Updates in Parkinson's Disease Treatment

March 2025

Andrea Fuentes, MD

Stanford University

Disclores

- None

Current Landscape

- Carbidopa/levodopa remains mainstay of therapy
  - But has its limitations – side effects, short acting → motor fluctuations
- Interest in longer acting medications to improve symptom management
- Need for disease-modifying therapies – to slow or halt disease progression

Presentation Goals

- Review recently approved PD treatments
  - What role do they serve? Who should use them?

- Highlight promising therapies in the drug development pipeline

Novel levodopa use

Crexont

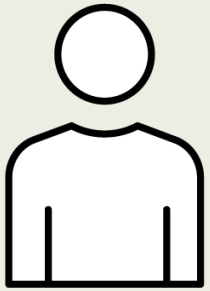
- Carbidopa/levodopa extended-release capsules
- Contains both immediate release and delayed release pellets
- Goals:
  - Improve “good ON time”
  - Reduce OFF time
  - Reduce dosing frequency
- FDA approved August 2024

JAMA Neurology

RCT: IPX203 vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease

POPULATION

396 Men, 234 Women



Patients with Parkinson disease aged ≥40 y experiencing a mean of ≥2.5 h daily off-time

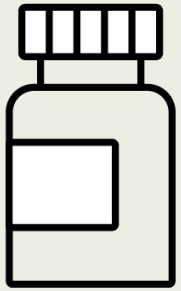
Mean age, 66.5 y

INTERVENTION

506 Patients randomized

3x per day (every 6 hours)

256 Extended-release carbidopa-levodopa (IPX203)
Double-blind, double-dummy treatment with IPX203 in a 13-wk maintenance period

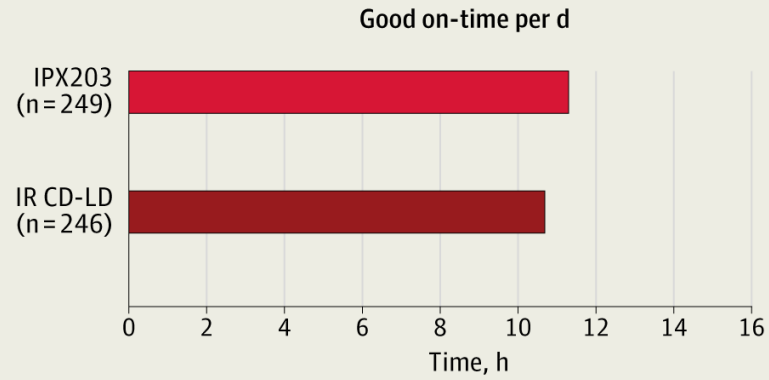


5x per day

250 Immediate-release carbidopa-levodopa (IR CD-LD)
Double-blind, double-dummy treatment with IR CD-LD in a 13-wk maintenance period

FINDINGS

There was a statistically significant improvement in good on-time per day for IPX203 compared with IR CD-LD



Least-squares mean change in good on-time:
IPX203: **−0.50 h (95% CI, −0.86 to −0.14)**
IR CD-LD: **−1.03 h (95% CI, −1.39 to −0.67)**

