

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Tremor: Treatments in the Pipeline

Alfonso Fasano, MD, PhD, FAAN

Chair in Neuromodulation, Professor of Medicine (Neurology) – University of Toronto, Canada

Clinician Investigator – Krembil Research Centre

Movement Disorders Centre, Toronto Western Hospital – UHN

Chairman of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Professor of Neurology, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy



UNIVERSITY OF
TORONTO



UHN

Krembil
Brain
Institute

HUMANITAS
NEURO CENTER

1

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Disclosures

- Receipt of grants/research supports:
 - BlueRock Therapeutics, Boston Scientific, CHIR, DMRF – Canada, **ES**, MSA Coalition, McLaughlin Centre, MJ Fox Foundation, **Medtronic**, **Praxis**, University of Toronto
- Receipt of honoraria or consultation fees:
 - **Abbott**, **Abbvie**, American Academy of Neurology, Annovis, AskBio, BlueRock Therapeutics, Brainlab, **Boston Scientific**, CADTH, Ceregate, Dompé, Gondola, Inbrain Pharma, Inbrain Neuroelectronics, Integra, International Parkinson and Movement Disorder Society, **Ipsen**, **Medtronic**, **Jazz Pharmaceuticals**, **Merz**, Springer, Sunovion, Syneos Health
- Participation in a company sponsored advisory board
 - **Abbott**, **Abbvie**, **Boston Scientific**, **Ipsen**, **Medtronic**, **Sunovion**

2

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

What (really) is Essential Tremor?

1. Isolated tremor syndrome of bilateral upper limb action tremor
2. At least 3 years duration
3. With or without tremor in other locations (e.g., head, voice, lower limbs)
4. Absence of other neurologic signs, such as dystonia, ataxia, parkinsonism



Bhatia et al, 2018

3

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Essential Tremor-Plus

1. Tremor with the characteristics of ET and additional neurological signs of uncertain significance such as:
 - impaired tandem gait,
 - questionable dystonic posturing,
 - memory impairment or
 - other mild neurologic signs of unknown significance
2. that do not suffice to make an additional syndrome classification or diagnosis.
 - ET with tremor at rest should be classified here.



Bhatia et al, 2018

4

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

'ET' evolution over 8 years

2015

2018

2023

5

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

ET evolution over 50 years

2005

2015

2018

6

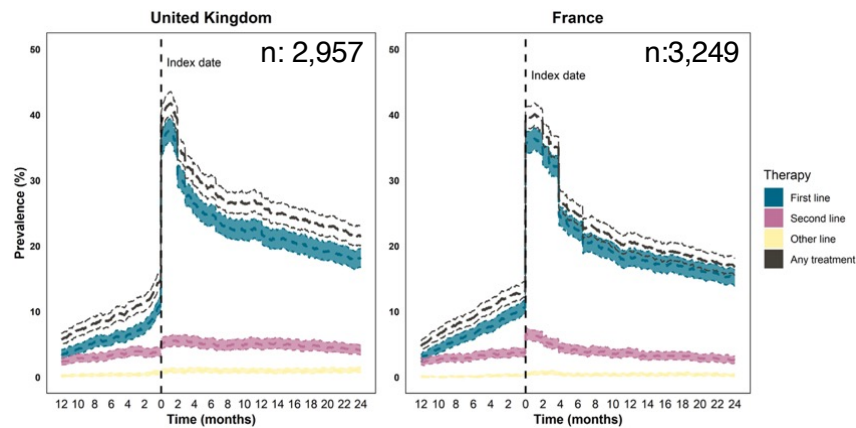
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

The Health Improvement Network



Antonazzo et al., 2024

7

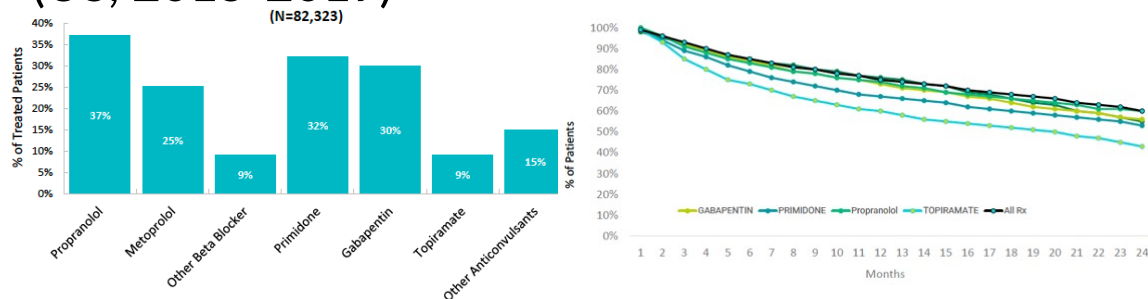
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Claims-based in >1 million of ET pts (US, 2015-2019)



- 64% patients received at least 1 pharmacological treatment
- Projected population suggests a further 1 million untreated

Vetterick et al., 2022

8

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Pharmacological approaches

- Enhancing GABA neurotransmission by activating extra-synaptic GABA receptors
- Reducing neuronal hyper-excitability
- Different overlapping mechanism?
 - electrical and/or degenerative disorder
- Other mechanisms: anti-AMPA, GluRd2 deficiency, dopamine (D3), adenosine A1 receptors, etc.

