

Project	AlphaDBS System	Phase	Post-Production Phase
Subsystem	Overall system	Document type	Summary of safety and clinical performance
Doc code	Doc6_SSCP_aDBS_COMP0 USER	Version number	5.0
Re-design code	RD[22]	Feedback number	FB[11]

AlphaDBS System – System Level

Post-Production Phase – Summary of safety and clinical performance

DOCUMENT REFERENCES		DOCUMENT TYPE	SECURITY	VALIDITY	
Doc6_SSCP_aDBS_COMP0.docx		SSCP	Newronika S.p.A.	Valid	
DOCUMENT SCOPE					
The summary of safety and clinical performance is intended to provide public access to an updated summary of clinical data and other information about the safety and clinical performance of the AlphaDBS System as required by Article 32 of MDR 2017/745.					
VER.	AUTHOR	REVIEWER	APPROVER	DATE AND SIGN	DESCRIPTION
1.0	C. Conti P. Zacchera C. Petrangeli	T. Campbell K. Drake	L. Rossi	29/06/2023	Obsolete
2.0	L. Thommi	C. Conti	L. Rossi	21/12/2023	Obsolete
3.0	T. Campbell	L. Rossi	L. Rossi	16/01/2024	Approved
4.0	C. Conti C. Petrangeli	L. Rossi	L. Rossi	09/08/2024	Approved
5.0	P.Raghunandan	L. Rossi	L. Rossi	14/07/2025	Approved
DOCUMENT CONTROL					
The intended audience of this document shall be internal Project Manager, Quality Manager and external Project Sponsor and Project Manager.					
DISTRIBUTION CONTROLLER					
Lorenzo Rossi (can be different by the approver)					

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DOCUMENT REVISION HISTORY	
VER.	CHANGE DESCRIPTION
1.0	First document release
2.0	Document has been updated.
3.0	Modified according to MDR submission screening review by IMQ (Classification Rule, EMDN Code and Component Categorization). No material changes to remaining content.
4.0	Updated due to IMQ requests
5.0	Updated to include details about the new catalogue number, accessories and components

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References

- [1] Regulation (EU) 2017/745 of the European parliament and of the council on medical devices
- [2] Doc4_CER_aDBS_COMP0 – Clinical Evaluation Report
- [3] Doc4_RMR_aDBS_COMP0 - Risk Management Report
- [4] Doc4_PMCF_aDBS_COMP0 – Post-market Clinical Follow-up plan
- [5] MDCG 2019-9 Rev.1 – Summary of safety and clinical performance; a guidance for manufacturers and notified body

Purpose

Articles 32 of the Regulation (EU) 2017/745 on medical devices requires that the manufacturer shall draw up a summary of safety and clinical performance (SSCP) for implantable devices and for class III devices, other than custom-made or investigational devices.

Summary of safety and clinical performance

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

This SSCP is not intended to replace an Implant card or the Instructions for Use to provide information on the safe use of the device.

The SSCP is not intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The information reported in this paragraph is intended for users/healthcare professionals.

Readability

The SSCP has one part for intended users/healthcare professionals, and a second part for patients. It provides clear information at an appropriate depth to reflect the healthcare professionals' and the patients' different levels of knowledge. The readability of the part of the SSCP intended for patients is assessed by a test given to lay persons.

The readability was assessed by providing the document to laypersons with different literacy background to read. All the lay persons who have read the document was able to understand the terms and details of the device properly. Also, they agreed that the document language was legible and understandable. The manufacturer used this method to confirm that the SSCP was written clearly to the patient. Medical terminology, relevant

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for the medical device and the clinical context, is used consistently throughout the part of the SSCP that is intended for healthcare professionals.

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1. Device identification and general information

1.1 Device trade names

Device category	Catalogue number (REF)	Trade name	Trade mark
Implantable neurostimulator and related accessories	AlphaDBSipg MV	AlphaDBSipg	αDBS Newronika
Implantable neurostimulator and related accessories	AlphaDBSipg DV	AlphaDBSipg	αDBS Newronika
Implantable neurostimulator and related accessories	AlphaDBSext	AlphaDBSext	αDBSext
Implantable neurostimulator and related accessories	NWKstation	NWKstation	αDBSnwkstation
Implantable neurostimulator and related accessories	AlphaDBSpat HP	AlphaDBSpat	αDBSPat
Implantable neurostimulator and related accessories	AlphaDBSpat LP	AlphaDBSpat	αDBSPat
Implantable neurostimulator and related accessories	AlphaDBS Screw Driver MV	AlphaDBS Screw Driver	/
Implantable neurostimulator and related accessories	AlphaDBS Screw Driver DV	AlphaDBS Screw Driver	/

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Implantable neurostimulator and related accessories	AlphaDBSLink	AlphaDBSLink	αDBS Link
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In this document

AlphaDBS System or AlphaDBS	Refers to the AlphaDBS Implantable Neuro Stimulators and related accessories as listed above
AlphaDBSipg	Refers to both the REF; AlphaDBSipg DV and AlphaDBSipg MV
AlphaDBSpat	Refers to both REF; AlphaDBSpat LP and AlphaDBSpat HP
AlphaDBS Screw Driver	Refers to both the REF; AlphaDBS Screw Driver DV and AlphaDBS Screw Driver MV

1.2 Manufacturer's name and address

Manufacturer identification: Newronika S.p.A.

Legal Office: Foro Buonaparte 57, 20121 Milano (MI) - Italy

Operative Labs: Via T. Tasso 1, 20093 Cologno Monzese (MI) - Italy

Tel: (+39) 02 8410 9381

Fax: (+39) 02 9287 8462

Website: www.newronika.com

1.3 Manufacturer's single registration number (SRN)

Manufacturer's SRN: IT-MF-000035433

1.4 Basic UDI-DI

The Basic UDI-DI codes as referred to in Part C of Annex VI of MDR 2017/745 assigned by Newronika to the AlphaDBS are the following:

Basic UDI-D1	AlphaDBSipg MV	805848093IPGMVKQ
	AlphaDBSipg DV	805848093IPGDVJV
	AlphaDBSext	805848093EXTR8
	NWKstation	805848093NWKSTQ2
	AlphaDBSpat LP	805848093PATLPLE
	AlphaDBSpat HP	805848093PATHPL2
	AlphaDBS Screw Driver MV	805848093SDMVM4

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	AlphaDBS Screw Driver DV	805848093SDDVL9
	AlphaDBSlink	805848093LINKKR

1.5 Medical device nomenclature

European Medical Device Nomenclature (EMDN) code:

- J02010101 - DEEP BRAIN STIMULATION (DBS) IMPLANTABLE NEUROSTIMULATORS, RECHARGEABLE

1.6 Class of device

Device classification: Class III as per MDR 2017/745 of Annex VIII, Rule No.8, 9 and 22

1.7 Year when the first certificate (CE) was issued covering the device

February 11th, 2021.

1.8 Authorized representative

The Newronika SpA is a European based company located in Italy. Therefore, Newronika SpA manufacturing AlphaDBS System does not require a European Authorized Representative.

1.9 Notified body's (NB) name and the NB's single identification number

Notified body: IMQ S.p.A.

Via Quintiliano 43 - 20138 Milano - Italia

Tel: (+39) 02 50 73 1

Fax: (+39) 02 50 99 15 00

Website: www.imq.it

Email: info@imq.it

NB identification number: 0051

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2. Intended use of the device

2.1. Intended purpose

AlphaDBS Implantable neurostimulators and related accessories are intended for conventional or adaptive deep brain stimulation (DBS) as an adjunctive therapy to reduce symptoms of levodopa-responsive Parkinson's Disease (PD) that are not adequately controlled by medications.

2.2. Indications and target population

Indications for use

AlphaDBS Implantable neurostimulators and related accessories are indicated for the management of Parkinson Disease (PD) symptoms such as tremor, rigidity, bradykinesia/akinesia and dyskinesia.

Intended target population

The target population of the AlphaDBS System consists of patients with levodopa-response Parkinson's disease who are not adequately controlled by medications. The target population is the same as for conventional DBS treatment.

Contraindications

The implantation of AlphaDBS system is contraindicated in the following cases:

- For patients in whom trial stimulation is ineffective.
- For patients who are unable to make the system work properly.
- Diathermic therapy. Patients with a neurostimulation system should not be subjected to shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (collectively referred to as 'diathermy'). The energy generated by diathermy can cross the implanted system and cause tissue damage at the site of implant, causing serious injury or death of the patient. Such injuries or damage may occur during diathermic treatment regardless of whether the neurostimulation system is switched on or off. All patients are advised to inform their doctor about the inability to expose themselves to diathermic treatment.
- Magnetic resonance imaging (MRI). Patients implanted with AlphaDBS should not undergo MRI. Since the magnetic resonance imaging energy can be transferred through the implanted system, there is the possibility of generating heat at the point where the electrodes are placed. This isolated rise in temperature can cause tissue damage at the electrode implantation site, resulting in serious injury or death of the patient. Injuries may occur during magnetic resonance treatment regardless of whether the neurostimulation system is switched on or off. All patients are advised

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to inform their physician of the inability to undergo magnetic resonance imaging (MRI).

Safety warnings

- Intracranial Hemorrhage. Special precautions should be taken for patients who are prone to hemorrhage including patients with coagulopathy, with high blood pressure, or who are using prescribed anticoagulants. Microelectrode penetration and DBS Lead insertion can put patients who have a likelihood of intracranial hemorrhages at greater risk.
- Electromagnetic Interference. Strong electromagnetic fields can potentially turn AlphaDBSipg off, cause temporary unpredictable changes in stimulation, or interfere with AlphaDBSpat or NWKstation communication. Patients should be counseled to avoid or exercise care around:
 - Theft detectors such as those used at entrances/exits of department stores, libraries, and other public establishments. The patient should proceed with caution, ensuring to move through the center of the detector as quickly as possible.
 - Security screeners, such as those used in Airport Security or at entrances to government buildings, including hand-held scanners. The patient should request assistance to bypass the device. If the patient must pass through the security screener, they should move quickly through the device staying as far from the physical device as allowable.
 - Power lines or power generators.
 - Electric steel furnaces and arc welders.
 - Large magnetized stereo speakers.
 - Strong magnets.
 - Automobiles or other motorized vehicles using a LoJack system or other anti-theft systems that can broadcast a radio frequency (RF) signal.
 - Other sources of electromagnetic interference, such as RF transmitters at television or radio broadcast stations or transceivers.
- Therapeutic Ionizing Radiation. Electronic components in AlphaDBSipg can be damaged by therapeutic ionizing radiation. Any damage to the implanted part of the AlphaDBSipg might not be immediately detectable.
- Heat Due to Charging. The charger, AlphaDBSpat, may become warm while charging the Stimulator. The Charger should be handled with care. The Patient should not charge while sleeping. This may result in a burn. If the patient experiences pain or discomfort, they should cease charging and contact their physician.
- Stimulator Damage. Chemical burns may result if the Stimulator housing is ruptured or pierced, exposing the patient's tissue to battery chemicals. Do not implant the AlphaDBSipg Stimulator if the housing is damaged.

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- **Suicide.** Depression, suicidal ideation, and suicide are risks previously reported in relation to DBS. If the patient reports depression or suicidal thoughts, consider adjustment of stimulation, discontinuing stimulation, adjusting medication, and/or psychiatric referral.
- **Other Active Implantable Devices.** Stimulators, such as the AlphaDBSipg, may interfere with the operation of implanted sensing stimulation devices such as pacemakers or cardioverter defibrillators. The effects of implanted stimulation devices on the neurostimulator AlphaDBSipg are unknown.
- **Automobiles and Equipment.** Patients should operate automobiles, other motorized vehicles, or potentially dangerous machinery/equipment with caution after receiving the AlphaDBS. Performing activities that would be dangerous if treated symptoms were to return, or instances in which stimulation changes occur, should be avoided.
- **Pregnancy** It is unknown whether this device may hurt an unborn baby.

Precaution

Physician training is required for usaging of the AlphaDBS. The implanting physician should be experienced in Stereotactic and Functional Neurosurgery. The following is a list of precautions that should be taken when implanting or using the AlphaDBSipg.

- **Connections.** Before inserting DBS Extension into any connector or header ports, including the AlphaDBSipg Hader, DBS Extension connectors, and operating room cable assembly, always wipe the connections with a dry cotton sponge. Contamination inside the ports may be difficult to remove and can cause high impedances, preventing electrical connectivity which may compromise the integrity of the stimulation circuit.
- **Components.** The use of components other than those supplied by Newronika and intended for use with the AlphaDBS may: damage the system, diminish the effectiveness of therapy, and/or put the patient at unknown risk.
- **Excess DBS Extension.** Coil excess DBS Extension around or below the AlphaDBSipg. Excess wire on top of the Stimulator may increase the potential for tissue erosion or damage during Stimulator replacement surgery and may interfere with charging.
- **Other Models of External Devices.** Only the NWKStation, AlphaDBSext, and AlphaDBSpat that were provided with the Newronika AlphaDBS should be used. Other models of these devices will not function with the AlphaDBS.
- **Stimulator Orientation.** To ensure proper charging, orient the Stimulator parallel to the skin surface and at a depth less than 1 cm below the skin. The etched writing "This Face Up" must be facing out of the pocket towards the patient's skin. Suboptimal placement of the Stimulator may result in the inability to recharge and/or a revision surgery.

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- **Setscrews.** Before tightening Setscrews, always test impedance to confirm electrical connectivity. Tightening a Setscrew onto a contact may damage the contact and may result in the need to replace the DBS Lead Extension.
- **Device Failure.** Implants can fail at any time due to random component failure, loss of battery functionality, or component breakage. Suddenly stopping brain stimulation can cause serious reactions to develop. If the Stimulator stops working even after complete charging, patients should be instructed to turn off the Stimulator and contact their physician immediately so that the system can be evaluated and appropriate medical care given to manage the return of symptoms.
- **Tissue Reaction.** Temporarily, there may be some pain in the area of the Stimulator as the incisions heal. If there is excessive redness around the wound area, it should be checked for infection. In rare cases, adverse tissue reaction to implanted materials can occur.
- **Cell Phones.** While interference with cell phones is not anticipated, the full effects of interaction with cell phones are unknown at this time. Advise patient to not place cell phone in his/her shirt pocket or directly on components of AlphaDBS. If some interferences happen, place cell phone on the other hear or turn off cellular.
- **Patient Activities.** During the two weeks following surgery, it is important for the patient to exercise extreme care so that appropriate healing will secure the implanted components. During this period, the patient should not attempt to move heavy objects. Instruct the patient to restrict head movements, including extension or flexion of the neck and rotation of the head, until healing is complete.
- **Massage Therapy.** Patients should avoid receiving massage therapy near the implanted system components. If a patient does receive massage therapy, the patient should inform the masseuse that they have an implanted device and show him/her where the Stimulator, DBS Extension, and DBS Leads are located. The patient should have the masseuse avoid these areas and proceed with caution.
- **Environmental Precautions.** Patients should avoid activities that could potentially involve large amounts of electromagnetic interference. Devices that contain permanent magnets, such as speakers, should not be placed near the Stimulator or other parts of AlphaDBS because they may cause the system to turn on or off.
- **Medical Devices/Therapies.** The AlphaDBSipg, also if the stimulation is turned off, could be associated to injuries to the patient or damages to the neurostimulator itself in case of:
 - **Electrocautery** – Electrocautery can transfer destructive current into the DBS Leads and/or Stimulator.
 - **Lithotripsy** – High frequency signals directed near the neurostimulator may damage circuitry.

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- Radiation Therapy – Lead shielding should be used over the Stimulator to prevent damage from high radiation. Any damage to the device by radiation may not be immediately detectable.
- Transcranial Stimulation – Safe use of electromagnetic therapies, such as transcranial magnetic stimulation, have not been established.
- External Defibrillation
- Ultrasound (US)
- If any of the above is required by medical necessity, the procedure(s) should be performed with the stimulation off and as far from the implanted components as possible. After having used one of the previous medical therapies, it is necessary to check functionalities of AlphaDBipg through NWKstation, trying to reset stimulation parameters and to measure impedance.
- Inspect packaging before use. Check the expiration date on the package before opening the sterile package and using the contents. Do not use the contents if the current date is past the expiration date, if the package is opened or damaged, or if contamination is suspected because of a defective sterile package seal.
- Inspect the seal integrity of the outer tray before use.
- Open the inner tray in the sterile field.
- If the Stimulator was dropped, do not implant it in a patient. The dropped Stimulator may have lost sterility, experienced a loss of hermeticity, or been otherwise damaged. Replace the dropped Stimulator with a new, sterile Stimulator prior to implantation. Return the damaged Stimulator to Newronika.
- Do not use any component that shows signs of damage.
- Do not use if “Use By” date has expired.
- AlphaDBS shall be used exclusively with certified intracranial electrodes.
- In the case of any malfunctioning, please immediately contact the manufacturer.
- AlphaDBS maintenance can be done only by the manufacturer.
- To avoid unintended stimulation, do not modify the operating system in any way. Do not use the application if the operating system has been compromised (jailbroken).
- Do not use AlphaDBS with sharp objects (pens, pencils, screwdrivers).
- Keep AlphaDBS away from kids in order to avoid asphyxiation and strangulation dangers.
- Inform the specialized staff when DBS is used in patients with other implanted devices, such as pacemakers, intracranial electrodes, defibrillators, or any other prosthesis.