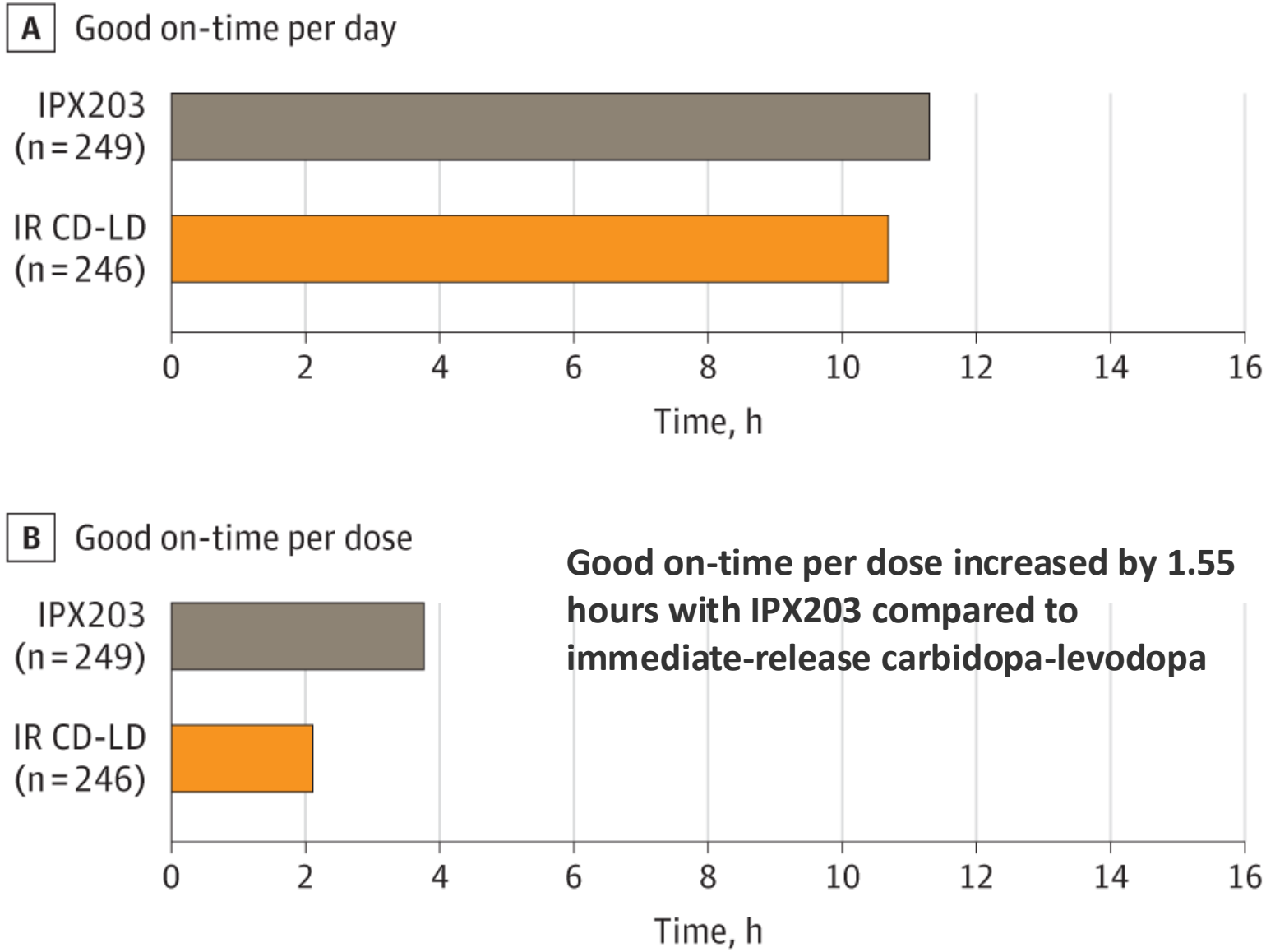
SETTINGS / LOCATIONS

105 Centers in the US and Europe

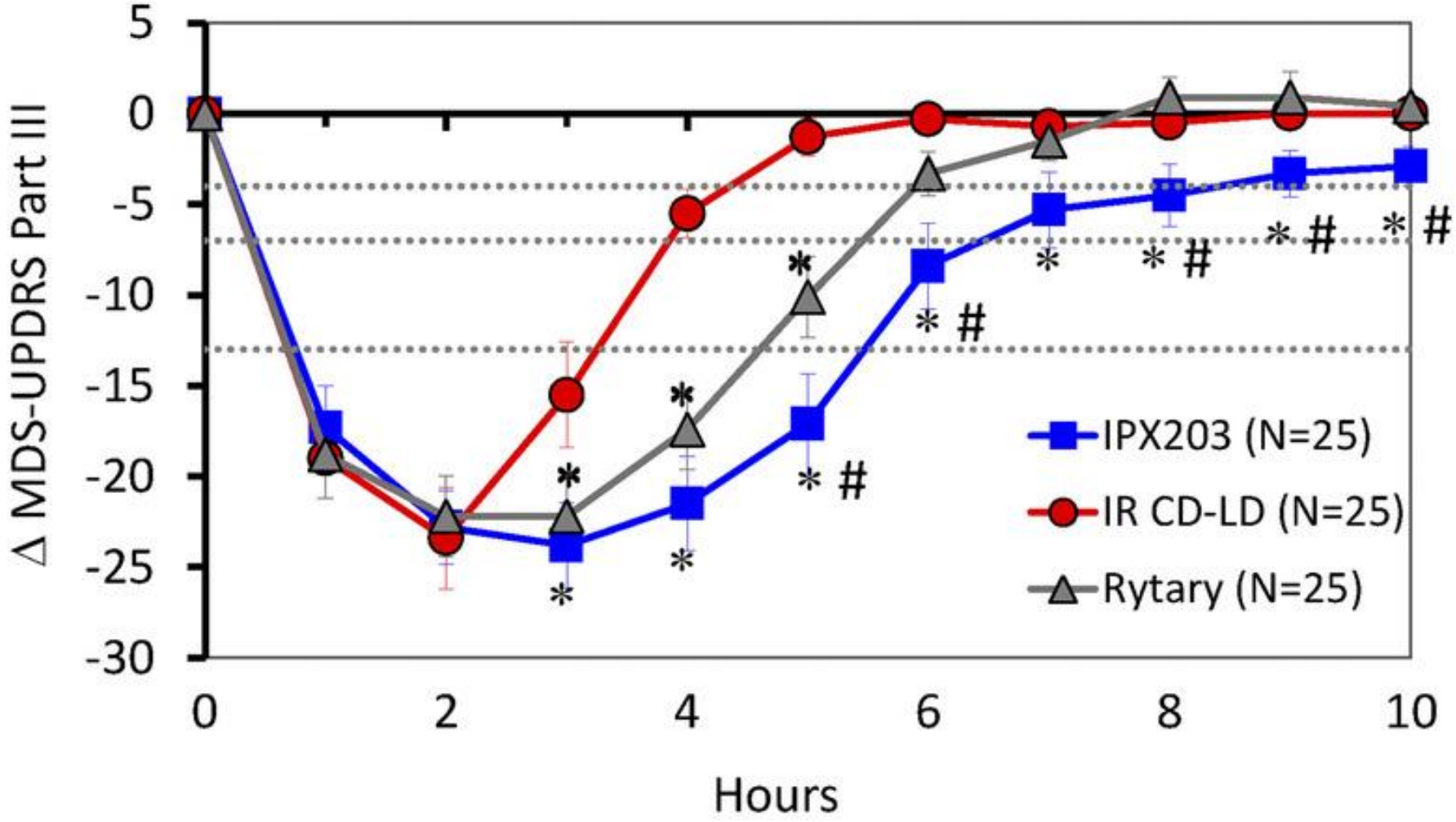
PRIMARY OUTCOME

Mean change from baseline in daily good on time (on-time without troublesome dyskinesia), averaged over 3 Parkinson disease diary days, to the end of the double-blind treatment period

Hauser RA, Espay AJ, Ellenbogen AL, et al. IPX203 vs immediate-release carbidopa-levodopa for the treatment of motor fluctuations in Parkinson disease: the RISE-PD randomized clinical trial. *JAMA Neurol*. Published online August 14, 2023. doi:10.1001/jamaneurol.2023.2679



Good on-time per dose increased by 1.55 hours with IPX203 compared to immediate-release carbidopa-levodopa



