Statistical Analysis Plan

Utilization of Target Ranges to Treat Patients with Parkinson's Disease by Objective Measurement Using the Personal KinetiGraph® (PKG®) compared to Standard of Care Assessment (TARGET-PD)- A Randomized Controlled Trial

Global Kinetics Corporation

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Approved By:

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1.Introduction

The purpose of this statistical analysis plan is to describe the methods that will be used to analyze and report the clinical utility of Personal KinetiGraph movement recording system data in the clinical management of Parkinson's disease (PD) using objective measurement and target ranges in neurology and movement disorders clinics in the U.S.

Subsequent versions of this analysis plan will document and describe any such changes. This plan is based on the protocol Version 1.0, dated June 6, 2019.

Prior to the planned protocol interim analysis, Global Kinetics notified all sites that enrollment was closed as of February 27, 2020. The contexts of this analysis plan will therefore reflect an adapted plan for all subjects enrolled prior to the notification of enrollment closure followed through the primary endpoint.

2.Abbreviations

- BKS: Bradykinesia Scores
- CGI-I: Clinician Global Impression of Improvement
- DKS: Dyskinesia Scores
- HCU: Healthcare resource utilization
- MDS: Movement Disorder Specialists
- PD: Parkinson's Disease
- PDQ-39: Parkinson's Disease Questionnaire - 39
- PGI-I: Patient Global Impression of Improvement
- PKG: Personal KinetiGraph
- MDS-UPDRS: Movement Disorder Specialist Unified Parkinson's Disease Rating Scale

3.Study Objectives

3.1. Primary Objective

This is a randomized controlled trial (RCT) to evaluate treating uncontrolled patients with Parkinson's Disease (PwP) to a target range established by published expert opinion. The study aims to evaluate clinical patient outcomes, quality of life measures and health care utilization of those patients specifically treated to a target range when using the PKG data in the clinical management of Parkinson's disease (PD) in routine clinical care (treatment group) compared to those managed with medical history and clinical evaluation alone (control group) performed by a neurologist experienced in PD management. Both groups will be recommended to undergo medication changes until they reach a "controlled state" that is determined by either the clinician using standard of

care (SOC) (PKG- Group) or using PKG based targets and SOC assessments (PKG+ Group). For subjects in the treatment arm (PKG+ Group) the references will be according to the following table for purposes of analysis using PKG scores. Subjects will either be considered bradykinetic (BKS scores exceed targets; BKS >25) or Dyskinetic (DKS scores exceed targets; DKS >9):

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25
Dyskinesia Score (DKS)	Median DKS 7-9

The main objective of this study is to evaluate whether PwP who are managed with the aid of objective measurement and use of target ranges have improved PD symptoms and outcomes as compared to individuals treated using only standard of care (medical history, neurological examination).

3.2. Hypothesis & Primary Endpoint

Primary Endpoint: The change in MDS-UPDRS Total score at 4 months from baseline defined as sections I, II, III and IV in PwP. The endpoint will be compared between those who are treated with standard of care and PKG data (PKG+ Group) and those who are treated per standard of care alone (PKG- Group).

The primary endpoint of change in total MDS-UPDRS at 4 months will be compared between the treatment group (PKG+ Group) and the control group (PKG- Group) based on a two-sample t-test. In the event normality assumptions are violated, a non-parametric analog will be used. A difference between groups of 5 points is assumed for the change in total MDS-UPDRS as well as a standard deviation of 13 based on historical data. With these assumptions, a sample size of 280 evaluable subjects will provide approximately 83% power for the statistical hypothesis test for the primary endpoint. To account for attrition of up to 20%, a total enrollment of 350 subjects is planned. Enrollment was stopped in the study at 41 subjects enrolled. These 41 subjects will be followed through the 4-month endpoint and will be analyzed.

The difference in the primary endpoint between randomized groups will be compared with a two-sample t-test of means at the 1-sided alpha of 0.025 (equivalent to a two-sided 0.05 alpha level). In the event normality assumptions are violated, a non-parametric analog will be used.

The primary analysis will be based on the intent-to-treat (ITT) population defined as all randomized subjects analyzed according to the treatment group assigned. Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analyses will be conducted using SAS version 9.4 or later (SAS

Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required. Continuous variables will be summarized with mean, standard deviation, median, max, min, and number of evaluable observations. Categorical variables will be summarized with frequency and percentages. Confidence intervals may be presented where appropriate using the t-distribution for continuous variables and Clopper-Pearson Exact method for categorical variables. Unless otherwise specified, statistical analyses will be performed using a one-sided 0.025 alpha level.