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- The use of device shall agree with the indications reported in the present manual.
Do not use AlphaDBS in a different manner.

Adverse Events

If any of these events occur, you should contact your physician as soon as possible to inform them.

The following is a list of known risks associated with the use of DBS treatment of Parkinson's disease. Note that some of these symptoms may be resolved or reduced by current steering, changing stimulation parameters, or by changing the position of the lead during surgery.

Risks Associated With Surgical Procedure and Post-Operative Period

- Allergic reaction to anesthesia or antibiotics including anaphylaxis.
- Anesthesia/neurosurgery risks, including unsuccessful implant, exposure to bloodborne pathogens.
- Embolism, including air embolism and pulmonary embolism.
- Hemorrhagic or ischemic stroke, immediate or delayed, which could result in temporary or permanent neurologic deficits such as muscle weakness, paralysis or aphasia.
- Injury to tissues adjacent to implant or within surgical field, such as blood vessels, peripheral nerves, brain (including pneumocephalus), or pleura (including pneumothorax).
- Blood clot formation in the extremities (e.g., in the veins of the legs).
- Blood clot or air forming in or traveling through the blood stream, which can block blood flow to parts of the lungs or other tissue that could be life-threatening.
- Confusion or problems with attention, thinking, or memory (acute or chronic).
- Death.
- Fibrosis (thickened skin and scarring) around the lead extension (including tightening, tethering, and bowstringing).
- Hemiparesis (muscular weakness or partial paralysis on one side of the body).
- Hemiballism (uncontrollable involuntary movements of a limb or limbs on one or both sides of the body).
- Intracranial hemorrhage (which can lead to stroke, paralysis, or death).
- Intraparenchymal cyst.
- Infection.
- Injury to areas next to the implant, such as blood vessels, nerves, the chest wall, and the brain.

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- Injury to the nerves in the armpit (brachial plexus) leading to pain or weakness of the arm or hand.
- Neurosurgery/anesthesia risks, including unsuccessful implant and pneumonia.
- Pain at the surgical site(s), headache or discomfort.
- Seizures.
- Speech or language difficulties.
- Subcutaneous hemorrhage or seroma.
- Stroke.
- Swelling or bruising of the muscles or skin in the area of the lead or of the IPG implant.

Possible Side-Effects of Stimulation

- Confusion or problems with attention, thinking, or memory.
- Gait difficulty (trouble walking) and falls.
- Pain, headache or discomfort.
- Pneumonia from difficulty with swallowing or from inhaling fluid.
- Psychiatric disturbances such as anxiety, depression, lessened interest or emotion, hypersexuality, aggression, mania or hypomania, psychosis, emotional sensitivity, sleep problems, suicide, or suicidal thoughts or attempts.
- Mentation impairment such as attention or cognitive deficits, memory disturbances, or confusion.
- Seizures.
- Sensory changes.
- Speech or language problems.
- Swallowing difficulty such as dysphasia, dysarthria or dysphagia, as well as complications of dysphagia such as aspiration pneumonia.
- Systemic effects such as rapid heartbeat, sweating, fever, dizziness, changes in kidney function, difficulty passing urine, sexual effects, nausea, difficulty having bowel movements, bloating.
- Weakness, muscle spasms, shaking, restlessness, or problems with movement.
- Undesirable sensations (e.g., tingling).
- Visual disturbances or periorbital symptoms, such as diplopia, eyelid movement difficulty, oculomotor difficulties or other visual field effects and eye-related symptoms.
- Weight changes.

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Device-Related Risks

- Allergic or immune system response to implanted materials.
- Failure or malfunction of any part of the device, including but not limited to: Battery leakage, battery failure, lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches, whether or not these problems require device removal and/or replacement.
- Implant site complications such as pain, poor healing, redness, warmth, swelling or wound reopening.
- Implanted neurostimulator may be cause skin erosion and/or move from original implanted location, which may lead to the need for additional surgery.
- Infection.
- Interference from external electromagnetic sources.
- Loss of adequate stimulation.
- Pain, headache or discomfort.
- Skin irritation or burns at the stimulator site.
- Stiffness in muscles or joints or worsening of disease symptoms, potentially caused by loss of stimulation, medication changes, surgery, or illness. In rare cases worsening can become a life-threatening crisis associated with varied symptoms such as mental status changes, fever, and muscle rigidity.
- Swelling, including fluid collecting around the device.

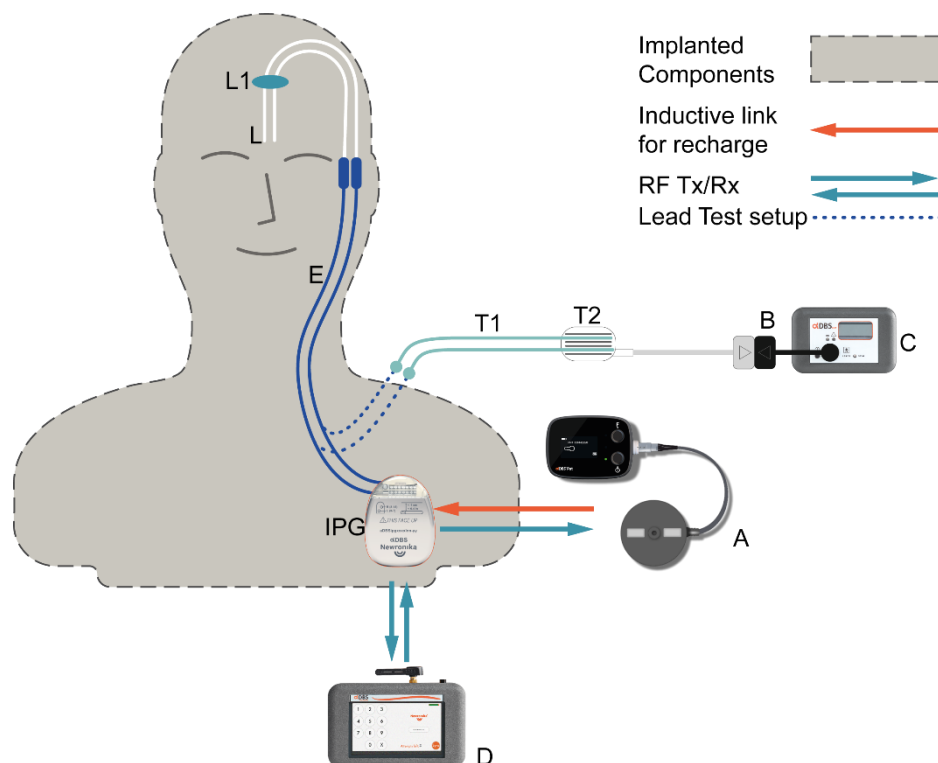
Note:

In case of reappearance of PD symptoms, pain/swelling in the area of the device implant or in case of any new symptom or for any other problems the patient should immediately contact the treating physician.

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3. Device description

3.1. Description of the device



The AlphaDBS System and Components (does not include implantable leads, lead extensions or trialing cable). (A. AlphaDBSpat, B. AlphaDBS Adapter Plug, C. AlphaDBSext, D. NWKstation, E. Lead Extensions (Medtronic), L. Lead Electrodes (Medtronic), L1. Leads, T1. Externalized leads extensions, T2. Multi-lead Trialing Cable.

This neuromodulation system is designed to deliver electrical impulses to nerve structures, and to simultaneously record and analyse neurophysiological signals AlphaDBS System also features algorithms that automatically vary stimulation parameters according to changes in input signals when programmed in adaptive mode. AlphaDBSipg is intended to be used with leads and associated extensions that are compatible with them.

Differently from other systems for Deep Brain Stimulation (DBS) on the market, the AlphaDBS Implantable neurostimulator can be programmed with two different types of stimulation: conventional DBS (cDBS), which is implemented also by other DBS systems,

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and adaptive DBS (aDBS) that automatically adjusts the energy delivered to patient using a biosignal, local field potential (LFP), in a closed-loop configuration.

The AlphaDBS System is composed of different components, and accessories that can be used in conjunction.

Catalogue Number	Trade Name	Photograph	Description
AlphaDBSipg MV	AlphaDBSi pg		Implantable pulse generator that both delivers chronic stimulation and records and analyzes the neuronal signals coming from the leads to adapt stimulation parameters AlphaDBSipg MV is designed to be compatible with the Medtronic leads (model 3389 and extensions model 37086). This is a single use sterile device, sterilized by

Project	AlphaDBS System	Phase	Post-Production Phase
Subsystem	Overall system	Document type	Summary of safety and clinical performance
Doc code	Doc6_SSCP_aDBS_COMP0 USER	Version number	5.0
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			Ethylene Oxide.
AlphaDBSipg DV	AlphaDBSipg		Implantable pulse generator that both delivers chronic stimulation and records and analyzes the neuronal signals coming from the leads to adapt stimulation parameters AlphaDBSipg DV is designed to be compatible with Abbott leads (Model 6170-6172) and Abbott extensions (Model 6371). This is a single use sterile device, sterilized by Ethylene Oxide.
Accessories			

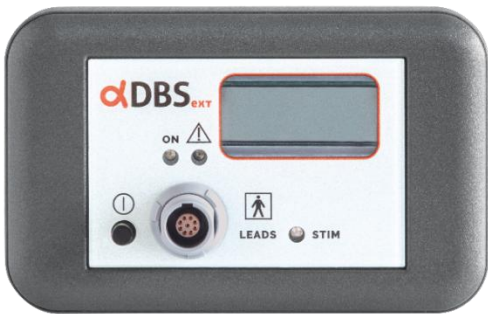
Project	AlphaDBS System	Phase	Post-Production Phase
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AlphaDBSpat HP	AlphaDBS pat	 The image shows the AlphaDBS Pat HP external controller, a black rectangular device with a small screen, a battery level indicator, and two large circular buttons labeled 'F' and 'ON'. Below the buttons is a green LED light. A charging coil with a cable is also shown, connected to the controller.	External controller that allows the patient to interact with AlphaDBSipg and to recharge it. The AlphaDBSpat HP is able to recharge the AlphaDBSipg through an inductive coil and to exchange information via radiofrequency with the AlphaDBSipg about its status and activity. When the patient wants to recharge its AlphaDBSipg, the user shall place the devices above the AlphaDBSipg implanted area
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Project	AlphaDBS System	Phase	Post-Production Phase
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AlphaDBSpat LP	AlphaDBS pat	 The image shows two components of the AlphaDBS system. The top component is the AlphaDBSpat LP, a black rectangular device with a small screen, a battery level indicator, and two large circular buttons labeled 'F' and 'ON'. The bottom component is an external controller, a circular device with a cable attached, used for recharging the AlphaDBSpat LP.	External controller that allows the patient to interact with AlphaDBSipg and to recharge it. The AlphaDBSpat LP is able to recharge AlphaDBSipg through an inductive coil and to exchange information via radiofrequency with AlphaDBSipg about its status and activity. When the patient wants to recharge its AlphaDBSipg, he/she shall place the devices above AlphaDBSipg implanted area
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Project	AlphaDBS System	Phase	Post-Production Phase
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NWKstation	NWKstation		External device that allows the physician to program both AlphaDBSext and AlphaDBSipg
AlphaDBSext	AlphaDBS ext		External pulse generator that measures the impedance of the implantable leads at the electrode contacts level during surgical procedures
AlphaDBS Screw Driver MV	AlphaDBS Screw Driver		Single-use accessory used during IPG implantation to fix leads extensions to AlphaDBSipg MV header using the stainless-steel screws.

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			This is a single use sterile device, sterilized by Ethylene Oxide.
AlphaDBS Screw Driver DV	AlphaDBS Screw Driver		Single-use accessory used during IPG implantation to fix leads extensions to AlphaDBSipg DV header using the stainless-steel screws. This is a single use sterile device, sterilized by Ethylene Oxide.
AlphaDBSlink	AlphaDBSlink		AlphaDBS Link is an external device that enables communication between the AlphaDBSipg and an external Bluetooth programming interface (AlphaDBSpad) by serving as a

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			transdecoder. It also connects the AlphaDBSipg with AlphaDBSstim, a mobile app that is installed on AlphaDBSpad
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3.2 A reference to previous generation(s) or variants, and a description of the differences

The device development process included the implementation of both types of DBS delivery, and has focused on aDBS, which is the innovation introduced by AlphaDBS System.

The initial generations of the device were external and were used mainly to prove the case for the use of aDBS.

In 2019, Newronika completed the development of its Implantable Pulse Generator (IPG) together with the subsystems that are part of the AlphaDBS System that was CE marked in 2021.

External prototypes

AlphaDBS system development started in 2006 and included the following steps:

LFPs recording during DBS: The first ever published methodology and apparatus (named FilterDBS) to record LFPs while DBS stimulation was on, was developed and patented in EU, US and Israel (Priori et al, European Patent EP1940508 - U.S. Patent No. 8,078,281 – Israel Patent n.191068).

First closed-loop external prototype: The first closed-loop prototype delivering adaptive DBS (AlphaDBSvext_V1) was developed in 2013 exploiting the results of basic neurophysiology research conducted on LFPs from 2006 to 2012. The system for clinical investigation was tested for general safety requirements (IEC 60601-1) and EMI compatibility (IEC 60601-1-2). The device had one stimulation channel and one recording channel with a single microprocessor unit. The device was designed to be connected to externalized intracranial leads in the time period between leads implant and IPG

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implantation, immediately following the stereotactic implant procedure. The prototype was able to provide stimulation in the adaptive (aDBS) and conventional DBS (cDBS) modes.

The AlphaDBSvext_V1 was tested in two case studies (CS1 and CS2) conducted in PD patients immediately after DBS electrodes implant. The adaptive algorithm was designed to avoid dyskinesia related to hyperstimulation: when levodopa administration reduced beta-band LFP activity, the voltage linearly diminished, avoiding hyperstimulation. The results of CS1 confirmed the ability of the algorithm to reduce dyskinesia related to hyperstimulation compared to cDBS. CS2 confirmed that the device is able to follow LFP activity precisely and that LFP activity correlates with clinical fluctuations. The data collected in these first patients were used to improve the algorithm that modulates the DBS stimulation voltage.

The same prototype (AlphaDBSvext_V1) with an improved/upgraded algorithm was used in two pilot study (PS1 and PS2, for a total of 23 patients) aimed at evaluating the safety and the efficacy of the investigational device.

External system upgrade: The AlphaDBSvext was upgraded (AlphaDBSvext_V2) to increase safety, to ensure longer battery life and to allow radiofrequency communication. The AlphaDBSvext_V2 is being used in a third pilot study (PS3), collecting data on patients chronically implanted with DBS and undergoing the surgery for IPG replacement, to compare the safety and the efficacy of cDBS and aDBS. This clinical investigation was designed to overcome limitations experienced in studying the effects of aDBS in the post-surgical period (all previous studies), immediately after leads implant, when symptom improvement may be in part attributed to lesional or implantation effects.

The AlphaDBSvext_V2 prototype was tested, for 24 hours, on 6 patients undergoing battery replacement. The AlphaDBSipg has successfully completed all bench tests and in vivo biocompatibility tests and usability tests, according with applicable standards. The CE mark process for the AlphaDBS system, with the only cDBS mode enabled, is ongoing.

First generation AlphaDBS implantable neurostimulator

The knowledge gained from the testing outlined above was transferred to further improvements in the implantable device AlphaDBSipg. The system is designed to deliver cDBS and aDBS, implementing the same adaptive algorithm used in the external prototype.

The AlphaDBS System development was completed in 2019 and CE marked in 2021 for cDBS under EU Directive 90/385/EEC on active implantable medical device directive (AIMDD).

In 2020, the Sponsor started a clinical investigation using the AlphaDBS System, with both cDBS and aDBS modes enabled. The first patient was implanted in January 2021.

The AlphaDBSpat was redesigned in 2022 and the previous version (part of the CE marked AlphaDBS System) is considered obsolete.

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The new design of the AlphaDBSpat was driven from experience gained during the first patients implanted in Pilot Study 4 that suggested an improvement of the recharging process.

This redesign affected both software and hardware part of the AlphaDBSpat. New version of the PCBs has been released including a change in the schematics, gerber and BOM files. The technical and safety tests have been redone in order to prove compliance of the new version of the AlphaDBSpat to the applicable standards.

List of Variants

There is just one configuration of the AlphaDBS System that is intended to be commercialized on the market.

