Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	Japan Post Market Adaptive Deep Brain Stimulation (aDBS) Study (Early Adapter) Part II
Clinical Investigation Plan Identifier	MDT20041
Clinical Investigation Plan Version	Version 6.0 and subsequent versions
Statistical Analysis Plan Version Date	12-MAY-2023
Sponsor/Local Sponsor	Medtronic Japan Co., Ltd. 1-2- 70 Konan, Minato-ku, Tokyo, Japan
The [redacted]	

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable. New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
aDBS	Adaptive Deep Brain Stimulation
AT	As Treated
BrainSense™	The family of features in the Percept PC system that make use of the system
BKS	Bradykinesia Score
cDBS	Continuous Deep Brain Stimulation
CC	Complete-Case
CIP	Clinical Investigation Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DBS	Deep Brain Stimulation
DD	Device Deficiency
DKS	Dyskinesia Score
EQ-5D-5L	Five-dimensional five-level generic measure designed to measure, compare and value health status across disease areas; developed by the EuroQol Group.
Event markers	Used to capture and record patient triggered events and provide additional information for analysis around patients outside the clinic.
GIC	Global Impression of Change
ICH	International Conference Harmonization
LCC	Lead Complete Case
LFP	Local Field Potential
INS	Implantable Neurostimulator
JSON	JavaScript Object Notation, a data file format
LEDD	Levodopa Equivalent Daily Dose
LFP	Local Field Potential
MedDRA	Medical Dictionary for Regulatory Activities
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
PD	Parkinson's Disease
PDQ-39	The 39-item Parkinson's Disease Questionnaire
PDQ-39 SI	PDQ-39 summary index
SAP	Statistical Analysis Plan
STN	Subthalamic Nucleus
TEED	Total Electrical Energy Delivered
UDysRS	Unified Dyskinesia Rating Scale
VAS	Visual Analog Scale

3. Introduction

3.1 Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease associated with both motor and non-motor symptoms. In the initial stages of PD, motor symptoms are often well controlled using dopaminergic drugs. However, chronic use of these levodopa medications is associated with symptom fluctuations, dyskinesia and other motor complications. Deep Brain Stimulation (DBS) Therapy may be used to treat some of the motor complications of PD that are not adequately controlled with medication. Deep Brain Stimulation Therapy is currently delivered in a continuous fashion (cDBS) where stimulation settings are constant over time and do not adjust to fluctuations in symptoms typically experienced by Parkinson's disease patients during medication On and Off states.

To make DBS more responsive to an individual patient's clinical state, investigators have explored the use of adaptive DBS (aDBS) therapy. Evidence generated by previous studies has demonstrated that aDBS is feasible. In addition, both dual and single threshold aDBS algorithms were well tolerated, were as effective or more effective than cDBS, may reduce DBS induced side effects and were associated with a significant reduction in DBS power usage compared to cDBS. Based on this evidence, this study will evaluate the efficacy of aDBS (preferred mode, single or dual threshold) in comparison to conventional cDBS.

The Early Adapter II trial is a prospective, randomized, single-blind, crossover, multicenter study of aDBS in subjects with Parkinson's disease.

3.2 Purpose

The purpose of this statistical analysis plan (SAP) is to document the analyses for the final study report. Revisions to the SAP may be required if the protocol changes impact to the analyses planned. The SAP has been prepared in agreement with Medtronic internal procedures and using the extension of Consolidated Standards of Reporting Trials (CONSORT) Statement[3] for crossover trial and International Conference Harmonization (ICH) guidelines E3, E6 and E9 as guidelines. The purpose of the study is to evaluate the efficacy of aDBS (preferred mode, single or dual threshold) vs standard continuous DBS (cDBS) in decreasing Total Electrical Energy Delivered (TEED).

3.3 Documents used to create SAP

Documents used to create the SAP include:

- Early Adapter Part II Clinical Investigational Plan
- Early Adapter Part II Data Management Plan
- Early Adapter Part II eCRF Requirement

4. Study Objectives

4.1 Primary objective

To demonstrate decreased Total Electrical Energy Delivered (TEED) during adaptive (aDBS) as compared to continuous DBS (cDBS).

4.2 Secondary objective

To demonstrate maintenance within an optimal beta local field potential (LFP) threshold during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower LFP threshold of beta LFP power preset for each patient.