An additional analysis will be conducted due to impacts from COVID-19 for the primary endpoint. This will include looking at instances where a partial UPDRS Part III was collected due to restrictions when conducting a telehealth video visit.

Subgroup Analysis of Primary Endpoint
Subgroup analyses will be conducted to examine the possible influence of baseline characteristics on the primary outcome. Subgroups of interest may include but are not limited to:

- Duration of disease – defined by years of disease (Date of Visit 1 - Year of PD Diagnosis)
- Stage of PD - defined by Hoehn & Yahr (1-5) at Visit 1
- History of fluctuation – defined by patient wearing off in last 30 days at Visit 1
- Gender
- Age – defined by Date of Visit - DOB
- Controlled PD at Baseline Visit in PKG+ and PKG- groups as defined by the PKG for both groups.
- Uncontrolled PD at Baseline Visit in PKG+ and PKG- groups as defined by the PKG for both groups.

3.3. Secondary Objective

The secondary objective is to determine the association between frequency of medication changes, the PKG information, and other clinical assessments among participants with and without a PKG report of their PD motor status available to the clinician at the time of evaluation.

3.4. Secondary Endpoints

The following secondary clinical outcomes will be measured at and compared between baseline and 4 months follow-up visits.

Secondary clinical outcomes will include:

1. **Percent "responders" for MDS-UPDRS Total score (based on a minimum clinically important change of >4 points)**

This is a comparison of the percent responders for the within-group change from baseline to 4 months for PKG+ and PKG- groups. This is a comparison of the percent responders for the within-subject change from baseline to 4 months for PKG+ and PKG- groups.

2. **Change in motor endpoints from baseline to 4 months including:**
    a. **MDS-UPDRS Part III**
        i. Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries. (example, 35 (4-month) – 45 (BL))
    b. **PKG Bradykinesia score (BKS),**
        i. Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries. (example, 25 (4-month) – 30 (BL))
    c. **PKG Dyskinesia score (DKS) and measurement of OFF time**
        i. Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries. (example, 5 (4-month) – 9 (BL))
        ii. Measurement of OFF time will not be included in this analysis

3. **Change in PDQ-39 from baseline to 4 months**

    Change in PDQ-39 from baseline to 4-months. Tabulate values and proportions and changes from baseline to each visit.

    Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

    The Parkinson's Disease Questionnaire will be completed by the patient at baseline, 4 months and annual follow-up visits concerning activities in the last month including self-care, walking ability, falling, mental stability, somnolence, etc. This a 5-point scale (never, occasionally, sometimes, often, always). A dimension score is calculated for each of 8 sections and a summary index is then calculated for the entire assessment.

4. **Change in MDS-UPDRS Part I from baseline to 4 months**

   Change in MDS-UPDRS Part I and subsections as noted on the MDS-UPDRS data collection from baseline to 4 months.

   Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

5. **Change in MDS-UPDRS Part II from baseline to 4 months**

   Change in MDS-UPDRS Part II and subsections as noted on the MDS-UPDRS data collection from baseline to 4 months.

   Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

6. **Change in MDS-UPDRS Part IV from baseline to 4 months**

   Change in MDS-UPDRS Part IV and subsections as noted on the MDS-UPDRS data collection from baseline to 4 months.

   Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

7. **Change in PKG Scores including BKS, DKS, PTT, FDS and PTI from baseline to 4 months**

   Change in PKG scores from baseline to interim1, interim 1 to interim2, interim 2 to interim3, interim3 to 4 months for those with interim visits conducted (uncontrolled) or baseline to 4 months for controlled.

   Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and positive change signifies a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

   PKG summary scores will be reported on the PKG at baseline, interims (if applicable for those uncontrolled), and 4 months including the following:

   - Bradykinesia Score

- Dyskinesia Score
- Fluctuation Score
- Percent Time Immobile (PTI)
- Percent Time Tremor Present (PTT)

Evaluation of individual patient and subgroup response from baseline assessed by change in PKG BK or DK scores from baseline to 4 months for controlled (in target range) and uncontrolled (out of target range) in PKG + and PKG- groups

- Rate of subjects who were uncontrolled at baseline (PKG Summary Scores exceeded targets) and then became controlled at the 4-month visit (PKG Summary Scores reduced to below targets).
- Rate of subjects unresponsive to medication changes (i.e. no change to PKG BK scores with LED increase)
- Rate of subjects who required treatment changes but were unwilling to make changes (this group may not show any impacts to outcomes)
- Rate of subjects who required treatment changes but were contraindicated to make changes (this group may not show any impacts on outcomes)

8. Change in LED from baseline to each interim visit and 4 months

Calculation of Levodopa Equivalent Dose (LED) at each visit for each patient and a comparison of change in LED at each visit for each patient. If a change is made at the scheduled visit, the change is calculated for the next visit (e.g., a change at the BL visit means the subject has started taking the new medication/dose/frequency change the day after the BL visit, etc.) – See Appendix for reference in calculating LED.

