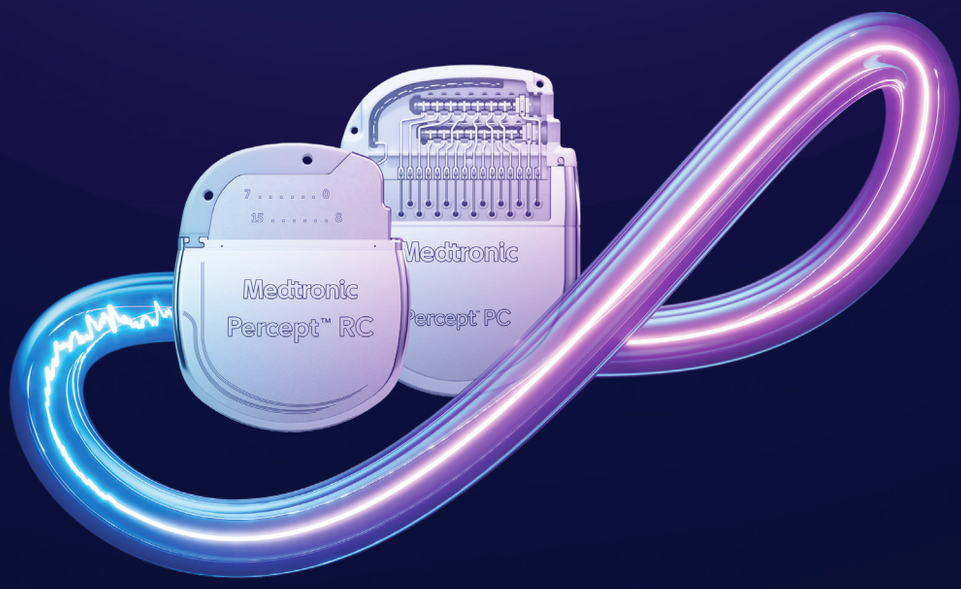
Medtronic

# BrainSense™ Adaptive DBS (aDBS)

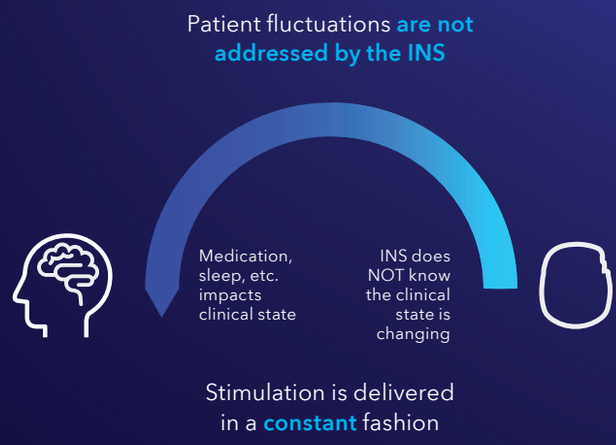
## ADAPT-PD clinical trial overview



# Managing the symptoms of Parkinson's disease can be complex.[1,2]

## Open-loop cDBS therapy

While open-loop DBS therapy – also called continuous DBS (cDBS) – is a proven therapy for treating symptoms of Parkinson's disease (tremor, bradykinesia, rigidity), patients may continue to exhibit fluctuations in their motor symptoms.[1,3,4]

