BMJ Open

A double-blind crossover protocol to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049955
Article Type:	Protocol
Date Submitted by the Author:	15-Feb-2021
Complete List of Authors:	Marceglia, Sara; Università degli Studi di Trieste, Dipartimento di Ingegneria e Architettura; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UO Neurofisiopatologia Conti, Costanza; Newronika SpA Svanidze, Oleg; Newronika SpA Foffani, Guglielmo; Hospital Universitario HM Puerta del Sur; Fundación del Hospital Nacional de Parapléjicos para la Investigación y la Integración Lozano, Andres M; University of Toronto, Department of Surgery; University Health Network, Department of Surgery Moro, Elena; Grenoble Institute of Neurosciences Volkmann, Jens; University of Wurzburg, Department of Neurology Arlotti, Mattia; Newronika SpA Rossi, Lorenzo; Newronika SpA Priori, Alberto; University of Milan, Department of Health Sciences; ASST Santi Paolo e Carlo
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Parkinson-s disease < NEUROLOGY, NEUROLOGY

A double-blind crossover protocol to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Sara Marceglia*[1], Costanza Conti*[2], Oleg Svanidze[2], Guglielmo Foffani[3,4], Andres M Lozano[5,6], Elena Moro[7,8], Jens Volkmann[9],Mattia Arlotti[2], Lorenzo Rossi[2], Alberto Priori[10,11]

[1] Department of Engineering and Architecture, University of Trieste, 34127 Trieste, Italy
[2] Newronika SpA
[3] CINAC, Hospital Universitario HM Puerta del Sur, Universidad CEU-San Pablo, Móstoles, Madrid, Spain
[4] Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain
[5] Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.
[6] Krembil Research Institute, University Health Network, Toronto, Ontario, Canada.
[7] Grenoble Institute of Neurosciences, INSERM U1216, University Grenoble Alpes, Grenoble, France
[8] Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France
[9] Department of Neurology, University of Wurzburg, Germany
[10] Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, 20142 Milan, Italy
[11]ASST Santi Paolo e Carlo, Milan, Italy

***The first two authors equally contributed to the work**

Corresponding Author:
Prof Sara Marceglia
Dipartimento di Ingegneria e Architettura
Università degli Studi di Trieste

Via Valerio 10
34127 Trieste, Italy
email:smarceglia@units.it
tel: +39 040 5583450

Abstract

Introduction: After several years of brain-sensing technology development and proof-of-concept studies, adaptive deep brain stimulation (aDBS) is ready to better treat Parkinson's disease (PD) using aDBS-capable implantable pulse generators (IPGs). New aDBS devices are capable of continuous sensing of neuronal activity from the subthalamic nucleus (STN) and contemporaneous stimulation automatically adapted to match the patient's clinical state estimated from the analysis of STN activity using proprietary algorithms. Specific studies are necessary to assess superiority of aDBS versus conventional DBS (cDBS) therapy. This protocol describes an original innovative multi-center international study aimed to assess safety and efficacy of aDBS versus cDBS using a new generation of DBS IPG in PD (AlphaDBS system by Newronika SpA, Milan, Italy).

Methods: The study involves six investigational sites (in Italy, Poland, and The Netherlands). The primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when used in cDBS and aDBS mode. Secondary objective will be to evaluate the potential efficacy of aDBS. After eligibility screening, 15 PD patients already implanted with DBS systems and in need of battery replacement will be randomized to enter a two-phases protocol, including a "short-term follow-up" and a "long-term follow-up". During the "short-term follow-up", randomized patients will undergo 2-day experimental sessions (i.e., one per each type of stimulation mode, cDBS, and aDBS, order randomized), in a well-controlled environment (during hospitalization). Then, in the "long-term follow-up" phase (1 month), patients not experiencing severe side effects will continue in their home environment, with stimulation delivered in aDBS or cDBS mode, for two weeks in each mode.

Ethics and Dissemination: The trial was approved as pre-market study by the Italian and Polish Competent Authorities, while the regulatory approval is underway in The Netherlands. Local COVID-19 emergencies permitting, four sites will start to enroll patients in January 2021.

Registration: ClinicalTrials.gov Identifier: NCT04681534

Strengths and limitations of this study

- New study protocols are necessary to ass outcomes form adaptive DBS versus conventional DBS. This specific study assesses the safety and efficacy of aDBS using a new implantable device.
- The study includes patients with Parkinson's disease in the need of IPG replacement, thus overcoming the limits of acute setting (stun effect) seen in de nove DBS patients.
- The use of an implantable device minimizes risks for the patients, as compared to the previously used aDBS external devices.
- The number of patients is low but the results will help to design larger studies.
- This is the first study assessing the good on time with aDBS.

Introduction

Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), but its progress has been hampered by stagnation in methodological, technological, and device development. DBS proved to be effective in improving major PD symptoms in long-term follow-up studies [1–7] and currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor fluctuations, dyskinesias, and refractory tremor [1]. 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 [7].

However, current devices deliver conventional DBS (cDBS) with constant stimulation parameters, not adapting real-time to clinical features, but leaving to reprogramming visits the possibility to improve patient's response and satisfaction [8].

Limitations of cDBS include lack of responsiveness to patients' needs, fixed therapeutic window, repeated hospital visits for stimulation adjustment thus ultimately leading to suboptimal and more expensive therapy [8]. In addition, the excessive and unnecessary electrical stimulation over time may interfere with the residual physiological functions of the basal ganglia, thus contributing [9] 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. Some of these stimulation-related side effects can be reversed by reprogramming [10].

A new approach to overcome cDBS limitations is now represented by adaptive DBS (aDBS) in which the intensity of stimulation is set automatically by real-time adaptation to the patient's clinical state, in a closed-loop fashion [11,12]. The patient's state is estimated by analyzing the local neural activity (local field potentials, LFPs) recorded through the implanted DBS lead while stimulation is ON[13]. Such biosignals, and more specifically the beta frequency band (8-35 Hz), are related to patient's clinical state and to levodopa intake [14–16], and are involved in movement preparation and execution [17–19] and more in general to motor state [20,21].

LFPs-based aDBS has already been tested in humans, demonstrating to be effective in reducing motor symptoms of PD, comparable or even better than cDBS [20,22–25]. In addition, it has been shown that aDBS significantly reduces side effects often associated with DBS therapy such as levodopa-induced dyskinesia [25] and speech impairments [26].

However, the information regarding the long-term safety and efficacy of aDBS remains limited. In fact, to date, studies comparing the efficacy and safety of aDBS to cDBS had intrinsic limitations, due to technical reasons. Initial studies were mostly performed in the immediate postoperative period, after surgery for DBS electrode implant, when the temporary presence of externalized electrodes allows the collection of data using external devices. This approach has several major limitations since symptom improvement may be in part attributed to lesional or implantation effects associated with surgery

[27,28] and the effects of DBS and adverse events in the "acute" (postoperative) period are known to differ from its "chronic" effects [29]. Recently, two studies confirmed the benefits of aDBS in patients at implantable pulse generator (IPG) replacement [30,31], and protocols studying aDBS in these patients have been proposed [32]. In addition, due to the lack of available implantable devices delivering aDBS, studies foresaw short periods of stimulation, with a maximum length of follow up to 24 hours [30]. Even though a new CE-marked implantable device able to record LFPs while DBS is ON (Medtronic Percept™) has been recently introduced, no data on long-term aDBS is available as well as specific protocols to compare aDBS and cDBS.

Here we present the protocol of a double-blind crossover study to assess the safety and potential benefits of aDBS delivered through a new implantable system capable of delivering both cDBS and aDBS, the AlphaDBS System (Newronika S.p.A.). This system will allow, for the first time, to overcome the limitations of the current experimental settings. Furthermore, in agreement with the results of basic research, we expect that the most interesting potential benefits of aDBS will be observed in the long-run, since aDBS may be able to improve axial signs and reduce fluctuations that are measured through patient's diaries and that cannot be assessed in the short-term.

Study objectives

The aim of this study is to assess the safety and the potential efficacy of personalized LFP-based aDBS, using the implantable AlphaDBS System, in PD patients, chronically implanted in the 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, 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.

Data collection using non-single patient use items, such as wearable systems and/or microphones that need to be sanitized, may be stopped in case of local COVID-19 emergency.

Study design

This study, sponsored by Newronika SpA, was designed as a crossover trial using cDBS as a control.

The study protocol is organized in two phases: the "short-term follow-up" and the "long-term follow-up" (Figure 1). During the "short-term follow-up", fully eligible patients will be randomized to undergo a 2-day experimental sessions (i.e. one per each type of stimulation mode, cDBS and aDBS), during hospitalization, to collect information on safety and efficacy endpoints as assessed by experienced neurologists.

Patients who will not experience severe side effects during the "short-term follow-up" and who will be deemed suitable by the neurologist, will be eligible to continue in the "long-term follow-up" phase (1 month) in their "home" environment. The AlphaDBS System will deliver the stimulation in aDBS or cDBS mode, for two weeks in each mode, following the same order as in the "short-term follow-up".

Methods and procedure

Study centers

The study involves six investigational sites (in Italy, Poland, and The Netherlands). In particular, four centers are located in Italy (the University of Padua, the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, the IRCCS Istituto Neurologico Besta of Milan, and the AOU Città della Salute e della Scienza of Torino), one in Poland (Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie, Warsaw), and one in The Netherlands (Maastricht UMC+, Maastricht).

Inclusion criteria

All patients included in the study must have been already implanted with DBS electrodes in the past. At the time of their first DBS implant (electrodes + first IPG now to be replaced), they were selected for DBS indication on the basis of the CAPSIT guidelines (Core Assessment Program for Surgical Interventional Therapies in PD, CAPSIT-PD, [33]).

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

Exclusion criteria

- Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score <10);
- 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.)
- 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.)
- Need to replace or reposition the leads during the IPG replacement procedure
- Patients with > 10 recurrent falls experienced in the 3 months prior to consent
- Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min
- Patients taking less than one levodopa dose per day
- Patients with no LFPs recorded intraoperatively from any contacts pair, during the IPG replacement procedure
- Pregnant or breastfeeding women.

Device description

The AlphaDBS System is a DBS system that includes the possibility for the neurologist to program the stimulation in conventional mode (cDBS) or in adaptive, closed-loop, mode (aDBS). When the AlphaDBS System is used in aDBS mode, it delivers DBS stimulation using an intelligent biofeedback mechanism to automatically modulate stimulation. AlphaDBS is able to record and analyze in real-time LFPs while DBS in ON from the same implanted lead, and automatically adjust stimulation.

The AlphaDBS System is composed of different subsystems (Figure 2): the AlphaDBSipg (IPG delivering stimulation inaDBS or cDBS mode and recording/analyzing LFPs from implanted DBS leads); AlphaDBSpat (external patient controller); NWKstation (external physician controller).

The AlphaDBSipg is an active implantable medical device that applies cDBS/aDBS. It is powered by a hermetically sealed rechargeable battery within a titanium case. The AlphaDBS System, manufactured by Newronika SpA (Milan, Italy), is currently under final stages of CE-mark certification procedures.

In cDBS mode, the AlphaDBSipg, with 16 independent stimulation current controlled outputs, delivers asymmetric biphasic balanced constant current pulse train. Stimulation can be delivered in bipolar or monopolar configuration by selecting a contact pair or one contact in each of the two available leads (stimulation parameters: pulse width (us), amplitude (V), and frequency (Hz)). In monopolar stimulation, the reference electrode is simulated by the IPG enclosure.

In aDBS mode, an adaptive algorithm will use LFP signals from implanted electrodes extracting information to decrease the energy of stimulation (amplitude) when the patient is responding

appropriately to pharmacological therapy and increasing the energy when the patient's symptoms are not well controlled. The algorithm that will be used in aDBS mode will be personalized based on LFP modulation in the 13-35 Hz frequency band (beta band), as described elsewhere [34].

Evaluations and procedures

After providing consent, each patient will undergo a Screening Period, during which demographic information and additional information on the medical management will be collected. Each patient will undergo a series of screening evaluations, including: evaluation of battery level, medical history, physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [33], measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery), assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be evaluated after the administration of a LEED morning dose + 30%.

Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization will be conducted in agreement with local standard practice for IPG replacement.

On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be connected to temporary extensions in order to check the integrity of the leads and the occurrence of ECG artifacts. The patients with ECG artifacts impairing LFP recording will not be excluded and will receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.

The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS current titration session will be performed to establish both the optimal cDBS parameters with AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the personalized beta band and peak previously defined.

At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to aDBS or cDBS treatment will take place on the following day.

On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one stimulation mode per day, according to the randomization schedule.

The experimental session will start around 7:30 am (expected time) and will last for about nine hours (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next washout period in the same mode.

At the beginning of the session, the stimulation will be switched off for at least 30 minutes of stimulation washout (stim-OFF/med-OFF condition), and then switched on.

Each experimental session will include the following assessments:

- T0: before the administration of the morning dopaminergic therapy and after at least 30 minutes of stimulation washout (stim-OFF/med-OFF) - UDysRS, UPDRS III and adverse events recording, speech analysis
- T1: before the administration of the morning dopaminergic therapy and after 1 hour of active stimulation (stim-ON/med-OFF) – UDysRS, UPDRS III and adverse event recording, speech analysis
- T2: around 1 hour after dopaminergic therapy administration, when the effect of dopaminergic therapy will reach its best effect (stim-ON/med-ON) – UDysRS, UPDRS III, adverse event recording, speech analysis
- T3: in the afternoon, around 4 pm or if the patient therapeutic schedule foresees a second dopaminergic therapy, when the effect of the therapy will reach its best effect (stim-ON/med-ON)- UDysRS, UPDRS III and adverse event recording
- T4: the following day (Day 3 or Day 4), in the morning, before starting any experimental procedure, when the stimulation is still ON, and before the administration of the morning dopaminergic therapy (stim-ON/med-OFF) - UDysRS, UPDRS III and adverse events recording, speech analysis.