3.3. Description of any accessories which are intended to be used in combination with the device

i. Accessories

CatalogueNumber	Image	Component	Accessory
<u>AlphaDBSext</u>	 The image shows the AlphaDBSext device, a rectangular unit with a black frame and a white faceplate. It features a small LCD screen at the top right, a power button and a warning symbol (triangle with exclamation mark) to its left, and a large circular connector port at the bottom left. Below the port are two smaller buttons labeled 'LEADS' and 'STIM'.	☐	☒

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<u>NWKstation</u>		☐	☒
<u>AlphaDBSpat HP</u>		☐	☒

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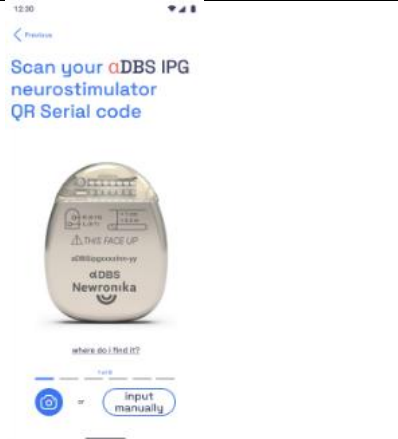
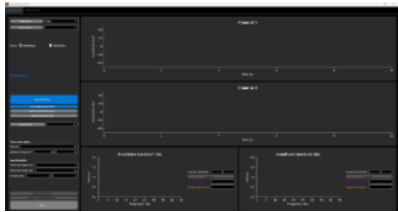
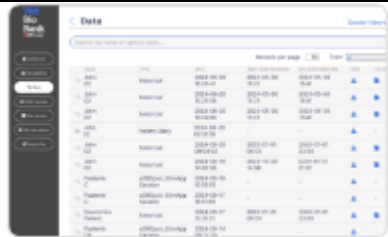
<u>AlphaDBSpat LP</u>			
<u>AlphaDBS Screw Driver DV</u>		☐	☒
<u>AlphaDBS Screw Driver MV</u>		☐	☒

Project	AlphaDBS System	Phase	Post-Production Phase
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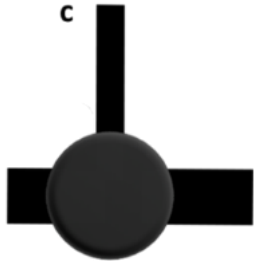
ii. Components

Catalogue Number	Device Image	Component	Optional Component
AlphaDBS Adapter Plug MV		☒	☐
AlphaDBS Adapter Plug DV		☒	☐
NWKpower supply		☒	☐
PAT power supply		☒	☐
PATreset		☐	☒
USB-MiniDin Cable		☐	☒

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AlphaDBSapp			☒
AlphaDBSdesk		☐	☒
AlphaDBSpad + AlphaDBSstim		☒	☐
AlphaDBSweb		☐	☒

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AlphaDBS Harness	 A diagram of a black harness with a central circular component and two horizontal straps. The letter 'c' is positioned above the central circle.	☐	☒
AlphaDBS T-Shirt_	 A diagram of a grey short-sleeved t-shirt with orange trim along the edges and a central zipper. The letter 'a' is positioned above the t-shirt.	☐	☒
AlphaDBS Clip	 A diagram of a grey clip with a curved shape and a central protrusion.	☐	☒
AlphaDBS Bag	 A photograph of a black zippered bag with a small red and white label that reads 'Newronika'.	☐	☒

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iPad Case		☐	☒
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3.4. Description of any other devices and products which are intended to be used in combination with the device

AlphaDBSipg MV and the AlphaDBSext are designed to be compatible with the Medtronic leads (model 3389 and extensions model 37086). AlphaDBSipg DV and the AlphaDBSext are designed to be compatible with the Abbott leads (Model 6170-6172 and extensions model 6371).

Therefore, the implant of AlphaDBS system with the Medtronic leads or Abbott Leads is considered a hybrid implant.

During the standard of care practice of lead implantation, the implanted leads drive electrical stimuli from the implanted neurostimulator to the target area in the brain.

Patients who have undergone Medtronic DBS leads implantation and are in need of IPG replacement, already have the following components implanted:

- Two (2) “implantable lead electrodes” (one for the left side, and one for the right side of the brain) with four contacts at each end; these electrodes allow stimulation of specific target areas in the brain;
- Two (2) “lead extensions” (distal end: 4 contacts – proximal end: 8 contacts) in order to connect the implantable electrodes with the AlphaDBSipg.

Patients who are in need for new leads implantation will undergo to Abbott leads + extensions implantation:

- Two (2) “implantable lead electrodes” (one for the left side, and one for the right side of the brain) with eight contacts at each end; these electrodes allow stimulation of specific target areas in the brain;
- Two (2) “lead extensions” (distal end: 8 contacts – proximal end: 8 contacts) in order to connect the implantable electrodes with the AlphaDBSipg.

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Newronika is now certifying only the implanted neurostimulator (the AlphaDBSipg) and is planning to use it on patients implanted with commercially available leads from Abbott, the AlphaDBSipg DV needs to be compatible in terms of functionality and mechanical interface with such leads.

Therefore, AlphaDBSipg MV and the AlphaDBSext are designed to be compatible with the Medtronic leads and can be directly connected without the need for additional adapters (leads model 3389 and extensions model 37086).

While, AlphaDBSipg DV and the AlphaDBSext are designed to be compatible with the Abbott leads and can be directly connected without the need for additional adapters (Model 6170-6172 and extensions model 6371).

4 Risks and warnings

4.1 Residual risks and undesirable effects

As per harmonized standard EN ISO 14971:2019/A11:2021, Newronika establishes, documents and maintains throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. Risk management process requirements set by EN ISO 14971:2019/A11:2021 has been fulfilled.

For AlphaDBS System, all the risks identified during development stage, and possibly associated to the clinical use of the devices have been mitigated through risk control measures.

After application and verification of all proposed control measures and after completion of the tests required by applicable Standards the residual risk is considered extremely limited, thanks to both decreasing harms occurrence probability and increasing in ability to apply immediately, the control measures. The risk management shows that, using design, procedure and informative risk control measures, occurrence, severity, and residual risk level remain within the acceptable limits.

After comparing the established benefits against the overall residual risk of AlphaDBS System, and since the criterion for overall risk acceptability is to have no unacceptable individual risks, the overall residual risk posed by the medical device is judged acceptable and it is deemed that the benefits of AlphaDBS System outweigh its risks.

The following is a list of known risks associated with the use of DBS treatment of Parkinson's disease. Note that some of these symptoms may be resolved or reduced by current steering, changing stimulation parameters, or by changing the position of the lead during surgery.

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Risks Associated with Surgical Procedure and Post-Operative Period (based on data collected from similar devices):

- Allergic reaction to anesthesia or antibiotics including anaphylaxis (4.8%, period of observation 3 yrs, *Medtronic Clinical Summary 2015*).
- Anesthesia/neurosurgery risks, including unsuccessful implant, exposure to bloodborne pathogens (1.2%, period of observations 3 yrs, *Medtronic Clinical Summary 2015*).
- Embolism, including air embolism and pulmonary embolism (1.6%, period of observations 2 yrs, *Medtronic Clinical Summary 2015*).
- Hemorrhagic or ischemic stroke, immediate or delayed, which could result in temporary or permanent neurologic deficits such as muscle weakness, paralysis or aphasia (1-2% of patients implanted and is recorded as immediate complications of the surgery, Ramirez-Zamora et al., 2013).
- Injury to tissues adjacent to implant or within surgical field, such as blood vessels, peripheral nerves, brain (including pneumocephalus (5.9%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), or pleura (including pneumothorax).
- Blood clot formation in the extremities (e.g., in the veins of the legs) (1.2%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Blood clot or air forming in or traveling through the blood stream, which can block blood flow to parts of the lungs or other tissue that could be life-threatening.
- Confusion or problems with attention, thinking, or memory (acute or chronic) (45.5%, period of observations 3 yrs, *Medtronic Clinical Summary 2015*).
- Death (device-related or DBS-related deaths are only reported in clinical study as complications of DBS implant procedure).
- Fibrosis (thickened skin and scarring) around the lead extension (including tightening, tethering, and bowstringing).
- Hemiparesis (muscular weakness or partial paralysis on one side of the body) (as consequence of stroke which occurs in relation to cerebral hemorrhage as reported below).
- Hemiballism (uncontrollable involuntary movements of a limb or limbs on one or both sides of the body).
- Intracranial hemorrhage (which can lead to stroke, paralysis, or death) (1-2% of patients implanted and is recorded as immediate complications of the surgery, Ramirez-Zamora et al., 2013).
- Intraparenchymal cyst (Anecdotal reporting, Ramirez-Zamora et al., 2013).
- Infection (7.5%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Injury to areas next to the implant, such as blood vessels, nerves, the chest wall, and the brain (7.5%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Injury to the nerves in the armpit (brachial plexus) leading to pain or weakness of the arm or hand.

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- Pain at the surgical site(s), headache or discomfort (22.5%-44.4%-4.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Seizures.
- Speech or language difficulties (58.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Subcutaneous hemorrhage or seroma.
- Stroke (1-2% of patients implanted and is recorded as immediate complications of the surgery, Ramirez-Zamora et al., 2013).
- Swelling or bruising of the muscles or skin in the area of the lead or of the IPG implant.

Possible Side-Effects of Stimulation:

- Confusion or problems with attention, thinking, or memory (15.5%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Gait difficulty (trouble walking) and falls (58.3%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Pain (22.5% at incision site, period of observation 3 yrs *Medtronic Clinical Summary 2015*), headache (44.4%, period of observation 3 yrs *Medtronic Clinical Summary 2015*) or discomfort (4.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Pneumonia from difficulty with swallowing or from inhaling fluid (pneumonia aspiration – 1.2%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Psychiatric disturbances such as anxiety (1.2%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), depression (59.9%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), lessened interest or emotion, hypersexuality (19.3%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), aggression, mania or hypomania, psychosis, emotional sensitivity, sleep problems (5.9%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), suicide, or suicidal thoughts or attempts.
- Mentation impairment such as attention or cognitive deficits (5.9%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), memory disturbances, or confusion.
- Seizures (1.2%, period of observation 3 yrs, *Medtronic Clinical Summary 2015*).
- Sensory changes (paraesthesia – 7%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Speech or language problems (58.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Swallowing difficulty such as dysphasia, dysarthria or dysphagia (57.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Systemic effects such as rapid heartbeat, sweating, fever (0.7%, period of observation 2 yrs *Medtronic Clinical Summary 2015*), dizziness (10.2%, period of

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- observation 3 yrs *Medtronic Clinical Summary 2015*), changes in kidney function, difficulty passing urine (7%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), sexual effects, nausea (16.6%, period of observation 3 yrs *Medtronic Clinical Summary 2015*), difficulty having bowel movements, bloating.
- Weakness, muscle spasms, shaking, restlessness, or problems with movement.
 - Undesirable sensations (e.g., tingling).
 - Visual disturbances or periorbital symptoms, such as diplopia, eyelid movement difficulty, oculomotor difficulties or other visual field effects and eye-related symptoms (9.1%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
 - Weight changes (increase – 7.5%, decrease – 5.4%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).

Residual Risks:

- Return of PD Symptoms (bradykinesia 46%, dystonia 55%, tremor 50.3%, motor dysfunction 46.5%, period of observation 3 yrs, *Medtronic Clinical Summary 2015*)
- Overstimulation side effects (dyskinesia, 3.6%, period of observation 3 yrs, *Medtronic Clinical Summary 2015*)
- Lead explant surgery side effects
- Internal tissue damage
- Electrical shock
- User inconvenience
- Skin irritation
- Nervous tissue irreversible damage
- Tissue damage due to temperature
- Infection (7.5%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).

Device-Related Risks are comparable to the risks:

- Allergic or immune system response to implanted materials (resulting in signs and symptoms reported below, e.g pain, redness, swelling, warmth, etc).
- Failure or malfunction of any part of the device, including but not limited to: Battery leakage, battery failure, lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches, whether or not these problems require device removal and/or replacement (3.8%, period of observation 2 yrs, *Medtronic Clinical Summary 2015*).
- Implant site complications such as pain, poor healing, redness, warmth, swelling or wound reopening (1%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Implanted neurostimulator may be cause skin erosion (1.2%, period of observation 3 yrs, *Medtronic Clinical Summary 2015*) and/or move from original implanted location, which may lead to the need for additional surgery (1%, period of observation, *Medtronic Clinical Summary 2015*).

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- Infection (7.5%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Interference from external electromagnetic sources.
- Loss of adequate stimulation (determining return of PD symptoms, see above).
- Pain (22.5% at incision site, period of observation 3 yrs *Medtronic Clinical Summary 2015*), headache (44.4%, period of observation 3 yrs *Medtronic Clinical Summary 2015*) or discomfort (4.8%, period of observation 3 yrs *Medtronic Clinical Summary 2015*).
- Skin irritation or burns at the stimulator site.
- Stiffness in muscles or joints or worsening of disease symptoms, potentially caused by loss of stimulation, medication changes, surgery, or illness. In rare cases worsening can become a life-threatening crisis associated with varied symptoms such as mental status changes, fever, and muscle rigidity.
- Swelling, including fluid collecting around the device.

Based on a Product Performance report from a commercially available conventional DBS product, adverse events associated with neurostimulator malfunction are rare (about 1.4%, or 55 events over 3,928 neurostimulators implanted from 2009 onward). In the event of a failure or malfunction, the IPG may need to be replaced. This is typically done under local anaesthesia. Such neurostimulator related events were classified as:

- High Impedance: 29 events (1% of neurostimulators implanted)
- Device Malfunction: 9 (1% of neurostimulators implanted)
- Low Impedance: 5 (1% of neurostimulators implanted)
- Premature Battery Depletion: 6 (0,3% of neurostimulators implanted)
- Electromagnetic Interference: 2 (1% of neurostimulators implanted)
- Device Issue: 1 (1% of neurostimulators implanted)
- Device Lead Issue: 1 (1% of neurostimulators implanted)
- Extension Migration: 1 (1% of neurostimulators implanted)
- Lead Insulation Failure: 1 (1% of neurostimulators implanted)

4.2. Warnings and precautions

Safety warnings - AlphaDBSipg Programming Manual, AlphaDBSipg Implant Manual, AlphaDBSlink Programming Manual

- **Intracranial Hemorrhage.** Special precautions should be taken for patients who are prone to hemorrhage including patients with coagulopathy, with high blood pressure, or who are using prescribed anticoagulants. Microelectrode penetration and DBS Lead insertion can put patients who have a likelihood of intracranial hemorrhages at greater risk.
- **Electromagnetic Interference.** Strong electromagnetic fields can potentially turn AlphaDBSipg off, cause temporary unpredictable changes in stimulation, or

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interfere with AlphaDBSpat or NWKstation communication. Patients should be counseled to avoid or exercise care around:

- Theft detectors such as those used at entrances/exits of department stores, libraries, and other public establishments. The patient should proceed with caution, ensuring to move through the center of the detector as quickly as possible.
- Security screeners, such as those used in Airport Security or at entrances to government buildings, including hand-held scanners. The patient should request assistance to bypass the device. If the patient must pass through the security screener, they should move quickly through the device staying as far from the physical device as allowable.
- Power lines or power generators.
- Electric steel furnaces and arc welders.
- Large magnetized stereo speakers.
- Strong magnets.
- Automobiles or other motorized vehicles using a LoJack system or other anti-theft systems that can broadcast a radio frequency (RF) signal.
- Other sources of electromagnetic interference, such as RF transmitters at television or radio broadcast stations or transceivers.
- **Therapeutic Ionizing Radiation.** Electronic components in AlphaDBSipg can be damaged by therapeutic ionizing radiation. Any damage to the implanted part of the AlphaDBSipg might not be immediately detectable.
- **Heat Due to Charging.** The recharger unit, AlphaDBSpat, may become warm while charging the Stimulator. The recharger unit should be handled with care. The Patient should not charge while sleeping. This may result in a burn. If the patient experiences pain or discomfort, they should cease charging and contact their physician.
- **Stimulator Damage.** Chemical burns may result if the Stimulator housing is ruptured or pierced, exposing the patient's tissue to battery chemicals. Do not implant the AlphaDBSipg Stimulator if the housing is damaged.
- **Suicide.** Depression, suicidal ideation, and suicide are risks previously reported in relation to DBS. If the patient reports depression or suicidal thoughts, consider adjustment of stimulation, discontinuing stimulation, adjusting medication, and/or psychiatric referral.
- **Other Active Implantable Devices.** Stimulators, such as the AlphaDBSipg, may interfere with the operation of implanted sensing stimulation devices such as pacemakers or cardioverter defibrillators. The effects of implanted stimulation devices on the neurostimulator AlphaDBSipg are unknown.
- **Automobiles and Equipment.** Patients should operate automobiles, other motorized vehicles, or potentially dangerous machinery/equipment with caution after receiving the AlphaDBS System. Performing activities that would be

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dangerous if treated symptoms were to return, or instances in which stimulation changes occur, should be avoided.

- **Pregnancy** It is unknown whether this device may hurt an unborn baby.

Safety warnings - AlphaDBSext Physician Manual for use and programming through NWKStation

- **Electromagnetic Interference.** Strong electromagnetic fields can potentially turn AlphaDBSext off, cause temporary unpredictable changes in stimulation, or interfere with NWKstation communication. Do not use the device in proximity to equipment that generates electromagnetic interference (EMI). Examples of common medical sources of EMI are magnetic resonance imaging and lithotripsy.
- **Pregnancy.** It is unknown whether this device may hurt an unborn baby.
- **Environment of use.** NWKstation and AlphaDBSext are not certified for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide. The consequences of using NWKstation and AlphaDBSext near flammable atmospheres are unknown.

