SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable multi-programmable deep brain stimulation system

Device Trade Name: Activa®, Percept™ and SenSight™ Deep Brain Stimulation Therapy System

Device Procode: NHL

Applicant's Name and Address: Medtronic, Inc.
Medtronic Neuromodulation
7000 Central Ave., N.E.
Minneapolis, MN 55432

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P960009/S478

Date of FDA Notice of Approval: February 20, 2025

Medtronic's Deep Brain Stimulator (DBS) System was approved for the following indications for use:

- P960009 approved on July 31, 1997: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

- P960009/S7 approved on January 14, 2002 (Modified in P960009/S229 approved on November 18, 2015): Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

- P960009/S219 approved on April 27, 2018: Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by

partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

The SSEDs to support the indication are available on the CDRH website and are incorporated by reference here:

https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009B.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007B.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S219B.pdf

The current supplement (S478) introduces a new optional programming feature called adaptive deep brain stimulation (aDBS) for Parkinson's Disease in existing devices in the DBS system for the Indications for Use specifically stated below.

II. INDICATIONS FOR USE

The Activa®, Percept™ and SenSight™ Deep Brain Stimulation Therapy System is indicated for bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

III. CONTRAINDICATIONS

General DBS contraindications
Implantation of a deep brain stimulation (DBS) system is contraindicated for these situations:

Diathermy - Patients exposed to diathermy. Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

Diathermy can also damage the neurostimulation system components, resulting in loss of therapy and requiring additional surgery for system explantation and replacement. Advise your patient to inform all their health care professionals that they should not be exposed to diathermy treatment.

Injury to the patient or damage to the device can occur during diathermy treatment when:

- the neurostimulation system is turned on or off.
- diathermy is used anywhere on the body—not just at the location of the neurostimulation system.
- diathermy delivers heat or no heat.
- any component of the neurostimulation system (lead, extension, neurostimulator) remains in the body.

Certain magnetic resonance imaging (MRI) procedures - Use of a full body transmit radio frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area is contraindicated for patients with the following implanted DBS systems or system components:

- Activa SC Model 37602 Neurostimulator
- Model 64001 and Model 64002 pocket adaptors implanted with any DBS system

Tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death, can occur if a contraindicated MRI scan is performed on a patient with any of these DBS systems.

Refer to the MRI guidelines for Medtronic deep brain stimulation systems Instructions for use manual associated with this product for comprehensive safety information and instructions.

Unable to operate patient devices - Patients who are unable, or do not have the necessary assistance, to properly operate the patient control device (e.g., patient programmer, therapy access controller) or a charging system (applicable to rechargeable DBS Systems only).

Transcranial magnetic stimulation (TMS) - Contraindicated for use in patients with an implanted DBS System.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic DBS System for PD labeling.

V. DEVICE DESCRIPTION

Medtronic DBS therapy uses an implantable multi-programmable neurostimulation system to deliver electrical stimulation to selected areas of the brain. The major components of the DBS systems include:

- Leads and Extensions – Conducts electrical stimulation to the intended target as part of a DBS system. The extension connects the lead to the neurostimulator. In

some cases, a pocket adaptor is also used to connect the extension to the neurostimulator.

- Implantable Neurostimulator (INS) – Generates electrical current that is conducted through DBS extensions and leads to the distal lead electrodes.
- Burr Hole Device – Used to anchor the lead to the skull.
- Clinician Programmer – Used by the clinician to configure and maintain the patient's therapy through adjustment of the available therapy parameters (amplitude, rate, pulse width, cycling, electrode configuration, etc.) and the creation of programs which consist of a specific set of values for each of the therapy parameters.
- Patient Programmer – Used by the patient to maintain their therapy within parameters configured by the clinician.
- Patient Recharger – Used by the patient to charge the battery of a rechargeable INS. A plug-in charger recharges the patient recharger.

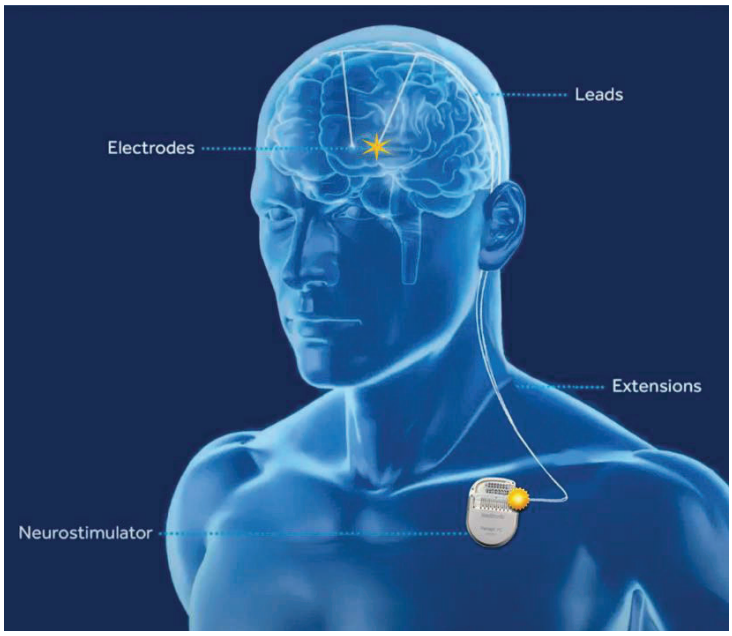

Figure 1: Representation of a Bilateral DBS System

The following Medtronic DBS system components that can be used with the aDBS software feature have been approved by FDA through the original submission and supplements to PMA P960009. Table 1 lists the system components and associated document control numbers for their market approval. There are no physical changes proposed for these devices.

Table 1: Medtronic DBS System Components

Component	Model	FDA Submission #	FDA Approval or Clearance Date
Neurostimulators	B35200 Percept PC INS	P960009/S361	June 24, 2020
	B35300 Percept RC INS	P960009/S438	January 08, 2024
Leads	3387S DBS Lead Kit 3389S DBS Lead Kit	P960009/S036	March 2, 2006
	B33005 SenSight Directional Lead Kit B33015 SenSight Directional Lead Kit	P960009/S391	May 25, 2021
Extensions	37085 Extension Kit	P960009/S051	March 27, 2009
	37086 Extension Kit	P960009/S134	February 3, 2012
	B34000 SenSight Extension Kit	P960009/S391	May 25, 2021
Implantable accessories	3550-25 Boots Accessory Kit	P960009/S026	October 31, 2002
	B31060 Connector Plug	P960009/S361	June 24, 2020
	B31000 Burr Hole Device B31020 SenSight Lead Cap Kit B31061 SenSight Connector Plug B32000 SenSight Burr Hole Device Kit	P960009/S391	May 25, 2021
Implant accessories	3550-05 Percutaneous Extension Kit	P960009	July 31, 1997
	3550-67 Screening Cable 3550-68 Screening Cable 37022 External Neurostimulator	P960009/S051	March 27, 2009
	3550-45 Torque Wrench Accessory Kit	P960009/R017	January 25, 2010
	B31010 SenSight Depth Stop and Cranial Tunneler Kit B31040 SenSight Lead Test Cable Kit B31050 SenSight Extension Test Cable Kit	P960009/S391	May 25, 2021
Clinician accessories	8880T2 Communicator A610 DBS Clinician Programmer Application	P960009/S304	May 26, 2018
Patient accessories	A620 DBS Patient Programmer Application	P960009/S333	July 3, 2019
	TH91 Handset and Communicator Package Kit	P960009/S361	June 24, 2020
	A90300 Recharger Application Software CD9000 Charging Dock	P960009/S365	June 25, 2020
	RS6230 DBS Recharging System WR9230 Wireless Recharger	P960009/S438	January 08, 2024

This PMA includes the following software version updates that are specific to the addition of the aDBS software:

- Model A610 Clinician Programmer Application (CPA) (Version 5.0)
  The aDBS programming option is part of version 5.0 of the Model A610 Clinician Programmer Application (CPA). This software update introduces the aDBS feature to the FDA approved Percept™ system of deep brain stimulation (DBS) devices (approved by FDA in P960009/S361 (Percept PC) and P960009/S438 (Percept RC). The aDBS feature was embedded (and disabled) as part of the approved Percept INS systems. In order to launch aDBS, the existing aDBS firmware needs to be enabled and no physical changes to the Percept INSs are required. Therefore, when the aDBS feature is enabled in a geography, it can be enabled in previously implanted Percept INSs as well as new Percept INSs.

- Model A620 Patient Programmer Application (PPA) (Versions 2.0 and 3.0)
  The Model A620 PPA is software used by patients to interrogate and adjust stimulation settings of the Medtronic DBS implantable neurostimulators within clinician determined limits. The Model A620 PPA will display aDBS screens once the patient programmer connects with an INS that has aDBS enabled. An important feature of the PPA software when applying aDBS as a programming option is that the Model A620 PPA can be used by patients to "pause" their aDBS therapy. Pausing Adaptive Therapy is not the same as turning stimulation off. When Adaptive Therapy is paused therapy reverts to a fixed cDBS level programmed by the clinician.

  No updates to the Model A620 PPA are in scope of this submission as the aDBS software was previously developed (and disabled) as part of the Percept PC and Percept RC INS systems. Therefore, the existing aDBS software will simply be enabled in the Model A620 PPA. Additionally, both Model A620 PPA version 2.0 and version 3.0 support the aDBS feature in the same way. Model A620 PPA version 2.0 supports the aDBS feature on Percept PC devices, and Model A620 PPA version 3.0 supports the aDBS feature on both Percept PC and Percept RC INS devices. In this way, existing patients who have a Percept PC INS and a patient programmer with Model A620 version 2.0 do not need to have updated or replacement patient programmers to have access to the aDBS feature. Similarly, patients who have a Percept PC or RC INS and a patient programmer with Model A620 version 3.0 do not need to have updated or replacement patient programmers to have access to the aDBS feature.

aDBS Software Feature Description

Commercially approved DBS is programmed to run continuously (cDBS) at specified programming parameters. The adaptive DBS (aDBS) algorithm individualizes DBS therapy by adjusting stimulation level based on local field potentials (LFPs) which represent population-level neuronal oscillations surrounding the DBS electrode. The aDBS feature automatically adjusts stimulation amplitude, within clinician-defined limits, based on changes in a patient's brain state measured using Alpha-Beta LFPs (8–30 Hz) as

a signal of interest (SOI). The aDBS feature can be enabled in one of two modes, Single Threshold Mode or Dual Threshold Mode, as described below.

- aDBS Single Threshold Mode
  Single threshold mode includes a single control threshold for the LFP SOI and aDBS makes changes to the stimulation amplitude based on the measured LFP and whether it is above or below the threshold. In this scheme, when the LFP SOI is above the threshold, then stimulation is incremented and when the LFP SOI is below the threshold, the stimulation is decremented. The maximum stimulation limits are set by the physician on an individual patient basis. This mode has shorter default stimulation ramp up and ramp down durations than dual mode. Figure 2 illustrates this aDBS mode.

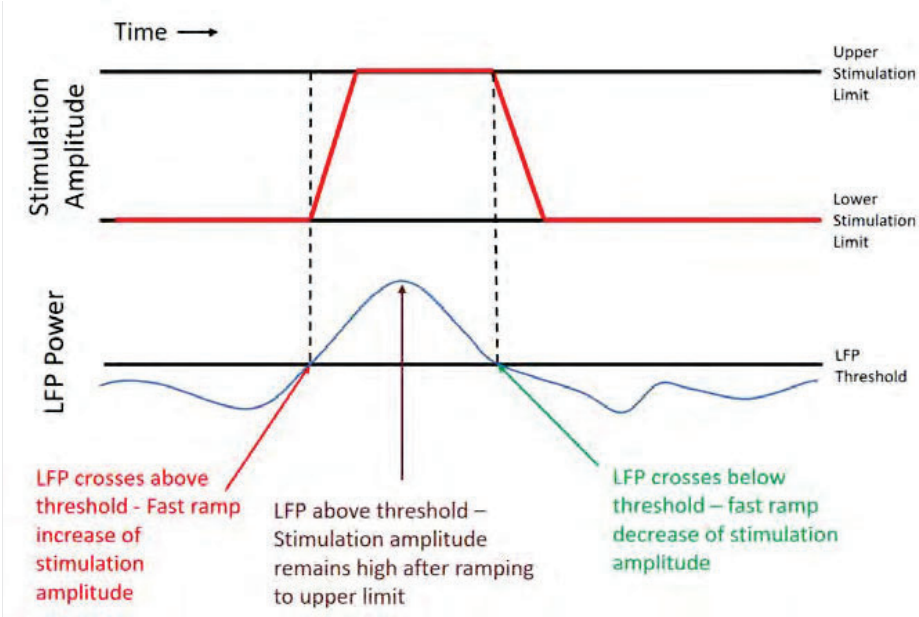

Figure 2: Single Threshold aDBS Mode

- aDBS Dual Threshold Mode
  Dual threshold mode includes both an upper and lower control threshold for the LFP SOI and aDBS makes changes to the stimulation amplitude to attempt to maintain the LFP SOI between the two thresholds. In this scheme, when the LFP SOI is "high", then stimulation is increased, whereas when the LFP SOI is "low" stimulation is decreased to control the LFP SOI. When the patient tailored LFP Alpha-Beta power SOI remains between the upper and lower thresholds, stimulation amplitude is held constant. When the Alpha-Beta power SOI exceeds the upper threshold, stimulation increments. When the Alpha-Beta power SOI dips below the lower threshold, stimulation decrements. The limits are set by the physician on an individual patient basis. Figure 3 illustrates this aDBS mode.

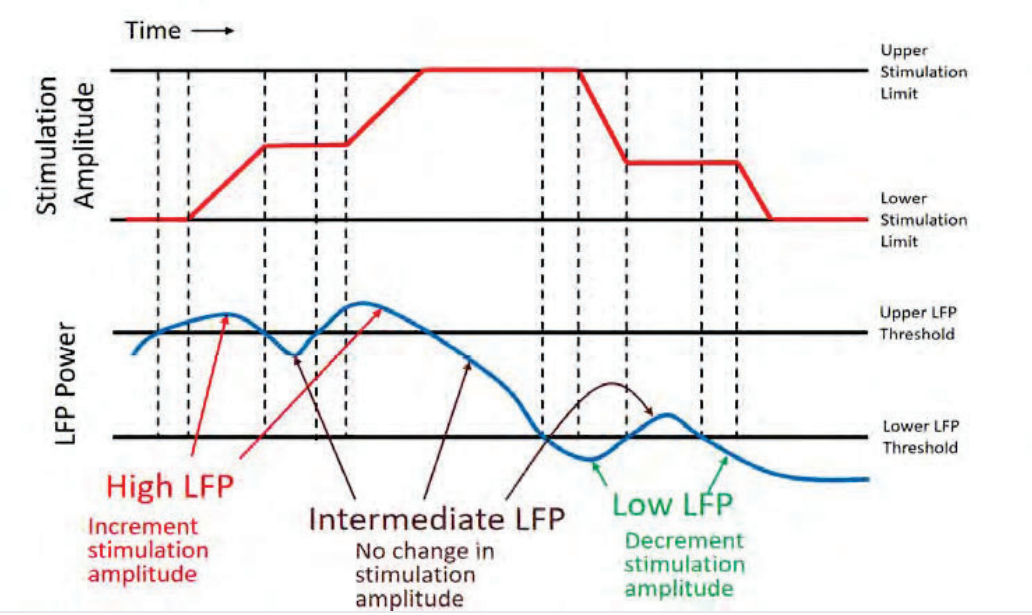

Figure 3: Dual Threshold aDBS Mode

Each mode has a set of default settings, some of which the clinician will have the ability to adjust. With both aDBS modes, the clinician is required to configure the upper and lower stimulation amplitude limits based on safe levels for each patient. Table 2 below lists the key configurable parameters in aDBS.