* $p<0.05$ compared with IR CD-LD

\# $p<0.05$ compared with Rytary

CREXONT comes in 4 dose strengths

Taken 2-4 times per day
Typically 1-2 capsules per dose

35 mg carbidopa
140 mg levodopa

52.5 mg carbidopa
210 mg levodopa

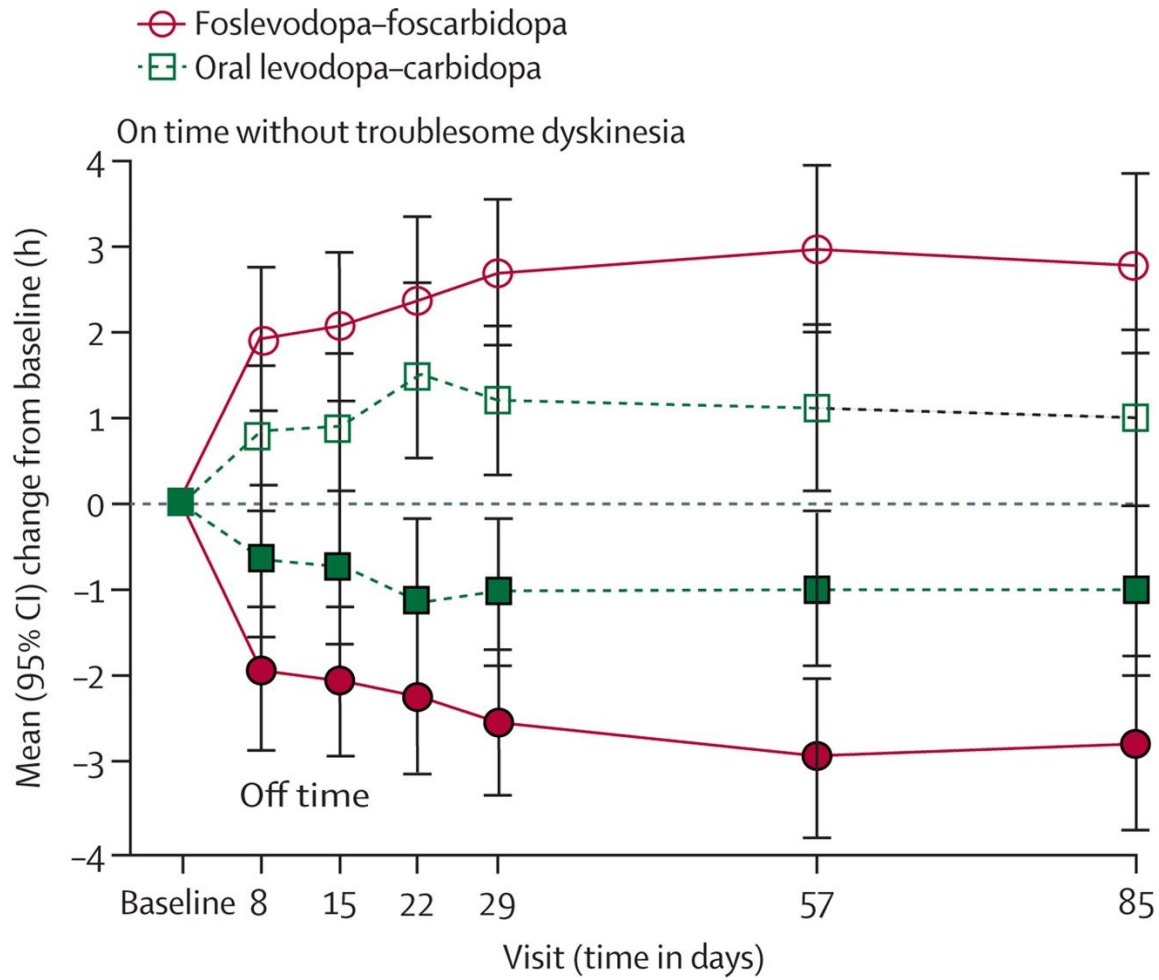
70 mg carbidopa
280 mg levodopa

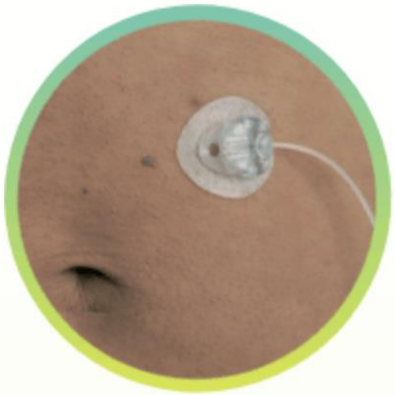
87.5 mg carbidopa
350 mg levodopa

Capsules shown are not actual size.

Vyalev

- Foscarbidopa/foslevodopa
  - Gets converted to carbidopa/levodopa
- Continuous, 24-hour infusion
- Subcutaneous (under the skin)
- Goals:
  - Reduce OFF time
  - Reduce dosing frequency
- FDA approved October 2024


Foslevodopa–foscarbidopa
Oral levodopa–carbidopa
On time without troublesome dyskinesia
Mean (95% CI) change from baseline (h)
4
3
2
1
0
−1
−2
−3
−4
Off time
Baseline
8
15
22
29
57
85
Visit (time in days)
Oral levodopa–carbidopa
n=67 65 63 39 62 62 62
Foslevodopa–foscarbidopa
n=73 70 66 39 54 47 47



Can be temporarily disconnected

Disconnect for up to 1 hour for water-based activities, such as swimming or showering

Small and less than 1 lb (0.63 lb)

Approximately the size of 2 stacked cell phones

Infusion Site Effects

- Redness 27%
- Pain 26%
- Swelling 12%

“mild to moderate severity”

- Infection 1%

Onapgo

- Subcutaneous apomorphine
- Mechanism: dopamine agonist
  - Stimulates dopamine receptors
- FDA approved February 2025
- Will be available in mid-late 2025

Help smooth the ups and downs in your day

ONAPGO provides a constant delivery of apomorphine through a wearable infusion device that is generally worn all day.