Precautions - AlphaDBSipg Programming Manual, AlphaDBSipg Implant Manual, AlphaDBSlink Programming Manual

Physician training is required for usaging of the AlphaDBS System. The implanting physician should be experienced in Stereotactic and Functional Neurosurgery. The following is a list of precautions that should be taken when implanting or using the AlphaDBSipg.

- **Connections.** Before inserting DBS Extension into any connector or header ports, including the AlphaDBSipg Hader, DBS Extension connectors, and operating room cable assembly, always wipe the connections with a dry cotton sponge. Contamination inside the ports may be difficult to remove and can cause high impedances, preventing electrical connectivity which may compromise the integrity of the stimulation circuit.
- **Components.** The use of components other than those supplied by Newronika and intended for use with the AlphaDBS System may: damage the system, diminish the effectiveness of therapy, and/or put the patient at unknown risk.
- **Excess DBS Extension.** Coil excess DBS Extension around or below the AlphaDBSipg. Excess wire on top of the Stimulator may increase the potential for tissue erosion or damage during Stimulator replacement surgery and may interfere with charging.
- **Other Models of External Devices.** Only the NWKStation, AlphaDBSext, and AlphaDBSpat that were provided with the Newronika AlphaDBS System should be used. Other models of these devices will not function with the AlphaDBS System.

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- **Stimulator Orientation.** To ensure proper charging, orient the Stimulator parallel to the skin surface and at a depth less than 1 cm below the skin. The etched writing “This Face Up” must be facing out of the pocket towards the patient's skin. Suboptimal placement of the Stimulator may result in the inability to recharge and/or a revision surgery.
- **Setscrews.** Before tightening Setscrews, always test impedance to confirm electrical connectivity. Tightening a Setscrew onto a contact may damage the contact and may result in the need to replace the DBS Lead Extension.
- **Device Failure.** Implants can fail at any time due to random component failure, loss of battery functionality, or component breakage. Suddenly stopping brain stimulation can cause serious reactions to develop. If the Stimulator stops working even after complete charging, patients should be instructed to turn off the Stimulator and contact their physician immediately so that the system can be evaluated, and appropriate medical care given to manage the return of symptoms.
- **Tissue Reaction.** Temporarily, there may be some pain in the area of the Stimulator as the incisions heal. If there is excessive redness around the wound area, it should be checked for infection. In rare cases, adverse tissue reaction to implanted materials can occur.
- **Cell Phones.** While interference with cell phones is not anticipated, the full effects of interaction with cell phones are unknown at this time. Advise patient to not place cell phone in his/her shirt pocket or directly on components of AlphaDBS System. If some interferences happen, place cell phone on the other ear or turn off cellular.
- **Patient Activities.** During the two weeks following surgery, it is important for the patient to exercise extreme care so that appropriate healing will secure the implanted components. During this period, the patient should not attempt to move heavy objects. Instruct the patient to restrict head movements, including extension or flexion of the neck and rotation of the head, until healing is complete.
- **Massage Therapy.** Patients should avoid receiving massage therapy near the implanted system components. If a patient does receive massage therapy, the patient should inform the masseuse that they have an implanted device and show him/her where the Stimulator, DBS Extension, and DBS Leads are located. The patient should have the masseuse avoid these areas and proceed with caution.
- **Environmental Precautions.** Patients should avoid activities that could potentially involve large amounts of electromagnetic interference. Devices that contain permanent magnets, such as speakers, should not be placed near the Stimulator or other parts of AlphaDBS System because they may cause the system to turn on or off.
- **Medical Devices/Therapies.** The AlphaDBSipg, also if the stimulation is turned off, could be associated to injuries to the patient or damages to the neurostimulator itself in case of:

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- Electrocautery – Electrocautery can transfer destructive current into the DBS Leads and/or Stimulator.
- Lithotripsy – High frequency signals directed near the neurostimulator may damage circuitry.
- Radiation Therapy – Lead shielding should be used over the Stimulator to prevent damage from high radiation. Any damage to the device by radiation may not be immediately detectable.
- Transcranial Stimulation – Safe use of electromagnetic therapies, such as transcranial magnetic stimulation, have not been established.
- External Defibrillation
- Ultrasound (US)
- If any of the above is required by medical necessity, the procedure(s) should be performed with the stimulation off and as far from the implanted components as possible. After having used one of the previous medical therapies, it is necessary to check functionalities of AlphaDBipg through NWKstation, trying to reset stimulation parameters and to measure impedance.
- **Inspect packaging before use.** Check the expiration date on the package before opening the sterile package and using the contents. Do not use the contents if the current date is past the expiration date, if the package is opened or damaged, or if contamination is suspected because of a defective sterile package seal.
 - Inspect the seal integrity of the outer tray before use.
 - Open the inner tray in the sterile field.
 - If the Stimulator was dropped, do not implant it in a patient. The dropped Stimulator may have lost sterility, experienced a loss of hermeticity, or been otherwise damaged. Replace the dropped Stimulator with a new, sterile Stimulator prior to implantation. Return the damaged Stimulator to Newronika.
 - Do not use any component that shows signs of damage.
 - Do not use if “Use By” date has expired.
- ***Note for clinical use: Treatment programming must be always performed according to applications already described in the literature. In any other case, clearance from competent regulatory bodies (e.g. local Ethical Committee or analogous) is required.***
- AlphaDBS System shall be used exclusively with certified intracranial electrodes.
- In the case of any malfunctioning, please immediately contact the manufacturer.
- AlphaDBS System maintenance can be done only by the manufacturer.
- To avoid unintended stimulation, do not modify the operating system in any way. Do not use the application if the operating system has been compromised (jailbroken).
- Do not use AlphaDBS System with sharp objects (pens, pencils, screwdrivers).

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- Keep AlphaDBS System away from kids in order to avoid asphyxiation and strangulation dangers.
- Inform the specialized staff when DBS is used in patients with other implanted devices, such as pacemakers, intracranial electrodes, defibrillators, or any other prosthesis.
- The use of device shall agree with the indications reported in the present manual. Do not use AlphaDBS System in a different manner.

Precautions - AlphaDBSpat Patient Manual

- **Device Failure.** Implants can fail at any time due to random component failure, loss of battery functionality, or component breakage. Suddenly stopping brain stimulation can cause serious reactions to develop. If the neurostimulator stops working even after complete charging, the patient should turn off the neurostimulator AlphaDBSipg and contact their physician immediately so that the system can be evaluated, and appropriate medical care given to manage the return of symptoms.
- **Tissue Reaction.** Temporarily, there may be some pain in the area of the Stimulator as the incisions heal. If there is excessive redness around the wound area, it should be checked for infection. In rare cases, adverse tissue reaction to implanted materials can occur.
- **Cell Phones.** While interference with cell phones is not anticipated, the full effects of interaction with cell phones are unknown at this time. Do not place your cell phone in your shirt pocket or directly on components of AlphaDBS System. If some interferences happen, place cell phone on the other ear or turn off cellular.
- **Patient Activities.** During the two weeks following surgery, it is important for you to exercise extreme care so that appropriate healing will secure the implanted components. During this period, you should not attempt to move heavy objects.
- **Massage Therapy.** You should avoid receiving massage therapy near the implanted system components. If you receive massage therapy, you should inform the masseuse that you have an implanted device and show him/her where the Stimulator, DBS Extension, and DBS Leads are located. You should have the masseuse avoid these areas and proceed with caution.
- **Use of AlphaDBSpat and its accessories.** Use the AlphaDBSpat and its accessories with care.
 - Do not use AlphaDBSpat and its accessories with sharp objects (pens, pencils, screwdrivers). Do not drop the AlphaDBSpat, because it may break.
 - For avoiding damage, the AlphaDBSpat and its power bank, do not submerge the devices, do not clean them with bleach or nails solvent, or mineral oil.
 - When using the AlphaDBSpat and its power supply, use special care near flammable or explosive atmospheres. An interaction between flammable or

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explosive atmospheres and the device or its battery can occur. The consequence of using a battery-powered device near flammable or explosive atmospheres are unknown.

- The AlphaDBSpat is not certified for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide. The consequences of using the device near flammable atmosphere are unknown.
- Keep AlphaDBSpat and its accessories away from kids to avoid asphyxiation and strangulation dangers. Always keep the device in its packaging when not used. The device is not intended to be used by kids or under 18 years old.
- **Exclusive use of Newronika devices and accessories.** Use only Newronika charging device and accessories to recharge your AlphaDBSipg and use only power supplier provided by Newronika for powering your AlphaDBSpat.
- **No modification of this equipment is allowed.** Modification of this equipment can result in damage to the device, causing the device to malfunction or become unusable.
- **Possible disturbances of other implanted devices.** Do not place the AlphaDBSpat above another active implantable medical device (e.g. pacemaker or defibrillator or other neurostimulator) because the recharger unit can accidentally modify the other device functionalities.
- **Electromagnetic interferences during radiofrequency communication.** When you use the AlphaDBSpat for communicating with your implanted AlphaDBSipg neurostimulator, be sure to be far away from equipment that may cause electromagnetic interference (EMI). The EMI may disturb and interrupt the communication between AlphaDBSpat and AlphaDBSipg. Example of common sources of EMI are powerful computer monitors, cell phones, speakers and motorized wheelchairs. All these sources should not be placed near the neurostimulator or the AlphaDBSpat because they may cause the system to turn on or off.

Precautions - AlphaDBSext Physician Manual for use and programming through NWKStation

Physician training is required for usage of the AlphaDBS System.

- **Components.** The use of components other than those supplied by Newronika and intended for use with the AlphaDBS System may damage the system, diminish the effectiveness of therapy, and/or put the patient at unknown risk.
- **Other Models of External Devices.** Only NWKstation and AlphaDBSext, which were provided with the Newronika's AlphaDBS System shall be used. Other models of these devices will not function with the AlphaDBS System.
- **Cell Phones.** While interference with cell phones is not anticipated, the full effects of interaction with cell phones are unknown at this time. Do not place the cell phone

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near or directly in contact with components of AlphaDBSext and NWKstation. If some interferences happen, move the cell phone far from the devices.

- **Environmental Precautions.** Do not use the device in proximity to equipment that generates electromagnetic interference (EMI). EMI may cause disruption in device function. Example of common medical sources of EMI are magnetic resonance imaging (MRI) and lithotripsy. Powerful computer monitors, cell phones, X-Ray equipment and other monitoring equipment may also generate EMI.
- **Warning.** No modification of this equipment is allowed. Modification of this equipment can result in damage to the device, causing the device to malfunction or become unusable.

The AlphaDBS must be turned on only by duly trained healthcare personnel that will be in charge of setting the programming parameters. The referral medical doctor will thoroughly assess the patient's clinical response to DBS treatment before discharging him/her and planning further monitoring visits.

Post-implant clinical visits will be conducted in agreement with standard-of-care for PD patients receiving DBS therapy. No specific follow-up visits are foreseen after AlphaDBS implant.

4.3. A summary of any field safety corrective action

Type of action	Issuing date	Scope of the FSCA	Status of the FSCA	Mnfr. Reference number	Rationale and description of action taken	Impacted regions
Nil	Nil	Nil	Nil	Nil	Nil	Nil

Since the products are yet to be introduced to the market for sale, there were no requirement of any field safety corrective actions during the past years.

5 Summary of clinical evaluation and relevant information on post-market clinical follow-up

5.1 Summary of clinical data related to equivalent devices

The conformity of the device was assessed and endorsed by the NB based on equivalence.

#	Equivalent Device Name	Brand Name	Manufacturer Name & Country
1.	AlphaDBS System and related accessories	AlphaDBS System	Newronika S.p.A & Italy

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The selected equivalent device is manufactured by Newronika S.p.A. and is certified under EU Directive 90/385/EEC (AIMDD). As per the comparison, there was no significant clinical differences related performance and safety between the subject device and equivalent device. Hence, the device under evaluation 'AlphaDBS System' is significantly equivalent to its Legacy Device 'AlphaDBS System'.

The AlphaDBS System, when used in cDBS operating mode, has been designed to deliver the same deep brain stimulation therapy to treat motor symptoms in PD as delivered by devices currently available in the market and CE marked, including from Medtronic, Boston Scientific and Abbott, for which technical equivalence and clinical equivalence has been established.

The AlphaDBSipg device belongs to the sub-category of the rechargeable devices, and we claim equivalence within this sub-category (when the system delivers cDBS), since clinical application, system design, physical structure, bio compatibility and principle of operations of the AlphaDBSipg are identical and/or comparable to the currently commercially available rechargeable IPG's with CE Mark.

Therefore, the safety and performance of the AlphaDBS System, when delivering cDBS can be assumed from clinical data on equivalent devices, as derived from the following sources:

- Clinical data published in peer-reviewed journals and regulatory dossiers as a result of clinical trials or observational studies (indicating the different class of evidence for each study). All studies considered used CE devices delivering DBS. Clinical trials report the use of devices manufactured by Medtronic, Abbott or Boston Scientific. When dividing the studies resulting from our literature search by the manufacturer we considered:
 - Studies using the Medtronic system: 31 (published from 2001 to 2022);
 - Study using the Abbott/St Jude system: 1 (Okun et al., 2012);
 - Studies using the Boston Scientific system: 2 (VANTAGE – reported by Timmerman et al., 2015 and INTREPID study – Vitek et al. 2020 and SSER related to Pre-Market Authorization P150031)
 - Studies using more than one DBS system: 5
 Other studies (observational) considered do not specify the device used.
- Result of meta-analysis and systematic reviews published in peer-reviewed journals.
- Information provided in reviews that address items of particular interest such as safety data.

Bilateral cDBS therapy is approved as an adjunctive therapy for patients with Parkinson's disease and provides persisting significant improvement of the OFF-related motor symptoms. Dyskinesias are also reduced due to the significant reduction of dopaminergic

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treatment after surgery. This improvement has been reported to range between 36% and 54% at 5-year evaluation (Kleiner-Fisman et al., 2003, Krack et al 2003 and 2017). Conventional DBS has become part of the standard clinical practice (NICE [IPG19], 2003) as treatment for PD and other disorders. Despite being associated with a number of possible adverse events (mainly during surgery and in the post-surgical period), the risk-benefit profile of cDBS is strongly in favour of benefits.

Summary of clinical data from investigations with AlphaDBS System before the CE-marking

The results of the clinical investigations conducted have been published in peer-reviewed papers (see reference close to study title). The clinical investigations results are not available in EUDAMED, since the studies were conducted when the EUDAMED system was not operational.

Pre-market study supporting the safety and efficacy of the AlphaDBS System in cDBS

Study PS3: A double blind cross over study to evaluate safety and efficacy of an adaptive Deep Brain Stimulation closed-loop method compared with conventional Deep Brain Stimulation in patients with Parkinson's Disease

Study design and methodology

This was an exploratory multicenter study, conducted in 4 Italian clinical sites, in which adaptive DBS (aDBS) delivered through the AlphaDBS external prototype (AlphaDBSVext), was tested in comparison with conventional DBS (cDBS) delivered by the same system and with conventional DBS delivered by a Medtronic commercial device, in PD patients, treated with DBS and hospitalized for IPG replacement surgery. Following personalized algorithm set up and «AlphaDBS» device calibration, patients were randomly assigned to either one of the stimulation mode sessions (i.e., aDBS or cDBS), for 24 hours, and were then switched to the other stimulation mode.

Eleven (11) patients underwent screening procedures. Of these 11 patients, 5 were excluded during the screening period and 6 were enrolled. Those 6 were randomized and entered the short-term follow up. Three of the patients completed the short-term follow-up (2 experimental days). Of the three who did not complete the short-term follow up, 1 had cardiac artifact and 2 experienced device deficiency (AlphaDBSVext did not provide sufficient stimulation due to external reference).

All study data were collected through an electronic Case Report Form (compliant with safety and data privacy requirements), managed by a CRO. The data quality (i.e., source data verification) and the compliance of the center to study procedures was verified by the CRO in charge of data monitoring.

Study results

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Device safety: The device safety was assessed during the follow up period, over a period of 3 days (from implant to Day 2). In the study, aDBS did not raise any safety concerns.

Some not serious procedure-related adverse events (mainly related to the presence of the externalized extensions) were recorded: 1 patient experienced a minor fall during the night that caused breakage of the extensions; 2 patients experienced sub-optimal stimulation which resulted in inadequate control of PD symptoms, due to device malfunction.

Device efficacy: PD motor symptoms were assessed through the use of the UPDRS III scale administered by a qualified Neurologist. Patients were treated in cDBS with a commercial Medtronic IPG. UPDRS II assessments were conducted during screening, follow up at multiple time points over two days during both states: randomized to conventional and adaptive operating modes.

All the patients showed improvement of motor symptoms after turning the stimulation ON (StimON/MedsOFF) and when the stimulation was combined with medical therapy administration (StimON/MedsON).

