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## 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

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# 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

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## 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 assess outcomes from 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 novo 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

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3 [27,28] and the effects of DBS and adverse events in the “acute” (postoperative) period are known to  
4 differ from its “chronic” effects [29]. Recently, two studies confirmed the benefits of aDBS in patients  
5 at implantable pulse generator (IPG) replacement [30,31], and protocols studying aDBS in these  
6 patients have been proposed [32]. In addition, due to the lack of available implantable devices delivering  
7 aDBS, studies foresaw short periods of stimulation, with a maximum length of follow up to 24 hours  
8 [30]. Even though a new CE-marked implantable device able to record LFPs while DBS is ON  
9 (Medtronic Percept™) has been recently introduced, no data on long-term aDBS is available as well as  
10 specific protocols to compare aDBS and cDBS.

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

### 28 **Study objectives**

29 The aim of this study is to assess the safety and the potential efficacy of personalized LFP-based aDBS,  
30 using the implantable AlphaDBS System, in PD patients, chronically implanted in the STN for DBS, at  
31 the time of IPG replacement.

32 The primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when  
33 used in cDBS and aDBS mode, based on the following endpoints:

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

36 Secondary objective will be to evaluate the potential efficacy of aDBS and AlphaDBS System usability.  
37 Efficacy will be evaluated from the following secondary measures:

- 38 • Evaluation of PD-related motor symptoms (i.e., bradykinesia, rigidity and tremor at rest) and  
39 their fluctuations through repeated clinical assessments (using the Unified Parkinson's Disease  
40 Rating Scale -UPDRS- part III)
- 41 • Evaluation of dyskinesia and their fluctuations through repeated clinical assessments (using the  
42 Unified Dyskinesia Rating Scale – UDysRS and wearable Systems)
- 43 • Evaluation of “Time On” with and without dyskinesia and “Time Off”, assessed through Patient  
44 Diary.

45 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 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

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3 appropriately to pharmacological therapy and increasing the energy when the patient's symptoms are  
4 not well controlled. The algorithm that will be used in aDBS mode will be personalized based on LFP  
5 modulation in the 13-35 Hz frequency band (beta band), as described elsewhere [34].  
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### 8 9 ***Evaluations and procedures***

11 After providing consent, each patient will undergo a Screening Period, during which demographic  
12 information and additional information on the medical management will be collected. Each patient will  
13 undergo a series of screening evaluations, including: evaluation of battery level, medical history,  
14 physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major  
15 psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [33],  
16 measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery),  
17 assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving  
18 informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-  
19 OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be  
20 evaluated after the administration of a LEED morning dose + 30%.  
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23 Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization  
24 will be conducted in agreement with local standard practice for IPG replacement.  
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27 On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be  
28 connected to temporary extensions in order to check the integrity of the leads and the occurrence of  
29 ECG artifacts. The patients with ECG artifacts impairing LFP recording will not be excluded and will  
30 receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.  
31  
32

33 The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be  
34 recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available  
35 electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best  
36 recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS  
37 current titration session will be performed to establish both the optimal cDBS parameters with  
38 AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the  
39 personalized beta band and peak previously defined.  
40  
41

42 At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to  
43 aDBS or cDBS treatment will take place on the following day.  
44  
45

46 On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one  
47 stimulation mode per day, according to the randomization schedule.  
48  
49

50 The experimental session will start around 7:30 am (expected time) and will last for about nine hours  
51 (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next  
52 washout period in the same mode.  
53  
54

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

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2  
3 stim ON-med ON including UDysRS, UPDRS III and DBS-IS scales, collection of possible side effects,  
4 speech analysis, and TEED (automatically collected from the AlphaDBSipg). Also, the  
5 patient/caregiver will provide his/her inputs related to the System usability for what concerns the IPG  
6 recharging process.  
7

8  
9 After the visit, the stimulation will be automatically switched to the other stimulation mode (as in Day  
10 3), and the patient will be sent home. The same protocol will be followed for two weeks until Day 32.  
11 Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a  
12 compatible commercially available IPG.  
13  
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15

### 16 17 *Randomization*

18  
19 Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a  
20 first treatment, based on a center-specific computer-generated randomization list.  
21

22 Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive  
23 study number will be automatically assigned. If the patient is eligible, the Investigators will randomize  
24 him/her and the eCRF will display a randomization code corresponding to the first free number from  
25 the randomization list.  
26  
27

28 At the beginning of each experimental day, the designated person in charge of DBS programming  
29 (unblind), will use the randomization code as PIN code to enter the Physician Programmer  
30 (NWKStation), to program the system in cDBS or aDBS according to randomization.  
31  
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## 34 35 **Methods: Statistical methods and data management**

### 36 37 *Sample size*

38 The objective of the study is to collect data that will allow calculation of the sample size needed for a  
39 pivotal study if the present study confirms the results obtained in a previous trial. This study will  
40 randomize at least 15 patients.  
41

42 Based on the figures obtained in the clinical trial with patients in the “acute” phase [25], and without  
43 considering corrections for multiple testing, this sample will allow using exploratory statistics to  
44 demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for  
45 an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05  
46 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the  
47 higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the  
48 patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse  
49 events (1-2%) are not considered since they were already described by other DBS devices  
50 manufacturers and thus expected.  
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### 59 60 *Data collection and management*

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3 All study data will be collected and stored through online eCRFs. The system will provide a safe  
4 environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data  
5 collection that can be shared among different operative units, allowing CRF signature and modifications  
6 tracking. A CRO is in charge of data management and quality assurance.  
7  
8  
9

### 10 **Monitoring**

11  
12  
13 The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO  
14 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will  
15 maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or  
16 retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the  
17 Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study  
18 Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot  
19 be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard  
20 Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).  
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### 28 **Data analysis**

29  
30 The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.  
31 The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints  
32 (i.e., UDysRS, UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS experimental  
33 sessions.  
34  
35 Safety will be evaluated on all patients randomized and receiving at least one of the treatments. It will  
36 include the comparison of: 1) TEED delivered to the patient during aDBS and cDBS experimental  
37 sessions, 2) AEs during the 2 treatments.  
38  
39 This is a first in man study not designed to claim efficacy of aDBS or superiority of aDBS over cDBS.  
40 Exploratory analysis will be only performed in order to obtain summary data to inform decisions on  
41 future clinical development phases. Clinical efficacy will be evaluated through intention-to-treat  
42 analysis.  
43  
44 Differences in clinical endpoints when patients receive aDBS or cDBS will be compared, as well as the  
45 time courses of UPDRS III scores, motor symptoms fluctuations, "Time Off"/"Time On", and UDysRS  
46 during aDBS and cDBS treatments. Data will be compared with repeated measures general linear model  
47 analyses. Tukey's honest significance test will be used for post hoc analysis. Differences will be  
48 considered significant at  $p < 0.05$  for the generation of hypotheses.  
49  
50 Since the protocol is a first in man study for the AlphaDBSipg, it includes various and repeated  
51 assessments to better evaluate patient's tolerability and response. However, these can be burdensome  
52 for the patients and minor protocol deviations might be expected. Minor deviations will be included in  
53 the analysis whereas major deviations will be excluded.  
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## **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 64<sup>th</sup> 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



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

22 Patients from an Italian PD association provided inputs on the definition of relevant benefits related to  
23 the results of this aDBS investigation and on device usability.  
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3 **Contributors:** SM and CC ideated and designed the protocol, wrote the protocol and documentation  
4 for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR,  
5 AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures  
6 and manuscript. All authors reviewed and approved the final version of this manuscript.  
7

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9 Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant  
10 number is not applicable.  
11

12 **Disclaimer:** All the scientific findings derived from this protocol are aimed to be made public  
13 through publication of articles in international journals.  
14

15 **Conflict of Interest statement:**

16 AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's  
17 scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are  
18 stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member  
19 of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of  
20 Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received  
21 honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston  
22 Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has  
23 served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of  
24 Functional Neuromodulation.  
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27 **Word count:** 3988  
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## 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