Table 2: Key aDBS Configurable Parameters

Configurable Parameter	Selection Range
Sensing Band	8-30 Hz
Threshold Mode	Dual or Single Threshold
Lower LFP Threshold	0.55-400µVrms Note: in Single Threshold Mode, Lower = Upper LFP Threshold
Upper LFP Threshold	0.55-400µVrms Note: in Single Threshold Mode, Lower = Upper LFP Threshold
Lower Stimulation Limit	0-25.5 mA
Upper Stimulation Limit	0-25.5 mA
Upper Threshold Onset Duration	Dual Threshold - 0 to 6 min Single Threshold - 0 to 30 seconds
Lower Threshold Onset Duration	Dual Threshold - 0 to 6 min Single Threshold - 0 to 30 seconds
Stimulation Ramp Up Duration	250ms-30 minutes
Stimulation Ramp Down Duration	250ms-30 minutes

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Several medical and surgical alternatives are available for the symptomatic treatment of Parkinson's disease (PD). The gold standard medical therapy for PD is levodopa combined with a peripheral decarboxylase inhibitor, such as carbidopa. Other medications may be used as an adjunct to levodopa including dopamine agonists, monoamine oxidase-B inhibitors, catechol-O methyltransferase inhibitors, apomorphine, amantadine, etc. Most patients respond to levodopa but "off" periods (increased symptoms when the medication dose wears off) can occur within 2 years of starting levodopa treatment. About 40% of patients experience dyskinesias after 4 to 6 years of levodopa treatment.[1]

In patients who no longer respond to medications or experience disabling motor complications, surgical treatments may offer benefit. Surgical treatments can involve destruction of designated brain targets (either radiofrequency or radiosurgery pallidotomy or thalamotomy) which are typically performed unilaterally due to the potential for serious adverse events with bilateral lesion procedures.[2] Magnetic resonance-guided focused ultrasound (MRgFUS) for thalamotomy in tremor-dominant PD is another therapeutic option and does not require a craniotomy and penetration of the brain.[3] Whether performed using radiofrequency, gamma knife or MRgFUS, no lesion procedures can safely address the bilateral nature of Parkinson's Disease progression, and therefore they cannot be considered state-of-the art treatment for the wider PD population. Furthermore, most unilateral procedures remain classified in guidelines as having insufficient evidence and being investigational for several key symptoms of PD, or having inferior benefit- risk ratios to DBS.[4]

DBS of the subthalamic nucleus (STN) or internal globus pallidus (GPi) is an alternative to lesioning procedures. DBS is the most common surgical treatment for PD and may reduce PD symptoms of bradykinesia, rigidity and tremor in patients who no longer have a predictable response to medication or who have dyskinesias resulting from the medication.[4]

Algorithms for the treatment of motor problems in Parkinson's disease using device-aided therapies have been proposed. For example, Dietrichs and Odin[5] developed a strategy for how best to treat PD patients at different stages of disease progression, as shown in Figure 4. The algorithm was based on recommendations from the Scandinavian countries and Germany, and, proposes several device-aided treatment options be used for later-stage treatment, including DBS, continuous subcutaneous infusion of apomorphine (CSAI)[6], or L-dopa-carbidopa intestinal gel (LCIG), which delivers the drug by portable pump through a percutaneous endoscopic gastrojejunostomy (PEG-J) tube, bypassing the stomach to eliminate variability associated with gastric emptying.[7] Relative to DBS, the other two alternative therapies have accumulated less clinical evidence supporting their use.[4,7]

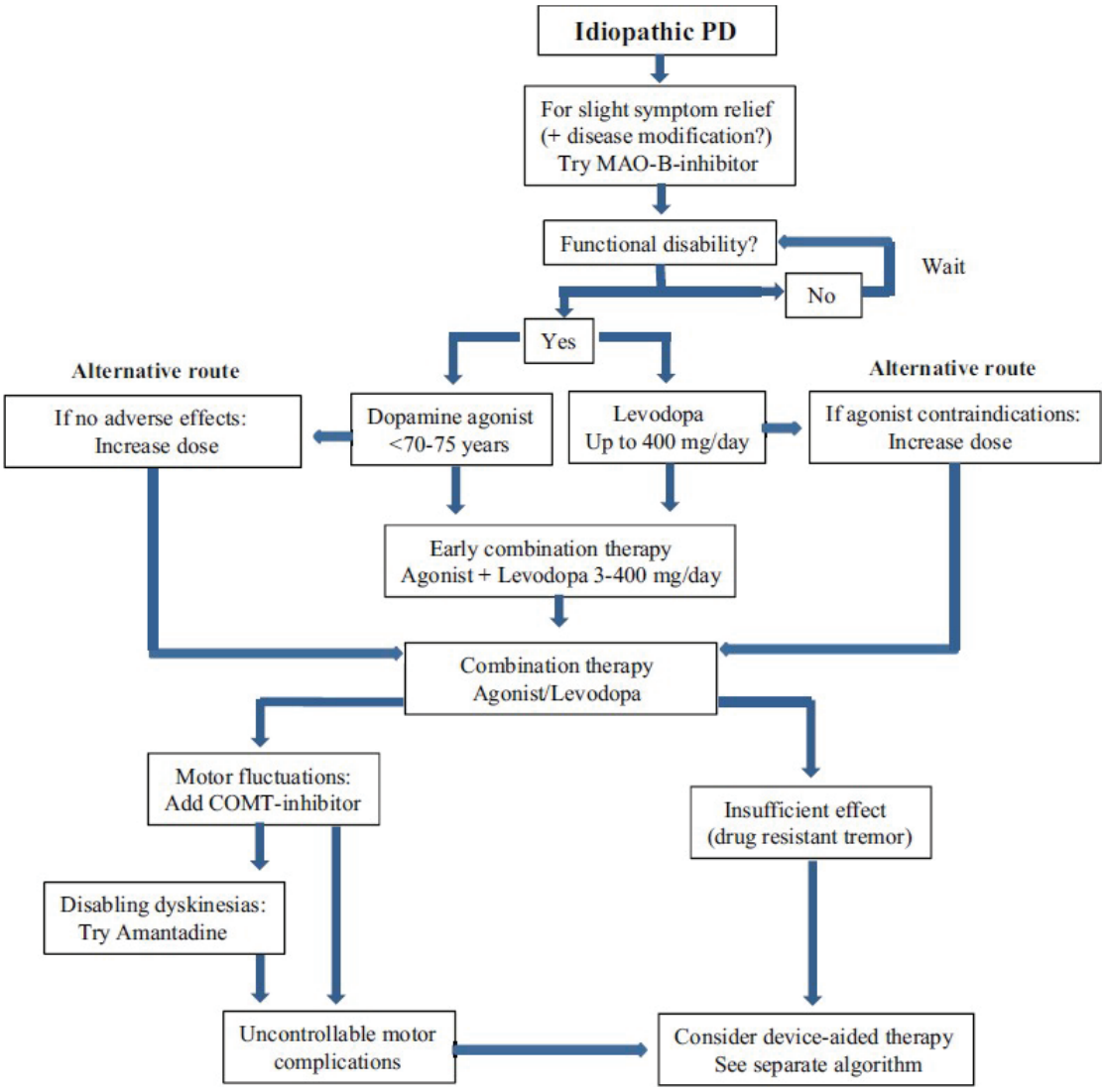

Figure 4: Algorithm for Medical Treatment of PD

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The adaptive deep brain stimulation (aDBS) feature has been marketed for Parkinson's Disease in Japan with Model B35200 Percept PC since May 2020 and with Model B35300 Percept RC since November 2022. The feature has been marketed for Parkinson's Disease in Europe with both Model B35200 Percept PC and Model B35300 Percept RC since January 2025.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device as identified in device labeling. Note that the potential adverse effects of the device on health for aDBS are the same as for cDBS.

Risks (potential adverse events) related to the lead, extension, or neurostimulator implant, explant, or revision procedures:

- Immediate intracranial hemorrhage or cerebral infarction which could be symptomatic, or which could result in temporary or permanent neurological injury or death
- Asymptomatic intracerebral hemorrhage or ischemia related to the DBS lead implant identified through postoperative imaging
- Complications related to anesthesia, including allergic reaction, hypotension, nausea and vomiting, headache, and other symptoms
- Complications or effects related to the device implantation or removal procedure, including lead insertion or removal difficulty, failure of the burr hole ring and cap, mechanical or electrical complications of the device, lead(s) not within target requiring replacement
- Complications or effects related to the tunneling procedure, including injury to nerve tissue (such as the spinal accessory nerve), vascular injury that may result in prolonged hospitalization, and tunneling through unintended anatomy (such as in between the ribs and entering the thoracic cavity)
- Cerebrospinal fluid leakage (also called CSF fistula)
- Pneumocephalus
- New onset seizures associated with the lead implant procedure
- General medical complications such as deep vein thrombosis, postoperative fever, and general postoperative discomfort

Risks (potential adverse events) after implantation of the lead(s), extension(s), or neurostimulator(s):

- Delayed intracranial hemorrhage or cerebral infarction which could be symptomatic, or which could result in temporary or permanent neurological injury or death
- Complications of the incision/surgical site, including inflammation, lack of healing, wound dehiscence, transient or persistent pain, seroma, or hematoma
- Infection of the incision/surgical site that could result in sepsis
- Meningitis, encephalitis, or brain abscess resulting from infection involving the brain and/or central nervous system
- Focal edema localized to the area around the lead
- Aseptic intraparenchymal cyst formation around the distal lead tip that may occur weeks to months after implant and may present as new neurological symptoms. Surgical removal of the lead may reduce the size of the cyst and the neurological symptoms caused by cyst formation.

- Erosion of the skin at the lead, extension, or neurostimulator site
- Migration or dislodgement of the lead, extension, or neurostimulator
- Lead, extension, or neurostimulator device complications, including lead or extension fracture, neurostimulator malfunction, neurostimulator setscrews not adequately tightened, and high impedance
- Fibrosis (including tightening, tethering, or bowstringing) at the extension or neurostimulator site may develop weeks to years after implant. It can be associated with pain, disfigurement, limited head mobility, and may require surgical intervention.
- Neurological symptoms, new or exacerbation of existing symptoms which might be transient or permanent, including:
  - vision disorders: diplopia, oculomotor difficulties, or other visual field disorders.
  - speech and swallowing disorders: dysphagia, dysarthria, dysphasia, drooling.
  - motor coordination and balance disorders: akinesia, "freezing," bradykinesia, dyskinesia, paresis, asthenia, muscle spasms/rigidity, tremor, loss of balance/coordination, gait disorder, dizziness, involuntary movements, tics, chorea, dystonia, facial muscle or limb partial paralysis.
  - sensory disturbances: paresthesia, hypoesthesia, burning sensation, headache.
  - mentation impairment: attention or cognitive deficits, dysgraphia, memory disturbances, confusion, somnolence, lethargy.
  - sleep disorders: insomnia, abnormal dreams.
  - déjà vu.
- Psychiatric and behavioral disorders, new or exacerbation of existing symptoms that might be transient or permanent, including:
  - new onset or worsening depression, suicidal ideation, suicide attempt, suicide.
  - anxiety, panic, restlessness.
  - irritability, anger, aggression, agitation.
  - changes or fluctuations in mood, apathy, fatigue.
  - other behavioral manifestations: changes in eating behaviors, obsessive-compulsive disorder, abnormal behavior.
  - hyperactivity or euphoria (hypomania).
  - psychosis, delusions, hallucinations, delirium, disinhibition, perseveration, abnormal thinking.
- New onset seizures during ongoing therapy
- Allergic or immune system response to the implanted materials
- Gastrointestinal disturbances
- Cough associated with DBS
- Transient uncomfortable stimulation (jolting or shocking sensation)
- Lack of effective therapy or loss of therapeutic effect
- Weight gain or loss

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

All components of the Medtronic DBS System for Parkinson's Disease are commercially approved as part of PMA P960009 and PMA Supplements. Pre-clinical studies (bench and animal) previously submitted to FDA in the Original PMA application (P960009) and supplements continue to support the safety of the commercially available Medtronic DBS System for Parkinson's Disease. The non-clinical testing discussed below has been provided to support the safety and effectiveness of the aDBS software feature of the device as an additional programming option for the therapy. Testing in this submission was limited to those associated with the addition of the aDBS feature.

A. Laboratory Studies

N/A

B. Animal Studies

N/A

C. Additional Studies

- Software
  To verify and validate changes associated with aDBS design verification and validation testing pertaining to aspects of the Model A610 CPA (Version 5.0) and Model A620 PPA (Version 3.0) impacted by the software changes. Acceptable documentation was provided in accordance with the requirements of the following FDA guidance documents:

  - *"Content of Premarket Submissions for Device Software Functions"* (June 14, 2023)
  - *"Off-The-Shelf Software Use in Medical Devices"* (September 9, 1999)
  - *"General Principles of Software Validation; Final Guidance for Industry and FDA Staff"* (January 11, 2002)
  - *"Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software*" (January 14, 2005)

- Firmware: Percept PC INS and Percept RC INS
  The aDBS feature was developed as part of the Model B35200 Percept PC INS and Model B35300 Percept RC INS Firmware systems. However, the feature was disabled and was not in scope of the previously approved submissions. In order to launch aDBS, the existing aDBS firmware simply needs to be enabled and no firmware changes or physical changes to the Percept INSs are required. There are no physical changes to the Percept PC INS in scope of this submission however, the new INS firmware update capability that is in the scope of this submission will deploy the latest approved firmware to Percept PC devices already in the field. The firmware version to be deployed with Model A610 CPA version 5.0 is

identical to the version approved in P960009/S445, therefore all testing provided in that submission remains valid. An updated version of firmware is not being deployed to Percept RC INSs because the latest approved version of firmware is currently used in all fielded devices. The Percept RC INS firmware remains identical to the version approved in P960009/S438.

- Regression Testing
  System end-to-end functionality of the Model A610 CPA (Version 5.0) and Model A620 PPA (Version 3.0) was demonstrated successfully via regression testing with unchanged released devices (Percept PC INS and Percept RC INS). The system operated as expected with these devices.

- Electromagnetic Compatibility (EMC)
  New to this submission is the enabling of the aDBS feature in both Model B35200 Percept PC and Model B35300 Percept RC devices. aDBS is considered essential performance, and behavior of the system while aDBS is operating could potentially pose a patient safety risk if not properly mitigated. Medtronic has performed a risk assessment on the aDBS feature consistent with Section IV.B of the FDA guidance document, "Electromagnetic Compatibility (EMC) of Medical Devices" (June 2022). This risk assessment addressed the risks associated with the inability to properly detect LFP due to EMI disturbances and demonstrated through testing that the risks are adequately mitigated.

  It's important to note that aDBS was not studied in the ADAPT-PD Trial with bilaterally implanted neurostimulators, and only subjects with single INS devices were eligible for the study. In the case that patients do have bilaterally implanted neurostimulators, a Percept device could sense the stimulation present from the opposite neurostimulator and adjust stimulation in response to that signal, rather than the desired response to the LFP SOI. Because of this interaction, the labeling instructs clinicians not to use aDBS with more than one implanted neurostimulator.

X. SUMMARY OF PRIMARY CLINICAL STUDY

With the introduction of the aDBS feature, there are no modifications to the existing PD indications, the contraindications, the PD patient population, the disease state, the DBS surgical procedure, the underlying medical condition, the symptoms of PD that are already indicated, or the brain targets already approved for DBS therapy for PD. The intended purpose of the aDBS feature is to be an optional tool for the clinician to use to automatically increment and decrement stimulation amplitude within the clinician-specified range based on the PD patient's LFPs (Alpha-Beta). DBS PD therapy itself is not changing with the aDBS feature and the clinical data provided in previous submissions under P960009 in support of the PD indications with cDBS is still applicable in support of the Percept system with aDBS.

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of aDBS as a programming option for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration in the ADAPT-PD Trial under IDE # G200179. The ADAPT-PD Trial evaluated the safety and effectiveness of aDBS in PD subjects with stable cDBS therapy. The study was conducted in 10 centers: 7 centers in the US, and one center each in Canada, the Netherlands, and France.

Data from this clinical study were the basis for the PMA approval decision for the programming option of the aDBS. A summary of the clinical study is presented below.

Refer to the Limitations of Study (**Section XIV.E**) for a discussion of the limitations associated with the study.

A. Study Design

Patients were treated between December 14, 2020, and March 22, 2023. The database for this Panel Track Supplement reflected data collected through December 15, 2023, and a total of 85 subjects were enrolled in the ADAPT-PD Trial (68 from the Primary Cohort and 17 from Directional Stimulation Cohort). The study was conducted in 10 centers: 7 centers in the US, and one center each in Canada, the Netherlands, and France. The study enrolled 63 (74.1%) subjects in US, 10 (11.8%) in the Netherlands, 7 (8.2%) in Canada, and 5 (5.9%) in France. In total, this study enrolled 22 (25.9%) subjects outside the US.

The study was a prospective, multicenter, single-arm, aDBS treatment mode blind, randomized crossover trial in subjects with Parkinson's Disease and DBS leads implanted either in the internal globus pallidus (GPi) or the subthalamic nucleus (STN) connected to a Medtronic Percept PC implantable neurostimulator capable of sensing LFPs.

The ADAPT-PD trial assessed both Single and Dual Threshold aDBS modes (algorithms). In cases where only one hemisphere had an Alpha-Beta Signal which met the inclusion criteria the following configurations were used to set up aDBS:

- Dual Threshold (DT) Mode:
  If only one hemisphere has Alpha-Beta signal ≥1.2µVp when setting up the Dual Threshold mode, *the clinician configured adaptive therapy in both hemispheres, using sensing from the hemisphere with Alpha-Beta signal ≥1.2µVp.*

- Single Threshold (ST) Mode:
  If only one hemisphere has Alpha-Beta signal ≥1.2μVp when setting up Single Threshold mode, *the clinician configured adaptive therapy in only that hemisphere with Alpha-Beta signal ≥1.2μVp. cDBS was set up in the hemisphere with the Alpha-Beta signal <1.2μVp.*

Subjects were assessed in the cDBS Baseline at enrollment, then entered the aDBS Adjustment Phase, followed by the aDBS Evaluation Phase in which subjects were randomized to 30 days of one mode (Single or Dual Threshold aDBS), then crossed over to 30 days of the other mode, if tolerated. A Long-Term Follow Up Phase and Extended Access Phase were also included in the study. See Figure 5.

The study consisted of two cohorts:

- Primary Cohort (PC): All subjects configured to ring mode monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side.

- Directional Stimulation Cohort (DS): All subjects configured to directional monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10).

