 2 of the study. This population will be used for all the efficacy analyses for Part 2.

3.4 Per Protocol Set

3.4.1 Per Protocol Set, Part 1

Per Protocol Set (PPS), Part 1 will consist of all subjects in the Efficacy Analysis Set, Part 1 without any important protocol deviations leading to exclusion from the PPS during the Part-1 period of the study. The PPS, Part 1 will be used as supportive analyses of primary and secondary endpoints for Part 1 only.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the correctness, accuracy, and / or reliability of the

study data or significantly affect a subject's rights, safety, or well-being. Section 3.4.2 details the deviations.

[redacted]

[redacted]

[redacted]

[redacted]

3.5 Safety Analysis Set

3.5.1 Safety Analysis Set, Part 1

All subjects treated with at least one dose of study medication in Part 1 of the study will be included in the Safety Analysis Set, Part 1. This population will be used for all the Safety analyses for Part 1.

3.5.2 Safety Analysis Set, Part 2

All subjects treated with at least one dose of study medication in Part 2 of the study will be included in the Safety Analysis Set, Part 2. This population will be used for all the Safety analyses for Part 2.

[redacted]

[redacted]

3.7 Pharmacokinetics Analysis Set, Part 1

The PK Analysis Set, Part 1 will include all subjects who received at least one dose of study medication in Part 1 of the study and had at least one blood sample taken at a later time to measure K0706 concentration level. This population will be used for PK-related analyses for Part 1.

3.8 All Enrolled Set, Part 2

All subjects who had a Part 2 visit, including the Part 2 baseline visit (e.g., eCRF Visit 13), will be included in the All Enrolled Set, Part 2. This population will be used for the summary of disposition, demographics and baseline characteristics for Part 2.

4. DATA HANDLING

4.1 Time Points and Visit Windows

4.1.1 General Definitions

All assessment days will be related to the first day of the first dose of study drug administration.

Day 1 is defined as the day when the first dose of the study drug is administered. [redacted]

The date of the first dose of study drug administration for each subject will be taken from the 'Study Drug' or 'Date Drug Admin Form' eCRF forms at the Baseline Visit. If the date in these eCRF forms is missing, alternatively, the date of randomization will be used.

For all Part 2 subjects, the date of the first dose of study drug administration in Part 2 will be taken from the 'Study Drug form-2' eCRF form at Visit 13/11 (Baseline visit for Part 2, Week 40). If the date in this eCRF form is missing, alternatively, the date of the Visit 13/11 (Baseline visit for Part 2, Week 40) will be used.

The date of the last dose of study drug administration for each subject will be taken from the "Last Study Drug Details" eCRF form. If the date on this eCRF form is missing, alternatively, the date of the last dose from the "DOSING" eCRF form will be used for the imputation.

4.1.2 Definition of Baseline Value for Part 1 and Part 2

For all subjects, the Baseline period for Part 1 is defined as the period from informed consent to the first dose of study drug administration. For some variables, data from more than one assessment within the Baseline Period are collected prior to the first dose of study drug administration.

Unless otherwise specified, the baseline value for a variable for Part 1 is defined as the value of the last non-missing assessment or observation collected before the first dose of study drug administration for Part 1.

Assessments carried out on the day of the first dose of study drug administration, i.e., Day 1, are considered to have taken place before the first dose of study drug administration if the corresponding times have not been recorded.

Unless otherwise specified, for all Part 2 subjects, the baseline value for a variable for Part 2 is defined as the non-missing value collected at Visit 11 (i.e., the Week 40 visit of Part 1). Note that the baseline visit for Part 2 is labeled as Visit 13, and the baseline value is simply taken from Visit 11, per the study schedule. Also, per the study schedule, the start (i.e., first dose) of the study drug for Part 2 is scheduled to be administered on the same day of the visit date of Visit 11. However, in some cases, the start of the study drug administration for Part 2 actually took place after the visit date of Visit 11. That is, the study drug start date in Part 2 can be greater than the visit date of Visit 11. In such cases, the non-missing assessment or observation immediately prior to the start of the study drug administration for Part 2 will be taken as the baseline value for Part 2.

[redacted]

4.1.3 Treatment Period

If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of study drug administration, the data collected at Day 1 will be assigned to the Baseline period. However, adverse events (AEs) and medications starting on Day 1 with missing onset time (HH:MM), will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date/time of the first dose of study drug administration up to and including the date of the last dose of study drug administration.

4.1.4 Visit Windows

4.1.4.1 Part 1

Table 3 provides the relative study day ranges to be applied to the assessment/sample collection dates to derive the analysis Visits for efficacy analyses and some safety assessments (vital signs, laboratory assessments, and C-SSRS, by Visits for Part 1).

The following considerations are to be followed when deriving the analysis Visits:

- [redacted]
- Both scheduled and unscheduled assessments are included for visit windowing
- [redacted]

- If both scheduled and unscheduled assessments fall within the same visit window, the scheduled assessment with non-missing assessment results will be used for analysis
- [redacted]
- [redacted]

[redacted]

[redacted]

4.1.4.2 Part 2

Table 4 provides the relative study day ranges to be applied to the assessment/sample collection dates to derive the analysis Visits for analyses of efficacy and safety assessments (vital signs, laboratory assessments, [redacted] by Visits for Part 2.

The above considerations for Part 1 are also to be followed when deriving the analysis Visits for Part 2.

[redacted]

4.2 Handling of Dropouts, Missing Data, and Outliers

4.2.1 Handling of Missing Efficacy Data

In general, missing efficacy data will not be imputed for efficacy analyses. The [redacted] analyses will be based on [redacted] The only exception is that a set of supplementary [redacted] of the primary efficacy variables at Week 40 will be performed on [redacted] imputed data.

4.2.2 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are described in Section 9.1. Unknown or partial medication and AE date imputations are given below and are to be used only for the assessment of prior/concomitant status for medications and treatment-emergent status for AEs.

4.2.3 Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications, and Last Dose of Study Drug

For AEs with partial or missing onset or stop dates:

- AE stop date will be imputed first as:
  - If the stop date is completely missing, assume it is ongoing (no imputation);
  - For a partial AE stop date:
    - the day is missing, then take the last day of the month
    - both day and month are missing, then take December 31st.
  - If the imputed AE stop date is after the End of the Study date, then the stop date will be set to the End of the Study date.
- Then AE onset date will be imputed as:
  - If the onset date is completely missing, the first dose date;
  - For a partial AE onset date:
    - Day is missing:
      - Partial date < the first dose date: last day of the month
      - Partial date = the first dose date: the first dose date
      - Partial date > the first dose date: first day of the month
    - Both day and month are missing, ie, only the year is available:
      - Partial date < the first dose date: 31st December
      - Partial date = the first dose date: the first dose date
      - Partial date > the first dose date: 1st January.
  - If the imputed AE onset date is after the AE stop date/imputed AE stop date, then the onset date will be set to the AE stop date/imputed AE stop date.

In the event that a partial date (month/year or year) for concomitant medication is available, concomitant medication start and stop dates will be imputed as:

- When both month and year are available – the first day of the month will be used for the start date, and the last day of the month will be used for the stop date.
- When only year is available – 01 January will be used for the start date and 31 December will be used for the stop date.

