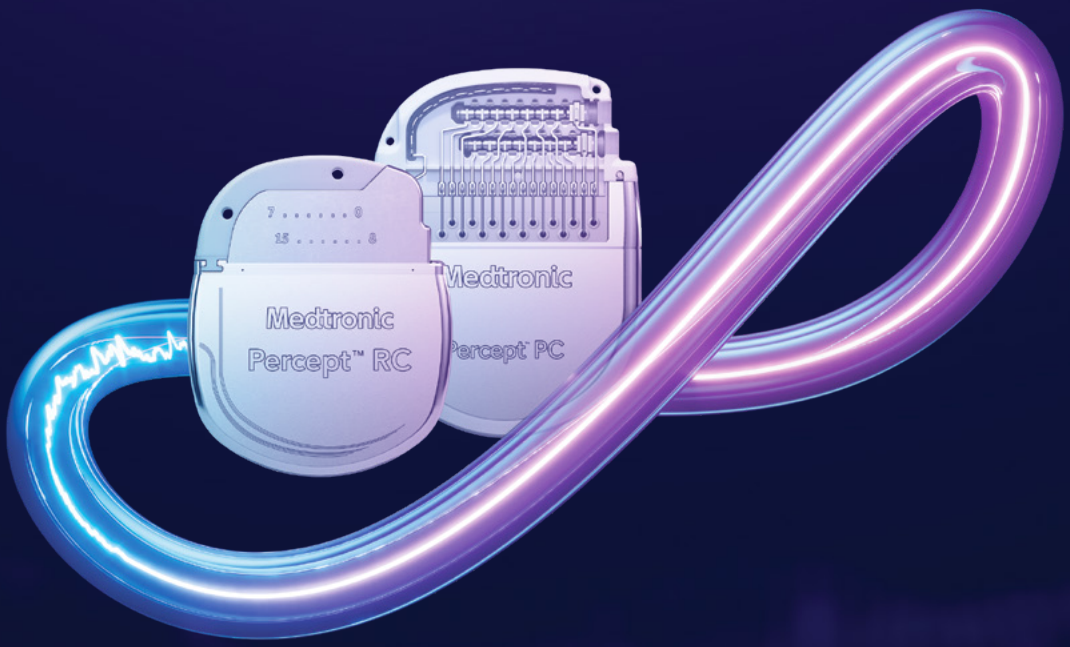
Medtronic

BrainSense™ Adaptive DBS (aDBS)

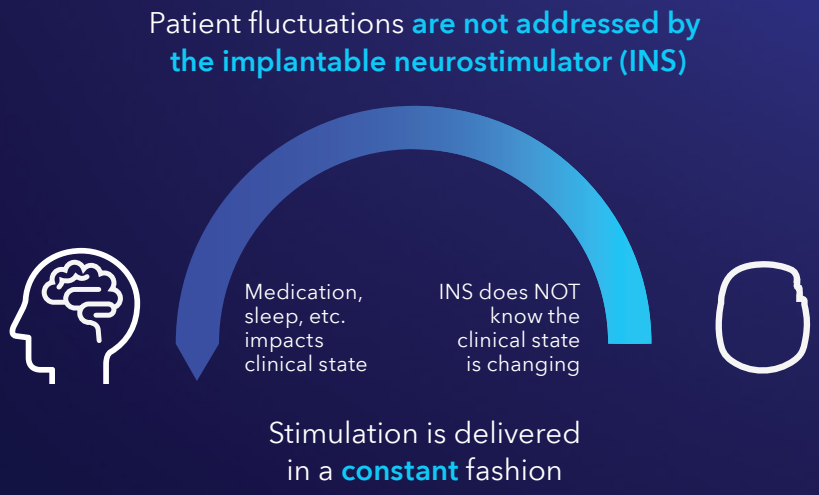
ADAPT-PD clinical trial overview



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.[1,3-5]

