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Sheffield Institute for Translational Neuroscience

# Parkinson's Disease: Clinical Definition and overview of current clinical trials

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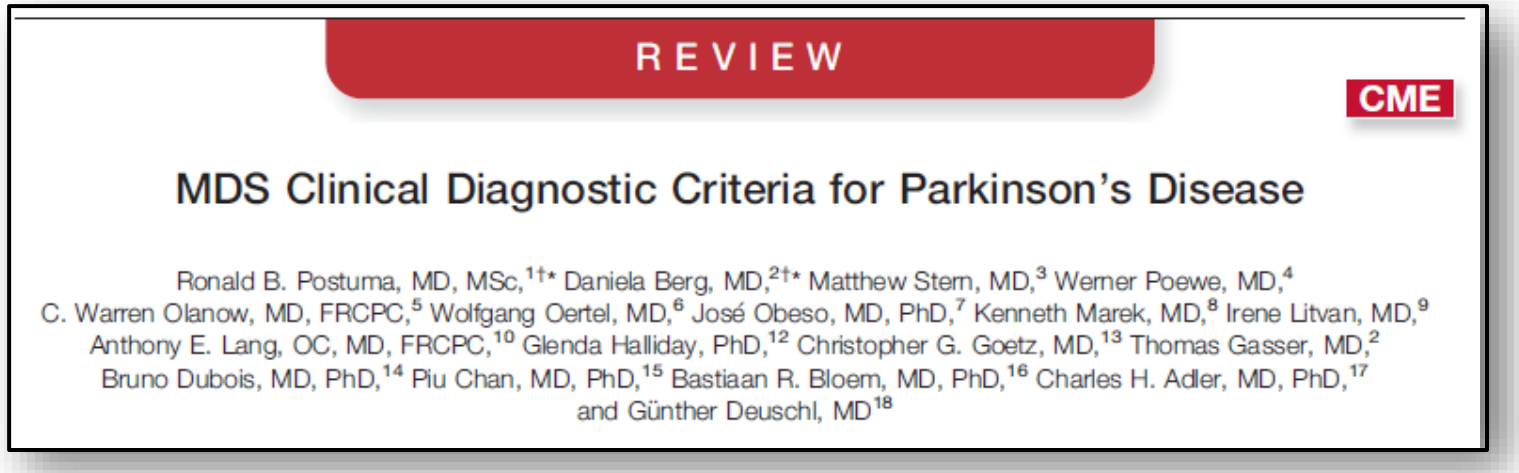
# Objectives:

- Introduction to MDS Clinical Diagnostic Criteria for PD
- Overview of recently completed PD neuroprotection studies
- (The future)

# The MDS Clinical Diagnostic Criteria for Parkinson's Disease

# MDS Clinical Diagnostic Criteria for PD/1


REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

- Intended for use in clinical research
- "May be used to guide clinical diagnosis"
- Critical aim to:
  - Standardize the diagnostic process
  - Make it reproducible across centres and applicable by clinicians with less PD expertise

*Movement Disorders, 2015*

# MDS Clinical Diagnostic Criteria for PD/2

- Benchmark for the MDS criteria is the ***expert clinical diagnosis***
  - Not biomarker-based (DAT-Scan, alpha-synuclein seeding assays, etc)

- **Two stage process:**
  - First, parkinsonism is defined – as **bradykinesia** in combination with either **rest tremor**, **rigidity** or **both**
  - Once diagnosed, the criteria then define whether this parkinsonism is attributable to PD (or due to atypical parkinsonism, WD, etc)

*Movement Disorders, 2015*

# From a diagnosis of parkinsonism to a diagnosis of Parkinson's disease

- **Diagnosis of clinically established PD:**
  - At least two supportive criteria
  - Absence of absolute exclusion criteria
  - No red flags

- **Supportive criteria:**
  - Clear, dramatic response to dopaminergic therapy
  - Presence of levodopa-induced dyskinesias
  - Rest tremor of a limb
  - Positive results from at least one ancillary diagnostic test with > 80% specificity for differential diagnosis of PD
    - Olfactory loss
    - Metaiodobenzylguanidine (MIG) scintigraphy clearly documenting cardiac denervation

# Exclusion criteria/red flags for the diagnosis of Parkinson's disease:

- **Absolute exclusion criteria:**
  - Unequivocal cerebellar signs
  - Downward vertical supranuclear gaze palsy/selective slowing of downward vertical saccades
  - Diagnosis of probable frontotemporal dementia
  - **Parkinsonian features restricted to the lower limbs for > 3 years (?)**
  - Treatment with dopamine-receptor blocker or a dopamine-depleting agent
  - **Absence of observable response to high-dose levodopa (≥ 600 mg) despite at least moderate severity of disease**
  - Unequivocal cortical sensory loss
  - Normal DAT scan
  - Documentation of alternative condition (i.e. MSA, PSP, but also Wilson disease etc)
- **Red flags:**
  - Rapid progression of gait impairment (wheelchair within 5 yr of onset)
  - Complete absence of progression of motor symptoms/signs over 5 or more years unless stability is related to treatment
  - Early bulbar dysfunction within the first 5 yr of disease
  - Inspiratory respiratory dysfunction (diurnal/nocturnal stridor or frequent inspiratory sighs)
  - **Severe autonomic failure in first 5 yr of disease**
  - Recurrent (>1/y) falls because of imbalance within 3 yr on onset
  - Presence of disproportionate anterocollis or hand/foot contractures in first 10 yr
  - **Absence of any common nonmotor features despite 5 yr disease duration (sleep dysfunction, autonomic dysfunction, hyposmia, psychiatric dysfunction) (?)**
  - Pyramidal tract signs
  - **Bilateral symmetric parkinsonism**

RESEARCH ARTICLE

# Clinical Diagnostic Accuracy of Parkinson's Disease: Where Do We Stand?

Sasivimol Virameteekul, MD, MSc,[1,2] Tamas Revesz, PhD, FRCPath,[1] Zane Jaunmuktane, MD, FRCPath,[1] Thomas T. Warner, FRCP, PhD,[1,2] and Eduardo De Pablo-Fernández, MD, PhD[1,2*]

- Post mortem study, diagnostic criteria retrospectively applied
- 271 patients with parkinsonism
  - PD: 141
  - Atypical parkinsonism: 126

- Diagnostic accuracy early (first five years) vs final stages:
  - **Experts: 91.5% -> 97.2%**
  - **MDS criteria: 89.5% -> 92.5%**
  - **Clinicians: 84.2% -> 90.3%**

EDITORIAL

The Clinical Diagnosis of Parkinson's Disease—We Are Getting Better

Ronald B. Postuma, MD, MSc,[1*] and Anthony E. Lang, MD[2]