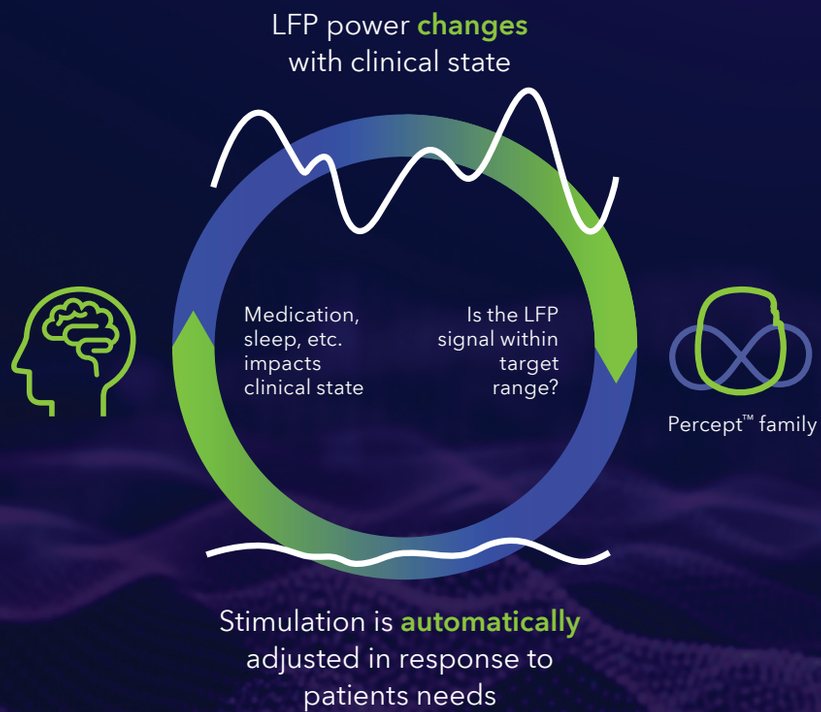



# Percept™ family with BrainSense™ aDBS†,‡ the only closed-loop DBS system

## BrainSense™ aDBS closed-loop therapy

### Addressing motor symptom fluctuations of Parkinson's disease

BrainSense™ aDBS continuously adapts to a patient's unique neurophysiological signals, allowing for a more personalized therapy throughout the day.




† The sensing feature of the Percept™ PC system and Percept™ RC system is intended for use in patients receiving DBS where chronically-recorded bioelectric data may provide useful, objective information regarding patient clinical status.

‡ aDBS is only approved for patients with Parkinson's disease.

# How does it work

BrainSense™ aDBS automates a patient's stimulation therapy within clinician-defined parameters, including minimum and maximum stimulation amplitude limits, and local field potential (LFP) thresholds.

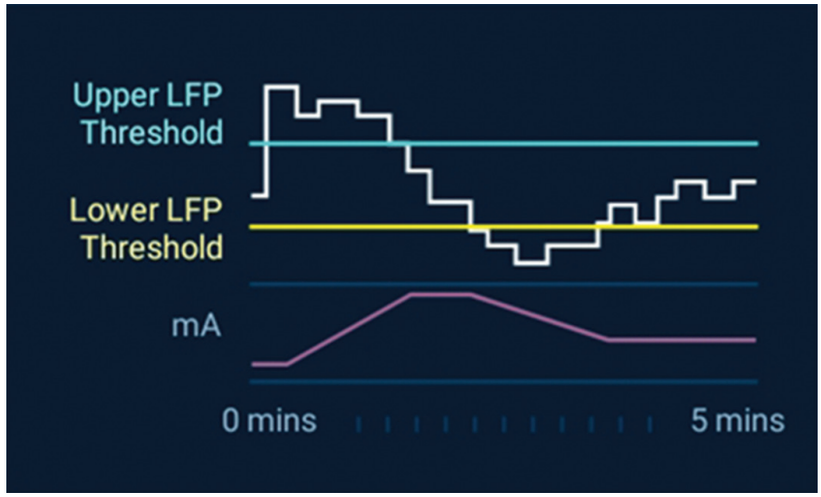
# Choose between two threshold modes

To help further personalize your patient's DBS therapy, BrainSense™ aDBS uses an automated algorithm that can be powered by two threshold modes: single threshold mode or dual threshold mode.

The neurostimulator responds to patient needs with varied stimulation based on your selected mode of either single or dual threshold mode.