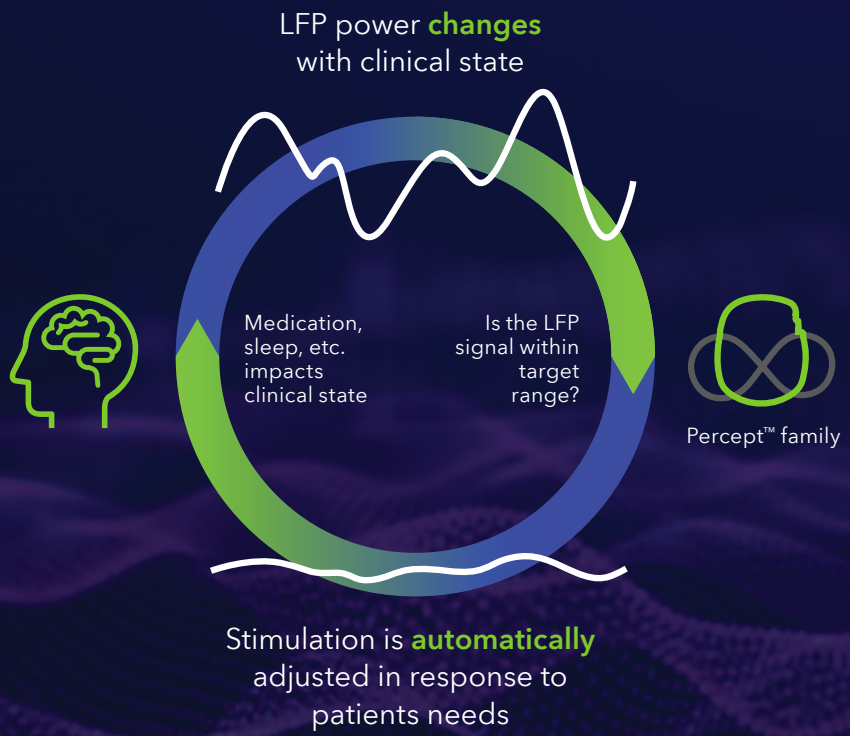


Percept™ family with BrainSense™ aDBS†,‡ the only closed-loop DBS system available

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.

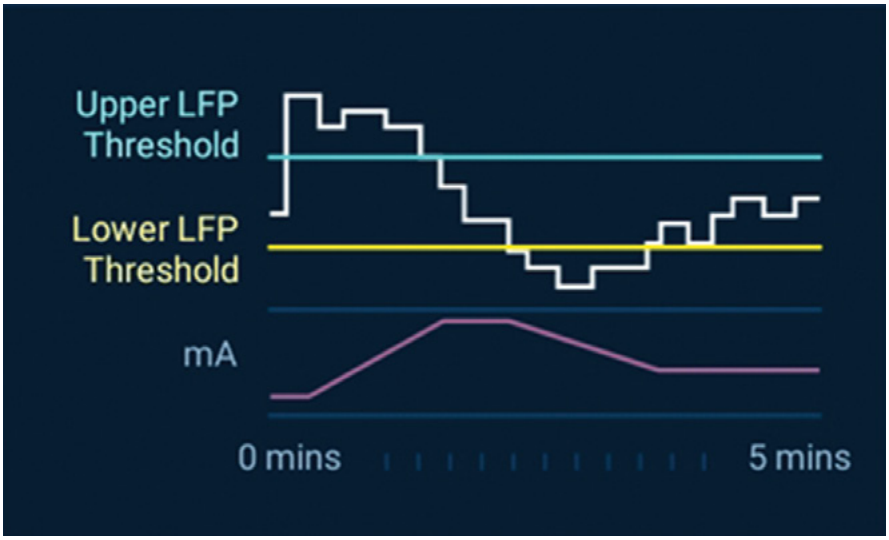
Choose between two threshold modes

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

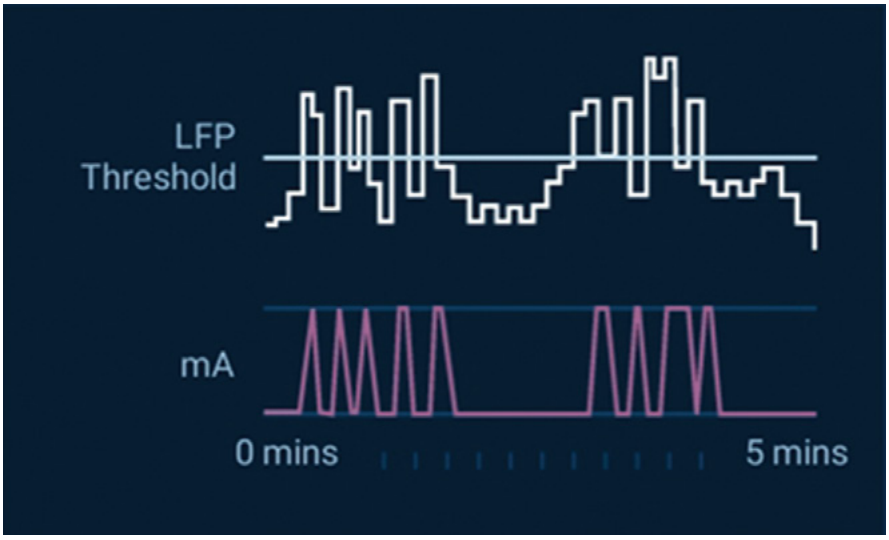
Slower (minutes) adaptation of therapy



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[6]

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.