Pan et al., 2020; Elan D. Louis & Kuo, 2022

9

The Parkinson's Disease Educational Course for Industry Professionals

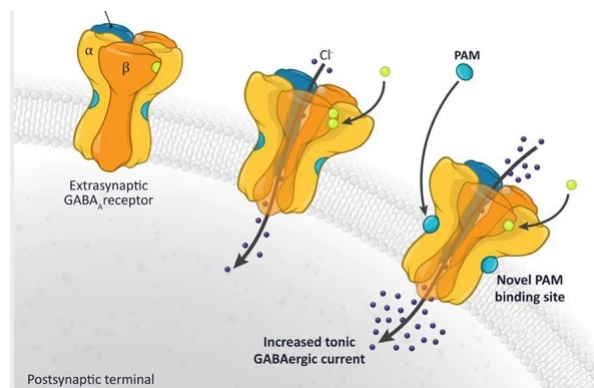
Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Positive allosteric modulators (PAMs)

- Ethanol is PAM of $\alpha 6$ subunit-containing GABAA receptors ($\alpha 6$ GABAARs)
- Expressed in the cerebellum, trigeminal ganglion, cochlear nuclei, the spinal trigeminal nucleus
- Similar action: gaboxadol, ketamine, flumazenil, 1-octanol, sodium oxybate
- Compound 6 (PZ-II-029), unclear if $\alpha 6$ GABAAR selective agonist (animal studies)



Handforth et al., 2023; Huang et al., 2023

10

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

SAGE-324/BIIB124 Sage Therapeutics

- SAGE has developed a series of GABA-A receptors PAMs
 - Reduction of occipital beta activity, a possibly biomarker for tremor
- Brexanolone (intravenous) and SAGE 217 (zuranolone, oral):
 - moderately reduced accelerometry power in short open label trials
 - Adverse events: dizziness, somnolence, and hypotension
 - FDA approved both for post-partum depression (iv discontinued)
- SAGE 324, oral with a longer half-life
 - Collaboration with Biogen
 - binding site different than endogenous GABA
 - In development also for status epilepticus and depressive disorders

11

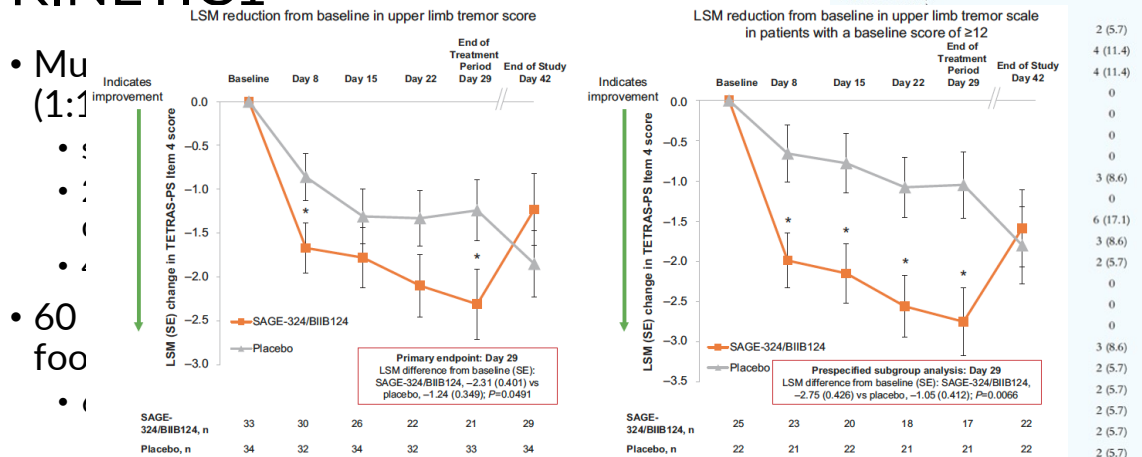
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

KINETIC1



Elble et al, 2024

12

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

KINETIC2

- Phase 2 dose-response trial (NCT05173012) in 147 subjects
- Double-blind, 4 arms: placebo, 15 30 60 mg
 - Screening: -28-0d, Treatment: 0-90d, FU period 91-104d
- Nighttime and gradual up-titration
 - Stratified based on propranolol use
- Completed in 2024
 - No significant effect on the item 4 of TETRAS-PS and ADL
- Biogen has terminated its right on the molecule, now tested as anti-seizure drug

Pahwa et al, unpublished

13

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

PRAX-114 Praxis Precision Medicines

- Neurosteroid GABA-A receptor PAM
- Developed for post-traumatic stress disorder, depression, seizure.
- A phase 2, randomized, double-blind, placebo-controlled trial testing 10 mg and 20 mg of PRAX-114 in adults with ET has been withdrawn in 2022 (NCT05387642).

14

The Parkinson's Disease Educational Course for Industry Professionals

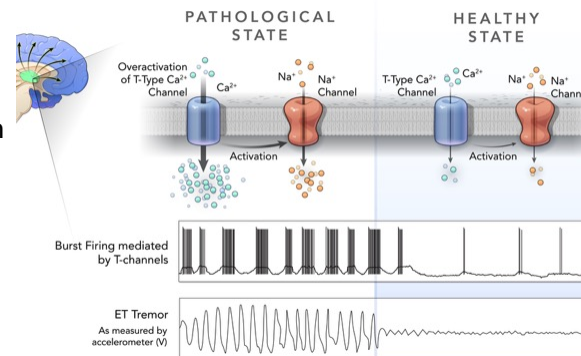
Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Reducing neuronal hyper-excitability

- **Low voltage-activated calcium channels (T-type, Cav3)**
 - 3 isoforms, Cav3.1 in cerebellum and thalamus
 - Zonisamide and ethosuximide known antagonists
- **Calcium-activated potassium channels**
 - SK channels, ie 'small conductance' for potassium
 - Activated by intracellular Ca^{2+} , causing neuronal repolarization after a spike