Each cohort followed the same study design.

Subjects received PD medications during the study and were expected to remain on stable medications through the aDBS Evaluation Phase.

During the Baseline Phase subjects were aware they were receiving cDBS and during the aDBS Setup and Adjustment Phase and aDBS Evaluation Phase subjects were aware that they were receiving either Single- or Dual-Threshold aDBS. Thus, subjects were aware of whether they were receiving an investigational or control treatment throughout the study. However, from the aDBS Setup and Adjustment Phase to the end of the aDBS Evaluation Phase, subjects were blinded to which aDBS mode they were receiving (Single-Threshold aDBS or Dual-Threshold aDBS).

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the ADAPT-PD Trial was limited to patients who met the following inclusion criteria:

   - Idiopathic PD
   - Implanted with Percept PC (Model B35200) and Medtronic DBS leads (Model 3387, 3389, B33005 or B33015) and extensions (Model 37085, 37086 or B34000) for directional cohort: Subject is implanted with Percept PC (Model B35200) and Medtronic SenSight DBS leads (Model B33005 or B33015) and extensions (Model B34000), bilaterally in the same target (physician confirmed), STN or GPi

- In the opinion of the investigator, the subject responds to DBS therapy.
- Based on the opinion of the investigator, the subject's cDBS parameters and PD medications were stable and expected to remain stable from enrollment through the end of the aDBS Evaluation phase
- Configured to ring mode monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10) on at least one side or, for subjects in the Directional Stimulation cohort, configured to directional monopolar or dual monopolar stimulation using contacts 1 and/or 2 (9 and/or 10).
    - Willing and able to attend all study-required visits and complete the study procedures (e.g. 1-month recall questionnaires, MDS-UPDRS III)
    - Ability to understand and provide written informed consent for participation in the study prior to the study-related procedures being conducted.
    - Male or non-pregnant female. If female of child-bearing potential, and if sexually active, must be using, or agree to use, a medically acceptable method of birth control as confirmed by the investigator.
    - For subjects with the SenSight leads: Subject was configured to the following stimulation rates: 55, 85, 110, 125, 145, 165 or 180 Hz (as required for sensing/aDBS)

    LFP Screening Criteria (start of cDBS Baseline visit): Subject had Alpha - Beta band (8-30 Hz) amplitude ≥ 1.2 μVp detected on either left and/or right DBS leads on sensing channels 0-2, 0-3, or 1-3; 8-10, 8-11, or 9-11.

    Patients were <u>not</u> permitted to enroll in the ADAPT-PD Trial if they met any of the following exclusion criteria:

    - Subject and/or caregiver were unable to utilize the patient programmer.
    - More than one lead in each hemisphere of the brain
    - Cortical leads or additional unapproved hardware implanted in the brain.
    - More than one INS
    - At enrollment, the subject's INS had a predicted battery life of <1 year.
    - Beck Depression Inventory II (BDI-II) > 25
    - Required diathermy, transcranial magnetic stimulation (TMS), or electroconvulsive therapy (ECT)
    - Metallic implant in the head, (e.g., aneurysm clip, cochlear implant)
    - Had, or planned to obtain, an implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemaker, defibrillator, spinal cord stimulator)
    - Had, or planned to obtain, an implanted medication pump for the treatment of Parkinson's disease (e.g., DUOPATM infusion pump) and/or portable infusion pump.
    - Based on the opinion of the investigator, the subject had an abnormal neurological examination that would preclude them from study participation

- Breastfeeding
- Under the age of 18 years
- Currently enrolled in or planned to enroll in any concurrent drug and/or device study that may confound the results of this study as determined by the Medtronic study team.
- Unable to use or tolerate wearable watch.
- Signal artifact on all 6 aDBS sense pathways (3 each on both DBS leads) which preclude the clinician from setting thresholds.

2. Follow-up Schedule

The study consisted of four phases following enrollment:

- The cDBS Baseline Phase (approximately 1 month) included LFP Screening (to ensure adequate LFPs per Inclusion Criteria above), Baseline cDBS data collection, and Off stimulation assessments.

- Subjects then entered the aDBS Setup and Adjustment Phase (up to 2 months) which included an aDBS Setup visit and additional optional visits during an aDBS Adjustment period. The purpose of the aDBS Adjustment Phase is to optimize aDBS with a combination of in-clinic and at-home use in which the clinician assesses each participant's response to aDBS while adjusting and optimizing stimulation amplitude ramping and limits and the LFP thresholds during unscheduled clinical visits.

- If, at the Setup visit, one aDBS mode cannot be set up, the subject should continue with the study using only the mode that can be set up and the subject will not be randomized. For modes that were setup, clinician, and participant satisfaction with each setup aDBS mode are assessed at the completion of the aDBS Adjustment period, and none, one or both modes are determined to be acceptable as compared to cDBS using a modified Global Impression of Change (GIC) score of ≤ 8 as a threshold for moving on to the Randomization and/or Evaluation Phase. Patients were excluded from the primary analysis set for any aDBS modes which they found unacceptable (GIC score > 8).

- The aDBS Evaluation Phase (approximately 2 months) included one-month treatment periods in each acceptable aDBS mode (Dual Threshold and/or Single Threshold) with aDBS evaluation visits at the end of each period. For subjects for whom both aDBS modes were acceptable, single- and dual-threshold aDBS mode evaluation periods were assigned in sequence via randomized crossover. Subjects for whom only one aDBS mode was acceptable underwent a single treatment period with the acceptable mode during the aDBS Evaluation Phase.

- The Long-Term Follow Up Phase (approximately 10 months) included four scheduled visits in the preferred aDBS mode.

An Extended Access Phase was optional and included additional visits in the preferred aDBS mode every 6 months until commercial approval of aDBS.

Figure 5 below depicts the study timeline.

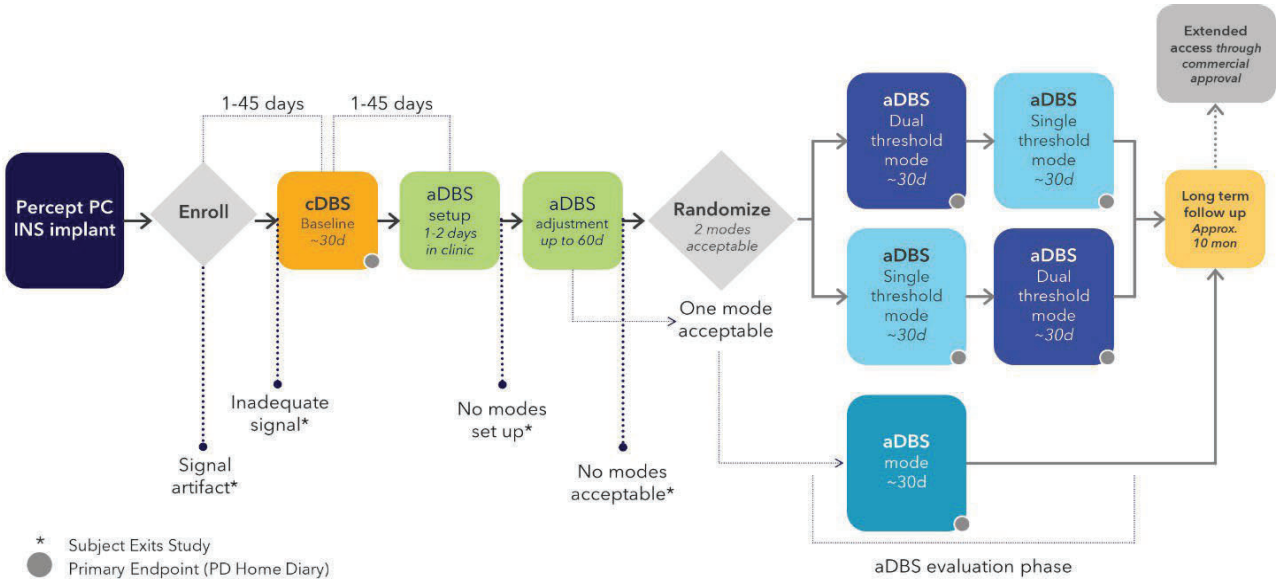

Figure 5: Study Timeline

3. Clinical Endpoints

Primary Safety Endpoints

With regards to safety, the following were characterized:

- Stimulation-related adverse events during the aDBS Evaluation and the cDBS Baseline Phases.
- Serious adverse events, adverse events and device deficiencies throughout the study.

Primary Effectiveness Endpoint

The study contains two primary endpoints, one for each aDBS mode. For each aDBS mode, the primary endpoint is a binary success/failure endpoint derived from a comparison of the subjects "On" time without troublesome dyskinesia (based on PD Home Diary) during the cDBS baseline phase and the aDBS evaluation phase applicable to that aDBS mode.

For each aDBS mode, a subject was considered a primary endpoint "success" when their daily average hours of "On" time without troublesome dyskinesia (based on the Parkinson's Disease Home Diary) during that mode's aDBS Evaluation Period exceeds a patient-specific threshold.

The patient-specific success threshold for these binary success/failure endpoints was revised post-hoc, from cDBS Baseline average "On" time without

troublesome dyskinesia *minus 1 standard deviation* to cDBS Baseline average "On" time without troublesome dyskinesia *minus 2 hours per day.* The change was made due to potential for type-I error inflation associated with formal statistical comparisons of the success rate derived from these endpoints (as they were originally defined) with a 50% performance goal. See Section: *Primary Effectiveness Analysis below* for more details. The revised success threshold is more conservative (requires *more* aDBS mode average "On" time without troublesome dyskinesia) than the original, and ameliorates previous type-I error concerns, but the revision precludes formal, confirmatory statistical inference since hypothesis tests are no longer fully prospective.

The primary effectiveness endpoint is based on Parkinson's Disease Home Diary, collected over at least three consecutive days, anytime during the cDBS baseline phase (subjects should be on stable cDBS stimulation from enrollment through the end of this period) and within 14 days of the aDBS Evaluation visit(s). The Parkinson's Disease Home Diary is a standard home diary to assess functional status in patients with PD. In 30-minute intervals, patients record whether they were in the "On" condition, with or without dyskinesia, "Off" condition, or asleep. In the On condition with dyskinesia, patients record whether they were On with troublesome or non-troublesome dyskinesia. For the purposes of the PD home diary, at least 3 consecutive days means at least 3 consecutive 24-hour periods.

During the aDBS Evaluation Phase, if the diary is collected more than 14 days prior to the visit, the diary may be used for analysis if there is no change in aDBS stimulation settings. Complete diary periods are defined as any diary period where at least 21 hours (defined as 42 30-minute records) of diary were completed during the 24-hour period, and only complete periods will be used for analysis. If the diary is collected for more than 3 complete periods, up to 7 which are closest to the visit will be used for the analysis, while if a subject has zero complete periods, their diary will be considered missing. Diaries with at least 1 complete period available will be used for analysis. Data from non-contiguous complete periods may also be used in the analysis.

Secondary Effectiveness Endpoint

The secondary endpoint was to demonstrate decreased total electrical energy delivered (TEED) during the aDBS Evaluation Phase as compared with continuous DBS (cDBS). TEED was defined as the total energy delivered by an electrical system through the DBS leads over an arbitrary period of time. TEED was determined by the stimulation parameters (e.g., pulse width, frequency, amplitude) and the measured impedance. The calculation of TEED when using constant voltage is:

$$TEED = (Voltage^2 * Frequency * Pulse\ width) / Impedance$$

The calculation of TEED when using constant current is:

$$TEED = Current^2 * Frequency * Pulse\ width * Impedance$$

The Total TEED for each mode is calculated as a sum of the energy use in the left and right leads. There will be one value per patient for each mode for which they were evaluated (cDBS, aDBS Dual Threshold, aDBS Single Threshold).

Two secondary endpoints, reduction in TEED associated with each applicable aDBS mode, is then calculated for each patient as the Total TEED for that aDBS mode minus the Total TEED during cDBS baseline.

Additional Assessments

To characterize aDBS during the Evaluation Phase as compared to cDBS (Primary Cohort). Additional objectives will be characterized for the CC unless otherwise specified:

- Voice Handicap Index (VHI): "best" and "worst" conditions
- Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III subscore (On stim/On med) of tremor, rigidity, and bradykinesia questions where a side can be determined: 3.3 b, c, d, e (rigidity), 3.4 a, b (finger taps/bradykinesia), 3.15 a, b (postural tremor of hands), 3.16 a, b (kinetic tremor of hands), and 3.17 a, b, c, d (rest tremor amplitude)
- MDS-UPDRS III (On stim/On med)
- MDS-UPDRS II: "best" and "worst" conditions
- MDS-UPDRS III speech question (On stim/On med) q 3.1
- MDS-UPDRS IV
- European Quality of Life - 5 dimensions (EQ-5D-5L)
- Parkinson's Disease Sleep Score 2 (PDSS-2)
- Data collected from wearable (for example: % of wear time tremor was detected, Dyskinesia Score [DKS], Bradykinesia Score [BKS], Fluctuation and Dyskinesia Score [FDS])
- Parkinson's Disease Questionnaire (PDQ)-39 Summary Index (SI) and subscores: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort
- Parkinson's Disease Questionnaire 39 (PDQ-39) – speech questions 34 and 35
- % of subjects with at least 25% increase in projected battery longevity as compared with cDBS
- Parkinson's Disease Home Diary: "On" time without troublesome dyskinesia, "On" time without dyskinesia, "On" time with non-troublesome dyskinesia, "On" time with troublesome dyskinesia, "Off" time, and asleep time [This analysis will use the FAS]
- Patient preference of aDBS vs cDBS (as assessed by Medtronic-developed patient preference questionnaire)
- Patient satisfaction with aDBS (as assessed by a Medtronic developed patient satisfaction questionnaire)

- Device data from JavaScript Object Notation (JSON) file, including BrainSense data

Long-term Follow-up Phase and Extended Access Phase Assessments
Complete adverse event data were collected during the Long-term Follow-up and Extended Access phases of the study. Effectiveness data at each Long-term Follow-up phase visit included the PDQ-39 and EQ-5D-5L and, at the sixth visit only, the patient satisfaction questionnaire (PSQ). The PDQ-39 and EQ-5D-5L were collected at each of the Extended Access phase visits.

4. Statistical Analysis Methods

Analysis Sets

- All-Consented (AC): includes all subjects who properly signed the study-specific informed consent (IC). This patient set will be used to summarize patient disposition.
- Single-Threshold Full Analysis Set (FAS): all Primary Cohort subjects who initiated a period of treatment using Single-Threshold aDBS during the aDBS Evaluation Phase.
- Dual-Threshold FAS: all Primary Cohort subjects who initiated a period of treatment using Dual Threshold aDBS during the aDBS Evaluation Phase.
- Total FAS: all Primary Cohort subjects who initiated the aDBS Evaluation Phase using the randomized treatment assignment for each subject that was randomized and the programmable treatment assignment for those subjects that were configured to one aDBS mode (dual or single threshold). The union of the Single- and Dual-Threshold FASs.
- Single-/Dual-Threshold As-treated (AT): all Primary Cohort subjects who are treated with continuous Deep Brain Stimulation (cDBS) and/or adaptive Deep Brain Stimulation (aDBS) during the cDBS Baseline Evaluation Phase, the aDBS Evaluation Phase and/or the Long-term Follow-up Phase; uses the observed treatment used for each subject in each phase.
- Single-/Dual-Threshold Complete-Case Sets (CC): Single-/Dual-Threshold FASs without imputation, includes all Primary Cohort FAS subjects with available measures for the respective analysis
- All-randomized (AR): all Primary Cohort subjects who were randomized in the aDBS Evaluation Phase
- Primary Cohort Single-/Dual-Threshold modified Intention-to-Treat (mITT) Set: all Primary Cohort subjects who were successfully setup for Single-/Dual-Threshold aDBS mode during the aDBS Setup and Evaluation Phase.
- Directional Stimulation As-Treated (DSAT)/Complete Case (DSCC): all Directional Stimulation Cohort subjects meeting analogous AT/CC criteria.

For each aDBS mode, primary and secondary objectives were analyzed using the mode-specific Full Analysis Set (FAS).

Primary effectiveness analysis

No formal statistical inferences are derived from the study's primary and secondary endpoint data, which are instead analyzed descriptively, because the patient-specific success threshold for these binary success/failure endpoints was revised post-hoc. As discussed in Section: *Primary Effectiveness Endpoint* above, the prespecified patient-specific success threshold was cDBS baseline daily average good "On" time *minus 1 standard deviation;* in the prespecified primary hypothesis test, the resulting success rate was to be compared with a performance goal set to 50% using a one-sided exact binomial test. However, the agency observed that, since the prespecified success threshold depended on the sample standard deviation, two key assumptions underpinning the exact binomial testing procedure were violated, causing type-I error inflation when the distribution of differences in good "On" time was skewed, as was the case for the Single-Threshold aDBS mode comparison. The revised success threshold (cDBS baseline daily average good "On" time *minus 2 hours per day)* is more conservative (requires *more* good "On" time) than the original and ameliorates these type-I error concerns. Still, formal confirmatory inference through hypothesis testing is precluded since the issue was identified post-hoc and addressed through substantive post-hoc revision of the primary endpoint definition.