Study drug last dose date (based on "Last Study Drug Details" eCRF page) will be used for calculating the exposure to study drug. If the study drug last dose date is missing, alternatively the date of the last dose from the "DOSING" eCRF page will be used for the imputation. This imputation of the study drug last dose date will be applied to both Part 1 and Part 2 of the study.

The imputed dates will not be listed. Study day relative to the first dose of the study drug and duration associated with missing or partial dates will not be displayed in AE and concomitant medication listings.

4.2.4 Handling of Plasma and CSF Concentrations that are Below the Lower Limit of Quantification

Plasma and CSF concentrations that are below the lower limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, the geometric mean and coefficient of variation (CV)% of the geometric mean will be reported as not calculated (NC).

5.0 STUDY CONDUCT

5.1 Subject Disposition and Definition of Completers for Part 1 and Part 2

Subject disposition for Part 1 of the study will be summarized by treatment group and overall, where appropriate, for the All Screened Set. The following information will be reported:

- Number of subjects for the following category:
  - Screened
- Number and percentage of subjects for the following categories:
  - Randomized,
  - Treated,
  - Not Treated,
  - Completed Part 1 of the study,
  - Ongoing in Part 1 of the study
  - Discontinued from Part 1 of the study,
  - Reasons for Part 1 study discontinuation.
- Number and percentage of subjects who failed and did not fail screening prior to randomization, including the primary reason for screen failure;

Subject disposition for Part 2 of the study will be summarized by treatment group and overall, where appropriate, for the All Enrolled Set, Part 2. The following information will be reported:

- Number and percentage of subjects for the following categories:
  - Completed Part 2 of the study,
  - Ongoing in Part 2 of the study
  - Discontinued from Part 2 of the study,
  - Reasons for Part 2 study discontinuation.

Moreover, the following information will be reported for the All Randomized Set, Part 1:

- Number and percentage of subjects included in each study population (All Randomized Set, Part 1; Efficacy Analysis Set, Part 1; Efficacy Analysis Set, Part 2; PPS, Part 1; Safety Analysis Set, Part 1; Safety Analysis Set, Part 2, BM Analysis Set, Part 1; and PK Analysis Set, Part 1);
- Number and percentage of subjects by country and site;
- Number and percentage of subjects by stratification factors [redacted] region [redacted], and use of an MAOB Inhibitor [redacted] at Baseline). Each [redacted] variable will be presented by the [redacted] collected in IWRS, except the use

of a MAOB Inhibitor at Baseline which will be presented both by the [redacted] collected in IWRS and the [redacted] collected in the eCRF.

The MAOB Inhibitors at the Baseline will be determined using the Chemical Subgroup (ATC-Level 4). The ATC-Level 4 that determines the MAOB Inhibitors is 'MONOAMINE OXIDASE B INHIBITORS' (ATC-Level 4 code: N04BD), based on WHO Drug Global Dictionary (version Mar 2022 or a later version if updated during the study), ATC Classification codes.

Completers of Part 1 and Part 2 of the study will be respectively defined as follows. A subject will be regarded as Part 1 completer if the subject attended the Visit 11 - Week 40 visit, at which the MDS-UPDRS Part III assessment on the subject was collected. A subject will be regarded as Part 2 completer if the subject attended the Visit 19 - Week 76 visit, at which the MDS-UPDRS Part III assessment on the subject was collected. A subject will be considered as having discontinued the study if the subject had an eCRF status of early study discontinuation. Otherwise, the subject will be considered as ongoing in the study.

A listing of all subjects with their treatment and study completion status, including the reason for study discontinuations, will be presented for the All Randomized Set, Part 1.

A listing of all screen-failed subjects with their reasons for screen failure will be presented for the All Screened Set. A separate listing of subjects who failed at least one inclusion/exclusion criteria, including a text description of the criterion failed, will be presented for the All Screened Set.

A listing of all randomized subjects with their randomization details, including first dose date and actual treatment received, will be presented for the All Randomized Set, Part 1.

A listing of all subjects with mis-stratification will be presented for the All Randomized Set, Part 1.

A listing of all subjects excluded from at least one analysis set will be presented for the All Randomized Set, Part 1.

5.2 Protocol Deviations

All important protocol deviations will be summarized for Parts 1 and 2 of the study separately, using the All Randomized Set, Part 1 and All Enrolled Set, Part 2, respectively, and all important protocol deviations leading to exclusion from the PPS, Part 1 (see Section 3.4.2) will be summarized for the Efficacy Analysis Set, Part 1 by treatment group and overall as described below:

- The number of unique subjects with at least one important protocol deviation as well as the number of subjects in each important protocol deviation category, will be presented by default descriptive summary statistics for categorical variables.
- The number of unique subjects with at least one important protocol deviation that led to exclusion from the PPS, Part 1 as well as the number of subjects in each important protocol deviation category, will be presented by default descriptive summary statistics for categorical variables.

A listing of the important protocol deviations will be presented for Parts 1 and 2 of the study separately, using the All Randomized Set, Part 1 and All Enrolled Set, and Part 2, respectively.

5.3 Measurement of Treatment Compliance

For scheduled visits [redacted], subjects are asked about compliance with study drug, and any deviation in compliance could feed into a protocol deviation.

The number of doses missed since the last visit is collected in the eCRF and taken into account for the derivations of study exposure. Details regarding these derivations are provided in Section 9.8.

5.4 Data Monitoring

The [redacted] independent of the study team and consisting of external members only, will be formed for this trial. The [redacted] will be responsible for the periodic review of the unblinded safety data and the ongoing monitoring of the safety of the study subjects according to the [redacted] Charter. When warranted due to safety concerns based on accumulated data and evidence, the [redacted] could make recommendations (such as dose reduction or trial termination) to the Sponsor. However, the decision of whether to follow [redacted] recommendation resides in the Sponsor.

6.0 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographic Characteristics

Demographic characteristics will be summarized for the All Randomized Set, Part 1, by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age at Screening (years)
- Weight (kg) at Screening
- Height (cm) at Screening
- Body mass index (kg/m^2) at Screening (calculated as [body weight / $height^2$] where weight is in kg and height is in m) and presented to one decimal precision

Total counts and percentages of subjects will be presented for the categorical variables of:

- Age group (years):
  - <= 65
  - > 65 to <= 75
  - > 75
- Gender
- Childbearing potential (females only; classified as [yes], [no, surgically sterile], [no, post-menopausal], [no, other])
- Race
- Ethnicity
- Weight category (kg) at Screening:
  - <= 90
  - > 90 kg

6.2 Baseline Characteristics

Baseline characteristics will be summarized for the All Randomized Set, Part 1 by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

Standard descriptive statistics will be presented for the continuous variables of:

- Baseline MDS-UPDRS (Part I total score, Part II total score, Part III total score, the sum of the Parts II and III total scores, the sum of the Parts I, II and III total scores)
- Time between onset of PD symptoms and initiation of study [redacted]
- Time between diagnosis of PD and initiation of the study [redacted]
- Number of years of education
- Montreal cognitive assessment score at Screening

Total counts and percentages of subjects will be presented for the categorical variables of:

- History of Sleep dysfunction [redacted]
- History of Autonomic dysfunction [redacted]
- History of Hyposmia [redacted]
- History of Psychiatric dysfunction ([redacted]
- Magnetic Resonance Imaging (MRI) scan of the brain suggestive of secondary Parkinsonism ([redacted]
- DaT SPECT scan performed to determine eligibility conclusion: [redacted]
- Meet criteria for clinically probable PD by MDS Clinical Diagnostic criteria: [redacted]
- Serological tests:
  - Hepatitis B Virus Surface Antigen: [redacted]
  - Hepatitis C Virus Antibody: [redacted]
  - Human Immunodeficiency Virus (HIV) 1 and 2 Antigen/Antibody: [redacted]
- Smoking history: [redacted]
- Alcohol consumption: [redacted]
- Caffeine consumption: [redacted]
- Currently working: [redacted]

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

6.3 Medical History

Medical history is defined as any condition, except for the study indication, that the subject may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

The medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0 or a later version if updated during the study) and will be presented by System Organ Class (SOC) and Preferred Term (PT).