- Most common misdiagnosis: **MSA**
  - 20% (16/80) with final clinical diagnosis of MSA had a pathological diagnosis of PD!
  - Only 1 of 73 autopsy-confirmed cases of MSA had clinical diagnosis of PD

*Movement Disorders, 2023*

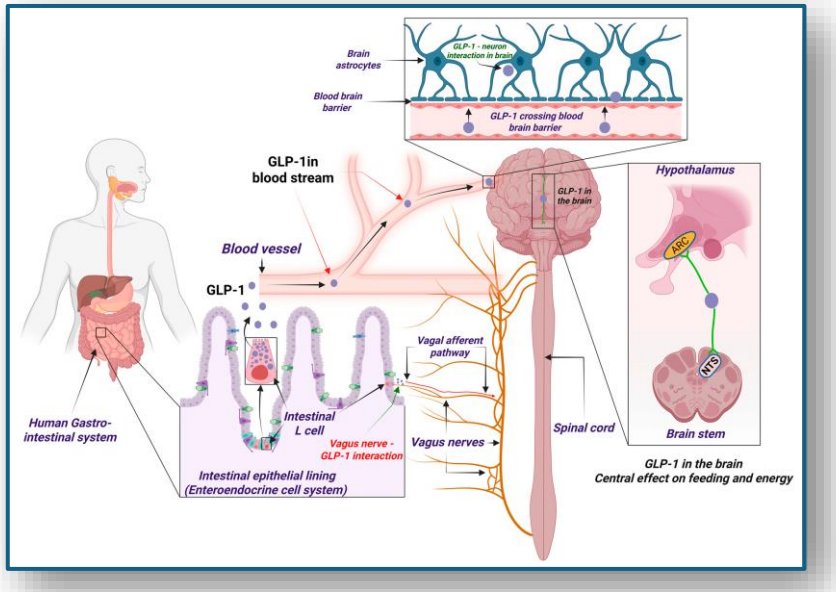
# Recently completed neuroprotection trials

# Recently completed neuroprotection trials

- GLP-1 Studies
- Stem cell trials
- Microbiome-related studies
- The (past and the) future of neuroprotection studies

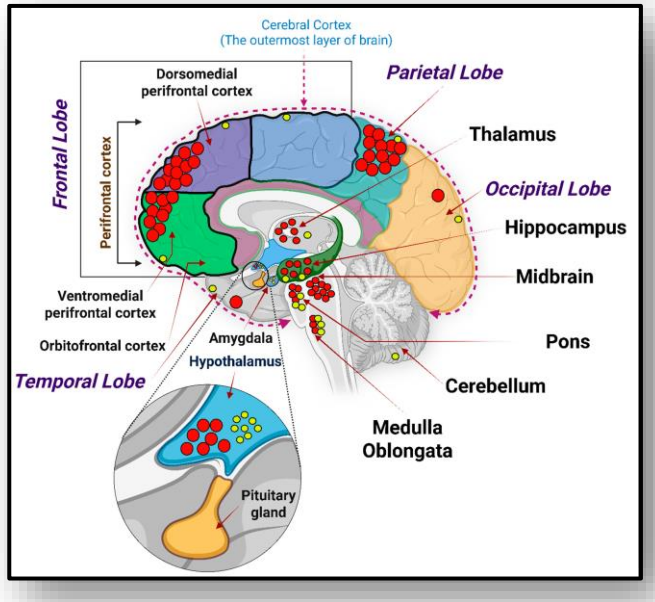
# GLP-1 agonist studies

# GLP-1 - Background



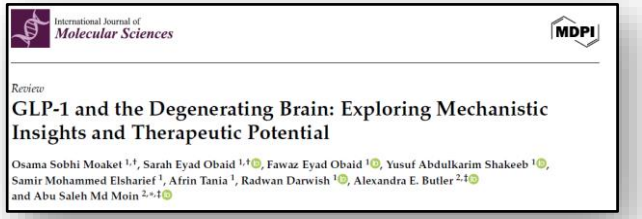

**GLP-1 produced in enteroendocrine C-cells**

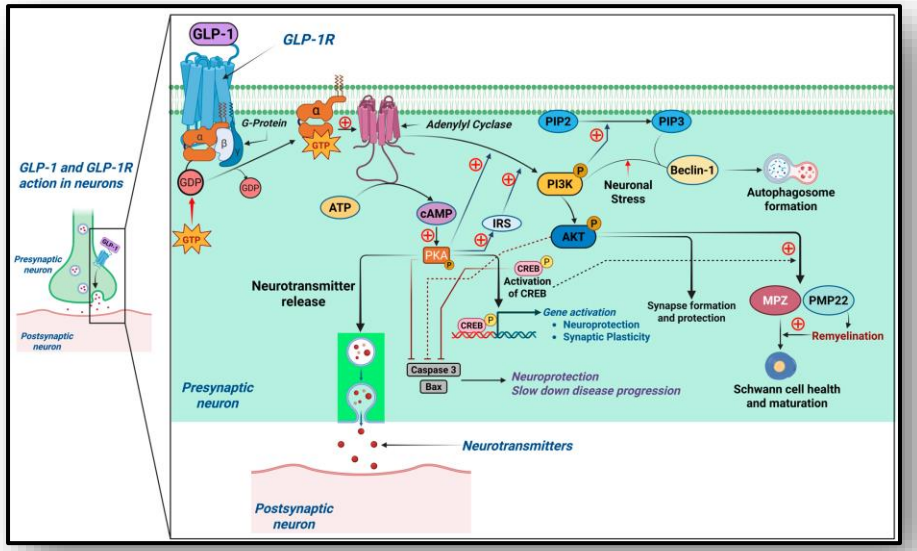
- Local effect on vagal nerve
- Systemic effect




**Widespread expression of GLP-1 receptors**

- Cortex
- Midbrain




**Activation of multiple neuroprotective mechanisms**

- Anti-inflammatory, Antiapoptotic, Synaptic plasticity, …


**Strong epidemiological evidence**

- Decreased risk of PD in DM pat on GLP-1 agonists

# Exenatide and the treatment of patients with Parkinson's disease

Iciar Aviles-Olmos,[1] John Dickson,[2] Zinovia Kefalopoulou,[1] Atbin Djamshidian,[3] Peter Ell,[2] Therese Soderlund,[2] Peter Whitton,[4] Richard Wyse,[5] Tom Isaacs,[5] Andrew Lees,[3] Patricia Limousin,[1] and Thomas Foltynie[1]