The timing of the assessments is indicative and variations up to 45 minutes are allowed.

Throughout the experimental session, to monitor motor symptoms fluctuations, the patient will wear a bracelet equipped with a three-axial accelerometer and will fill in his/her Patient's Diary, for the whole duration of the experimental session. Speech analysis will be performed with Semantic and phonemic evaluations will be recorded with the VF test (Delis-Kaplan Executive Function System), and control word repetition tasks.

The parameters to calculate the TEED at T4 will be automatically collected from the AlphaDBS System.

On Day 4, if the neurologist will deem the patient suitable for the "long-term follow-up" phase, the patient will undergo another clinical assessment and will be discharged. The clinical assessment will take place about 1 hour after morning dopaminergic therapy administration, when the effect of the therapy will reach its best effect (stim-ON/med-ON), administering UDysRS and UPDRS III scales and examining possible side effects. After the visit, the stimulation will be automatically switched to the stimulation mode, randomly allocated on Day 2.

After the examination, patients (blinded to treatment) will receive the training on how to use the device, and then be discharged from the hospital and sent to their "home" environment for two weeks in each stimulation mode.

During this follow-up period, a research fellow/nurse will monitor the patient remotely every day to assess the patient status, check Concomitant Medications and record adverse events.

After two weeks of treatment, on Day 18, the patient will provide diaries completed in the last three days before the visit and will undergo a clinical assessment (performed by a blinded neurologist) in

stim ON-med ON including UDysRS, UPDRS III and DBS-IS scales, collection of possible side effects, speech analysis, and TEED (automatically collected from the AlphaDBSipg). Also, the patient/caregiver will provide his/her inputs related to the System usability for what concerns the IPG recharging process.

After the visit, the stimulation will be automatically switched to the other stimulation mode (as in Day 3), and the patient will be sent home. The same protocol will be followed for two weeks until Day 32. Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a compatible commercially available IPG.

Randomization

Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a first treatment, based on a center-specific computer-generated randomization list.

Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive study number will be automatically assigned. If the patient is eligible, the Investigators will randomize him/her and the eCRF will display a randomization code corresponding to the first free number from the randomization list.

At the beginning of each experimental day, the designated person in charge of DBS programming (unblind), will use the randomization code as PIN code to enter the Physician Programmer (NWKStation), to program the system in cDBS or aDBS according to randomization.

Methods: Statistical methods and data management

Sample size

The objective of the study is to collect data that will allow calculation of the sample size needed for a pivotal study if the present study confirms the results obtained in a previous trial. This study will randomize at least 15 patients.

Based on the figures obtained in the clinical trial with patients in the "acute" phase [25], and without considering corrections for multiple testing, this sample will allow using exploratory statistics to demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse events (1-2%) are not considered since they were already described by other DBS devices manufacturers and thus expected.

Data collection and management

All study data will be collected and stored through online eCRFs. The system will provide a safe environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data collection that can be shared among different operative units, allowing CRF signature and modifications tracking. A CRO is in charge of data management and quality assurance.

Monitoring

The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).

Data analysis

The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.

The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints (i.e., UDysRS, UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS experimental sessions.

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 treatments.

This is a first in man study not designed to claim efficacy of aDBS or superiority of aDBS over cDBS. Exploratory analysis will be only performed in order to obtain summary data to inform decisions on future clinical development phases. Clinical efficacy will be evaluated through intention-to-treat analysis.

Differences in clinical endpoints when patients receive aDBS or cDBS will be compared, as well as the time courses of UPDRS III scores, motor symptoms fluctuations, “Time Off”/”Time On”, and UDysRS during aDBS and cDBS treatments. Data will be compared with repeated measures general linear model analyses. Tukey's honest significance test will be used for post hoc analysis. Differences will be considered significant at $p<0.05$ for the generation of hypotheses.

Since the protocol is a first in man study for the AlphaDBSipg, it includes various and repeated assessments to better evaluate patient’s tolerability and response. However, these can be burdensome for the patients and minor protocol deviations might be expected. Minor deviations will be included in the analysis whereas major deviations will be excluded.

Ethics and dissemination

Risk-benefit analysis

Potential risks and benefits of aDBS will be clearly explained to the patients in the Informed Consent Form that will be provided at screening, prior to start the study protocol.

If the results of the trial will be promising, PD patients will have a new innovative device for DBS that will allow the delivery of aDBS. In any case, new long-term LFP recordings will be available thanks to the implantation of the AlphaDBS system thus improving the understanding of PD neurophysiology.

Patients treated with aDBS could experience a reduction of symptoms, better quality of life, and a simplification of patient management, reducing the number of visits and calls to the treating neurologist to fine-tune DBS programming settings. In addition, patients involved in the study could experience personal benefits, possibly including: overall reduction of the electrical energy delivered to the tissues, and of the patient's OFF time (compared to cDBS), overall increase of the patient's ON time without troublesome dyskinesia, improvement of efficacy in reducing bradykinesia, rigidity, and tremor (compared to cDBS), reduction "levodopa-induced dyskinesia", improvement in speech, balance, and gait problems related to stimulation.

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. An additional risk may occur in patients choosing to replace the AlphaDBSipg with a commercial IPG at the end of the long-term follow-up.

COVID-19 seriously impacted on the conduction of experimental trials and research activity [35]. A COVID-19 risk assessment, related to the study conduct was prepared, in agreement with the indications provided in the "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic (Version 3, 28/04/2020)" issued by the European Commission and coordinated by EMA.

Informed consent, IEC/IRB approval, and MoH approval

The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013.

The protocol, Subject Information Sheet, Informed Consent Form and the Data Privacy Consent Form were reviewed and approved, prior to initiating any trial-related activity, by the Ethical Committees of each institution involved namely: Comitato Etico Milano Area 2 (Milano), Comitato Etico Fondazione

IRCCS Istituto Neurologico C. Besta (Milano), Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino (Torino), Comitato Etico per la Sperimentazione Clinica della Provincia di Padova (Padova); Bioethics Committee at the National Institute of Oncology of Maria Skłodowska-Curie (Warsaw), De Medisch Ethisch Toetsingscommissie van Maastricht UMC (in The Netherlands, approval pending upon revision of study documentation). As the AlphaDBS System is an investigational device, the trial required the approval, as pre-market study, of competent authorities, namely: the Italian Ministry of Health, Directorate General for Medical Devices and Pharmaceutical service, the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and the Dutch Central Committee on Research Involving Human Subjects.

Patient and Public Involvement

Patients from an Italian PD association provided inputs on the definition of relevant benefits related to the results of this aDBS investigation and on device usability.

References

1 Krack P, Martinez-Fernandez R, del Alamo M, *et al.* Current applications and limitations of surgical treatments for movement disorders: Surgical Treatments For Movement Disorders. *Movement Disorders* 2017;**32**:36–52. doi:10.1002/mds.26890

2 Kleiner-Fisman G, Herzog J, Fisman DN, *et al.* Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 2006;**21 Suppl 14**:S290-304. doi:10.1002/mds.20962

3 Bronstein JM, Tagliati M, Alterman RL, *et al.* Deep Brain Stimulation for Parkinson Disease: An Expert Consensus and Review of Key Issues. *Arch Neurol* 2011;**68**. doi:10.1001/archneurol.2010.260

4 Deuschl G, Schade-Brittinger C, Krack P, *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;**355**:896–908. doi:10.1056/NEJMoa060281

5 Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. *Mov Disord* 2012;**27**:1718–28. doi:10.1002/mds.25214

6 Odekerken VJJ, Boel JA, Schmand BA, *et al.* GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. *Neurology* 2016;**86**:755–61. doi:10.1212/WNL.0000000000002401

7 Cavallieri F, Fraix V, Bove F, *et al.* Predictors of Long-Term Outcome of Subthalamic Stimulation in Parkinson Disease. *Ann Neurol* 2021;:ana.25994. doi:10.1002/ana.25994

8 Koeglsperger T, Palleis C, Hell F, *et al.* Deep Brain Stimulation Programming for Movement Disorders: Current Concepts and Evidence-Based Strategies. *Front Neurol* 2019;**10**:410. doi:10.3389/fneur.2019.00410

9 Chen CC, Brücke C, Kempf F, *et al.* Deep brain stimulation of the subthalamic nucleus: a two-edged sword. *Curr Biol* 2006;**16**:R952-953. doi:10.1016/j.cub.2006.10.013

10 Picillo M, Lozano AM, Kou N, *et al.* Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. *Brain Stimulation* 2016;**9**:425–37. doi:10.1016/j.brs.2016.02.004

11 Priori A, Foffani G, Rossi L, *et al.* Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Exp Neurol* 2013;**245**:77–86. doi:10.1016/j.expneurol.2012.09.013

12 Mitchell KT, Starr PA. Smart neuromodulation in movement disorders. In: *Handbook of Clinical Neurology*. Elsevier 2020. 153–61. doi:10.1016/B978-0-444-63934-9.00012-3

13 Marceglia S, Rossi L, Foffani G, *et al.* Basal ganglia local field potentials: applications in the development of new deep brain stimulation devices for movement disorders. *Expert Rev Med Devices* 2007;**4**:605–14. doi:10.1586/17434440.4.5.605

14 Arlotti M, Rosa M, Marceglia S, *et al.* The adaptive deep brain stimulation challenge. *Parkinsonism Relat Disord* 2016;**28**:12–7. doi:10.1016/j.parkreldis.2016.03.020

15 Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord* 2003;**18**:357–63. doi:10.1002/mds.10358

16 Priori A, Foffani G, Pesenti A, *et al.* Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;**189**:369–79. doi:10.1016/j.expneurol.2004.06.001

17 Marceglia S, Fumagalli M, Priori A. What neurophysiological recordings tell us about cognitive and behavioral functions of the human subthalamic nucleus. *Expert Rev Neurother* 2011;**11**:139–49. doi:10.1586/ern.10.184

18 Marceglia S, Fiorio M, Foffani G, *et al.* Modulation of beta oscillations in the subthalamic area during action observation in Parkinson's disease. *Neuroscience* 2009;**161**:1027–36. doi:10.1016/j.neuroscience.2009.04.018

19 Foffani G, Bianchi AM, Baselli G, *et al.* Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol (Lond)* 2005;**568**:699–711. doi:10.1113/jphysiol.2005.089722

20 Arlotti M, Marceglia S, Foffani G, *et al.* Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology* 2018;**90**:e971–6. doi:10.1212/WNL.0000000000005121

21 Neumann W-J, Degen K, Schneider G-H, *et al.* Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease: Correlation of Subthalamic B Oscillations and PD Symptoms. *Mov Disord* 2016;**31**:1748–51. doi:10.1002/mds.26759

22 Little S, Pogosyan A, Neal S, *et al.* Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;**74**:449–57. doi:10.1002/ana.23951

23 Little S, Beudel M, Zrinzo L, *et al.* Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J Neurol Neurosurg Psychiatr* 2016;**87**:717–21. doi:10.1136/jnnp-2015-310972

24 Rosa M, Arlotti M, Ardolino G, *et al.* Adaptive deep brain stimulation in a freely moving Parkinsonian patient. *Mov Disord* 2015;**30**:1003–5. doi:10.1002/mds.26241

25 Rosa M, Arlotti M, Marceglia S, *et al.* Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Mov Disord* 2017;**32**:628–9. doi:10.1002/mds.26953

26 Little S, Tripoliti E, Beudel M, *et al.* Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. *Journal of Neurology, Neurosurgery & Psychiatry* 2016;:jnnp-2016-313518. doi:10.1136/jnnp-2016-313518

27 Mann JM, Foote KD, Garvan CW, *et al.* Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 2009;**80**:794–7. doi:10.1136/jnnp.2008.159558

28 Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord* 2016;**31**:290–6. doi:10.1002/mds.26500

29 Rosa M, Giannicola G, Servello D, *et al.* Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neurosignals* 2011;**19**:151–62. doi:10.1159/000328508

30 Arlotti M, Palmisano C, Minafra B, *et al.* Monitoring subthalamic oscillations for 24 hours in a freely moving Parkinson's disease patient. *Mov Disord* 2019;**34**:757–9. doi:10.1002/mds.27657

31 Piña-Fuentes D, Little S, Oterdoom M, *et al.* Adaptive DBS in a Parkinson's patient with chronically implanted DBS: A proof of principle. *Mov Disord* 2017;**32**:1253–4. doi:10.1002/mds.26959

32 Piña-Fuentes D, Beudel M, Little S, *et al.* Adaptive deep brain stimulation as advanced Parkinson's disease treatment (ADAPT study): protocol for a pseudo-randomised clinical study. *BMJ Open* 2019;**9**:e029652. doi:10.1136/bmjopen-2019-029652

33 Defer GL, Widner H, Marié RM, *et al.* Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;**14**:572–84. doi:10.1002/1531-8257(199907)14:4<572::aid-mds1005>3.0.co;2-c

34 Arlotti M, Rossi L, Rosa M, *et al.* An external portable device for adaptive deep brain stimulation (aDBS) clinical research in advanced Parkinson's Disease. *Med Eng Phys* 2016;**38**:498–505. doi:10.1016/j.medengphy.2016.02.007

35 Priori A, Baisi A, Banderali G, *et al.* The Many Faces of Covid-19 at a Glance: A University Hospital Multidisciplinary Account From Milan, Italy. *Front Public Health* 2021;**8**:575029. doi:10.3389/fpubh.2020.575029

Contributors: SM and CC ideated and designed the protocol, wrote the protocol and documentation for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR, AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures and manuscript. All authors reviewed and approved the final version of this manuscript.