4.3 Safety assessment

To assess safety in the following items:

- Stimulation-related adverse events during the aDBS treatment phase
- Serious adverse events which occur through the study after consent and for which the relationship with Percept PC cannot be ruled out: for all subjects
- Any-cause of death throughout the study: for all subjects.
- Device (Percept PC) deficiencies that potentially involve a serious adverse event throughout the study: for all subjects

4.4 Additional objectives

To characterize clinical outcomes of aDBS (preferred mode) vs. cDBS, and by aDBS mode in the following items:

- EQ-5D-5L
- Parkinson's Disease Questionnaire (PDQ)-39
- Unified Dyskinesia Rating Scale (UDysRS)
- Movement Disorder Society-Sponsored Revision of Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II ("best" and "worst" conditions)*
- MDS-UPDRS III and IV
- LFP dynamics based on out of clinic patient event markers and PD Medication cycle
- Movement data collected from Apple Watch (will be correlated with Percept Device data and clinical measures)
- To assess a patient-specific anatomy using a visualization tool of lead location and simulated volume of neural activation based on Pre-op/post-op imaging data of Percept PC implant.
- Patient preference of aDBS (preferred mode) vs cDBS
- Patient satisfaction with aDBS (preferred mode)
- Global Impression of Change (GIC) with aDBS
- Assess the average function of the subjects during the past week, including the assessment date, when they were in the "best conditions" and "worst conditions".

* "Best conditions" is the time period when PD subjects are receiving relief from their Parkinson's disease symptoms, also known as "on" time or "on" period. "Worst conditions" is the time period when PD subjects are not receiving relief from their Parkinson's disease symptoms, also known as "off" time or "off" period.

5. Investigation Plan

This is a prospective, randomized, single-blind, crossover, multicenter study of aDBS in subjects with Parkinson's disease. The study is expected to be conducted at two centers located in Japan. It is

estimated that approximately 20-30 subjects will be enrolled (implanted with a commercially available Medtronic DBS system with Percept PC INS) to obtain a study population of 20 subjects who complete the aDBS treatment phase. These subjects will roll over from the Early Adapter part I study or will qualify on the basis of demonstrated aDBS acceptability.

The expected study duration of the study is approximately 3 years. It is estimated an enrollment period of 14 months to enroll 20-30 subjects.

Study visits and/or phases include (see Figure 5-1 and Figure 5-2):

- Enrollment Visit: Consent
- Baseline: Demographics, Medical & surgical history, PD history, Device Information, MRI/ CT image data, Signal Test/LFP threshold setting, aDBS washout, Concomitant medications (non-PD), PD medication, Preference questionnaire and Device data programming session upload
- Randomization: 7 days or more after cDBS has been set and within 30 days after the baseline visit, subjects will be randomly assigned to aDBS mode (single or dual threshold) or cDBS.

- aDBS Treatment phase [Period A initiation (Visit A), Post Period A (Visit 2), Post Period B (Visit 3)]: Concomitant medications (non-PD), PD medications, Programming session upload, with device interrogation and BrainSense data included in the JSON session data report, PDQ-39, EQ-5D-5L MDS-UPDRS II ("best" conditions), MDS-UPDRS II ("worst" conditions), MDS-UPDRS III (On stim (cDBS)/On med) – trained rater, MDS-UPDRS IV – trained rater, UDysRS, Upload data collected from Apple Watch, including movement and sleep data
- Follow-up phase [Visit4, Visit5, Visit6]