*Proof of concept study, JCI, 2013*

JAMA Neurology | Original Investigation

## Utility of Neuronal-Derived Exosomes to Examine Molecular Mechanisms That Affect Motor Function in Patients With Parkinson Disease

A Secondary Analysis of the Exenatide-PD Trial

Dilan Athauda, MRCP, PhD; Seema Gulyani, PhD; Hanuma kumar Karnati, PhD; Yazhou Li, PhD; David Tweedie, PhD; Maja Mustapic, PhD; Sahil Chawla, BSc; Kashfia Chowdhury, MSc; Simon S. Skene, PhD; Nigel H. Greig, PhD; Dimitrios Kapogiannis, MD; Thomas Foltynie, MRCP, PhD

Confirmation of Akt activation

## Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

*Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie*

*Phase 2 study, Lancet 2017*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Trial of Lixisenatide in Early Parkinson's Disease

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houéto, M. Anheim, I. Benatru, T. Boraud, C. Brefel-Courbon, N. Carrière, H. Catala, M. Charif, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, C. Geny, A. Georget, C. Germain, S. Grimaldi, C. Hardy, L. Hopes, P. Krystkowiak, B. Laurens, R. Lefaucheur, L.-L. Mariani, A. Marques, C. Marse, F. Ory-Magne, V. Rigalleau, H. Salhi, A. Saubion, S.R.W. Stott, C. Thalamas, C. Thiriez, M. Tir, R.K. Wyse, A. Benard, and O. Rascol, for the LIXIPARK Study Group*

*Phase 2 study, NEJM 2024*

## Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial

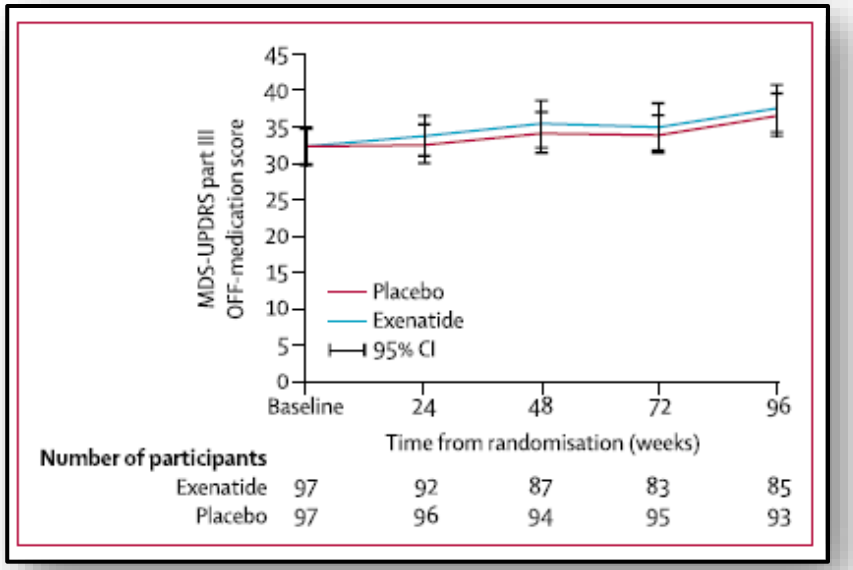
*Nirosen Vijiaratnam, Christine Girges, Grace Auld, Rachel McComish, Alexa King, Simon S Skene, Steve Hibbert, Alan Wong, Sabina Melander, Rachel Gibson, Helen Matthews, John Dickson, Camille Carroll, Abigail Patrick, Jemma Inches, Monty Silverdale, Bethan Blackledge, Jessica Whiston, Michele Hu, Jessica Welch, Gordon Duncan, Katie Power, Sarah Gallen, Jacqueline Kerr, K Ray Chaudhuri, Lucia Batzu, Silvia Rota, Edwin Jabbari, Huw Morris, Patricia Limousin, Nigel Greig, Yazhou Li, Vincenzo Libri, Sonia Gandhi, Dilan Athauda, Kashfia Chowdhury, Tom Foltynie*

*Phase 3 study, Lancet 2025*

# Exenatide Phase 3 trial

- Multicentre, double-blind, parallel group, randomised, placebo-controlled trial
- H/Y stage ≤ 2.5
- 97 patients on Exenatide 2 mg once weekly vs 97 patients on placebo
- Duration: 96 weeks
- Primary outcome: UPDRS/part III
- **No** beneficial effect

*Why?*

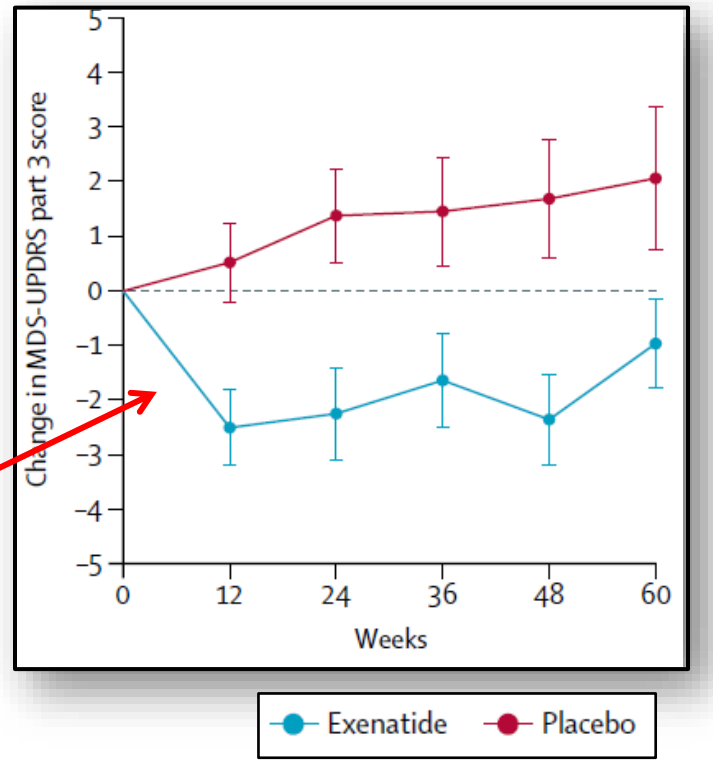


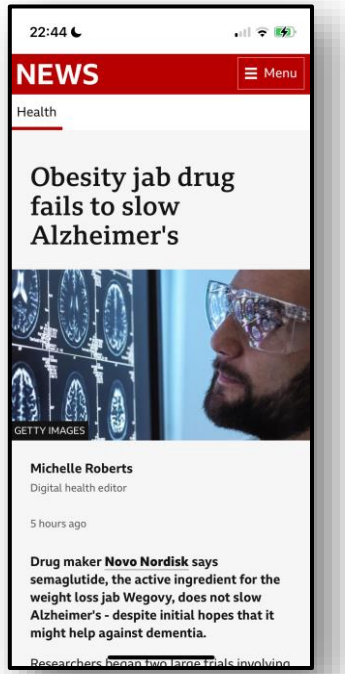

*Mean MDS-UPDRS part III off score*

# Possible explanations for negative outcome of phase 3 Exenatide trial

- Greater weight loss in phase 2 study – unblinding?
  - Phase 2: 2.6 kg  Phase 3: 1.8 kg
- ***CSF concentration only 1% of plasma Exenatide concentration!***
- No differential effect on neurodegeneration as quantified by DaT-SPECT (36 in Exenatide group, 27 in placebo group
- ***CSF alpha-synuclein seeding assay:***
  - ***Exenatide arm: 31/31 (100%) ASS +***
  - ***Placebo arm: 32/35 (91%) ASS+***