Active medical history is defined as ticked on eCRF as ongoing (with or without treatment) and otherwise is defined as past.

Active and past medical history records will be summarized separately for the All Randomized Set, Part 1 by treatment group and overall as follows:

- The number and percentage of subjects with at least one active/past medical history record will be presented.
- The number and percentage of subjects with at least one active/past medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using the descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

7.0 CONCOMITANT MEDICATIONS

It is expected that during the development of the study, the events defined in this section will take place. The aim of this section is to define flags to be created in the efficacy datasets and to facilitate the analysis of the efficacy endpoints as defined in Section 8.

7.1 Start Date of Symptomatic PD Medications for Part 1

The start of symptomatic PD medications will be derived according to the following algorithm:

(1) For subjects who are PD treatment naïve at baseline, medication treatment for symptomatic PD includes the following medications received by the subjects during Part 1: [redacted] Dopamine agonists [redacted]; COMT inhibitors [redacted]; Monoamine Oxidase type B (MOA-B) inhibitors [redacted]; other anti-Parkinson drugs [redacted]; Anticholinergics [redacted]; Anti-nausea [redacted]

The symptomatic PD medications will be selected using the following criteria from the WHODrug dictionary: ATC Class Level 2 equals to "ANTI-PARKINSON DRUGS" (Class code: N04).

For subjects on MAO-B inhibitors at baseline, the list of symptomatic PD medications will be the same as the above with the exclusion of the MAO-B inhibitors.

MAO-B inhibitors will be selected from the concomitant medications where ATC Class Level 4 equals to "MONOAMINE OXIDASE B INHIBITORS" (Class code: N04BD).

For subjects on MAO-B inhibitors at baseline, an increase from baseline in daily dose (mg/day) during Part 1 will be considered an intake of symptomatic PD medication as well.

(2) The date (in Part 1) when the first symptomatic PD medications were received or when an increase in the daily dose (mg/day) of MAOB inhibitors happened (whichever was the first occurrence) will be marked as the "symptomatic PD medications start date."

(3) All visits or assessments with a date after the date of the first intake of symptomatic PD medication during Part 1 will be marked as "after the start date of symptomatic PD medications".

7.2 Start Date of Symptomatic PD Medications for Part 2

Subjects who started symptomatic PD medications in Part 1 will be withdrawn from the study and cannot enter Part 2. Subjects entering Part 2 are either still naïve to symptomatic PD medications or on MAO-B inhibitors (without an increase in dose) since the Part 1 baseline.

The start of symptomatic PD medications for Part 2 should be after the start of the study drug administration for Part 2. The start date of symptomatic PD medications for Part 2 will be derived and flagged using the same algorithm as above.

8.0 EFFICACY ANALYSES

All efficacy analyses for Part 1 (the double-blind treatment phase) of the study will be performed on the Efficacy Analysis Set, Part 1, and subjects will be included in the treatment group as randomized.

All efficacy analyses for Part 2 (the long-term extension phase) of the study will be performed on the Efficacy Analysis Set, Part 2, and subjects will be included in the treatment group as assigned at the baseline visit (Visit 13) of Part 2.

For all efficacy analyses, the values of stratification strata (for example, baseline user status of MAO-B inhibitors) as collected in the eCRF will be used instead of the values entered by the investigator into the IWRS, except for the supplementary analyses described in Section 8.1.6 below.

8.1 Primary Efficacy Analyses (Part 1)

The week 40 visit of Part 1 is a landmark time-point for this trial when the last assessment of the primary efficacy outcome for the double-blind treatment phase will be collected. The primary efficacy outcome variable is the MDS-UPDRS III total score, which is the sum of the rater-based Motor Examination ([redacted]). The primary endpoint is the change from baseline to Week 40 in the MDS-UPDRS Part III total score.

8.1.1 Primary [redacted]

This trial seeks to clarify the efficacy of K0706 in delaying the progress of PD in the ideal scenario of no intercurrent events and full adherence to the assigned 40-week treatment regimen dosed once daily in all randomized subjects. It is thus appropriate to employ the hypothetical [redacted] for the primary efficacy analyses, with the use of a hypothetical strategy for handling intercurrent events. The primary [redacted] is described by five attributes as follows.

- • **Treatment**: the treatment condition of interest includes the [redacted] high dose and the [redacted] low dose of K0706 in [redacted] formulation administered once daily for 40 weeks. The alternative treatment condition to which the comparison will be made is Placebo in [redacted] formulation administered once daily for 40 weeks.
- • **Target Population**: subjects aged ≥ 50 years in whom an initial diagnosis of PD was within 3 years of the screening visit, who score on a modified Hoehn and Yahr stage ≤ 2, [redacted] who meet the protocol-specified inclusion and exclusion criteria.
- • **Endpoint**: Change from Baseline to Week 40 in the MDS-UPDRS Part III total score

- [redacted]
- [redacted]

During the course of this trial, the COVID-19 pandemic broke out. There were occasionally virtual visits (or say, remote assessments) and possibly early discontinuation of treatment directly or indirectly related to the pandemic. Virtual visits in the pandemic environment will not be handled [redacted]. Subjects who dropped out for a reason related to the COVID-19 pandemic will be handled as if they would have dropped out for other reasons if the pandemic had not happened. The hypothetical strategy for handling [redacted] will be used to clarify the efficacy of K0706 had there been no occurrence of [redacted] regardless of being COVID-19 related or not.

8.1.2 Method of Estimation

Mean changes from baseline in the MDS-UPDRS Part III score will be analyzed using the [redacted] The analysis will be performed by fitting the [redacted] model with an unstructured [redacted] in which the change from the baseline in the Part III total score (Weeks 4, 8, 12, 20, 28, 36, 40) will be the dependent variable based on the observed case data. The analysis will include treatment arm, analysis visit, region ([redacted]), baseline MAOB inhibitor user status ([redacted] and the interaction term of treatment by analysis visit as the fixed, categorical effects, and will include the interaction term of baseline Part III score by analysis visit as the continuous, fixed covariates. An unstructured covariance structure will be used to model the within-subject error. In case of the convergence problem with the [redacted] model with the [redacted] matrix, the following structures will be used in the order of [redacted] to the best fit will be used as the primary analysis.