When considering the difference between the efficacy (namely UPDRS III in StimON/MedsOFF) of stimulation delivered in cDBS mode by the AlphaDBS System and a commercial, substantially equivalent system (in terms of clinical operation, i.e., Medtronic Activa) the mean difference is 0.333 which is largely below the minimally clinically important difference (MCID =4.83). This is confirmed by the estimation of the effect size (Cohen's d: 0.039) which supports the hypothesis of no difference between the two systems.

Similarly, the mean difference between the efficacy (namely UPDRS III in StimON/MedsOFF) of stimulation delivered in cDBS mode and aDBS mode by the AlphaDBS is -0.667 which is largely below the MCID, with an effect size of -0.069, thus supporting equivalence.

Pre-market studies supporting the safety and efficacy of the AlphaDBS System in aDBS

PS1: Clinical Study for Adaptive Deep Brain Stimulation (aDBS) Controlled by Intracerebral Activity in Parkinson's Disease (NCT02154724) (Rosa et al., 2017)

Study Design

This was a randomized, monocentric study on Parkinson's disease patients, who underwent surgery for STN DBS electrode implantation in the neurosurgery unit at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan from September 2013 to September 2015. Patients without experiencing any surgical complication and meeting all selection criteria, were enrolled in the study. The objective of the study was to compare the safety and efficacy of aDBS vs. cDBS in freely moving PD patients, with a specific focus on the concurrent administration of levodopa treatment.

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The experimental sessions (i.e., each session lasting for two hours, one day with aDBS and the other with cDBS in random order) took place the 5th and the 6th day after surgery. The patient was blind to the type of DBS received during the session. For the clinical assessment, the Unified Parkinson's Disease Rating Scale, part III, motor part (UPDRS III), the Unified Dyskinesias Rating Scale (UdysRS), part 3 and 4, and the adverse events experienced by the patient were collected. The patient and the neurologist who performed the clinical assessment were blinded to the DBS type. A second blinded neurologist (video rater) evaluated the patients by viewing the video recordings (rigidity scores were excluded from the analysis). The total electrical energy delivered (TEED) was used for the assessment of energy efficiency.

Both aDBS and cDBS were delivered using the AlphaDBS V-ext that has two modes, cDBS (the stimulation is delivered with fixed parameters, at the effective stimulation amplitude), and aDBS (stimulation parameters are changed linearly according to the beta band power, with the stimulation amplitude ranging from 0 to the effective stimulation amplitude). AlphaDBS V-ext was calibrated the day before the first experimental session, according to the procedures described in (Rosa et al., 2015), in order to provide a personalized aDBS algorithm.

Both aDBS and cDBS were delivered unilaterally, to the hemisphere in which the recorded LFPs showed the highest beta peak. LFPs used as a feedback signal for aDBS were recorded from the electrode contact pair that exhibited the highest beta peak, and the contact located between these contacts was used for stimulation delivery (the same for aDBS and cDBS sessions).

Each experimental session lasted at least 2 hours, during which the patient was evaluated three times: (1) after a baseline assessment (OFF DBS and OFF medication, StimOFF/MedOFF, after a night withdrawal of medication), (2) after the stimulation was turned on and before levodopa administration (StimON/MedOFF, at least 30 minutes after DBS was turned on), and (3) 40 minutes after the administration of the usual patient's levodopa dose increased by 50% (StimON/MedON condition). Clinical assessments included an evaluation of motor performance, measured via the Unified Parkinson Disease Rating Scale (UPDRS) III and dyskinesia, measured via the Unified Dyskinesia Rating Scale (UdysRS, III and IV parts).

Disposition

A total of 17 Parkinson's disease patients undergoing DBS surgery were screened and 14 were enrolled in the study. Of them, 4 withdrew from the study: three patients were dropped after the first experimental session because of intolerability to medication withdrawal, and one patient was dropped after the second experimental session because of fatigue. Ten patients completed all of the experimental sessions and were analyzed.

Safety results

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In addition to the 4 patients who were dropped from the study prior to completing the second experimental session (3 patients because of intolerability to medication withdrawal and one patient because of fatigue), 3 additional patients, who completed the study, reported heaviness (2) and dizziness (1).

Efficacy Results

The clinical scores were not significantly different between the 2 experimental sessions at baseline (StimOFF/MedOFF UPDRS III, aDBS vs cDBS: 37.0 ± 16.8 vs 36.6 ± 16.2 ; $P > 0.05$).

When the patient was on both levodopa and DBS (StimON/MedON), a similar improvement on motor symptoms with aDBS or cDBS was observed (UPDRS III percentage change from baseline, aDBS vs cDBS: $-46.1\% \pm 10.5\%$ vs $-40.1\% \pm 17.5\%$; $P > 0.05$). Conversely, aDBS was more effective on dyskinesias than cDBS (UdysRS score, aDBS vs cDBS: 11.7 ± 67 vs 15.0 ± 8.7 ; $P=0.02$). As expected, aDBS showed significant saving of electrical energy delivered to the tissue, an average of $73.6\% \pm 22.9\%$ in aDBS compared with cDBS (mean TEED aDBS vs cDBS: 44.6 ± 47.9 IW vs 158.7 ± 69.7 IW; $P=0.0005$).

Conclusions

These results support the hypothesis that aDBS, administered concomitantly to levodopa, could reduce the severity of dyskinesia induced by the transient summation of DBS stimulation and pharmacological therapy.

PS2bis: Title: Optimization of Deep Brain Stimulation therapy in Parkinson Disease according to the patient clinical state, using adaptive stimulation: 8-hour sessions cDBS vs aDBS (Bocci et al, NPJ, 2022)

Objectives

The primary objective of the study was to compare, in an 8-hour time frame, the safety and clinical efficacy of aDBS and cDBS, in freely moving PD patients.

Study design

Patients with advanced PD, who underwent surgery for STN DBS electrode implantation in the Neurosurgery Unit at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan without experiencing any surgical complication and meeting all selection criteria, were enrolled in the study.

The experimental sessions took place after DBS surgery, before the leads were connected to the subcutaneous pulse generator. The experimental protocol included two 8-hour sessions (one per day) conducted using an external portable «AlphaDBS» system prototype: Day 1: cDBS ON, LFP recordings ON; Day 2: aDBS ON, LFP recordings ON. After 12 hours of medication withdrawal, each session started with a baseline assessment

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(Med OFF, Stim OFF), then the patient was assessed whenever his/her medication was effective (Med ON, Peak dose, about 45-60 minutes after medication intake) and then when the medication ended its effects (Med OFF, End dose, 60-90 minutes after the Peak dose). For the clinical assessment, the Unified Parkinson's Disease Rating Scale, part III, motor part (UPDRS III), the Unified Dyskinesia Rating Scale (UdysRS), parts 3 and 4, and the adverse events experienced by the patient were collected.

Methods

The experiment took place five days after the electrode implantation surgery, and consisted of three sections lasting in total 2 days:

- Session 1: baseline assessment and aDBS calibration (day 5);
- Session 2: 8 hours cDBS (day 5);
- Session 3: 8 hours aDBS (day 6).

Session 1. aDBS calibration. After overnight PD medication withdrawal, a baseline assessment including the Unified Parkinson's Disease Rating Scale (UPDRS)-III, the Rush filming protocol, and the Dyskinesias Rating Scale (RDRS) REF was performed by an experienced physician. Then, the calibration phase was comprised of three steps: a) Electrode contact selection: all the contact combinations were probed and recorded to select the pair with a prominent non-artefactual beta peak. B) Stimulation threshold: a stimulation contact was selected based on the best clinical outcome on rigidity sub-scores, assessed for both lower and upper limbs, and an experienced neurologist assessed the therapeutic window (V_{min} = minimum voltage providing a benefit to the patient, namely at least 20% improvement in rigidity; V_{max} = maximum voltage before the occurrence of side effects). Frequency and pulse width remained constant for every patient and were set to 130 Hz and 60 μ s respectively. C) Beta peak selection: the frequency of the beta peak (frequency with the maximum beta power) was selected as the center of a personalized beta band (maximum frequency $\pm$ 2 Hz) on the contact pair chosen in step a) and set as a biomarker for aDBS. aDBS amplitude was therefore set to change its value in the V_{min} - V_{max} window, according to the change in the amplitude of the beta band (linear adaptation).

Session 2. Eight hours of cDBS. After baseline assessment and calibration, cDBS was turned on and the first Levodopa administration was given. cDBS was delivered for 8 hours with an amplitude of V_{max} -20%. Meanwhile, the regular intake of Levodopa was resumed during the session. UPDRS-III and DRS evaluations were performed by an experienced neurologist during the peak (PeakDose) and the end (EndDose) of Levodopa efficacy. At the end of the session, cDBS was turned OFF.

Session 3. Eight hours of aDBS. On the second day (day 6 after the implantation surgery), after overnight medication withdrawal, aDBS was turned ON for 8 hours using the

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parameters chosen in calibration (personalized beta band and therapeutic window). Then, the experimental session was repeated as in the day before.

The relative UPDRS III scores (i.e., raw UPDRS III normalized by the maximum change recorded in each patient), Rush-DRS scores, and TEED were analyzed using non-parametric statistics (two tailed Wilcoxon's rank sum test and two tailed paired signed rank tests); effect size r estimated for non-parametric tests as reported in Fritz et al., 2012.

Disposition

A total of 8 patients with PD were screened and analyzed in the study, representing the ITT population.

Results

The primary outcome was motor improvement comparing aDBS with cDBS, in terms of both dyskinesias and motor scores, as assessed by UPDRS-III; the secondary outcome referred to changes in TEEDs. Baseline values (after overnight withdrawal of DBS and medication) did not differ between the two sessions (UPDRS-III, cDBS 20.86 ± 3.53 and aDBS: 20.29 ± 3.90 , Rush-CDRS, cDBS: 2.50 ± 1.13 and aDBS: 1.67 ± 0.53). UPDRS-III relative score was significantly lower in the aDBS than in the cDBS session (relative UPDRS, cDBS: 0.46 ± 0.05 , aDBS: 0.33 ± 0.04 , $p = 0.015$, effect size $r = 0.24$, Wilcoxon's rank sum test).

Considering sub-scores, whereas Rest Tremor and Upper Limb Bradykinesia did not differ between aDBS and cDBS sessions, rigidity was higher during cDBS session (UPDRS-III rigidity subset mean score, cDBS: 2.9143 ± 0.6551 and aDBS: 2.1429 ± 0.5010 , $p = 0.034$, effect size $r = 0.47$, Wilcoxon's signed rank test). The reduction compared to baseline values was also calculated both for UPDRS-III and the rigidity sub-score, during either cDBS or aDBS, confirming a significant improvement during adaptive stimulation (UPDRS-III: aDBS = $47.1 \pm 7.5\%$; cDBS = $33.2 \pm 9.1\%$; rigidity subset: aDBS = $56 \pm 6.7\%$; cDBS = $35.25 \pm 7.9\%$).

Moreover, the dyskinesia score was significantly lower in the aDBS than in the cDBS session (Rush scale, cDBS 2.79 ± 0.39 versus aDBS 1.57 ± 0.23 , $p = 0.037$, effect size $r = 0.24$ Wilcoxon's rank sum test). The TEEDs was calculated for 6 patients (2 patients were excluded due to a different impedance recording methodology), and it was significantly higher in the cDBS than in the aDBS session (cDBS TEEDs mean: $28.75 \pm 3.36 \mu\text{s}^{-1}$, aDBS TEEDs mean: 16.47 ± 3.33 , $p = 0.032$, effect size $r = 0.32$ Wilcoxon's sign rank test).

Conclusions

The results further confirmed the safety and effectiveness of aDBS, as compared to cDBS, both in terms of motor performance and of DBS side effects, in a day-long time window.

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Study PS3: A double blind cross over study to evaluate safety and efficacy of an adaptive Deep Brain Stimulation closed-loop method compared with conventional Deep Brain Stimulation in patients with Parkinson's Disease

The study design, objectives and methodology were already summarized in Section 3.5.2.1. Here we summarize the main results regarding UPDRS III changes between the MedOFF/StimOFF condition and the MedON/StimON condition, useful to assess the equivalence of aDBS and cDBS in terms of motor improvement.

Results

Considering the StimON/MedOFF condition, the improvement in UPDRS III observed in aDBS (mean 32%; range 10-53%) is comparable to the improvement observed in cDBS (mean 29%; range 14-53%) and to the improvement observed at the screening visit, when the patient was stimulated in cDBS with a commercial implantable device (mean 35%; range 10-53%), as previously described (Section 3.5.2.1).

Considering the StimON/MedOn condition, all patients showed a significant improvement in motor scores compared to the MedOFF/StimON condition. The improvement in UPDRS III observed in aDBS (mean 18 ± 5.3 points corresponding to 51% improvement, range 36-77%) is comparable to the improvement observed in cDBS (mean 21 ± 4.9 points corresponding to 58% improvement, range 47-68%). The average difference between cDBS and aDBS delivered with the Newronika AlphaDBS-Vext device was 3.3 points (SD 9.1).

Study PS4: A double blind cross over study to evaluate safety and efficacy of adaptive Deep Brain Stimulation delivered through the AlphaDBS system in patients with Parkinson's Disease

Study design and methodology

This is the first study that implemented the use of the AlphaDBS System in humans. The study was designed to assess the safety of the device and its potential efficacy, including the aDBS closed-loop method in patients with PD. The study was designed as a multicenter crossover randomized trial that uses conventional DBS (cDBS) as a control.

Objectives

The primary objective of the study was to evaluate the safety and tolerability of the «AlphaDBS» System, when used in cDBS and aDBS mode. The determination of safety and tolerability is based on the occurrence of device related adverse events.

Efficacy was evaluated through the following secondary measures:

- Evaluation of PD-related motor symptoms (i.e. bradykinesia, rigidity and tremor at rest) and their fluctuations through repeated clinical assessments (using the Unified Parkinson's Disease Rating Scale -UPDRS- part III).

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- Evaluation of dyskinesia and their fluctuations through repeated clinical assessments (using the Unified Dyskinesia Rating Scale – UDysRS, Patient Diary and wearable systems).
- Evaluation of “time on” with and without dyskinesia and “time off”, assessed through Patient Diary.
- Total Electrical Energy Delivered (TEED) to the patient.
- Patient preferences (assessed considering the stimulation mode chosen by the blinded patient at the end of the “long term follow up”).

The study was approved by the National Competent Authorities in Italy, Poland, and Netherlands.

Clinical sites that participated in the investigation were:

- Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico (Milano)-Italy
- IRCCS Istituto Neurologico Carlo Besta (Milano)- Italy
- AOU Città della Salute e della Scienza di Torino (Torino)- Italy
- Azienda Ospedaliera Università Padova (Padova)- Italy
- IRCCS Policlinico Gemelli (Roma)-Italy
- Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie -, (Warszawa) -Poland
- Copernicus Podmiot Leczniczy Sp. z o.o., (Gdańsk) -Poland

Maastricht University Medical Center - Netherlands

PD patients in need of IPG replacement are screened for enrollment eligibility. The study protocol is organized in two phases: the “short-term follow-up” and the “long-term follow-up”.

During the screening visit, each patient is assessed for motor symptoms (UPDRS III and UDysRS scales) while being treated with cDBS delivered through a Medtronic Activa device. Following screening, the patients undergo surgery for IPG replacement and receive the AlphaDBSipg and are randomized. After a day of DBS calibration, in which appropriate stimulation settings are entered into the Physician Programmer, randomized patients undergo 2 days of experimental sessions (i.e., one day for each type of stimulation mode: cDBS and aDBS), in a well-controlled environment (i.e., during hospitalization) (“short term follow-up phase”). The allocation of the first type of stimulation is determined by randomization (implemented by the CRO, through the eCRF system) and both the patient and the clinicians in charge of patient assessment are blind to the mode of stimulation.

During “short term follow-up” patients undergo thorough repeated clinical assessments (in standardized conditions) to detect any possible adverse event or stimulation/procedure-related side effects and stimulation induced changes in motor and non -motor symptoms.

At the conclusion of short-term follow-up phase, patients who do not experience severe side effects and who are deemed suitable by the neurologist, continue in the “long-term follow-up” phase (i.e., 1 month) in their “home” environment with the AlphaDBS System

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delivering the stimulation in aDBS or cDBS mode (two weeks in each mode over the 1 month). The type of stimulation used in the first two weeks of the long-term follow up (aDBS or cDBS) is determined by randomization and both the patient and the clinicians in charge of patient assessment remain blind to the mode of stimulation for the entire duration of the follow-up.

At the conclusion of the long-term follow-up phase, the patient returns to the hospital and undergoes an interim follow-up visit. During the visit the Investigator collects the patient diaries (completed at home in the three days before the visit) and assesses motor and non-motor symptoms in the MedON/StimON condition. After the assessment, the IPG is switched to the alternative stimulation mode (i.e., patients that received cDBS first are switched to aDBS and vice versa) and the patient is re-evaluated. If no AEs occur, the patient is discharged for two additional weeks. At the end of the second two weeks follow-up the patient returns to the hospital for the final follow-up visit. During the visit the Investigator collects the patient diaries (completed at home in the three days before the visit) and assesses motor and non-motor symptoms in the MedON/StimON condition.