Rate and change in PD medications including medication type, dosing, increase, decrease from baseline to interim1, interim2, interim3, and 4 months.

An analysis to look at medication change amount and frequency and impact on outcome of MDS-UPDRS and PKG BKS will be performed. Patients will be ranked by amount of LED change at each visit and grouped by number of times they had medication changes at a visit (e.g. 0, 1, 2 times, etc.) from baseline to the 4 month visit and correlated to the outcome of MDS-UPDRS and PKG score of BKS at 4 months.

- Rate of subjects who were marked as uncontrolled but had no medication changes will be noted.
- Rate of subjects who had medication changes but were less than 100mg LED will be noted.

9. **PKG Patient Survey at 4 months**
PKG Patient Survey at 4 months. Tabulate values and proportions and changes from baseline to each visit.

The rate at 4 months will be calculated for the PKG+ and PKG- groups for each section of the survey.

Within-subject changes will be calculated as visit value minus 4-Month value such that a positive change indicates an improvement and a negative change a deterioration. Summaries of improved/same/worsened will be provided along with the continuous summaries.

This assessment is completed by the patient at 4 months.. The assessment contains 2 parts including PKG Use and PKG Impact on Care. The PKG Use is a 5-point scale from strongly disagree to strongly agree concerning PKG training, ease of use, compliance with medication reminders, willingness to use again in PD management. The PKG Impact on Care is a 5-point scale from not valuable to very valuable concerning medication reminders, explanation of symptoms, movement during daily activity and overall value.

3.5. Ancillary Endpoints

Ancillary endpoints will include measurements as indicated below:

- Rate of protocol defined adverse events affecting health care utilization including: hospitalizations, emergency department, urgent care or unanticipated clinic visits from at 4 months
- Rate of protocol defined adverse events and potential contraindications for increasing dopaminergic therapy including: falls, orthostatic hypotension, bothersome hallucinations, delirium, and impairment that prohibits interaction with the PKG watch at 4 months
- Rate of uncontrolled subjects in PKG+ group who are unable to be brought into Target Range through follow-up visits (BKS < = 25 or DKS < = 9). This will also be run for a threshold of a PKG score of BKS < = 26 at 4-months.

4.Study Design

This is a prospective, multi-center, single-blind randomized (1:1) controlled, longitudinal follow-up study (1, 2, 3 years).

This is a randomized controlled trial (RCT) to evaluate treating uncontrolled patients with Parkinson's Disease (PwP) to a target range established by a published expert opinion manuscript. The study aims to evaluate clinical patient outcomes, quality of life measures and health care utilization of those patients specifically treated to a target range when using the PKG data in the clinical management of Parkinson's disease (PD) in routine clinical care (treatment group) compared to those managed with medical history and clinical evaluation alone (control group) performed by a neurologist experienced in PD management. Both groups will be recommended to undergo medication changes until they reach a "controlled state" that is determined by either the clinician using standard of care (SOC) (PKG- Group) or using PKG based targets and SOC assessments (PKG+ Group). For subjects in the treatment arm (PKG+ Group) the references will be according to the following table for purposes of analysis using PKG scores*:

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25
Dyskinesia Score (DKS)	Median DKS 7-9

The main objective of this study is to evaluate whether PwP who are managed with the aid of objective measurement and use of target ranges have improved PD symptoms and outcomes as compared to individuals treated using only standard of care (medical history, neurological examination).

4.1. Sample Size

Based on the original planned sample size, approximately 350 subjects were to be consented to provide an estimated 280 subjects followed through the 4-Month follow-up period (assuming 20% attrition). However, enrollment was stopped in the study at 41 subjects enrolled prior to any protocol defined interim analysis milestones being achieved. These 41 subjects will be followed through the 4-month endpoint and will be analyzed.

4.2. Randomization

Subjects will be randomized during the screening/enrollment visit. Randomization will be performed prior to the start of the study with a 1:1 allocation ratio PKG-:PKG+. Randomization assignments will be created by the statistician and be accessed through the trial electronic database.

4.3. Blinding

The subject will be blinded to the randomization assignment throughout the follow-up phase. For the PKG- group, both the subject and the study staff will remain blinded to the PKG scores throughout the study.

