HÔPITAL FONDATION
Adolphe de ROTHSCHILD
LA RÉFÉRENCE TÊTE ET COU

Statistical Analysis Plan

Evaluation of a Millimeter Wave Emission Bracelet -Type Medical Device for Improving Parkinson's Disease Symptoms: Multicenter, Double-blind Randomized Controlled Trial

BOMP

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1. Statistical Analysis Plan from the Protocol

1.1. Objectives

1.1.1. Primary Objective
To assess the effectiveness of two months of use of the medical device Remedee Endorphin Band in the significant improvement of motor disorders in patients with Parkinson's disease.

1.1.2. Secondary Objectives
To evaluate the effectiveness of two months of use of the Remedee Endorphin Band on:

1. The motor disorders of patients;
2. Non-motor experiences in daily life;
3. Motor experiences in daily life;
4. Motor complications;
5. Quality of life;
6. Pain;
7. Walking;
8. The evolution of the average number of steps per week (only for patients who agreed to wear a second specific bracelet);
9. The evolution of sleep (only for patients who agreed to wear a second specific bracelet);
10. The evolution of heart rate (only for patients who agreed to wear a second specific bracelet);
11. The medication regimen;
12. The effectiveness of the treatment as perceived by the primary caregiver;
13. The effectiveness of the treatment as perceived by the patient.

After two months of use, the medical devices will be collected, and new active medical devices will be provided to the patients in both arms.
The elements evaluated for the primary objective and secondary objectives 1 to 10 will be described at M4 and M6 to document the evolution of the effect of the medical device using millimeter wave stimulation.

14. To describe the effectiveness perceived by the patient after discontinuing the device use: biweekly phone follow-ups for 2 months after use.
15. To assess the tolerance of the medical device.
16. To assess the acceptability and usability of the medical device.
17. Description of compliance with the use of the device.

1.2. Judgment Criteria

1.2.1. Primary Judgment Criterion
Comparison between the two treatment arms (VERUM bracelet and SHAM bracelet) of the percentage of patients showing an improvement of at least -3.25 points in the Movement Disorder Society – Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III), 2 months after randomization.
The MDS-UPDRS III score (Appendix 1) will be assessed in ON Dopa conditions, blind to the randomization arm.

1.2.2. Secondary Judgment Criteria

1. Mean change in MDS-UPDRS III score in ON Dopa conditions.

2. Mean change in MDS-UPDRS I score (Appendix 2) in ON Dopa conditions.
3. Mean change in MDS-UPDRS II score (Appendix 3) in ON Dopa conditions.
4. Mean change in MDS-UPDRS IV score (Appendix 4) in ON Dopa conditions.
5. Mean change in the Parkinson Disease Questionnaire -39 (PDQ 39) score (Appendix 5) in ON Dopa conditions.
6. Mean change in King's PD Pain Scale (KPPS) score (Appendix 6) in ON Dopa conditions.
7. Change in the time (in seconds) required for the Stand-Walk-Sit (SWS) test (Appendix 7) in ON Dopa conditions. This change will be expressed as a percentage of time change, defined as the difference between the time required at baseline and 2 months after randomization, divided by the baseline time.
8. Slope of the change in the average number of steps per week measured with an activity bracelet (Fitbit 4) between D-2 weeks and D+8 weeks, for patients who agreed to wear this second bracelet.
9. Evolution of the average number of hours of weekly sleep and the average weekly hours of deep, paradoxical, light sleep, and night wakefulness, measured with an activity bracelet (Fitbit 4) between D-2 weeks and D+8 weeks, for patients who agreed to wear this second bracelet.
10. Evolution of the average weekly heart rate measured with an activity bracelet (Fitbit 4) between D-2 weeks and D+8 weeks, for patients who agreed to wear this second bracelet.
11. Percentage of patients without any modification (in drug molecule or dosage) in their medication regimen or with a reduction in medication dosage.
12. Score on the Clinical Global Impression of Change (CGI) questionnaire (Appendix 8) at M2, using the baseline (D0) provided in person or by phone by the person designated as the primary caregiver.
13. Score on the CGI questionnaire (Appendix 8) at M2, using D0 as the reference.
14. CGI score at M6, using M2 as the reference, and then every 2 weeks for two months through phone interviews. For phone evaluations, the patient will be asked to use the situation two weeks prior (during the previous CGI score evaluation) as the reference.
15. Description of adverse events reported during the study: number, intensity, severity, duration in each arm.
16. Acceptability and usability questionnaire completed by the patient at M6 (Appendix 10).
17. Compliance evaluated based on the medical device log file (number of sessions/day, session duration, pause times).