The [redacted] will be used to estimate the denominator degrees of freedom. Three contrasts of group mean (i.e., difference in least-square means for each active dose and the pooled dose of the K0706 *vs.* placebo) at Week 40 will be estimated from the interaction term of treatment by analysis visit based on the [redacted] model. These contrasts at Week 40 will serve as the primary comparison. Test of significance for each contrast will be performed by using a [redacted] confidence interval estimate for

each contrast will be constructed. The analysis will be implemented using the [redacted]

In addition to the above main estimates at Week 40, the LS mean and its [redacted] CI for each treatment group, together with the LS mean difference and its [redacted] CI and [redacted] p-value for the comparison of each active dose and the pooled dose of K0706 *versus* placebo at each post-baseline visit prior to Week 40 will be extracted from the same [redacted] A negative value of the contrast estimate with Placebo as the reference group would clinically favor the K0706 group.

The Part III total score at baseline and at each post-baseline visit and the change from baseline will also be summarized by the treatment group using standard descriptive statistics. Mean values of the Part III total score together with their [redacted] CI or SE, will be plotted over time (weeks) by treatment group.

8.1.3 Subgroup Analyses for the Primary Efficacy Endpoint

Two subgroups of interest are defined as follows. [redacted] is obtained by excluding subjects with the mild motor-predominant subtype at baseline. ([redacted]) proposed clinical criteria for dividing PD patients into [redacted] based on a [redacted] of the data on the de novo treatment-naïve PD patients from the [redacted] study [redacted] The proposed criteria will be adapted to define [redacted] The Proseek cohort is considerably similar in demographics and baseline disease characteristics to the de novo PD cohort in the [redacted] study [redacted] This similarity justifies the use of the subtyping criteria developed by [redacted]

[redacted] is defined as having the composite motor score and all the three non-motor scores below the [redacted] where the [redacted] is the sum of the MDS-UPDRS Part II and III total scores, and the three non-motor scores are of SCOPA-AUT, MoCA and Rapid Eye Movement Sleeping Disorder (RBDSQ) respectively. [redacted] a "no" answer to the general sleeping disorder [redacted] is obtained by excluding subjects of the mild motor-predominant subtype from the Efficacy Analysis Set (for Part 1 period) (Appendix 3).

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]
).
[redacted]

[redacted]

[redacted]

Raw (unadjusted) p-values for individual hypotheses will be extracted from the [redacted] for the [redacted] visit. [redacted] p-values for the two comparisons at [redacted] will be calculated by utilizing the correlation of the test statistics between the two comparisons. [redacted] for the randomization ratio 1:1:1.

8.1.5 Supplementary Analysis Addressing the Effect of a [redacted]

A small percentage of subjects may have conflicting values in the baseline [redacted] MAO-B inhibitors usage status [redacted] resulting from different data sources (eCRF versus IWRS). If such a percentage [redacted] in any treatment group, the primary efficacy analysis will be repeated by using the values from the IWRS.

8.1.6 [redacted] Analyses

The mean change-from-baseline at Week 40 in the MDS-UPDRS Part III score will be analyzed by using [redacted] with treatment as a fixed main effect, and with baseline Part III total score, region [redacted] and baseline MAOB

inhibitors user status (from eCRF) as covariates. Of note, the change-from-baseline data at Week 40 will be imputed using [redacted] approach for the above analysis.

The primary efficacy analyses will be repeated on the Per Protocol Set, Part 1. If any clinical sites are identified by audit as having had non-compliance issues prior to database lock, the primary efficacy analyses will be repeated on the data excluding the non-compliant sites.

The distribution-free permuation test ([redacted]) will be used to test the robustness of the overall treatment effect (for the pairwise comparison of each dose group, and the pooled dose group vs the placebo group) over repeated assessments of the primary efficacy outcome during Part 1. Specifically, the [redacted] for the observed mean difference at each post-baseline assessment will be calculated, and thus the mean [redacted] over repeated assessments will be calculated based on the actual data of the trial. In order to calculate the corresponding p-value, the permutation test will be conducted in which subjects will be permuted randomly (without breaking repeated observations at each subject) between 3 treatment arms. The process will be repeated [redacted] times in order to construct frequency distribution for the simulated [redacted]. The [redacted] p-value for each pairwise comparison (using the placebo group as the reference group) will be computed by calculating the percentage of the simulated mean [redacted] that are more favorable (i.e., having larger treatment effect) than the actual observed mean [redacted] A small [redacted] p-value tends to support the presence of the overall treatment effect over multiple assessments.

Model fit of the primary [redacted] analysis will be examined. If the model fit calls into question, additional [redacted] analyses will be performed post-hoc.

If the dropout rate is differential across treatment groups, additional [redacted] analyses will be performed post hoc.

8.2 Secondary Efficacy Analyses

8.2.1 Part 1 (Day 1 to Week 40)

The secondary efficacy variables or endpoints of interest for Part 1 of the study are as follows.

- Change from baseline through Week 40 in the sum of the MDS-UPDRS Parts II and III total scores.
- Change from baseline through Week 40 in the MDS-UPDRS Part IA sub-score, Part IB sub-score, Part I total score, Part II total score, and the four sub-scores of Part III [redacted].
- Change from baseline through Week 40 in the grand sum of the MDS-UPDRS Parts I, II and III total scores.

- Evaluation of slopes of the mean change in MDS-UPDRS Parts III total score over time during Part 1 by treatment group.
- Time from first dose of study drug in Part 1 to initiation of symptomatic PD medications in Part 1.
- Change in HRQoL using the EQ-5D-5L scale from Baseline to Week 40.
- Change in severity of PD using the CGIS scale from Baseline to Week 40.
- Change in autonomic nervous system dysfunction related to PD using the SCOPA-AUT scale from Baseline to Week 40.

8.2.1.1 The [redacted] analysis

Analyses of other efficacy endpoints pertaining to the MDS-UPDRS scores will be performed by using the same [redacted] model for the primary efficacy analysis. [redacted]

The same [redacted] analysis will also be performed for all time points prior to Week 40 for each of the above-mentioned efficacy endpoints.

[redacted]

- [redacted]

A random coefficients regression analysis with random terms for intercept and slope (i.e., time is a linear random effect) will be used to estimate mean changes from baseline in UPDRS Part III total score over time (in weeks).

Change-from-baseline MDS-UPDRS Part III total score over time will be analyzed using a structured random coefficient model with the inclusion of treatment, time (as a continuous variable in weeks), region ([redacted]), baseline user status of MAOB inhibitors [redacted], the treatment-by-time interaction, and the baseline score-by-time interaction as the explanatory variables.

Like the data handling rule for the primary efficacy analysis, if any MDS-UPDRS assessments are collected on or after the day of the subject's start of symptomatic PD medications, such assessments will be set as missing.

From the [redacted] the mean change-from-baseline in the MDS-UPDRS Part III total score at each time point and its associated SE and the LS mean difference (using

Placebo as the reference group) at each time point will be estimated. A c[redacted] p-value for testing the LS mean difference at each time-point will be extracted from the model. And p-values for the treatment main effect, the main effect of time, and treatment-by-time interaction will be extracted from the model. The linear trend of the estimated mean change-from-baseline in the MDS-UPDRS Part III total score will be displayed graphically by treatment group for the Part 1 period.

The same analysis as the above for the MDS-UPDRS Part III total score will be repeated for the sum of the MDS-UPDRS Parts II and III total scores.

8.2.1.3 Time to Event Analysis

- To determine if K0706 slows early-stage PD progression by increasing the time to significant worsening of PD, as compared to placebo.