Womack et al., 2004; Yazdi et al., 2007; Handforth, 2016

15

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Suvecaltamide (JZP385) Jazz Pharmaceuticals

- Developed by CAVION (CX-8998) in mouse model
 - Highly selective Cav3 antagonist with good CNS penetration, a 10-13h half-life
- T-CALM (NCT03101241)
 - Phase 2a in 95 patients
 - 10 mg BID vs placebo for 28 days
 - Improvement in tremor and ADL but primary efficacy endpoint not met
 - Dropout secondary to adverse events 17% (vs 6% in placebo)
 - Dizziness very common (42% vs 21%).
- Phase 2b (NCT05122650)
 - 400 ET patients, 12-week double-blind placebo-controlled
 - Primary endpoint not met: TETRAS composite outcome (performance + ADL) score at 12 weeks
 - Dizziness (21%) and headache (8%) most common AEs
- Program in ET has been discontinued
 - Phase 2b for PD tremor (NCT05642442), results unavailable

Papapetropoulos et al., 2019; 2021

16

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Ulixacaltamide (PRAX-944) Praxis Precision Medicines

- Selective T-type blocker, high binding affinity to the CaV3.1 pore domain
 - Robust sigma band EEG power reduction in rodents and healthy human
 - Sleep spindle-related activity (sigma) during NREM sleep: biomarker of functional T-type blockade
- ESSENTIAL 1 (PRAX-944-222, NCT05021991)
 - Phase 2, double-blind, placebo-controlled, dose range (20-100mg)
 - Phase 2b testing 60mg vs 100mg vs placebo
 - No difference between 60 mg and 100 mg
 - Synergistic effect of propranolol (post-hoc)

Olhaye et al., 2022

17

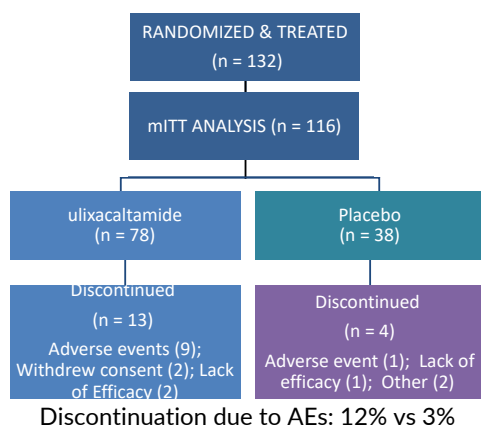
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Essential1 (NCT05021991)



	ULIXACALTAMIDE (n = 78)	PLACEBO (n = 38)
AGE, mean (min, max)	70.4 (32, 86)	67.7 (29, 88)
GENDER (Male / Female, %)	59% / 41 %	58% / 42%
FAMILY HISTORY OF ET	59 (76%)	23 (61%)
PROPRANOLOL USE	27 (35%)	9 (24%)
mADL SCORE, mean (min, max)	20.6 (12, 32)	20.8 (12, 34)
ADL SCORE, mean (min, max)	29.0 (20, 38)	28.6 (19, 39)
mADL EXCLUDING PS , mean (min, max)	16.4 (9, 25)	16.4 (8, 25)

Olhaye et al., 2022

18

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Primary endpoint: mADL scale

TETRAS ADL measures observed:

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task
12. Social Impact

Each measure is individually scored from 0-4:

- 0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with ____
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

TOTAL SCORE OF UP TO 48

Modified ADL measures observed:

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task
12. ~~Social Impact~~ PS6. Spirals (Left, Right)
PS7. Handwriting

Each measure is individually scored from 0-3:

- 0 = Slightly abnormal. Tremor is present but does not interfere with ____
1 = Mildly abnormal. Spills a little.
2 = Moderately abnormal. Spills a lot or changes strategy to complete task.
3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

TOTAL SCORE OF UP TO 42

Olhaye et al., 2022

19

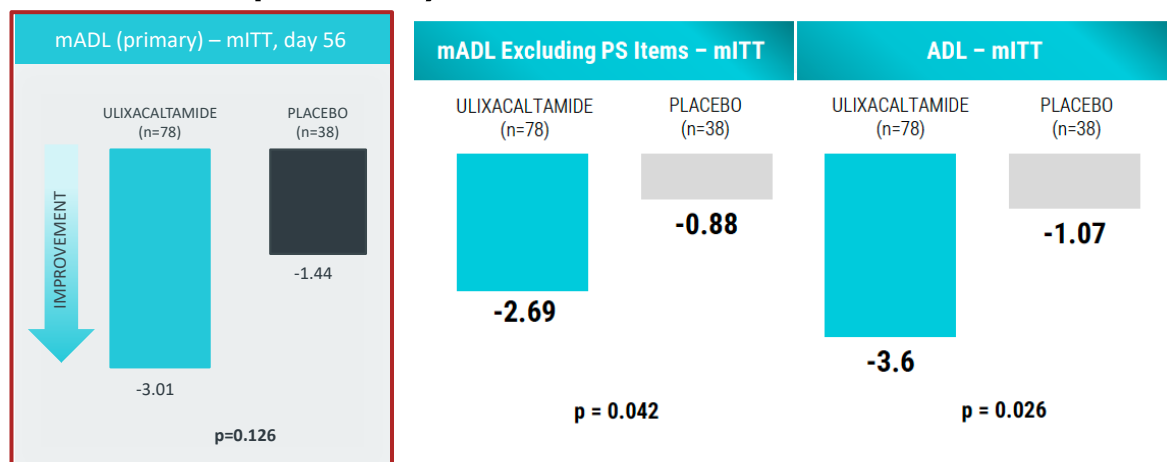
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Results (primary not met), 1