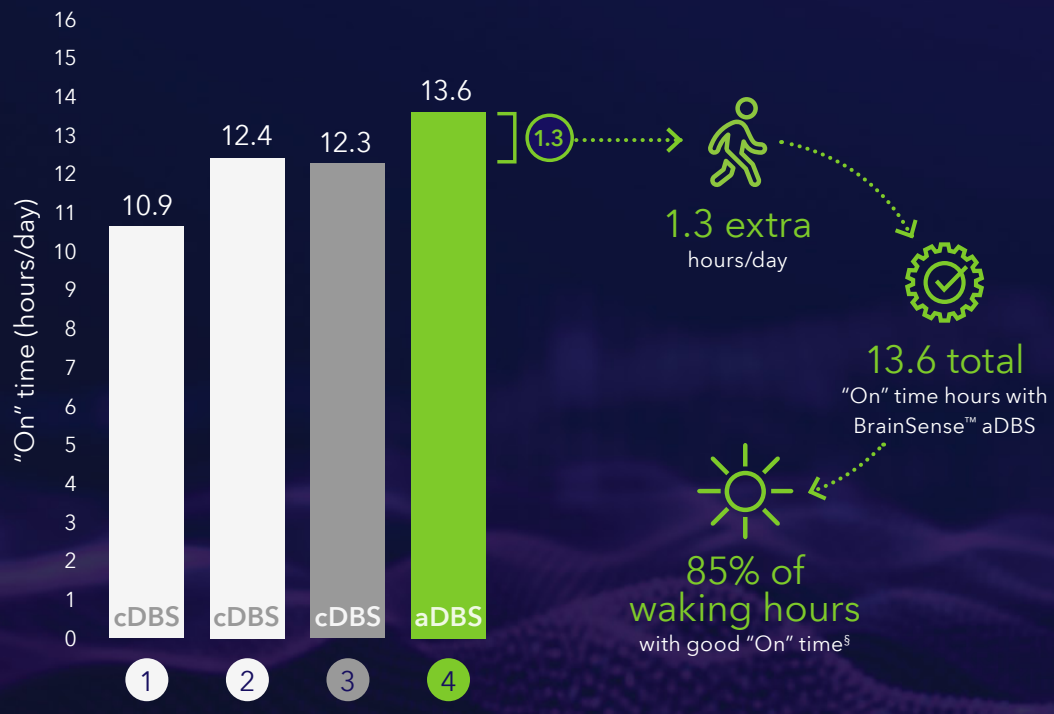
Additionally, the trial helped to inform the overall user experience and workflow optimization to simplify BrainSense™ aDBS programming.

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†,6

Common reasons for preferring aDBS compared to cDBS‡,11

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'.§,7

aDBS is safe◊,6

- As with cDBS, stimulation-related adverse events (AEs) are expected during initial aDBS setup.
- All but one stimulation-related AEs resolved with reprogramming in the aDBS setup and adjustment phase (insomnia).
- Similar safety profiles between single and dual threshold.
- Stimulation-related adverse events occurred at a higher rate during aDBS Set-up and Adjustment Phase, with events largely categorized as worsening of PD symptoms (n = 12, 22.6% of patients) and dyskinesias (n = 13, 24.5% of patients) as would be expected when modifying DBS settings.

aDBS Evaluation Phase

Stimulation-related AEs during the aDBS Evaluation Phase are presented below. All stimulation-related events were resolved during the aDBS evaluation phase. Additionally, no unexpected serious or adverse device events were reported, and no subject deaths were reported. Overall, the safety profile observed in this study for aDBS is consistent with those described in cDBS.

aDBS Evaluation Phase AEs

aDBS Mode		
Stimulation-related AEs	**Single Threshold (N = 35)**	**Dual Threshold (N = 40)**
17 events	11 events	6 events
(13 subjects/45)	(8 [22.9%] subjects)	(5 [12.5%] subjects)
None serious	None serious	None serious

aDBS Setup and adjustment phase

All but one stimulation-related adverse event resolved with reprogramming.