The event of interest is the significant worsening of PD during Part 1. [redacted] ≥ [redacted]

AEs associated with PD symptoms will be identified by using the following AE preferred terms: [redacted] based on MedDRA version 23.0 or newer. The final list of preferred terms associated with PD symptoms will be provided in the 'Analysis Set Specification' document.

[redacted]

[redacted]

For the Part 1 early discontinued subject having not had the event of interest during Part 1, the subject will be [redacted] at the date of early treatment discontinuation, or loss to follow-up, or death, whichever occurs first. Of note, the maximum time-point of Week 44 [redacted] will be applied to this [redacted].Time in weeks to [redacted] – [redacted]

For the on-going subject having not had the event of interest during Part 1, [redacted] –

The number and percentage of subjects who had the event of interest or who were censored will be tabulated by the treatment group.

Time to event (or say, survival time in weeks) will be analyzed using [redacted]. The [redacted] percentile, median, and [redacted] percentile of the survival time together with [redacted] CI will be estimated by treatment group. The [redacted] CI estimates will be computed based on [redacted] with the use of a log-log transformation. The cumulative survival experience in weeks will be displayed graphically by treatment group using the [redacted].

The equality (*vs.* inequality) in the survival time between each dose of K0706 *vs.* placebo will be tested using the [redacted], with Region ([redacted]) and baseline MAO-B inhibitors usage status ([redacted]) as the stratification factor. [redacted]-sided p-value for each comparison will be extracted from the test.

In addition, [redacted] will be performed with the inclusion of Region ([redacted]) and baseline MAO-B inhibitors usage status ([redacted] as covariates for the model. The [redacted] ratio (with placebo being the reference group) and its [redacted] CI, and the [redacted]-sided p-value for each test (for testing [redacted] ratio = [redacted] *against* [redacted] ratio [redacted] will be estimated and extracted based on the proportional [redacted] model.

The above analyses will be repeated for the comparison of the pooled dose of K0706 *vs.* placebo.

- To determine if K0706 delays the initiation of symptomatic PD medications or the early withdrawal due to PD-related AEs, as compared to placebo.

The event of interest consists of two sub-events as follows. [redacted]

AEs. Subjects without the event of interest will be [redacted] The [redacted] rule and the time-to-event analyses will be similar to that described in the preceding paragraph.

- To determine if K0706 delays the initiation of symptomatic PD medications, as compared to placebo.

The event of interest is the initiation of symptomatic PD medications as defined above in this subsection, Subjects without the event of interest will be censored. The [redacted] rule and the time-to-event analyses will be similar to that described in the preceding paragraph.

- To determine if K0706 delays the worsening of PD in terms of the MDS-UPDRS Part III total scores, as compared to placebo.

The event of interest is the increase [redacted] ≥ [redacted] points from baseline in the MDS-UPDRS Part III total score. Subjects without the event of interest will be [redacted] The [redacted] rule and the time-to-event analyses will be similar to that described in the preceding paragraph.

8.2.1.4 [redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

8.2.2 Part 2 (Week 40 to Week 80)

There are 3 treatment groups for Part 2: ([redacted]). Note that, for some analyses for Part 2, groups (2) and (3) will be pooled together as a single "[redacted] group, in addition to being separate.

The secondary efficacy analyses for Part 2 are specified as follows.

- Change from Week 40 (Baseline for Part 2) through Week 76 (EOT visit for Part 2) in the MDS-UPDRS Part III total score.

The baseline value for Part 2 is defined as the value collected at the end-of-trial visit (i.e., the Week 40 visit) of Part 1. But there are exceptions in some circumstances. Refer to Section 4.1.2 for the definition of baseline value for Part 2.

The MDS-UPDRS Part III total score [redacted] at baseline and at each post-baseline analysis visit (as derived per Table 5) during Part 2, and the change from baseline will be summarized by the treatment group using standard descriptive statistics. Moreover, the mean values of the MDS-UPDRS Part-III total score together with the corresponding SEs or [redacted] CIs will be displayed graphically (plotted) by dose group over the Week (Analysis Visit).

- Change from Week 40 (Baseline visit for Part 2) through Week 76 (EOT visit for Part 2) in the MDS-UPDRS Part IA sub-score, Part IB sub-score, Part I total score, Part II total score, sub-scores of the Part III sub-domains, the sum of Parts II and III total scores, and the grand sum of Parts I, II and III total scores.

The MDS-UPDRS Part IA sub-score is the sum of [redacted] The Part IB sub-score is the sum of [redacted]. The Part I total score is the sum of Items [redacted] The Part II total score is the sum of [redacted] The Part III tremor sub-score is the sum of [redacted] The Part III rigidity sub-score is simply the [redacted]. The Part III [redacted] sub-score is the sum of [redacted]. The Part III axial symptoms sub-score is the sum of [redacted]

Analyses for each of the above-mentioned efficacy variables will be similar to that for the Part III total score in the preceding paragraph.

- Time from Week 40 (Baseline for Part 2) to the initiation of symptomatic PD medications in Part 2.

The event of interest is the initiation of symptomatic PD medications in Part 2. The [redacted] rule and the time-to-event analyses for Part 2 will be similar to that for Part 1. Of note, the starting time-point for this time-to-event analysis is Day 1 (first dose date) of Part 2.

8.3 [redacted]

[redacted]

8.3.1 Part 1 (Day 1 to Week 40)

Biomarker analyses for Part 1 will be performed on [redacted]. [redacted]

The biomarker variables or endpoints of interest for Part 1 are:

- Skin pathological findings that correlate with PD, [redacted] α[redacted]
- Blood and CSF levels of emerging biomarkers [redacted] that predict or track PD progression or target engagement of K0706.
- Brain DaT SPECT - an imaging tool that is a marker of presynaptic dopamine transporter levels.

Biomarker analyses for Part 1 are pre-specified as follows:

- To evaluate the effect of K0706 on skin pathology markers of PD.

Specific skin pathology biomarkers (parameters) of interest for PD have not yet been fully determined at the time of writing this SAP. [redacted]. Samples of skin biopsies will be collected at baseline and Week 36 (Visit 10). For each parameter, assayed values at each visit and the change from baseline value at each visit will be summarized by dose group by using standard descriptive statistics (such as Mean, SD, Median, and Quartiles). For each parameter, graphical displays in the forms of Tukey box and whisker plots will be used to summarize the data by dose group and by visit

- To evaluate the effect of K0706 on blood and cerebrospinal fluid (CSF) biomarkers linked to PD and target engagement of K0706.

The specific blood and CSF biomarkers (parameters) linked to PD have not yet been fully determined at the time of the writing of this SAP. Potential parameters may include α-synuclein, total Tau, ratio of total Tau/α-synuclein, amyloid, etc. For each parameter, graphical displays in the forms of mean plots and Tukey box and whisker plots will be used to summarize the data by dose group and visit.

In addition, the statistical correlation of each biomarker parameter with the efficacy endpoint will be explored in the following ways. (1) Pearson's and Spearman's correlation coefficient (and its [redacted] CI) between the change-from-baseline parameter value and the change-from-baseline MDS-UPDRS Part III score at the end of Part 1 (Week 40) will be estimated. (2) Subjects will be divided into 3 categories (roughly corresponding to "worse off," "little changes", and "improvement") with respect to the primary clinical outcome. Unless otherwise specified, the tertiles of change-from-baseline at Week 40 in the Part-III score will be used as the cutoffs. Tukey's box and whisker plots of the change-from-baseline at Week 40 in each biomarker parameter will be plotted by category of the primary clinical outcome.