Figure 5-1. Study Schematic

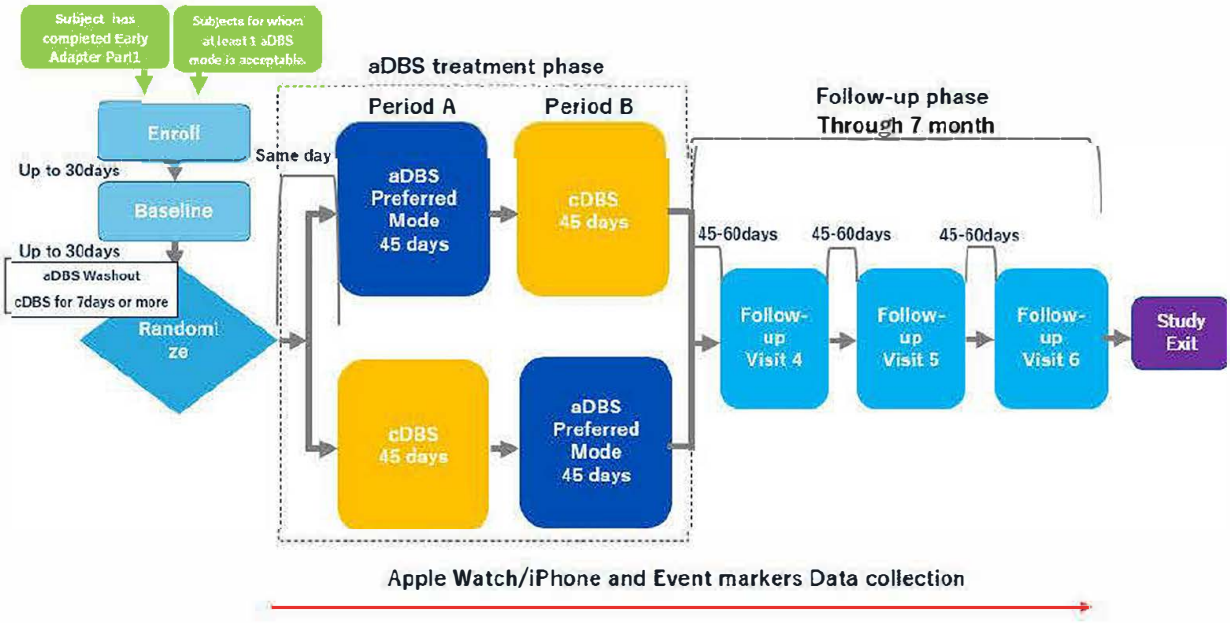

Figure 5--2. Study Procedures and Data Collection by Visit

Visit	Enrollment	Baseline	Randomization	aDBS Treatment Phase					Follow-up phase			Exit
				Visit 1	Out of clinic	Visit 2	Out of clinic	Visit 3	Visit 4	Visit 5	Visit 6	
Visit ranges (From the previous visit)		Up to 30 days		Up to 30 days		45 days[4]		45 days[4]	45-60 days[4]	45-60 days[4]	45-60 days[4]	
Informed Consent	X											
Demographics		X[1]										
Medical & surgical history		X[1]										
PD history		X[1]										
Device Information		X[1]										
MRI/ CT image data		X[1]										
Signal Test/LFP threshold setting		X[1]										
aDBS washout (7 days or more)		X										

Visit	Enrollment	Baseline	Randomization	aDBS Treatment Phase					Follow-up phase			Exit
				Visit 1	Out of clinic	Visit 2	Out of clinic	Visit 3	Visit 4	Visit 5	Visit 6	
Visit ranges (From the previous visit)		Up to 30 days		Up to 30 days		45 days[4]		45 days[4]	45-60 days[4]	45-60 days[4]	45-60 days[4]	
Randomization			X									
Concomitant medications (non-PD)		X		X		X		X	X	X	X	
PD medication		X		X		X		X	X	X	X	
Program initiation (cDBS or aDBS)				X		X						
PDQ-39				X		X		X	X	X	X	
EQ-5D-5L				X		X		X	X	X	X	
UDysRS				X		X		X	X	X	X	
MDS-UPDRS II ("best" conditions)				X		X		X	X	X	X	
MDS-UPDRS II ("worst" conditions)				X		X		X	X	X	X	
MDS-UPDRS III				X		X		X	X	X	X	
MDS-UPDRS IV				X		X		X	X	X	X	
DBS GIC						X		X				
Preference questionnaire		X[1]						X[5]				
Satisfaction questionnaire								X[5]			X	
Apple Watch/iPhone distribution and programming				X								
Apple Watch/iPhone data collection				X	X[2]	X	X[2]	X	X	X	X	
Device data		X[3]		X		X		X	X	X	X	
Event markers (Option)					X		X		X	X	X	
Adverse Events	As they occur											
Device Deficiencies	As they occur											
Protocol Deviations	As they occur											

Visit	Enrollment	Baseline	Randomization	aDBS Treatment Phase					Follow-up phase			Exit
				Visit 1	Out of clinic	Visit 2	Out of clinic	Visit 3	Visit 4	Visit 5	Visit 6	
Visit ranges (From the previous visit)		Up to 30 days		Up to 30 days		45 days[4]		45 days[4]	45-60 days[4]	45-60 days[4]	45-60 days[4]	
Reason for exit												X

1 Not required if data collected prior to Early Adapter Part II
2 PD Medication cycle, every 14 days during 45 days of Period A and B; Calendar reminders set on Apple Watch, with instructions
3 If Signal test was implemented
4 Visit ranges ±7days
5 Perform before unblinding subjects
6 Perform after unblinding subjects

6. Determination of Sample Size

Based on the registry data and the bench testing, when a conservative estimate for the first quartile of TEED data for initial devices in the registry is used, TEED is expected to decrease between 35 and 22 units for aDBS single threshold mode and aDBS dual threshold mode, respectively [1,2]. A standard deviation of 36 results in a medium to large effect size of 0.7858. Based on these assumptions, the sample size was estimated using a two-sided (alpha=0.05) paired T-Test means (PASS 2019) to compare the difference in aDBS TEED to cDBS TEED of 28 and a standard deviation of 36, a minimum of 20 subjects achieves at least 90% power for the detection of an effect size of 0.78. It is anticipated that around 25% of subjects will have unilateral DBS and so they will be excluded from the primary analysis. Considering this information, it is estimated that between 20-30 subjects implanted with a commercially available Medtronic DBS system with Percept PC INS will be enrolled to obtain a study population of 20 (bilateral DBS).

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated according to the extension of CONSORT Statement1 for crossover trial and attrition will be identified and summarized. The number of subjects enrolled, randomized, and who underwent cDBS and aDBS adjustment phases will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

CIP deviations will be listed and the number of deviations will be summarized by associated visit, type and overall.