**Possible clue in phase 2 results:**
***All the improvement occurred in first 12 weeks***



# Stem cell trials

Cell

CellPress
OPEN ACCESS

Article

## Phase 1/2a clinical trial of hESC-derived dopamine progenitors in Parkinson's disease

Jin Woo Chang,[1,11] Han Kyu Na,[2,11] Kyung Won Chang,[3,11] Chan Wook Park,[2,4,11] Do-Hun Kim,[4,5] Sanghyun Park,[4] Chul-Yong Park,[4,5] Jang Hyeon Eom,[5] Seung Taek Nam,[5] Ki-Sang Jo,[5] Mi-Young Jo,[5] Sung Kyoung Choi,[5] Hye-Jin Hur,[5] Sarang Kim,[5] Minseok Kim,[6] Dae-Sung Kim,[7] Dong-Youn Hwang,[8] Myoung Soo Kim,[9] Inkyung Jung,[6] Jongwan Kim,[5] Myung Soo Cho,[5] Phil Hyu Lee,[2,*] and Dong-Wook Kim[4,5,10,12,*]

*Cell 2025*

## Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease

https://doi.org/10.1038/s41586-025-08700-0

Received: 9 August 2024

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Published online: 16 April 2025

Nobukatsu Sawamoto[1,2], Daisuke Doi[2,3], Etsuro Nakanishi[1,2], Masanori Sawamura[1,2], Takayuki Kikuchi[2], Hodaka Yamakado[1], Yosuke Taruno[1], Atsushi Shima[1], Yasutaka Fushimi[4], Tomohisa Okada[4], Tetsuhiro Kikuchi[2], Asuka Morizane[2], Satoe Hiramatsu[2], Takayuki Anazawa[5], Takero Shindo[6], Kentaro Ueno[7], Satoshi Morita[7], Yoshiki Arakawa[3], Yuji Nakamoto[4], Susumu Miyamoto[3], Ryosuke Takahashi[1,2] & Jun Takahashi[2,3]

*Nature 2025*

## Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease

https://doi.org/10.1038/s41586-025-08845-y

Received: 26 July 2024

Accepted: 26 February 2025

V. Tabar[1,2,3], H. Sarva[4], A. M. Lozano[5,6], A. Fasano[6,7,8], S. K. Kalia[5,6], K. K. H. Yu[7], C. Brennan[1], Y. Ma[9,10], S. Peng[9], D. Eidelberg[9,10], M. Tomishima[11], S. Irion[11], W. Stemple[11], N. Abid[11], A. Lampron[11], L. Studer[2,12,14] & C. Henchcliffe[13,14]

*Nature 2025*

# Comparison of recent PD stem cell trials

| Study | Number of patients | Duration | Placebo | Type of stem cell | Immune suppression | Key outcomes |
|---|---|---|---|---|---|---|
| Sawamoto et al | **n=7** (single dose) | 24 months | No | iPS derived from peripheral blood of single donor | Tacrolimus for 15 months | 1. Save<br>2. Average improvement by **9.5** points (OFF/MDS-UPDRS/III)<br>3. No graft-induced dyskinesias |
| Tabar et al | **n=12**<br>Two cohorts:<br>Low dose (**n=5**)<br>High dose **(n=7**) | 18 months (interim) | No | iPS derived from human embryonic stem cell line<br>(Bemdaneprosel/ MSK-DA01) | Tacrolimus for 12 months | 1. Save<br>2. Average improvement by **8.6** vs **23** points (OFF/MDS-UPDRS/III) in **low** vs **high** dose cohort<br>3. No graft-induced dyskinesias |
| Chang et al | **n=12**<br>Two cohorts:<br>Low dose (**n=6**)<br>High dose (**n=6**) | 12 months (interim) | No | iPS derived from human embryonic stem cell line<br>(A9-DPC) | Tacrolimus for 12 months | 1. Save<br>2. Average improvement by **12.7** vs **15.5** points (OFF/MDS-UPDRS/III) in **low** vs **high** dose cohort<br>3. No graft-induced dyskinesias |

# Stem cell therapy for PD – what will the future hold?

- Extremely encouraging data from 2025 early phase clinical trials
- No placebo arm…
- Spread of pathology to transplant…
- Non-motor symptoms will not be addressed
- Early or late (or not at all)?

**Advanced Therapies Clinic 2030**

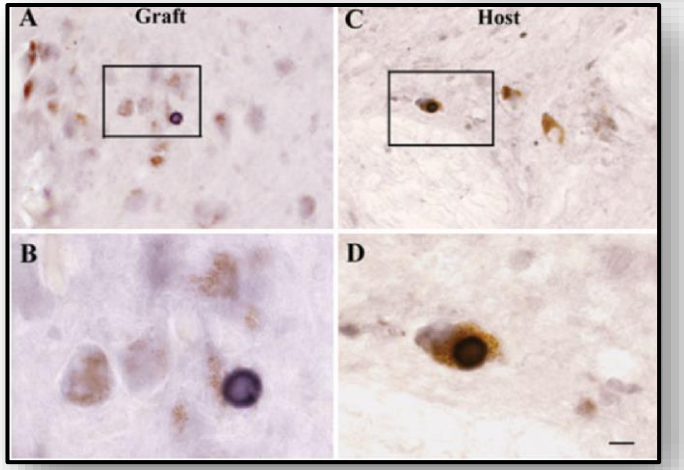
**DBS?** | **Apomorphine?** | **s.c. L-Dopa?** | **Stem cell transplant?**