- To investigate genetic and clinical markers that predict the degree of progression of early-stage PD and / or response to K0706.

Specific genetic and clinical biomarkers (parameters) may be identified as potential candidates predictive of the degree of progression of early-stage PD. For each parameter, the exploratory analyses will be similar to those in the preceding paragraph.

- To evaluate the effect of K0706 on dopamine cell health in PD as detected via Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT) brain imaging.

DaT SPECT brain imaging will be performed at baseline and at the EOT visit (Week 40). The following parameters or quantities may be of relevance: left caudate Striatal Binding Ratio (SBR), right caudate SBR, left putamen SBR, right putamen SBR, and minimum putamen SBR, etc. For each parameter, the exploratory analyses will be similar to those in the preceding paragraph.

8.3.2 Part 2 (Week 40 to Week 80)

For the exploratory efficacy analyses for Part 2, treatment groups are defined identically to that for the secondary efficacy analyses for Part 2. See Section 8.2.2.

The exploratory efficacy analyses are pre-specified as follows:

- Change in the MDS-UPDRS Part III total score, compared between the early and delayed groups at 76 weeks.

For Part 2 of the study, the change from Week 40 (Baseline for Part 2) to Week 76 (EOT visit for Part 2) in the MDS-UPDRS Part III score will be presented for the early-start and delayed-start K0706 groups. The early-start and delayed-start cohorts will be defined as:

- Early-start – the cohort of subjects randomized to K0706 treatment groups in Part 1 (called 'K0706 Pooled' in the summary tables).
- Delayed-start – the cohort of subjects randomized to Placebo treatment group in Part 1 and transitioned to K0706 High dose therapy at the beginning of Study Part 2 (called 'Prior Placebo transitioned to K0706 High Dose' in the summary tables).

The above summaries are covered in the first bullet under the Secondary Efficacy Analysis for Part 2.

- Evaluation of slopes of the mean change in MDS-UPDRS Part-III total score over time in Part 2 for the early treatment groups as compared to the delayed treatment group.

The random coefficient regression analyses for Part 2 will be similar to that for Part 1. Note that the prior Placebo group transitioned to K0706 high dose will be used as the reference group for the testing and estimating for the LS mean difference at each time-point during Part-2. Note that the starting time-point for this Part 2 analysis is Part 2's baseline. The same analysis for the Part III total score will be repeated for the analysis of the sum of Parts II and III total scores.

- Proportion of subjects initiating symptomatic treatment.

The difference (and its 90% CI) in the proportion of subjects initiating symptomatic PD medications in Part 2 between each dose of K0706 versus the Prior Placebo transitioned to

K0706 High dose arm will be calculated. In addition, the above statistics will also be presented for the comparison of the early-start group versus delayed-start group.

9.0 SAFETY ANALYSES

All safety data will be summarized for Parts 1 and 2 of the study separately, using the Safety Analysis Set, Part 1 and Safety Analysis Set, Part 2, respectively.

9.1 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary (version 23.0 or a later version if updated during the study) and classified as either pre-treatment AEs or TEAEs for Part 1 or Part 2 of the study as follows:

- Pre-treatment AEs are events that start prior to the start of the Treatment Period.
- TEAEs are either events with start date / time on or after the start of the Treatment Period, or events with start date / time prior to the start of the Treatment Period whose severity worsens on or after the start of the Treatment Period.
- TEAEs for Part 1 of the study are all TEAEs for those subjects not participating in Part 2 of the study and those TEAEs with start date / time before the date of first dose for Part 2 of the study for subjects participating in Part 2 of the study.
- TEAEs for Part 2 of the study are those TEAEs with start date / time on or after the date of first dose for Part 2 of the study.
- Serious TEAEs will be defined as TEAEs regarded by the investigator as Serious = "Yes".
- The relationship between TEAE and study medication is assessed as certainly, probably, possibly, unlikely or unrelated. A study treatment related TEAE will be defined as a TEAE considered by the investigator as certainly, probably, or possibly related to study medication or with missing relationship to study medication.
- Assessment of AE severity will be characterized as mild, moderate, severe, life-threatening and death.
- TEAEs leading to discontinuation of study are defined as TEAEs where "Did AE caused subject to discontinue from the study?" is indicated as "Yes".
- TEAEs leading to discontinuation of study treatment are defined as TEAEs where "Action taken with Study Medication" is indicated as "Drug Discontinued".

AEs will be summarized by default descriptive summary statistics for categorical variables by treatment group and overall, for Parts 1 and 2 of the study separately, using the Safety Analysis Set, Part 1 and Safety Analysis Set, Part 2 respectively, as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:

- Any TEAE
  - Leading to discontinuation of study treatment
  - Leading to death
  - Severity: mild
  - Severity: moderate
  - Severity: severe
  - Severity: life-threatening
  - Severity: death
- Any study treatment-related TEAE
  - Leading to discontinuation of study treatment
  - Leading to death
- Any serious TEAE
  - Leading to discontinuation of study treatment
  - Leading to death
- Any serious study treatment-related TEAE
  - Leading to discontinuation of study treatment
  - Leading to death
- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
  - TEAEs
  - TEAEs Leading to Discontinuation of Study Treatment
  - TEAEs Leading to Death
  - TEAEs by Maximum Severity
  - TEAEs by Relationship to Treatment
  - TEAEs by Relationship and Maximum Severity
  - Study Treatment-Related TEAEs
  - Study Treatment-Related TEAEs Leading to Discontinuation of Study Treatment
  - Study Treatment-Related TEAEs Leading to Death

- Serious TEAEs
- Serious TEAEs Leading to Discontinuation of Study Treatment
- Serious TEAEs Leading to Death
- Study Treatment-Related Serious TEAEs
- Study Treatment-Related Serious TEAEs Leading to Discontinuation of Study Treatment
- Study Treatment Related Serious TEAEs Leading to Death

- The number and percentage of subjects who died will be summarized
- The number and percentage of subjects reporting each TEAE and the number of events will be summarized by PT

[redacted]

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

AEs for Part 1 of the study will be summarized by default descriptive summary statistics for categorical variables by formulation category and overall, using the Safety Analysis Set, Part 1, as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type above.
- The number and percentage of subjects reporting each TEAE and the number of events will be summarized by SOC and PT.
- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by PT.

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included in the overall count of subjects with TEAEs, but will not be included in the counts of subjects with TEAEs within a SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where PTs tie, PTs will be sorted alphabetically.

[redacted] statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those subjects who received at least one dose of study treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented for Parts 1 and 2 of the study separately, using the Safety Analysis Set, Part 1 and Safety Analysis Set, Part 2, respectively:

- Listing of Deaths
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs resulting in death
- Listing of Serious AEs

9.2 Laboratory Evaluations

Data for the following hematology, serum chemistry, urinalysis, serology, lipid profile and coagulation analytes received from central laboratory and recorded in the eCRF are to be measured at the scheduled visits indicated in the study flowchart (Table 5).