7.1.3 Analysis Sets

The following subject sets will be used for the analysis:

- Complete Case (CC): includes all subjects with bilateral aDBS who initiate the aDBS treatment phase and have complete data for the respective analysis. This set will be used for the primary analysis.
- As-Treated (AT): includes all subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) at enrollment and/or the aDBS treatment phase and uses the observed treatment used for each subject in each phase regardless unilateral or bilateral DBS. This set will be used for the safety assessment.
- Lead Complete Case (LCC): includes all subjects with aDBS who initiate the aDBS treatment phase and have complete data for the respective analysis regardless of unilateral or bilateral aDBS. This set will be used for the supporting analysis.

7.2 General Methodology

A formal analysis for the Early Adapter Part II study will occur when all active subjects have completed the aDBS treatment phase of the study. Analysis will include both the primary/secondary endpoints. Safety assessment and additional objectives will be addressed based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the study or have been exited. The main analysis will include data from both contributing centers.

The subjects' baseline will be summarized with descriptive statistics. Summary statistics will be presented for continuous measures (N, means, medians, standard deviations, minimum and maximums) and categorical measures (N, percentage, frequency distributions) with 95% confidence intervals as appropriate. For events that can occur more than once in a single subject, such as adverse events, the percentage will be based on subjects experiencing the event; both subject and event counts will be reported. Summary statistics will be provided for each randomization group and period.

7.3 Center Pooling

All investigators will conduct the study according to a common protocol and utilize the same Case Report Forms (CRFs) to collect study data. Any efforts will be made to ensure consistency among sites in selection of patients and conduct of the study procedures. In addition, a poolability assessement based on the descriptive statistics of the primary and key secondary endpoints by center will be performed.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

No imputation will be used. However, all attempts will be made to minimize missing data.

7.5 Adjustments for Multiple Comparisons

No adjustment will be performed for evaluations of the additional study objectives.

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for the CC set. This will at least include:

- Baseline demographics: Age and Sex
- Medical and Surgery history: Disease name and Surgery name
- PD history: PD duration, Dyskinesia duration, Location of dyskinesias, Motor fluctuation duration, Dominant Side, Duration of L-DOPA treatment, Duration of dopamine agonist treatment
- Device identification information, including historical DBS implant information
- Signal test/LFP threshold setting
- aDBS washout (7 days or more)
- Patient preference questionnaire
- Concomitant medications (non-PD)
- PD medication
- Programming session upload, with device interrogation and BrainSense data included in the JSON session data report

The statistical evaluations will use some derived variables as listed below.

New Variable	Derivation
PD duration	Visit Year – PD diagnosis Year
Dyskinesia duration	Visit Year – Dyskinesia start Year
Motor fluctuation duration	Visit Year – Motor fluctuation start Year
Duration of L-DOPA treatment	Visit Year – L-DOPA treatment start Year
Duration of dopamine agonist treatment	Visit Year – L-DOPA treatment start Year
Study Exposure (days)	(Study Exit date – Consent date)/30.44

7.7 Treatment Characteristics

Device data will be summarized with descriptive statistics as described in section 7.2.

In addition, duration of study exposure will be measured in days starting from the point of enrollment (informed consent completed) through and including the time of study exit: duration of study exposure (days) = (study exit date – date of consent). Extent of study exposure will be presented in a summary table and supporting data listing if needed.

7.8 Interim Analyses

No interim analysis is planned for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The primary objective is to demonstrate decreased Total Electrical Energy Delivered (TEED) during adaptive (aDBS) as compared to continuous DBS (cDBS).

7.9.1.1 Endpoint definition

The endpoint is the energy use as measured by TEED during the aDBS as compared with TEED during the cDBS during the aDBS treatment phase (from period A to period B). Denote by $TEED_{aDBS}$ the TEED on aDBS and by $TEED_{cDBS}$ the corresponding value for cDBS . For each patient the difference between $TEED_{aDBS}$ and $TEED_{cDBS}$ will be calculated ($TEED_{aDBS}$ - $TEED_{cDBS}$ =$TEED_{DIFF}$).

7.9.1.2 Hypothesis

The hypothesis that $TEED_{DIFF}$ <0 will be tested by means of the Student's paired t-test and a p-value less than, or equal to, 0.05 will be regarded statistically significant. As a robustness analysis the hypothesis will be tested by means of the Wilcoxon signed rank test as well.

The formal hypothesis testing is:

$$H_0: \mu TEED_{aDBS} - \mu\, TEED_{cDBS} = 0 \quad \text{vs.} \quad H_a: \mu TEED_{aDBS} - \mu\, TEED_{cDBS} < 0,$$

where the difference $\mu TEED_{DIFF} = \mu TEED_{aDBS} - \mu\, TEED_{cDBS}$ is the mean electrical energy saving.

TEED is defined as the total energy delivered by an electrical system through the DBS leads over an arbitrary period of time.

7.9.1.3 Sample size justification

The sample size justification for the primary objective is provided in section 6.

7.9.1.4 Analysis methods

The primary analysis will use the CC set as described in section 7.1.3. TEED is determined by the stimulation parameters (e.g., pulse width, frequency, amplitude) and the measured impedance.