Actor portrayal

Attaches to your skin with a small cannula and connecting line, similar to insulin devices

About the size and weight of an average smartphone

Side Effects

- “The most common adverse events were skin reactions, nausea, and somnolence”
- Commonly started with an anti-nausea medication

“Adjunct” therapies

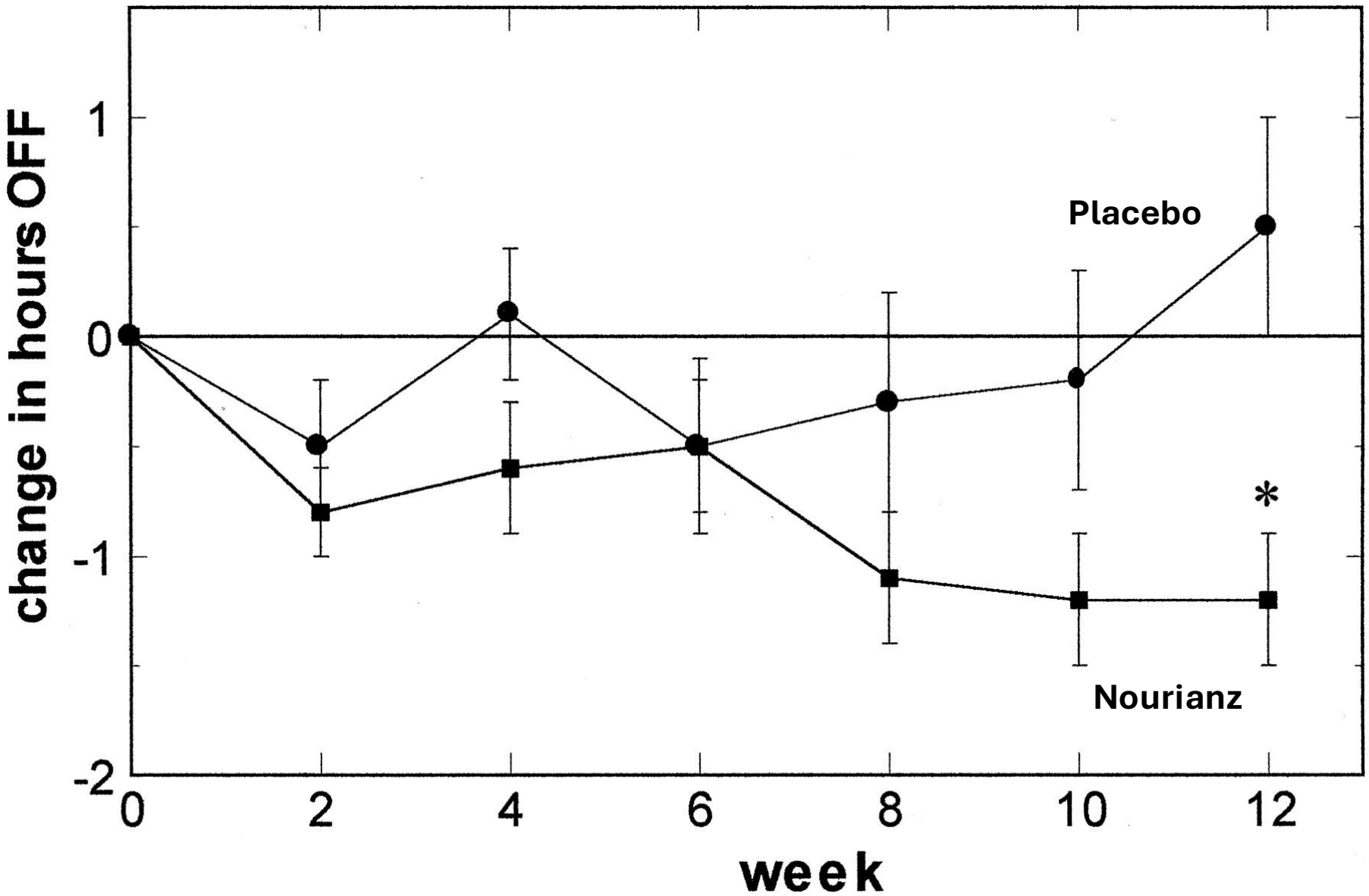
- *supplemental*

Ogentys

- Opicapone
- Longer acting version of entacapone
- Mechanism: COMT inhibitor
  - Reduces the *breakdown* of dopamine
- Goal: reduce OFF time
- FDA approved April 2020

Nourianz

- Istradefylline
- Mechanism: new, acts on adenosine pathways, different than dopamine
- Goal: reduce OFF time
- FDA approved August 2019


change in hours OFF
1
0
-1
-2
0
2
4
6
8
10
12
week
Placebo
Nourianz