**Dual threshold**

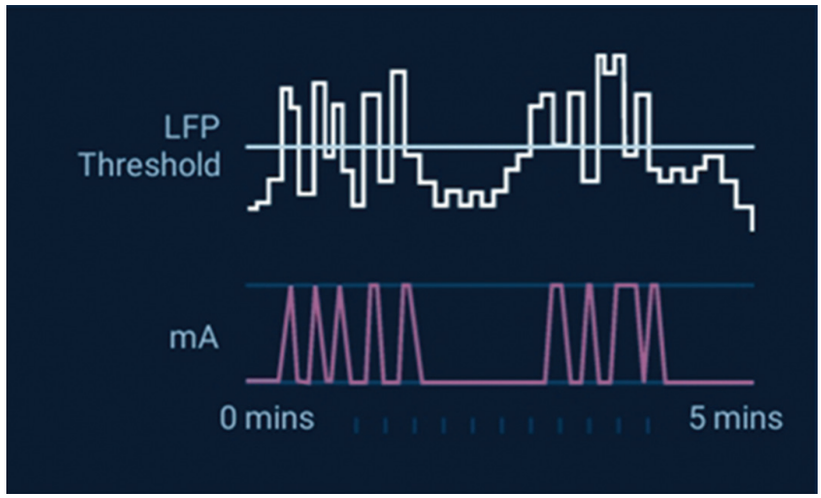
Slower (minutes) adaptation of therapy




Setting two thresholds

**Single threshold**

Rapid (milliseconds) adaptation of therapy




Setting one threshold

# Breaking new ground in Parkinson's disease research

## ADAPT-PD clinical trial

The ADAPT-PD clinical trial's intent was to determine safety and effectiveness of the adaptive feature within a clinical workflow and with the practicality and efficiency desired by clinicians managing Parkinson's disease.

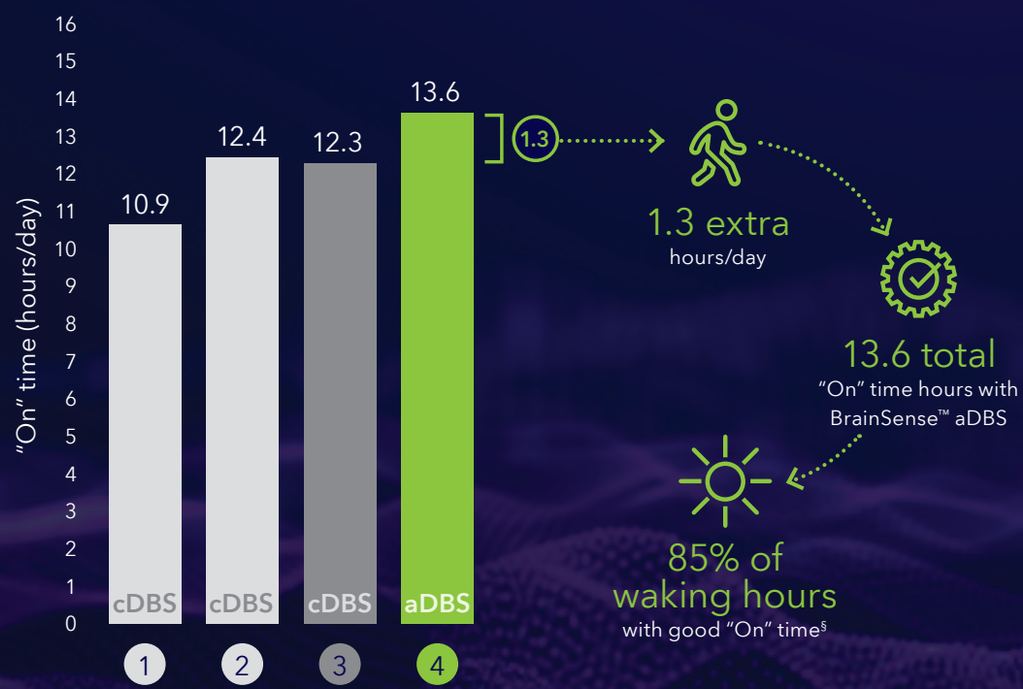
Additionally, the trial helped to inform the overall user experience and workflow optimization to simplify BrainSense™ aDBS programming.