The calculation of TEED when using constant voltage is:

$$TEED = voltage^2 \times frequency \times pulse\ width / impedance$$

The calculation of TEED when using constant current is:

$$TEED = current^2 \times frequency \times pulse\ width \times impedance$$

The previous formulas can be used without modification with DBS lead models 3387 or 3389. When the lead is the SenSight™ system and it is programmed in Directional Stim Mode or Ring Mode Stimulation, each contact is considered independent. For each segment that is activated, TEED will be calculated individually using the formulas above, and then summed to obtain the total TEED for the lead. Leads programmed with monopolar settings will use the electrode unipolar impedance between the case and the active electrode. If 2 cathodes are used (dual monopolar settings), TEED will be calculated for each contact separately, and total TEED will be determined for the lead as the sum of the two TEED. Leads programmed to bipolar will use the impedance between the active electrodes.

Directional Stim Mode may be programmed during the follow-up phase. The primary endpoint on the difference in TEED will be assessed by means paired t-test to compare the difference in TEED for aDBS (preferred mode, single or dual threshold) to cDBS. Normality of the outcome will be assessed with the Shapiro-Wilk test. If large violations to the normality assumption are observed ($p<0.05$), the primary analysis will use a Wilcoxon signed-rank test to assess statistical significance. To compute TEED using the formula above, the average current drain from the JSON session data will be computed using the average stimulation currents from the timeline feature in the 14 days prior to the visit. This will be computed as the average of the currents from the timeline feature using the epochs that align with the analysis set (e.g., As-Treated analysis set uses the actual aDBS mode as reported from the device). The pulse-width, frequency, and impedance will be determined from the JSON session data as per study procedure. TEED calculation will be provided by Rune Labs.

7.9.1.5 Supporting analyses

In order to demonstrate the decreased TEED during adaptive (aDBS) as compared to continuous DBS (cDBS), using a within-subject comparison in this crossover design, it is necessary to test for period effects (where the treatment effect is dependent upon which treatment was applied first) and carryover effects (where the treatment effect from the first crossover period affects the response during the second period). The average TEED will be analyzed using a general linear model appropriate for a two-treatment, two-period crossover design to inspect the period effect and carry-over effect. A significance level of 0.15 will be applied to the analysis of period effect and carry-over effect to allow for a more conservative analysis. Should any significant period or carryover effects be detected, data from the first crossover period may be compared between randomized groups in a parallel-design fashion.

7.9.1.6 Handling of missing data

All attempts will be made to minimize missing data. If missing data are observed, no imputation will be used for this analysis.

7.9.2 Secondary Objective

The secondary objective is to demonstrate maintenance within an optimal beta LFP threshold of beta LFP power during aDBS mode compared to cDBS. This objective will be assessed on the CC set.

7.9.2.1 Endpoint definition

The secondary endpoint is the mean percent time within an optimal beta LFP threshold of beta LFP power during aDBS mode compared to cDBS. The optimal beta LFP threshold indicates values between upper and lower LFP threshold preset for each patient.

7.9.2.2 Hypothesis

The formal hypothesis testing is:

$$H_0: \mu LFP_{aDBS} - \mu\, LFP_{cDBS} = 0 \quad \text{vs.} \quad H_a: \mu LFP_{aDBS} - \mu\, LFP_{cDBS} \neq 0,$$

where the difference ($\mu LFP_{aDBS} - \mu\, LFP_{cDBS}$) is the mean LFP change.

7.9.2.3 Analysis methods

The secondary endpoint will be assessed based on data collected from the Percept device using Brain Sense Timeline View function. Denote the LPF on aDBS by LFP_{aDBS} and the corresponding value for cDBS by LFP_{cDBS}. For each patient the difference between LFP_{aDBS} and LFP_{cDBS} will be calculated (LFP_{aDBS} - LFP_{cDBS} =LFP_{DIFF}). The mean percent time within an optimal threshold calculation will be provided by Rune Labs according to the Appendix A. The endpoint will be analyzed using a Paired T-test or nonparametric Wilcoxon Rank-Sum Test according the LFP normal or non-normal distribution between percent of time in the window for the preferred aDBS mode vs cDBS.

7.9.2.4 Handling of missing data

All attempts will be made to minimize missing data. If missing data are observed, no imputation will be used for this analysis.

7.9.3 Additional Objectives

The additional objectives will be summarized by reporting:

- mean score in cDBS,
- mean score in aDBS,
- the estimated difference from aDBS to cDBS and the 95% confidence interval (CI) and reported separately by aDBS (preferred mode, single or dual threshold).

The Complete Case analysis set will be used for the additional objectives. No multiplicity adjustment will be performed for evaluations of the additional study objectives and no imputation of missing data will be used.