Funding: This study is sponsored by Newronika SpA, a spin off company of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant number is not applicable.

Disclaimer: All the scientific findings derived from this protocol are aimed to be made public through publication of articles in international journals.

Conflict of Interest statement:

AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of Functional Neuromodulation.

Word count: 3988

FIGURES AND FIGURE LEGENDS

Figure 1- The trial time-line in patients participating to both the short and long term follow-up phases: after completing the experimental procedures foreseen in Day 1, Day 2 and Day 3, on Day 4, in the morning, the patient will be discharged with the AlphaDBSipg delivering aDBS or cDBS for 2 weeks. On Day 18 the patient will undergo a clinical assessment. After the assessment the stimulation mode will be switched and the patient will undergo a new clinical assessment. If the second clinical assessment (with changed stimulation mode ON) will be successfully completed, the patient will be discharged with the AlphaDBS device delivering aDBS or cDBS for additional 2 weeks. On Day 32 the patient will undergo the last clinical assessment.

Figure 2 – AlphaDBS system overview

Figure 3- Summary of examinations foreseen at each time point of the experimental sessions (Day 2 and Day 3). Note that timing is indicative and may vary up to 45 min. per session

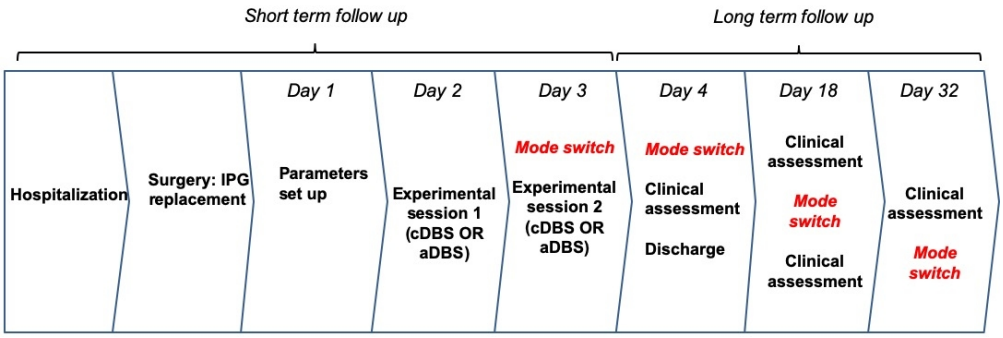

Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

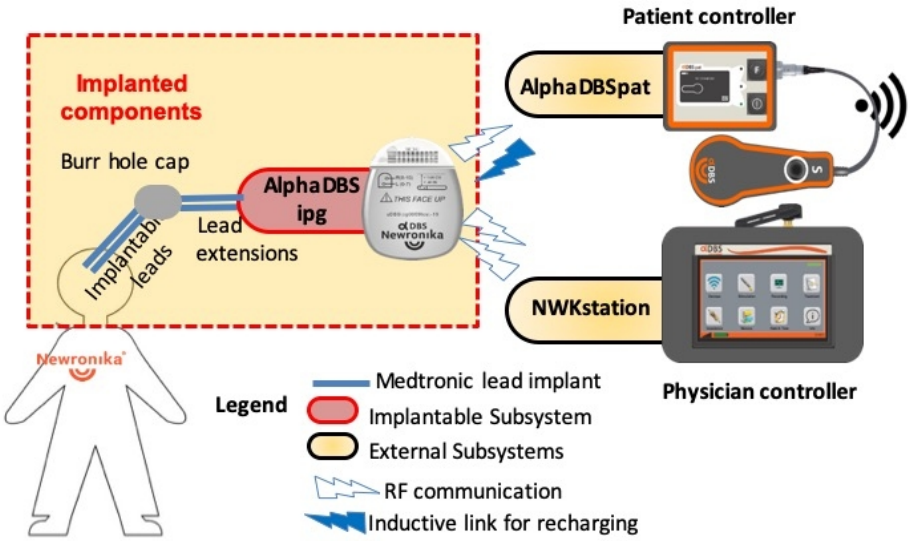

Figure 2 - AlphaDBS system components

264x171mm (72 x 72 DPI)

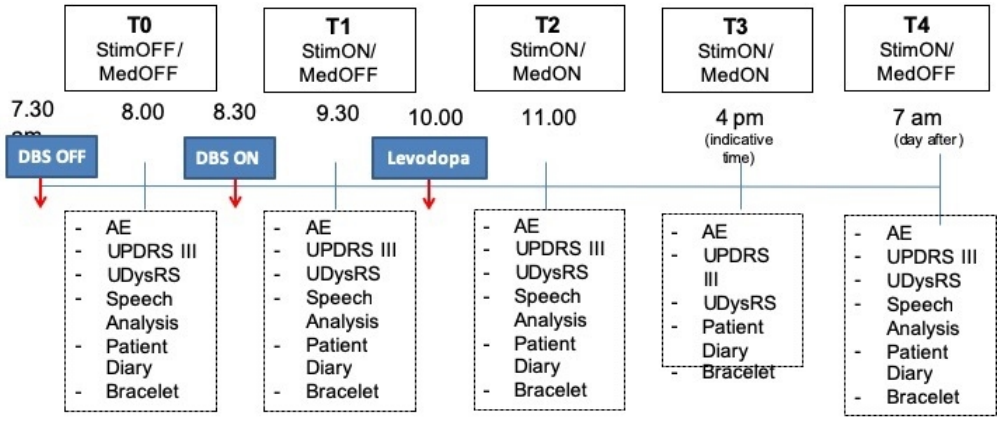

Figure 3 - Short term follow-up: Experimental session details

60x25mm (300 x 300 DPI)

BMJ Open

A double-blind crossover pilot trial to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049955.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Oct-2021
Complete List of Authors:	Marceglia, Sara; Università degli Studi di Trieste, Dipartimento di Ingegneria e Architettura; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UO Neurofisiopatologia Conti, Costanza; Newronika SpA Svanidze, Oleg; Newronika SpA Foffani, Guglielmo; Hospital Universitario HM Puerta del Sur; Fundación del Hospital Nacional de Parapléjicos para la Investigación y la Integración Lozano, Andres M; University of Toronto, Department of Surgery; University Health Network, Department of Surgery Moro, Elena; Grenoble Institute of Neurosciences Volkmann, Jens; University of Wurzburg, Department of Neurology Arlotti, Mattia; Newronika SpA Rossi, Lorenzo; Newronika SpA Priori, Alberto; University of Milan, Department of Health Sciences; ASST Santi Paolo e Carlo
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Parkinson-s disease < NEUROLOGY, NEUROLOGY

A double-blind crossover pilot trial to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Sara Marceglia*[1], Costanza Conti*[2], Oleg Svanidze[2], Guglielmo Foffani[3,4], Andres M Lozano[5,6], Elena Moro[7,8], Jens Volkmann[9], Mattia Arlotti[2], Lorenzo Rossi[2], Alberto Priori[10,11]

[1] Department of Engineering and Architecture, University of Trieste, 34127 Trieste, Italy
[2] Newronika SpA
[3] CINAC, Hospital Universitario HM Puerta del Sur, Universidad CEU-San Pablo, Móstoles, Madrid, Spain
[4] Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain
[5] Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.
[6] Krembil Research Institute, University Health Network, Toronto, Ontario, Canada.
[7] Grenoble Institute of Neurosciences, INSERM U1216, University Grenoble Alpes, Grenoble, France
[8] Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France
[9] Department of Neurology, University of Wurzburg, Germany
[10] Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, 20142 Milan, Italy
[11] ASST Santi Paolo e Carlo, Milan, Italy

***The first two authors equally contributed to the work**

Corresponding Author:
Prof Sara Marceglia
Dipartimento di Ingegneria e Architettura
Università degli Studi di Trieste

Via Valerio 10
34127 Trieste, Italy
email:smarceglia@units.it
tel: +39 040 5583450

Abstract

Introduction: After several years of brain-sensing technology development and proof-of-concept studies, adaptive deep brain stimulation (aDBS) is ready to better treat Parkinson's disease (PD) using aDBS-capable implantable pulse generators (IPGs). New aDBS devices are capable of continuous sensing of neuronal activity from the subthalamic nucleus (STN) and contemporaneous stimulation automatically adapted to match the patient's clinical state estimated from the analysis of STN activity using proprietary algorithms. Specific studies are necessary to assess superiority of aDBS versus conventional DBS (cDBS) therapy. This protocol describes an original innovative multi-center international study aimed to assess safety and efficacy of aDBS versus cDBS using a new generation of DBS IPG in PD (AlphaDBS system by Newronika SpA, Milan, Italy).

Methods: The study involves six investigational sites (in Italy, Poland, and The Netherlands). The primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when used in cDBS and aDBS mode. Secondary objective will be to evaluate the potential efficacy of aDBS. After eligibility screening, 15 PD patients already implanted with DBS systems and in need of battery replacement will be randomized to enter a two-phases protocol, including a "short-term follow-up" (2-days experimental sessions during hospitalization, 1 day per each mode) and a "long-term follow-up" (1 month at home, 15 days per each mode).

Ethics and Dissemination: The trial was approved as pre-market study by the Italian, Polish, and Dutch Competent Authorities: Bioethics Committee at National Oncology Institute of Maria Skłodowska-Curie – National Research Institute in Warsaw; Comitato Etico Milano Area 2; Comitato Etico IRCCS Istituto Neurologico C. Besta; Comitato Etico interaziendale AOUC Città della Salute e della Scienza – AO Ordine Mauriziano di Torino – ASL Città di Torino; De Medisch Ethisch Toetsingscommissie van Maastricht UMC. The study started enrolling patients in January 2021.

Registration: ClinicalTrials.gov Identifier: NCT04681534

Strengths and limitations of this study

- New study protocols are necessary to ass outcomes form adaptive DBS versus conventional DBS. This specific study assesses the safety and efficacy of aDBS using a new implantable device.
- The study includes patients with Parkinson's disease in the need of IPG replacement, thus overcoming the limits of acute setting (stun effect) seen in de nove DBS patients.
- The use of an implantable device minimizes risks for the patients, as compared to the previously used aDBS external devices.
- The number of patients is low but the results will help to design larger studies.
- This is the first study assessing the good on time with aDBS.

Introduction

Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), but its progress has been hampered by stagnation in methodological, technological, and device development. DBS proved to be effective in improving major PD symptoms in long-term follow-up studies [1–7] and currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor fluctuations, dyskinesias, and refractory tremor [1]. 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 [7].

However, current devices deliver conventional DBS (cDBS) with constant stimulation parameters, not adapting real-time to clinical features, but leaving to reprogramming visits the possibility to improve patient's response and satisfaction [8].

Limitations of cDBS include lack of responsiveness to patients' needs, fixed therapeutic window, repeated hospital visits for stimulation adjustment thus ultimately leading to suboptimal and more expensive therapy [8]. In addition, the excessive and unnecessary electrical stimulation over time may interfere with the residual physiological functions of the basal ganglia, thus contributing [9] 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. Some of these stimulation-related side effects can be reversed by reprogramming [10].

A new approach to overcome cDBS limitations is now represented by adaptive DBS (aDBS) in which the intensity of stimulation is set automatically by real-time adaptation to the patient's clinical state, in a closed-loop fashion [11,12]. The patient's state is estimated by analyzing the local neural activity (local field potentials, LFPs) recorded through the implanted DBS lead while stimulation is ON[13]. Such biosignals, and more specifically the beta frequency band (8-35 Hz), are related to patient's clinical state and to levodopa intake [14–16], and are involved in movement preparation and execution [17–19] and more in general to motor state [20,21].

LFPs-based aDBS has already been tested in humans, demonstrating to be effective in reducing motor symptoms of PD, comparable or even better than cDBS [20,22–25]. In addition, it has been shown that aDBS significantly reduces side effects often associated with DBS therapy such as levodopa-induced dyskinesia [25] and speech impairments [26].

However, the information regarding the long-term safety and efficacy of aDBS remains limited. In fact, to date, studies comparing the efficacy and safety of aDBS to cDBS had intrinsic limitations, due to technical reasons. Initial studies were mostly performed in the immediate postoperative period, after surgery for DBS electrode implant, when the temporary presence of externalized electrodes allows the collection of data using external devices. This approach has several major limitations since symptom improvement may be in part attributed to lesional or implantation effects associated with surgery

[27,28] and the effects of DBS and adverse events in the "acute" (postoperative) period are known to differ from its "chronic" effects [29]. Recently, two studies confirmed the benefits of aDBS in patients at implantable pulse generator (IPG) replacement [30,31], and protocols studying aDBS in these patients have been proposed [32]. In addition, due to the lack of available implantable devices delivering aDBS, studies foresaw short periods of stimulation, with a maximum length of follow up to 24 hours [30]. Even though a new CE-marked implantable device able to record LFPs while DBS is ON (Medtronic Percept™) has been recently introduced, no data on long-term aDBS is available as well as specific protocols to compare aDBS and cDBS.

Here we present the protocol of a double-blind crossover study to assess the safety and potential benefits of aDBS delivered through a new implantable system capable of delivering both cDBS and aDBS, the AlphaDBS System (Newronika S.p.A.). This system will allow, for the first time, to overcome the limitations of the current experimental settings. Furthermore, in agreement with the results of basic research, we expect that the most interesting potential benefits of aDBS will be observed in the long-run, since aDBS may be able to improve axial signs and reduce fluctuations that are measured through patient's diaries and that cannot be assessed in the short-term.

Study objectives

The aim of this study is to assess the safety and the potential efficacy of personalized LFP-based aDBS, using the implantable AlphaDBS System, in PD patients, chronically implanted in the 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, based on the following endpoints:

- Occurrence of device-related adverse events
- Decrease in the Total Electrical Energy Delivered (TEED) to the patient.