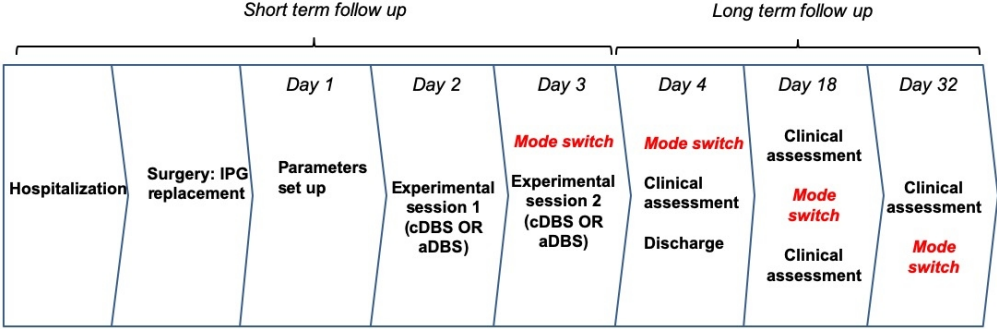


Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

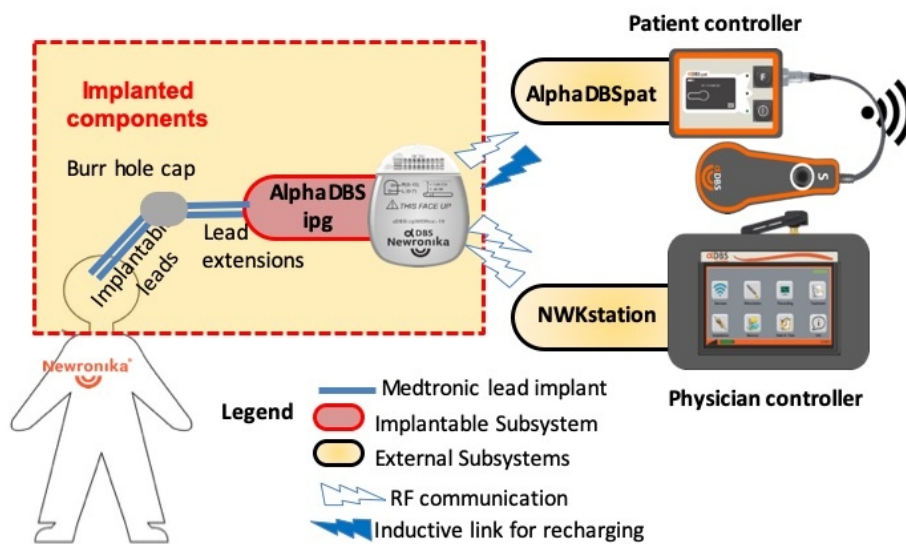


Figure 2 - AlphaDBS system components

264x171mm (72 x 72 DPI)

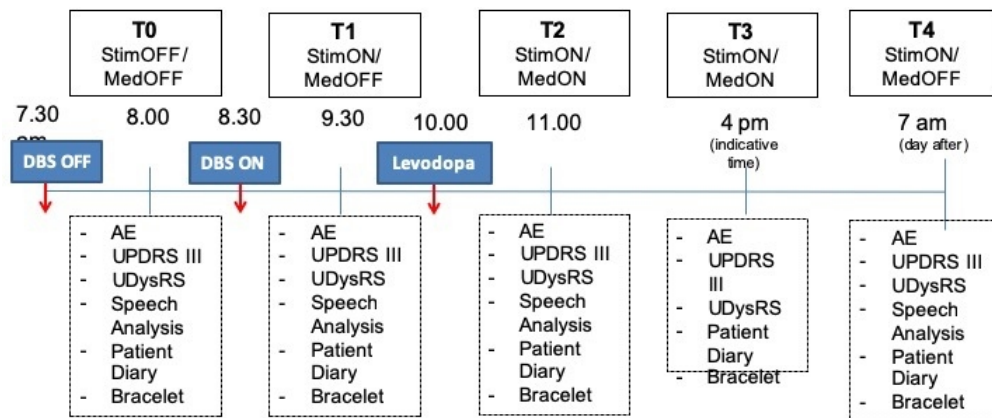


Figure 3 - Short term follow-up: Experimental session details

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

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<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Parkinson-s disease < NEUROLOGY, NEUROLOGY

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Manuscripts



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4 1 **A double-blind crossover pilot trial to evaluate the safety and**  
5 2 **preliminary efficacy of long-term adaptive Deep Brain Stimulation**  
6 3 **in patients with Parkinson's Disease**  
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8 5 **Sara Marceglia\*<sup>1</sup>, Costanza Conti\*<sup>2</sup>, Oleg Svanidze<sup>2</sup>, Guglielmo Foffani<sup>3,4</sup>, Andres M Lozano<sup>5,6</sup>,**  
9 6 **Elena Moro<sup>7,8</sup>, Jens Volkmann<sup>9</sup>, Mattia Arlotti<sup>2</sup>, Lorenzo Rossi<sup>2</sup>, Alberto Priori<sup>10,11</sup>**  
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3 **1 Abstract**

4 **2 Introduction:** After several years of brain-sensing technology development and proof-of-concept  
5 studies, adaptive deep brain stimulation (aDBS) is ready to better treat Parkinson's disease (PD) using  
6 aDBS-capable implantable pulse generators (IPGs). New aDBS devices are capable of continuous  
7 sensing of neuronal activity from the subthalamic nucleus (STN) and contemporaneous stimulation  
8 automatically adapted to match the patient's clinical state estimated from the analysis of STN activity  
9 using proprietary algorithms. Specific studies are necessary to assess superiority of aDBS versus  
10 conventional DBS (cDBS) therapy. This protocol describes an original innovative multi-center  
11 international study aimed to assess safety and efficacy of aDBS versus cDBS using a new generation  
12 of DBS IPG in PD (AlphaDBS system by Newronika SpA, Milan, Italy).

13 **12 Methods:** The study involves six investigational sites (in Italy, Poland, and The Netherlands). The  
14 primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when used in  
15 cDBS and aDBS mode. Secondary objective will be to evaluate the potential efficacy of aDBS. After  
16 eligibility screening, 15 PD patients already implanted with DBS systems and in need of battery  
17 replacement will be randomized to enter a two-phases protocol, including a "short-term follow-up" (2-  
18 days experimental sessions during hospitalization, 1 day per each mode) and a "long-term follow-up"  
19 (1 month at home, 15 days per each mode).

20 **20 Ethics and Dissemination:** The trial was approved as pre-market study by the Italian, Polish, and Dutch  
21 Competent Authorities: Bioethics Committee at National Oncology Institute of Maria Skłodowska-  
22 Curie – National Research Institute in Warsaw; Comitato Etico Milano Area 2; Comitato Etico IRCCS  
23 Istituto Neurologico C. Besta; Comitato Etico interaziendale AOUC Città della Salute e della Scienza  
24 – AO Ordine Mauriziano di Torino – ASL Città di Torino; De Medisch Ethisch Toetsingscommissie  
25 van Maastricht UMC. The study started enrolling patients in January 2021.

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27 **27 Registration:** ClinicalTrials.gov Identifier: NCT04681534  
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## Strengths and limitations of this study

- New study protocols are necessary to assess outcomes from 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 novo 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.

## 1 Introduction

2  
3 Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), but its progress  
4 has been hampered by stagnation in methodological, technological, and device development. DBS  
5 proved to be effective in improving major PD symptoms in long-term follow-up studies [1–7] and  
6 currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor  
7 fluctuations, dyskinesias, and refractory tremor [1]. In particular, DBS of the subthalamic nucleus  
8 (STN) has been shown to improve motor symptoms of PD, levodopa-induced complications and overall  
9 quality of life [7].