To characterize clinical outcomes of aDBS (preferred mode) vs. cDBS, and by aDBS mode in the following items:

- EQ-5D-5L
- Parkinson's Disease Questionnaire (PDQ)-39
- Unified Dyskinesia Rating Scale (UDysRS)
- Movement Disorder Society-Sponsored Revision of Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II ("best" and "worst" conditions)*
- MDS-UPDRS III and IV
- LFP dynamics based on out of clinic patient event markers and PD Medication cycle
- Movement and sleep data collected from Apple Watch (will be correlated with Percept Device data and clinical measures)
- To assess a patient-specific anatomy using a visualization tool of lead location and simulated volume of neural activation based on Pre-op/post-op imaging data of Percept PC implant.
- Patient preference of aDBS (preferred mode) vs cDBS
- Patient satisfaction with aDBS (preferred mode)
- Global Impression of Change (GIC) with aDBS
- Assess the average function of the subjects during the past week, including the assessment date, when they were in the "best conditions" and "worst conditions".

* "Best conditions" is the time period when PD subjects are receiving relief from their Parkinson's disease symptoms. "Worst conditions" is the time period when PD subjects are not receiving relief from their Parkinson's disease symptoms.

7.9.3.1 EQ-5D-5L

To characterize the EQ-5D-5L of the preferred aDBS mode as compared to cDBS Baseline.

Endpoint definition

The European Quality of Life – 5 Dimensions, version 5L (EQ-5D-5L) will be collected at visit 2 and visit 3.

Analysis methods

The European Quality of Life – 5 Dimensions, version 5L (EQ-5D-5L) will assess generic health status by five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on 5 levels of severity (no problems, slight problems, moderate problems, severe problems, extreme problems) and by the visual analogue scale (VAS). The responses to the five EQ-5D dimensions (i.e. an EQ-5D health state or profile) will be converted into an index value using the Japanese value set. The EQ-5D dimensions will be summarized as categorical measures and the index value and visual analog scale (VAS) will be summarized as continuous measures for both cDBS and aDBS and by aDBS preferred mode.

7.9.3.2 PDQ-39

To characterize the Parkinson's Disease Questionnaire (PDQ)-39 Summary Index (SI) and subscores: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort.

Endpoint definition

The Parkinson's Disease Questionnaire is a self-completion Patient Reported Outcome (PRO) designed to address aspects of functioning and well-being for those affected by Parkinson's disease. The PDQ-39 will be collected at cDBS and at each aDBS adjustment phase.

Analysis methods

The PDQ-39 is a 39 questions assessment with 8 discrete scales:

- mobility (10 items, questions number 1 to 10)
- activities of daily living (6 items, questions number 11 to 16)
- emotional well-being (6 items, questions number 17 to 22)
- stigma (4 items, questions number 23 to 26)
- social support (3 items, questions number 27 to 29)
- cognitions (4 items, questions number 30 to 33)
- communication (3 items, questions number 34 to 36)
- bodily discomfort (3 items, questions number 37 to 39)

Patients are asked to think about their health and general well-being and to consider how often in the last month they have experienced certain events (e.g. difficulty walking 100 yards). Each patient is asked to indicate the frequency of each event using a rate on a 5 points scale (ranging from 0 to 4 reflecting the subject's rating; never/occasionally/sometimes/often/always or cannot do at all), higher scores indicating higher frequency of each event. Each domain is calculated as a scale from 0 to 100, where 0 represents no problem at all and 100 represents the maximum level of problem.

The formula for scoring each domain is:

$$\frac{\text{sum of scores of each question in domain}}{4 \times \text{number of questions in domain}} \times 100$$

The PDQ-39-SI is scored as:

$$\frac{\text{sum of all domain scores}}{8}$$

The PDQ-39 Summary Index (SI) and the 8 subscales will be summarized for this outcome2 by summary statistics as mean, standard deviations and 95% confidence intervals (CIs). The PDQ-39 Summary Index (SI) and sub-scores will be summarized for both cDBS and aDBS and by aDBS preferred mode. If the response to a question is missing, no scale score is calculated for that individual for that domain. This precludes the calculation of the PDQ-39 summary index score.

7.9.3.3 UDysRS

To characterize the Unified Dyskinesia Rating Scale (UDysRS).

Endpoint definition

The Unified Dyskinesia Rating Scale (UDysRS) is developed to evaluate involuntary movements often associated with treated Parkinson's disease. The UDysRS will be collected at cDBS and at each aDBS adjustment phase.