ADAPT-PD clinical trial is the **first** to study:

- **Chronic aDBS study** (>1 year)
- **aDBS in subthalamic nucleus (STN) & internal globus pallidus (GPi)**
- **Comparison of two aDBS modes** (single and dual thresholds)
- **aDBS with directional stimulation**

**ADAPT-PD trial: comparable cDBS efficacy to two previous randomized control trials**
**+ an increase, on average, in "On" time compared to cDBS**

### Historical view of "On" time without troublesome dyskinesia†,‡,3,4




1. Weaver et al., 2009 (N = 121) compared best medical therapy to cDBS at 6 mo follow-up postoperatively
2. Schuepbach et al., 2013 (N = 105) compared best medical therapy to cDBS at 24 mo
3. Medtronic cDBS ADAPT-PD (n = 40) Prospective open-label, outcomes at 1 mo
4. Medtronic aDBS ADAPT-PD in Dual Threshold Mode (n = 40) Prospective open-label, outcomes at 1 mo

† Study sizes, designs, and populations vary. Patients in the Medtronic ADAPT-PD study were previously implanted and on stable cDBS. Patients in other studies were newly implanted. The figure legend provides additional study details.

‡ Compared to continuous DBS (cDBS). Results presented for dual threshold aDBS. n = 40. Based on results from an open-label trial.

§ 16 hours. Study data in 45 patients, 40 patients evaluated on Dual Threshold mode.

0.6 hours/day more "On" time without troublesome dyskinesias with single threshold (n = 35)

# BrainSense™ aDBS means patients living with Parkinson's have more ways to manage their symptoms

**98%** preferred BrainSense™ Adaptive DBS over traditional DBS after using for 30 days†

### Common reasons for preferring aDBS compared to cDBS

66%
Address symptom fluctuations

63%
Improving motor symptoms

45%
Manage side effects

**While aDBS was preferred over cDBS, no clear preference for one mode was reported by patients:** 11 (39.3%) preferred Dual Threshold mode, 10 (35.7%) preferred Single Threshold mode, 6 (21.4%) had no preference, and one 'didn't know'.

# aDBS is safe

The safety profile observed with aDBS is consistent with cDBS

- Of all adverse events collected during the ADAPT-PD trial, 30% (155 events) were related to aDBS.
- Falls were commonly reported, but 93% deemed unrelated to aDBS and determined to be related to Parkinson's disease as rates matched published literature.

As with initial cDBS programming, stimulation-related adverse events are expected during aDBS initial setup.

- In the ADAPT-PD trial, stimulation-related adverse events occurred during the aDBS Set-up and Adjustment phase, with most events categorized as worsening of PD cardinal symptoms (35% of events), as would be expected when modifying DBS settings.

Stimulation-related events are expected to resolve with reprogramming and it's important to ensure patients have regular follow up visits to optimize programming. aDBS is an optional programming feature and may not work for everyone.

- In the ADAPT-PD trial, all but one stimulation-related event resolved with reprogramming during the aDBS Set-up and Adjustment phase.

### Stimulation-related events (subjects, % of subjects)

| Study phase | Enrollment through cDBS baseline phase (N = 85, ~1mo) | aDBS setup and adjustment phase (N = 70, ~2mo) | aDBS evaluation phase (N = 60, 1mo) | Long-term follow-up phase (N = 59, 10mo) | Extended access phase (N = 54, 5.5mo) |
|---|---|---|---|---|---|
| All events (155) | 4 (4, 4.7%) | 75 (39, 55.7%) | 23 (17, 28.3%) | 24 (17, 28.8%) | 29 (15, 27.8%) |
| #Subjects with event/month | 4 | 19.5 | 17 | 1.7 | 2.7 |

† Data from 45 patients who were previous stable on traditional DBS (cDBS).