For each aDBS mode, the proportion of subjects who met the primary "success" criteria – aDBS mode daily average "On" time without troublesome dyskinesia exceeding a patient-specific threshold defined as cDBS baseline daily average "On" time without troublesome dyskinesia minus 2 hours per day – is computed on that aDBS mode's Full Analysis Set (FAS). The lower bounds of 97.5% binomial exact confidence intervals are reported.

Secondary effectiveness analysis

Since formal hypothesis testing for the primary analysis was not possible due to post-hoc revisions to the primary endpoint definition, and the primary analysis was intended to gatekeep secondary hypothesis testing, secondary endpoints are analyzed descriptively. The total stimulation energy (TEED) under each aDBS mode during the aDBS Evaluation Phase is compared to cDBS mode during the cDBS Baseline Phase. Means and associated standard errors are reported for each aDBS mode, derived from the mode's FAS.

Missing data handling

For each aDBS mode, missing primary endpoint data is imputed using multiple imputation if missingness is unrelated to that aDBS mode's effectiveness or tolerability, and is imputed as a failure otherwise. Missing secondary endpoint data is imputed using multiple imputation.

B. Accountability of PMA Cohort

The ADAPT-PD Trial was conducted at 10 investigational sites in a total of 85 subjects (68 from the Primary Cohort and 17 from Directional Stimulation Cohort). The study enrolled 63 (74.1%) subjects in US and 22 (25.9%) subjects outside US.

Of the 85 subjects enrolled in the study, 70 subjects completed the cDBS Baseline Phase, 60 subjects entered the aDBS Evaluation Phase (43 were randomized and 17 had only one acceptable mode), and 60 subjects completed the aDBS Evaluation Phase. All active subjects (54) have completed the Long-term Follow-up Phase.

Thirty-three (33) subjects were discontinued early from the study. Among these early discontinuations, 25 subjects discontinued prior to the aDBS Evaluation Phase, none during the aDBS Evaluation Phase, and 8 after the aDBS Evaluation Phase.

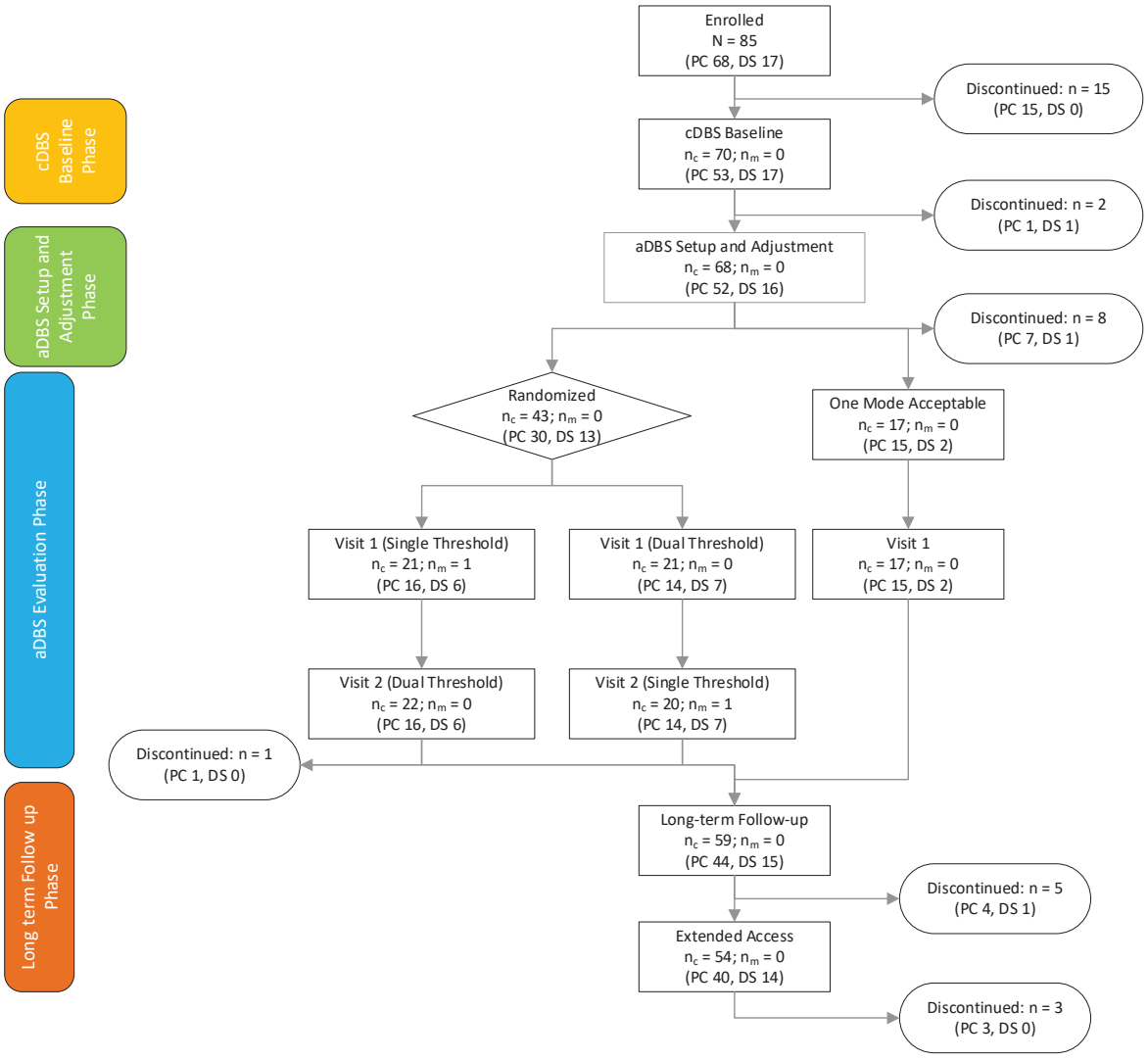

Figure 6: Subject Disposition
Note: Counts at each visit indicate the number of subjects who completed the visit (denoted as nc) and number of subjects who missed the visit (denoted as nm);
PC: Primary Cohort, DS: Directional Stimulation Cohort

Table 3 below documents counts of subject discontinuations by Cohort, study phase, and discontinuation type. There was a total of 34 withdrawals/terminations following informed consent.

Table 3: Subject Disposition by Phase

Phase	Discontinuation reason category[1]	Specific Reason (n)	All Consented
Enrollment Through LFP Screening	LFP Screen Failure	LFP Screen Failure (6)	6
	Screen Failure	Patient enrolled in competing study (1)	1
	Physician Decision	Stress/Anxiety of being in study (1)	1
	Subject Decision	Concerns with withholding medications (1)	1
		Sub total	**9**
LFP Screening Through cDBS Baseline	LFP Screen Failure	LFP Screening Failure (4)	4
	Subject Decision	Travel concerns (1) Being OFF medication perceived as intolerable (1)	2
		Sub total	**6**
cDBS Baseline Through aDBS Setup and Adjustment	Physician Decision	Exited due to treatment of hallucinations (1)	1
	Subject Decision	Not in best interest of subject physical and mental well-being (1)	1
		Sub total	**2**
aDBS Setup and Adjustment Through Randomization	LFP Screen Failure	LFP Screening Failure/aDBS unable to be set up (2)	2
	Subject Decision	Felt better on cDBS than either aDBS mode (1) Travel and/or reimbursement concerns (2) Unable to comply with study requirements (1)	4
	Physician Decision	Unable to make study visits (1)	1
	Subject & Physician Decision	Poor tolerance to both aDBS modes	1
		Sub total	**8**
Long-Term Follow-Up Phase	Subject Decision	aDBS Evaluation Phase Completed, Prefer cDBS (3) Travel difficulty (1)	4
	Physician Decision	aDBS not adequately controlling symptoms (1) Unclear that aDBS was better than cDBS and overall higher stimulation settings on aDBS followed by a fall (1)	2
		Sub total	**6**
Extended Access Phase	Subject Decision	aDBS Evaluation Phase Completed, Prefer cDBS (1) Travel difficulty (1)	2
	Death[2]	Death[2]	1
		Sub total	**3**
TOTALS		LFP Screen Failure/Unable to set up aDBS	12
		Better on cDBS than aDBS	6
		Travel problems/Unable to make visits or comply with study requirements/Reimbursement	7
		Stress/anxiety/well-being of being in study	3
		Concerns with withholding medications	2
		Other	2
		Screen Failure (enrolled in competing study)	1
		Death[2]	1
		Total	**34**

Abbreviations: aDBS=adaptive deep brain stimulation, cDBS=continuous deep brain stimulation.
[1] Nine subjects discontinued after the aDBS Evaluation Phase for a total of 34 subjects.
[2] Assessed by both the investigator and CEC as not related to the study device, procedure, therapy, or
stimulation.

Local Field Potential (LFP) Screening Results

Among the total 85 consented subjects, during the initial LFP screening period, 84.7% (72/85) had LFP screening success (i.e., a control signal was identified) and 14.1% (12/85) were LFP screening failures during initial LFP screening. Of the 12 subjects that failed LFP screening, 4 subjects had the peak band amplitude < 1.2μVp on both hemispheres and 6 subjects reported signal artifact.

Additionally, there were 2 LFP Screen failures during the aDBS setup and adjustment period through randomization because in one subject aDBS was not able to be set up and in the other an adequate LFP signal was not obtained. No additional subjects exited the study due to the loss of LFP signals starting from the aDBS Evaluation Phase to the Extended Access Phase of the study. See Table 4 below for a summary of all LFP screening results.

Table 4: Summary of LFP Screening Result

LFP Screening Results	All Consented (N=85)
Success	72 (84.7%)
Failure	12 (14.1%)
NA	1 (1.2%)

Post-Screening Exclusions from Primary Cohort's Full Analysis Sets

The primary and secondary analyses of each aDBS mode is conducted on that mode's Full Analysis Set, defined as the set of subjects in the Primary Cohort who initiated a period of treatment using that mode during the aDBS Evaluation Phase of the study. At the end of the Screening Phase, 53 subjects in the Primary Cohort continued to the cDBS Baseline Phase. 52/53 Primary Cohort subjects continued to the aDBS Setup and Adjustment Phase. Each of these continuing Primary Cohort subjects were potentially eligible for both mode-specific Full Analysis Sets.

At the start of the aDBS Setup and Adjustment Phase, investigators attempted to setup each aDBS mode; if subjects could not be setup for an aDBS mode (due to LFP exclusion or other reasons), they were not assigned treatment using that mode during the aDBS Evaluation Phase and were excluded from that mode's FAS and primary analysis. In the Primary Cohort, 3/52 (5.8%) subjects discontinued the study during the aDBS Setup and Adjustment Phase due to logistical reasons and were removed from both Single-Threshold and Dual-Threshold FASs. Additionally, Single-Threshold and Dual-Threshold aDBS modes could not be setup in 6/52 (11.5%) and

3/52 (5.8%) Primary Cohort subjects, respectively. See Table 5. After accounting for these exclusions, the Single- and Dual-Threshold mITT sets of all subjects who were successfully setup under Single- and Dual-Threshold mode during the aDBS Setup and Adjustment Phase contained 43 and 46 subjects, respectively.

Table 5: Discontinuations and Setup Exclusions from FAS during aDBS Setup and Adjustment Phase

Reason for Exclusion from FAS	**Single Threshold FAS**	**Dual Threshold FAS**
	N = 52 continued post cDBS Baseline	
Discontinued study: Logistical Issues	3	3
Unable to setup: LFP Screen Fail	1	1
Unable to setup: Other	5	2
Total setup	43	46

For each successfully setup aDBS mode, stimulation parameters were optimized over additional in-clinic or remote visits as needed during an adjustment period lasting up to 60 days and then assessed using a modified Global Impression of Change (GIC) scale comparing efficacy and side-effects to cDBS. None, one or both modes were determined to be "acceptable" using a GIC score of ≤8 as a threshold. See white and grey shaded boxes in Table 6 below for "acceptable" and "unacceptable" GIC ratings. Patients with an "unacceptable" GIC rating for a given aDBS mode were not assigned treatment using that mode during the aDBS Evaluation Phase and were excluded from that mode's FAS and primary analysis. In the primary cohort, Single-Threshold and Dual-Threshold aDBS modes were "unacceptable" in 8/43 (18.6%) and 6/46 (13.0%) subjects, respectively, who could otherwise setup the mode and continue participation in the study. See Table 7.

Table 6: aDBS Global Impression of Change Score Grid

Efficacy	*None*	*Does not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Side effects experienced outweigh efficacy*
Vast improvement	01	02	Fail:10	Fail:11
Decided improvement	03	04	Fail:12	Fail:13
Slight improvement	05	06	Fail:14	Fail:15
Unchanged	07	08	Fail:16	Fail:17
Worse	Fail:18	Fail:19	Fail:20	Fail:21

Table 7: Post-aDBS-Setup exclusions from FAS due to worse efficacy or poor tolerance during aDBS Setup and Adjustment Phase

Reason for Exclusion from FAS	Single Threshold FAS (N=43 setup)	Dual Threshold FAS (N=46 setup)
Discontinued: poor tolerance to both aDBS modes	1	1
Discontinued: felt worse on both aDBS modes than cDBS	1	1
GIC: worse efficacy	3	1
GIC: side-effects significantly interfere with patient's functioning	2	1
GIC: both worse efficacy and significantly inferring side-effects	1	2
Total exclusions (% of subjects setup) due to worse efficacy/poor tolerance	**8 (18.6%)**	**6 (13.0%)**

aDBS Mode Randomization

Table 8 below summarizes the randomization or one mode assignment for subjects who entered the aDBS Evaluation Phase. Of the 85 enrolled subjects, 25 had early discontinuations and 60 entered the aDBS Evaluation Phase. 43 subjects received treatment with both aDBS modes in randomized order, and 17 received treatment with only one mode. Of the 43 randomized subjects, 22 (36.7%) subjects were randomized to receive Single Threshold mode first followed by Dual Threshold mode, and 21 (35%) subjects were randomized to receive Dual Threshold mode first followed by Single Threshold. Of the 17 subjects that received one mode, 5 (8.3%) received Single Threshold and 12 (20%) received Dual Threshold.

Table 8: Summary of Randomization or One Mode Assignment

Randomization assignment	Primary (N=45)	Directional Stimulation (N=15)	Total (N=60)
	n (%)		
Single threshold -> Dual threshold	16 (35.6%)	6 (40.0%)	22 (36.7%)
Dual threshold -> Single threshold	14 (31.1%)	7 (46.7%)	21 (35.0%)
One mode, Dual Threshold	10 (22.2%)	2 (13.3%)	12 (20.0%)
One mode, Single Threshold	5 (11.1%)	0 (0.0%)	5 (8.3%)

Analysis Sets

The numbers of subjects included in each analysis set are summarized in Table 9. Primary and secondary analyses were conducted on the Single-Threshold and Dual-Threshold FAS, respectively containing 35 and 40 subjects. The Total FAS, which included all subjects in either the Single-Threshold or Dual-Threshold FAS (or both), contained 45 subjects.

Table 9: Efficacy and Safety Data Sets Analyzed

Efficacy Data Sets	Number of Subjects
Full Analysis Set (FAS)	**ST: 35, DT: 40** **Total: n=45**
Complete Case (CC)	Primary Objective, ST: 30, DT: 38 Secondary Objective, ST: 32, DT: 39
As-Treated (AT)	Primary Objective, ST: 29, DT: 37 Secondary Objective, ST: 31, DT: 38
Directional Stimulation Complete Case (DSCC)	Primary Objective, ST: 13, DT: 15 Secondary Objective, ST: 13, DT: 14
Primary Cohort Modified Intention-to-Treat Set	ST: 43, DT: 46
Safety Data Sets	**Number of Subjects**
All Consented	Total: 85

Abbreviations: ST=Single Threshold. DT=Dual Threshold

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the US.

Investigational Sites

As shown in Table 10, a total of 85 subjects were enrolled in the study, 70 subjects have completed the cDBS Baseline Phase, 60 subjects have entered the aDBS Evaluation Phase, and 60 subjects have completed the aDBS Evaluation Phase. Fifty-four (54) active subjects entered the Extended Access Phase. Investigational sites are presented in the order of the number of subjects enrolled at the site, largest to smallest.

Table 10: Subject Disposition by Investigational Site

Investigational site	Subjects enrolled (STN:GPi)	Subjects completed the cDBS Baseline Phase	Subjects entered the aDBS Evaluation Phase (Randomized: one mode)	Subjects completed the aDBS Evaluation Phase (Randomized: one mode)	Subjects entered the Long- term Follow-up Phase	Subjects entered the Extended Access Phase
Massachusetts General Hospital	13 (9:4)	13	12 (8:4)	12 (8:4)	11	10
University of Florida Health Shands Hospital	11 (2:9)	10	8 (8:0)	8 (8:0)	8	7
Amsterdam UMC-locatie AMC	10 (10:0)	6	6 (3:3)	6 (3:3)	6	6
University of California San Francisco at Mount Zion	9 (6:3)	8	7 (2:5)	7 (2:5)	7	6
Duke University Medical Center	8 (7:1)	6	6 (5:1)	6 (5:1)	6	5
Stanford University Medical Center	8 (8:0)	8	7 (6:1)	7 (6:1)	7	7
Vanderbilt University Medical Center	8 (7:1)	7	6 (6:0)	6 (6:0)	6	6
Toronto Western Hospital	7 (6:1)	6	4 (2:2)	4 (2:2)	4	4
Cleveland Clinic	6 (5:1)	3	2 (2:0)	2 (2:0)	2	2
CHU de Grenoble	5 (5:0)	3	2 (1:1)	2 (1:1)	2	1
Total	**85 (65:20)**	**70**	**60 (43:17)**	**60 (43:17)**	**59**	**54**

Baseline Characteristics

Of the 85 enrolled subjects, the mean age was 61.8 years (SD 7.96) with 24 (28.2%) females, mean PD duration was 12.4 years (SD 6.61), the mean dyskinesia duration was 6.0 years (SD 4.52) for those with dyskinesia, and mean fluctuation years was 7.6 years (SD 4.44) for those with fluctuation. See Table 11 below.