As aDBS can be considered as a new treatment, all device related AEs will be reported and analyzed against other devices on the market. Particular attention will be given to unexpected AEs and to those related to aDBS malfunctioning. In addition, TEED is an objective measure of the amount of energy transferred by DBS amplitude to the patient's brain. Previous works showed a significant reduction of TEED in aDBS compared to cDBS. Since TEED is correlated to dyskinesia occurrence [33], which is one of the stimulation-related side effects that aDBS may be able to control [25], TEED was also included as a quantitative safety endpoint.

Since this is the first study on the use of AlphaDBS System and on the chronic application of its aDBS implementation, 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 MDS-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 (see supplementary materials).
Exploratory objectives include evaluation of DBS associated deficits, through the DBS Impairment Scale (DBS-IS) [34] and evaluation of the effects of aDBS on speech.
Data collection using non-single patient use items, such as wearable systems and/or microphones that need to be sanitized, may be stopped in case of local COVID-19 emergency.

Study design

This study, sponsored by Newronika SpA, was designed as a crossover trial using cDBS as a control.
The study protocol is organized in two phases: the "short-term follow-up" and the "long-term follow-up" (Figure 1). During the "short-term follow-up", fully eligible patients will be randomized to undergo a 2-day experimental sessions (i.e. one per each type of stimulation mode, cDBS and aDBS), during hospitalization, to collect information on safety and efficacy endpoints as assessed by experienced neurologists.
Patients who will not experience severe side effects during the "short-term follow-up" and who will be deemed suitable by the neurologist, will be eligible to continue in the "long-term follow-up" phase (1 month) in their "home" environment. The AlphaDBS System will deliver the stimulation in aDBS or cDBS mode, for two weeks in each mode, following the same order as in the "short-term follow-up".

Methods and procedure

Study centers

The study involves six investigational sites (in Italy, Poland, and The Netherlands). In particular, four centers are located in Italy (the University of Padua, the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, the IRCCS Istituto Neurologico Besta of Milan, and the AOU Città della Salute e della Scienza of Torino), one in Poland (Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie, Warsaw), and one in The Netherlands (Maastricht UMC+, Maastricht).

Inclusion criteria

All patients included in the study must have been already implanted with DBS electrodes in the past. At the time of their first DBS implant (electrodes + first IPG now to be replaced), they were selected for DBS indication on the basis of the CAPSIT guidelines (Core Assessment Program for Surgical Interventional Therapies in PD, CAPSIT-PD, [35]). Even though some of the listed inclusion/exclusion criteria are similar to that used for DBS indication, we decided to reconsider them because of the time elapsed from DBS first implant.

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

Exclusion criteria

- Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score <10);
- 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.)
- 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.)
- Need to replace or reposition the leads during the IPG replacement procedure
- Patients with > 10 recurrent falls experienced in the 3 months prior to consent
- Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min
- Patients taking less than one levodopa dose per day
- Patients with no LFPs recorded intraoperatively from any contacts pair, during the IPG replacement procedure
- Pregnant or breastfeeding women.

Device description

The AlphaDBS System is a DBS system that includes the possibility for the neurologist to program the stimulation in conventional mode (cDBS) or in adaptive, closed-loop, mode (aDBS). When the AlphaDBS System is used in aDBS mode, it delivers DBS stimulation using an intelligent biofeedback mechanism to automatically modulate stimulation. AlphaDBS is able to record and analyze in real-time LFPs while DBS in ON from the same implanted lead, and automatically adjust stimulation.

The AlphaDBS System is composed of different subsystems (Figure 2): the AlphaDBSipg (IPG delivering stimulation in aDBS or cDBS mode and recording/analyzing LFPs from implanted DBS leads); AlphaDBSpat (external patient controller); NWKstation (external physician controller).

The AlphaDBSipg is an active implantable medical device that applies cDBS/aDBS. It is powered by a hermetically sealed rechargeable battery within a titanium case. The AlphaDBS System, manufactured by Newronika SpA (Milan, Italy), is currently under final stages of CE-mark certification procedures.

In cDBS mode, the AlphaDBSipg, with 16 independent stimulation current controlled outputs, delivers asymmetric biphasic balanced constant current pulse train. Stimulation can be delivered in bipolar or monopolar configuration by selecting a contact pair or one contact in each of the two available leads (stimulation parameters: pulse width (us), amplitude (V), and frequency (Hz)). In monopolar stimulation, the reference electrode is simulated by the IPG enclosure.

In aDBS mode, an adaptive algorithm will use LFP signals from implanted electrodes extracting information to decrease the energy of stimulation (amplitude) when the patient is responding appropriately to pharmacological therapy and increasing the energy when the patient's symptoms are not well controlled. The algorithm that will be used in aDBS mode will be personalized based on LFP modulation in the 13-35 Hz frequency band (beta band), as described elsewhere [36].

The AlphaDBS System has several innovative features that implement a distributed architecture allowing data collection and management that make it a reliable platform for aDBS and closed-loop neuromodulation applications. Major innovations reside in the technology for artifact-free recordings [36–38] that is stimulation agnostic, electrode configuration independent, and needless for back-end processing. This implies that LFPs can be recorded with stimulation ON from all contact pairs, not necessarily symmetrical around the stimulation contact, and with different stimulation types. In addition, the artifact rejection methodology is implemented at the chip level and not at the system level, thus leaving the whole computational capacity free for closed-loop algorithm implementation. Another important feature is the ability of the system both to provide on-demand real-time streaming of LFPs both in ON and OFF without the need of additional receivers worn by the patient, but using directly the clinician controller (NWKStation) and to provide continuous embedded data storage that is always ON 24/7 whatever the stimulation mode (OFF, cDBS, aDBS). Thanks to the data management infrastructure, the embedded data storage guarantees no data loss for memory overwriting because data are automatically downloaded to the patient controller (AlphaDBSpat) during recharging, using the same device. This is crucial to allow full biomarker tracking for future aDBS optimization.

Evaluations and procedures

After providing consent, each patient will undergo a Screening Period, during which demographic information and additional information on the medical management will be collected. Each patient will

undergo a series of screening evaluations, including: evaluation of battery level, medical history, physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [35], measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery), assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be evaluated after the administration of a LEED morning dose + 30%.

Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization will be conducted in agreement with local standard practice for IPG replacement.

On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be connected to temporary extensions in order to check the integrity of the leads and the occurrence of ECG artifacts. The patients with ECG artifacts impairing LFP recording will ~~not~~ be excluded and will receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.

The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS current titration session will be performed to establish both the optimal cDBS parameters with AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the personalized beta band and peak previously defined.

At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to aDBS or cDBS treatment will take place on the following day.

On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one stimulation mode per day, according to the randomization schedule.

The experimental session will start around 7:30 am (expected time) and will last for about nine hours (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next washout period in the same mode.

At the beginning of the session, the stimulation will be switched off for at least 30 minutes of stimulation washout (stim-OFF/med-OFF condition), and then switched on.

Each experimental session will include the following assessments:

- T0: before the administration of the morning dopaminergic therapy and after at least 30 minutes of stimulation washout (stim-OFF/med-OFF) - UDysRS, UPDRS III and adverse events recording, speech analysis
- T1: before the administration of the morning dopaminergic therapy and after 1 hour of active stimulation (stim-ON/med-OFF) – UDysRS, UPDRS III and adverse event recording, speech analysis

- T2: around 1 hour after dopaminergic therapy administration, when the effect of dopaminergic therapy will reach its best effect (stim-ON/med-ON) – UDysRS, UPDRS III, adverse event recording, speech analysis
- T3: in the afternoon, around 4 pm or if the patient therapeutic schedule foresees a second dopaminergic therapy, when the effect of the therapy will reach its best effect (stim-ON/med-ON)- UDysRS, UPDRS III and adverse event recording
- T4: the following day (Day 3 or Day 4), in the morning, before starting any experimental procedure, when the stimulation is still ON, and before the administration of the morning dopaminergic therapy (stim-ON/med-OFF) - UDysRS, UPDRS III and adverse events recording, speech analysis.

The timing of the assessments is indicative and variations up to 45 minutes are allowed.

Throughout the experimental session, to monitor motor symptoms fluctuations, the patient will wear a bracelet equipped with a three-axial accelerometer and will fill in his/her Patient's Diary, for the whole duration of the experimental session. Speech analysis will be performed with Semantic and phonemic evaluations will be recorded with the VF test (Delis-Kaplan Executive Function System), and control word repetition tasks.

The parameters to calculate the TEED at T4 will be automatically collected from the AlphaDBS System.

On Day 4, if the neurologist will deem the patient suitable for the "long-term follow-up" phase, the patient will undergo another clinical assessment and will be discharged. The clinical assessment will take place about 1 hour after morning dopaminergic therapy administration, when the effect of the therapy will reach its best effect (stim-ON/med-ON), administering UDysRS and UPDRS III scales and examining possible side effects. After the visit, the stimulation will be automatically switched to the stimulation mode, randomly allocated on Day 2.

After the examination, patients (blinded to treatment) will receive the training on how to use the device, and then be discharged from the hospital and sent to their "home" environment for two weeks in each stimulation mode.

During this follow-up period, a research fellow/nurse will monitor the patient remotely every day to assess the patient status, check Concomitant Medications and record adverse events.

After two weeks of treatment, on Day 18, the patient will provide diaries completed in the last three days before the visit and will undergo a clinical assessment (performed by a blinded neurologist) in stim ON-med ON including UDysRS, UPDRS III and DBS-IS scales, collection of possible side effects, speech analysis, and TEED (automatically collected from the AlphaDBSipg). Also, the patient/caregiver will provide his/her inputs related to the System usability for what concerns the IPG recharging process.

After the visit, the stimulation will be automatically switched to the other stimulation mode (as in Day 3), and the patient will be sent home. The same protocol will be followed for two weeks until Day 32.

Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a compatible commercially available IPG.

Randomization

Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a first treatment, based on a center-specific computer-generated randomization list.

Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive study number will be automatically assigned. If the patient is eligible, the Investigators will randomize him/her and the eCRF will display a randomization code corresponding to the first free number from the randomization list.

At the beginning of each experimental day, the designated person in charge of DBS programming (unblind), will use the randomization code as PIN code to enter the Physician Programmer (NWKStation), to program the system in cDBS or aDBS according to randomization.

Methods: Statistical methods and data management

Sample size

The objective of the study is to collect data, such as the degree of correlation between GOT in aDBS and cDBS, that will allow calculation of the sample size needed for a pivotal study if the present study confirms the results obtained in a previous trial. This study will randomize at least 15 patients.

Based on the figures obtained in the clinical trial with patients in the “acute” phase [25], and without considering corrections for multiple testing, this sample will allow using exploratory statistics to demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse events (1-2%) are not considered since they were already described by other DBS devices manufacturers and thus expected. Also, rare hardware related are usually observable in studies with longer observation periods than that included in this study (1 month) which is thus not ideal to assess this type of information, which in any case will be collected.

Data collection and management

All study data will be collected and stored through online eCRFs. The system will provide a safe environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data collection that can be shared among different operative units, allowing CRF signature and modifications tracking. A CRO is in charge of data management and quality assurance.

Monitoring

The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).

Data analysis

The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.

The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints (i.e., UDysRS, UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS experimental sessions.

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 treatments.

This is a first in man study not designed to claim efficacy of aDBS or superiority of aDBS over cDBS. Exploratory analysis will be only performed in order to obtain summary data to inform decisions on future clinical development phases. Clinical efficacy will be evaluated through intention-to-treat analysis.

Differences in clinical endpoints when patients receive aDBS or cDBS will be compared, as well as the time courses of UPDRS III scores, motor symptoms fluctuations, “Time Off”/”Time On”, and UDysRS during aDBS and cDBS treatments. Data will be compared with repeated measures general linear model analyses. Tukey's honest significance test will be used for post hoc analysis. Differences will be considered significant at $p<0.05$ for the generation of hypotheses.

Since the protocol is a first in man study for the AlphaDBSipg, it includes various and repeated assessments to better evaluate patient’s tolerability and response. However, these can be burdensome for the patients and minor protocol deviations might be expected. Minor deviations will be included in the analysis whereas major deviations will be excluded.

Ethics and dissemination

Risk-benefit analysis

Potential risks and benefits of aDBS will be clearly explained to the patients in the Informed Consent Form that will be provided at screening, prior to start the study protocol.

If the results of the trial will be promising, PD patients will have a new innovative device for DBS that will allow the delivery of aDBS. In any case, new long-term LFP recordings will be available thanks to the implantation of the AlphaDBS system thus improving the understanding of PD neurophysiology.

Patients treated with aDBS could experience a reduction of symptoms, better quality of life, and a simplification of patient management, reducing the number of visits and calls to the treating neurologist to fine-tune DBS programming settings. In addition, patients involved in the study could experience personal benefits, possibly including: overall reduction of the electrical energy delivered to the tissues, and of the patient's OFF time (compared to cDBS), overall increase of the patient's ON time without troublesome dyskinesia, improvement of efficacy in reducing bradykinesia, rigidity, and tremor (compared to cDBS), reduction "levodopa-induced dyskinesia", improvement in speech, balance, and gait problems related to stimulation.

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. An additional risk may occur in patients choosing to replace the AlphaDBSipg with a commercial IPG at the end of the long-term follow-up.

COVID-19 seriously impacted on the conduction of experimental trials and research activity [39]. A COVID-19 risk assessment, related to the study conduct was prepared, in agreement with the indications provided in the "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic (Version 3, 28/04/2020)" issued by the European Commission and coordinated by EMA.

Informed consent, IEC/IRB approval, and MoH approval

The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013.

