A double-blind crossover study to evaluate the safety and efficacy of adaptive Deep Brain Stimulation delivered through AlphaDBS System in patients with Parkinson*s Disease

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The aim of this study is to assess the safety and the potential efficacy of personalized Local Field Potential (LFP)-based adaptive Deep Brain Stimulation (aDBS), using the implantable pulse generator (IPG), «AlphaDBS» System, in Parkinson*s Disease...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON55259

Source
ToetsingOnline

Brief title
A study with adaptive DBS in patients with Parkinson*s Disease.

Condition

- Movement disorders (incl parkinsonism)

Synonym
Morbus Parkinson, Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Newronika SpA
Source(s) of monetary or material Support: industry

Intervention

Keyword: adaptive DBS, AlphaDBS, Deep Brain Stimulation, Parkinson's Disease

Outcome measures

Primary outcome

Safety Analysis (primary objective): safety will be evaluated on all patients randomized and receiving at least one of the treatments. It will include the comparison of: 1) TEED delivered to the patient during aDBS and cDBS experimental sessions; 2) AEs during the 2 stimulation modes.

Secondary outcome

Preliminary Efficacy Analysis (secondary objective): clinical efficacy will be evaluated through intention-to-treat analysis. Exploratory analysis will be performed to obtain summary data to inform decisions on future clinical development phases. Differences in clinical endpoints when patients receive aDBS or cDBS will be compared by appropriate statistical tests. The time courses of UPDRS III scores, motor symptoms fluctuations, *time off* and *time on* as collected by Patient Diaries and UDysRS during aDBS and cDBS treatments will be compared.

Study description

Background summary

Dopaminergic medications are effective in treating PD motor symptoms, but their

efficacy wanes over time. The use of levodopa, the most effective PD medication, is associated with the development of motor fluctuations in the near term, and with irreversible motor fluctuations during long-term use. Deep Brain Stimulation (DBS) uses a medical device, similar to a cardiac pacemaker, to deliver carefully controlled electrical stimulation to precisely targeted areas in the basal ganglia.
DBS proved to be effective in improving major Parkinson*s Disease (PD) symptoms in long-term follow-up studies (Kleiner-Fishman et al, 2003; Krack et al, 2003) and currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor fluctuations, dyskinesias, and refractory tremor. In particular, DBS of the subthalamic nucleus (STN) has been shown to improve motor symptoms of PD, levodopa-induced complications and overall quality of life.
However, current devices deliver DBS with constant stimulation parameters, thus not controlling typical clinical fluctuations, and do not adapt stimulation parameters to clinical features, therefore:
1) There is a transient summation of the effects due to DBS and to pharmacological therapy that leads to a motor (dyskinesias and dystonia) and non-motor side effects (hypomania or impulse control disorders) in many patients;
2) The excessive and unnecessary electrical stimulation over time may interfere with the residual physiological functions of the basal ganglia, thus contributing (Chen et al, 2006) to the development of neurological complications such as impairment of speech, balance, and gait, and, possibly, cognition. In particular, the decline in verbal fluency, which is the most frequent side effect of STN-DBS, was associated with the influence of stimulation on sounding neural pathways.
Adaptive DBS (aDBS) strategies have been proposed to automatically adapt moment-by-moment stimulation parameters to the patient*s clinical symptoms, in a closed-loop fashion (Marceglia et al, 2007; Priori et al, 2013), thus avoiding the above-mentioned limitations.
Newronika has developed the «AlphaDBS» System, the first stand-alone system that can deliver stimulation in a closed-loop adaptive *real-time* fashion, using a biosignal recorded from the same macro-electrodes routinely implanted for DBS, as an input variable. AlphaDBS was ideated and created to provide optimized and personalized control of PD symptoms.

The «AlphaDBS» System records and processes the beta band power and uses it as an input variable to the adaptive algorithm that computes a new stimulation amplitude every second, providing the patient only *real* needed stimulation.

However, the information regarding the long-term safety and efficacy of aDBS remains limited. In facts, so far, studies comparing the efficacy and safety of aDBS to cDBS had intrinsic limitations, due to technical reasons.
The availability of the AlphaDBSipg, which is the Implantable Pulse Generator (IPG) component of the «AlphaDBS» System, will allow, for the first time, to

overcome such limitations.

In this first-in-man study, we plan to assess the safety and potential benefits of aDBS delivered through the «AlphaDBS» System.

Study objective

The aim of this study is to assess the safety and the potential efficacy of personalized Local Field Potential (LFP)-based adaptive Deep Brain Stimulation (aDBS), using the implantable pulse generator (IPG), «AlphaDBS» System, in Parkinson*s Disease (PD) patients, chronically implanted in subthalamic nucleus (STN) for DBS, at the time of IPG replacement.
The primary objective will be to evaluate the safety and tolerability of the «AlphaDBS» System, when used in cDBS and aDBS mode. The determination of safety and tolerability will be based on the following endpoints:
• Occurrence of device-related adverse events.
• Decrease in the Total Electrical Energy Delivered (TEED) to the patient.
Secondary objective will be to evaluate the potential efficacy of aDBS and «AlphaDBS» System usability.
Efficacy will be evaluated from the following secondary measures:
• Evaluation of PD-related motor symptoms (i.e. bradykinesia, rigidity and tremor at rest) and their fluctuations through repeated clinical assessments (using the Unified Parkinson's Disease Rating Scale -UPDRS- part III).
• Evaluation of dyskinesia and their fluctuations through repeated clinical assessments (using the Unified Dyskinesia Rating Scale - UDysRS and wearable Systems).
• Evaluation of *Time On* with and without dyskinesia and *Time Off*, assessed through Patient Diary.
Usability will be evaluated by means of usability questionnaires.