EXPEDITED PUBLICATION

A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease

C. Warren Olanow, MD,[1] Christopher G. Goetz, MD,[2] Jeffrey H. Kordower, PhD,[2] A. Jon Stoessl, MD,[3] Vesna Sossi, PhD,[3] Mitchell F. Brin, MD,[1] Kathleen M. Shannon, MD,[2] G. Michael Nauert, MD,[4] Daniel P. Perl, MD,[5] James Godbold, PhD,[6] and Thomas B. Freeman, MD[4]

Ann Neurol 2003;54:403–414




**Lewy body in grafted DA neuron**

**Lewy body in Substantia nigra**

Ann Neurol 2009;66:591–596

# Microbiome-related trials

# The rationale for microbiome-related clinical trials in Parkinson's disease

- Multiple studies have demonstrated clear microbiome abnormalities in PD
- Microbiome abnormalities already present in prodromal PD, suggesting that these abnormalities may not just be secondary to constipation etc
- Plausible link with the gut-brain axis hypothesis

**However…**

- Proposed underlying mechanisms linking the microbiome and neurodegeneration are only tentative at best
  - Functional link between distinct microbiome strains and their beneficial/detrimental effect on PD related patho-mechanisms is typically absent or purely hypothetical
  - Hypotheses include but are not limited to:
    - Effect on alpha-synuclein spreading
    - Gut inflammation -> brain inflammation
    - "Leaky gut", leading to abnormal short chain fatty acid (SCFA) levels in PD
    - Impaired endogenous GLP-1 secretion
    - Bile acid dyshomeostasis
    - …..

# Fecal microbiota transplantation studies in PD

| Author and year | Study type | Patient population | Sample size | The FMT preparation | Route | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|
| Segal et al. (2021) | Case series | 3 male vs. 3 femal | 6 FMT | Fresh stool (65 g) from each donor was immediately mixed in a blender with 300 mL of 0.9% sterile saline for several seconds until it developed a smooth consistency. The stool suspension was then filtered through a gauze pad to remove large particles. The stool suspension was mixed with glycerol (final concentration of 10%). 50 mL aliquots of the mixed suspension were prepared and frozen in − 80 ∘C to create a stool bank. | Colonoscopy | UPDRS-III, NMSS, Wexner constipation and BSS scores | 2, 4, 8, 12, 16, 20, and 24 weeks |
| Kuai et al. (2021) | Cohort (open-label pilot study) | 7 male vs. 4 femal | 11 FMT | Frozen fecal microbiota was obtained from the China fmtBank (Nanjing, China) | Nasojejunal | the Hoehn-Yahr (H-Y) grade, UPDRS score, NMSS, PAC-QOL score and Wexner constipation score | 12 weeks |
| Cheng et al. (2023) | RCT with open-label follow-up | 32 male vs. 22 femal | 27 FMT vs. 27 placebo | For stool donation for this trial, each donor provided stools for making FMT capsules for about 7 patients, and each patient in the FMT group was given 16 FMT capsules at each time, which are made from approximately 50 g of donated stool | Oral | the MDS-UPDRS score, safety (adverse effects), and evaluation for gastrointestinal disorders (including the IBS-SSS, GSRS, Bristol stool form scale, and IBS QOL scale scores) and evaluation for mental health (including the PHQ-9 scale, GDS-15 scale, GAD-7 scale, Montreal Cognitive Assessment, Mini-mental State Examination scores), and alterations in gut microbiota | 4, 8 and 12 weeks |
| DuPont et al. (2023) | RCT with open-label follow-up | 9 male vs. 3 femal | 8 FMT vs. 4 placebo | We administer a dose of 100 g of donor feces,lyophilized to 1.5 g of powder, contained in 10 capsules | Oral | safety(adverse effects), Microbiome changes, Self-reported clinical global improvement using a 100 point visual analog scale | 4, 8 and 12 weeks |
| Bruggeman et al. (2024) | RCT with open-label follow-up | 29 male vs. 17 femal | 22 FMT vs. 24 placebo | The faecal product was diluted with sterile saline and subsequently homoge nized anaerobically and filtered using a stomacher. Glycerol (10%) was added as a cryoprotectant to the filtered product resulting in a total volume of 200 mL. The faecal suspension was stored at −80 ∘C | Nasojejunal | the MDS-UPDRS score, Radiopaque pellets test, Levodopa-equivalent daily dose(LEDD), NMSS score, Parkinson's Disease Quality of Life Questionnaire (PDQ-39), Wexner Constipation Scale, Geriatric Depression Scale(GDS), Parkinson Anxiety Scale (PAS), Lille Apathy Rating Scale(LARS), Parkinson's Disease Sleep Scale(PDSS), Parkinson's Fatigue Scale(PFS), Montreal Cognitive Assessment(MoCA) | 3,6, 12 months |
| Scheperjans et al. (2024) | RCT with open-label follow-up | 25 male vs. 20 femal | 30 FMT vs. 15 placebo | Active treatment was a freeze-stored prepara tion of 30 g of feces from 1 of 2 donors, mixed with 150 mL of sterile physiological saline and 20 mL of 85% glycerol for cryoprotection to improve viability of microbes | Colonoscopy | the MDS-UPDRS score, the Hoehn-Yahr (H-Y) grade, Levodopa-equivalent daily dose(LEDD), TUG test (off medication), MoCA score, NMSS score, PDQ-39 SI score, IBS-SSS score, BDI-II score, BAI score, Wexner constipation score, Bowel movements, Intestinal volumes, Retained ROM markers | 6, 12 months |

Safety and efficacy of fecal microbiota transplantation in the treatment of Parkinson's disease: a systematic review of clinical trials