The protocol, Subject Information Sheet, Informed Consent Form and the Data Privacy Consent Form were reviewed and approved, prior to initiating any trial-related activity, by the Ethical Committees of each institution involved namely: Comitato Etico Milano Area 2 (Milano), Comitato Etico Fondazione IRCCS Istituto Neurologico C. Besta (Milano), Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino (Torino), Comitato Etico per la Sperimentazione Clinica della Provincia di Padova (Padova); Bioethics Committee at the

National Institute of Oncology of Maria Skłodowska-Curie (Warsaw), De Medisch Ethisch Toetsingscommissie van Maastricht UMC (The Netherlands). As the AlphaDBS System is an investigational device, the trial required the approval, as pre-market study, of competent authorities, namely: the Italian Ministry of Health, Directorate General for Medical Devices and Pharmaceutical service, the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and the Dutch Central Committee on Research Involving Human Subjects.

Patient and Public Involvement

Patients from an Italian PD association provided inputs on the definition of relevant benefits related to the results of this aDBS investigation and on device usability.

References

1 Krack P, Martinez-Fernandez R, del Alamo M, *et al.* Current applications and limitations of surgical treatments for movement disorders: Surgical Treatments For Movement Disorders. *Movement Disorders* 2017;**32**:36–52. doi:10.1002/mds.26890

2 Kleiner-Fisman G, Herzog J, Fisman DN, *et al.* Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 2006;**21 Suppl 14**:S290-304. doi:10.1002/mds.20962

3 Bronstein JM, Tagliati M, Alterman RL, *et al.* Deep Brain Stimulation for Parkinson Disease: An Expert Consensus and Review of Key Issues. *Arch Neurol* 2011;**68**. doi:10.1001/archneurol.2010.260

4 Deuschl G, Schade-Brittinger C, Krack P, *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;**355**:896–908. doi:10.1056/NEJMoa060281

5 Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. *Mov Disord* 2012;**27**:1718–28. doi:10.1002/mds.25214

6 Odekerken VJJ, Boel JA, Schmand BA, *et al.* GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. *Neurology* 2016;**86**:755–61. doi:10.1212/WNL.0000000000002401

7 Cavallieri F, Fraix V, Bove F, *et al.* Predictors of Long-Term Outcome of Subthalamic Stimulation in Parkinson Disease. *Ann Neurol* 2021;:ana.25994. doi:10.1002/ana.25994

8 Koeglsperger T, Palleis C, Hell F, *et al.* Deep Brain Stimulation Programming for Movement Disorders: Current Concepts and Evidence-Based Strategies. *Front Neurol* 2019;**10**:410. doi:10.3389/fneur.2019.00410

9 Chen CC, Brücke C, Kempf F, *et al.* Deep brain stimulation of the subthalamic nucleus: a two-edged sword. *Curr Biol* 2006;**16**:R952-953. doi:10.1016/j.cub.2006.10.013

10 Picillo M, Lozano AM, Kou N, *et al.* Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. *Brain Stimulation* 2016;**9**:425–37. doi:10.1016/j.brs.2016.02.004

11 Priori A, Foffani G, Rossi L, *et al.* Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Exp Neurol* 2013;**245**:77–86. doi:10.1016/j.expneurol.2012.09.013

12 Mitchell KT, Starr PA. Smart neuromodulation in movement disorders. In: *Handbook of Clinical Neurology*. Elsevier 2020. 153–61. doi:10.1016/B978-0-444-63934-9.00012-3

13 Marceglia S, Rossi L, Foffani G, *et al.* Basal ganglia local field potentials: applications in the development of new deep brain stimulation devices for movement disorders. *Expert Rev Med Devices* 2007;**4**:605–14. doi:10.1586/17434440.4.5.605

14 Arlotti M, Rosa M, Marceglia S, *et al.* The adaptive deep brain stimulation challenge. *Parkinsonism Relat Disord* 2016;**28**:12–7. doi:10.1016/j.parkreldis.2016.03.020

15 Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord* 2003;**18**:357–63. doi:10.1002/mds.10358

16 Priori A, Foffani G, Pesenti A, *et al.* Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;**189**:369–79. doi:10.1016/j.expneurol.2004.06.001

17 Marceglia S, Fumagalli M, Priori A. What neurophysiological recordings tell us about cognitive and behavioral functions of the human subthalamic nucleus. *Expert Rev Neurother* 2011;**11**:139–49. doi:10.1586/ern.10.184

18 Marceglia S, Fiorio M, Foffani G, *et al.* Modulation of beta oscillations in the subthalamic area during action observation in Parkinson's disease. *Neuroscience* 2009;**161**:1027–36. doi:10.1016/j.neuroscience.2009.04.018

19 Foffani G, Bianchi AM, Baselli G, *et al.* Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol (Lond)* 2005;**568**:699–711. doi:10.1113/jphysiol.2005.089722

20 Arlotti M, Marceglia S, Foffani G, *et al.* Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology* 2018;**90**:e971–6. doi:10.1212/WNL.0000000000005121

21 Neumann W-J, Degen K, Schneider G-H, *et al.* Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease: Correlation of Subthalamic B Oscillations and PD Symptoms. *Mov Disord* 2016;**31**:1748–51. doi:10.1002/mds.26759

22 Little S, Pogosyan A, Neal S, *et al.* Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;**74**:449–57. doi:10.1002/ana.23951

23 Little S, Beudel M, Zrinzo L, *et al.* Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J Neurol Neurosurg Psychiatr* 2016;**87**:717–21. doi:10.1136/jnnp-2015-310972

24 Rosa M, Arlotti M, Ardolino G, *et al.* Adaptive deep brain stimulation in a freely moving Parkinsonian patient. *Mov Disord* 2015;**30**:1003–5. doi:10.1002/mds.26241

25 Rosa M, Arlotti M, Marceglia S, *et al.* Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Mov Disord* 2017;**32**:628–9. doi:10.1002/mds.26953

26 Little S, Tripoliti E, Beudel M, *et al.* Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. *Journal of Neurology, Neurosurgery & Psychiatry* 2016;:jnnp-2016-313518. doi:10.1136/jnnp-2016-313518

27 Mann JM, Foote KD, Garvan CW, *et al.* Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 2009;**80**:794–7. doi:10.1136/jnnp.2008.159558

28 Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord* 2016;**31**:290–6. doi:10.1002/mds.26500

29 Rosa M, Giannicola G, Servello D, *et al.* Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neurosignals* 2011;**19**:151–62. doi:10.1159/000328508

30 Arlotti M, Palmisano C, Minafra B, *et al.* Monitoring subthalamic oscillations for 24 hours in a freely moving Parkinson's disease patient. *Mov Disord* 2019;**34**:757–9. doi:10.1002/mds.27657

31 Piña-Fuentes D, Little S, Oterdoom M, *et al.* Adaptive DBS in a Parkinson's patient with chronically implanted DBS: A proof of principle. *Mov Disord* 2017;**32**:1253–4. doi:10.1002/mds.26959

32 Piña-Fuentes D, Beudel M, Little S, *et al.* Adaptive deep brain stimulation as advanced Parkinson's disease treatment (ADAPT study): protocol for a pseudo-randomised clinical study. *BMJ Open* 2019;**9**:e029652. doi:10.1136/bmjopen-2019-029652

33 Prenassi M, Arlotti M, Borellini L, *et al.* The Relationship Between Electrical Energy Delivered by Deep Brain Stimulation and Levodopa-Induced Dyskinesias in Parkinson's Disease: A Retrospective Preliminary Analysis. *Front Neurol* 2021;**12**:643841. doi:10.3389/fneur.2021.643841

34 Maier F, Lewis CJ, Eggers C, *et al.* Development and validation of the deep brain stimulation impairment scale (DBS-IS). *Parkinsonism & Related Disorders* 2017;**36**:69–75. doi:10.1016/j.parkreldis.2017.01.002

35 Defer GL, Widner H, Marié RM, *et al.* Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;**14**:572–84. doi:10.1002/1531-8257(199907)14:4<572::aid-mds1005>3.0.co;2-c

36 Arlotti M, Rossi L, Rosa M, *et al.* An external portable device for adaptive deep brain stimulation (aDBS) clinical research in advanced Parkinson's Disease. *Med Eng Phys* 2016;**38**:498–505. doi:10.1016/j.medengphy.2016.02.007

37 Priori A, Foffani G, Rossi L. Apparatus for treating neurological disorders by means of adaptive electro-stimulation retroacted by biopotentials. 2005.

38 Rossi L, Foffani G, Marceglia S, *et al.* An electronic device for artefact suppression in human local field potential recordings during deep brain stimulation. *J Neural Eng* 2007;**4**:96–106. doi:10.1088/1741-2560/4/2/010

39 Priori A, Baisi A, Banderali G, *et al.* The Many Faces of Covid-19 at a Glance: A University Hospital Multidisciplinary Account From Milan, Italy. *Front Public Health* 2021;**8**:575029. doi:10.3389/fpubh.2020.575029

Contributors: SM and CC ideated and designed the protocol, wrote the protocol and documentation for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR, AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures and manuscript. All authors reviewed and approved the final version of this manuscript.

Funding: This study is sponsored by Newronika SpA, a spin off company of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant number is not applicable.

Disclaimer: All the scientific findings derived from this protocol are aimed to be made public through publication of articles in international journals.

Conflict of Interest statement:

AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of Functional Neuromodulation.

Word count: 4410

FIGURES AND FIGURE LEGENDS

Figure 1- The trial time-line in patients participating to both the short and long term follow-up phases: after completing the experimental procedures foreseen in Day 1, Day 2 and Day 3, on Day 4, in the morning, the patient will be discharged with the AlphaDBSipg delivering aDBS or cDBS for 2 weeks. On Day 18 the patient will undergo a clinical assessment. After the assessment the stimulation mode will be switched and the patient will undergo a new clinical assessment. If the second clinical assessment (with changed stimulation mode ON) will be successfully completed, the patient will be discharged with the AlphaDBS device delivering aDBS or cDBS for additional 2 weeks. On Day 32 the patient will undergo the last clinical assessment.

Figure 2 – AlphaDBS system overview

Figure 3- Summary of examinations foreseen at each time point of the experimental sessions (Day 2 and Day 3). Note that timing is indicative and may vary up to 45 min. per session

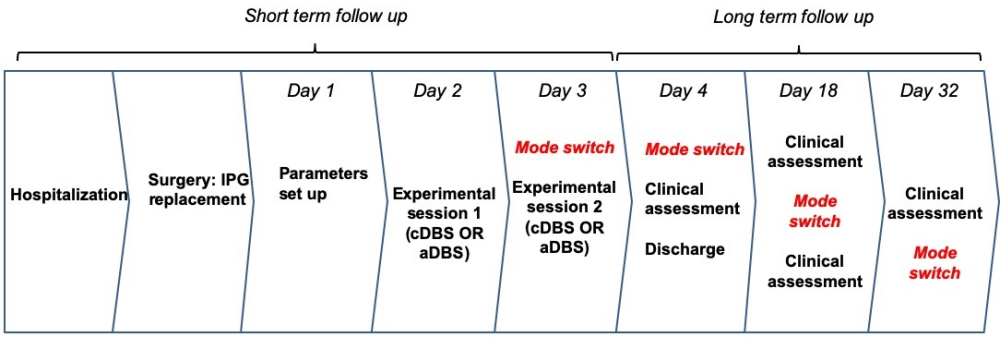

Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

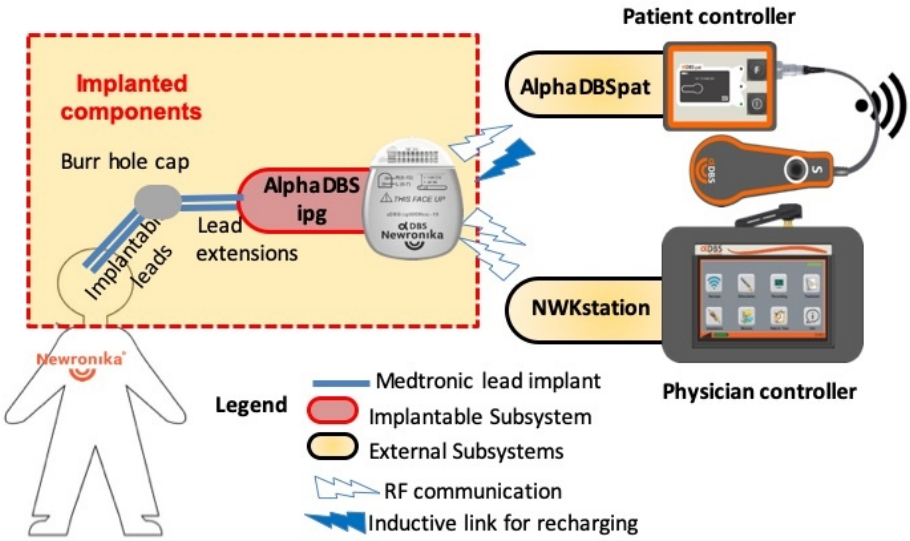

Figure 2 - AlphaDBS system components

264x171mm (72 x 72 DPI)