Enrollment through long-term follow-up

No serious adverse device events (N= 44)

† Data from 45 patients (primary cohort) who were previous stable on traditional DBS (cDBS).
‡ Results based on the complete case set of the primary cohort, Single threshold, n=33. Dual threshold, n=40.
§ Results based on the all randomized set minus the subject who missed Visit 2 and did not complete the questionnaires, n=28
◊ Data from the Primary cohort

Adaptive **D**BS **A**lgorithm for **P**ersonalized **T**herapy in **P**arkinson's **D**isease (ADAPT-PD) Trial[6]

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,[8] 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 evaluation 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 with moderate to advanced PD and who is responsive to DBS.
- LFP peak power amplitude ≥1.2 µVp in the Alpha-Beta band (8-30 Hz) 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[9]

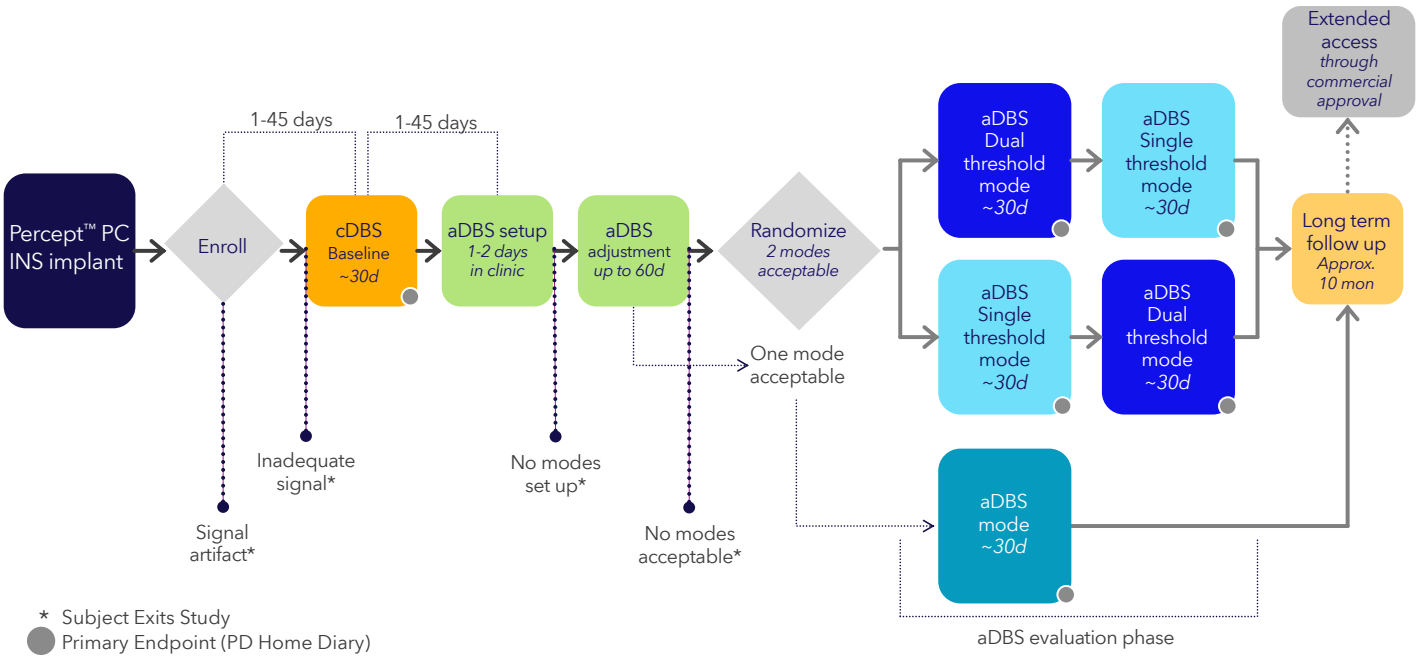


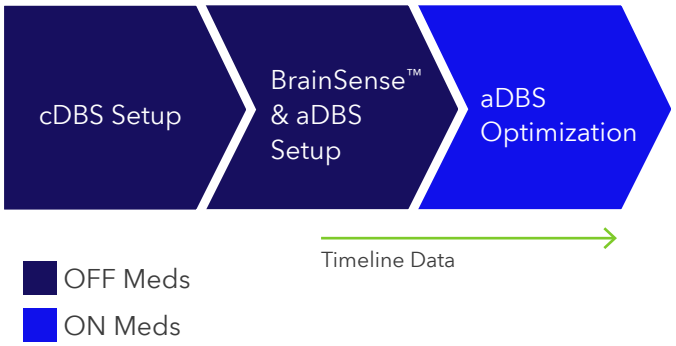
Figure from Stanslaski et al., 2024. https://doi.org/10.1038/s41531-024-00772-5.

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.