Kewei Chen[1], Lirong Sun[1], Yilan Liu[1] and Ran Chen[2]*

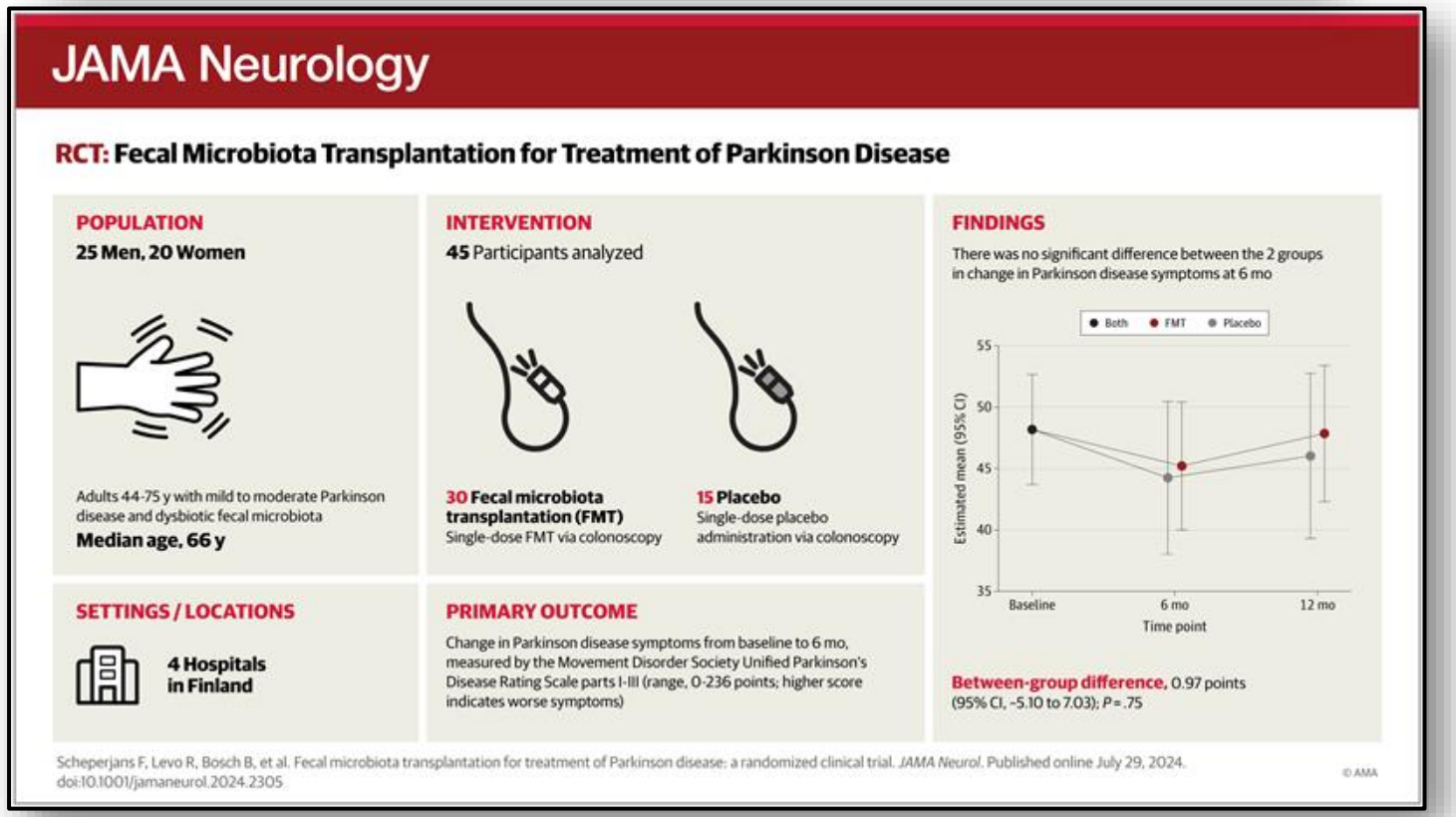
frontiers | Frontiers in Neuroscience

TYPE Systematic Review
PUBLISHED 20 August 2025
DOI 10.3389/fnins.2025.1639911

JAMA Neurology | Original Investigation

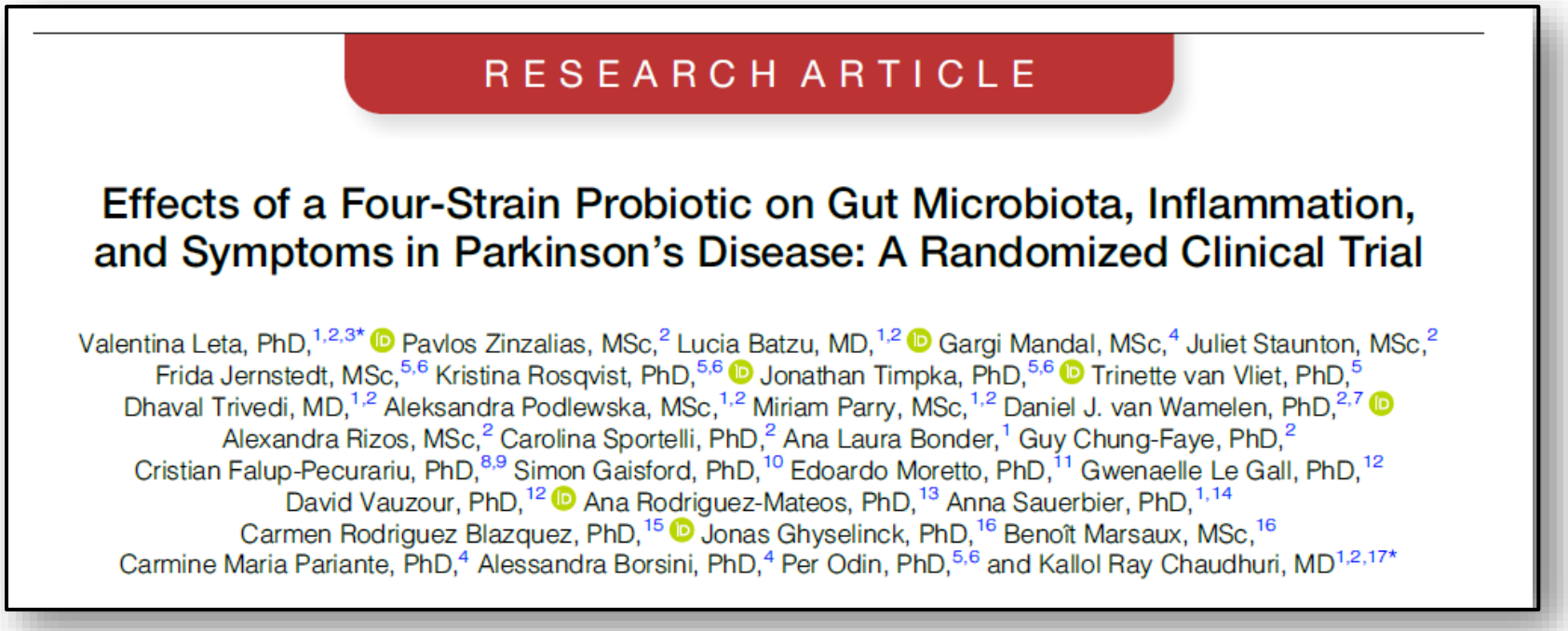
# Fecal Microbiota Transplantation for Treatment of Parkinson Disease
## A Randomized Clinical Trial

Filip Scheperjans, MD, PhD; Reeta Levo, RN; Berta Bosch, MSc; Mitja Lääperi, PhD; Pedro A. B. Pereira, PhD; Olli-Pekka Smolander, PhD; Velma T. E. Aho, PhD; Nora Vetkas, MD; Lotta Toivio, MSc; Veera Kainulainen, PhD; Tatyana D. Fedorova, MD, PhD; Perttu Lahtinen, MD, PhD; Rebekka Ortiz, MD, PhD; Valtteri Kaasinen, MD, PhD; Reetta Satokari, PhD; Perttu Arkkila, MD, PhD




- No benefit of FMT on primary outcome
- Gastrointestinal adverse events more common in FMT (53%) vs placebo group (7%)
- Dysbiosis status was reversed more frequently in placebo group (!)
- Some improvement of axial motor scores and cognition in placebo group (!)
- Beneficial effect of gut cleansing?