Olhaye et al., 2022

20

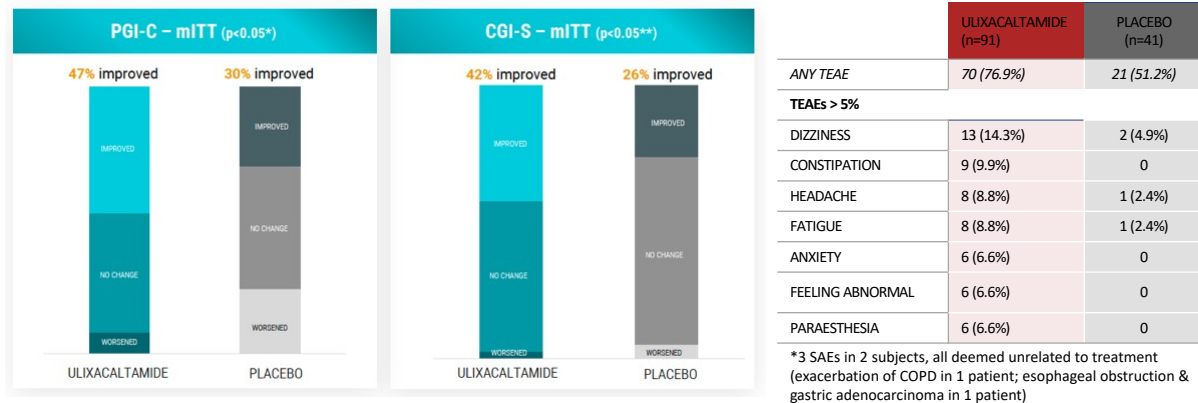
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Other outcomes



Olhaye et al., 2022

21

The Parkinson's Disease Educational Course for Industry Professionals

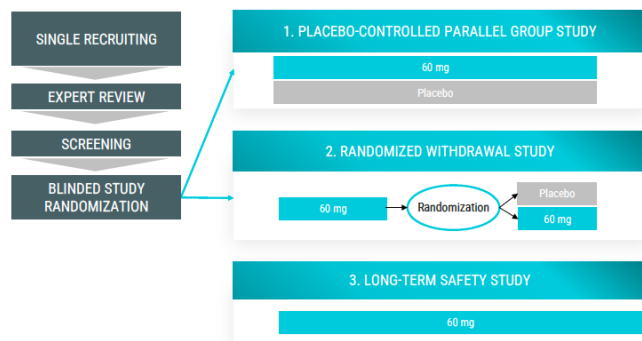
Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Essential 3 (PRAX-944-321, NCT06087276)

- Phase 3, multi-study including 3 phase 3 pivotal studies (up to 1,000 pts)
- Composite sum of items 1 to 11 of TETRAS-ADL (mADL11) as primary endpoint.
- Decentralized design (www.essential3study.com)



Interim analysis of Study 1 suggested the study to be stopped for futility. Given the advanced state of enrollment for both Study 1 and Study 2, the company has decided to continue both studies, with results expected in the third quarter of 2025.

<https://investors.praxismedicines.com/news-releases/news-release-details/praxis-precision-medicines-provides-update-essential3-and>

22

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

Rimtuzalcap (CAD-1883) Cadent Therapeutics

- PAM of small conductance Ca^{2+} activated K^+ channels (SK channels)
 - Modulation of SK channel could restore a normalized firing pattern and reduce tremor by desynchronizing Purkinje cell output
 - CAD-1883 also decreases measures of ataxic gait in a mouse model
- Phase I in healthy volunteers: well-tolerated at doses of up to 1200 mg/d
- CADENCE-1 (NCT03688685): phase 2a in 25 patients
 - open, safe and effective (blind analysis of objective measures)
- A large multicenter, placebo-controlled phase 2b clinical trial was completed in December 2024
 - Company acquired by Novartis, both ET and SCA programs abandoned

Adelman et al, 2012; Lin et al., 2014; Brown et al., 2020

23

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

NBI-827104/ACT-7099478 Neurocrine

- Supposed (not confirmed) effect on T-type channel
- Phase 1: tremor reduction in ET patients
- Phase 2 (NCT04880616): primary endpoint: accelerometer, cross-over 28 days/arm
 - Negative: program discontinued

24

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

ES-481 ES Therapeutics Australia Pty Ltd

- Transmembrane AMPA receptors regulatory proteins (TARP) inhibitor
- Phase 2a trial in Canada (NCT05234762)
- Double-blind, 28 subjects, up to 75 mg BID
 - No ET-Plus
 - No Alcohol
- 7/11 randomized terminated early due to Aes
- Safety Review Committee met in June 2022 and determined that the trial can continue at a fixed dose of 25 mg QD
 - No results yet