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 primary cohort of the trial, receiving non-directional stimulation from legacy leads, or from SenSight™ leads set to ring mode. 17 additional participants enrolled in the directional cohort, receiving directional stimulation from SenSight™ leads. Here results from this primary cohort are presented. 45 participants entered 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. (%) (n=68)	
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

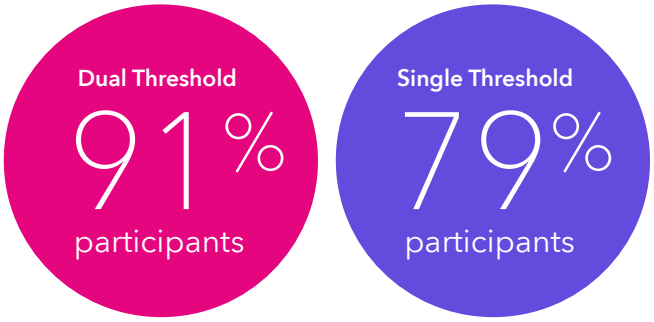
- LFP signal present to set up aDBS in 84% (57/68) of patients at enrollment at On-medication
- aDBS tolerable and successfully set up in 87% (45/52) of patients

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 79% (n = 35).

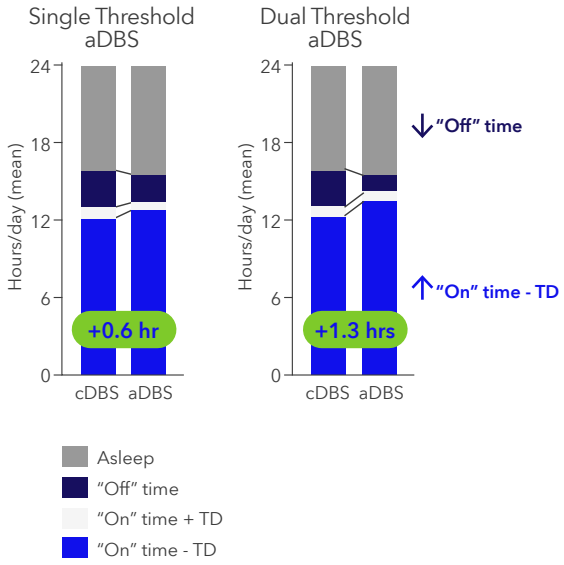
Primary endpoint success criteria: No worse than -2 hour loss of "On" time without troublesome dyskinesia during aDBS relative to cDBS



Motor diary data

There was a clinically meaningful improvement in "On" time without troublesome dyskinesia of 1.3 hours/day and a clinically meaningful 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 meaningful for the Single Threshold mode.

Change in motor diary



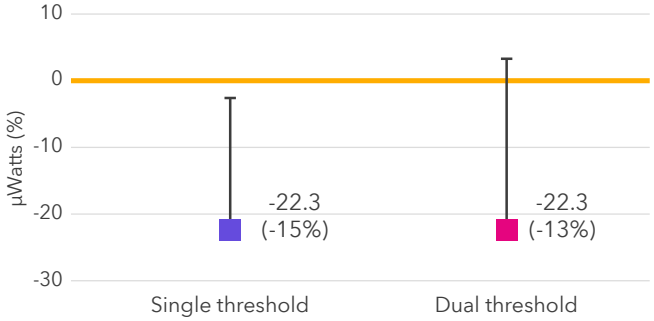
Motor diary data at baseline continuous deep brain stimulation (cDBS) and adaptive deep brain stimulation (aDBS). Change in diary data listed by hour. Note: changes >1 hour are clinically meaningful.[10,11]
TD = troublesome dyskinesia

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.

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

Brief Statement:

This material should not be considered the exclusive source of information, it does not replace or supersede information contained in the device manual(s). Please note that the intended use of a product may vary depending on geographical approvals. See the device manual(s) for detailed information regarding the intended use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For a MRI compatible device(s), consult the MRI information in the device manual(s) before performing a MRI. If a device is eligible for eIFU usage, instructions for use can be found at Medtronic's website manuals. medtronic.com. Manuals can be viewed using a current version of any major internet browser. For best results, use Adobe Acrobat® Reader with the browser. on European markets comply with EU and UK legislation (if applicable) on medical devices. For any further information, contact your local Medtronic representative and/or consult Medtronic's websites.

Medtronic

Europe
Medtronic International
Trading Sàrl.
Route du Molliau 31
Case postale
CH-1131 Tolochenaz
www.medtronic.eu
Tel: +41 (0)21 802 70 00
Fax: +41 (0)21 802 79 00

United Kingdom/Ireland
Medtronic Limited
Building 9, Croxley Park
Hatters Lane,
Watford
Herts WD18 8WW
www.medtronic.co.uk
Tel: +44 (0)1923 212213
Fax: +44 (0)1923 241004

medtronic.eu

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