# **A**daptive **D**BS **A**lgorithm for **P**ersonalized **T**herapy in **P**arkinson's **D**isease (ADAPT-PD) Trial

## Conclusions

**The ADAPT-PD clinical trial demonstrated that aDBS (Single and Dual Threshold modes) is effective relative to cDBS as an optional programming feature to be used with legacy or SenSight™ leads implanted in the STN or GPi targets.**

## Objectives

- While the feasibility of aDBS in a naturalistic environment has been demonstrated,[5] aDBS had not been validated as safe and effective, studied in the GPi, administered chronically (~1 year), nor made clinically available outside of Japan.
- The ADAPT-PD clinical trial was designed to address these gaps in understanding and to seek commercial approval of the adaptive feature.

### Primary endpoint

To meet the primary objective, at least 50% of participants for each aDBS mode must have met the primary success criteria - no worse than 2 hours/day less of "On" time without troublesome dyskinesia (i.e. Good "On" Time) during aDBS compared to cDBS. "On" time was based on a self-reported motor diary completed by participants every 30 minutes over 24 hours on at least 3 consecutive days prior to the evalution visit.

### Secondary endpoint: energy delivered

To demonstrate reduced total electrical energy delivered (TEED) during aDBS compared to cDBS.

### Safety and additional objectives

Stimulation-related AEs, AEs, and device deficiencies. Wearable device data, Voice Handicap Index, MDS-UPDRS, EQ-5D-5L, PDSS-2, PDQ-39, and patient preference and satisfaction.

## Methods

### Study purpose and design

- The ADAPT-PD clinical trial aimed to demonstrate the safety and effectiveness of chronic dual and single threshold aDBS in patients with Parkinson's disease (PD).
- Multicenter, prospective, randomized single-blind crossover (between dual and single threshold modes of aDBS) with open-label comparison between aDBS and cDBS. All patients were implanted with Medtronic Percept™ PC.

### Notable inclusion criteria

- Stable STN or GPi DBS and medication therapy for PD.
- Patient is responsive to DBS.
- LFP peak power amplitude ≥1.2 µVp in the Alpha-Beta band on left and/or right DBS leads. (This peak amplitude is recommended for aDBS.)

## ADAPT-PD study phases

1. **cDBS baseline phase (gold):** 30-day evaluation on stable cDBS settings
2. **aDBS setup and adjustment phase (green):** up to 60-day programming on both modes
3. **aDBS evaluation phase (blue):** 30-day evaluation in one or both aDBS modes (if both deemed acceptable)
4. **Long-term follow-up phase (yellow):** ~10 months of aDBS in the mode selected by the patient