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

13 Limitations of cDBS include lack of responsiveness to patients' needs, fixed therapeutic window,  
14 repeated hospital visits for stimulation adjustment thus ultimately leading to suboptimal and more  
15 expensive therapy [8]. In addition, the excessive and unnecessary electrical stimulation over time may  
16 interfere with the residual physiological functions of the basal ganglia, thus contributing [9] to the  
17 development of neurological complications such as impairment of speech, balance, and gait, and,  
18 possibly, cognition. In particular, the decline in verbal fluency, which is the most frequent side effect  
19 of STN-DBS, was associated with the influence of stimulation on sounding neural pathways. Some of  
20 these stimulation-related side effects can be reversed by reprogramming [10].

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

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

32 However, the information regarding the long-term safety and efficacy of aDBS remains limited. In fact,  
33 to date, studies comparing the efficacy and safety of aDBS to cDBS had intrinsic limitations, due to  
34 technical reasons. Initial studies were mostly performed in the immediate postoperative period, after  
35 surgery for DBS electrode implant, when the temporary presence of externalized electrodes allows the  
36 collection of data using external devices. This approach has several major limitations since symptom  
37 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

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3 1 All patients included in the study must have been already implanted with DBS electrodes in the past.  
4 2 At the time of their first DBS implant (electrodes + first IPG now to be replaced), they were selected  
5 3 for DBS indication on the basis of the CAPSIT guidelines (Core Assessment Program for Surgical  
6 4 Interventional Therapies in PD, CAPSIT-PD, [35]). Even though some of the listed inclusion/exclusion  
7 5 criteria are similar to that used for DBS indication, we decided to reconsider them because of the time  
8 6 elapsed from DBS first implant.

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

### 13 14 ***Exclusion criteria***

- 15 • Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score <10);
- 16 • Patients with major psychiatric issues or any other condition that, based on the physician  
17 opinion, could interfere with the study conduct (e.g., severe depression, psychosis, etc.)
- 18 • Patients with any medical conditions potentially interfering with DBS battery replacement  
19 surgery (e.g., severe hypertension, active cancer, intake of drugs interfering with the  
20 coagulation, etc.)
- 21 • Need to replace or reposition the leads during the IPG replacement procedure
- 22 • Patients with > 10 recurrent falls experienced in the 3 months prior to consent
- 23 • Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min
- 24 • Patients taking less than one levodopa dose per day
- 25 • Patients with no LFPs recorded intraoperatively from any contacts pair, during the IPG  
26 replacement procedure
- 27 • Pregnant or breastfeeding women.

### 28 29 ***Device description***

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



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3 1 The AlphaDBS System is composed of different subsystems (Figure 2): the AlphaDBSipg (IPG  
4 2 delivering stimulation in aDBS or cDBS mode and recording/analyzing LFPs from implanted DBS  
5 3 leads); AlphaDBSpat (external patient controller); NWKstation (external physician controller).

6  
7  
8 4 The AlphaDBSipg is an active implantable medical device that applies cDBS/aDBS. It is powered by  
9 5 a hermetically sealed rechargeable battery within a titanium case. The AlphaDBS System,  
10 6 manufactured by Newronika SpA (Milan, Italy), is currently under final stages of CE-mark certification  
11 7 procedures.

12 8 In cDBS mode, the AlphaDBSipg, with 16 independent stimulation current controlled outputs, delivers  
13 9 asymmetric biphasic balanced constant current pulse train. Stimulation can be delivered in bipolar or  
14 10 monopolar configuration by selecting a contact pair or one contact in each of the two available leads  
15 11 (stimulation parameters: pulse width (us), amplitude (V), and frequency (Hz)). In monopolar  
16 12 stimulation, the reference electrode is simulated by the IPG enclosure.

17 13 In aDBS mode, an adaptive algorithm will use LFP signals from implanted electrodes extracting  
18 14 information to decrease the energy of stimulation (amplitude) when the patient is responding  
19 15 appropriately to pharmacological therapy and increasing the energy when the patient's symptoms are  
20 16 not well controlled. The algorithm that will be used in aDBS mode will be personalized based on LFP  
21 17 modulation in the 13-35 Hz frequency band (beta band), as described elsewhere [36].

22 18 The AlphaDBS System has several innovative features that implement a distributed architecture  
23 19 allowing data collection and management that make it a reliable platform for aDBS and closed-loop  
24 20 neuromodulation applications. Major innovations reside in the technology for artifact-free recordings  
25 21 [36–38] that is stimulation agnostic, electrode configuration independent, and needless for back-end  
26 22 processing. This implies that LFPs can be recorded with stimulation ON from all contact pairs, not  
27 23 necessarily symmetrical around the stimulation contact, and with different stimulation types. In  
28 24 addition, the artifact rejection methodology is implemented at the chip level and not at the system level,  
29 25 thus leaving the whole computational capacity free for closed-loop algorithm implementation. Another  
30 26 important feature is the ability of the system both to provide on-demand real-time streaming of LFPs  
31 27 both in ON and OFF without the need of additional receivers worn by the patient, but using directly the  
32 28 clinician controller (NWKStation) and to provide continuous embedded data storage that is always ON  
33 29 24/7 whatever the stimulation mode (OFF, cDBS, aDBS). Thanks to the data management  
34 30 infrastructure, the embedded data storage guarantees no data loss for memory overwriting because data  
35 31 are automatically downloaded to the patient controller (AlphaDBSpat) during recharging, using the  
36 32 same device. This is crucial to allow full biomarker tracking for future aDBS optimization.

### 33 34 ***Evaluations and procedures***

35 35 After providing consent, each patient will undergo a Screening Period, during which demographic  
36 36 information and additional information on the medical management will be collected. Each patient will



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3 1 undergo a series of screening evaluations, including: evaluation of battery level, medical history,  
4 2 physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major  
5 3 psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [35],  
6 4 measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery),  
7 5 assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving  
8 6 informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-  
9 7 OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be  
10 8 evaluated after the administration of a LEED morning dose + 30%.

11 9 Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization  
12 10 will be conducted in agreement with local standard practice for IPG replacement.

13 11 On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be  
14 12 connected to temporary extensions in order to check the integrity of the leads and the occurrence of  
15 13 ECG artifacts. The patients with ECG artifacts impairing LFP recording will not be excluded and will  
16 14 receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.

17 15 The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be  
18 16 recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available  
19 17 electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best  
20 18 recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS  
21 19 current titration session will be performed to establish both the optimal cDBS parameters with  
22 20 AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the  
23 21 personalized beta band and peak previously defined.

24 22 At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to  
25 23 aDBS or cDBS treatment will take place on the following day.

26 24 On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one  
27 25 stimulation mode per day, according to the randomization schedule.

28 26 The experimental session will start around 7:30 am (expected time) and will last for about nine hours  
29 27 (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next  
30 28 washout period in the same mode.

31 29 At the beginning of the session, the stimulation will be switched off for at least 30 minutes of stimulation  
32 30 washout (stim-OFF/med-OFF condition), and then switched on.

33 31 Each experimental session will include the following assessments:

- 34 32 ○ T0: before the administration of the morning dopaminergic therapy and after at least 30  
35 33 minutes of stimulation washout (stim-OFF/med-OFF) - UDysRS, UPDRS III and adverse  
36 34 events recording, speech analysis
- 37 35 ○ T1: before the administration of the morning dopaminergic therapy and after 1 hour of  
38 36 active stimulation (stim-ON/med-OFF) – UDysRS, UPDRS III and adverse event  
39 37 recording, speech analysis

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

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

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

17 The parameters to calculate the TEED at T4 will be automatically collected from the AlphaDBS System.  
18 On Day 4, if the neurologist will deem the patient suitable for the "long-term follow-up" phase, the  
19 patient will undergo another clinical assessment and will be discharged. The clinical assessment will  
20 take place about 1 hour after morning dopaminergic therapy administration, when the effect of the  
21 therapy will reach its best effect (stim-ON/med-ON), administering UDysRS and UPDRS III scales and  
22 examining possible side effects. After the visit, the stimulation will be automatically switched to the  
23 stimulation mode, randomly allocated on Day 2.

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

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

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

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

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3 1 Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a  
4 2 compatible commercially available IPG.  
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#### 8 4 *Randomization*

9 5 Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a  
10 6 first treatment, based on a center-specific computer-generated randomization list.  
11 7 Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive  
12 8 study number will be automatically assigned. If the patient is eligible, the Investigators will randomize  
13 9 him/her and the eCRF will display a randomization code corresponding to the first free number from  
14 10 the randomization list.