25

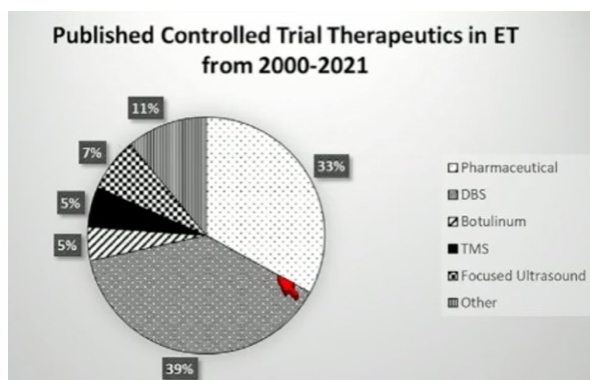
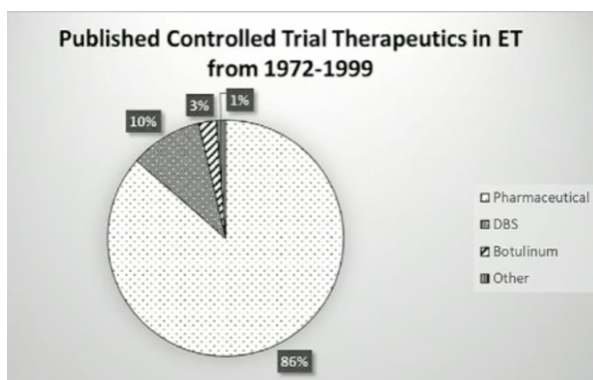
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Clinical trials in ET



Zesiewicz et al 2022

26

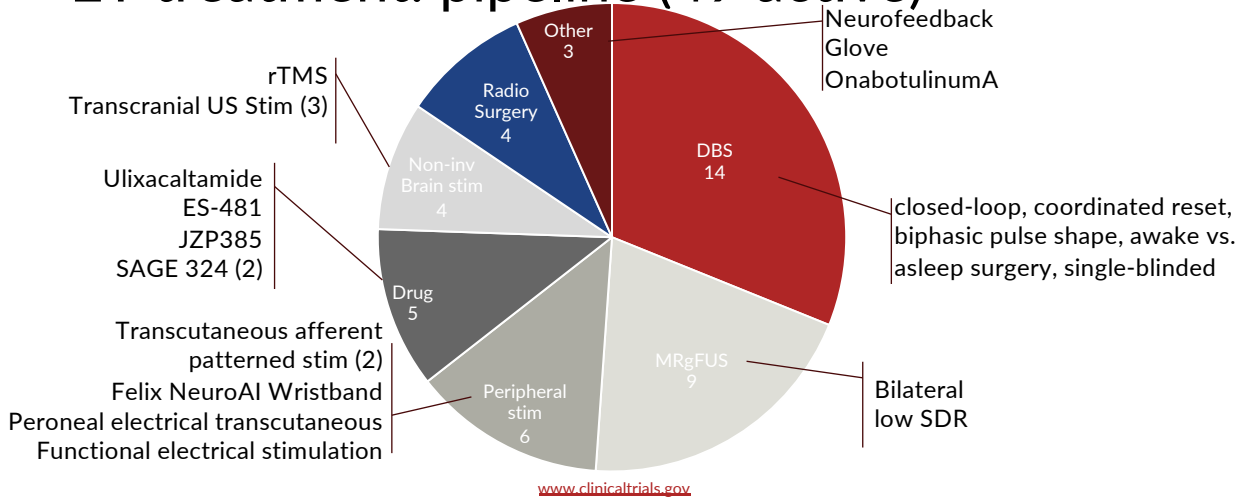
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

ET treatment: pipeline (49 active)



27

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

MR-guided Focused Ultrasound



28

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Bilateral MRgFUS thalamotomy

Baseline

After **left** Vim procedure

After **right** Vim procedure

Iorio-Morin, Yamamoto et al., 2021

29

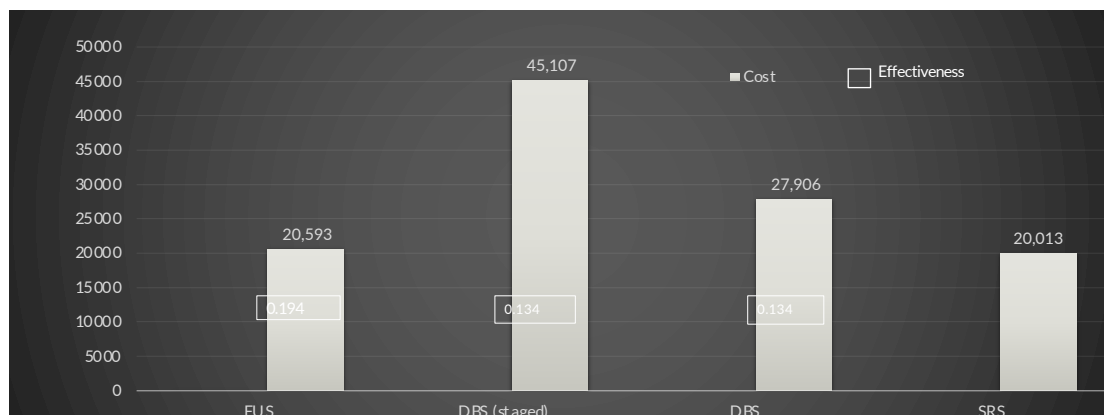
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Cost-Effectiveness of MRgFUS, GKRS and DBS for ET