# ADAPT-PD study design[6]

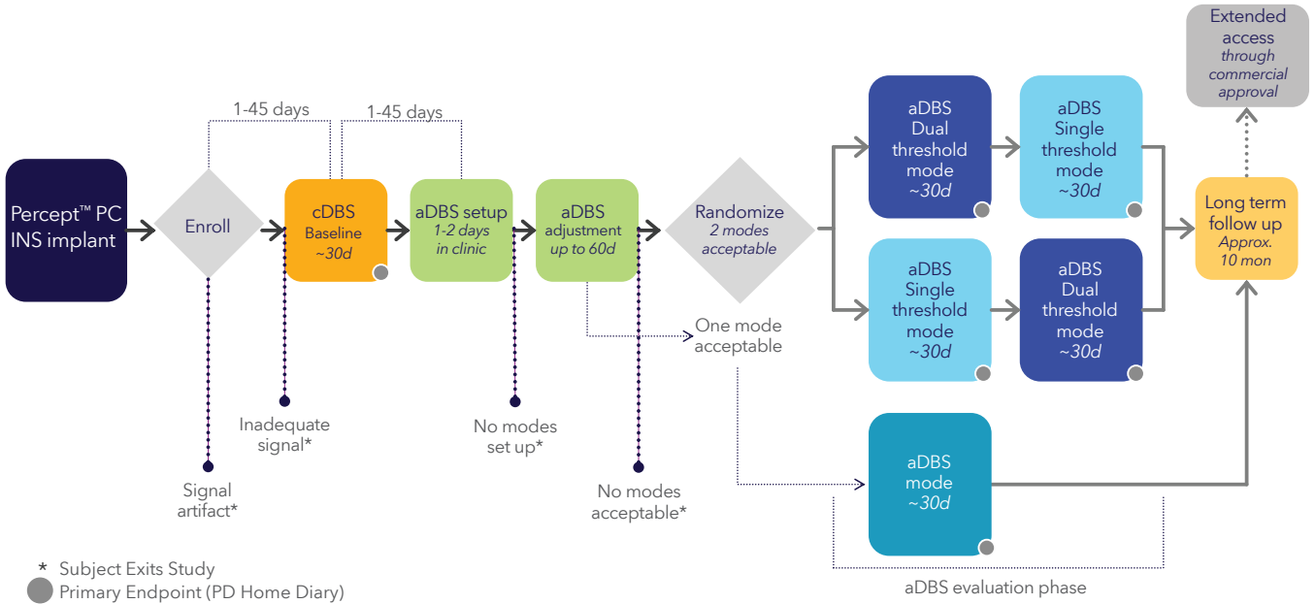



Figure from Stanslaski et al., 2024. https://doi.org/10.1038/s41531-024-00772-5.

# Commercial workflow

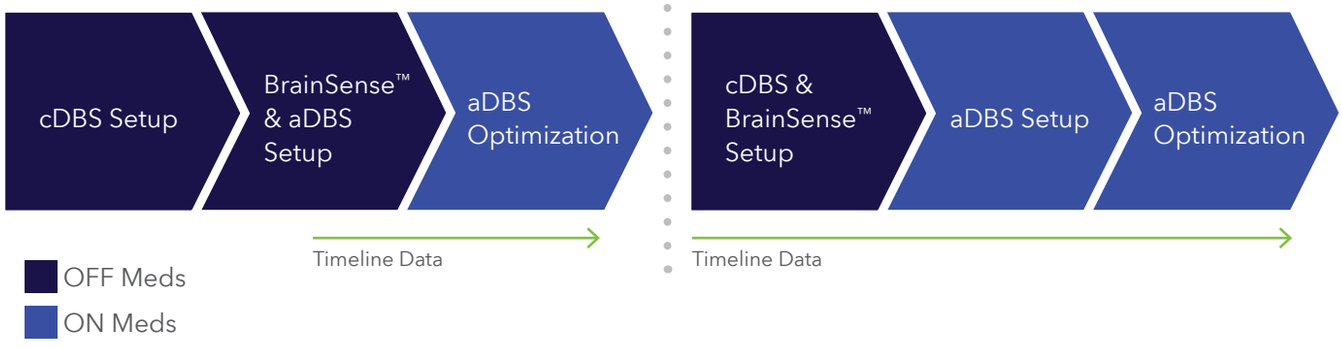
**Leveraging lessons from the ADAPT-PD study to drive efficient, successful aDBS setups**

## ADAPT-PD

- aDBS Setup was **based primarily on in-office exam**.
- The study protocol required deviation from the typical DBS programming workflow adding time, visits, and necessity to go 'OFF' Medication.
- The average number of visits to program BOTH aDBS modes was 4.1 +/- 2.2 visits (Visits include setting up aDBS modes and follow-up visits).[9]

## Commercial workflow

- aDBS can be set up **based on both in-clinic and chronic data** from the start (as it was in the adjustment phases of the study)
- No extra 'OFF' Med visits beyond standard-of-care initial programming visit are needed for aDBS Setup.



# Results

## Participants

68 participants enrolled in the trial with 45 entering the aDBS evaluation phase (30 randomized to both aDBS modes). After the evaluation phase 44/45 participants chose to remain on aDBS and entered the long-term follow-up phase.