15 11 At the beginning of each experimental day, the designated person in charge of DBS programming  
16 12 (unblind), will use the randomization code as PIN code to enter the Physician Programmer  
17 13 (NWKStation), to program the system in cDBS or aDBS according to randomization.  
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### 26 15 **Methods: Statistical methods and data management**

#### 27 16 *Sample size*

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29 17 The objective of the study is to collect data, such as the degree of correlation between GOT in aDBS  
30 18 and cDBS, that will allow calculation of the sample size needed for a pivotal study if the present study  
31 19 confirms the results obtained in a previous trial. This study will randomize at least 15 patients.

32 20 Based on the figures obtained in the clinical trial with patients in the “acute” phase [25], and without  
33 21 considering corrections for multiple testing, this sample will allow using exploratory statistics to  
34 22 demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for  
35 23 an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05  
36 24 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the  
37 25 higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the  
38 26 patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse  
39 27 events (1-2%) are not considered since they were already described by other DBS devices  
40 28 manufacturers and thus expected. Also, rare hardware related are usually observable in studies with  
41 29 longer observation periods than that included in this study (1 month) which is thus not ideal to assess  
42 30 this type of information, which in any case will be collected.  
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#### 53 32 *Data collection and management*

54 33 All study data will be collected and stored through online eCRFs. The system will provide a safe  
55 34 environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data  
56 35 collection that can be shared among different operative units, allowing CRF signature and modifications  
57 36 tracking. A CRO is in charge of data management and quality assurance.  
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## 2 **Monitoring**

3 The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO  
4 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will  
5 maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or  
6 retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the  
7 Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study  
8 Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot  
9 be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard  
10 Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).

11

## 12 **Data analysis**

13 The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.  
14 The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints  
15 (i.e., UDysRS, UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS experimental  
16 sessions.

17 Safety will be evaluated on all patients randomized and receiving at least one of the treatments. It will  
18 include the comparison of: 1) TEED delivered to the patient during aDBS and cDBS experimental  
19 sessions, 2) AEs during the 2 treatments.

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

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

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

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## 34 **Ethics and dissemination**

## 35 **Risk-benefit analysis**

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3 1 Potential risks and benefits of aDBS will be clearly explained to the patients in the Informed Consent  
4 2 Form that will be provided at screening, prior to start the study protocol.

5  
6 3 If the results of the trial will be promising, PD patients will have a new innovative device for DBS that  
7 4 will allow the delivery of aDBS. In any case, new long-term LFP recordings will be available thanks to  
8 5 the implantation of the AlphaDBS system thus improving the understanding of PD neurophysiology.

9  
10 6 Patients treated with aDBS could experience a reduction of symptoms, better quality of life, and a  
11 7 simplification of patient management, reducing the number of visits and calls to the treating neurologist  
12 8 to fine-tune DBS programming settings. In addition, patients involved in the study could experience  
13 9 personal benefits, possibly including: overall reduction of the electrical energy delivered to the tissues,  
14 10 and of the patient's OFF time (compared to cDBS), overall increase of the patient's ON time without  
15 11 troublesome dyskinesia, improvement of efficacy in reducing bradykinesia, rigidity, and tremor  
16 12 (compared to cDBS), reduction "levodopa-induced dyskinesia", improvement in speech, balance, and  
17 13 gait problems related to stimulation.

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21 15 Given the extensive bench testing and animal and clinical studies conducted, there is a reasonable  
22 16 expectation that the device will be technically successful and that it will function as intended.

23  
24 17 The replacement of a DBS IPG involves risks, and we expect that the patient implanted with the  
25 18 AlphaDBSipg will be exposed to the same procedure-related risks reported for other DBS Systems on  
26 19 the market. These risks are the ones commonly associated with IPG replacement surgery. An additional  
27 20 risk may occur in patients choosing to replace the AlphaDBSipg with a commercial IPG at the end of  
28 21 the long-term follow-up.

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30 22 COVID-19 seriously impacted on the conduction of experimental trials and research activity [39]. A  
31 23 COVID-19 risk assessment, related to the study conduct was prepared, in agreement with the  
32 24 indications provided in the "Guidance on the management of clinical trials during the COVID-19  
33 25 (coronavirus) pandemic (Version 3, 28/04/2020)" issued by the European Commission and coordinated  
34 26 by EMA.

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### 28 ***Informed consent, IEC/IRB approval, and MoH approval***

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39 30 The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64<sup>th</sup>  
40 31 General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013.

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42 32 The protocol, Subject Information Sheet, Informed Consent Form and the Data Privacy Consent Form  
43 33 were reviewed and approved, prior to initiating any trial-related activity, by the Ethical Committees of  
44 34 each institution involved namely: Comitato Etico Milano Area 2 (Milano), Comitato Etico Fondazione  
45 35 IRCCS Istituto Neurologico C. Besta (Milano), Comitato Etico Interaziendale A.O.U. Città della Salute  
46 36 e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino (Torino), Comitato Etico  
47 37 per la Sperimentazione Clinica della Provincia di Padova (Padova); Bioethics Committee at the

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3 1 National Institute of Oncology of Maria Skłodowska-Curie (Warsaw), De Medisch Ethisch  
4 2 Toetsingscommissie van Maastricht UMC (The Netherlands). As the AlphaDBS System is an  
5 3 investigational device, the trial required the approval, as pre-market study, of competent authorities,  
6 4 namely: the Italian Ministry of Health, Directorate General for Medical Devices and Pharmaceutical  
7 5 service, the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal  
8 6 Products and the Dutch Central Committee on Research Involving Human Subjects.  
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### 14 8 ***Patient and Public Involvement***

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16 9 Patients from an Italian PD association provided inputs on the definition of relevant benefits related to  
17 10 the results of this aDBS investigation and on device usability.  
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3 1 **Contributors:** SM and CC ideated and designed the protocol, wrote the protocol and documentation  
4 2 for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR,  
5 3 AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures  
6 4 and manuscript. All authors reviewed and approved the final version of this manuscript.  
7

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9 6 Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant  
10 7 number is not applicable.  
11

12 8 **Disclaimer:** All the scientific findings derived from this protocol are aimed to be made public  
13 9 through publication of articles in international journals.  
14

15 10 **Conflict of Interest statement:**

16 11 AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's  
17 12 scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are  
18 13 stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member  
19 14 of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of  
20 15 Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received  
21 16 honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston  
22 17 Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has  
23 18 served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of  
24 19 Functional Neuromodulation.  
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26 20  
27 21 **Word count:** 4410  
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3 **1 FIGURES AND FIGURE LEGENDS**  
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5 **2**

6 **3 Figure 1-** The trial time-line in patients participating to both the short and long term follow-up phases:  
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8 4 after completing the experimental procedures foreseen in Day 1, Day 2 and Day 3, on Day 4, in the  
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10 5 morning, the patient will be discharged with the AlphaDBSipg delivering aDBS or cDBS for 2 weeks.  
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12 6 On Day 18 the patient will undergo a clinical assessment. After the assessment the stimulation mode  
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14 7 will be switched and the patient will undergo a new clinical assessment. If the second clinical  
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16 8 assessment (with changed stimulation mode ON) will be successfully completed, the patient will be  
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18 9 discharged with the AlphaDBS device delivering aDBS or cDBS for additional 2 weeks. On Day 32  
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20 10 the patient will undergo the last clinical assessment.  
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23 **13 Figure 2 –** AlphaDBS system overview  
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27 **16 Figure 3-** Summary of examinations foreseen at each time point of the experimental sessions (Day 2  
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29 17 and Day 3). Note that timing is indicative and may vary up to 45 min. per session  
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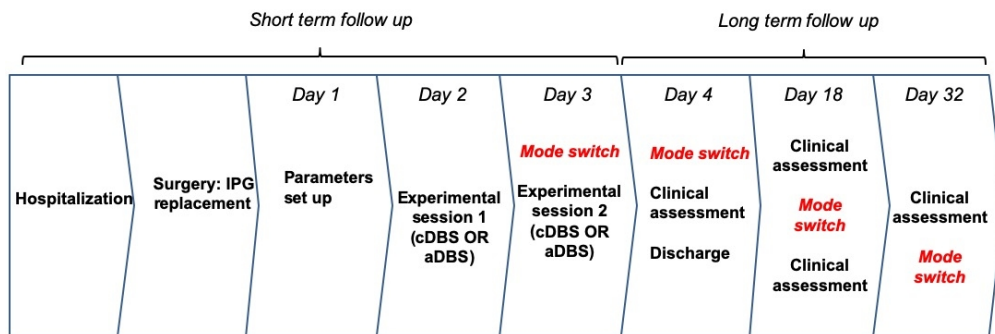


Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

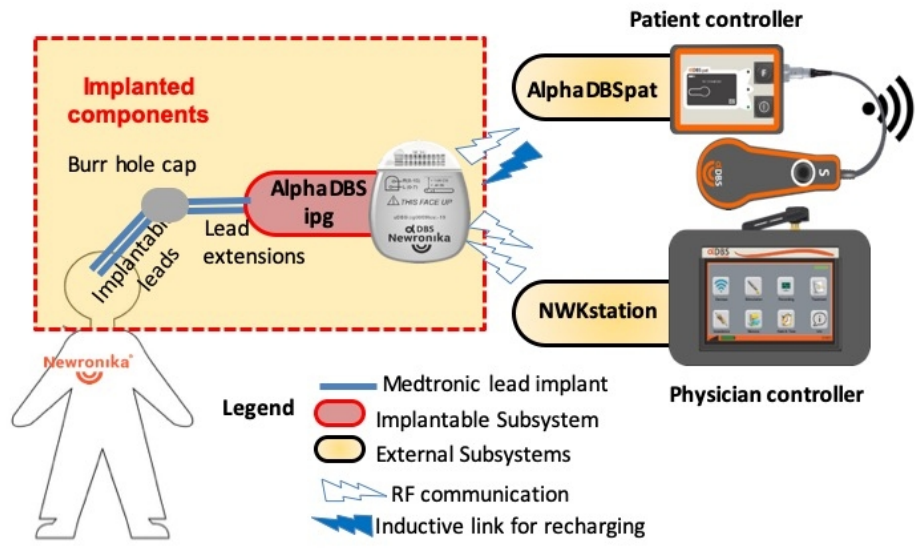


Figure 2 - AlphaDBS system components

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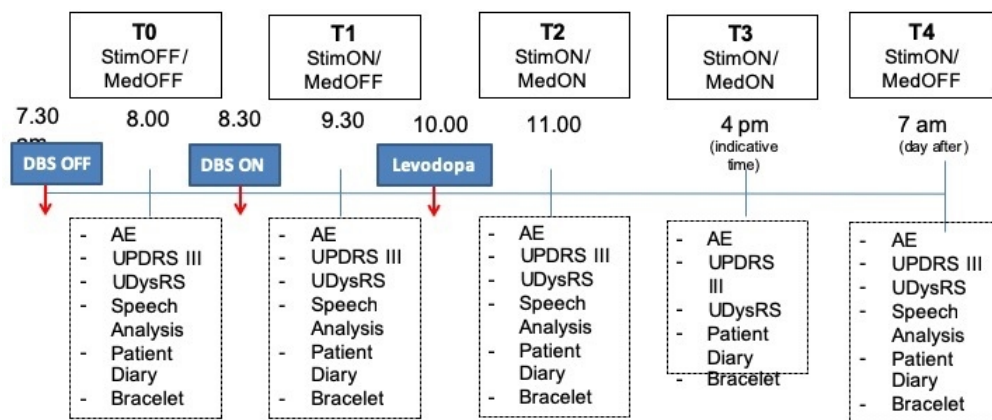






Figure 3 - Short term follow-up: Experimental session details





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## 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?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you find it is easy to turn on the patient remote control (both parts)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand clearly when the neurostimulator is communicating with the patient remote control?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand clearly the battery level of the implanted neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Considerations about screens and alarms</b>					
Do you hear the alarms?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The information provided in the display of the patient programmer are clear and exhaustive?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Is it clear what is shown on the display when you connect the 2 parts of the patient remote control?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand if the charging procedure is correctly ongoing?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand when the charging process is interrupted due to misalignment of the patient remote control with the implanted neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand how to check the battery level of your neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



<b>Consideration about the patient remote control and its accessories</b>					
Device dimension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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Patient remote control portability	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
AlphaDBS T-shirt	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
AlphaDBS Collar	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>User Information</b>					
AlphaDBSpat Patient Manual	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Peer review only

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# 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

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# 1 A double-blind crossover pilot trial protocol to evaluate the safety and 2 preliminary efficacy of long-term adaptive Deep Brain Stimulation 3 in patients with Parkinson's Disease

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1  
2  
3 **1 Abstract**

4 **2 Introduction:** After several years of brain-sensing technology development and proof-of-concept  
5 studies, adaptive deep brain stimulation (aDBS) is ready to better treat Parkinson's disease (PD) using  
6 aDBS-capable implantable pulse generators (IPGs). New aDBS devices are capable of continuous  
7 sensing of neuronal activity from the subthalamic nucleus (STN) and contemporaneous stimulation  
8 automatically adapted to match the patient's clinical state estimated from the analysis of STN activity  
9 using proprietary algorithms. Specific studies are necessary to assess superiority of aDBS versus  
10 conventional DBS (cDBS) therapy. This protocol describes an original innovative multi-center  
11 international study aimed to assess safety and efficacy of aDBS versus cDBS using a new generation  
12 of DBS IPG in PD (AlphaDBS system by Newronika SpA, Milan, Italy).

13 **12 Methods:** The study involves six investigational sites (in Italy, Poland, and The Netherlands). The  
14 primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when used in  
15 cDBS and aDBS mode. Secondary objective will be to evaluate the potential efficacy of aDBS. After  
16 eligibility screening, 15 PD patients already implanted with DBS systems and in need of battery  
17 replacement will be randomized to enter a two-phases protocol, including a "short-term follow-up" (2-  
18 days experimental sessions during hospitalization, 1 day per each mode) and a "long-term follow-up"  
19 (1 month at home, 15 days per each mode).

20 **20 Ethics and Dissemination:** The trial was approved as pre-market study by the Italian, Polish, and Dutch  
21 Competent Authorities: Bioethics Committee at National Oncology Institute of Maria Skłodowska-  
22 Curie – National Research Institute in Warsaw; Comitato Etico Milano Area 2; Comitato Etico IRCCS  
23 Istituto Neurologico C. Besta; Comitato Etico interaziendale AOUC Città della Salute e della Scienza  
24 – AO Ordine Mauriziano di Torino – ASL Città di Torino; De Medisch Ethisch Toetsingscommissie  
25 van Maastricht UMC. The study started enrolling patients in January 2021.

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27 **27 Registration:** ClinicalTrials.gov Identifier: NCT04681534  
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## Strengths and limitations of this study

- New study protocols are necessary to assess outcomes from 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 novo 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.

## 1 Introduction

2  
3 Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), but its progress  
4 has been hampered by stagnation in methodological, technological, and device development. DBS  
5 proved to be effective in improving major PD symptoms in long-term follow-up studies [1–7] and  
6 currently, DBS is the surgical treatment of choice for PD patients with medication-resistant motor  
7 fluctuations, dyskinesias, and refractory tremor [1]. In particular, DBS of the subthalamic nucleus  
8 (STN) has been shown to improve motor symptoms of PD, levodopa-induced complications and overall  
9 quality of life [7].

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

13 Limitations of cDBS include lack of responsiveness to patients' needs, fixed therapeutic window,  
14 repeated hospital visits for stimulation adjustment thus ultimately leading to suboptimal and more  
15 expensive therapy [8]. In addition, the excessive and unnecessary electrical stimulation over time may  
16 interfere with the residual physiological functions of the basal ganglia, thus contributing [9] to the  
17 development of neurological complications such as impairment of speech, balance, and gait, and,  
18 possibly, cognition. In particular, the decline in verbal fluency, which is the most frequent side effect  
19 of STN-DBS, was associated with the influence of stimulation on sounding neural pathways. Some of  
20 these stimulation-related side effects can be reversed by reprogramming [10].