Table 11: Baseline Characteristics of the Study Population

	All Consented [N][1]	**Full Analysis Set [N][1]**	**Directional Simulation [N][1]**
Age - yr (mean ± std) (range)	61.8 ± 8.0 (36-75) [83]	61.4 ± 8.8 (36-75) [45]	60.1 ± 6.0 (48-72) [15]
PD duration - yr (mean ± std)	12.4 ± 6.6 [81]	13.4 ± 7.6 [45]	7.9 ± 3.0 [15]
Dyskinesia - yr (mean ± std)	6.0 ± 4.5 [51]	6.7 ± 5.0 [26]	3.7 ± 3.0 [13]
Motor fluctuations - yr (mean ± std)	7.6 ± 4.4 [61]	6.5 ± 3.7 [32]	6.8 ± 3.7 [13]
Duration of levodopa treatment – yr (mean ± std)	10.0 ± 5.7 [76]	10.6 ± 6.8 [43]	7.3 ± 2.9 [14]
Duration of treatment with dopamine agonist - yr (mean ± std)	8.8 ± 4.8 [54]	8.3 ± 5.0 [29]	5.6 ± 3.0 [10]
Levodopa equivalent daily dose – mg (mean ± std)	514.3 ± 521.0 [74]	509.7 ± 460.7 [45]	372.1 ± 283.2 [15]
Sex			
Male (%)	71.8% [61]	66.7% [30]	73.3% [11]
Female (%)	28.2% [24]	33.3% [15]	26.7% [4]
PD subtype (%)	[75]	[45]	[15]
Akinetic Rigid	62.7%	60.0%	46.7%
Tremor Dominant	25.3%	28.9%	40.0%
Mixed	12.0%	11.1%	13.3%
MDS-UPDRS III	[75]	[45]	[15]
Mean (SD)	45.7 (15.74)	47.5 (15.38)	47.7 (19.45)
Min to Max	16.0 to 86.0	23.0 to 86.0	16.0 to 80.0
Hoehn and Yahr Stage (n, %)	[75]	[45]	[15]
2	49 (65.3%)	27 (60.0%)	12 (80.0%
3	17 (22.7%)	12 (26.7%)	1 (6.7%)
4	7 (9.3%)	4 (8.9%)	4 (8.9%)
1	1 (1.3%)	1 (2.2%)	0 (0.0%)
5	1 (1.3%)	1 (2.2%)	0 (0.0%)

[1] All Consented (85 subjects), Full Analysis Set (45 subjects), Directional Stimulation Complete Case (15 subjects but not all subjects with screen failures provided PD history

Device Characteristics

Table 12 describes the device characteristics of the products that were used in the study. All neurostimulator systems (INS, extension, leads) were implanted prior to enrollment. The two lead types are legacy leads (models 3387 or 3389) and SenSight leads (models B33005 or B33015). Each subject had two leads (left and right hemispheres) with two target site locations. Since the two lead types and two target site locations for each subject were the same, summaries of lead type and target site by subject are presented. Most subjects (76.5%, 65/85) were implanted with their first DBS system an average of 0.5 years prior to enrollment. Most subjects (76.5%, 65/85) had the target site in the STN.

Table 12: Device Characteristics of Patients Enrolled

Characteristics	All Consented (N=85)	Full Analysis Set (N=45)	Directional Simulation (N=15)
New or Replacement Neurostimulator			
New (%)	76.5%	75.6%	100.0%
Replacement (%)	23.5%	24.4%	0.0%
Time from the current neurostimulator implant to consent – yr	0.5 ± 0.29	0.5 ± 0.29	0.5 ± 0.17
Mean ± std	0.5 ± 0.29	0.5 ± 0.29	0.5 ± 0.17
Minimum to Maximum	0.0-1.3	0.1 to 1.3	0.3-0.9
Lead type by subject			
Lead models 3387 or 3389 (%)	63.5%	75.6%	0.0%
SenSight lead models B33005 or B33015 (%)	36.5%	24.4%	100.0%
Time from the current lead implant to consent – yr			
Mean ± std	2.9 ± 3.19	2.7 ± 3.31	0.5 ± 0.17
Minimum to Maximum	0.2-11.3	0.2-11.3	0.3-0.9
Target site by subject			
STN (%)	76.5%	68.9%	86.7%
GPi (%)	23.5%	31.1%	13.3%

D. Safety and Effectiveness Results

Refer to the Limitations of Study (**Section XIV.E**) for a discussion of the limitations associated with the study and results.

Protocol Deviations

There were 54 protocol deviations that occurred in 36 subjects during the aDBS Evaluation Phase (Table 13). These are the protocol deviations that occurred during the collection of the data for the primary endpoint analysis.

Table 13: Protocol deviations during aDBS Evaluation Phase

Study visit	Deviation Type	Number of deviations
Randomization	Visit occurred outside of window	9
	Study treatment deviation - switched to cDBS at night - switched to Directional Stimulation due to AE	2
	Visit not completed	1
Visit 1	Study assessment/data collection not completed - Wearable: <7 days x13 - Diary: incomplete diary x2, missing x3	18
	Visit occurred outside of window	3
	Study assessment completed outside window	2
	Study treatment deviation - Subject not randomized and exited	1

Study visit	Deviation Type	Number of deviations
	Subject unblinding	1
	Visit not completed - switched mode not tolerated	1
Visit 2	Study assessment/data collection not completed - Wearable: <7 days x3, missing x1 - Diary: incomplete x3, missing x1 - Missing Questionnaire: switched mode not tolerated x1	9
	Visit occurred outside of window	3
	Study assessment completed outside window	1
	Study treatment deviation - aDBS off during Evaluation phase	1
	Unauthorized use of investigational device - Investigational tablet used during exit visit	1
	Visit not completed - switched mode not tolerated	1
Total		54

Note: Subjects may have more than 1 deviation.

All Randomized subjects completed the aDBS Evaluation Phase of the study. However, 3 subjects did not complete the aDBS Evaluation Phase as Randomized. Two subjects were unable to complete the evaluation period for Single-Threshold aDBS mode due to side effects and switched to the Dual-Threshold aDBS mode without completing the required Single-Threshold mode evaluations. One subject was inadvertently reprogrammed to cDBS throughout the aDBS Evaluation Phase. These subjects were included in the analysis for the primary endpoint, imputing data for the subject inadvertently switched to cDBS using multiple imputation, and imputing data for subjects who switched modes due to side effects as failures. Subjects with otherwise missing primary and secondary endpoint data had data imputed using multiple imputation.

1. Safety Results

   The analysis of safety was based on the All-Consented cohort of 85 subjects from enrollment through the Extended Access Phase of the study. The key safety outcomes for this study are presented below in Table 14 to Table 20.

   Adverse effects that occurred in the PMA clinical study:

   Table 14 below presents an overview of the adverse events (AEs).

   - Overall, the incidence of adverse events was 78.8%, and 56.5% for adverse device events.
   - Serious adverse events were reported in 17.6% of subjects with 1 subject experiencing 2 serious adverse device events (fall [1 event], spinal fracture [1 event]) in the Extended Access Phase.

Table 14: Brief Overview of Adverse Events

Event type	Events (Subjects, % of Subjects)	
	All Consented (N = 85)	
	ADE	Total
All AEs	155 (48, 56.5%)	510 (67, 78.8%)
SAE	2 (1, 1.2%)	23 (15, 17.6%)

Abbreviations: AE=adverse event, SAE=serious adverse event, ADE=adverse device event.

Among all consented subjects from enrollment through the Extended Access Phase, there were 23 SAEs in 15 subjects (17.6%, Table 15). All subjects were implanted with a Percept PC device and stable on their medications and programming prior to enrollment in the ADAPT-PD Trial.

Table 15: Serious Adverse Events

	Events (Subjects, % of Subjects)
	All Consented subjects (N = 85)
All Serious Adverse Events	**23 (15, 17.6%)**
Fall	4 (3, 3.5%)
Pneumothorax	2 (2, 2.4%)
Urinary tract infection	2 (2, 2.4%)
Abdominal pain	1 (1, 1.2%)
Arthritis	1 (1, 1.2%)
Choking[1]	1 (1, 1.2%)
Craniocerebral injury	1 (1, 1.2%)
Dislocation of vertebra	1 (1, 1.2%)
Dizziness	1 (1, 1.2%)
Giardiasis	1 (1, 1.2%)
Myocardial infarction	1 (1, 1.2%)
Nephrolithiasis	1 (1, 1.2%)
Radiculopathy	1 (1, 1.2%)
Rib Fracture	1 (1, 1.2%)
Skull fracture	1 (1, 1.2%)
Spinal fracture	1 (1, 1.2%)
Spinal osteoarthritis	1 (1, 1.2%)
Sternal fracture	1 (1, 1.2%)

[1] Choking led to death was unrelated to the study device, procedure, stimulation, or therapy

Significant Adverse Events

- Death
  One subject death was reported in the optional Extended Access Phase of the study. This death was assessed by the investigator and the CEC as unrelated to the study device, procedure, therapy or stimulation.

- Suicidality
  There were no suicidal ideations, behaviors, or self-injurious behaviors without suicidal intent reported in the study.

- Intracranial hemorrhage
  One patient had a skull fracture resulting from a fall. This was classified as an SAE and a CT scan revealed that they had intraparenchymal, subarachnoid, and subdural hemorrhage. The event was considered by the investigator to be unlikely related to the stimulation or therapy and probably related to the disease under study.

- Device-related infections
  There were no device-related infections reported in the study.

Display of adverse events (All Consented data set)
The most frequently occurring adverse events are summarized in Table 16. A total of 510 adverse events in 67 subjects (78.8%) were reported. The adverse events with the highest frequencies were falls (40.0%), worsening of Parkinson's disease symptoms (34.1%), and dyskinesia (22.4%). Note that documented pre-existing conditions (i.e., Parkinson's disease, Dyskinesia, Tremor) that worsened in intensity, duration, or frequency from the time of enrollment to study exit and/or closure were considered reportable events.

Table 16: Top 5% of Adverse Events from Enrollment to Extended Access Phase, by Preferred Term

Preferred term	Events (Subjects, % of Subjects) All Consented subjects (N = 85)
All Adverse Events	**510 (67, 78.8%)**
Fall	88 (34, 40.0%)
Parkinson's disease	41 (29, 34.1%)
Dyskinesia	34 (19, 22.4%)
COVID-19	22 (19, 22.4%)
Tremor	23 (17, 20.0%)
Gait disturbance	11 (11, 12.9%)
Dizziness	10 (10, 11.8%)
Contusion	9 (8, 9.4%)
Urinary tract infection	9 (8, 9.4%)
Freezing phenomenon	9 (7, 8.2%)
Arthralgia	7 (7, 8.2%)

Preferred term	Events (Subjects, % of Subjects) All Consented subjects (N = 85)
Dystonia	8 (6, 7.1%)
Insomnia	6 (6, 7.1%)
Skin abrasion	8 (5, 5.9%)
Balance Disorder	5 (5, 5.9%)
Pain in extremity	5 (5, 5.9%)

Table 17 presents stimulation-related adverse events by System Organ Class (SOC), preferred term (PT), and phase of the study. Among the total 155 stimulation-related adverse events, 23 (17/60, 28.3%) were reported during the aDBS Evaluation Phase. Stimulation adjustments based on subject's observations requiring reprogramming were reported as AEs. None of these events required system modifications.

Table 17: Frequency of Stimulation-related AEs by System Organ Class, Preferred Term, and Phase

SOC Preferred term	Events (Subjects, % of Subjects)				
	Enrollment through cDBS Baseline Phase (N = 85)	aDBS Setup and Adjustment Phase (N = 70)	aDBS Evaluation Phase (N = 60)	Long-Term Follow-up Phase (N = 59)	Extended Access Phase (N = 54)
All Adverse Events	**4 (4, 4.7%)**	**75 (39, 55.7%)**	**23 (17, 28.3%)**	**24 (17, 28.8%)**	**29 (15, 27.8%)**
Psychiatric disorders					
Insomnia	0 (0, 0%)	2 (2, 2.9%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)
Apathy	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Bradyphrenia	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)
Depressed mood	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)
Impulse-control disorder	1 (1, 1.2%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Nervous system disorders					
Parkinson's disease	0 (0, 0%)	14 (13, 18.6%)	9 (8, 13.3%)	6 (6, 10.2%)	6 (5, 9.3%)
Dyskinesia	0 (0, 0%)	22 (16, 22.9%)	3 (2, 3.3%)	4 (3, 5.1%)	3 (3, 5.6%)
Tremor	1 (1, 1.2%)	7 (6, 8.6%)	2 (2, 3.3%)	4 (2, 3.4%)	2 (2, 3.7%)
Dystonia	0 (0, 0%)	2 (1, 1.4%)	0 (0, 0%)	1 (1, 1.7%)	3 (3, 5.6%)
Freezing phenomenon	1 (1, 1.2%)	0 (0, 0%)	2 (2, 3.3%)	2 (2, 3.4%)	0 (0, 0%)
Paraesthesia	0 (0, 0%)	4 (3, 4.3%)	1 (1, 1.7%)	0 (0, 0%)	0 (0, 0%)
Dizziness	0 (0, 0%)	4 (4, 5.7%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Dysarthria	1 (1, 1.2%)	2 (2, 2.9%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)
Parkinsonian rest tremor	0 (0, 0%)	3 (3, 4.3%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)
On and off phenomenon	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)
Altered state of consciousness	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Balance disorder	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Bradykinesia	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Brain fog	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Hemiparaesthesia	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Muscle contractions involuntary	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Slow speech	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)
Speech disorder	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)

SOC Preferred term	Events (Subjects, % of Subjects)				
	Enrollment through cDBS Baseline Phase (N = 85)	aDBS Setup and Adjustment Phase (N = 70)	aDBS Evaluation Phase (N = 60)	Long-Term Follow-up Phase (N = 59)	Extended Access Phase (N = 54)
Eye disorders					
Blepharospasm	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Vascular disorders					
Hot flush	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Respiratory, thoracic and mediastinal disorders					
Dysphonia	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	1 (1, 1.9%)
Gastrointestinal disorders					
Nausea	0 (0, 0%)	2 (2, 2.9%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Oral discomfort	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)
Musculoskeletal and connective tissue disorders					
Muscle twitching	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)
Musculoskeletal stiffness	0 (0, 0%)	0 (0, 0%)	2 (2, 3.3%)	0 (0, 0%)	0 (0, 0%)
Muscle rigidity	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Pain in extremity	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)
Pain in jaw	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)	0 (0, 0%)
General disorders and administration site conditions					
Gait disturbance	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	4 (4, 7.4%)
Asthenia	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)	0 (0, 0%)
Propulsive gait	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)	0 (0, 0%)
Sluggishness	0 (0, 0%)	1 (1, 1.4%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)
Injury, poisoning and procedural complications					
Fall	0 (0, 0%)	0 (0, 0%)	1 (1, 1.7%)	0 (0, 0%)	3 (3, 5.6%)
Spinal fracture	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	0 (0, 0%)	1 (1, 1.9%)

Abbreviations: cDBS=continuous deep brain stimulation, aDBS=adaptive deep brain stimulation

Unscheduled Visits for Stimulation Related AEs

Visits conducted outside of the required, scheduled protocol visits (e.g., Enrollment, LFP, cDBS Baseline, Randomization, Evaluation Visits, Long-term, Extended Access Visits) for aDBS programming adjustments/optimization/telehealth visits or for programming for stimulation-related AE resolution were documented on case report forms. Table 18 summarizes the number of visits, 132 unscheduled (AE, Programming adjustments, Other) and 51 protocol required, that were conducted for reprogramming of stimulation-related AEs reported for all phases. The average number of visits required for resolution of a stimulation related adverse event was 1.2 visits/stimulation-related events however, some events did not require a follow-up visit for AE resolution and no action was required.

Table 18: Summary of Visits Conducted for Reprogramming of Stimulation-related Adverse Events (n=183)

Events	Unscheduled visit			Protocol required visits that included programming for stimulation- related AE
	Primary Reason for Unscheduled visit – *Adverse event*	**Primary Reason for Unscheduled visit – *Programming adjustment***	**Primary Reason for unscheduled visit - Other**	
Stimulation - related AE (N=149)	99	29	4	51

Table 19 summarizes the number of visits conducted for resolution of a stimulation-related AE by Phase and the temporary aDBS therapy pauses/suspensions, medication changes, and programming adjustments conducted for resolution of stimulation-related AEs. Most visits for AE resolution of a stimulation-related AE were conducted during the aDBS Setup and Adjustment Phase. Once stimulation adjustments were completed in the aDBS Setup and Adjustment Phase the number of visits reported for stimulation-related AEs decreased and remained around 20% for the remainder of the follow-up period.