1.3. Reminder on the Calculation of the Required Sample Size

This is a pilot study, as the bracelet has not yet been studied in patients with motor disorders in Parkinson's disease. We therefore planned to include 30 subjects per group.
Since the percentage of patients improving in the control arm is expected to be close to zero, a sample size of 30 patients per arm will allow us to detect a difference in percentage of 15% of improved patients versus 0.1% in the control arm, with a power of 80% and a bilateral alpha risk of 5%.
Patients lost to follow-up between the inclusion visit and randomization will be replaced.

1.4. Description of Statistical Methods

1.4.1. Descriptive Analysis

A flowchart, created according to CONSORT guidelines, will summarize the number of patients screened, included, randomized, lost to follow-up, and analyzed for each randomization arm. The reasons for non-participation at each step will be described.
A descriptive analysis of the data will be performed. This will include point estimates,

numbers, and percentages for qualitative variables, mean, standard deviation, median, and range for quantitative variables. The normality of continuous variables will be assessed graphically and using a normality test (e.g., Shapiro-Wilk). A description of missing data for each variable (sample size and percentage) will also be provided.

1.4.2. Comparison at Baseline

Comparability at baseline between the experimental and control arms will be assessed using a Student's t-test (or Wilcoxon-Mann-Whitney test if needed) for continuous parameters and a Chi-square test (or Fisher's exact test if necessary) for qualitative parameters.

1.4.3. Analysis of the Primary Judgment Criterion

The primary judgment criterion will be analyzed using logistic regression with a center effect. A Per Protocol sensitivity analysis will be conducted, including only patients who adhered to the medical device. A patient will be considered adherent if they completed more than 80% of the planned sessions, considering a low-frequency usage of 2 sessions per day.

1.4.4. Analysis of Secondary Judgment Criteria

Quantitative secondary criteria to be compared between the two treatment arms (criteria 1 to 7, 12, and 13) will be analyzed using multiple linear regression with a center effect and an adjustment for the initial value of the parameter being studied.
Judgment criterion number 8 (change in the average number of steps per week) will be assessed graphically and using mixed linear regression with weekly steps as the dependent variable, with the randomization arm and time (from D0-2 weeks to D0+8 weeks) as fixed effects, and the patient as a random effect. The p-value for the interaction term will be used to assess the significance of the evolution based on the treatment arm. The same type of analysis will be used for criteria 9 and 10.
Qualitative criterion 11 will be analyzed as the primary judgment criterion.
Criteria 14 to 17 will be analyzed using descriptive statistics as described in section 2.4.1.

1.5. Statistical Significance Level

Alpha risk set at 5%.

1.6. Method for Handling Missing, Unused, or Invalid Data

Analyses will be performed on complete data. If missing data for the primary judgment criterion exceeds 10%, a sensitivity analysis will be conducted after multiple imputation.

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2. Modifications Made to the Protocol's Analysis Plan

Definition of the PP Population:
The protocol and the SAP did not specify the definition of the per-protocol population. This population includes all randomized patients who:

- Received the medical device and adhered to the randomization arm,
- Met the eligibility criteria,
- Were adherent, meaning they followed at least 80% of the scheduled sessions, i.e., 2 sessions of 30 minutes per day during the first 2 months of follow-up.

Description of Baseline Characteristics:
In accordance with current recommendations, baseline group comparisons were not performed.

Analysis of the Primary Criterion:
All patients in the study were included by the HFAR center, so a fixed-effects logistic regression was conducted instead of the initially planned random-effects center logistic regression.

Analysis of Secondary Criteria:

- Secondary analyses were conducted on the ITT population and available data, with no imputation performed.
- Since the distribution of quantitative secondary judgment criteria (criteria 1 to 8, 12, and 13) did not follow a normal distribution, the originally planned linear regressions were not performed. Instead, median differences and their 95% confidence intervals, calculated using the Mood method, were used for comparisons between the two treatment arms. The variation between scores at each time point and the initial score was also calculated when the baseline score was available.
- The protocol was not followed for criterion 8 (evolution of the average number of steps per week) because very few patients agreed to wear the Fitbit watch, and it was given to them simultaneously with the device. Consequently, the before/after comparison of wearing the bracelet could not be performed. Available data was described for informational purposes only.
- Criterion 11 (percentage of patients without treatment modification) was not analyzed using a logistic model, as the results were identical between the two groups.
- Heart rate and sleep hours (criteria 9 and 10) were not analyzed due to the absence of data.

Secondary analyses are exploratory, and no alpha risk adjustment for multiplicity was performed.

All statistical analyses were performed using R software (version 4.3.0).