At the end of the study, the patient, also considering the Investigators' advice, decides whether to keep the AlphaDBS System (open label study extension) or to switch to a commercial neurostimulator. If the patient keeps the AlphaDBS System, he/she chooses, in blinded fashion, which is his/her preferred mode of stimulation (based on the benefits received during the two follow-up periods).

The study protocol is published in a peer-reviewed journal (Marceglia et al, 2022).

In the second half of 2022 the study protocol was amended in two Italian centers to also include PD patients receiving "de novo" DBS implants.

Study interim Results

Safety

One subject was observed with pulmonary embolism due to COVID-19, not related to the study procedure or the device, while the second was a difficulty in recharging the device. This event might be associated with a suboptimal IPG implant position due to anatomical features (i.e. large size of the subcutaneous pocket and presence of adipose tissue), as the tests conducted in the explanted device revealed that the device recharged properly as per its specification.

Device related AE

The following device related AEs were reported during the study:

- Worsening of PD symptoms, associated to probable interruption of stimulation (3 patients)
- Difficulty in recharging (2 patients)

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No stimulation-related AEs (nor in cDBS nor in aDBS) were recorded during the study follow up.

Evaluation of PD motor symptoms

Short term follow-up data

The short term follow-up data showed that the AlphaDBS system induced a marked improvement on PD motor symptoms (assessed through the UPDRS III scale) both in cDBS and in aDBS.

In particular, the average improvement was of 32.6 (56%) points (SD 16.7) and 31.5 (54%) points (SD 17.7) of the UPDRS III scale, in cDBS and aDBS respectively, when the patient received the stimulation only (StimON/MedOFF condition).

Such improvement increased to 40 (66%) points (SD 19.5) and 35.4 (61%) points (SD 17.9) of the UPDRS III scale, in cDBS and aDBS respectively, when the patient received both the stimulation and the medical therapy (StimON/MedON condition).

Long term follow up data

The effect of the stimulation on PD motor symptoms reduction was maintained over the 2 weeks observation period (long term follow up).

In particular, the average improvement was of 22.30 (53%) points (SD 7.66) and 18.64 (60%) points (SD 6.90) of the UPDRS III scale, in cDBS and aDBS respectively, in StimON/MedON condition.

There was a trend suggesting that patients have higher benefits on motor symptoms control when stimulated in aDBS, compared to cDBS.

Evaluation of dyskinesia

The patients showed low levels of dyskinesias during the assessments conducted in the short term follow up. However, on comparing the worst UDysRS scored obtained across all assessments conducted in aDBS and cDBS some reduction in dyskinesia when the patients were treated in aDBS was observed.

Evaluation of TEED

Average of the Total energy delivered (TEED) when the patients were treated in aDBS and cDBS, during the long-term follow up was cDBS: 106.11±42.31 and aDBS: 114.62±67.72

Recording performances

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During hospitalization (short-term follow up) LFPs were recorded both in the streaming and in the embedded mode. LFP streaming consists in the real-time wireless transmission of LFP data to an external receiver (NWKstation) that, due to the high-power demand and consequent fast battery drain for the maintenance of a permanent external receiver link, was limited to a short time window. The embedded mode is a less power consuming solution for chronic neural activity monitoring that consists of collecting data in an embedded memory located inside the IPG and can be maintained always ON.

LFP streaming was used to choose the best contact pair to be used in chronic recording. More specifically, LFPs were recorded and streamed out from all the possible contact pairs (excluding the one used for stimulation) that, considering bilateral monopolar configuration, it includes 6 differential traces, 3 per side. The patients were in the MedOFF/StimOFF condition and were asked to stay in resting posture during the data streaming. Each recording lasted 10 seconds, to minimize the time in which the patients experienced the return of motor symptoms (MedOFF/StimOFF condition). The power spectra were directly visualized for each trace, and the contact pair showing higher beta (10-35Hz) activity was selected for chronic recording during DBS treatment. The recorded beta band is defined as ± 5 Hz from the peak frequency in the beta band (personalized beta band).

At the end of the experimental session with LFP data streaming, LFP chronic recording (embedded mode) was activated and consisted in storing physiological data inside the IPG on a not-volatile memory for chronic recording and offline downloading and processing (Arlotti et al, 2021).

Data streamed showed limited data loss (average 2%) and no cardiac artifact in any recordings. The signal-to-noise ratio (SNR) calculated on the beta peak was always greater than 3 logs, suggesting an optimal recording performance. A significant beta peak was found in at least one side per each patient.

From the internal memory of the IPG we downloaded the power spectral density (PSD) of the contact pair selected from streamed LFPs, thus allowing a full monitoring of LFP fluctuation over time. The AlphaDBSipg stored the power spectrum every 10 minutes and downloaded it (together with the beta power value every minute and the stimulation value every 10 minutes) on the AlphaDBSpat at each recharging. The embedded mode provided high-quality data that was successfully used for closed-loop stimulation. Note that for two patients the recording configuration was symmetric (stimulation contact between recording contacts) whereas for the third patient it was asymmetric (stimulation contact outside recording contacts). Iterative storing and downloading allowed for chronic data collection, providing highlights on the system functioning in terms of beta power tracking, closed loop implementation, and neurophysiological monitoring (Arlotti et al, 2021).

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Summary of clinical data from other sources, if applicable

Clinical Data Registry

A clinical data registry is an interactive database that collects, organizes, and displays healthcare information. The purpose of a data registry is to evaluate and improve outcomes for a population defined by a particular condition, disease, or exposure. Specifically, registries use observational study methods to collect and harmonize data about the treatment, outcomes, and well-being of patients who receive care over time. They aggregate large data sets and analyze trends or patterns in treatments and outcomes. Medical device manufacturers like us use registries to track and understand the effectiveness, safety, and value of medical devices or therapies and drugs entering or on the market. We rely on advanced analytics and data science to transform data into meaningful insights that are useful, usable, and used by a variety of stakeholders to achieve a desired outcome.

Medical Device Registry:

A medical device registry is focused on tracking the effectiveness, safety, and value of medical devices. Device registries come in several forms. Medical specialty organizations may collect data on various devices used for procedures or conditions, as part of their clinical data registries. Medical device companies establish registries and use registry data to support post-market surveillance.

The uses of the clinical data registries are:

- Decision support
- Guideline development
- Measure development
- Regulatory and public reporting
- Value based reimbursement and payment
- Patient engagement
- Post market surveillance
- Registry based clinical trials
- Education development
- Certification and accreditation

The value of clinical data registries are:

- Physicians and providers use high-quality; data-driven insights to better understand expected outcomes, make evidence-based decisions, and share best practices.
- Patients share timely and personal data about their condition and outcomes and gain a greater understanding of their care that leads to informed shared decision-making.

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- Researchers and developers use registry data as the foundation for registry-enhanced or registry-based research, clinical trials, or post-market surveillance studies.

Examples of clinical data registries are:

1. Clinicaltrials.gov: ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.
2. Clinicaltrialsregister.eu: The European Union Clinical Trials Register allows you to search for protocol and results information on interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA); clinical trials conducted outside the EU / EEA that are linked to European pediatric-medicine development.

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Studies referred from device registries are given below:

Sl.no	Registry	Study No	Country	Study Title	Study Phase	Type of study	Number of subjects	Inference
1.	https://clinicaltrials.gov/study/NCT01221948?term=Deep%20brain%20stimulator%20system%20for%20Parkinson%E2%80%99s%20disease&rank=1	NCT01221948	Austria, France, Germany, Italy, Spain, United Kingdom	VANTAGE STUDY Vercise™ Implantable Stimulator for Treating Parkinson's Disease	Phase 2	Interventional	53	High-frequency deep brain stimulation (DBS) with a single electrical source is effective for motor symptom relief in patients with Parkinson's disease. We can conclude that a multiple-source, constant-current device that permits well defined distribution of current would lead to motor improvement in patients with Parkinson's disease.
2.	https://clinicaltrials.gov/study/NCT01703598?term=Deep%20brain%20stimulator%20system%20for%20Parkinson%E2%80%99s%20disease&page=2&rank=11	NCT01703598	United States	Clinical Outcomes of Deep Brain Stimulator Electrodes Placed Using Intraoperative Computed Tomography and Frameless Stereotaxis Versus Microelectrode Recording and Frame-based Stereotaxis	NA	Interventional	69	Asleep DBS for PD improved motor outcomes over 6 months on par with or better than awake DBS, was superior with regard to speech fluency and quality of life, and should be an option considered for all patients who are candidates for the treatment.

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The advantage of referring the data from a third-party registry is usually centered on patients or cases, which provides a sufficient level of traceability and detail for the study of our product. Using registries can be less expensive than initiating new and private device registries. The data in these registries might be relevant but may not contain the exact attributes needed to document/demonstrate clinical performance.

Hence, we cannot completely rely on the above registries to collect enough data for our devices. We have referred these registries only to gather information on similar devices and the study methodology.

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Real-world evidences

a. Published Adverse Events for Similar Medical Devices

The adverse events databases USA, UK, Germany & Australia are selected for collection of information about events with similar medical devices.

i. USFDA Database (Maude)

Year	FDA Code	Event Type	Total Results	Applicable Events	Event Details	Ref. Risk ID#
2018	MHY	Death	30	00	--	--
		Injury	1720	00	--	--
		Malfunction	2758	00	--	--
2019	MHY	Death	31	00	--	--
		Injury	1374	05	01-High Impedance 01-Unintended use error 02-Rapid Battery depletion 01-Trouble in Charging	HZ03.05 HZ03.07 HZ03.10 HZ03.14 HZ03.23 HZ03.30 HZ12.11 HZ12.18 HZ12.25 HZ15.02 HZ15.03 HZ15.24 HZ15.29 HZ15.31 HZ21.03 HZ21.06 HZ21.07 HZ21.08 HZ21.10 HZ21.13 HZ21.18 HZ21.22 HZ21.23 HZ24.10
		Malfunction	1410	00	--	--
2020	MHY	Death	19	00	--	--
		Injury	1393	06	02-Unitended Use Error 01-Component Failure 01-Impedance Issue	HZ03.05 HZ03.07 HZ03.10 HZ03.14 HZ03.23

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					01-Mild Shocking Feeling or Discomfort 01- Lead Damage	HZ03.30 HZ12.11 HZ12.18 HZ12.25 HZ15.02 HZ15.03 HZ15.24 HZ15.29 HZ15.31 HZ21.03 HZ21.06 HZ21.07 HZ21.08 HZ21.10 HZ21.13 HZ21.18 HZ21.22 HZ21.23 HZ24.10 HZ14.01 HZ14.02 HZ14.04 HZ14.13 HZ14.17 HZ14.18 HZ14.19 HZ14.20 HZ14.21 HZ14.22 HZ19.14 HZ13.01 HZ13.02 HZ13.03 HZ13.04 HZ13.05 HZ13.06 HZ13.07 HZ13.08 HZ13.09 HZ14.02 HZ14.04 HZ14.05 HZ14.07 HZ14.13 HZ14.14
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						HZ14.15
						HZ14.16
						HZ14.18
						HZ14.28
						HZ14.29
						HZ15.02
						HZ19.21
						HZ19.35
						HZ19.53
						HZ19.55
						HZ19.68
						HZ21.07
						HZ21.08
						HZ22.05
						HZ23.01
						HZ23.02
						HZ23.03
						HZ23.04
						HZ23.05
						HZ23.06
						HZ23.07
						HZ23.08
						HZ23.12
						HZ11.14
						HZ11.15
						HZ11.16
						HZ11.17
						HZ11.40
						HZ11.58
						HZ11.71
						HZ12.11
						HZ12.18
						HZ12.25
						HZ14.23
						HZ15.24
						HZ15.29
						HZ15.31
						HZ16.01
						HZ17.01
						HZ17.02
						HZ17.03
						HZ17.04
						HZ17.05
						HZ18.01
						HZ18.02
						HZ18.03
						HZ19.11
						HZ19.28

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						HZ19.42 HZ19.57 HZ21.03 HZ21.18 HZ21.23 HZ22.09 HZ22.13 HZ24.10 HZ24.12
		Malfunction	1252	00	--	
2021	MHY	Death	05	00	--	--
		Injury	1346	01	01-Unintended use error	HZ03.05 HZ03.07 HZ03.10 HZ03.14 HZ03.23 HZ03.30 HZ12.11 HZ12.18 HZ12.25 HZ15.02 HZ15.03 HZ15.24 HZ15.29 HZ15.31 HZ21.03
		Malfunction	1083	00	--	
2022	MHY	Death	12	00	--	--
		Injury	1283	00	--	--
		Malfunction	946	00		
2023 (Till OCT)	MHY	Death	11	00	--	--
		Injury	954	00	--	--
		Malfunction	525	00		

Year	Total Recalls	No. of Applicable Recalls	Recall Reason	Is this covered in Risk Management?	Ref. Risk ID#
2018	01	00	--	--	--
2019	00	--	--	--	--
2020	01	01	01-Software Issue	Yes	HZ14.05, HZ14.06,

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					HZ14.08, HZ14.09, HZ14.10, HZ14.11, HZ14.12
2021	04	01	01-Cycling issue and Log fill issue 01-Software Issue	Yes	HZ14.05, HZ14.06, HZ14.08, HZ14.09, HZ14.10, HZ14.11, HZ14.12
2022	01	01	01-Communication issue between Neurostimulator and Clinician Programmer	Yes	HZ07.03
2023 (Till OCT)	01	01	01-Incorrect Labelling (Use by date)	Yes	HZ10.27 HZ10.29 HZ10.31

ii. UK Database (MHRA)

Year	Therapeutic Area	Key word	Total Results	Applicable Events	Event Details	Ref. Risk ID#
2018	Neurology	Deep Brain Stimulation	00	--	--	--
2019	Neurology	Deep Brain Stimulation	01	00	--	--
2020	Neurology	Deep Brain Stimulation	00	--	--	--
2021	Neurology	Deep Brain Stimulation	06	04	01-Premature Battery depletion 03-Software issue	HZ15.06, HZ15.13, HZ19.53 HZ14.05, HZ14.06, HZ14.08, HZ14.09, HZ14.10, HZ14.11, HZ14.12

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2022	Neurology	Deep Brain Stimulation	02	01	01-Communication issue between Neurostimulator and Clinician Programmer	HZ07.03
2023 (Till OCT)	Neurology	Deep Brain Stimulation	01	00	--	--

iii. Germany Database (BfArM)

Year	Therapeutic Area	Key word	Total Results	Applicable Events	Event Details	Ref. Risk ID#
2018	Neurology	Deep Brain Stimulation	01	00	--	--
2019	Neurology	Deep Brain Stimulation	03	00	--	--
2020	Neurology	Deep Brain Stimulation	00	--	--	--
2021	Neurology	Deep Brain Stimulation	00	--	--	--
2022	Neurology	Deep Brain Stimulation	00	--	--	--
2023 (Till OCT)	Neurology	Deep Brain Stimulation	00	--	--	--

iv. Australia Database (DAEN)

Year	Therapeutic Area	Key word	Total Results	Applicable Events	Event Details	Ref. Risk ID#
2018	Neurology	Deep Brain Stimulation	01	00	--	--
2019	Neurology	Deep Brain Stimulation	00	--	--	--
2020	Neurology	Deep Brain Stimulation	00	--	--	--
2021	Neurology	Deep Brain Stimulation	00	--	--	--

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2022	Neurology	Deep Brain Stimulation	00	--	--	--
2023 (Till OCT)	Neurology	Deep Brain Stimulation	00	--	--	--

The identified applicable events and related possible hazards are already evaluated as part of our AlphaDBS risk management and there were no known foreseeable events. Hence, we can conclude that our AlphaDBS is safe to use for its intended purpose.