Table 19: Visits for Stimulation-related AEs by Phase (n=149 Stimulation-related AEs)

	Visits (% visits)				
	Enrollment to cDBS Baseline	**aDBS Setup and Adjustment Phase**	**Evaluation Phase**	**Long Term Follow-up Phase**	**Extended Access Phase**
Total visits (n=183)	3[a] (1.6%)	77 (42%)	33 (18%)	38 (21%)	33 (18%)

[a] one event resolved over the phone without a visit.

Other actions taken that included temporary aDBS therapy pauses/suspensions, medication changes, group changes within a mode, and changes from ring mode to directional stimulation that were associated with a stimulation-related AE resolution are summarized in Table 20. As shown in Table 20, other actions taken to resolve a stimulation-related AE involved temporary pauses in aDBS therapy and/or in some cases PD medication changes. The ability to pause aDBS was put in place as a measure to return patients to cDBS therapy if experiencing AEs. The majority of aDBS therapy pauses/suspensions were reported during the aDBS Setup and Adjustment Phase. Once the programming was optimized and subjects entered the Evaluation Phase the number of temporary aDBS therapy pauses/suspensions decreased and remained consistent throughout the remainder of the follow-up phases.

Table 20: Visits for Stimulation-related AEs by Phase (n=149 Stimulation-related AEs) and Actions Taken

Other Actions Taken	Enrollment to cDBS Baseline N=3	aDBS Setup and Adjustment Phase n=77	Evaluation Phase N=3	Long Term Follow-up Phase N=38	Extended Access Phase N=33
Temporary aDBS Therapy Pauses/Suspensions *#Visits with aDBS pauses (subjects, % visits)*	1 (1, 1%)	48 (25, 65%)	10 (7, 13%)	10 (9, 13%)	5 (4, 7%)
Medication Changes	0	2	1	2	7
Change in Group with the same aDBS mode	N/A	N/A	0	0	2
Change from Ring to/from Directional Stimulation	N/A	N/A	0	2[a]	1

[a.] one event resolved over the phone without a visit.

2. Effectiveness Results

The analysis of effectiveness was based on the 45 evaluable patients in the FAS (35 in Single Threshold FAS and 40 in Dual Threshold FAS) at the end of the aDBS Evaluation Phase. Key effectiveness outcomes are presented in Table 21 to Table 33.

Primary Endpoint Results

The primary objective of this study was to provide descriptive statistics of the proportion of aDBS subjects who met the primary "success" criteria – aDBS mode daily average "On" time without troublesome dyskinesia exceeding a patient-specific threshold defined as cDBS baseline daily average "On" time without troublesome dyskinesia minus 2 hours.

In the Single-Threshold and Dual-Threshold FAS, 85.7% (30/35) had PD home diaries for Single Threshold and 95% (38/40) had diaries for Dual Threshold. Multiple imputation was applied to treat missing data in the primary analysis, with the exception of 2 subjects in the Single-Threshold FAS who were imputed as failures because their assessments were missing due to poor tolerance to the mode.

For Single Threshold aDBS, the proportion of success was 78.9% with exact 97.5% lower confidence limit at 59.4%; for Dual Threshold aDBS, the proportion of success was 91% with exact 97.5% lower confidence limit at 75.6% (See Table 21).

Table 21: Primary Analysis of the Primary Objective (Full Analysis Set)

aDBS Mode	No. of subjects (FAS)	Proportion of success[1]	Exact 97.5% lower confidence limit [1]
Single Threshold	35	78.9%	59.4%
Dual Threshold	40	91.0%	75.6%

Abbreviations: aDBS=adaptive deep brain stimulation, FAS=full analysis set, No=number. Statistical test associated with analysis:
[1] Multiple Imputation Clopper-Pearson mean success approach

Primary Endpoint Sensitivity Analyses

A sensitivity analysis for the primary endpoint was conducted using the Complete Case (CC), As-Treated (AT), and Primary Cohort modified Intention-to-Treat (PC mITT) data sets (Table 22 . In addition, the Directional Stimulation cohort was added to the analysis to include the subjects across the entire study accounting for a combined analysis of both legacy and SenSight leads and programming in ring mode (omnidirectional) and directional configurations (CC+DSCC). On the CC, AT, and CC+DSCC analysis sets, the lower bounds of 97.5% Confidence Intervals for the primary success rate were at least 67.2% for Single-Threshold aDBS mode and at least 76.0% for Dual-Threshold aDBS mode. On the Single- and Dual-Threshold PC mITT sets, which included all FAS subjects as well as subjects who were successfully setup for the respective aDBS mode but found that mode unacceptable during the aDBS Setup and Adjustment Phase, 97.5% Confidence Interval lower bounds for the primary success rate were 46.0% and 62.6%, respectively.

Table 22: Sensitivity and combined analysis for the Primary Objective (Complete Case, As- Treated, and CC+DSCC data sets)

	Single Threshold		Dual Threshold	
Dataset	n	n/N, %Success (% LCB)	n	n/N, %Success (% LCB)
CC	30	25/30, 83.3% (62.7%)	38	35/38, 92.1% (76.6%)
AT	29	25/29, 86.2% (65.7%)	37	34/37, 91.9% (76.0%)
CC + DSCC	43	36/43, 83.7% (67.2%)	53	48/53, 90.6% (77.6%)
PC mITT	43	64.2%[1] (46.0%)	46	79.1%[1] (62.6%)

Abbreviations: LCB=exact 97.5% lower confidence limit, CC=Complete Case, DSCC=Directional Stimulation Complete- Case.
Statistical test associated with analysis:
[1] n/N not applicable since proportions were derived using multiple imputation.

Primary Endpoint Additional Analyses

Subjects were asked to record their mobility in a motor diary (PD home diary) over at least 3 consecutive days at the end of the cDBS Baseline Phase and each aDBS Evaluation Phase visit. In 30-minute intervals, the subject recorded whether he or she was in "On" time with/without troublesome dyskinesia; "Off" time; or

asleep. An improvement of 1 hour/day for "On" time without troublesome dyskinesia and "Off" time is considered clinically significant. Table 23 shows motor diary results for both aDBS and cDBS for the FAS.

Table 23: Comparisons of Motor Diaries, aDBS vs cDBS by Mode (Full Analysis set)

Motor diaries	Comparison	Single Threshold		Dual Threshold	
		n	Mean ± SE (% chg)	n	Mean ± SE (% chg)
"On" time without troublesome dyskinesia (hours/day)	cDBS	35	12.24 ± 0.57	40	12.30 ± 0.57
	aDBS	35	12.87 ± 0.66	40	13.62 ± 0.46
	aDBS – cDBS	35	0.6 ± 0.6 (5%)	40	1.3 ± 0.5 (11%)
"On" time with troublesome Dyskinesia (hours/day)	cDBS	35	0.83 ± 0.30	40	0.73 ± 0.27
	aDBS	35	0.54 ± 0.27	40	0.59 ± 0.29
	aDBS – cDBS	35	-0.3 ± 0.2 (-36%)	40	-0.1 ± 0.2 (-19%)
"Off" time (hours/day)	cDBS	35	2.77 ± 0.50	40	2.83 ± 0.52
	aDBS	35	2.09 ± 0.62	40	1.26 ± 0.32
	aDBS – cDBS	35	-0.7 ± 0.6 (-25%)	40	-1.6 ± 0.4 (-55%)
Asleep time (hours/day)	cDBS	35	8.12 ± 0.25	40	8.12 ± 0.23
	aDBS	35	8.37 ± 0.32	40	8.54 ± 0.23
	aDBS – cDBS	35	0.3 ± 0.3 (3%)	40	0.4 ± 0.2 (5%)

Abbreviations: cDBS=continuous deep brain stimulation, aDBS=adaptive deep brain stimulation, chg=change, SE=standard error. Statistical test associated with p-values:
Notes: For the measures of Time with good mobility without troublesome dyskinesia and Asleep time, higher values (positive mean changes) indicate an improvement for aDBS as compared with cDBS. For the measures of Time with troublesome dyskinesia and Time with impaired mobility, lower values (negative values) indicate an improvement for aDBS as compared with cDBS. Subjects were taking their regular medication regimen during the recording of these data.
Motor diaries were rated every 30 minutes (0.5 h) over 24 hours on at least 3 consecutive days. A subject's diary results for a day were included in the analysis if valid entries were made for at least 42*0.5 hours per day (=21 hours per day).

Figure 7 and Figure 8 below show results of "On" time without troublesome dyskinesia from the cDBS baseline phase to the aDBS evaluation for the CC data set for ST and DT.

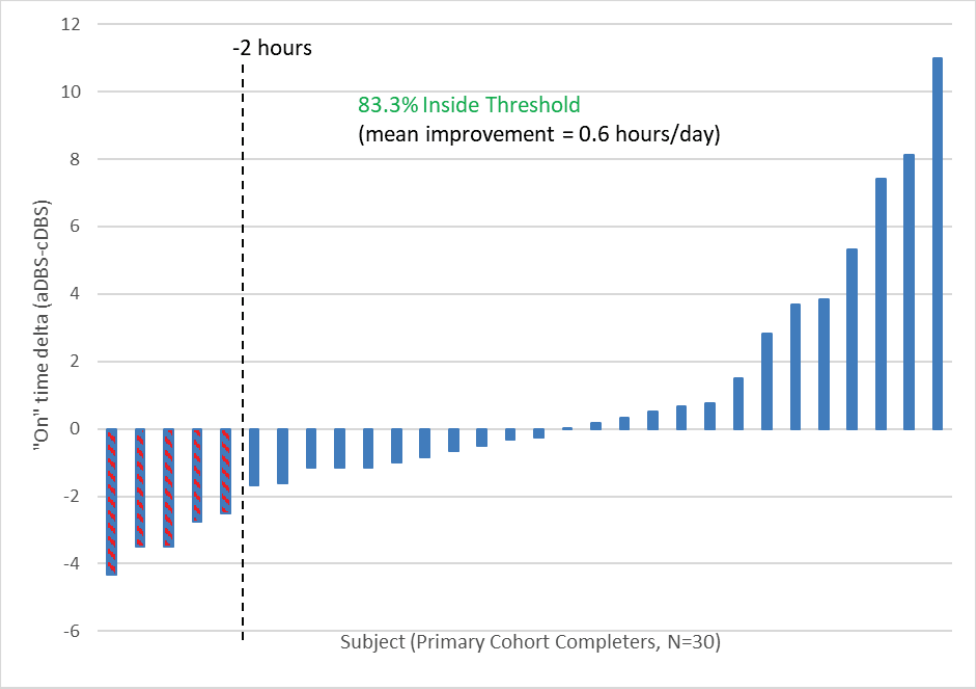

Figure 7: Changes of "On" Time without Troublesome Dyskinesia from the cDBS Baseline to aDBS Evaluation for Single Threshold (Complete Case Set)

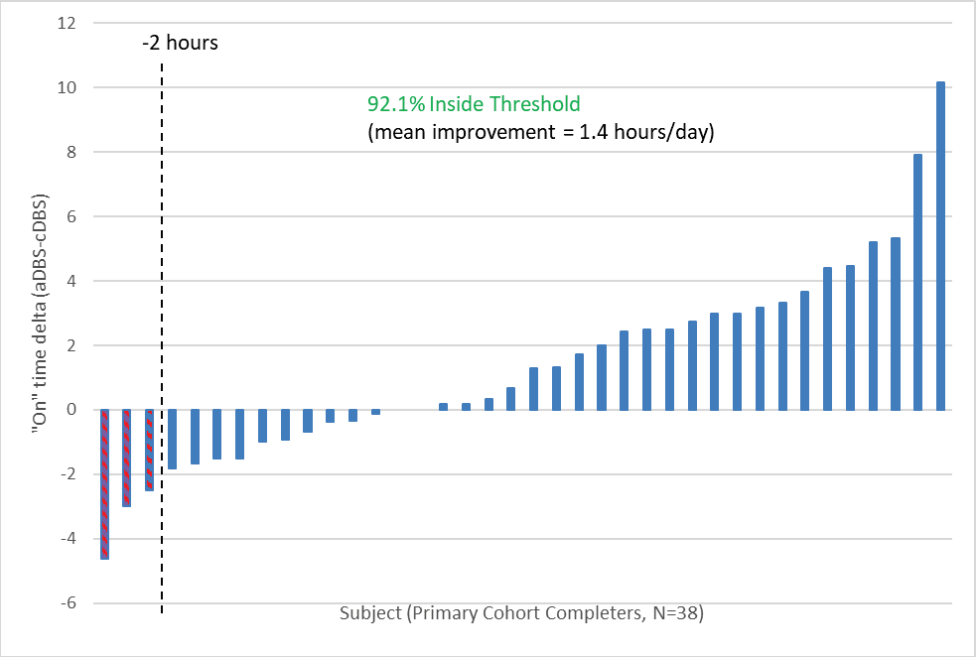

Figure 8: Changes of "On" Time without Troublesome Dyskinesia from the cDBS Baseline to aDBS Evaluation for Dual Threshold (Complete Case Set)

Secondary outcome measure

The secondary objective was to demonstrate decreased stimulation energy use during the aDBS Evaluation Phase as compared with cDBS using the Total Electrical Energy Delivered (TEED). TEED is defined as the total energy delivered by an electrical system through the DBS leads over an arbitrary period of time. TEED is determined by the stimulation parameters (pulse width, frequency, amplitude) and the measured impedance. The mean decrease in TEED between aDBS and cDBS was 22.3 μWatts for both Single-Threshold and Dual-Threshold modes, as reported below in Table 24 along with associated standard errors.

Table 24: Comparison of TEED, aDBS vs cDBS by mode (Full Analysis set)

Endpoint	Comparison	Single Threshold		Dual Threshold	
		n	Mean ± SE (% chg)	n	Mean ± SE (% chg)
TEED (μWatts)	aDBS – cDBS	35	-22.3 ± 8.37 (-15%)	40	-22.3 ± 10.98 (-13%)

Abbreviations: TEED=total electrical energy delivered, cDBS=continuous deep brain stimulation, aDBS=adaptive deep brain stimulation, chg=change, SE=standard error.

A sensitivity analysis for the secondary endpoint was conducted using the Complete Case (CC), As-Treated (AT), and combined Primary Cohort CC and Directional Stimulation Cohort CC (CC+DSCC) data sets in Table 25. Across sensitivity analysis sets, Single-Threshold aDBS mode mean TEED reduction was generally larger than in the FAS, ranging from 23.5 μWatts (CC+DSCC) to 28.8 μWatts (AT); for Dual-Threshold aDBS mode, mean TEED reduction was also generally larger across sensitivity analysis sets as compared with the FAS, ranging from 23.6 μWatts (CC) to 28.1 μWatts (AT).

Table 25: Sensitivity and Combined Analysis for TEED μWatts , aDBS vs cDBS by Mode (Complete Case, As-Treated, and CC+DSCC data sets)

Dataset	Comparison	Single Threshold		Dual Threshold	
		n	Mean ± SD (%chg)	n	Mean ± SD (%chg)
Complete Case	aDBS – cDBS	32	-23.7 ± 50.8 (-13%)	39	-23.6 ± 69.1 (-11%)
As-Treated	aDBS – cDBS	31	-28.8 ± 42.3 (-14%)	38	-28.1 ± 64.0 (-11%)
CC + DSCC	aDBS - cDBS	45	-23.5 ± 46.1 (-12%)	53	-26.7 ± 63.5 (-12%)

Abbreviations: TEED=total electrical energy delivered, cDBS=continuous deep brain stimulation, aDBS=adaptive deep brain stimulation, SD=standard deviation, %chg=median % change, CC=Complete Case, DSCC=Directional Stimulation Complete-Case.

Note: Negative changes (lower values) indicate an improvement for aDBS as compared with cDBS.

Additional Endpoints

Table 26 summarizes at a high level the results of the additional endpoint analyses comparing the change in cDBS Baseline results to the aDBS Evaluation Phase results for the CC dataset. Because there were many additional endpoints, only total scores are included in the table and although subscores were also collected they have not been included. Results from the PD Home Diary are summarized above in Table 23, Figure 7, and Figure 8. Data were also collected with Global Kinetics Corporation (GKC) Personal KinetiGraph (PKG) wearable device. Correlations between the wearable endpoints and the various standard endpoints were not achieved. This could be due to multiple factors including that the algorithms of the wearable scores were not sensitive enough to detect small changes in this population or that the watch was worn on one wrist while the disease affects the entire body and would not pick up on motor complications of the feet or the non-measured hand.