Ravikumar et al. 2017

30

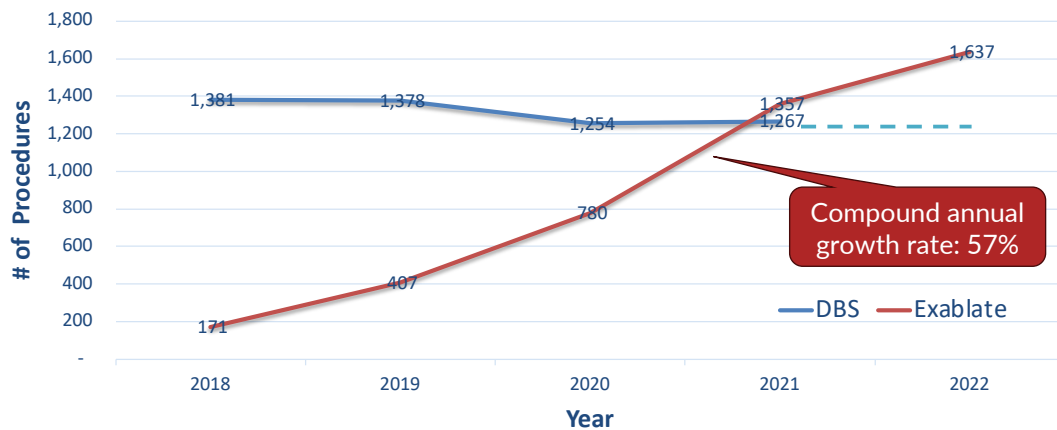
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

U.S. ET Procedures



Carevovance, Healthcare Claims Database

31

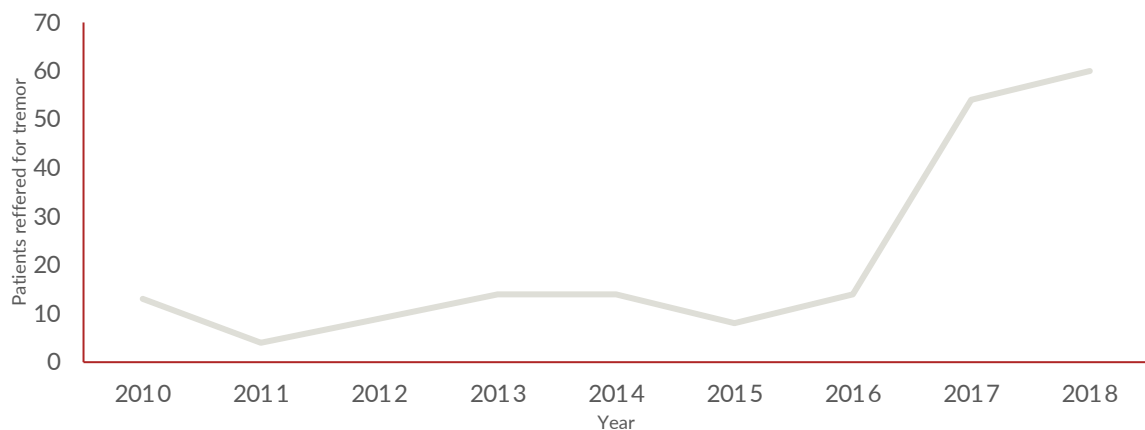
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

The MRgFUS effect



Balachandar et al., 2022

32

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

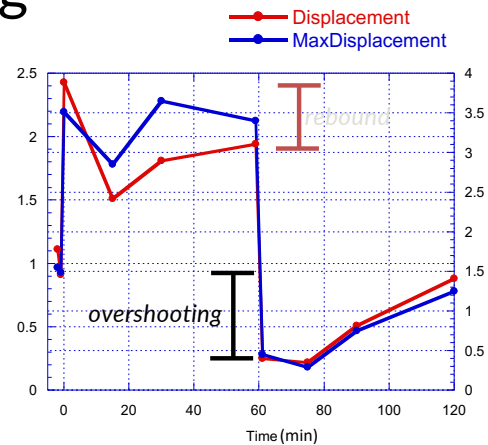
Rebound and overshooting

Unilateral R VIM DBS for ET (escaper)

ON →

OFF →

back ON



Courtesy of Drs Daniel Di Luca and Rodger Elble

33

The Parkinson's Disease Educational Course for Industry Professionals

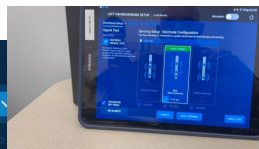
Honolulu, Hawaii, USA | October 4, 2025



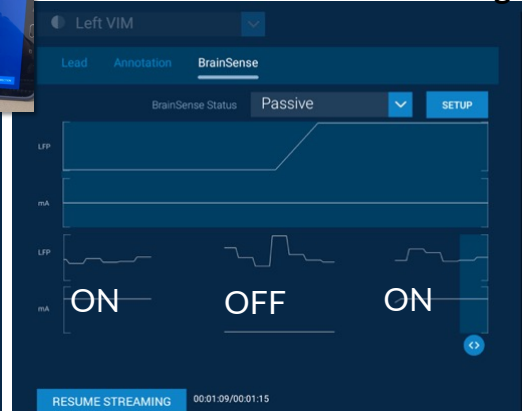
International Parkinson and Movement Disorder Society

New insights from chronic sensing

Timeline (chronic sensing)



Streaming



34

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025

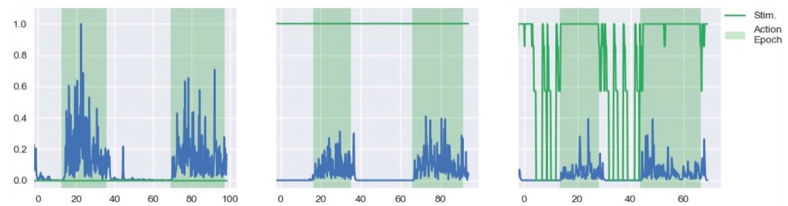


International Parkinson and
Movement Disorder Society

aDBS for ET

Controlling signal:

- Thalamic LFPs
- Alternative approaches:
 - External markers of tremor amplitude and phase measured by EMG or accelerometers.
 - Decoding movement with thalamic LFPs
 - Decoding movement with M1/S1 LFPs