Screening of scientific literature and other sources of clinical data:

Criteria for Literature Selection

Inclusion criteria

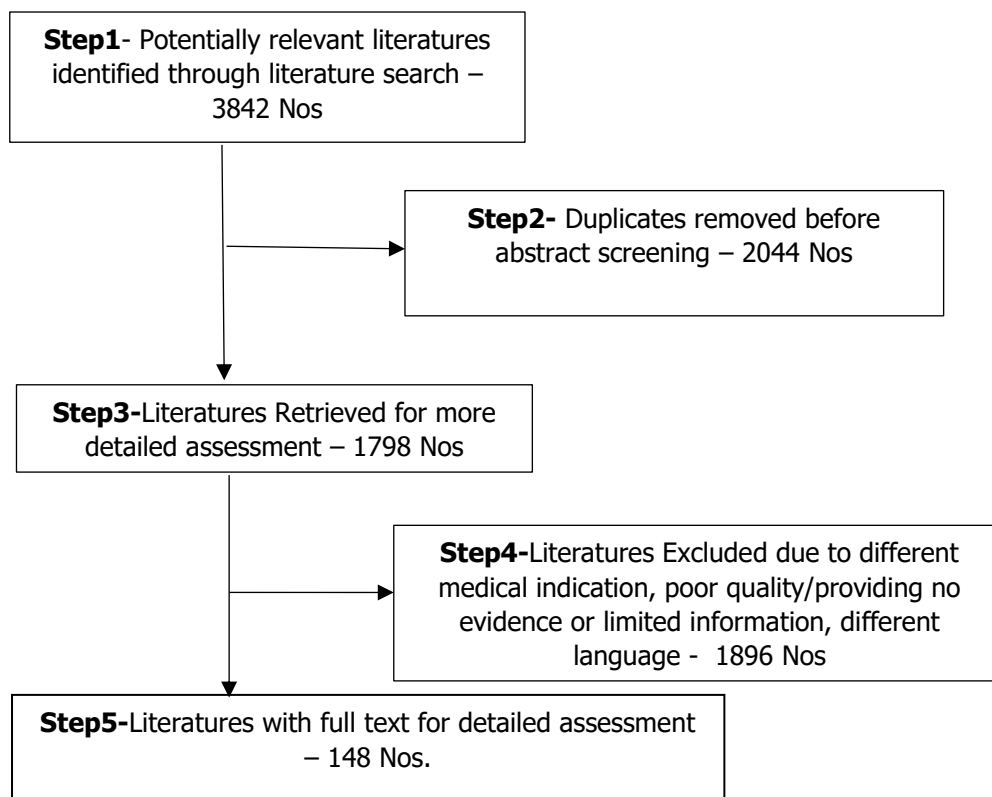
#	Criteria Aspect
Criteria 1	Study Type (Prospective studies, Comparative studies, Controlled randomized prospective clinical trials (RCT), Treatment studies, Retrospective studies, Reviews and Meta-Analyses)
Criteria 2	Treatment or medical condition
Criteria 3	Related to device under evaluation, benchmark device, similar device and other device
Criteria 4	Related to medical alternatives available to the intended patient population
Criteria 5	Related to demonstrating the medical device performance
Criteria 6	Related safety aspect, describing complications from the medical device intended use
Criteria 7	Related to state-of-the-art of the medical device
Criteria 8	Availability of favourable and un-favourable data

Exclusion criteria (non-relevant articles)

- No abstract or truncated abstract,
- Biochemical studies,
- Animal studies (reviewed related the relevance for preclinical data),
- Published in other languages than English,
- Duplications (unless the data was used to elicit different conclusions).
- Papers that focused on the treatment/therapy of a specific disease state, rather than an evaluation of the devices in question were excluded. Dissimilar devices and studies whose outcomes were unrelated to device performance (e.g. general evaluation of disease state) were also excluded.

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Literature Selection Flowchart



An overall summary of the clinical performance and safety

Final considerations on the safety and efficacy of cDBS

Safety

DBS devices for PD are on the market since 1998 so long term safety data are available, however additional unknown risks cannot be excluded.

Several studies have proven the efficacy of STN-DBS and GPi-DBS in alleviating off-motor symptoms and dyskinesias, however, some studies and reviews suggest that DBS is associated with higher adverse events (Pouratian et al., 2012) or with more severe adverse events as compared to medical treatment (Deuschl et al., 2006).

Most severe AEs occur as a direct consequence of surgery or during the first few months after surgery (Vergani et al., 2010 and Lachenmayer et al., 2021).

Major complications (including intracranial hemorrhages, lead malpositioning, delayed adverse events, lead infections, IPG infections requiring removal of the device, and lead

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displacement) accounted for 15% (Deuschl et al., 2013). A recent analysis of databases analyzing adverse events occurring in DBS routine practice in North America indicates that 24.2% of PD patients implanted with DBS undergo lead revision or removal (Moro et al, 2016). Another recent analysis of data of 6,058 DBS surgeries for PD, registered in the US Nationwide Readmissions Database indicates that the large majority of patients were discharged home (95.3%). Non-elective readmission was rare (4.9%), even compared to non-elective readmission rates observed for common procedures such as upper gastrointestinal endoscopy (16.2%), colonoscopy (14.0%), and cardiac defibrillator and pacemaker procedures (11.1%) (Schneider et al, 2020).

Systematic reviews of AEs associated with DBS in PD concluded that:

- The most common procedure-related AEs of STN and GPi DBS were mental status/behavioral changes, present in 18.4% and 9.3% of patients, respectively. The most common mental status/behavioral change reported was confusion in 10.2% and 6.2% in STN and GPi respectively (Videnovic et al., 2008).
- Among hardware-related AEs:
 - Infections accounted for from 4.2% (Rasiah et al, 2022) to 2.4% (Videnovic et al, 2008).
 - Surgical site complications accounted for 2.8% (Rasiah et al, 2022)
 - Intracranial hemorrhage accounted for from 3.1% (Lachenmayer et al, 2021) to 2.4% (Rasiah et al, 2022)
 - Revision 4.9% (Rasiah et al, 2022)
 - Lead malposition 3.3% (Rasiah et al, 2022)
 - Hardware-related complications 2.4% (Rasiah et al, 2022)
 - Seizure 1.9% (Rasiah et al, 2022)
- Stimulation/Disease Progression-Related AEs: A clear distinction between stimulation-dependent and stimulation-independent AEs was documented only in 12 reports (i.e., 265 patients with STN DBS and 17 patients with GPi DBS). This distinction was based on whether the AE resolved when the stimulator was turned off (stimulation-dependent) or whether it persisted. The most common AEs in the STN group were weight gain (37.5%), speech disturbance (12.8%), eyelid opening apraxia (11.3%), and cognitive decline (5.8%). In the GPi group, the most common AEs included weight gain, gait ignition failure (17.6% each), and dysarthria (11.8%) (Videnovic et al, 2008). A more recent review also includes respiratory issues, postural instability, and dysphagia among DBS related AEs (Jörg et al, 2020).
- Medication-related complications, including impulse control disorder, cognitive slowing, mania or hypomania, sleepiness, and dyskinesia, may improve post-operatively by reducing medication doses (Zhang et al, 2021)

A number of reports focus on possible psychiatric and behavioral side effects of STN-DBS (Volkman et al., 2001). The most common mood disorder reported is depression, which is more frequent in patients treated with DBS, particularly with STN-DBS than in patients

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treated with best available medical therapy. However, some authors suggest that such mood disorders might be associated with the withdrawal of medications (Pouratian et al., 2012). For what concerns the association between suicidality and DBS, 2 meta-analysis and 2 systematic reviews revealed increased rates of suicidality after DBS. A comparative analysis of suicidality DBS at two different neurological targets (GPi vs. STN) showed a markedly lower rate in the GPi group. It was postulated that GPi DBS might be protective against the development of depression or suicidal behaviors because it is comparable to STN DBS concerning motor outcomes but does not require post-operative reduction of dopaminergic medications as is usually the case for STN DBS (Costanza et al, 2022).

Clinical efficacy

A huge body of literature shows that cDBS improves PD motor symptoms. However, many studies show methodological limitations (e.g., unblinded assessment, uncontrolled studies). The results of the first randomized controlled study comparing DBS to best medical treatment was published only in 2006 (Deuschl et al., 2006), while the first randomized controlled trial, in which both groups underwent DBS implant was published in 2012 (Okun et al., 2012). The latest clinical trial on DBS (INTREPID study), which foresees also sham stimulation to allow more reliable blinding, confirms previous positive effects of DBS in the short follow up.

The randomized trial, meta-analysis, and reviews agree on the fact that the three cardinal signs of PD (tremor, bradykinesia, rigidity), as well as medication-induced dyskinesias, all respond to cDBS.

For what concerns the efficacy of cDBS:

- All studies showed a significant reduction of motor symptom severity when in the stimulation on/medication off state after surgery as compared with the medication off-state before surgery, as measured with the UPDRS part III. For STN-DBS the reduction varied between 25% (Follett et al., 2010) and 41% (Deuschl et al., 2006) for the controlled studies. In the analysis of the 22 uncontrolled studies, (Kleiner-Fisman et al., 2006) an average improvement of 52% is reported. The largest meta-analysis published in recent years suggests that STN-DBS efficacy on UPDRS III is 50.5%. The efficacy in the reduction of UPDRS III scores observed in the study conducted with the AlphaDBS System is slightly superior (61% of improvement) but such results should be interpreted with caution since the patient population is small and constituted by patients at elective IPG replacement. Other studies conducted in the same patient population indicate no statistically significant changes in the motor functions of patients after elective IPG replacement, despite changes in impedances and TEED after IPG replacement with concurrent Pocket Adapter implantation (Nieman et al., 2020). Similarly, a systematic review, comparing the effect of constant current and constant voltage stimulation on PD

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patients with STN-DBS, report no change in motor and non-motor symptoms after device exchange (Abdollahifard et al., 2022).

- Long-term data are available for STN stimulation from studies with follow-up of 5 years (Krack et al., 2003, Moro et al., 2010, Deuschl et al., 2013) and of 8–10 years of follow-up (Fasano et al., 2010; Castrioto et al., 2011). They demonstrate that a considerable proportion of the patients can improve in the long term. The important points are that the UPDRS III and even the UPDRS II (ADL) scores in the off-state are worsened over time but still remain better than baseline scores. Treatment efficacy decreased over time, with dopaminergic medication alone losing efficacy more quickly than STN-DBS alone but not when combined with STN-DBS (Lau et al, 2020).
- Almost every study of cDBS to the STN reports a significant reduction in the use of medications, but reports on the effect of DBS to the GPi on medication use are less consistent.
- There is an ongoing discussion concerning the relative efficacy of stimulating the STN versus the GPi in treating tremor-dominant symptoms, freezing, and medication-induced dyskinesias. Follett et al. report a similar improvement in GPi and STN stimulation (Follett et al., 2010), while other authors suggest the superiority of STN.
- Recently two meta-analyses suggested that DBS has a positive effect on gait problems:
 - Compared to other targets (GPi and PPN) STN-DBS ranks first in improving PD gait and motor symptoms and can greatly increase the stride length and increase the gait speed in the drug withdrawal state, while the rhythm remains mostly unchanged (Chen et al, 2021).
 - For freezing of gait, low-frequency stimulation was superior to high-frequency stimulation, but efficacy of DBS seems to decrease with time (Razmkon et al., 2022)
- DBS alleviates pain associated with PD, as reported by a recent meta-analysis (Diao et al, 2022)
- DBS seems to improve sleep problems. A prospective uncontrolled study shows that STN-DBS has a significant and lasting positive effect on overall sleep quality and determines a significant reduction in the proportion of patients with severe sleep abnormalities from 31% preoperatively to 12% at 12 months. Such improvement is also reported in sub-scores related to nocturnal motor symptoms and restlessness, and daytime dozing (Bjerknes et al, 2020)
- There is little consensus on:
 - The effectiveness of DBS on falls and near falls (Nilson et al., 2011).
 - The effect of DBS on late-stage disability milestones associated to PD, associated with a possible neuroprotective effect of the stimulation, which could slow down the degeneration of dopaminergic neurons in PD (Mahlknecht et al., 2022). Some authors suggest that DBS can induce

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gradual reorganization of neural circuits through enhanced synaptic plasticity and neurogenesis.

- Data on survival are not conclusive but seem to point to a potential survival benefit in favour of DBS, with the largest of the studies calculated a mean gain in lifetime of 7.6 months (Mahlknecht et al., 2022).
- The effect of DBS on speech. A recent review indicates that most studies report a deterioration of the vocal parameters on subjective voice quality evaluation. For speech, the findings were more contrasted. The stimulated anatomical region may have a significant role since the stimulation of the pallidal area was mainly associated with voice quality improvement, in contrast with other regions (Baudoulin et al., 2020)
- The effect of DBS on urinary problems. A recent systematic review indicates that STN-DBS led to a significant increase in maximum bladder capacity but had no clinically relevant effects on other urodynamic parameters (Jorg et al.2021).
- Some authors suggest the efficacy of STN-DBS in improving posture difficulties associated with PD (Artusi et al., 2017)
- Some authors suggest that GPi-DBS is associated with fewer psychological complications and with better outcomes on mood (Xu et al., 2016, Mansouri et al., 2017).

More recent studies also take into consideration the effects of DBS on specific patient subgroups. DBS is effective both in young onset and late onset PD (Kim et al., 2021) and in different disease forms (e.g., malignant, intermediate etc.) (Artusi et al., 2021).

Regarding gender differences related to DBS procedure, a large study suggests that women are disproportionally underrepresented in referrals to DBS centers compared to the general PD population and their probability of undergoing DBS after positive indication evaluations is lower than in men. Preoperatively, female patients have longer disease severity and more severe symptoms. However, DBS is equally clinically efficacious in women and men (Jost et al., 2022)

A recent meta-analysis suggests that monogenic PD patients have variable DBS benefit depending on the mutated gene. The overall benefit of DBS in SNCA, GBA and LRRK2 p.T2031S mutations may be compromised due to rapid progression of cognitive and neuropsychiatric symptoms. In the presence of other mutations, the motor changes in DBS-treated monogenic PD patients appear comparable to those of the general PD population (Kuusimäki et al., 2020).

Final considerations on the safety and efficacy of aDBS

The total number of patients in which the safety and efficacy of aDBS was assessed is 31 with 13 studied at IPG replacement (chronic patients) and 18 studied immediately after DBS electrode implant (de novo patients in acute condition). Ten patients received the

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AlphaDBSipg implantable device (PS4) whereas the others received aDBS and cDBS through the AlphaDBSext external device.

When considering all the studies including de novo DBS patients (PS2bis and PS1), on a population of 18 subjects, cDBS showed an average improvement of 17.2 ± 12.8 points (52.1%), and aDBS of 19.6 ± 13.5 points (58.4%), corresponding to an average difference of -2.32 with an effect size of -0.18. Similarly, in chronic DBS patients (PS3 and PS4), on a population of 13 subjects, cDBS showed an average improvement of 37.5 ± 19.4 points (65.4%), and aDBS of 35.0 ± 19.7 points (62.0%), corresponding to an average difference of 2.56 with an effect size of 0.13. Note that the improvement in de novo DBS patients obtained with externalized leads 5/6 days after electrode implant is in line (or even superior) with that reported in the literature for similar patients (30-35%, Little et al 2013; Little et al, 2016), and is lower than that in chronic patients because of the transitory changes in the electrode-tissue interface occurring during the very acute phase.

At the individual level, with an overall standard deviation of the MedOFF/StimOFF vs MedON/StimON improvement of 18.1 points, all patients show an equivalent improvement between aDBS and cDBS.

Dyskinesia, when visible (PS1 and PS2bis) were better controlled by aDBS.

Therefore, despite the heterogeneity of conditions, the data available so far show that both aDBS and cDBS provide satisfactory clinical efficacy, in, at least, an equivalent way.

Ongoing or planned post-market clinical follow-up

During 2022, the company continued the implementation of the activities defined in its 5-year PMCF plan. Since the company did not start device commercialization, activities concentrated on:

1. The Implant registry: the Company **designed the AlphaDBS System implant registry** together with domain experts. The design has been submitted to FDA for assessment since the Company aims to use it for international clinical study.
2. Analysis of long term performance of AlphaDBS system, with particular focus on the recording function: This activity has partially been **implemented in the context of a clinical study** aimed at comparing an innovative stimulation mode (defined as adaptive DBS or aDBS) against an **active comparator (constituted by the conventional DBS mode)**, both delivered by AlphaDBS System.

Since the study uses an investigational device that is constituted by the CE marked AlphaDBS System with the additional feature of implementing aDBS (that uses as feedback variable LFPs), the **data collected when the system delivers conventional DBS will serve to gain knowledge on the long term performances of the recording function and long term analysis.**

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The company will continue the implementation of the activities defined in the 5-year PMCF plan in 2023. The results from the studies performed in 2022 have not yet been documented in a PMCF Report, as the company made the decision to concentrate its efforts in preparing the MDR Technical Documentation ready for MDR Certification. As such, the Clinical Research Manager will draw the PMCF report, for the years 2022 and 2023 as part of the EU MDR Technical Documentation submission.

6 Possible therapeutic alternatives

Parkinson's disease: Epidemiology and burden of disease

PD is among the most prevalent neurodegenerative conditions. Age-adjusted prevalence estimations range between 70.9 and 173.8 per 100,000 population, and age-adjusted incidence rates range from 6.1 to 17.4 per 100,000 population per year in Western Countries (Abbas et al., 2018). The male-to-female ratio is estimated to be 1.9 (Baker et al., 2006). People suffering from PD utilize health services significantly more often than healthy individuals, and this is associated with costs that are approximately double that of a control population (Elsner et al., 2016).

PD is a serious burden for the patient not only for the symptoms related to it but also for the comorbidities to which it is accompanied, such as musculoskeletal disorders, falls, mental health problems, dysfunction of the autonomic nervous system. Despite this, many patients and their family members are unaware of the relationship between PD and these concomitant non-motor symptoms.

Management of PD patients

There is no disease-modifying therapy for PD. Different medical and surgical alternatives are currently available to control motor and non-motor symptoms associated to PD.

In addition, several non-pharmacological treatments are available (physiotherapy speech therapy, tai-chi, etc.).