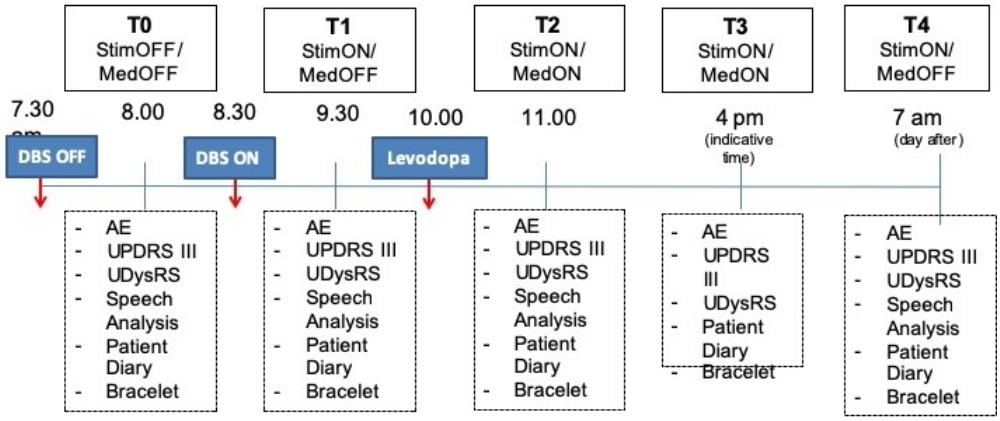

Figure 3 - Short term follow-up: Experimental session details

60x25mm (300 x 300 DPI)

NWK_AlphaDBS_FIM_2019
Usability Questionnaire, version 1.0 dated 23 June 2020

Newronika®

USABILITY QUESTIONNAIRE

Please, indicate your level of satisfaction:

Functions	 1	2	3	4	 5
Do you find it easy to connect the 2 parts of the Patient Programmer?	○	○	○	○	○
Do you find it is easy to turn on the patient remote control (both parts)?	○	○	○	○	○
Do you understand clearly when the neurostimulator is communicating with the patient remote control?	○	○	○	○	○
Do you understand clearly the battery level of the implanted neurostimulator?	○	○	○	○	○
Considerations about screens and alarms					
Do you hear the alarms?	○	○	○	○	○
The information provided in the display of the patient programmer are clear and exhaustive?	○	○	○	○	○
Is it clear what is shown on the display when you connect the 2 parts of the patient remote control?	○	○	○	○	○
Do you understand if the charging procedure is correctly ongoing?	○	○	○	○	○
Do you understand when the charging process is interrupted due to misalignment of the patient remote control with the implanted neurostimulator?	○	○	○	○	○
Do you understand how to check the battery level of your neurostimulator?	○	○	○	○	○

Date: ___/___/_____

NWK_AlphaDBS_FIM_2019
Usability Questionnaire, version 1.0 dated 23 June 2020

Newronika®

Consideration about the patient remote control and its accessories	☹				☺
Device dimension	○	○	○	○	○
Buttons dimension	○	○	○	○	○
Patient remote control portability	○	○	○	○	○
AlphaDBS T-shirt	○	○	○	○	○
AlphaDBS Collar	○	○	○	○	○
User Information	☹				☺
AlphaDBSpat Patient Manual	○	○	○	○	○

Date: ___/___/_____

BMJ Open

A double-blind crossover pilot trial protocol to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049955.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2021
Complete List of Authors:	Marceglia, Sara; Università degli Studi di Trieste, Dipartimento di Ingegneria e Architettura; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UO Neurofisiopatologia Conti, Costanza; Newronika SpA Svanidze, Oleg; Newronika SpA Foffani, Guglielmo; Hospital Universitario HM Puerta del Sur; Fundación del Hospital Nacional de Parapléjicos para la Investigación y la Integración Lozano, Andres M; University of Toronto, Department of Surgery; University Health Network, Department of Surgery Moro, Elena; Grenoble Institute of Neurosciences Volkmann, Jens; University of Wurzburg, Department of Neurology Arlotti, Mattia; Newronika SpA Rossi, Lorenzo; Newronika SpA Priori, Alberto; University of Milan, Department of Health Sciences; ASST Santi Paolo e Carlo
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Parkinson-s disease < NEUROLOGY, NEUROLOGY

A double-blind crossover pilot trial protocol to evaluate the safety and preliminary efficacy of long-term adaptive Deep Brain Stimulation in patients with Parkinson's Disease

Sara Marceglia*[1], Costanza Conti*[2], Oleg Svanidze[2], Guglielmo Foffani[3,4], Andres M Lozano[5,6], Elena Moro[7,8], Jens Volkmann[9], Mattia Arlotti[2], Lorenzo Rossi[2], Alberto Priori[10,11]

[1] *Department of Engineering and Architecture, University of Trieste, 34127 Trieste, Italy*
[2] *Newronika SpA*
[3] *CINAC, Hospital Universitario HM Puerta del Sur, Universidad CEU-San Pablo, Móstoles, Madrid, Spain*
[4] *Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain*
[5] *Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.*
[6] *Krembil Research Institute, University Health Network, Toronto, Ontario, Canada.*
[7] *Grenoble Institute of Neurosciences, INSERM U1216, University Grenoble Alpes, Grenoble, France*
[8] *Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France*
[9] *Department of Neurology, University of Wurzburg, Germany*
[10] *Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, 20142 Milan, Italy*
[11] *ASST Santi Paolo e Carlo, Milan, Italy*

***The first two authors equally contributed to the work**

Corresponding Author:
Prof Sara Marceglia
Dipartimento di Ingegneria e Architettura
Università degli Studi di Trieste

Via Valerio 10
34127 Trieste, Italy
email:smarceglia@units.it
tel: +39 040 5583450

Abstract

Introduction: After several years of brain-sensing technology development and proof-of-concept studies, adaptive deep brain stimulation (aDBS) is ready to better treat Parkinson's disease (PD) using aDBS-capable implantable pulse generators (IPGs). New aDBS devices are capable of continuous sensing of neuronal activity from the subthalamic nucleus (STN) and contemporaneous stimulation automatically adapted to match the patient's clinical state estimated from the analysis of STN activity using proprietary algorithms. Specific studies are necessary to assess superiority of aDBS versus conventional DBS (cDBS) therapy. This protocol describes an original innovative multi-center international study aimed to assess safety and efficacy of aDBS versus cDBS using a new generation of DBS IPG in PD (AlphaDBS system by Newronika SpA, Milan, Italy).

Methods: The study involves six investigational sites (in Italy, Poland, and The Netherlands). The primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when used in cDBS and aDBS mode. Secondary objective will be to evaluate the potential efficacy of aDBS. After eligibility screening, 15 PD patients already implanted with DBS systems and in need of battery replacement will be randomized to enter a two-phases protocol, including a "short-term follow-up" (2-days experimental sessions during hospitalization, 1 day per each mode) and a "long-term follow-up" (1 month at home, 15 days per each mode).

Ethics and Dissemination: The trial was approved as pre-market study by the Italian, Polish, and Dutch Competent Authorities: Bioethics Committee at National Oncology Institute of Maria Skłodowska-Curie – National Research Institute in Warsaw; Comitato Etico Milano Area 2; Comitato Etico IRCCS Istituto Neurologico C. Besta; Comitato Etico interaziendale AOUC Città della Salute e della Scienza – AO Ordine Mauriziano di Torino – ASL Città di Torino; De Medisch Ethisch Toetsingscommissie van Maastricht UMC. The study started enrolling patients in January 2021.

Registration: ClinicalTrials.gov Identifier: NCT04681534

Strengths and limitations of this study

- New study protocols are necessary to ass outcomes form adaptive DBS versus conventional DBS. This specific study assesses the safety and efficacy of aDBS using a new implantable device.
- The study includes patients with Parkinson's disease in the need of IPG replacement, thus overcoming the limits of acute setting (stun effect) seen in de nove DBS patients.
- The use of an implantable device minimizes risks for the patients, as compared to the previously used aDBS external devices.
- The number of patients is low but the results will help to design larger studies.
- This is the first study assessing the good on time with aDBS.

Introduction

Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), but its progress has been hampered by stagnation in methodological, technological, and device development. DBS proved to be effective in improving major PD symptoms in long-term follow-up studies [1–7] and currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor fluctuations, dyskinesias, and refractory tremor [1]. 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 [7].

However, current devices deliver conventional DBS (cDBS) with constant stimulation parameters, not adapting real-time to clinical features, but leaving to reprogramming visits the possibility to improve patient's response and satisfaction [8].

Limitations of cDBS include lack of responsiveness to patients' needs, fixed therapeutic window, repeated hospital visits for stimulation adjustment thus ultimately leading to suboptimal and more expensive therapy [8]. In addition, the excessive and unnecessary electrical stimulation over time may interfere with the residual physiological functions of the basal ganglia, thus contributing [9] 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. Some of these stimulation-related side effects can be reversed by reprogramming [10].

A new approach to overcome cDBS limitations is now represented by adaptive DBS (aDBS) in which the intensity of stimulation is set automatically by real-time adaptation to the patient's clinical state, in a closed-loop fashion [11,12]. The patient's state is estimated by analyzing the local neural activity (local field potentials, LFPs) recorded through the implanted DBS lead while stimulation is ON[13]. Such biosignals, and more specifically the beta frequency band (8-35 Hz), are related to patient's clinical state and to levodopa intake [14–16], and are involved in movement preparation and execution [17–19] and more in general to motor state [20,21].

LFPs-based aDBS has already been tested in humans, demonstrating to be effective in reducing motor symptoms of PD, comparable or even better than cDBS [20,22–25]. In addition, it has been shown that aDBS significantly reduces side effects often associated with DBS therapy such as levodopa-induced dyskinesia [25] and speech impairments [26].

However, the information regarding the long-term safety and efficacy of aDBS remains limited. In fact, to date, studies comparing the efficacy and safety of aDBS to cDBS had intrinsic limitations, due to technical reasons. Initial studies were mostly performed in the immediate postoperative period, after surgery for DBS electrode implant, when the temporary presence of externalized electrodes allows the collection of data using external devices. This approach has several major limitations since symptom improvement may be in part attributed to lesional or implantation effects associated with surgery

[27,28] and the effects of DBS and adverse events in the "acute" (postoperative) period are known to differ from its "chronic" effects [29]. Recently, two studies confirmed the benefits of aDBS in patients at implantable pulse generator (IPG) replacement [30,31], and protocols studying aDBS in these patients have been proposed [32]. In addition, due to the lack of available implantable devices delivering aDBS, studies foresaw short periods of stimulation, with a maximum length of follow up to 24 hours [30]. Even though a new CE-marked implantable device able to record LFPs while DBS is ON (Medtronic Percept™) has been recently introduced, no data on long-term aDBS is available as well as specific protocols to compare aDBS and cDBS.

Here we present the protocol of a double-blind crossover study to assess the safety and potential benefits of aDBS delivered through a new implantable system capable of delivering both cDBS and aDBS, the AlphaDBS System (Newronika S.p.A.). This system will allow, for the first time, to overcome the limitations of the current experimental settings. Furthermore, in agreement with the results of basic research, we expect that the most interesting potential benefits of aDBS will be observed in the long-run, since aDBS may be able to improve axial signs and reduce fluctuations that are measured through patient's diaries and that cannot be assessed in the short-term.

Study objectives

The aim of this study is to assess the safety and the potential efficacy of personalized LFP-based aDBS, using the implantable AlphaDBS System, in PD patients, chronically implanted in the 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, based on the following endpoints:

- Occurrence of device-related adverse events
- Decrease in the Total Electrical Energy Delivered (TEED) to the patient.

As aDBS can be considered as a new treatment, all device related AEs will be reported and analyzed against other devices on the market. Particular attention will be given to unexpected AEs and to those related to aDBS malfunctioning. In addition, TEED is an objective measure of the amount of energy transferred by DBS amplitude to the patient's brain. Previous works showed a significant reduction of TEED in aDBS compared to cDBS. Since TEED is correlated to dyskinesia occurrence [33], which is one of the stimulation-related side effects that aDBS may be able to control [25], TEED was also included as a quantitative safety endpoint.

Since this is the first study on the use of AlphaDBS System and on the chronic application of its aDBS implementation, 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 MDS-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 (see supplementary materials).
Exploratory objectives include evaluation of DBS associated deficits, through the DBS Impairment Scale (DBS-IS) [34] and evaluation of the effects of aDBS on speech.
Data collection using non-single patient use items, such as wearable systems and/or microphones that need to be sanitized, may be stopped in case of local COVID-19 emergency.

Study design

This study, sponsored by Newronika SpA, was designed as a crossover trial using cDBS as a control.
The study protocol is organized in two phases: the "short-term follow-up" and the "long-term follow-up" (Figure 1). During the "short-term follow-up", fully eligible patients will be randomized to undergo a 2-day experimental sessions (i.e. one per each type of stimulation mode, cDBS and aDBS), during hospitalization, to collect information on safety and efficacy endpoints as assessed by experienced neurologists.
Patients who will not experience severe side effects during the "short-term follow-up" and who will be deemed suitable by the neurologist, will be eligible to continue in the "long-term follow-up" phase (1 month) in their "home" environment. The AlphaDBS System will deliver the stimulation in aDBS or cDBS mode, for two weeks in each mode, following the same order as in the "short-term follow-up".

Methods and procedure

Study centers

The study involves six investigational sites (in Italy, Poland, and The Netherlands). In particular, four centers are located in Italy (the University of Padua, the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, the IRCCS Istituto Neurologico Besta of Milan, and the AOU Città della Salute e della Scienza of Torino), one in Poland (Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie, Warsaw), and one in The Netherlands (Maastricht UMC+, Maastricht).

Inclusion criteria

All patients included in the study must have been already implanted with DBS electrodes in the past. At the time of their first DBS implant (electrodes + first IPG now to be replaced), they were selected for DBS indication on the basis of the CAPSIT guidelines (Core Assessment Program for Surgical Interventional Therapies in PD, CAPSIT-PD, [35]). Even though some of the listed inclusion/exclusion criteria are similar to that used for DBS indication, we decided to reconsider them because of the time elapsed from DBS first implant.

