HÔPITAL FONDATION
Adolphe de ROTHSCHILD
LA RÉFÉRENCE TÊTE ET COU

Title	**Evaluation of a Millimeter Wave Emission Bracelet -Type Medical Device for Improving Parkinson's Disease Symptoms: Multicenter, Double-blind Randomized Controlled Trial**
Acronym	**BOMP**
Sponsor	Hôpital Fondation Adolphe de Rothschild
Principal Investigator	Dr Cécile Hubsch
Research justification	Idiopathic Parkinson's disease is a common neurodegenerative disorder, with a prevalence of approximately 2% among individuals over 65 years old in France, corresponding to 120,455 patients (ranging from 94,861 to 151,896) [1]. This disease primarily affects the dopaminergic pathway (damage to the nigrostriatal pathway leads to cardinal symptoms such as rigidity, bradykinesia, and tremor), but it also impacts other systems: cholinergic, noradrenergic, and serotonergic [2]. The symptoms of Parkinson's disease are therefore motor, initially with a good response to dopaminergic treatments, but also non-motor, including sleep disturbances, loss of smell, cognitive, psychiatric, digestive, urinary, dysautonomic, and painful issues [3]. All these symptoms contribute to a significant reduction in the quality of life of patients, who, together with clinicians, are still constantly seeking solutions to improve management. Continuous dopaminergic stimulation is desirable to reduce motor fluctuations in patients, who experience motor fluctuations such as wearing-off, dyskinesias, and freezing [4]. Invasive techniques (deep brain stimulation, gamma knife lesioning, ultrasound) or devices that are heavy, invasive, and costly (duodopa pumps, apokinon pumps) have provided benefits for patients [5]. There is an ongoing need to explore clinical improvements using less expensive and lighter devices. The Remedee Endorphin Band is a device that emits electromagnetic waves in the millimeter waveband on the inner side of the wrist, an area rich in nerve endings. The device stimulates subcutaneous nerve endings and activates a physiological response that triggers the release

	of endorphins in the brain. Endorphins are involved in several physiological processes, including pain control. Mu-opioid receptor (MOR) agonists not only relieve pain but also have effects related to dopaminergic mesolimbic pathways [6,7]. Indeed, the opioid and dopaminergic systems are closely linked at the cellular level [8]. Endorphins, by inhibiting the release of the neurotransmitter GABA when binding to the μ receptor, are also related to an increase in dopamine. The Remedee Endorphin Band is CE-marked for well-being and sleep indications. It is undergoing clinical trials at the University Hospital of Grenoble as a medical device for the management of postoperative pain (NCT03889288), as well as for pain related to osteoarthritis (authorization requests ongoing) and migraines (NCT04568252). Several individuals using this band for well-being/sleep purposes have reported benefits on the motor symptoms of their Parkinson's disease to Remedee Labs. This is why we aim to evaluate the contribution of the Remedee Band to the motor symptoms of Parkinson's disease.
Primary objective and outcome	**Evaluate the effectiveness of two months of using the Remedee Endorphin Band medical device on the significant improvement of motor symptoms in patients with Parkinson's disease.** **Primary outcome measure:** Comparison between the two treatment arms (VERUM band and SHAM band) 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) score, 2 months after randomization [9]. The evaluation of the MDS-UPDRS III score (Annex 1) will be conducted under ON Dopa conditions and in a blinded manner regarding the randomization arm.
Secondary objectives and outcomes	**Evaluate the effectiveness of two months of using the Remedee Endorphin Band medical device on:** 1. Motor symptoms in patients 2. Non-motor experiences in daily life 3. Motor experiences in daily life 4. Motor complications 5. Quality of life 6. Pain 7. Gait 8. Evolution of the average number of steps per week (only for patients who agreed to wear a second specific bracelet) 9. Evolution of sleep (only for patients who agreed to wear a second specific bracelet)