Analysis methods

The Unified Dyskinesia Rating Scale (UDysRS) has two primary sections:

- Historical (from question 1 to 15):
  Part 1 (On-Dyskinesia)
  Part 2 (Off-Dystonia)
- Objective (from question 16 to 26):
  Part 3 (Impairment)
  Part 4 (Disability)

Each sub-score will be calculated as the sum or scores within the section (see Figure 7-1). The total UDysRS score will be calculated as the sum of the Historical and Objective sub-score. Results will be presented overall and separately by sub-score by summary statistics as mean, standard deviations and 95% confidence intervals (CIs) and summarized for both cDBS and aDBS and by aDBS preferred mode

Figure 7-1. UDysRS score summary

Historical	Score	Objective	Score
1. Time dyskinesia		16. Face	
2. Speech		17. Neck	
3. Chewing/Swallowing		18. Right Hand/arm/shoulder	
4. Eating tasks		19. Left Hand/arm/shoulder	
5. Dressing		20. Trunk	
6. Hygiene		21. Right foot/leg/hip	
7. Handwriting		22. Left foot/leg/hip	
8. Doing hobbies/activities		23. Communication	
9. Walking/balance		24. Drinking	
10. Public/social		25. Dressing	
11 Exciting situations		26. Ambulation	
12 Time Off dystonia			
13. Dystonia effects on activities (not pain)			
14. Effect of Pain from dystonia			
15. Dystonia pain severity			
Historical sub-score (sum)		Objective sub-score (sum)	
Total UDysRS score (Historical + Objective):			

7.9.3.4 MDS-UPDRS

To characterize the Movement Disorder Society-Sponsored Revision of Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Endpoint definition

The MDS-UPDRS part II (best and worst), part III and part IV will be used to assess motor PD symptoms.

Analysis methods

The MDS-UPDRS is a comprehensive assessment of both motor and non-motor PD symptoms. The assessment has four parts:

- Part I (non-motor experiences of daily living) not included in this study
- Part II Best (motor experiences of daily living) condition and Part II Worst (motor experiences of daily living) condition
- Part III (motor examination)
- Part IV (motor complications)

Each question is scored from 0 to 4 reflecting the subject's usual level of function; Normal, Slight, Mild, Moderate and Severe. Each part can be reported as sub-scores.

The MDS-UPDRS II (best and worst) is a 13 questions assessment of experiences of daily living. Each parkinsonian sign or symptom from 2.1 to 2.13 is rated on a 5 points scale (ranging from 0 to 4 reflecting the subject's usual level of function; Normal, Slight, Mild, Moderate and Severe), with higher scores indicating more severe impairment. The maximum total MDS-UPDRS II score is 52, indicating the worst

possible experiences of daily living. These items will be summarized by summary statistics for both cDBS and aDBS and by aDBS preferred mode.

The MDS-UPDRS III is a 18 questions assessment of motor PD symptoms. Each parkinsonian sign or symptom from 3.1 to 3.18 is rated on a 5 points scale (ranging from 0 to 4 reflecting the subject's usual level of function; Normal, Slight, Mild, Moderate and Severe), with higher scores indicating more severe impairment. The maximum total MDS-UPDRS III score is 72, indicating the worst possible motor disability from PD. These items will be summarized by summary statistics for both cDBS and aDBS and by aDBS preferred mode.

The MDS-UPDRS IV is a 6 questions assessment of motor PD complication. Each parkinsonian sign or symptom from 4.1 to 4.6 is rated on a 5 points scale (ranging from 0 to 4 reflecting the subject's usual level of function; Normal, Slight, Mild, Moderate and Severe), with higher scores indicating more severe impairment. The maximum total MDS-UPDRS III score is 24, indicating the worst possible motor complication. These items will be summarized by summary statistics for both cDBS and aDBS and by aDBS preferred mode.

7.9.3.5 Patient preference

To characterize the Patient preference of DBS mode.

Endpoint definition

Patient preference for DBS modes will be assessed by the Patient preference questionnaire at the screening Visit and at the end of the aDBS treatment phase.

Analysis methods

The Patient preference questionnaire assesses subject preference for DBS modes on two items: disease-related symptoms (shaking, slowness, stiffness) and any side effects (trouble swallowing, change in mood, tingling). At screening, subjects will reply that they prefer the single threshold, double threshold, no preference, or do not know. At Visit 3, subjects will reply that they prefer the DBS mode received during period A, the DBS mode received during period B, no preference, or do not know. The responses will be summarized as categorical measures.

7.9.3.6 LFP dynamics

To characterize the LFP dynamics based on out of clinic patient event markers and PD Medication cycle

Endpoint definition

LFP will be recorded through Rune Labs database.

Analysis methods

Subjects may choose to participate in optional data collection of Events with LFP capture (snapshots). The clinician may set up a maximum of 4 event types, selected from the following options: dyskinesia, tremor, rigidity, freezing, sleep disturbance, took PD medication.

7.9.3.7 Percept Device and Apple Watch

To assess correlation among movement and sleep data collected from Apple Watch, Percept Device data and clinical measures.

Endpoint definition

Percept Device data, Apple Watch data and clinical outcomes (GIC, PDQ-39 SI, MDS-UPDRS III, UDysRS and EQ-5D-5L). Percept Device and Apple Watch data will be provided by Rune Labs (see Appendix A).

Analysis methods

The parameters summarized with the device data from Percept Device and Apple Watch are listed in Appendix A. Summary statistic will be reported in aDBS, cDBS and by aDBS preferred mode. Correlations will be assessed visually as appropriate.

7.9.3.8 Patient Satisfaction

To assess Patient satisfaction with aDBS (preferred mode).