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

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

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

1 [27,28] and the effects of DBS and adverse events in the “acute” (postoperative) period are known to  
2 differ from its “chronic” effects [29]. Recently, two studies confirmed the benefits of aDBS in patients  
3 at implantable pulse generator (IPG) replacement [30,31], and protocols studying aDBS in these  
4 patients have been proposed [32]. In addition, due to the lack of available implantable devices delivering  
5 aDBS, studies foresaw short periods of stimulation, with a maximum length of follow up to 24 hours  
6 [30]. Even though a new CE-marked implantable device able to record LFPs while DBS is ON  
7 (Medtronic Percept™) has been recently introduced, no data on long-term aDBS is available as well as  
8 specific protocols to compare aDBS and cDBS.

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

## 17 **Study objectives**

18 The aim of this study is to assess the safety and the potential efficacy of personalized LFP-based aDBS,  
19 using the implantable AlphaDBS System, in PD patients, chronically implanted in the STN for DBS, at  
20 the time of IPG replacement.

21 The primary objective will be to evaluate the safety and tolerability of the AlphaDBS System, when  
22 used in cDBS and aDBS mode, based on the following endpoints:

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

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

32 Since this is the first study on the use of AlphaDBS System and on the chronic application of its aDBS  
33 implementation, secondary objective will be to evaluate the potential efficacy of aDBS and AlphaDBS  
34 System usability.

35 Efficacy will be evaluated from the following secondary measures:



- 1 • Evaluation of PD-related motor symptoms (i.e., bradykinesia, rigidity and tremor at rest) and  
2 their fluctuations through repeated clinical assessments (using the Unified Parkinson's Disease  
3 Rating Scale MDS-UPDRS- part III)
- 4 • Evaluation of dyskinesia and their fluctuations through repeated clinical assessments (using the  
5 Unified Dyskinesia Rating Scale – UDysRS and wearable Systems)
- 6 • Evaluation of “Time On” with and without dyskinesia and “Time Off”, assessed through Patient  
7 Diary.

8 Usability will be evaluated by means of usability questionnaires (see supplementary materials).

9 Exploratory objectives include evaluation of DBS associated deficits, through the DBS Impairment  
10 Scale (DBS-IS) [34] and evaluation of the effects of aDBS on speech.

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

## 15 **Study design**

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

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

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

## 27 **Methods and procedure**

### 28 **Study centers**

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

### 35 **Inclusion criteria**

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3 1 All patients included in the study must have been already implanted with DBS electrodes in the past.  
4 2 At the time of their first DBS implant (electrodes + first IPG now to be replaced), they were selected  
5 3 for DBS indication on the basis of the CAPSIT guidelines (Core Assessment Program for Surgical  
6 4 Interventional Therapies in PD, CAPSIT-PD, [35]). Even though some of the listed inclusion/exclusion  
7 5 criteria are similar to that used for DBS indication, we decided to reconsider them because of the time  
8 6 elapsed from DBS first implant.

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

### 13 14 ***Exclusion criteria***

- 15 • Patients with severe cognitive decline, as resulting from MoCA assessment (MoCA score <10);
- 16 • Patients with major psychiatric issues or any other condition that, based on the physician  
17 opinion, could interfere with the study conduct (e.g., severe depression, psychosis, etc.)
- 18 • Patients with any medical conditions potentially interfering with DBS battery replacement  
19 surgery (e.g., severe hypertension, active cancer, intake of drugs interfering with the  
20 coagulation, etc.)
- 21 • Need to replace or reposition the leads during the IPG replacement procedure
- 22 • Patients with > 10 recurrent falls experienced in the 3 months prior to consent
- 23 • Patients that cannot tolerate an interruption of DBS stimulation for at least 30 min
- 24 • Patients taking less than one levodopa dose per day
- 25 • Patients with no LFPs recorded intraoperatively from any contacts pair, during the IPG  
26 replacement procedure
- 27 • Pregnant or breastfeeding women.

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

### 31 32 ***Device description***

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

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

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

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

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

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

20 The AlphaDBS System has several innovative features that implement a distributed architecture  
21 allowing data collection and management that make it a reliable platform for aDBS and closed-loop  
22 neuromodulation applications. Major innovations reside in the technology for artifact-free recordings  
23 [36–38] that is stimulation agnostic, electrode configuration independent, and needless for back-end  
24 processing. This implies that LFPs can be recorded with stimulation ON from all contact pairs, not  
25 necessarily symmetrical around the stimulation contact, and with different stimulation types. In  
26 addition, the artifact rejection methodology is implemented at the chip level and not at the system level,  
27 thus leaving the whole computational capacity free for closed-loop algorithm implementation. Another  
28 important feature is the ability of the system both to provide on-demand real-time streaming of LFPs  
29 both in ON and OFF without the need of additional receivers worn by the patient, but using directly the  
30 clinician controller (NWKStation) and to provide continuous embedded data storage that is always ON  
31 24/7 whatever the stimulation mode (OFF, cDBS, aDBS). Thanks to the data management  
32 infrastructure, the embedded data storage guarantees no data loss for memory overwriting because data  
33 are automatically downloaded to the patient controller (AlphaDBSpat) during recharging, using the  
34 same device. This is crucial to allow full biomarker tracking for future aDBS optimization.

### 35 *Evaluations and procedures*

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3 1 After providing consent, each patient will undergo a Screening Period, during which demographic  
4 2 information and additional information on the medical management will be collected. Each patient will  
5 3 undergo a series of screening evaluations, including: evaluation of battery level, medical history,  
6 4 physical, neurological and psychiatric examinations to assess cognitive decline (i.e. MoCA) and major  
7 5 psychiatric issues (e.g. severe depression, psychosis, etc.), as suggested in CAPSIT-PD guidelines [35],  
8 6 measurement of vital signs (as performed in normal clinical practice before IPG replacement surgery),  
9 7 assessment of prior and concomitant medications, of adverse events (AEs) occurring after giving  
10 8 informed consent, and evaluation of MDS-UPDRS and UDysRS at (1) stim-ON/med-OFF, (2) stim-  
11 9 OFF (1h)/med-OFF, (3) stim-OFF/med-ON, (4) stim-ON(1h)/med-ON. The med-ON condition will be  
12 10 evaluated after the administration of a LEED morning dose + 30%.

13 11 Patients with a confirmed need for battery replacement will be qualified for surgery. Hospitalization  
14 12 will be conducted in agreement with local standard practice for IPG replacement.

15 13 On Day 0, during routine surgery for IPG replacement, after IPG removal, the exposed leads will be  
16 14 connected to temporary extensions in order to check the integrity of the leads and the occurrence of  
17 15 ECG artifacts. The patients with ECG artifacts impairing LFP recording will not be excluded and will  
18 16 receive a standard of care new IPG implant. Otherwise, the patient will be enrolled.

19 17 The day after surgery (Day 1), the patients will undergo personalized algorithm setup. LFPs will be  
20 18 recorded synchronously, through the AlphaDBSipg device, for about 30 minutes, from all available  
21 19 electrode pairs in the med-OFF/stim-OFF condition (no DBS and no levodopa) to establish (1) the best  
22 20 recording pair, (2) the peak LFPs frequency, and (3) the LFPs band of interest. Then, a routine DBS  
23 21 current titration session will be performed to establish both the optimal cDBS parameters with  
24 22 AlphaDBSipg, and the therapeutic window. Finally, the AlphaDBS System will be calibrated using the  
25 23 personalized beta band and peak previously defined.

26 24 At the end of the personalized algorithm setup, patients will be assigned to cDBS; randomization to  
27 25 aDBS or cDBS treatment will take place on the following day.

28 26 On 2 consecutive days after the algorithm setup (Day 2 and Day 3) aDBS and cDBS will be tested, one  
29 27 stimulation mode per day, according to the randomization schedule.