	10. Evolution of heart rate (only for patients who agreed to wear a second specific bracelet) 11. Medication treatment 12. Treatment effectiveness as perceived by the primary caregiver 13. Treatment effectiveness as perceived by the patient After two months of use, the medical devices will be collected, and new devices (all active) will be provided to patients in both arms. The elements assessed for the primary and secondary objectives 1 to 10 will be described at M4 and M6 to document the evolution of the effect of the millimeter-wave stimulation medical device. The following secondary objectives will be purely descriptive: 14) Describe the effectiveness perceived by the patient after discontinuing the use of the device: bi-weekly follow-up phone calls for 2 months after use. 15) Evaluate the tolerance of the medical device. 16) Evaluate the acceptability and usability of the medical device. 17) Description of the device usage compliance. **Secondary Outcome Measures:** 1. Average change in MDS-UPDRS III score under ON Dopa conditions 2. Average change in MDS-UPDRS I score (Annex 2) under ON Dopa conditions 3. Average change in MDS-UPDRS II score (Annex 3) under ON Dopa conditions 4. Average change in MDS-UPDRS IV score (Annex 4) under ON Dopa conditions 5. Average change in Parkinson Disease Questionnaire-39 (PDQ-39) score (Annex 5) under ON Dopa conditions 6. Average change in King's PD Pain Scale (KPPS) score (Annex 6) under ON Dopa conditions 7. Change in time (in seconds) required for the Stand-Walk-Sit (SWS) test (Annex 7) under ON Dopa conditions. This change will be expressed as a percentage change in time, defined as the difference between the time required at baseline and 2 months after randomization, divided by the baseline time. 8. Slope of the evolution in the average number of steps per week measured using an activity tracker (Fitbit 4) between -2 weeks and +8 weeks, for patients who agreed to wear this second bracelet. 9. Evolution of the average number of hours of weekly sleep and average weekly hours of deep, paradoxical, light sleep, and nighttime wakefulness, measured

	using an activity tracker (Fitbit 4) between -2 weeks and +8 weeks, for patients who agreed to wear this second bracelet. 10. Evolution of the average weekly heart rate measured using an activity tracker (Fitbit 4) between -2 weeks and +8 weeks, for patients who agreed to wear this second bracelet. 11. Percentage of patients with no change (in drug type or dosage) or a decrease in medication dosage. 12. Score on the Clinical Global Impression of Change (CGI) questionnaire (Annex 8) at M2, taking J0 as the reference point, reported in person or by phone by the person identified by the patient as the primary caregiver. 13. Score on the Clinical Global Impression of Change (CGI) questionnaire (Annex 8) at M2, taking J0 as the reference point. 14. CGI score at M6, taking M2 as the reference, then every 2 weeks for two months via phone interviews. For phone assessments, the patient will be asked to use the situation from 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 of the two arms. 16. Acceptability and usability questionnaire completed by the patient at M6 (Annex 10). 17. Compliance assessed using the medical device log file (number of sessions/day, duration of sessions, start and end times, pause times).
Study design	**Multicenter, controlled, randomized, parallel two-arm, double-blind efficacy trial.** Randomization will be performed with a 1:1 ratio and will be stratified by center.
Population	Patients will be recruited via neurology consultations for the management and monitoring of their Parkinson's disease.
Selection criteria	**Inclusion Criteria** • Patient aged over 18 years • Follow-up for Parkinson's disease with progression for more than 5 years • Stable treatment for at least 3 months • Maintained sufficient autonomy to participate in the study • Non-faller: Hoehn and Yahr score in ON DOPA <4 (Annex 9) • Informed and has signed consent to participate in the study • Affiliated or beneficiary of a social security scheme