4.4. Study Assessments and Missing Data

In the event inaccurate and/or incomplete PKG data collection occurs (e.g., subject wore PKG successfully but for less than the required duration, subject PKG Watch was not sufficiently secured creating PKG artifacts precluding interpretation, subject performed activities, such as the use of power tools, for a sufficient duration that interfered with PKG data collection, data collection completed when subject was OFF), data collection may be repeated one time. A note will be made in the case report form (CRF) that documents the reason for the repeated data collection and the initial and final test results will be recorded in the medical record. Only the final results will be recorded on the CRF and used for analysis purposes. Techniques will not be used to impute missing data; evaluable data will be utilized.

Due to the impact of COVID-19 on ability to collect select data, notations have been made in the protocol deviation section of the data extract and will be provided as a summary categorization for analysis purposes.

Specifically, for the MDS-UPDRS Part III data was either:

- Completely collected for baseline and/or 4-months visit
- Partially collected for baseline and/or 4 months visit (i.e., rigidity (Q 3.3) and postural stability (Q3.12) questions not collected if a telehealth visit)
- Not collected for baseline and/or 4-month visit

4.5. Analysis Populations

The primary analysis will be based on the intent-to-treat (ITT) population defined as all randomized subjects analyzed according to the treatment group assigned.

In addition, analyses based on the per-protocol (PP) population will be performed for the primary and secondary endpoints. The PP population is defined as all subjects who are randomized and adhere to the study protocol requirements, including: meeting all of the subject selection criteria, completion of the PKG Watch wear period, inability for investigator to further make treatment changes due to known contraindication, completion of subject surveys and completion of follow-up visits.

Subject selection criteria can be found in the study protocol.

5.Methods

5.1. General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using {SAS version 9.3 or later (SAS Institute Inc., Cary, NC)} or other widely accepted statistical or graphical software as required.

5.1.1. Descriptive Statistics

Continuous variables will be summarized with mean, standard deviation, median, max, min, and number of evaluable observations. Categorical variables will be summarized with frequency and percentages. Confidence intervals may be presented where appropriate using the t-distribution for continuous variables and Clopper - Pearson Exact method for categorical variables.

5.2. P-Values

Unless otherwise specified, statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "< 0.001." If a p-value is greater than 0.999 it will be reported as "> 0.999."

6.References

ICH Guidelines. E9: *Statistical Principals for Clinical Trials* http://www.ich.org/ich5e.html.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001 14;357:1191-4.

Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry November 2019;https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

Farzanehfar P, Woodrow H, Braybrook M, McGregor S, Evans A, Nicklason F, Horne M. Objective measurement in routine care of people with Parkinson's disease improves outcomes. *npj Parkinson's Disease*. 2018 4:10; doi: 10.1038/s41531-018-0046-4.

Shulman LM, Gruber-Baldini AL, Anderson KE, et al. (2010) The Clinically Important Difference on the Unified Parkinson's Disease Rating Scale. Arch Neurol ; 67(1): 64-70.

Odin P, Chaudhuri KR, Volkmann J, et al. (2018) Viewpoint and practical recommenda-tions from a movement disorder specialist panel on objective measurement in the clin-ical management of Parkinson's disease. NP J Parkinsons Dis. May 10;4:14. doi: 10.1038/s41531-018-0051-7.

Pahwa R, Isaacson SH, Torres-Russotto D, Nahab FB, Lynch PM,Kotschet KE (2018) Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's dis-ease: Recommendations from an expert panel. Expert Rev Neurother 18, 669-680.

7. Appendix 1 - LED Calculation

LED Used for Parkinson's Studies- 28Jan2020

Reference Tomlinson article Table 2 or order in calculating the LED.

Medication	**Conversion Factor (mg)**	
Levodopa (immediate release)	X 1	
Levodopa CR (controlled release)	X 0.75	
Levodopa ER (extended release) "Rytary"	X 0.5	
Entacapone (or Stalevo™)	LD x 0.33	
Duodopa™	X 1.11	*"When entering dose, consider total mg infused per day"*
Pramiprexole	X 100	
Ropinirole	X 20	
Rotigotine	X 30	
Selegiline (oral)	X 10	
Selegiline (sublingual)	X 80	
Cabergoline	X 100	
Rasagiline	X 100	
Amantadine	X 1	
Apomorphine	X 10 (total mg per day)	*"When entering dose, consider total mg infused per day"*
Bromocripine	X 10	
Pergolide	X 100	
Benzhexol	No L-dopa equivalent	

Benztropine	No L-dopa equivalent	
Biperiden	No L-dopa equivalent	

Tomlinson et al. Systematic Levodopa Equivalent Review in Parkinson's Disease. *Movement Disorders* (2010).

Rytary Instructions for Use Label – Table 1

8. Appendix 2 – Statistical Tables (see attachment)