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

Exclusion criteria

- Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score <10);
- 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.)
- 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.)
- Need to replace or reposition the leads during the IPG replacement procedure
- Patients with > 10 recurrent falls experienced in the 3 months prior to consent
- Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min
- Patients taking less than one levodopa dose per day
- Patients with no LFPs recorded intraoperatively from any contacts pair, during the IPG replacement procedure
- Pregnant or breastfeeding women.

According to exclusion criterion in the second bullet point, the neurologist has the possibility to exclude patients whenever a condition reducing the compliance is observed, including moderate cognitive impairment.

Device description

The AlphaDBS System is a DBS system that includes the possibility for the neurologist to program the stimulation in conventional mode (cDBS) or in adaptive, closed-loop, mode (aDBS). When the AlphaDBS System is used in aDBS mode, it delivers DBS stimulation using an intelligent biofeedback

mechanism to automatically modulate stimulation. AlphaDBS is able to record and analyze in real-time LFPs while DBS in ON from the same implanted lead, and automatically adjust stimulation.

The AlphaDBS System is composed of different subsystems (Figure 2): the AlphaDBSipg (IPG delivering stimulation in aDBS or cDBS mode and recording/analyzing LFPs from implanted DBS leads); AlphaDBSpat (external patient controller); NWKstation (external physician controller).

The AlphaDBSipg is an active implantable medical device that applies cDBS/aDBS. It is powered by a hermetically sealed rechargeable battery within a titanium case. The AlphaDBS System, manufactured by Newronika SpA (Milan, Italy), is currently under final stages of CE-mark certification procedures.

In cDBS mode, the AlphaDBSipg, with 16 independent stimulation current controlled outputs, delivers asymmetric biphasic balanced constant current pulse train. Stimulation can be delivered in bipolar or monopolar configuration by selecting a contact pair or one contact in each of the two available leads (stimulation parameters: pulse width (us), amplitude (V), and frequency (Hz)). In monopolar stimulation, the reference electrode is simulated by the IPG enclosure.

In aDBS mode, an adaptive algorithm will use LFP signals from implanted electrodes extracting information to decrease the energy of stimulation (amplitude) when the patient is responding appropriately to pharmacological therapy and increasing the energy when the patient's symptoms are not well controlled. The algorithm that will be used in aDBS mode will be personalized based on LFP modulation in the 13-35 Hz frequency band (beta band), as described elsewhere [36].

The AlphaDBS System has several innovative features that implement a distributed architecture allowing data collection and management that make it a reliable platform for aDBS and closed-loop neuromodulation applications. Major innovations reside in the technology for artifact-free recordings [36–38] that is stimulation agnostic, electrode configuration independent, and needless for back-end processing. This implies that LFPs can be recorded with stimulation ON from all contact pairs, not necessarily symmetrical around the stimulation contact, and with different stimulation types. In addition, the artifact rejection methodology is implemented at the chip level and not at the system level, thus leaving the whole computational capacity free for closed-loop algorithm implementation. Another important feature is the ability of the system both to provide on-demand real-time streaming of LFPs both in ON and OFF without the need of additional receivers worn by the patient, but using directly the clinician controller (NWKStation) and to provide continuous embedded data storage that is always ON 24/7 whatever the stimulation mode (OFF, cDBS, aDBS). Thanks to the data management infrastructure, the embedded data storage guarantees no data loss for memory overwriting because data are automatically downloaded to the patient controller (AlphaDBSpat) during recharging, using the same device. This is crucial to allow full biomarker tracking for future aDBS optimization.

Evaluations and procedures

After providing consent, each patient will undergo a Screening Period, during which demographic information and additional information on the medical management will be collected. Each patient will undergo a series of screening evaluations, including: evaluation of battery level, medical history, physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [35], measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery), assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be evaluated after the administration of a LEED morning dose + 30%.

Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization will be conducted in agreement with local standard practice for IPG replacement.

On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be connected to temporary extensions in order to check the integrity of the leads and the occurrence of ECG artifacts. The patients with ECG artifacts impairing LFP recording will ~~not~~ be excluded and will receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.

The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS current titration session will be performed to establish both the optimal cDBS parameters with AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the personalized beta band and peak previously defined.

At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to aDBS or cDBS treatment will take place on the following day.

On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one stimulation mode per day, according to the randomization schedule.

The experimental session will start around 7:30 am (expected time) and will last for about nine hours (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next washout period in the same mode.

At the beginning of the session, the stimulation will be switched off for at least 30 minutes of stimulation washout (stim-OFF/med-OFF condition), and then switched on.

Each experimental session will include the following assessments:

- T0: before the administration of the morning dopaminergic therapy and after at least 30 minutes of stimulation washout (stim-OFF/med-OFF) - UDysRS, MDS-UPDRS III and adverse events recording, speech analysis

- T1: before the administration of the morning dopaminergic therapy and after 1 hour of active stimulation (stim-ON/med-OFF) – UDysRS, MDS-UPDRS III and adverse event recording, speech analysis
- T2: around 1 hour after dopaminergic therapy administration, when the effect of dopaminergic therapy will reach its best effect (stim-ON/med-ON) – UDysRS, MDS-UPDRS III, adverse event recording, speech analysis
- T3: in the afternoon, around 4 pm or if the patient therapeutic schedule foresees a second dopaminergic therapy, when the effect of the therapy will reach its best effect (stim-ON/med-ON)- UDysRS, MDS-UPDRS III and adverse event recording
- T4: the following day (Day 3 or Day 4), in the morning, before starting any experimental procedure, when the stimulation is still ON, and before the administration of the morning dopaminergic therapy (stim-ON/med-OFF) - UDysRS, MDS-UPDRS III and adverse events recording, speech analysis.

The timing of the assessments is indicative and variations up to 45 minutes are allowed.

Throughout the experimental session, to monitor motor symptoms fluctuations, the patient will wear a bracelet equipped with a three-axial accelerometer and will fill in his/her Patient's Diary, for the whole duration of the experimental session. Speech analysis will be performed with Semantic and phonemic evaluations will be recorded with the VF test (Delis-Kaplan Executive Function System), and control word repetition tasks.

The parameters to calculate the TEED at T4 will be automatically collected from the AlphaDBS System.

On Day 4, if the neurologist will deem the patient suitable for the "long-term follow-up" phase, the patient will undergo another clinical assessment and will be discharged. The clinical assessment will take place about 1 hour after morning dopaminergic therapy administration, when the effect of the therapy will reach its best effect (stim-ON/med-ON), administering UDysRS and MDS-UPDRS III scales and examining possible side effects. After the visit, the stimulation will be automatically switched to the stimulation mode, randomly allocated on Day 2.

After the examination, patients (blinded to treatment) will receive the training on how to use the device, and then be discharged from the hospital and sent to their "home" environment for two weeks in each stimulation mode.

During this follow-up period, a research fellow/nurse will monitor the patient remotely every day to assess the patient status, check Concomitant Medications and record adverse events.

After two weeks of treatment, on Day 18, the patient will provide diaries completed in the last three days before the visit and will undergo a clinical assessment (performed by a blinded neurologist) in stim ON-med ON including UDysRS, MDS-UPDRS III and DBS-IS scales, collection of possible side effects, speech analysis, and TEED (automatically collected from the AlphaDBSipg). Also, the patient/caregiver will provide his/her inputs related to the System usability for what concerns the IPG recharging process.

After the visit, the stimulation will be automatically switched to the other stimulation mode (as in Day 3), and the patient will be sent home. The same protocol will be followed for two weeks until Day 32. Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a compatible commercially available IPG.

Randomization

Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a first treatment, based on a center-specific computer-generated randomization list.

Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive study number will be automatically assigned. If the patient is eligible, the Investigators will randomize him/her and the eCRF will display a randomization code corresponding to the first free number from the randomization list.

At the beginning of each experimental day, the designated person in charge of DBS programming (unblind), will use the randomization code as PIN code to enter the Physician Programmer (NWKStation), to program the system in cDBS or aDBS according to randomization.

Methods: Statistical methods and data management

Sample size

The objective of the study is to collect data, such as the degree of correlation between GOT in aDBS and cDBS, that will allow calculation of the sample size needed for a pivotal study if the present study confirms the results obtained in a previous trial. This study will randomize at least 15 patients.

Based on the figures obtained in the clinical trial with patients in the “acute” phase [25], and without considering corrections for multiple testing, this sample will allow using exploratory statistics to demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse events (1-2%) are not considered since they were already described by other DBS devices manufacturers and thus expected. Also, rare hardware related are usually observable in studies with longer observation periods than that included in this study (1 month) which is thus not ideal to assess this type of information, which in any case will be collected.

Data collection and management

All study data will be collected and stored through online eCRFs. The system will provide a safe environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data

collection that can be shared among different operative units, allowing CRF signature and modifications tracking. A CRO is in charge of data management and quality assurance.

Monitoring

The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).

Data analysis

The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.

The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints (i.e., UDysRS, MDS-UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS experimental sessions.

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 treatments.

This is a first in man study not designed to claim efficacy of aDBS or superiority of aDBS over cDBS. Exploratory analysis will be only performed in order to obtain summary data to inform decisions on future clinical development phases. Clinical efficacy will be evaluated through intention-to-treat analysis.

Differences in clinical endpoints when patients receive aDBS or cDBS will be compared, as well as the time courses of MDS-UPDRS III scores, motor symptoms fluctuations, “Time Off”/”Time On”, and UDysRS during aDBS and cDBS treatments. Data will be compared with repeated measures general linear model analyses. Tukey's honest significance test will be used for post hoc analysis. Differences will be considered significant at $p<0.05$ for the generation of hypotheses.

Since the protocol is a first in man study for the AlphaDBSipg, it includes various and repeated assessments to better evaluate patient’s tolerability and response. However, these can be burdensome for the patients and minor protocol deviations might be expected. Minor deviations will be included in the analysis whereas major deviations will be excluded.

Ethics and dissemination

Risk-benefit analysis

Potential risks and benefits of aDBS will be clearly explained to the patients in the Informed Consent Form that will be provided at screening, prior to start the study protocol.

If the results of the trial will be promising, PD patients will have a new innovative device for DBS that will allow the delivery of aDBS. In any case, new long-term LFP recordings will be available thanks to the implantation of the AlphaDBS system thus improving the understanding of PD neurophysiology.

Patients treated with aDBS could experience a reduction of symptoms, better quality of life, and a simplification of patient management, reducing the number of visits and calls to the treating neurologist to fine-tune DBS programming settings. In addition, patients involved in the study could experience personal benefits, possibly including: overall reduction of the electrical energy delivered to the tissues, and of the patient's OFF time (compared to cDBS), overall increase of the patient's ON time without troublesome dyskinesia, improvement of efficacy in reducing bradykinesia, rigidity, and tremor (compared to cDBS), reduction "levodopa-induced dyskinesia", improvement in speech, balance, and gait problems related to stimulation.

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. An additional risk may occur in patients choosing to replace the AlphaDBSipg with a commercial IPG at the end of the long-term follow-up.

COVID-19 seriously impacted on the conduction of experimental trials and research activity [39]. A COVID-19 risk assessment, related to the study conduct was prepared, in agreement with the indications provided in the "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic (Version 3, 28/04/2020)" issued by the European Commission and coordinated by EMA.

Informed consent, IEC/IRB approval, and MoH approval

The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013.

The protocol, Subject Information Sheet, Informed Consent Form and the Data Privacy Consent Form were reviewed and approved, prior to initiating any trial-related activity, by the Ethical Committees of each institution involved namely: Comitato Etico Milano Area 2 (Milano), Comitato Etico Fondazione IRCCS Istituto Neurologico C. Besta (Milano), Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino (Torino), Comitato Etico

per la Sperimentazione Clinica della Provincia di Padova (Padova); Bioethics Committee at the National Institute of Oncology of Maria Skłodowska-Curie (Warsaw), De Medisch Ethisch Toetsingscommissie van Maastricht UMC (The Netherlands). As the AlphaDBS System is an investigational device, the trial required the approval, as pre-market study, of competent authorities, namely: the Italian Ministry of Health, Directorate General for Medical Devices and Pharmaceutical service, the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and the Dutch Central Committee on Research Involving Human Subjects.

Patient and Public Involvement

Patients from an Italian PD association provided inputs on the definition of relevant benefits related to the results of this aDBS investigation and on device usability.