Exploratory objectives include evaluation of DBS associated deficits, through the DBS Impairment Scale (DBS-IS) and evaluation of the effects of aDBS on speech.
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Study design

This is a first-in-man study of the IPG that is part of «AlphaDBS» System, and it is designed to assess the safety of the device and the potential efficacy of aDBS closed-loop method in patients with PD.
The study has been designed as a crossover trial that uses conventional DBS (cDBS) as a control.

The study protocol is organized in two phases: the *short-term follow-up* and the *long-term follow-up*.

PD patients in need of IPG replacement will be screened to identify for enrollment eligibility.
For the *short-term follow-up*, randomized patients will undergo 2 days of experimental sessions (i.e. one per each type of stimulation mode, cDBS and aDBS), in a well-controlled environment (i.e. during hospitalization). This part of the study will collect information on safety and efficacy endpoints as assessed by experienced neurologists.
Patients, who will not experience severe side effects and who will be deemed suitable by the neurologist, will be eligible to continue in the *long-term follow-up* phase (i.e. 1 month) in their *home* environment. The «AlphaDBS» System will deliver the stimulation in aDBS or cDBS mode, for two weeks in each mode.

Intervention

The study treatment, adaptive DBS (aDBS), will be tested in comparison with conventional DBS (cDBS). Following personalized algorithm set up and «AlphaDBS» System calibration, patients will be randomly assigned to either one of the stimulation mode sessions (i.e. aDBS or cDBS).

The study will consist of a hospitalization phase in which patients will undergo surgery for removal of the old IPG, implant of the «AlphaDBS» System and set up of the personalized algorithm. Then, patients will be randomized to either aDBS or cDBS stimulation (one day in each mode), and on fourth day discharged to the second phase of the protocol (home) where they will be exposed to additional 28 days of DBS (14 days in each mode).

Study burden and risks

Anticipated adverse events and adverse device effects;
Given the extensive bench testing and animal and clinical studies conducted, there is a reasonable expectation that the device will be technically successful and that it will function as intended.
The replacement of a DBS IPG involves risks, and we expect that the patient implanted with the AlphaDBSipg will be exposed to the same procedure-related risks reported for other DBS Systems on the market.
These risks are the ones commonly associated with IPG replacement surgery and described in the protocol at section 7.5.
Possible DBS complications may occur which also are described under section 7.5.

Anticipated clinical benefits
The potential benefits of this study are twofold:
Personal benefits: If patients agree to participate in the study they could or not experience individual benefits. In fact, the «AlphaDBS» System is the first DBS system able to deliver adaptive and conventional DBS. The expected benefits of using the aDBS approach include:

o overall reduction of the electrical energy delivered to the tissues
o overall reduction of the patient*s OFF time (comparable to what observed in cDBS)
o overall increase of the patient*s ON time without troublesome dyskinesia
o improvement of efficacy in reducing bradykinesia, rigidity, and tremor (comparable to what observed in cDBS)
o reduction *levodopa-induced dyskinesia*
o improvement in speech, balance, and gait problems related to stimulation.

General benefits: If the results of the trial will be promising. PD patients will have a new innovate device for DBS that will allow the delivery of adaptive DBS.
The neurologist and/or the patient will, therefore, have the possibility to choose between cDBS and aDBS. Patients treated with aDBS could experience a better quality of life and, a simplification of patient management during the *stabilization period* normally occurring in patients after DBS implant, reducing the number of visits and calls to the treating neurologist to fine tune DBS programming settings. More in general, there will be benefits for the entire PD community

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of idiopathic PD;
2. Subject is bilaterally treated with DBS in the STN using a Medtronic Activa PC or Activa RC IPG (mono-channnel or dual channel);
3. DBS implant for at least 3 years and in need of battery replacement within 12 months after consent;
4. Patients must be able to understand and sign the informed consent document.

Exclusion criteria

1. Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score < 10);
2. Patients with major psychiatric issues or any other condition that, based on the physician opinion, could interfere with the study conduct (e.g. severe depression, psychosis, etc.);
3. Patients with any medical conditions potentially interfering with DBS battery replacement surgery (e.g. severe hypertension, active cancer, intake of drugs interfering with the coagulation etc.);
4. Need to replace or reposition the leads during the IPG replacement procedure;
5. Patients with > 10 recurrent falls experienced in the 3 months prior to consent;
6. Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min;
7. Patients taking less than one levodopa dose per day;
8. Patients without suitable LFPs recordings or with significant artifacts
9. Pregnant or breastfeeding women.

Study design

Design

Study type:	Interventional

Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Generic name:	AlphaDBS system
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO

Date:	19-05-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04681534
CCMO	NL73291.068.20