Graupe et al., 2010; Cagnan et al., 2017; Tan et al. 2019; Ferleger et al., 2020; Opri et al., 2020; Guehl et al., 2023

35

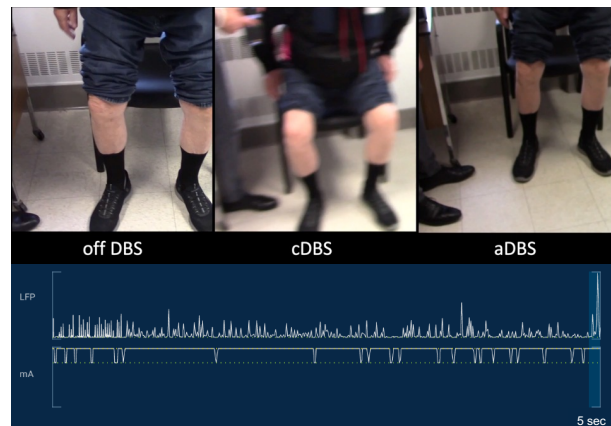
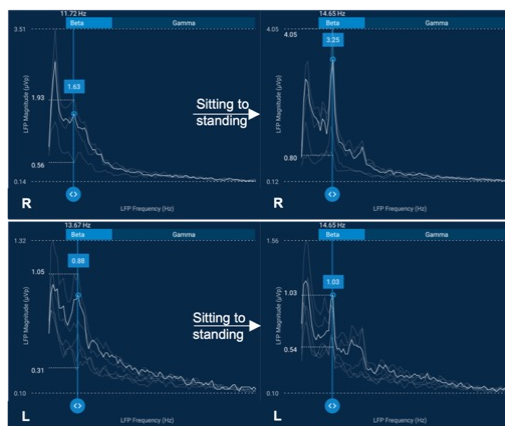
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society

aDBS for orthostatic tremor



Fung et al., 2025

36

The Parkinson's Disease Educational Course for Industry Professionals

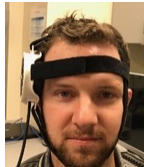
Honolulu, Hawaii, USA | October 4, 2025



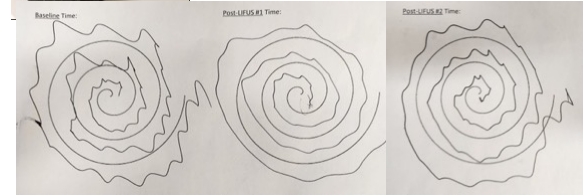
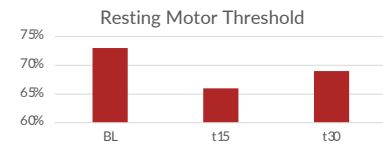
International Parkinson and Movement Disorder Society

Low-Intensity Focused Ultrasound

- 8 sessions of VIM-TUS
 - Brainsonix Pulsar 1002
 - 30 s on/30 s off for 10 min
- 8/10 ET improved
 - unblinded



- Dentate Nucleus in SCA12



Deveney et al 2024; Robert Chen's lab, in preparation

37

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025

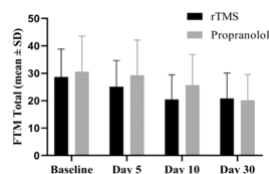


International Parkinson and Movement Disorder Society

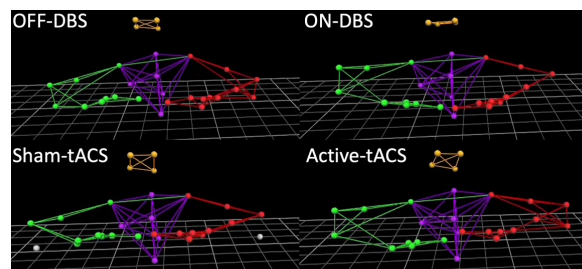
Other Non-Invasive Neuromodulations

1-Hz bil cerebellar rTMS

- Single-blinded, 30-day prospective, randomized
 - 1200 pulses, 90% of the resting MT for 10 days (n: 20 pts)
 - Propranolol titrated to 90 mg/day (n: 18 pts)