Table 5: Laboratory Tests

Hematology Test (SI unit)	**Serum Chemistry Test (SI unit)**	**Urinalysis (dipstick)**

• Hemoglobin (g/L)
• Hematocrit (%)
• WBC Count (10^9/L)
• Differential WBC (10^9/L and %)
  ○ Neutrophils
  ○ Lymphocytes
  ○ Eosinophils
  ○ Basophils
  ○ Monocytes
• Platelet count (10^9/L)
	• Sodium (mmol/L)
	• Potassium (mmol/L)
	• Chloride (mmol/L)
	• CO_2 (mmol/L)
	• Glucose (mmol/L)
	• BUN (mmol/L)
	• Creatinine (mmol/L)
	• Calcium (mmol/L)
	• ALT (U/L)
	• AST (U/L)
	• Alkaline phosphatase (U/L)
	• Total bilirubin (mmol/L)
	• Total protein (g/L)
	• Albumin (g/L)
	• Amylase (U/L)
	• Lipase (U/L)
		• pH
		• Specific Gravity
		• Protein
		• Glucose
		• Ketones
		• Bilirubin
		• Urobilinogen
		• Blood
		• Nitrite
		• Leukocyte esterase
		• Microscopic examination of the sediment only if abnormality seen on routine tests

Serology	**Lipid Profile (SI unit)**	**Coagulation**

• HIV-1/2 Antigen/Antibody
• Hepatitis panel
  ○ Hepatitis B Virus Surface Antigen
  ○ Hepatitis C Virus Antibody
	• Total Cholesterol (mmol/L)
	• HDL (mmol/L)
	• LDL (mmol/L)
	• Triglycerides (mmol/L)
		• Prothrombin Intl. Normalized Ratio
		• Activated Partial Thromboplastin Time

SI = International System of Units; WBC = White Blood Cell; CO_2 = Carbon Dioxide; BUN = Blood Urea Nitrogen; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; HIV = Human Immunodeficiency Virus; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein.

[redacted]

Central laboratory data will be summarized by analysis visit (as defined in and) using default descriptive summary statistics for continuous variables for Parts 1 and 2 of the study separately, by treatment group and overall. Changes from Baseline will also be summarized.

All central laboratory data will be reported [redacted] and all local laboratory data will be reported [redacted]. All quantitative central laboratory test values at each assessed visit will be compared with the relevant reference range [redacted] and all quantitative local laboratory test values at each assessed visit will be compared with the relevant reference range in [redacted] and categorized as:

[redacted]

For summaries which present the worst value with respect to the reference range at the subject level, low and high are each chosen in preference to normal values. For parameters with both lower and upper limits of the reference range, subjects who have assessments within both low and high ranges will be counted within each category for worst value summary tables.

The number and percentage of subjects with worst post-baseline categorized (low, normal and high) values relative to the reference range will be summarized for Parts 1 and 2 of the study separately, by laboratory analyte, treatment group and overall.

Listings of all clinical laboratory data including derived change from Baseline and listings of clinically significantly abnormal values will be provided for Parts 1 and 2 of the study separately. [redacted]

9.3 Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- Systolic blood pressure in supine position (mmHg);
- Systolic blood pressure in standing position (mmHg);
- Diastolic blood pressure in supine position (mmHg);
- Diastolic blood pressure in standing position (mmHg);
- Pulse rate in supine position (bpm);
- Pulse rate in standing position (bpm);

- Weight (kg);
- An investigator assessment of both, systolic and diastolic blood pressure in supine position, systolic and diastolic blood pressure in standing position, pulse rate in supine position and pulse rate in standing position classified as Normal / Abnormal, Not Clinically Significant / Abnormal, Clinically Significant.

In accordance with the Baseline value definitions for Part 1 and Part 2 in Section 0. For Part 1, the absolute change from Baseline at post-Baseline analysis visits (as defined in) will be derived as follows:

[redacted] – [redacted]

[redacted]

[redacted] – [redacted]

The following will be summarized by treatment group and overall for Parts 1 and 2 of the study separately:

- Observed values and change from Baseline at each analysis visit (as defined in and) for each vital sign parameter using default summary statistics for continuous variables.
- The worst post-Baseline investigator assessment will be summarized for the blood pressure (both supine and standing position together), and pulse rate (both supine or standing position together) by providing number and percentage of subjects within each assessment category.

A listing of all vital signs data including derived change from Baseline will be provided for Parts 1 and 2 of the study separately, using the Safety Analysis Set, Part 1 and Safety Analysis Set, Part 2, respectively.

9.4 Electrocardiograms

The following ECG assessments will be taken in triplicate for Part 1 of the study only:

- Heart rate (bpm);
- PR interval (msec);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);

- Fridericia corrected QT (QTcF) interval (msec).

[redacted]

The average QTcF interval (msec) values and changes from Baseline will be summarized at each analysis visit (as defined in) by treatment group and overall using default summary statistics for the Safety Analysis Set, Part 1.

In accordance with the Baseline value definitions for Part 1 in Section 0. For Part 1, the absolute change from Baseline at post-Baseline analysis visits (as defined in) will be derived as follows:

[redacted]

The maximum post-Baseline average QTcF interval values will be classified in accordance with the ICH E14 [redacted]) Boundaries as presented in [redacted]

Table 6: QTcF Interval ICH E14 Boundaries

QTcF Interval	Criteria (msec)
Observed Average QTcF interval	<= 450 msec > 450 to <= 480 msec > 480 to <= 500 msec > 500 msec
Change from Baseline in Average QTcF interval	<= 30 msec > 30 to <= 60 msec > 60 msec

A categorical summary of QTcF classification according to ICH E14 boundaries will be provided using counts and percentages for the maximum post-Baseline value by treatment group and overall for the Safety Analysis Set, Part 1.

A listing of all ECG data including derived change from Baseline for average QTcF interval will be provided for the Safety Analysis Set, Part 1.

9.5 Physical Examinations

Abnormalities identified from physical examination are recorded in the eCRF as AEs and will be listed and summarized as such (See Section 6.3 [Medical History] and Section 9.1 [Adverse Events]).

In accordance with the Baseline value definitions for Part 1 and Part 2 in Section 4.1.2, for each physical examination body system, the number and percentage of subjects with abnormalities at Baseline will be summarized by treatment group and overall for Parts 1 and 2 of the study separately.

Physical examination findings (Normal / Abnormal, Not Clinically Significant / Abnormal, Clinical Significant) and details of abnormalities will be listed for each subject at each scheduled visit for Parts 1 and 2 of the study separately.

9.6 Other Safety Outcomes

A categorical summary of the [redacted] composite endpoints at Baseline, at each analysis visit and the worst post-Baseline result will be provided using counts and percentages by treatment group and overall for Parts 1 and 2 of the study separately. See Section 13.5 on the [redacted] composite endpoints.

9.7 Prior and Concomitant Medications

All medications will be coded using the World Health Organization (WHO) Drug Global Dictionary, (version Mar 2022 or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) classification codes.

Prior and concomitant medications are defined as follows:

- Prior medications are those medications with a stop date prior to the start of the Treatment Period.
- Concomitant medications are those with a start date on or after the start of the Treatment Period, or those with a start date before the start of the Treatment Period and either a stop date on or after the start of the Treatment Period, or are ongoing at the end of the study.
- Concomitant medications for Part 1 of the study are all concomitant medications for those subjects not participating in Part 2 of the study and those concomitant medications with start date before the date of first dose for Part 2 of the study for subjects participating in Part 2 of the study.
- Concomitant medications for Part 2 of the study are those concomitant medications with start date on or after the date of first dose for Part 2 of the study.