### Baseline characteristics of study population

| Characteristic | Mean ± standard deviation |
|---|---|
| Age - yr (n = 66) (range) | 62.2 ± 8.4 (36 – 75) |
| PD duration - yr (n = 64) | 13.5 ± 6.8 |
| Dyskinesia - yr (n = 37) | 6.9 ± 4.8 |
| Motor fluctuations - yr (n = 46) | 7.6 ± 4.6 |
| Duration of levodopa treatment – yr (n = 60) | 10.7 ± 6.1 |
| Levodopa equivalent daily dose - mg | 561.9 ± 568.3 |
| Sex - no. (%) | |
| Male | 48 (70.6%) |
| Female | 20 (29.4%) |
| Target site by participant - no. (%) | |
| STN | 51 (75.0%) |
| GPi | 17 (25.0%) |
| Years from the lead implant to consent | 3.4 ± 3.3 |
| MDS-UPDRS part III (Off stim/Off meds) (n = 58) | 45.7 (14.9) |
| Tremor | 8.8 (6.4) |
| Rigidity | 8.3 (3.6) |
| Bradykinesia | 22.9 (8.3) |
| Axial | 5.6 (3.0) |

Primary Cohort Consented N = 68. On and off medication examination completed at enrollment and screening visits.

## aDBS is feasible and tolerable

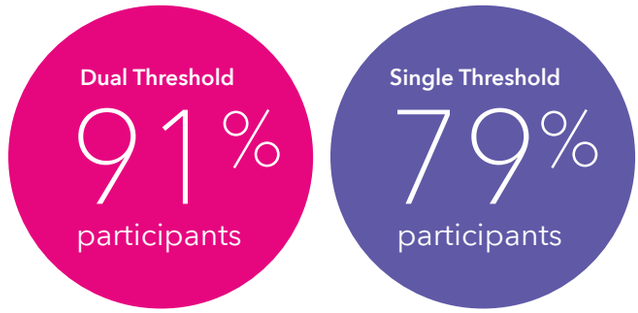
- LFP signal present to set up aDBS in 85% (57/68) of patients at enrollment
- aDBS tolerable and successfully set up in 87% (45/52) of patients

## aDBS is effective

**Primary objective met: Effectiveness**

Dual Threshold aDBS proportion of success was 91% (n = 40); and Single Threshold aDBS proportion of success was 78.9% (n = 35).

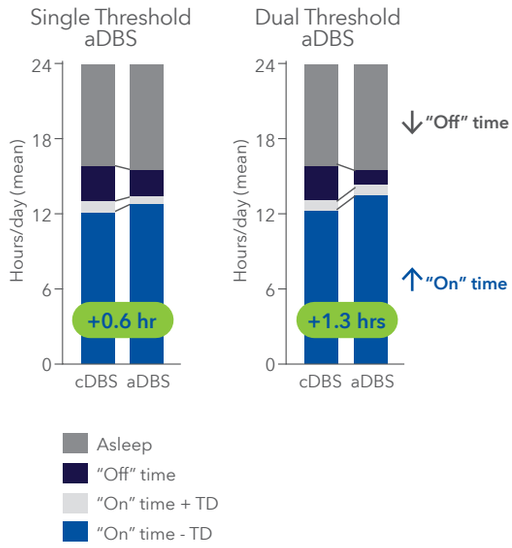
**Primary endpoint success criteria: No worse than -2 hour loss of "On" time without troublesome dyskinesia during aDBS relative to cDBS**



## Motor diary data

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. The mean change in "On" time without troublesome dyskinesias (+0.6 hrs/day) and mean reduction in "Off" time (-0.7 hrs/day) were not clinically significant for the Single Threshold mode.