	• Negative urinary pregnancy test for women who are not postmenopausal **Exclusion Criteria** • Genetic forms of the disease • EVA > 7 in the previous week • Moderate to severe cognitive disorders • Pathology or condition (other than Parkinson's disease) that could cause motor disturbances • Allergy to metals and/or silicone • Dermatological pathology on the wrists, such as weeping dermatosis, excessive sweating, or an unhealed lesion • Metal object on one of the wrists (implanted metal, piercing) • Presence of a tattoo on one of the wrists • Wrist circumference <14.5 cm or >21 cm, i.e., wrist size incompatible with the device model • Inability of the patient to apply and/or wear the medical device • Patient under legal protection • Pregnant or breastfeeding woman **Secondary Exclusion Criteria**: None specified in the protocol
Trial procedures	**Experimental Therapeutic Intervention** Medical device Remedee Endorphin Band with millimeter wave emission activated for a duration of 6 months, to be used according to the following schedule: one 30-minute session in the morning and one session in the evening. Additional sessions may be added if desired by the patient, up to a maximum of 4 sessions per day. **Control Therapeutic Intervention** Medical device Remedee Endorphin Band without millimeter wave emission for two months, followed by the Remedee Endorphin Band with millimeter wave emission activated for a duration of 4 months, to be used according to the following schedule: one 30-minute session in the morning and one session in the evening. Additional sessions may be added if desired by the patient, up to a maximum of 4 sessions per day.
Conduct of the trial	Patients seen during consultations/Day Hospital and meeting the inclusion and non-inclusion criteria will be offered the opportunity to participate in the study. If they agree, a visit will be scheduled (within 2 to 4 weeks) to perform the various tests and provide the medical device to the patient (VERUM or SHAM according to the randomization group).

	Patients will be randomized into two parallel groups (1:1 ratio) via an online randomization module. The doctor enrolling the patient in the study will not be aware of the randomization group.
	
	• **Experimental Group (VERUM)**: Provision of an active medical device for a period of 2 months. Then, provision of a second active medical device for a duration of 4 months.
	• **Control Group (SHAM)**: Provision of an inactive medical device for a duration of 2 months, followed by the provision of an active medical device from Month 2 to Month 6 after enrollment.
	
	Inclusion Visit (J0-2 to -4 weeks)
	
	• Verification of inclusion and non-inclusion criteria
	• Information and obtaining written informed consent from the patient
	• Information to the patient regarding the Fitbit 4 and the option to use it
	• Trial fitting of the Remedee Endorphin Band device
	
	Visit 1 (J0)
	
	• Confirmation of patient's willingness to participate
	• Randomization
	• Provision of the medical device and instructions on its use
	• Administration of the various assessment tests (if necessary, after administration of Modopar dispersible):
	  ○ MDS-UPDRS (I, II, III, and IV)
	  ○ PDQ39
	  ○ KPPS
	  ○ SWS
	
	Phone Call at J7 and M1: Verification that the patient does not encounter any difficulties in using the device (call by the TEC)
	
	Visit 2 (M2)
	
	• Administration of the various assessment tests (if necessary, after administration of Modopar dispersible):
	  ○ MDS-UPDRS (I, II, III, and IV)
	  ○ PDQ39
	  ○ KPPS
	  ○ SWS
	• CGS score from the caregiver (in-person or by phone)
	• CGS score from the patient

	• Retrieval of usage data from the medical device (log file)
	• Retrieval of the first medical device (active or inactive) and provision of an active medical device to all patients.
	
	Visit 3 (M4)
	
	• Administration of the various assessment tests (if necessary, after administration of Modopar dispersible):
	  o MDS-UPDRS (I, II, III, and IV)
	  o PDQ39
	  o KPPS
	  o SWS
	• Retrieval of usage data from the medical device (log file)
	
	Visit 4 (M6)
	
	• Administration of the various assessment tests (if necessary, after administration of Modopar dispersible):
	  o MDS-UPDRS (I, II, III, and IV)
	  o PDQ39
	  o KPPS
	  o SWS
	• Administration of the acceptability and usability questionnaire for the medical device
	• CGS score from the patient
	• Retrieval of usage data from the medical device (log file)
	• Retrieval of the millimeter-wave emitting bracelet
	• Retrieval of the Fitbit4 for patients who accepted its use
	
	Phone Calls at M6+2 weeks, M6+4 weeks, M6+6 weeks, and M6+8 weeks: CGS score from the patient, and at M6+8 weeks, the patient will also be asked if they would have liked to continue using the medical device bracelet.

Sample size	60 (30 per arm)
Statistical analysis	The primary endpoint will be analysed using logistic regression with a centre effect.
Planning	Enrollement : 24 months Study participation for each patient : 8 months Total study length : 32 months