Table 26: Additional Endpoints – Change in cDBS Baseline to the aDBS Evaluation Phase (Complete Case Set)

Measure	Subject Characteristics	Single Threshold (N=33)	Dual Threshold (N=40)
VHI "Best" Condition Total Score	Mean (SD) Median Min to Max 95% Confidence Interval	0.1 (13.66) 0 -29.0 to 35.0 (-4.7, 5.0)	0.4 (13.95) 0 -25.0 to 39.0 (-4.1, 4.9)
VHI "Worst" Condition Total Score	Mean (SD) Median Min to Max 95% Confidence Interval	-0.7 (14.49) 0 -28.0 to 48.0 (-5.9, 4.4)	0.1 (16.31) 0 -44.0 to 52.0 (-5.1, 5.3)
MDS-UPDRS III Subscore Left by Side (On stim/On med)	Mean (SD) Median Min to Max 95% Confidence Interval	0.9 (4.33) 0 -9.0 to 13.0 (-0.6, 2.4)	0.9 (3.13) 0.5 -5.0 to 8.0 (-0.1, 1.9)
MDS-UPDRS III Subscore Right by Side (On stim/On med)	Mean (SD) Median Min to Max 95% Confidence Interval	-0.1 (3.84) 0 -11.0 to 9.0 (-1.5, 1.2)	0.2 (4.05) 0 -10.0 to 9.0 (-1.1, 1.5)
MDS-UPDRS III More Affected Side	Mean (SD) Median Min to Max 95% Confidence Interval	0.6 (4.23) 0 -9.0 to 13.0 (-0.9, 2.1)	1.1 (4.07) 1 -10.0 to 9.0 (-0.2, 2.4)
MDS-UPDRS III Less Affected Side	Mean (SD) Median Min to Max 95% Confidence Interval	0.2 (4.01) 0 -11.0 to 9.0 (-1.2, 1.6)	0.1 (3.07) 0 -5.0 to 8.0 (-0.9, 1.1)
MDS-UPDRS III Score	Mean (SD) Median Min to Max 95% Confidence Interval	1.7 (9.92) 1 -26.0 to 25.0 (-1.8, 5.2)	2.6 (7.23) 2 -15.0 to 22.0 (0.2, 4.9)

Measure	Subject Characteristics	Single Threshold (N=33)	Dual Threshold (N=40)
MDS-UPDRS III Speech Question (On stim/On med)	Mean (SD) Median Min to Max 95% Confidence Interval	0.2 (0.62) 0 -1.0 to 2.0 (-0.1, 0.4)	0.1 (0.63) 0 -1.0 to 1.0 (-0.1, 0.3)
MDS-UPDRS II Best Condition	Mean (SD) Median Min to Max 95% Confidence Interval	-0.2 (5.57) 1 -10.0 to 18.0 (-2.1, 1.8)	0.0 (4.94) 0 -11.0 to 13.0 (-1.6, 1.6)
MDS-UPDRS II Worst Condition	Mean (SD) Median Min to Max 95% Confidence Interval	0.8 (5.34) 0 -8.0 to 22.0 (-1.0, 2.7)	0.8 (6.22) 1 -12.0 to 20.0 (-1.2, 2.8)
MDS-UPDRS IV	Mean (SD) Median Min to Max 95% Confidence Interval	0.6 (3.17) 0 -9.0 to 6.0 (-0.5, 1.7)	1.2 (3.64) 1 -8.0 to 8.0 (0.1, 2.4)
EQ-5D-5L Index Value	Mean (SD) Median Min to Max 95% Confidence Interval	0.03 (0.190) 0 -0.45 to 0.73 (-0.04, 0.10)	0.03 (0.169) 0.01 -0.31 to 0.49 (-0.02, 0.08)
EQ VAS	Mean (SD) Median Min to Max 95% Confidence Interval	1.18 (13.992) 2 -30.00 to 35.00 (-3.78, 6.14)	-3.05 (12.011) -3.5 -35.00 to 25.00 (-6.89, 0.79)
PDSS-2 Total Score	Mean (SD) Median Min to Max 95% Confidence Interval	0.9 (7.04) 0 -14.0 to 18.0 (-1.6, 3.4)	-0.3 (8.77) 1 -31.0 to 14.0 -3.1, 2.6)
PDQ-39 Summary Index	Mean (SD) Median Min to Max 95% Confidence Interval	N=32 -0.8 (9.71) 0.1 -38.7 to 14.6 (-4.3, 2.7)	N= 39 -0.3 (9.03) 0 -22.1 to 18.0 (-3.3, 2.6)
PDQ-39 Speech Question 34: Had difficulty with speech	Mean (SD) Median Min to Max 95% Confidence Interval	-0.3 (0.99) 0 -3.0 to 2.0 (-0.7, 0.0)	-0.2 (0.86) 0 -2.0 to 2.0 (-0.4, 0.1)
PDQ-39 Speech Question 35: Felt Unable to communicate properly	Mean (SD) Median Min to Max 95% Confidence Interval	-0.3 (1.04) 0 -3.0 to 2.0 (-0.6, 0.1)	-0.1 (0.97) 0 -2.0 to 2.0 (-0.4, 0.2)

Abbreviations: cDBS=continuous deep brain stimulation, aDBS=adaptive deep brain stimulation, SD=standard deviation, VHI=Voice Handicap Index, MDS-UPDRS=Movement Disorder Society- Unified Parkinson's Disease Rating Scale, EQ-5D-5L=European Quality of

Life 5 Dimensions 5 Level Version, PDSS-2=Parkinson's disease sleep scale 2nd version, PDQ-39=Parkinson's disease questionnaire.
Note: Positive changes indicate an improvement for aDBS as compared with cDBS.

Battery Longevity

Due to patient-to-patient variability the aDBS function does not have the same predictability with respect to battery life as the currently approved output modes available on the Medtronic DBS Therapy for PD devices (i.e., cDBS or cDBS plus sensing). However, to give some idea of how battery life may be affected by aDBS, the estimated battery life in months, was extracted from the device programming data from cDBS Baseline and aDBS Evaluation Visit 1. Data from the Visit 2 in aDBS Evaluation Phase was not included in analysis to avoid potential bias towards aDBS due to depletion during evaluation phase. The change from cDBS to aDBS was calculated as the standardized change of estimated battery life at aDBS minus that at cDBS. A positive change represents an improvement using aDBS over the aDBS Evaluation Phase. This analysis provides a general estimate of how using aDBS may affect battery life, but the effects are highly dependent on programmed parameters and the Estimated Battery Life Remaining feature of the device should be used by the clinician for each individual subject to better predict effects of aDBS on individual patients.

An analysis focused on actual longevity influence for each patient enrolled in the ADAPT-PD study was performed (see Table 27 below). The longevity change for Dual Threshold Mode at the 50th percentile is 5% per year longevity improvement over cDBS, or an 8% per year improvement over cDBS + continuous passive sensing (passive sensing results in a -3% longevity change from cDBS). The longevity changes for Single Threshold Mode at the 50th percentile is a 4% per year longevity loss over cDBS, or 1% per year loss when compared to cDBS + continuous passing sensing. The extra cost for Single Threshold Mode is in part due to the higher sample rate required to run the single threshold algorithm (20Hz vs 5Hz for Dual Threshold). Use of aDBS may also affect the recharge interval and the Percept RC Recharge Interval Calculator will estimate the recharge interval for given settings so that clinicians and patients can review the recharge intervals in consideration of the potential therapeutic results of using aDBS, and decide whether the influence to recharging intervals is not outweighed by the benefit of using aDBS. These longevity influences are expected when running the aDBS feature and may be a necessary tradeoff for a clinician and patient to weigh against the potential clinical benefits of aDBS.

Table 27: ADAPT PD study patient % longevity/year impact. (+ value is longevity improvement over cDBS)

	Median 50% study patient	**Low 20% study patient**	**High 80% study patient**
DT	5.00%	0.00%	12.00%
ST	-4.00%	-10.00%	-1.00%

3. Subgroup Analyses
The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: geographic location (US vs OUS), target site (STN vs GPI), and lead type (legacy vs SenSight) and no statistically or clinically significant differences were observed.

The study was not specifically powered for these subgroups.

No analyses were performed for sex-, age-, race-, or ethnicity subgroups.

4. Programming Characteristics – aDBS Evaluation Phase
Table 28 describes the aDBS output characteristics used during the aDBS Evaluation Phase.

Table 28: aDBS Characteristics during the aDBS Evaluation Phase (Complete Case and Directional Stimulation Complete Case Sets)

Characteristics	Single Threshold (N=72 leads)	Dual Threshold (N=103 leads)
Amplitude – mA (mean ± std)	2.3 ± 0.9	2.5 ± 1.0
Frequency – Hz (mean ± std)	135.7 ± 22.0	136.1 ± 23.6
Pulse width – μs (mean ± std)	68.8 ± 18.5	68.7 ± 18.9
Ramp up rate - ms for Single, min for Dual (mean ± std)	664.1 ± 1088.3 Median: 250	2.1 ± 0.7 Median: 2.5
Used default ramp up rate (n, %)	46 (64.8%)	73 (72.3%)
Ramp down rate - ms for Single, min for Dual (mean ± std)	1102.1 ± 3422.6 Median: 250	5.1 ± 2.1 Median: 5
Used default ramp down rate (n, %)	58 (81.7%)	74 (73.3%)
Detection blank – ms (mean ± std)	572.9 ± 106.2 Median: 550	1680.0 ± 529.5 Median: 2000
Used default detection blank (n, %) Single: 550 ms; Dual: 2000 ms	43 (61.4%)	73 (73.0%)
Upper stimulation limits – mA (mean ± std)	2.8 ± 1.0	3.0 ± 1.0
Lower stimulation limits – mA (mean ± std)	2.1 ± 0.9	2.1 ± 0.9
Difference between upper and lower limits – mA (mean ± std)	0.8 ± 0.5	0.9 ± 0.6
Percent time aDBS is running - % (mean ± std)	97.2 ± 14.0	98.6 ± 7.3
Percent time above threshold - % (mean ± std)	39.9 ± 31.3	25.9 ± 27.0
Percent of time below (ST) or between and below (DT) threshold - % (mean ± std)	60.1 ± 31.3	72.6 ± 27.3

Abbreviations: ST=Single Threshold, DT=Dual Threshold, ms=milliseconds, min=minutes, mA=milliamps.

5. Long-term Follow-up Phase
The EQ-5D-5L Index Value and the PDQ-39 were collected during the Long-term Follow-up phase of the study. Table 29 summarizes the results from EQ-5D-5L Index Value at the cDBS Baseline and Long-term Follow-up Phase using CC set. These results show no clinically significant change from cDBS baseline but consistent performance in quality of life using aDBS for at least a year.

Table 29: Summary of EQ-5D-5L Index Value at the cDBS Baseline and Long-term Follow-up Phase (Complete Case Set)

EQ-5D-5L Index Value	cDBS Baseline	Visit 3	Visit 4	Visit 5	Visit 6
Measure Available	44	44	41	41	39
Mean (SD)	0.76 (0.163)	0.77 (0.179)	0.76 (0.169)	0.76 (0.169)	0.73 (0.185)
Median	0.8	0.81	0.76	0.76	0.78
Min to Max	0.28 to 1.00	0.26 to 1.00	0.31 to 1.00	0.31 to 1.00	0.24 to 1.00

Figure 9 shows the PDQ-39 Summary Index (SI) by visits at the cDBS Baseline and Long-term Follow-up Phase. These results show no clinically significant change from cDBS baseline but consistent performance in quality of life using aDBS for at least a year.

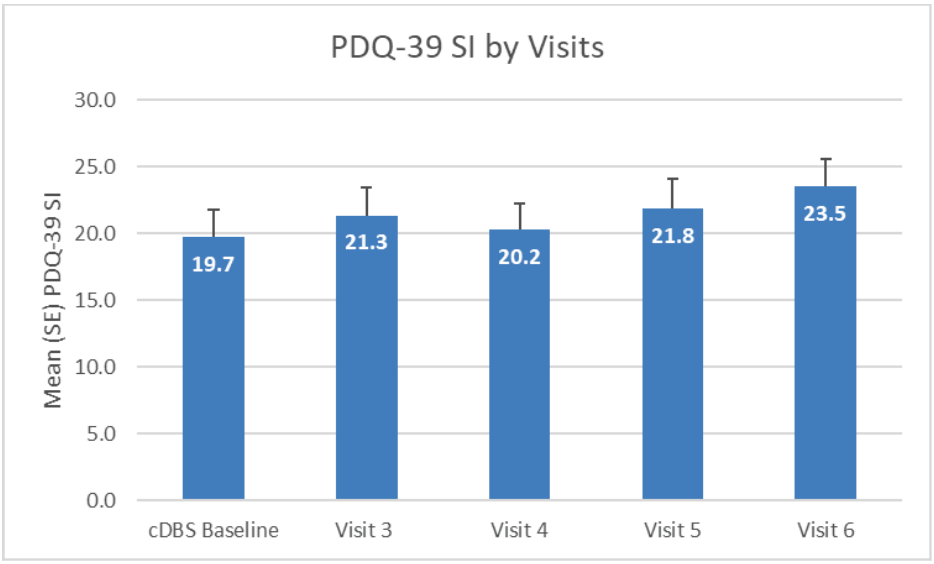

Figure 9: PDQ-39 Summary Index at the cDBS Baseline and Long-term Follow-up Phase(Complete Case Series)

6. Extended Access Phase

The Extended Access Phase was designed as an optional phase where the subjects could stay in the study to continue being programmed in aDBS. The PDQ-39 and EQ-5D-5L were collected during this phase and results of the PDQ-39 Summary Index and EQ-5D-5L Index Value are shown below in Table 30 and Table 31.

Table 30: Extended Access Phase (EAP) PDQ-39 Summary Index Results

PDQ-39 Summary Index - EAP	Visit 1	Visit 2	Visit 3
Measure Available	35	26	12
Mean (SD)	24.74 (15.67)	29.86 (17.89)	32.98 (22.84)
Median	21.25	29.53	30.31
Min to Max	0.00 – 62.50	0.00 - 82.29	0.00 – 88.28

Table 31: Extended Access Phase (EAP) EQ-5D-5L Index Value Results

EQ-5D-5L Index Value	Visit 1	Visit 2	Visit 3
Measure Available	36	25	12
Mean (SD)	0.68 (0.204)	0.70 (0.177)	0.65 (0.229)
Median	0.72	0.7	0.71
Min to Max	0.17 to 1.00	0.33 to 1.00	0.09 to 1.00

7. Patient Preference and Patient Satisfaction

At the end of the aDBS Evaluation Phase, subjects were surveyed about their overall preference between aDBS and cDBS. Results for the CC analysis set are shown in Table 32 below. 66.7% (22/33) of subjects preferred Single-Threshold aDBS mode to cDBS, while 21.2% (7/33) preferred cDBS; 70.0% (28/40) of subjects preferred Dual-Threshold aDBS mode to cDBS, while 10.0% (4/40) preferred cDBS. When subjects were able to choose which mode they preferred for the Long-Term Follow-up phase, 97.8% (44/45) of Primary Cohort subjects who entered the aDBS Evaluation Phase subjects chose to remain on aDBS during long term follow-up over returning to cDBS mode and exiting the study.

Table 32: Patient Preference for DBS Mode Over Past 14 Days (CC Set)

Subject Characteristics	Single Threshold	Dual Threshold
Overall do you prefer the DBS therapy you received during the past 14 days or the DBS therapy you were receiving prior to joining the research study? (n, %)		
Measure Available	33	40
Strongly prefer the DBS therapy received during the last 14 days	13 (39.4%)	20 (50.0%)
Somewhat prefer the DBS therapy received during the last 14 days	9 (27.3%)	8 (20.0%)
No preference between the two	4 (12.1%)	8 (20.0%)
Somewhat prefer the DBS therapy I was receiving prior to joining the research	4 (12.1%)	3 (7.5%)
Strongly prefer the DBS therapy I was receiving prior to joining the research	3 (9.1%)	1 (2.5%)

Patient satisfaction with aDBS was also assessed using a Medtronic-developed questionnaire. This assessment was completed either in person, or a copy was sent to the subject to be completed a maximum of 7 days prior to the study visit. It was completed at Visit 6 of the Long-term follow-up Phase. Thirty-eight (38) of the 40 subjects completing visit 6 in the Complete Case Set completed the patient satisfaction questionnaire. Seventy-eight-point nine percent (78.9%) (30/38) of subjects responded that they would definitely recommend aDBS to other DBS patients with PD, 15.8% (6/38) probably would, and 5.3% (2/38) were neutral. Sixty-eight-point four percent (68.4%) (26/38) of subjects were very satisfied

with the aDBS received during the Long-term Follow-up Phase and 31.6% (12/38) were somewhat satisfied. See Table 33.

Table 33: Summary of Patient Satisfaction Questions at Visit 6 during Long-term Follow-up Phase (Complete Case Set)

Subject Characteristics	Total (N=38[a])
Would you recommend adaptive DBS to other DBS patients with PD? (n, %)	
Measure Available	38
Definitely yes	30 (78.9%)
Probably yes	6 (15.8%)
Neutral	2 (5.3%)
Overall how satisfied or unsatisfied are you with the adaptive DBS you received during the long term follow up phase of this study? (n, %)	
Measure Available	38
Very satisfied	26 (68.4%)
Somewhat satisfied	12 (31.6%)

[a]2 subjects completed Visit 6 but didn't provide answers to the questions.

8. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The ADAPT-PD clinical study included 12 investigators, of which none were full-time or part-time employees of the sponsor, and 3 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payments of other sorts (excluding payments for conducting clinical study): 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0
- Medtronic royalty-earning consultant: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

N/A

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness evaluation for each aDBS mode is based on the mode-specific Full Analysis Set (FAS) of Primary Cohort subjects who initiated a period of treatment with that mode during the aDBS Evaluation Phase of the study. Subjects in the FAS were carefully screened to meet: aDBS setup criteria, requiring adequate LFP signal for adaptive stimulation; and "acceptability" criteria, requiring clinician and participant satisfaction (after an aDBS parameter adjustment period lasting up to 2 months) that aDBS efficacy was no worse than cDBS and did not cause side-effects that significantly interfered with the patient's functioning. Among the total 85 consented subjects, the percentage of LFP screen successes through randomization was 84.7% (72/85); of the 49 Primary Cohort subjects that continued the study through the aDBS Setup and Adjustment Phase, 71.4% (35/49) met setup and "acceptability" criteria for ST aDBS evaluation, and 81.6% met setup and "acceptability" criteria for DT aDBS evaluation.

The originally planned primary effectiveness endpoint was discovered to be statistically inadequate during review of the PMA supplement submission and therefore, a post-hoc descriptive analysis was performed using a revised primary effectiveness endpoint that measures the proportion of subjects in the FAS with aDBS Evaluation Phase "On" time without troublesome dyskinesia exceeding a subject-specific success threshold defined as cDBS Baseline Phase "On" time without troublesome dyskinesia minus 2 hours per day.

The proportion (97.5% CI lower bound) of FAS subjects meeting the primary success threshold was 78.9% (59.4%) for Single Threshold and 91.0% (75.6%) for Dual Threshold. Thus, among DBS patients who met aDBS setup and "acceptability" criteria, most had no worse than 2 hours per day less "Good On Time" using aDBS, as compared with cDBS. While the mean change in "On" time without troublesome dyskinesias and mean reduction in "Off" time were not clinically significant for the Single Threshold mode, there was a clinically significant improvement in "On" time without troublesome dyskinesia of 1.3 hours/day and a clinically significant reduction in "Off" time of 1.6 hours/day with Dual Threshold mode.

Regarding patient preference, at the end of the aDBS Evaluation Phase, 66.7% (22/33) of subjects who were programmed to Single-Threshold aDBS mode during the aDBS Evaluation Phase (CC Set) preferred Single-Threshold aDBS mode to cDBS, and 70.0% (28/40) of subjects programmed to Dual-Threshold aDBS mode during the aDBS Evaluation Phase preferred Dual-Threshold aDBS mode to cDBS. Further, subjects were able to choose which mode they preferred for the Long-Term Follow-up phase. 97.8% (44/45) of subjects who were programmed to at least one aDBS mode during the aDBS Evaluation Phase chose to remain on aDBS during long term follow-up over switching back to cDBS and exiting the study.

Regarding patient satisfaction, 78.9% (30/38) of subjects responded that they would definitely recommend aDBS to other DBS patients with PD, 15.8% (6/38) probably would, and 5.3% (2/38) were neutral. 68.4% (26/38) of subjects were very satisfied with the aDBS received during the Long-term Follow-up Phase and 31.6% (12/38) were somewhat satisfied.

The secondary objective evaluated the reduction in TEED between cDBS and aDBS in the aDBS Evaluation Phase. The TEED results were not clinically significant for either Single Threshold aDBS or Dual Threshold aDBS.

Due to patient-to-patient variability the aDBS function does not have the same predictability with respect to battery life as the currently approved output modes available on the Medtronic DBS Therapy for PD devices (i.e., cDBS or cDBS plus sensing). However, to give some idea of how battery life in general may be affected by aDBS, the estimated battery life in months, was extracted from the device programming data. This analysis showed that the longevity increased by 5% for Dual Threshold Mode at the 50th percentile, or an 8% per year improvement over cDBS + continuous passive sensing. When compared to cDBS, the longevity decreased by 4% per year for Single Threshold Mode at the 50th percentile, or 1% per year loss when compared to cDBS + continuous passive sensing. The Estimated Battery Life Remaining feature of the device should be used by the clinician for each individual subject to better predict effects of aDBS on individual patients. These longevity influences are expected when running the aDBS feature and may be a necessary tradeoff for a clinician and patient to weigh against the potential clinical benefits of aDBS.

The study has demonstrated the effectiveness of aDBS as a programming option in carefully selected subjects based on the following:

- A significant proportion of subjects enrolled could be programmed to at least one aDBS mode
- The primary success endpoint was met for both aDBS modes
- 98% of subjects chose to remain on aDBS during long term follow-up
- The large majority of subjects were satisfied with aDBS and would recommend aDBS to other DBS patients with PD

It should be noted however that there were several limitations to the study as described in **Section XIV.E.**

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

Over the entire study, a total of 67 subjects reported 510 AEs (78.8%), 48 subjects reported 155 stimulation-related AEs (56.5%), and 15 subjects reported 23 serious adverse events (17.6%). One subject death was reported in the Extended Access Phase that was not related to the study device, procedure, therapy, or stimulation.

Only 4 stimulation-related AEs in 4 subjects (4.7%) were reported in enrollment through cDBS baseline phase. The rate of stimulation-related AEs on aDBS is as follows: 75 events in 39 subjects (55.7%) during aDBS setup and adjustment phase, 23 events in 17 subjects (28.3%) during aDBS evaluation phase, 23 events in 17 subjects (28.8%) during long-term follow-up phase, and 24 events in 12 subjects (22.2%) during aDBS extended access phase.

The most frequently reported stimulation-related AEs (above 5%) were worsening of Parkinson's disease symptoms (28.2%, 24/85), dyskinesia (20.0%, 17/85), tremor (15.3%, 13/85), and freezing phenomenon (5.9%, 5/85). Most of the stimulation-related events resolved (142, 95.3%) at the time of the database snapshot date of December 15, 2023. Reprogramming, switching modes or temporarily pausing aDBS therapy resolved most stimulation related events (127). Changes in medications with and without reprogramming resolved 12 events or no action resolved the remaining 3 events.

Although falls were one of the most frequently reported adverse events in the trial, the majority (93%) were deemed by the investigators as unrelated to the study, device, stimulation, procedure and/or therapy.

One subject death was reported in the Extended Access Phase that was not related to the study device, procedure, therapy, or stimulation.

The overall safety profile observed in this study is consistent with earlier studies described in Section VIII of this summary.

C. Benefit-Risk Determination

Important to interpreting the data associated with the benefits and risks of this study is the fact that with the introduction of the aDBS feature, there are no modifications to the existing PD indications, the contraindications, the PD patient population, the disease state, the DBS surgical procedure, the underlying medical condition, the symptoms of PD that are already indicated, or the brain targets already approved for

DBS therapy for PD. The intended purpose of the aDBS feature is to be an optional tool for the clinician to use to automatically increment and decrement stimulation amplitude within the clinician-specified range based on the PD patient's LFPs (Alpha-Beta). DBS therapy itself is not changing with the aDBS feature and the clinical data provided in previous submissions under P960009 in support of the PD indications with cDBS is still applicable in support of the Percept system with aDBS. While the automatic adjustment of stimulation amplitude is new with aDBS, the stimulation waveform itself is unchanged. Like the patient control limits, aDBS always stays between clinician-defined upper and lower stimulation limits.

Benefits

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

In carefully screened and selected subjects, the trial has shown that patients may receive benefit from aDBS as a programming option. aDBS achieved a performance level no worse than -2 hours per day of "Good on Time" without troublesome dyskinesia as compared to cDBS for some PD patients, offering an alternative DBS programming option. A margin of -2 hours per day demonstrates that, while aDBS may not be as effective in "On" time without troublesome dyskinesia (GOT) as cDBS on the per-patient level, most patients who entered the long-term follow-up Phase as demonstrated by patient preference and patient satisfaction questionnaires collected in the Long-Term follow-up phase of the study decided to continue with aDBS. Due to the many limitations associated with the study (**Section XIV.E**), the study results preclude a definitive conclusion regarding the effectiveness of aDBS over cDBS. However, it provides adequate effectiveness data to show that some carefully selected patients may benefit from aDBS as a new programming option for select PD patients.

Risks

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The overall safety profile observed in this study is consistent with earlier studies described in Section VIII of this summary.

Most of the stimulation-related events resolved (142, 95.3%) at the time of the database snapshot date of December 15, 2023. Reprogramming, switching modes, or temporarily pausing aDBS therapy (i.e., reverting to a fixed cDBS level programmed by the clinician) resolved most stimulation related events.

Additional factors

There are potential subpopulations of PD patients who could benefit from aDBS programming feature. Based on ADAPT-PD trial, the specific characteristics of this subpopulation who may benefit from this new programming feature is unclear. However, adequate mitigation strategies can be implemented for patient selection for aDBS programming, monitoring, and management of potential stimulation-related adverse events. Device labeling is implemented to implement these mitigations. Some of these include:

- An important feature of the device software when applying aDBS as a programming option is that the patient programmer can be used by patients to "pause" their aDBS therapy if they experience undesirable stimulation-related side effects or inadequate symptom control. When aDBS is paused, therapy reverts to a fixed cDBS level programmed by the clinician.

- Clinicians may consider aDBS as a programming option after careful patient selection, allocating sufficient time during the initial aDBS set up and adjustment session to ensure optimal programming, based on ADAPT-PD experience.

- Ensuring patients have regular follow up visits to monitor response to therapy, optimize programming, and manage any stimulation-related side effects promptly, especially within aDBS adjustment and set up periods (at least within the first two months of aDBS programming).

- Providing patients with prompt access to unscheduled visits to address any unexpected complications or stimulation-related adverse events. This availability is crucial given that over 55% of patients experienced such events on aDBS during the aDBS Setup and Adjustment Phase (in the first few months) in the ADAPT-PD trial. Once stimulation adjustments were complete the number of unscheduled visits for stimulation-related AEs decreased.

- Clinicians and patients should be aware that despite the attempt to set up aDBS programming and adjustment sessions, some patients may experience intolerable adverse event or unfavorable responses compared to cDBS, requiring discontinuation of aDBS therapy.

- Clinicians should educate patients and caregivers thoroughly about the potential risks and benefits of aDBS and how to manage potential stimulation-related adverse events as a result of over stimulation or under stimulation on aDBS modes.

Patient Perspective

Patient perspectives considered during the review included patient preferences when entering the long-term study and patient satisfaction at the end of the study.

In conclusion, given the available information above, the data support that for aDBS feature as a programming option, the probable benefits outweigh the probable risks with risk mitigation strategies.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness, for carefully selected patients, of the aDBS feature as a programming option for PD patients when used in accordance with the indications for use and labeling. The effectiveness data demonstrated that aDBS achieved a level of acceptable therapeutic function in a significant proportion of subjects and patient preference and satisfaction were extremely strong in favor of aDBS. The safety analysis did not reveal any death, suicide, or severe adverse event related to aDBS and the overall safety profile observed in this study is consistent with earlier studies described in Section VIII of this summary. An important consideration is that patients will always have the ability to pause aDBS therapy and return to cDBS if they feel that they are not receiving adequate benefit or experiencing increased side effects from aDBS.

E. Limitations of the Study

When interpreting the results of this study the following study limitations were considered:

- Subjects enrolled in the study were already implanted with a Percept PC neurostimulator, were required to be stable on their PD medications, and in the opinion of the investigator, were responders to cDBS Therapy. Baseline assessments, including VHI, MDS-UPDRS, EQ-5D-5L, PDSS-2, PDQ-39, showed that subjects were well-controlled with minimal to moderate PD-related symptoms and quality of life.

- This study was open label between cDBS and aDBS, i.e., all subjects knew whether or not they received aDBS. Randomized, double blind trials are considered the 'gold-standard' for judging the benefits of a treatment. Open label studies can cause an overestimation of the treatment effect in investigator and subject ratings. Also, the open-label study design does not allow for characterization of the extent or duration of potentially confounding effects which may be associated with the assignment of experimental aDBS treatment, such as placebo effect or regression to the mean, that could contribute significantly or in part to the observed therapeutic effects of aDBS. Additionally, the effectiveness of aDBS mode was assessed using a within-subject comparison between cDBS mode and aDBS mode; for all subjects, cDBS mode was evaluated before aDBS

mode. Thus, resulting treatment effects may be confounded by period and carryover effects which cannot be probed statistically due to the study's design.

- Subjects were carefully screened during the Screening and aDBS Setup and Adjustment phase for the "acceptability" of one or both of the aDBS modes prior to the study endpoint evaluation phase. The study endpoint evaluation cohort consisted of subjects who had already passed the aDBS LFP screening, had tolerance of aDBS, and for whom aDBS was determined "Acceptable" compared to cDBS in terms of efficacy and side-effects using a modified clinician Global Impression of Change (GIC) scale. In particular, the primary analysis of Single- and Dual-Threshold aDBS mode effectiveness relative to cDBS excludes (respectively) 8 of 43 (18.6%) and 6 of 46 (13.0%) of patients who attempted treatment with that mode during a trial and adjustment period lasting up to 60-days but found it "unacceptable" in terms of efficacy and/or tolerability relative to cDBS. Thus, the study results reflect those of carefully screened subjects and not all study enrolled subjects, but may overestimate the proportion of patients for whom an aDBS mode performs similarly to cDBS in the overall population of patients who attempt treatment with that mode.

- The patient-specific success threshold for these binary success/failure endpoints was revised post-hoc due to potential for type-I error inflation associated with formal statistical comparisons of the success rate derived from these endpoints (as they were originally defined) with a 50% performance goal. For each aDBS mode, a subject was considered a primary endpoint "success" when their daily average hours of "On" time without troublesome dyskinesia (based on the Parkinson's Disease Home Diary) during that mode's aDBS Evaluation Period exceeds their daily average hours of "On" time without troublesome dyskinesia during the cDBS Baseline Phase minus 2 hours. A margin of -2 hours per day acknowledges that, while the new treatment may not be as effective in "On" time without troublesome dyskinesia (GOT) as the comparator on the per-patient level, it could still offer an improvement for the patient on a different endpoint, or still be a patient preference.

- The study did not explicitly control for physicians who may have pre-screened subjects for LFP signal before the enrollment visit. This may have underestimated study drop-out and screening failure rates or may have biased estimates of how many patients may be suitable for aDBS based on a detectable LFP signal. Another consideration is that LFP detection rate or estimate of number of subjects that may be eligible for aDBS may be underestimated because the sample was a majority of patients who had legacy leads rather than SenSight leads that were designed for sensing LFP signals.

- Missing data may affect the accuracy of the results obtained in a clinical study. Subjects who are receiving little or no benefit from a treatment may be more likely to discontinue their participation during the course of the study which may

skew later results favorably from what would have been observed if all subjects were included.

- Given the limited sample size, this study was not intended to establish aDBS as an overall superior therapy, but rather to demonstrate the safety and efficacy relative to standard cDBS (a performance level no worse than -2 hours per day of "Good on Time" without troublesome dyskinesia as compared to cDBS) in and out-of-the-clinic.

- The aDBS Evaluation Phase was limited to 30 days per mode to enable a feasible duration for therapy effects to be realized. To bolster the limited evaluation period, a Long-Term Follow-up and Extended Access Phases were incorporated into the design where subjects could choose the aDBS mode that they preferred or had the most benefit from and be followed for at least a year on aDBS.

XV. CDRH DECISION

CDRH issued an approval order on February 20, 2025.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

1. Stanslaski, S., Summers, R.L.S., Tonder, L. et al. Sensing data and methodology from the Adaptive DBS Algorithm for Personalized Therapy in Parkinson's Disease (ADAPT-PD) clinical trial. npj Parkinsons Dis. 10, 174 (2024). https://doi.org/10.1038/s41531-024-00772-5. Figure reuse via open access: https://creativecommons.org/licenses/by/4.0/

2. Ahlskog J, Muenter M. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Movement disorders : official journal of the Movement Disorder Society*. 2001;16(3):448-458. doi:10.1002/mds.1090

3. Lee D, Dallapiazza R, Vloo PD, Lozano A. Current surgical treatments for Parkinson's disease and potential therapeutic targets. Neural regeneration research. 2018;13(8):1342-

1345. doi:10.4103/1673-5374.235220

4. Martinez-Fernandez R, Pineda-Pardo J. Magnetic resonance-guided focused ultrasound for movement disorders: clinical and neuroimaging advances. Current opinion in neurology. 2020;33(4):488-497. doi:10.1097/WCO.0000000000000840

5. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Movement Disorders. 2018;33(8):1248-1266. doi:10.1002/mds.27372

6. Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. Acta neurologica Scandinavica. 2017;136(5):378-385. doi:10.1111/ane.12733

7. Pessoa R, Moro A, Munhoz R, HAG T, Lees A. Apomorphine in the treatment of Parkinson's disease: a review. Arquivos de neuro-psiquiatria. 2018;76(12):840-848. doi:10.1590/0004- 282X20180140

8. Wirdefeldt K, Odin P, Nyholm D. Levodopa–Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. CNS Drugs. 2016;30(5):381-404. doi:10.1007/s40263-016-0336-5