**Change in motor diary**



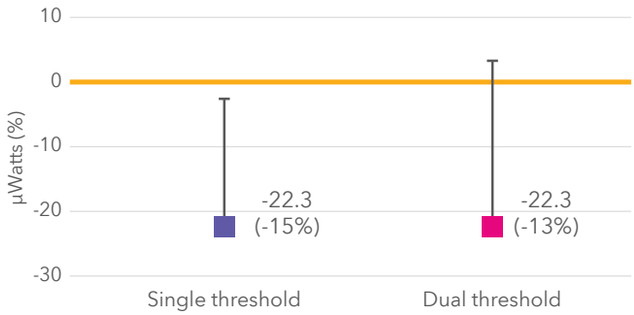

Motor diary data at baseline continuous deep brain stimulation (cDBS) and adaptive deep brain stimulation (aDBS). Change in diary data listed by hour. Note: changes >1 hour are clinically meaningful.[7,8]
TD = troublesome dyskinesia

## aDBS impact on energy and battery

**Secondary objective met: Total electrical energy delivered (TEED)**

Total energy delivered during aDBS compared to cDBS demonstrated a mean decrease of 22.3 (SE: 8.37) µWatts during Single Threshold aDBS and 22.3 (SE: 10.98) µWatts during Dual Threhold aDBS.

**Change in TEED**




- Patients programmed in Dual Threshold mode showed a median aDBS longevity improvement of 5%/year vs cDBS.
- Patients programmed in Single Threshold mode showed a median aDBS longevity reduction of -4%/year vs cDBS.

## Study limitations

1. **Not an RCT:** The comparison between cDBS and aDBS was not blinded or randomized and Medtronic cannot conclude superiority of aDBS over cDBS.
2. **Modest sample size:** While 30 patients were able to be programmed in both modes, an additional 15 patients were set up to one mode. Therefore, 45 patients contributed to the primary outcome calculation.
3. **Drop outs:** 34% (N=23) drop out before aDBS evaluation largely due to screening criteria and personal reasons.
4. **Some physicians pre-screened:** a few centers reported pre-screening for an LFP signal meeting inclusion criteria prior to consent.

## References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6. 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. Licensed under CC BY 4.0: https://creativecommons.org/licenses/by/4.0/
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9. Data on file, Medtronic.


**For scientific conversations regarding the ADAPT-PD results, please contact Medical Affairs at rs.neuromedicalaffairs@medtronic.com.**

# Brief Statement: Medtronic DBS Therapy for Parkinson's Disease

**Product labeling must be reviewed prior to use for detailed disclosure of risks.**

**INDICATIONS:**
**Medtronic DBS Therapy for Parkinson's Disease:** 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.

**CONTRAINDICATIONS:** Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if the patient has an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

**WARNINGS:** There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths and a potential risk to drive tremor (cause tremor to occur at the same frequency as the programmed frequency) using low frequency settings. Extreme care should be used with lead implantation in patients with an increased risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as implanted cardiac devices (e.g., pacemaker, defibrillator), external defibrillation/cardioversion, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious and permanent injury including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Abrupt cessation of stimulation should be avoided as it may cause a return of disease symptoms, in some cases with intensity greater than was experienced prior to system implant ("rebound" effect). New onset or worsening depression, suicidal ideations, suicide attempts, and suicide have been reported.

Patients should avoid activities that may put undue stress on the implanted components of the neurostimulation system. Activities that include sudden, excessive or repetitive bending, twisting, or stretching can cause component fracture or dislodgement that may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component. Patients should avoid manipulating the implanted system components or burr hole site as this can result in component damage, lead dislodgement, skin erosion, or stimulation at the implant site. Patients should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA) as this could damage the neurostimulation system, before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their clinician. Patients using a rechargeable neurostimulator must not place the recharger over a medical device with which it is not compatible (eg, other neurostimulators, pacemaker, defibrillator, insulin pump). The recharger could accidentally change the operation of the medical device, which could result in a medical emergency. Patients should not use the recharger on an unhealed wound as the recharger system is not sterile and contact with the wound may cause an infection.

**PRECAUTIONS:** Loss of coordination in activities such as swimming may occur. Patients using a rechargeable neurostimulator for Parkinson's disease should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist.

**ADVERSE EVENTS:** Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy and weight gain or loss.

Safety and effectiveness has not been established for patients with neurological disease other than idiopathic Parkinson's disease, previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, patients who are pregnant, or patients under 18 years.

USA Rx only Rev 10/24

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