Endpoint definition

Patient satisfaction questionnaire

Analysis methods

The patient satisfaction questionnaire will assess the overall satisfaction and satisfaction on specific items on 5 levels of satisfaction (very satisfied, somewhat satisfied, neutral, somewhat unsatisfied and very unsatisfied) and by the recommendation of adaptive DBS to other DBS patients with Parkinson's Disease. The responses will be summarized as categorical measures only for aDBS mode (any preferred mode).

7.9.3.9 Global Impression of changes

To assess Global Impression of changes (GIC) with aDBS (preferred mode).

Endpoint definition

DBS Global Impression of Change score (DBS GIC)

Analysis methods

GIC scores can be used to help assess for acceptability of aDBS for an individual subject. A lower number is better in terms of acceptability (ie, greater efficacy with minimal side effects). The responses will be summarized as categorical measures.

7.10 Safety Evaluation

All reportable adverse events (AEs) and all device deficiencies (DDs) will be collected throughout the study once the informed consent form is signed. The safety evaluation will be performed on the all screened subjects or as treated (AT) set as appropriate and presented with summary tables and supporting data listings.

AEs and DDs will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Summaries include the number of events, the number of subjects who experience an event, and the percentage of subjects who experienced one or more events. The denominator will include the

appropriate number of subjects for each respective phase and period. In particular, the following objectives will be reported separately:

- Stimulation-related adverse events during the aDBS treatment Phase.
- Serious adverse events which occur through the study after consent and which causal relationship with Percept PC cannot be ruled out.
- Any-cause death throughout the study after Screening Visit starts.
- Device (Percept PC) deficiencies that involves or potentially involves a serious adverse event throughout the study after the randomization.

7.11 Changes to Planned Analysis

Any change to the data analysis methods described in the SAP will require an amendment only if it changes a principal feature of the SAP. Any other change to the data analysis methods described in the SAP, and the justification for making the change, will be described in the clinical study report.

8. Validation Requirements

All collected data will be reviewed for completeness correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment the data. Statistical programming code that affects the result of the main analysis (e.g., not including sensitivity or supporting analyses) for the primary objective shall be validated using Level I validation. Programming code for randomization and programming code that affects the result of the main analysis for the secondary objective(s) shall be validated using at least Level II validation. In addition, those main statistical analyses that are planned for publication and have not been previously validated should be validated using at least Level II validation. The CIP deviation summary shall be validated using at least Level III validation and the high-level adverse event summary shall be validated using at least Level II validation. Additional measures where a p-value or confidence interval has been generated may need to be validated using at least Level II validation.

9. References

1. Simon Little, MA, MBBS, Alex Pogosyan, PhD, Spencer Neal, BEng (Hons),Baltazar Zavala, BA, Ludvic Zrinzo, PhD, Marwan Hariz, PhD, et al. Adaptive Deep Brain Stimulation in Advanced Parkinson Disease. Little et al. 2013;74(3):449-457.
2. Simon Little, Martijn Beudel, Ludvic Zrinzo, Thomas Foltynie, Patricia Limousin, Marwan Hariz, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. Neurosurg Psychiatry 2016;87:717–721. Epub;2015
3. CONSORT 2010 statement: extension to randomised crossover trials. BMJ 2019; 366:l4378

10. Appendix A

For each subject, two weeks prior to each adjustment visit will be used for this analysis. Data will be provided for aDBS treatment phase 1 and follow-up phase. The following data from JSON, BrainSense and Apple Watch will be provided from Rune Labs.

Source	Parameter	Value/ Category	Description
OC	ID	XXX	the patient ID will be as from OC
	Phase	1/2	1= aDBS treatment phase 2 = follow-up phase
	Next Visit	1/2/3/4/5/6	
Percept data	Group	A/B/C/D	
	N hours available within 2 weeks prior to the visit	Number	
	Sensor contacts (L, R)	Categorical	(0-3, 0-2, 1-3, etc..)
	LFP Power (L, R)	Number	mean, std, min, q1, median, q3, max
	Lower LFP Threshold (L, R)	Number	
	Upper LFP Threshold (L, R)	Number	
	Measured Lower LFP (L, R)	Categorical	
	Measured Upper LFP (L, R)	Categorical	
	DBS Mode	Categorical	aDBS, cDBS
	Stim Electrodes (L, R)	Categorical	
	TEED	Number	mean, std, min, q1, median, q3, max
	Use of event markers	Categorical	
	Time spent below the thresholds (L, R)	%time	
	Time spent between thresholds (L, R)	%time	
	Time spent above thresholds (L, R)	%time	
Apple Watch Data	Dyskinesia Probability AUC	Number	AUC (Area Under the Curve)
	Dyskinesia % time	%time	with Probability≥20%, 30%, 40%, 50%
	Tremor Probability AUC	Number	AUC (Area Under the Curve)
	Tremor % time	%time	with Probability≥20%, 30%, 40%, 50%
	Medication Cycle	On/off	