See Section [redacted] for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized by treatment group and overall for Parts 1 and 2 of the study separately, using the All Randomized Set, Part 1 and All Enrolled Set, Part 2, respectively, as follows:

- The number and percentage of subjects with at least one prior / concomitant medication will be presented.
- The number and percentage of subjects with at least one prior / concomitant medication within each Therapeutic Subgroup (ATC-Level 2), Chemical Subgroup (ATC-Level 4), and PT will be presented. The summary will be sorted using numerical counts by descending order of Therapeutic Subgroup, then descending order of Chemical Subgroup, then descending order of PT in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications will be listed for the All Randomized Set, Part 1. Concomitant medications for Parts 1 and 2 of the study will be listed separately, using the All Randomized Set, Part 1 and All Enrolled Set, Part 2, respectively. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date of study drug in the corresponding Part period and will be presented for those subjects who received at least one dose of study drug. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

9.8 Extent of Exposure

Duration of exposure will be calculated in weeks as:

[redacted] –

Duration of exposure will be summarized by treatment group and overall for Parts 1 and 2 of the study separately.

The total number and percent of doses administered per subject (and the number of subjects with doses administered since previous visit) at each scheduled site visit will be summarized using descriptive statistics by treatment group and overall.

The percentage of doses administered per subject will be calculated as the total number of doses administered divided by the total planned doses, expressed as a percentage.

Total number of doses administered per Visit will be defined as:

- For Part 1 of the study:

- For the first post-Baseline visit → (Date of the visit – date of first dose for Part 1 – number of doses missed since last visit)
- For subsequent visits → (Date of the visit – date of the prior visit – number of doses missed since last visit)
- For the last on-treatment visit → (Date of the last dose for Part 1 – date of the prior visit – number of doses missed since last visit + 1)

- For Part 2 of the study:
  - For the first post-Baseline visit → (Date of the visit – date of first dose for Part 2 – number of doses missed since last visit)
  - For subsequent visits → (Date of the visit – date of the prior visit – number of doses missed since last visit)
  - For the last on-treatment visit → (Date of the last dose for Part 2 – date of the prior visit – number of doses missed since last visit + 1)

Total number of doses administered in Part 1 or Part 2 will be calculated as the sum of the doses administered per Visits in Part 1 or Part 2, respectively.

[redacted]

- [redacted]
  - [redacted] → [redacted] – [redacted]
  - [redacted] → [redacted] – [redacted]
  - [redacted] → [redacted] – [redacted]
- [redacted]
  - [redacted] → [redacted] – [redacted]
  - [redacted] → [redacted] – [redacted]
  - [redacted] → [redacted] – [redacted]

[redacted]

A listing of overall treatment exposure data, including the first and last dates of treatment, transition dates from capsules to powder formulation, and dates of the study treatment dose reductions will be presented for Parts 1 and 2 of the study separately, using the Safety Analysis Set, Part 1 and Safety Analysis Set, Part 2, respectively.

10.0 PHARMACOKINETIC ANALYSES

Pharmacokinetic (PK) analyses will be performed on the PK Analysis Set, Part 1. There is no PK study in Part 2. [redacted]

See Section 4.2.4 for the handling of plasma and CSF concentrations that are BLQ.

K0706 plasma and CSF concentration data will be summarized by dose group and assessment time-point by using descriptive statistics (such as number of subjects, mean, standard deviation, geometric mean, coefficient of variation (CV%), minimum, median, and maximum values).

PK analyses and modelling will be detailed in a separate SAP.

[redacted]

[redacted]

[redacted]

[redacted]

12.0 CONVENTIONS

12.1 Software

The Statistical Analysis System® (SAS®, version 9.4 or newer) will be used for all statistical analysis and reporting.

12.2 General rules for Statistical Reporting

In general, statistical reporting and analyses will be created separately for Part 1 and Part 2.

The default summary statistics for quantitative variables will be the number of observations (n), mean, SD, median, minimum (min) and maximum (max), for those subjects with data. In addition, geometric mean and CV% of geometric mean will be reported for PK parameters.

All summary statistics will be rounded (using the [redacted]) and presented to 1 more decimal place than the raw value, except for the SD and SE values that will be presented to 2 more decimal places than the raw value, and minimum and maximum values that will be presented with the same decimal precision as the raw value. All summary statistics for PK data will be rounded (using the [redacted]) and presented to 3 significant figures, except for the geometric CV values that will be presented to 1 decimal place.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. The number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in Tables, Figures and Listings (TFL) mock shell(s).

All statistical comparisons and tests will be performed at the [redacted]-sided [redacted] significance level unless specifically stated otherwise.

All central laboratory test results will be provided in International System of Units (SI) and all local laboratory test results will be provided in conventional units.

For the TFL, the results will be summarized or presented in [redacted] Refer to Appendix of the TLF mock shells for the SI unit corresponding to each laboratory test and the precision level in which each laboratory test is reported by the central laboratory.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

13.0 RATING SCALES: SCORING AND HANDLING OF MISSING DATA

13.1 MDS-UPDRS

The MDS-UPDRS contains questions/ratings, which are divided into Part I (13 items), Part II (13 items), and Part III [redacted] The total score of each part will be calculated as the sum of individual items' scores within the corresponding Part. [redacted]

In case of missing item scores, prorated scores for each part of the MDS-UPDRS will be calculated as the sum of the available individual item scores multiplied by the number of total items in the complete part of the MDS-UPDRS, and this result was divided by the number of items with actual scores. The number of permissible missing items for generating a valid prorated score is 1 missing item for Part I, 1 missing item for Part II and 3 missing items for Part III. If the number of missing item scores exceeds the number of permissible missing items, then the prorated score will not be valid and will be kept missing. If the total score for either Part II or Part III is missing, then the sum of MDS-UPDRS Parts II and III total scores will be missing.

For the primary and secondary efficacy analyses, if any assessment on MDS-UPDRS is captured on or after the day of the initiation of symptomatic PD medications, it will be treated as a missing value.

13.2 CGIS

The CGIS is rated on a [redacted], with the severity of illness scale using a range of responses [redacted]

13.3 EQ-5D-5L

The [redacted]

13.4 SCOPA-AUT

The SCOPA-AUT is a specific 23-item self-completed questionnaire for the assessment of autonomic dysfunction in subjects with PD. [redacted]

In case of a valid SCOPA-AUT score (i.e., with a valid response on [redacted] of the questions), the SCOPA-AUT total score will be transformed to a scale from 0 to 100 points.

[redacted]

If the number of items with a valid response is [redacted] then the SCOPA-AUT total score will keep blank, i.e., a missing value.

[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]

Appendix 3: Schedule of Assessments

Table 7: Schedule of Assessments for All Subjects – Screening Period Only

[redacted]

[redacted]

Table 8: Schedule of Assessments – Treatment Period: Subjects NOT in the Biomarker Sub-study

[redacted]

[redacted]

[redacted]

Table 9: Schedule of Assessments – Treatment Period: Subjects in the [redacted]

[redacted]

[redacted]

[redacted]

Table 10: Schedule of Assessments – Long Term Extension Period: Optional

[redacted]

[redacted]

[redacted]

[redacted]

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