30 28 The experimental session will start around 7:30 am (expected time) and will last for about nine hours  
31 29 (Figure 3). At the end of the experimental session, the stimulation will continue overnight until the next  
32 30 washout period in the same mode.

33 31 At the beginning of the session, the stimulation will be switched off for at least 30 minutes of stimulation  
34 32 washout (stim-OFF/med-OFF condition), and then switched on.

35 33 Each experimental session will include the following assessments:

- 36 34 ○ T0: before the administration of the morning dopaminergic therapy and after at least 30  
37 35 minutes of stimulation washout (stim-OFF/med-OFF) - UDysRS, MDS-UPDRS III and  
38 36 adverse events recording, speech analysis

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

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

15 Throughout the experimental session, to monitor motor symptoms fluctuations, the patient will wear a

16 bracelet equipped with a three-axial accelerometer and will fill in his/her Patient's Diary, for the whole

17 duration of the experimental session. Speech analysis will be performed with Semantic and phonemic

18 evaluations will be recorded with the VF test (Delis-Kaplan Executive Function System), and control

19 word repetition tasks.

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

21 On Day 4, if the neurologist will deem the patient suitable for the "long-term follow-up" phase, the

22 patient will undergo another clinical assessment and will be discharged. The clinical assessment will

23 take place about 1 hour after morning dopaminergic therapy administration, when the effect of the

24 therapy will reach its best effect (stim-ON/med-ON), administering UDysRS and MDS-UPDRS III

25 scales and examining possible side effects. After the visit, the stimulation will be automatically

26 switched to the stimulation mode, randomly allocated on Day 2.

27 After the examination, patients (blinded to treatment) will receive the training on how to use the device,

28 and then be discharged from the hospital and sent to their "home" environment for two weeks in each

29 stimulation mode.

30 During this follow-up period, a research fellow/nurse will monitor the patient remotely every day to

31 assess the patient status, check Concomitant Medications and record adverse events.

32 After two weeks of treatment, on Day 18, the patient will provide diaries completed in the last three

33 days before the visit and will undergo a clinical assessment (performed by a blinded neurologist) in

34 stim ON-med ON including UDysRS, MDS-UPDRS III and DBS-IS scales, collection of possible side

35 effects, speech analysis, and TEED (automatically collected from the AlphaDBSipg). Also, the

36 patient/caregiver will provide his/her inputs related to the System usability for what concerns the IPG

37 recharging process.

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3 1 After the visit, the stimulation will be automatically switched to the other stimulation mode (as in Day  
4 2 3), and the patient will be sent home. The same protocol will be followed for two weeks until Day 32.  
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6 3 Then, the patient will be able to choose whether to keep the AlphaDBS System or replace it with a  
7 4 compatible commercially available IPG.  
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#### 10 6 *Randomization*

11 7 Each recruited patient will be randomly assigned to one of the stimulation modes to be allocated as a  
12 8 first treatment, based on a center-specific computer-generated randomization list.

13 9 Each eligible patient will be recorded on the online Case Report Form (eCRF) system and a progressive  
14 10 study number will be automatically assigned. If the patient is eligible, the Investigators will randomize  
15 11 him/her and the eCRF will display a randomization code corresponding to the first free number from  
16 12 the randomization list.

17 13 At the beginning of each experimental day, the designated person in charge of DBS programming  
18 14 (unblind), will use the randomization code as PIN code to enter the Physician Programmer  
19 15 (NWKStation), to program the system in cDBS or aDBS according to randomization.  
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### 29 17 **Methods: Statistical methods and data management**

#### 30 18 *Sample size*

31 19 The objective of the study is to collect data, such as the degree of correlation between GOT in aDBS  
32 20 and cDBS, that will allow calculation of the sample size needed for a pivotal study if the present study  
33 21 confirms the results obtained in a previous trial. This study will randomize at least 15 patients.

34 22 Based on the figures obtained in the clinical trial with patients in the “acute” phase [25], and without  
35 23 considering corrections for multiple testing, this sample will allow using exploratory statistics to  
36 24 demonstrate a difference in TEED during cDBS and aDBS sessions through a non-parametric test-for  
37 25 an effect size of 1.14, assuming the following parameters, using type I error probability equal to 0.05  
38 26 and power of 99%: TEED = 44.6 in aDBS, TEED = 158.7 in cDBS, SD = 100, multiplying by 4.5 the  
39 27 higher SD observed. Also, 15 patients will allow to observe adverse events occurring in 5-10% of the  
40 28 patients, but not rare events in the range 1-2%. However, at this stage, rare hardware-related adverse  
41 29 events (1-2%) are not considered since they were already described by other DBS devices  
42 30 manufacturers and thus expected. Also, rare hardware related are usually observable in studies with  
43 31 longer observation periods than that included in this study (1 month) which is thus not ideal to assess  
44 32 this type of information, which in any case will be collected.  
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#### 56 34 *Data collection and management*

57 35 All study data will be collected and stored through online eCRFs. The system will provide a safe  
58 36 environment suitable for multicenter studies, with de-identified patients' data and clinical forms for data  
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60



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

### 3 4 **Monitoring**

5 The study monitoring will be conducted in agreement with Good Clinical Practice regulations (ISO  
6 14155:2011). The designated CRO will oversee the conduct of the trial. The Study Monitor will  
7 maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or  
8 retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the  
9 Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Study  
10 Monitor will perform periodic, interim monitoring visits. In case that on-site monitoring visits cannot  
11 be completed, Remote Monitoring Visit will be implemented and conducted according to the Standard  
12 Operating Procedure of the CRO in charge of study monitoring (e.g., during sanitary emergency).

### 13 14 **Data analysis**

15 The CRO will carry out all steps of analysis related to clinical efficacy and safety assessment.  
16 The effect of randomization will be explored by descriptive statistics analyzing the clinical endpoints  
17 (i.e., UDysRS, MDS-UPDRS III, etc.) in Stim-OFF/Med-OFF condition before aDBS and cDBS  
18 experimental sessions.

19 Safety will be evaluated on all patients randomized and receiving at least one of the treatments. It will  
20 include the comparison of: 1) TEED delivered to the patient during aDBS and cDBS experimental  
21 sessions, 2) AEs during the 2 treatments.

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

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

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

### 35 36 **Ethics and dissemination**



### 1 **Risk-benefit analysis**

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

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

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

15  
16 Given the extensive bench testing and animal and clinical studies conducted, there is a reasonable  
17 expectation that the device will be technically successful and that it will function as intended.

18 The replacement of a DBS IPG involves risks, and we expect that the patient implanted with the  
19 AlphaDBSipg will be exposed to the same procedure-related risks reported for other DBS Systems on  
20 the market. These risks are the ones commonly associated with IPG replacement surgery. An additional  
21 risk may occur in patients choosing to replace the AlphaDBSipg with a commercial IPG at the end of  
22 the long-term follow-up.