*JAMA Neurology 2024*



RESEARCH ARTICLE

# Effects of a Four-Strain Probiotic on Gut Microbiota, Inflammation, and Symptoms in Parkinson's Disease: A Randomized Clinical Trial

Valentina Leta, PhD,[1,2,3*] Pavlos Zinzalias, MSc,[2] Lucia Batzu, MD,[1,2] Gargi Mandal, MSc,[4] Juliet Staunton, MSc,[2] Frida Jernstedt, MSc,[5,6] Kristina Rosqvist, PhD,[5,6] Jonathan Timpka, PhD,[5,6] Trinette van Vliet, PhD,[5] Dhaval Trivedi, MD,[1,2] Aleksandra Podlewska, MSc,[1,2] Miriam Parry, MSc,[1,2] Daniel J. van Wamelen, PhD,[2,7] Alexandra Rizos, MSc,[2] Carolina Sportelli, PhD,[2] Ana Laura Bonder,[1] Guy Chung-Faye, PhD,[2] Cristian Falup-Pecurariu, PhD,[8,9] Simon Gaisford, PhD,[10] Edoardo Moretto, PhD,[11] Gwenaelle Le Gall, PhD,[12] David Vauzour, PhD,[12] Ana Rodriguez-Mateos, PhD,[13] Anna Sauerbier, PhD,[1,14] Carmen Rodriguez Blazquez, PhD,[15] Jonas Ghyselinck, PhD,[16] Benoît Marsaux, MSc,[16] Carmine Maria Pariante, PhD,[4] Alessandra Borsini, PhD,[4] Per Odin, PhD,[5,6] and Kallol Ray Chaudhuri, MD[1,2,17*]

- 74 participants randomised
  - 35 patients in treatment (probiotic) arm
  - 33 patients in control (placebo) arm
- Duration: 12 weeks
- Only patients with functionally significant constipation included

*Movement Disorders 2025*

# Probiotic study - results

**TABLE 2** *Changes in plasma levels of inflammatory cytokines in the active and placebo groups*

| | Active (n = 22) | | | Placebo (n = 19) | | |
|---|---|---|---|---|---|---|
| Cytokine (pg/mL) | Baseline | Follow-up | *P* | Baseline | Follow-up | *P* |
| IFN-γ | 6.60 ± 4.19 | 6.09 ± 5.00 | 0.372 | 3.90 ± 2.30 | 12.93 ± 41.58 | 0.778 |
| TNF-α | 2.04 ± 1.40 | 1.69 ± 0.93 | **0.024** | 1.37 ± 0.42 | 1.69 ± 0.63 | **0.005** |
| IL-6 | 1.01 ± 0.49 | 0.81 ± 0.45 | **0.028** | 1.16 ± 1.23 | 1.45 ± 2.34 | **0.040** |
| IL-8 | 13.00 ± 4.37 | 11.69 ± 3.91 | 0.149 | 11.49 ± 5.23 | 11.17 ± 3.97 | 0.520 |
| IL-10 | 0.33 ± 0.34 | 0.32 ± 0.49 | 0.115 | 0.19 ± 0.09 | 0.19 ± 0.08 | 0.809 |

**TABLE 3** *Changes in motor and non-motor outcomes in the active and placebo groups*

| | Active (n = 35) | | | | Placebo (n = 33) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | *P* | *d* | Baseline | Follow-up | *P* | *d* |
| *On*-MDS-UPDRS-III | 35.49 ± 17.59 | 30.88 ± 16.76 | 0.149 | 0.366 | 35.85 ± 16.15 | 30.60 ± 14.99 | 0.058 | 0.505 |
| MDS-UPDRS-IV | 3.86 ± 3.71 | 4.54 ± 4.05 | 0.133 | 0.440 | 3.82 ± 3.98 | 3.42 ± 3.00 | 0.740 | 0.082 |
| Time-to-*on* (min) | 31.43 ± 25.22 | 23.95 ± 27.50 | **0.027** | 0.709 | 32.70 ± 38.31 | 27.65 ± 28.74 | 0.260 | 0.362 |
| NMSS | 70.71 ± 45.22 | 61.34 ± 47.20 | **0.005** | 0.704 | 56.88 ± 30.43 | 54.36 ± 36.29 | 0.440 | 0.191 |

- No overall change in differential microbiome abundance (primary outcome)
- No change in SCFA
- Some enrichment of gut microbiota with putative beneficial effect
- Significant change of TNF-alpha
- Marked improvement of NMSS, in particular constipation
- Shortened time-to-on…

***….due to improved constipation?***

# FMT and Probiotic trials – comment and context

*"We suggest that future FMT (and probiotic) trials should incorporate blood, metabolites, urine and functional neuroimaging biological markers and control dietary, lifestyle comorbidities, medication intake and/or other potential variables, and to ensure optimal evaluation of interactions between the gut microbes and brain outcomes prospectively over a longer time frame."*

*Tan et al, Brain 2025*

RESEARCH ARTICLE

**Constipation Is Linked to Neuroinflammation in Early Parkinson's Disease**

Marta Camacho, PhD,[1*] Julia C. Greenland, MRCP, PhD,[1] Alexander R.D. Peattie, PhD,[1] Lennart R.B. Spindler, PhD,[1,2] Jonathan Holbrook, PhD,[1] Lakmini Kahanawita, MS,[1] Tim D. Fryer, PhD,[1,3] Young T. Hong, PhD,[1,3] and Caroline H. Williams-Gray, FRCP, PhD[1]