*

Adverse events	Placebo, n = 29	Istradefylline	
		5/10/20 mg/d, n = 26	10/20/40 mg/d, n = 28
Nausea	2 (6.9)	9 (34.6)	6 (21.4)
Dyskinesia aggravated	4 (13.8)	5 (19.2)	4 (14.3)
Dizziness	1 (3.4)	4 (15.4)	3 (10.7)
Vomiting	2 (6.9)	3 (11.5)	2 (7.1)
Insomnia	3 (10.3)	3 (11.5)	2 (7.1)
PD aggravated		3 (11.5)	1 (3.6)
Nasopharyngitis	1 (3.4)	2 (7.7)	2 (7.1)
Lipase increased		3 (11.5)	1 (3.6)
Anxiety		2 (7.7)	1 (3.6)
Upper respiratory tract infection		1 (3.8)	2 (7.1)
Urinary tract infection	1 (3.4)	1 (3.8)	2 (7.1)
Postural hypotension	3 (10.3)		3 (10.7)

Values are n (%).

PD = Parkinson's disease.

Xadago

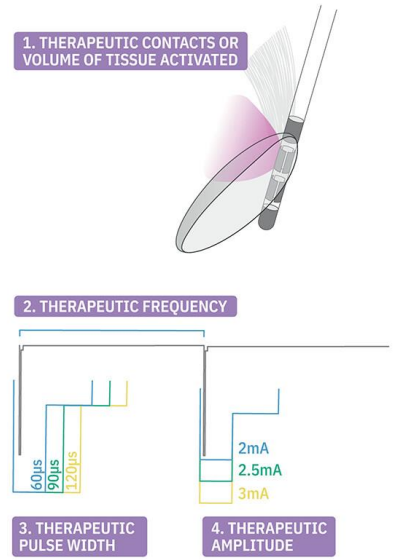
- Safinamide
- Mechanism: MAO-B inhibitors
  - Reduces the *breakdown* of dopamine
- Goal: reduce OFF time
- FDA approved March 2017