Cerebellar Transcranial Alternating Current Stimulation



Lv et al., 2023; Olivier et al 2023

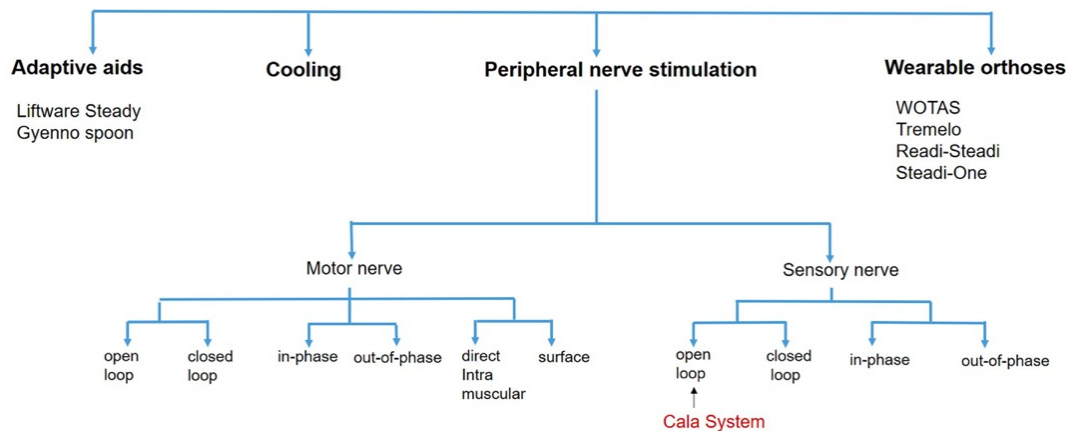
38

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society



Isaacson et al., 2020; Brillman et al., 2023; Wagle Shukla et al., 2023

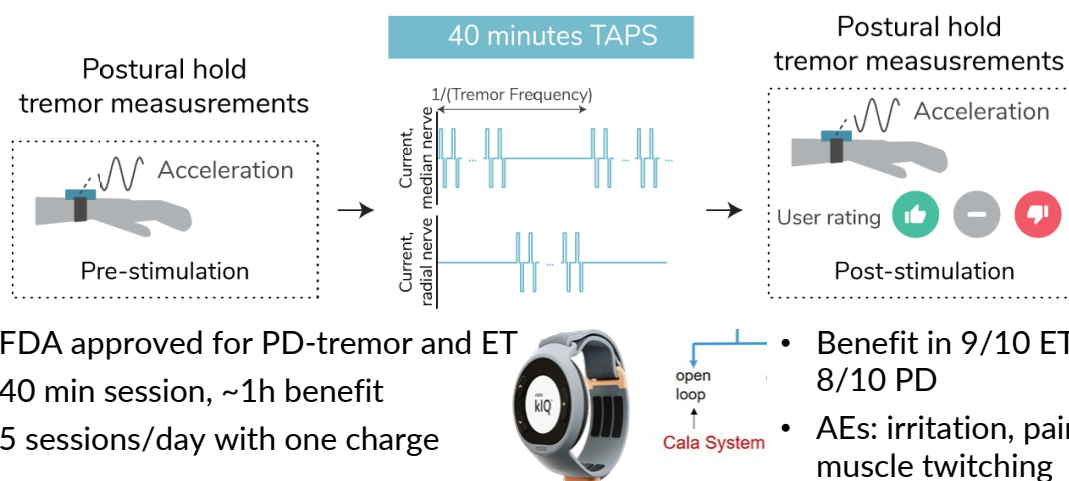
39

The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and
Movement Disorder Society



Isaacson et al., 2020; Brillman et al., 2023; Wagle Shukla et al., 2023

40

The Parkinson's Disease Educational Course for Industry Professionals

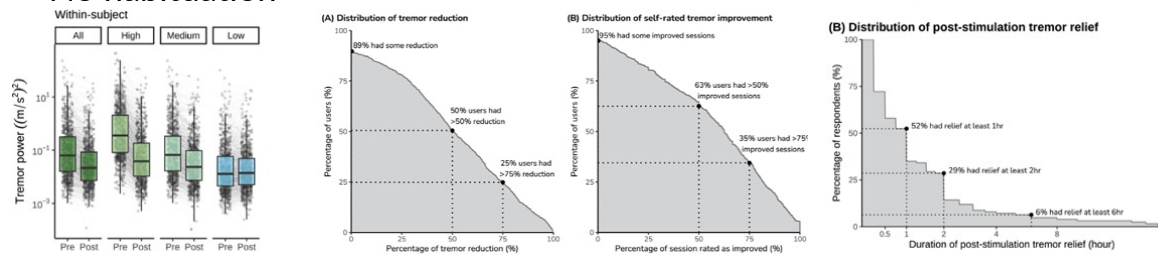
Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Transcutaneous afferent patterned stimulation

- Retrospective post-market in 1,223 ET pts
- Age 73.0 ± 9.7 years
- Beyond 90 days (up to 1,233), ~5.6 sessions/week
- No habituation



Lu et al., 2023

41

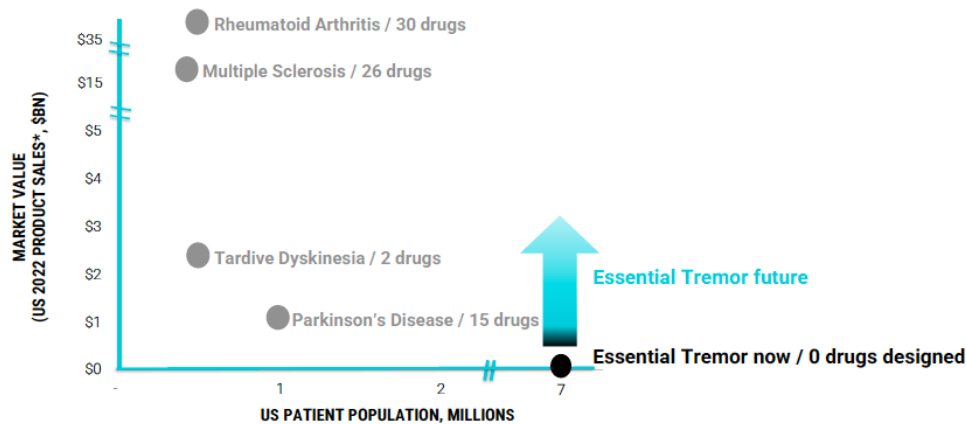
The Parkinson's Disease Educational Course for Industry Professionals

Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society

Large market potential and limited competition compared to other diseases



Source: Evaluate Pharma US Sales by Product, (#) number of drugs with branded revenue report by company *US products sales are not indication specific

42



Thank you

@alfonso.fasano@uhn.ca

@DrAlfonsoFasano

The Parkinson's Disease Educational Course for Industry Professionals
Honolulu, Hawaii, USA | October 4, 2025



International Parkinson and Movement Disorder Society