Medical treatment

Medical therapy for motor symptoms has been primarily focused on restoring dopamine levels through the administration of levodopa, dopamine agonists, or monoamine oxidase B (MAO-B) inhibitors. Current standards for patient care recommend dopamine agonist or levodopa as the first line of therapy for the symptomatic control during the early, uncomplicated stages of PD.

Other medical therapy may be used to treat multiple symptoms of PD.

The following table summarizes the main pharmacological classes of drugs currently used to treat PD.

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Class	Symptomatic treatment	Prevention of disease progression	Description
Dopaminergic drugs	Efficacious	Insufficient evidence	In the initial stages of the disease, levodopa therapy is the most effective for improving motor symptoms in PD. However, long-term treatment is accompanied by fluctuations in motor performance, dyskinesias, and neuropsychiatric complications. Furthermore, as PD progresses, patients develop features that do not respond well to levodopa therapy, such as freezing episodes, autonomic dysfunction, falling, and dementia, and symptoms related to the administration of other drugs (Horskin et al., 2006a and Horskin et al., 2006b). Recent reviews claim that the efficacy of levodopa for the prevention of clinical progression (Goetz et al., 2005) or neuroprotection (Horskin et al., 2006a) is not proven.
Dopamine agonists	Efficacious		Levodopa is more efficacious than any orally active dopamine agonist. The proportion of patients able to remain on agonist monotherapy falls progressively over time to <20% after 5 years of treatment (Horskin et al., 2006a). However, Class I randomized, controlled trials demonstrate how early use of an agonist can reduce the incidence of motor complications versus levodopa.
Catechol-O-methyltransferase (COMT) inhibitors	Efficacious	--	These drugs enhance the bioavailability of L-dopa and, therefore, are not used in clinical situations other than as adjuncts to L-dopa. With regard to safety issues, tolcapone is considered Acceptable but Requiring Special Monitoring in fluctuating patients who have failed other therapies, but Unacceptable in patients who otherwise can be treated. (Goetz et al., 2005).

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Class	Symptomatic treatment	Prevention of disease progression	Description
Anticholinergic Therapies	Likely efficacious	insufficient evidence	Data is insufficient to establish the long-term efficacy of anticholinergic treatment (MDS task force, 2002).
monoamine oxidase B (MAO-B) inhibitors	Efficacious	insufficient evidence	Rasagiline use is Acceptable Without Specialized Monitoring. For 'Clinical Practice Implications', rasagiline is considered Useful as a monotherapy in early PD and Investigational in all other settings (MDS taskforce, 2002). As with any dopaminergic drug, MAO-B inhibitors can induce a variety of dopaminergic adverse reactions (Goetz et al., 2005).

Main pharmacological classes of drugs currently used to treat PD.

The following tables summarize the NICE guidelines (NICE guideline [NG71]) in relation to the side effects of widely used treatments for PD.

	Levodopa	Dopamine agonists	MAOB inhibitors
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviation: MAOB, monoamine oxidase B.

* Excessive sleepiness, hallucinations, and impulse control disorders.

Potential benefits and harms of dopamine agonists, levodopa and MAOB inhibitors.

	Dopamine agonists	MAOB inhibitors	COMT inhibitors	Amantadine
Motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms

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Activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
Off time	More off time reduction	Off time reduction	Off time reduction	No studies reporting this outcome
Adverse events	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
Hallucinations	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this outcome
Abbreviations: MAOB, monoamine oxidase B; COMT, catecholOomethyl transferase.				

Potential benefits and harms of dopamine agonists, MAOB inhibitors, COMT inhibitors, and amantadine

Surgical treatments

Current medical therapies for PD produce a marked improvement in PD symptoms. However, chronic use of levodopa is often limited by the appearance of its long-term side effects including an overall loss of drug effect throughout the course of the day (“wearing off”), fluctuations in efficacy (“on–off” fluctuations), and involuntary movements now recognized as levodopa-induced dyskinesia (LIDs). These complications are observed in as many as 45% of patients treated with levodopa for more than 5 years (Strauss et al., 2014). Non-motor fluctuations are also often reported. Non-motor fluctuations are non-motor symptoms (dysautonomic, cognitive, psychiatric and sensory/pain) that vary according to dopaminergic treatment in a manner similar to motor fluctuations.

Surgical treatments have been typically reserved for patients with severe motor impairment from PD and motor complications in the form of fluctuations and dyskinesias (Goetz et al., 2005).

Surgical treatment aims to correct the imbalance created by the diminished function of the substantia nigra. Surgery alters, through either destruction or electrical stimulation, the function of brain nuclei - such as the thalamus, globus pallidus or subthalamus - that interact functionally with the substantia nigra (NICE, [IPG19], 2003).

Current available surgical treatments for PD are listed (revised from Fox et al., 2018).

	Efficacy conclusions	Implication for clinical practice	Risks
Bilateral STN cDBS	Efficacious	Clinical useful	
Bilateral GPi cDBS	Efficacious	Clinical useful	

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Unilateral pallidotomy	Efficacious	Clinical useful	Acceptable risk with specialized monitoring.
Unilateral thalamotomy	Insufficient evidence	Investigational	
Thalamic stimulation (uni or bilateral)	Insufficient evidence	Investigational	
Subthalamotomy	Insufficient evidence	Investigational	

Surgical treatments for PD.

Deep Brain Stimulation

Conventional DBS is an established treatment for advanced PD. The US Food and Drug Administration approved DBS as a treatment for Parkinson's disease in 2002. DBS consists of delivering chronic high-frequency stimulation through electrodes neurosurgical implanted in the basal ganglia and connected to an IPG positioned in the supraclavicular region. The GPi and the STN are the most common targets for DBS.

Despite the fact that DBS of both the GPi and the STN were approved for the treatment of PD, the STN has been the target of choice for most neurosurgeons and neurologists.

Conventional DBS is characterized by hardware components, mode, and pattern of stimulation that did not change over time (since the first applications in the 1990s). The IPG implanted in the STN delivers continuous stimulation resulting in a spherical shape of the electric field around the electrodes (Aström et al, 2009). Stimulation settings for chronic conventional DBS (lead contact/contacts, stimulation mode – monopolar/bipolar, frequency, voltage, pulse width, and polarity) are decided based on screening of the four electrode contacts for effect and side effects, during the programming phase that takes place around two weeks after stereotactic neurosurgery for electrode implant. This procedure is sometimes a laborious exercise for the programming clinician and the patient and may need incremental repetitive adjustments after surgery, over periods of weeks and months in some patients.

The NICE guidelines suggest considering cDBS for people with advanced PD whose symptoms are not adequately controlled by best medical therapy (NICE, [IPG19], 2003).

7 Suggested profile and training for users

AlphaDBS System has three main types of user.

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1. PD patients with DBS implant and their caregivers who will use the AlphaDBSpat to recharge their neurostimulator (i.e. AlphaDBSipg).
2. Caregivers who will use the AlphaDBSpat to recharge the patient's neurostimulator (i.e. AlphaDBSipg).
3. Physicians (neurologists and neurosurgeons, DBS experts):
 - DBS expert neurologists and neurosurgeons will use NWKstation to program the AlphaDBSext and the AlphaDBSipg.
 - DBS expert neurosurgeons will implant the AlphaDBSipg and will connect it to DBS lead extensions.

PD patients

- Age: the mean PD age of onset in 58-60 year, so usually PD patient are elderly
- Gender: based on epidemiology, the prevalence of PD is slightly higher in males
- Linguistic and cultural background: various
- Professional competence: various
- Strength and stamina: very low due to PD symptoms
- Physical dexterity, flexibility, and coordination: very low due to PD symptoms
- Cognitive abilities: long term PD is often associated with cognitive, including memory, impairments. However, the reference guidelines (CAPSIT-PD guidelines) recommend to evaluate cognitive status as part of the pre-surgical visit in de novo DBS patients and to exclude patients with severe decline. Furthermore, neurologists consider that rechargeable DBS systems are appropriate only for patients with a relatively good cognitive status. Therefore we can consider that AlphaDBSipg will only be implanted in patients showing good cognitive performances.
- Mental and emotional state could be compromised. Anxiety and related emotional states could worsen PD symptoms. However, the reference guidelines (CAPSIT-PD guidelines) recommend to the patient psychiatric status as part of the pre-surgical visit in de novo DBS patients and to exclude patients that are more likely to have psychiatric side effects.
- Literacy and language skills: various but depending on disease level. PD patients could have limitations in to speaking properly
- General health status: compromised. PD is a neuro-degenerative disease that worsen over time
- General knowledge of similar types of devices: not very high considering they are approaching DBS treatment for the first time. This aspect could vary for patients that have a previous implanted DBS rechargeable system.

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- Willingness and motivation to use a new device: could be various but in general patients could be highly motivated in using a new device to improve their quality of life
- Ability to learn and adapt to a new device: in the immediate post-surgical period patients could experience discomfort and pain. Abilities to learn new task and technological device could be limited by age related issues.

Level of training that users are expected to have and/or to receive: patients are expected to receive exhaustive and detailed training, before starting to use the AlphaDBSpat and information sheet in lay language. Physicians are expected to train their patients about the use of the device in a domestic environment, especially for what concerns the daily recharging sessions. If the patient is not able to manage the device by itself, caregivers shall be train as well to support the patient.

Caregivers

- Age: typically caregivers are family members of the PD patient (e.g. partner or sons/daughters). As the mean PD age of onset around 60 years, PD patients' partners are often elderly.
- Gender: typically caregivers are most often females
- Linguistic and cultural background: various
- Professional competence: various
- Strength and stamina: could be lower due to elder age
- Physical dexterity, flexibility, and coordination: could be lower due to elder age
- Cognitive abilities: could be lower due to elder age
- Mental and emotional state: should be normal
- Literacy and language skills: various
- General health status: could be compromised due to elder age
- General knowledge of similar types of devices: not very high considering they are approaching DBS treatment for the first time. This aspect could vary for caregivers of patients with an implanted DBS rechargeable system and will be evaluated.
- Willingness and motivation to use a new device: could be various but in general caregivers could be highly motivated in using a new device to improve the quality of life of the cared one
- Ability to learn and adapt to a new device: abilities to learn new task and technological device could be limited by age related issues.

Level of training that users are expected to have and/or to receive: caregivers are expected to receive exhaustive and detailed training, before starting to use the AlphaDBSpat and information sheet in lay language.

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Physicians

- Age: various but usually older than 30 years old and younger than 70
- Gender: various
- Linguistic and cultural background: medicine degree
- Professional competence: these physicians are neurologists and neurosurgeons with high expertise in DBS
- Strength and stamina: this group is used to work in a complex environment, to deal with patients affected by Parkinson's disease and to work under stress
- Cognitive abilities (including memory) and sensory abilities (i.e., vision, hearing, tactile sensitivity): generally good
- General knowledge of similar types of devices: physicians group has high experience and knowledge of similar types of devices, including implantable device for DBS
- Willingness and motivation to use a new device: ability to learn how to use a new device and willingness and motivation in understanding a new device that could improve patient quality of life
- Ability to learn and adapt to a new device: physicians group is used to work with new technological devices and has a consolidated knowledge regarding technology in general, technical and digital skills.

Level of training that users are expected to have and/or receive: physicians are expected to receive exhaustive level of training about tasks that need to be performed with AlphaDBSipg, NWKstation and AlphaDBSext.

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8 Reference to any harmonized standards and CS applied

List of Applicable Standards

#	Standard ID	Current Issue	Title	Partial/ Full compliance
Quality Management System Requirements				
1.	EN ISO 13485	2016/A11:2021	Medical devices - Quality management systems - Requirements for regulatory purposes	Full compliance
Risk Management Requirements				
2.	EN ISO 14971	2019/A11:2021	Medical devices - Application of risk management to medical devices	Full compliance
3.	EN ISO/TR 24971	2020	Medical devices – Guidance on the application of ISO 14971	Full compliance
Usability				
4.	EN 60601-1-6	2010+ A1: 2015 + A2:2020	Medical electrical equipment Part 1-6 General requirements for safety - Collateral Standard: Usability	Full compliance
5.	EN 62366-1	2015+AC:2015+AC:2016+ A1:2020	Medical devices – Part 1: Application of usability engineering to medical devices	Full compliance
Biological Risk Evaluation Requirements				
6.	EN ISO 10993-1	2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	Full compliance
7.	EN ISO 10993-3	2014	Biological evaluation of medical devices - Part 3: Tests for Genotoxicity	Full compliance
			Biological evaluation of medical devices - Part 3: Tests for Carcinogenicity	Full compliance
8.	EN ISO 10993-5	2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity	Full compliance

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9.	EN ISO 10993-6	2016	Biological evaluation of medical devices - Part 6: Tests for Implantation Effects	Full compliance
10.	EN ISO 10993-10	2023	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization	Full compliance
11.	EN ISO 10993-11	2018	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity	Full compliance
12.	EN ISO 10993-12	2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials	Full compliance
13.	EN ISO 10993-23	2021	Biological evaluation of medical devices - Part 23: Tests for irritation	Full compliance
14.	EN ISO 10993-15	2023	Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys	Full compliance
15.	EN ISO 10993-17	2009	Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents	Full compliance
16.	EN ISO 10993-18	2020	Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process	Full compliance
Labels & Symbols Requirements				
17.	EN ISO 15223-1	2021	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Full compliance
Instruction For Use Requirements				
18.	EN ISO 20417	2021	Information supplied by the manufacturer of medical devices	Full compliance
Post Market Surveillance Requirements				

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19.	ISO/ TR 20416	2020	Medical devices – Post market surveillance for manufacturers	Full compliance
Medical Device “Active” Requirements				
20.	EN 60601-1	2006+A1:2013+AC:2014+A12:2014+A2:2020	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance	Partial Compliance
21.	EN 60601-1-2	2015+A1:2020	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests	Partial Compliance
22.	EN 62311	2020	Assessment of electronic and electrical equipment related to human exposure restrictions for electromagnetic fields (0 Hz to 300 GHz)	Partial Compliance
Particular Standard Requirements				
23.	ISO 14708-1	2014	Implants for surgery - Active implantable medical devices -- Part 1: General requirements for safety, marking and for information to be provided by the manufacturer	Full compliance
24.	ISO 14708-3	2017	Implants for surgery -- Active implantable medical devices -- Part 3: Implantable neurostimulators	Full compliance
25.	EN 45502-1	2015	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer	Full compliance
Medical Device “Active + Software” Requirements				
26.	EN 62304	2006+A1:2015	Medical device software - Software life-cycle Processes	Full compliance
DIRECTIVE 2014/53/EU – RED				

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27.	ETSI EN 301 489-1	(V2.2.3)	Electromagnetic Compatibility (EMC) standard for radio equipment and services; Part 1: Common technical requirements; Harmonized Standard covering the essential requirements. of article 3.1(b) of Directive 2014/53/EU and the essential requirements of article 6 of Directive 2014/30/EU	Full compliance
28.	ETSI EN 301 489-3	(V2.3.2)	Electromagnetic Compatibility (EMC) standard for radio equipment and services; Part 3: Specific conditions for Short Range Devices (SRD) operating on frequencies between 9 kHz and 246 GHz; Harmonized Standard for Electromagnetic Compatibility	Full compliance
29.	ETSI EN 301 489-17	(V3.2.6)	Electromagnetic Compatibility (EMC) standard for radio equipment and services; Part 17: Specific conditions for Broadband Data Transmission Systems; Harmonized Standard for Electromagnetic Compatibility	Full compliance
30.	ETSI EN 300 440	(V2.2.1)	Short Range Devices (SRD); Radio equipment to be used in the 1 GHz to 40 GHz frequency range; Harmonized Standard covering the essential requirements of article 3.2 of Directive 2014/53/EU	Partial Compliance
31.	ETSI EN 300 328	(V2.2.2)	Wideband transmission systems; Data transmission equipment operating in the 2,4 GHz band; Harmonised Standard for access to radio spectrum	Partial Compliance
Medical Device “REUSE” Requirements				
32.	EN ISO 17664-1	2021	Processing of health care products - Information to be provided by the medical device manufacturer for the processing of medical devices - Part 1: Critical and semi-critical medical devices	Full compliance

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Medical Device “Active – Home Use” Requirements

33.	EN 60601-1-11	2015+A1:2020	Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment	Full compliance
Sterilization Requirements				
34.	EN ISO 11607-1	2019/Amd 1: 2023	Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems — Amendment 1: Application of risk management	Full compliance
35.	EN ISO 11607-2	2019/Amd 1: 2023	Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes — Amendment 1: Application of risk management	
36.	EN ISO 11135-1	2014+A1:2019	Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	Full compliance

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9 Revision history

SSCP Ver. number	Date issued	Change description and modified paragraph	Revision validated by the Notified Body
1.0	14/03/2023	First document release	☐ Yes Validation language: English ☐ No
2.0	21/12/2023	Document update	☐ Yes Validation language: English ☐ No
3.0	16/01/2024	Document update	☐ Yes Validation language: English ☐ No
4.0	09/08/2024	Document update	☐ Yes Validation language: English ☐ No
5.0	14/07/2025	Document update	☐ Yes Validation language: English ☐ No