Device-Assisted Therapy

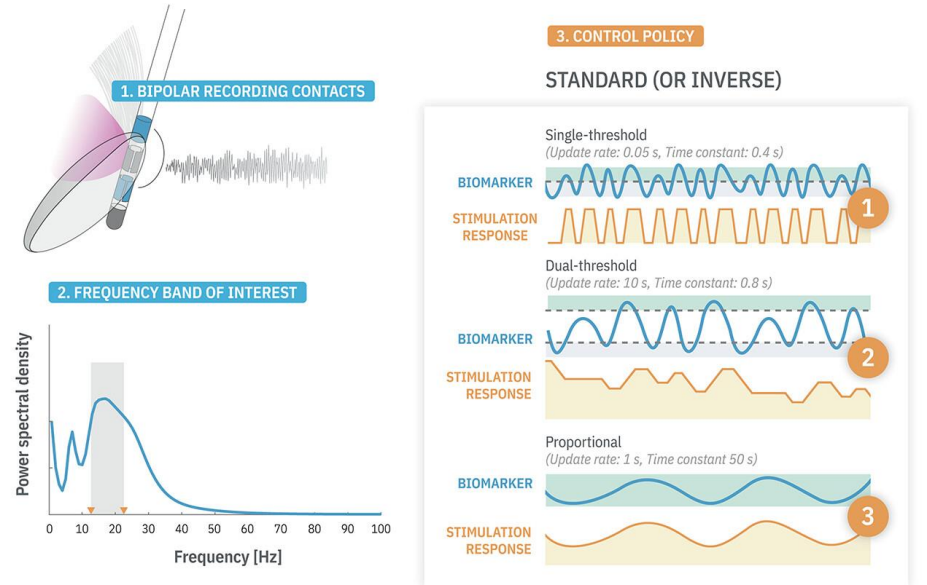
Adaptive DBS

- “closed loop” – automatically adjusts stimulation parameters based on a person’s real-time brain activity
- Goal: reduce motor fluctuations
- FDA approved February 2025

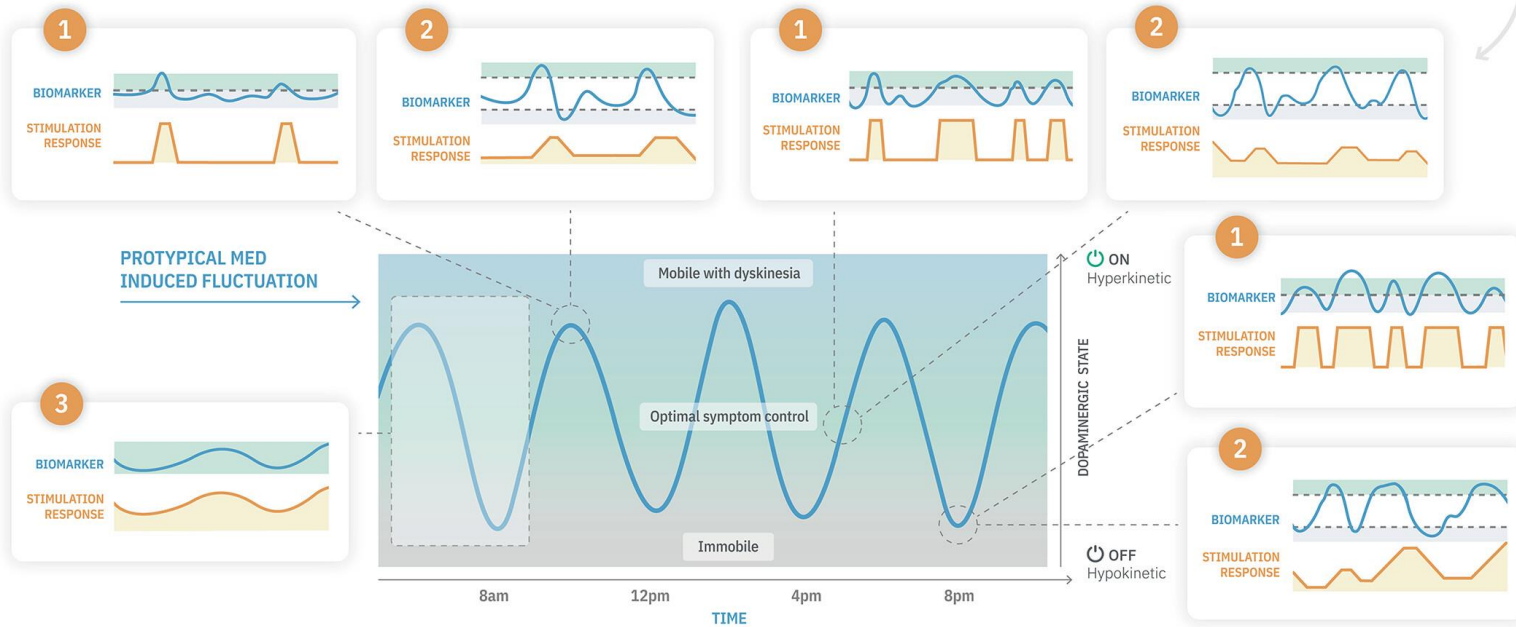
A Conventional DBS parameters



B Additional adaptative DBS parameters



C Prototypical Medication Induced Fluctuations



Emerging Therapies & Research Updates

Monoclonal antibodies

- Anti-alpha-synuclein targeting
- Goal: reduce neuronal toxicity
- Prasinezumab
  - 586 participants with early PD (PADOVA study)
  - Placebo vs prasinezumab infusion
  - Trend towards improvement in motor symptoms in prasinezumab group, although not statistically significant
- Minzasolmin
  - >450 participants with early PD (ORCHESTRA study)
  - Placebo vs minzasolmin oral med
  - Found no effect on PD, stopped testing