References

1 Krack P, Martinez-Fernandez R, del Alamo M, *et al.* Current applications and limitations of surgical treatments for movement disorders: Surgical Treatments For Movement Disorders. *Movement Disorders* 2017;**32**:36–52. doi:10.1002/mds.26890

2 Kleiner-Fisman G, Herzog J, Fisman DN, *et al.* Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 2006;**21 Suppl 14**:S290-304. doi:10.1002/mds.20962

3 Bronstein JM, Tagliati M, Alterman RL, *et al.* Deep Brain Stimulation for Parkinson Disease: An Expert Consensus and Review of Key Issues. *Arch Neurol* 2011;**68**. doi:10.1001/archneurol.2010.260

4 Deuschl G, Schade-Brittinger C, Krack P, *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;**355**:896–908. doi:10.1056/NEJMoa060281

5 Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. *Mov Disord* 2012;**27**:1718–28. doi:10.1002/mds.25214

6 Odekerken VJJ, Boel JA, Schmand BA, *et al.* GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. *Neurology* 2016;**86**:755–61. doi:10.1212/WNL.0000000000002401

7 Cavallieri F, Fraix V, Bove F, *et al.* Predictors of Long-Term Outcome of Subthalamic Stimulation in Parkinson Disease. *Ann Neurol* 2021;:ana.25994. doi:10.1002/ana.25994

8 Koeglsperger T, Palleis C, Hell F, *et al.* Deep Brain Stimulation Programming for Movement Disorders: Current Concepts and Evidence-Based Strategies. *Front Neurol* 2019;**10**:410. doi:10.3389/fneur.2019.00410

9 Chen CC, Brücke C, Kempf F, *et al.* Deep brain stimulation of the subthalamic nucleus: a two-edged sword. *Curr Biol* 2006;**16**:R952-953. doi:10.1016/j.cub.2006.10.013

10 Picillo M, Lozano AM, Kou N, *et al.* Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. *Brain Stimulation* 2016;**9**:425–37. doi:10.1016/j.brs.2016.02.004

11 Priori A, Foffani G, Rossi L, *et al.* Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Exp Neurol* 2013;**245**:77–86. doi:10.1016/j.expneurol.2012.09.013

12 Mitchell KT, Starr PA. Smart neuromodulation in movement disorders. In: *Handbook of Clinical Neurology*. Elsevier 2020. 153–61. doi:10.1016/B978-0-444-63934-9.00012-3

13 Marceglia S, Rossi L, Foffani G, *et al.* Basal ganglia local field potentials: applications in the development of new deep brain stimulation devices for movement disorders. *Expert Rev Med Devices* 2007;**4**:605–14. doi:10.1586/17434440.4.5.605

14 Arlotti M, Rosa M, Marceglia S, *et al.* The adaptive deep brain stimulation challenge. *Parkinsonism Relat Disord* 2016;**28**:12–7. doi:10.1016/j.parkreldis.2016.03.020

15 Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord* 2003;**18**:357–63. doi:10.1002/mds.10358

16 Priori A, Foffani G, Pesenti A, *et al.* Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;**189**:369–79. doi:10.1016/j.expneurol.2004.06.001

17 Marceglia S, Fumagalli M, Priori A. What neurophysiological recordings tell us about cognitive and behavioral functions of the human subthalamic nucleus. *Expert Rev Neurother* 2011;**11**:139–49. doi:10.1586/ern.10.184

18 Marceglia S, Fiorio M, Foffani G, *et al.* Modulation of beta oscillations in the subthalamic area during action observation in Parkinson's disease. *Neuroscience* 2009;**161**:1027–36. doi:10.1016/j.neuroscience.2009.04.018

19 Foffani G, Bianchi AM, Baselli G, *et al.* Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol (Lond)* 2005;**568**:699–711. doi:10.1113/jphysiol.2005.089722

20 Arlotti M, Marceglia S, Foffani G, *et al.* Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology* 2018;**90**:e971–6. doi:10.1212/WNL.0000000000005121

21 Neumann W-J, Degen K, Schneider G-H, *et al.* Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease: Correlation of Subthalamic B Oscillations and PD Symptoms. *Mov Disord* 2016;**31**:1748–51. doi:10.1002/mds.26759

22 Little S, Pogosyan A, Neal S, *et al.* Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;**74**:449–57. doi:10.1002/ana.23951

23 Little S, Beudel M, Zrinzo L, *et al.* Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J Neurol Neurosurg Psychiatr* 2016;**87**:717–21. doi:10.1136/jnnp-2015-310972

24 Rosa M, Arlotti M, Ardolino G, *et al.* Adaptive deep brain stimulation in a freely moving Parkinsonian patient. *Mov Disord* 2015;**30**:1003–5. doi:10.1002/mds.26241

25 Rosa M, Arlotti M, Marceglia S, *et al.* Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Mov Disord* 2017;**32**:628–9. doi:10.1002/mds.26953

26 Little S, Tripoliti E, Beudel M, *et al.* Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. *Journal of Neurology, Neurosurgery & Psychiatry* 2016;:jnnp-2016-313518. doi:10.1136/jnnp-2016-313518

27 Mann JM, Foote KD, Garvan CW, *et al.* Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 2009;**80**:794–7. doi:10.1136/jnnp.2008.159558

28 Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord* 2016;**31**:290–6. doi:10.1002/mds.26500

29 Rosa M, Giannicola G, Servello D, *et al.* Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neurosignals* 2011;**19**:151–62. doi:10.1159/000328508

30 Arlotti M, Palmisano C, Minafra B, *et al.* Monitoring subthalamic oscillations for 24 hours in a freely moving Parkinson's disease patient. *Mov Disord* 2019;**34**:757–9. doi:10.1002/mds.27657

31 Piña-Fuentes D, Little S, Oterdoom M, *et al.* Adaptive DBS in a Parkinson's patient with chronically implanted DBS: A proof of principle. *Mov Disord* 2017;**32**:1253–4. doi:10.1002/mds.26959

32 Piña-Fuentes D, Beudel M, Little S, *et al.* Adaptive deep brain stimulation as advanced Parkinson's disease treatment (ADAPT study): protocol for a pseudo-randomised clinical study. *BMJ Open* 2019;**9**:e029652. doi:10.1136/bmjopen-2019-029652

33 Prenassi M, Arlotti M, Borellini L, *et al.* The Relationship Between Electrical Energy Delivered by Deep Brain Stimulation and Levodopa-Induced Dyskinesias in Parkinson's Disease: A Retrospective Preliminary Analysis. *Front Neurol* 2021;**12**:643841. doi:10.3389/fneur.2021.643841

34 Maier F, Lewis CJ, Eggers C, *et al.* Development and validation of the deep brain stimulation impairment scale (DBS-IS). *Parkinsonism & Related Disorders* 2017;**36**:69–75. doi:10.1016/j.parkreldis.2017.01.002

35 Defer GL, Widner H, Marié RM, *et al.* Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;**14**:572–84. doi:10.1002/1531-8257(199907)14:4<572::aid-mds1005>3.0.co;2-c

36 Arlotti M, Rossi L, Rosa M, *et al.* An external portable device for adaptive deep brain stimulation (aDBS) clinical research in advanced Parkinson's Disease. *Med Eng Phys* 2016;**38**:498–505. doi:10.1016/j.medengphy.2016.02.007

37 Priori A, Foffani G, Rossi L. Apparatus for treating neurological disorders by means of adaptive electro-stimulation retroacted by biopotentials. 2005.

38 Rossi L, Foffani G, Marceglia S, *et al.* An electronic device for artefact suppression in human local field potential recordings during deep brain stimulation. *J Neural Eng* 2007;**4**:96–106. doi:10.1088/1741-2560/4/2/010

39 Priori A, Baisi A, Banderali G, *et al.* The Many Faces of Covid-19 at a Glance: A University Hospital Multidisciplinary Account From Milan, Italy. *Front Public Health* 2021;**8**:575029. doi:10.3389/fpubh.2020.575029

Contributors: SM and CC ideated and designed the protocol, wrote the protocol and documentation for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR, AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures and manuscript. All authors reviewed and approved the final version of this manuscript.

Funding: This study is sponsored by Newronika SpA, a spin off company of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant number is not applicable.

Disclaimer: All the scientific findings derived from this protocol are aimed to be made public through publication of articles in international journals.

Conflict of Interest statement:

AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of Functional Neuromodulation.

Word count: 4410

FIGURES AND FIGURE LEGENDS

Figure 1- The trial time-line in patients participating to both the short and long term follow-up phases: after completing the experimental procedures foreseen in Day 1, Day 2 and Day 3, on Day 4, in the morning, the patient will be discharged with the AlphaDBSipg delivering aDBS or cDBS for 2 weeks. On Day 18 the patient will undergo a clinical assessment. After the assessment the stimulation mode will be switched and the patient will undergo a new clinical assessment. If the second clinical assessment (with changed stimulation mode ON) will be successfully completed, the patient will be discharged with the AlphaDBS device delivering aDBS or cDBS for additional 2 weeks. On Day 32 the patient will undergo the last clinical assessment.

Figure 2 – AlphaDBS system overview

Figure 3- Summary of examinations foreseen at each time point of the experimental sessions (Day 2 and Day 3). Note that timing is indicative and may vary up to 45 min. per session

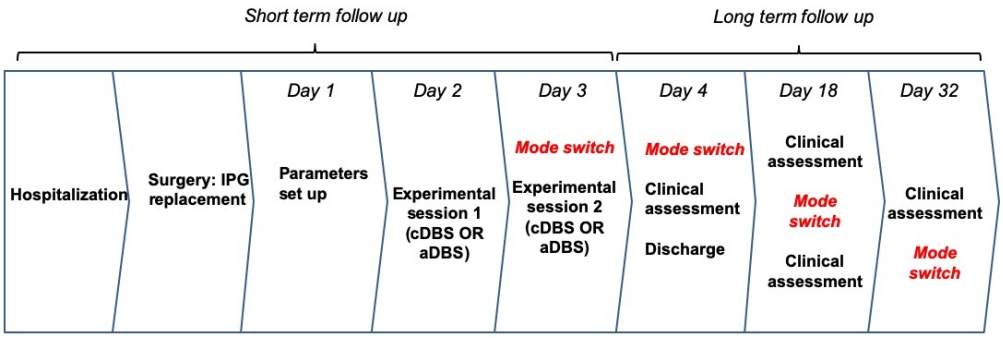

Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

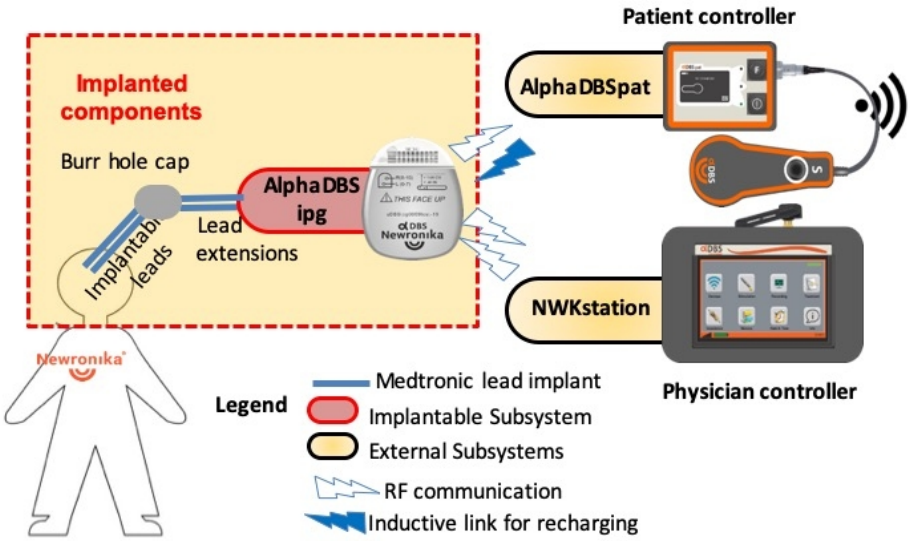

Figure 2 - AlphaDBS system components

264x171mm (72 x 72 DPI)

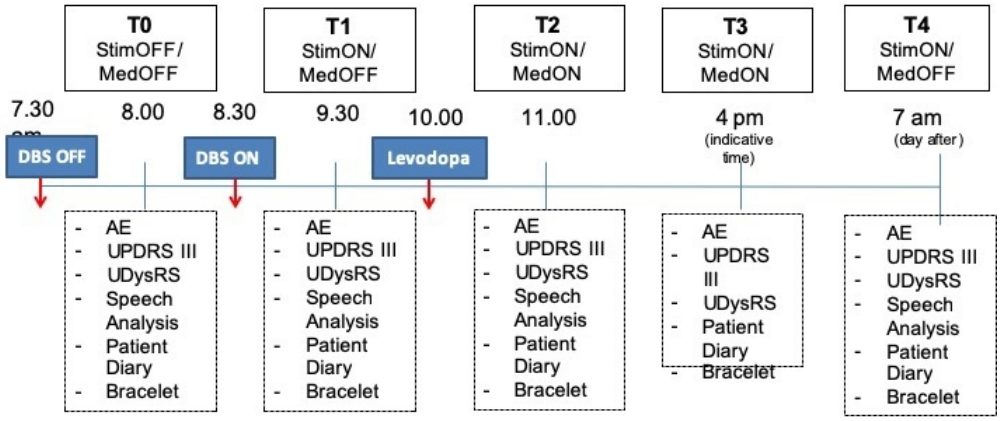

Figure 3 - Short term follow-up: Experimental session details

60x25mm (300 x 300 DPI)

NWK_AlphaDBS_FIM_2019
Usability Questionnaire, version 1.0 dated 23 June 2020

Newronika®

USABILITY QUESTIONNAIRE

Please, indicate your level of satisfaction:

Functions	 1	2	3	4	 5
Do you find it easy to connect the 2 parts of the Patient Programmer?	○	○	○	○	○
Do you find it is easy to turn on the patient remote control (both parts)?	○	○	○	○	○
Do you understand clearly when the neurostimulator is communicating with the patient remote control?	○	○	○	○	○
Do you understand clearly the battery level of the implanted neurostimulator?	○	○	○	○	○
Considerations about screens and alarms					
Do you hear the alarms?	○	○	○	○	○
The information provided in the display of the patient programmer are clear and exhaustive?	○	○	○	○	○
Is it clear what is shown on the display when you connect the 2 parts of the patient remote control?	○	○	○	○	○
Do you understand if the charging procedure is correctly ongoing?	○	○	○	○	○
Do you understand when the charging process is interrupted due to misalignment of the patient remote control with the implanted neurostimulator?	○	○	○	○	○
Do you understand how to check the battery level of your neurostimulator?	○	○	○	○	○

Date: ___/___/_____

NWK_AlphaDBS_FIM_2019
Usability Questionnaire, version 1.0 dated 23 June 2020

Newronika®

Consideration about the patient remote control and its accessories	☹				☺
Device dimension	○	○	○	○	○
Buttons dimension	○	○	○	○	○
Patient remote control portability	○	○	○	○	○
AlphaDBS T-shirt	○	○	○	○	○
AlphaDBS Collar	○	○	○	○	○
User Information	☹				☺
AlphaDBSpat Patient Manual	○	○	○	○	○

Date: ___/___/_____