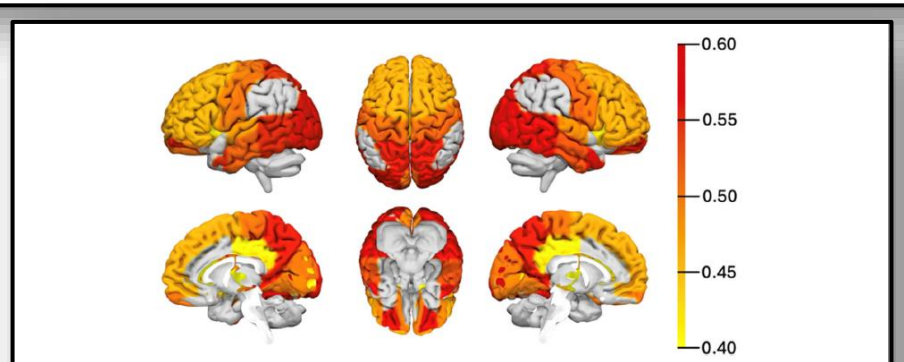



FIG. 2. Regions of interest (ROIs) with significant partial correlations ($P < 0.05$) between regional $^{11}$C-PK11195 $BP_{ND}$ and GIDS-PD constipation scores, adjusted for age and sex (n = 27). Color bar denotes the strength of the partial correlation, with red being the highest correlation strength. $BP_{ND}$, non-displaceable binding potential; GIDS-PD, Gastrointestinal Dysfunction Scale for Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

Significant correlation between constipation and:

- 11C-PK11195 binding in the brain
- Higher CSF lymphocyte count
- Higher blood T helper cells

***How much are any observed effects in FMT/probiotic trials simply due to improved constipation?***

*Movement Disorders 2025*

# The past and the future

# 1993 - First neuroprotection trial in PD

176 THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 21, 1993

**EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON'S DISEASE**

THE PARKINSON STUDY GROUP*

- 800 patients, 4 treatment arms:
  - Deprenyl (MAO-B inhibitor)
  - Tocopherol (vitamin E)
  - Deprenyl and Tocopherol
  - Placebo

- Primary outcome –UPDRS/part III
- Trial duration: 24 months

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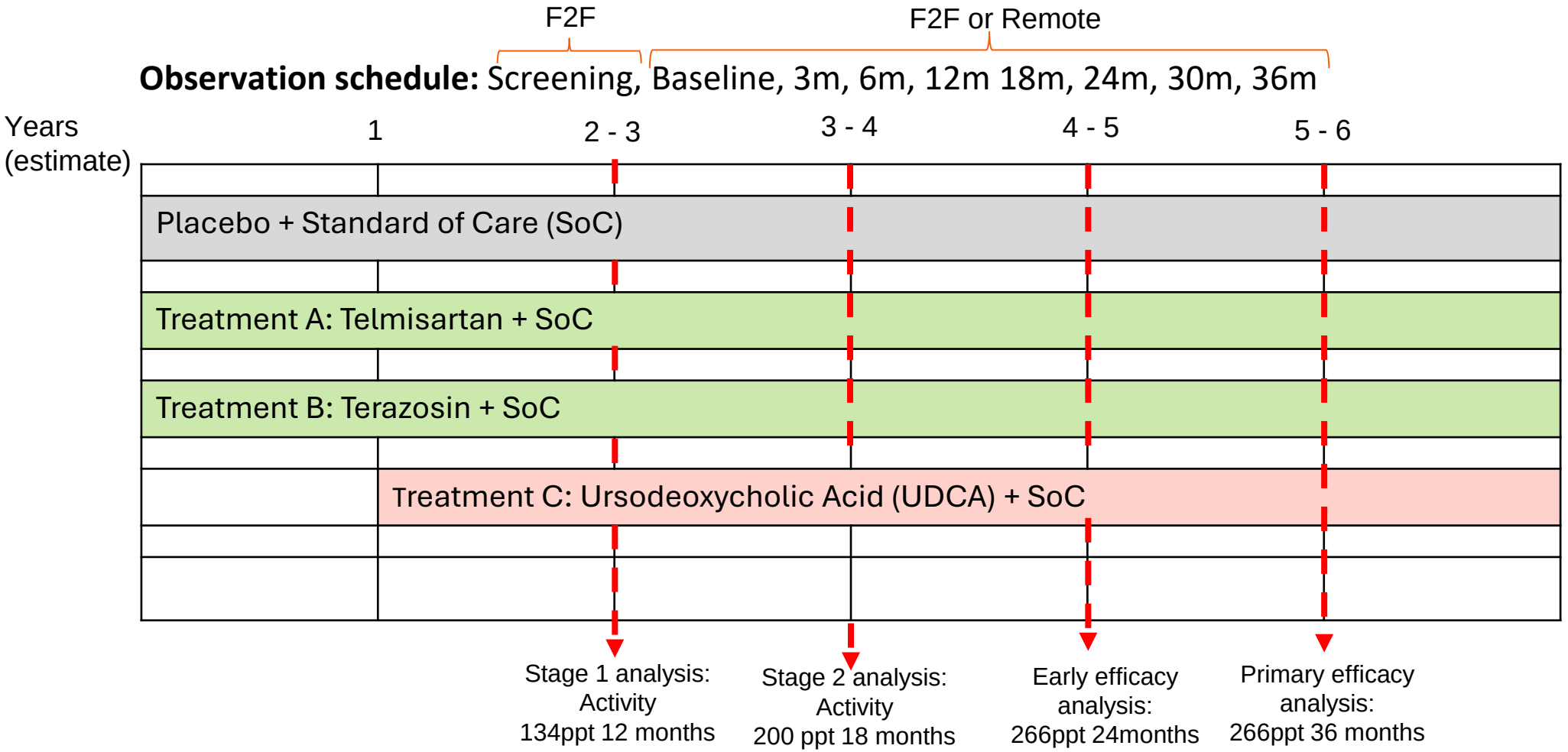
  - Deprenyl and Tocopherol
  - Placebo

- Primary outcome –UPDRS/part III
- Trial duration: 24 months

- *No objective biomarker*
- *Symptomatic effect of "neuroprotective" treatment*
- *How long should a definitive phase 3 trial be for PD?*

# The future has arrived…

# Trial design overview:



# EJS-ACT-PD trial outline

- ***Recruitment target: 1600 patients (400 per treatment arm)***
- Recruitment rate: 400 patients per year
- Site target: 40 sites across the UK
- ***Treatment duration: 36 months***
- Stratification: Sex, site tier, age, Hoehn& Yahr
- ***Primary endpoint: 30% reduction in rate of progression on MDS-UPDRS part 1+2***
- Interim analysis outcome: Inverse variance weighted MDS-UPDRS part 1, 2 and remote 3

**Patient-reported outcomes**

# Conclusion

- Neuroprotection research for PD has become a highly active landscape
- EJS-ACT-PD, if successful, will transform the PD trial landscape forever
- Similar platform approaches required for phase 2 trials
- Novel trial concepts must be explored
  - Basket trials, n=1 trials, drug combination therapy trials, etc
- Non-pharmacological interventions underexplored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Clinical Trial Highlights

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]