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

### 28 **Informed consent, IEC/IRB approval, and MoH approval**

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

31 The protocol, Subject Information Sheet, Informed Consent Form and the Data Privacy Consent Form  
32 were reviewed and approved, prior to initiating any trial-related activity, by the Ethical Committees of  
33 each institution involved namely: Comitato Etico Milano Area 2 (Milano), Comitato Etico Fondazione  
34 IRCCS Istituto Neurologico C. Besta (Milano), Comitato Etico Interaziendale A.O.U. Città della Salute  
35 e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino (Torino), Comitato Etico  
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3 1 per la Sperimentazione Clinica della Provincia di Padova (Padova); Bioethics Committee at the  
4 2 National Institute of Oncology of Maria Skłodowska-Curie (Warsaw), De Medisch Ethisch  
5 3 Toetsingscommissie van Maastricht UMC (The Netherlands). As the AlphaDBS System is an  
6 4 investigational device, the trial required the approval, as pre-market study, of competent authorities,  
7 5 namely: the Italian Ministry of Health, Directorate General for Medical Devices and Pharmaceutical  
8 6 service, the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal  
9 7 Products and the Dutch Central Committee on Research Involving Human Subjects.  
10 8

### 9 ***Patient and Public Involvement***

10 Patients from an Italian PD association provided inputs on the definition of relevant benefits related to  
11 the results of this aDBS investigation and on device usability.  
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3 1 **Contributors:** SM and CC ideated and designed the protocol, wrote the protocol and documentation  
4 2 for regulatory purposes and ethical committee approvals, and drafted the manuscript. OS, MA, LR,  
5 3 AP ideated and designed the protocol. AL, GF, EM, JV critically reviewed the protocol procedures  
6 4 and manuscript. All authors reviewed and approved the final version of this manuscript.  
7

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9 6 Ca' Granda Ospedale Maggiore Policlinico of Milan and of the University of Milan. Award/Grant  
10 7 number is not applicable.  
11

12 8 **Disclaimer:** All the scientific findings derived from this protocol are aimed to be made public  
13 9 through publication of articles in international journals.  
14

15 10 **Conflict of Interest statement:**

16 11 AP, GF, and SM are founders and shareholders of Newronika Spa, and are member of Newronika's  
17 12 scientific advisory board. LR is founder, shareholder and CEO of Newronika SpA. M.A. and O.S. are  
18 13 stock option holder and work for Newronika S.p.A. C.C. works for Newronika SpA. E.M. is member  
19 14 of the scientific advisory board of Newronika SpA, J.V. is member of the scientific advisory board of  
20 15 Newronika SpA and works as a consultant to Boston Scientific and Medtronic, and has received  
21 16 honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston  
22 17 Scientific and Medtronic, A.M.L. is member of the scientific advisory board of Newronika SpA, has  
23 18 served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of  
24 19 Functional Neuromodulation.  
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26 20  
27 21 **Word count:** 4410  
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3 **1 FIGURES AND FIGURE LEGENDS**  
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5 **2**

6 **3 Figure 1-** The trial time-line in patients participating to both the short and long term follow-up phases:  
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8 **4** after completing the experimental procedures foreseen in Day 1, Day 2 and Day 3, on Day 4, in the  
9  
10 **5** morning, the patient will be discharged with the AlphaDBSipg delivering aDBS or cDBS for 2 weeks.  
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12 **6** On Day 18 the patient will undergo a clinical assessment. After the assessment the stimulation mode  
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14 **7** will be switched and the patient will undergo a new clinical assessment. If the second clinical  
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16 **8** assessment (with changed stimulation mode ON) will be successfully completed, the patient will be  
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18 **9** discharged with the AlphaDBS device delivering aDBS or cDBS for additional 2 weeks. On Day 32  
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20 **10** the patient will undergo the last clinical assessment.  
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23 **12**  
24 **13 Figure 2 –** AlphaDBS system overview  
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28 **16 Figure 3-** Summary of examinations foreseen at each time point of the experimental sessions (Day 2  
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30 **17** and Day 3). Note that timing is indicative and may vary up to 45 min. per session  
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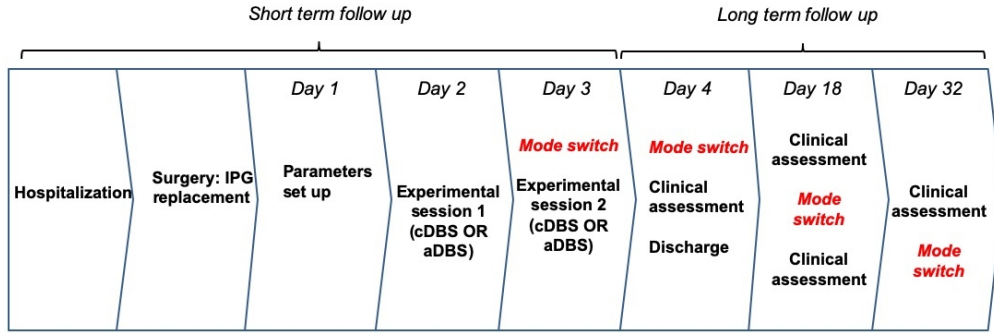


Figure 1 - experimental protocol overview

382x129mm (72 x 72 DPI)

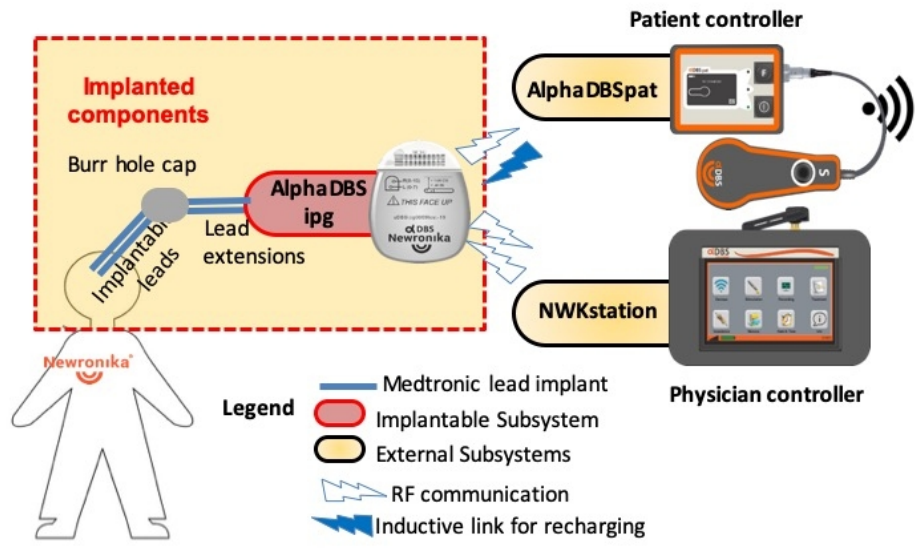


Figure 2 - AlphaDBS system components

264x171mm (72 x 72 DPI)

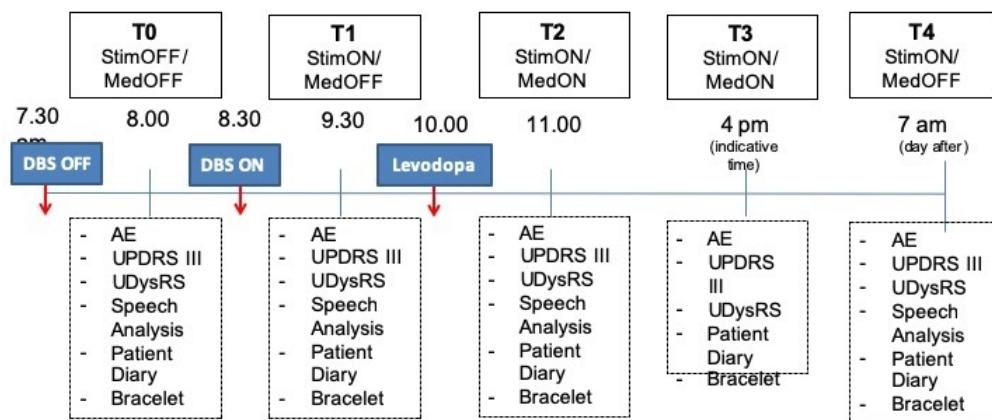










Figure 3 - Short term follow-up: Experimental session details

60x25mm (300 x 300 DPI)

## 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?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you find it is easy to turn on the patient remote control (both parts)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand clearly when the neurostimulator is communicating with the patient remote control?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand clearly the battery level of the implanted neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Considerations about screens and alarms</b>					
Do you hear the alarms?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The information provided in the display of the patient programmer are clear and exhaustive?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Is it clear what is shown on the display when you connect the 2 parts of the patient remote control?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand if the charging procedure is correctly ongoing?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand when the charging process is interrupted due to misalignment of the patient remote control with the implanted neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Do you understand how to check the battery level of your neurostimulator?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

<b>Consideration about the patient remote control and its accessories</b>					
Device dimension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Buttons dimension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Patient remote control portability	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
AlphaDBS T-shirt	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
AlphaDBS Collar	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>User Information</b>					
AlphaDBSpat Patient Manual	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Peer review only

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