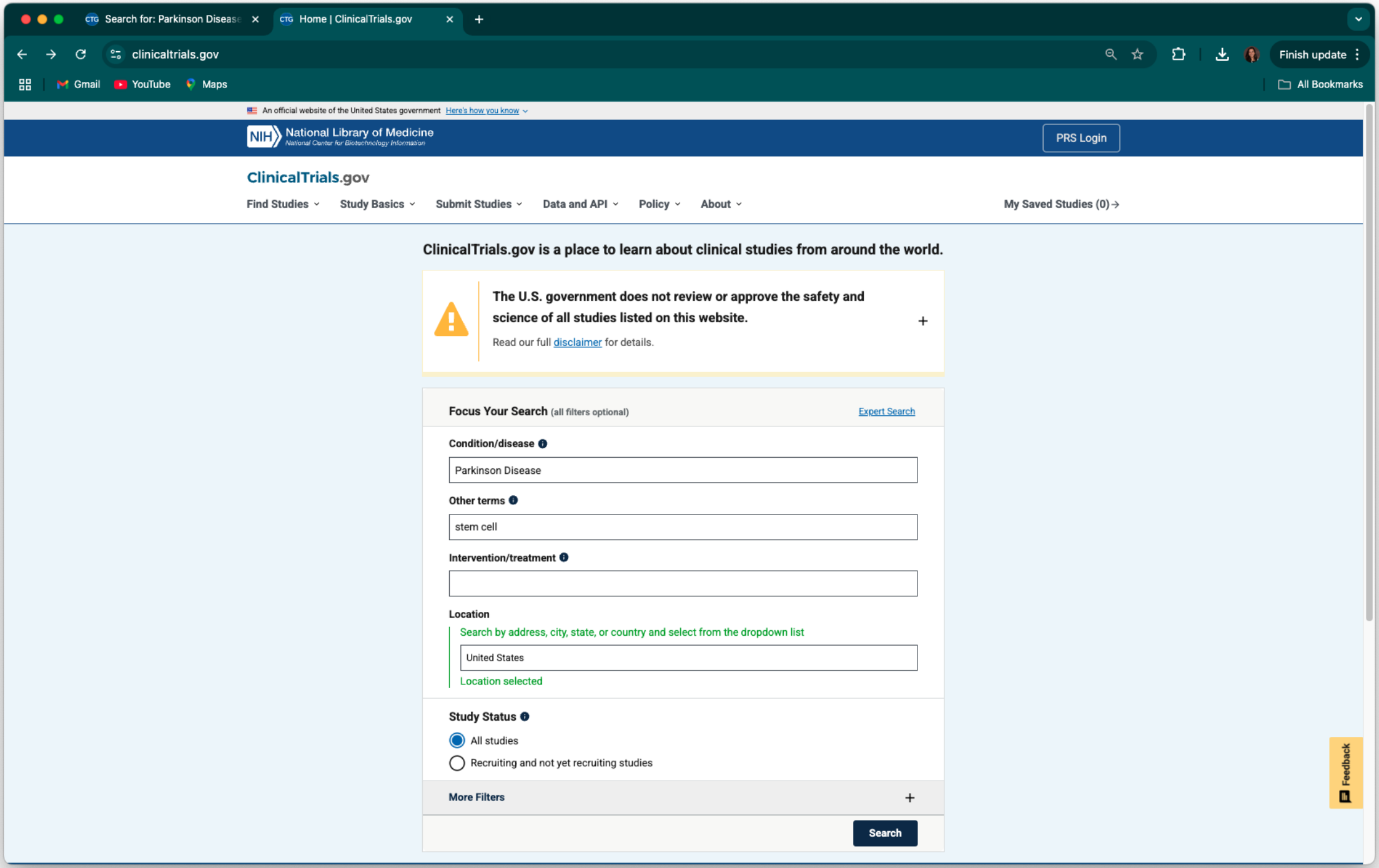
GLP-1 receptor agonists?

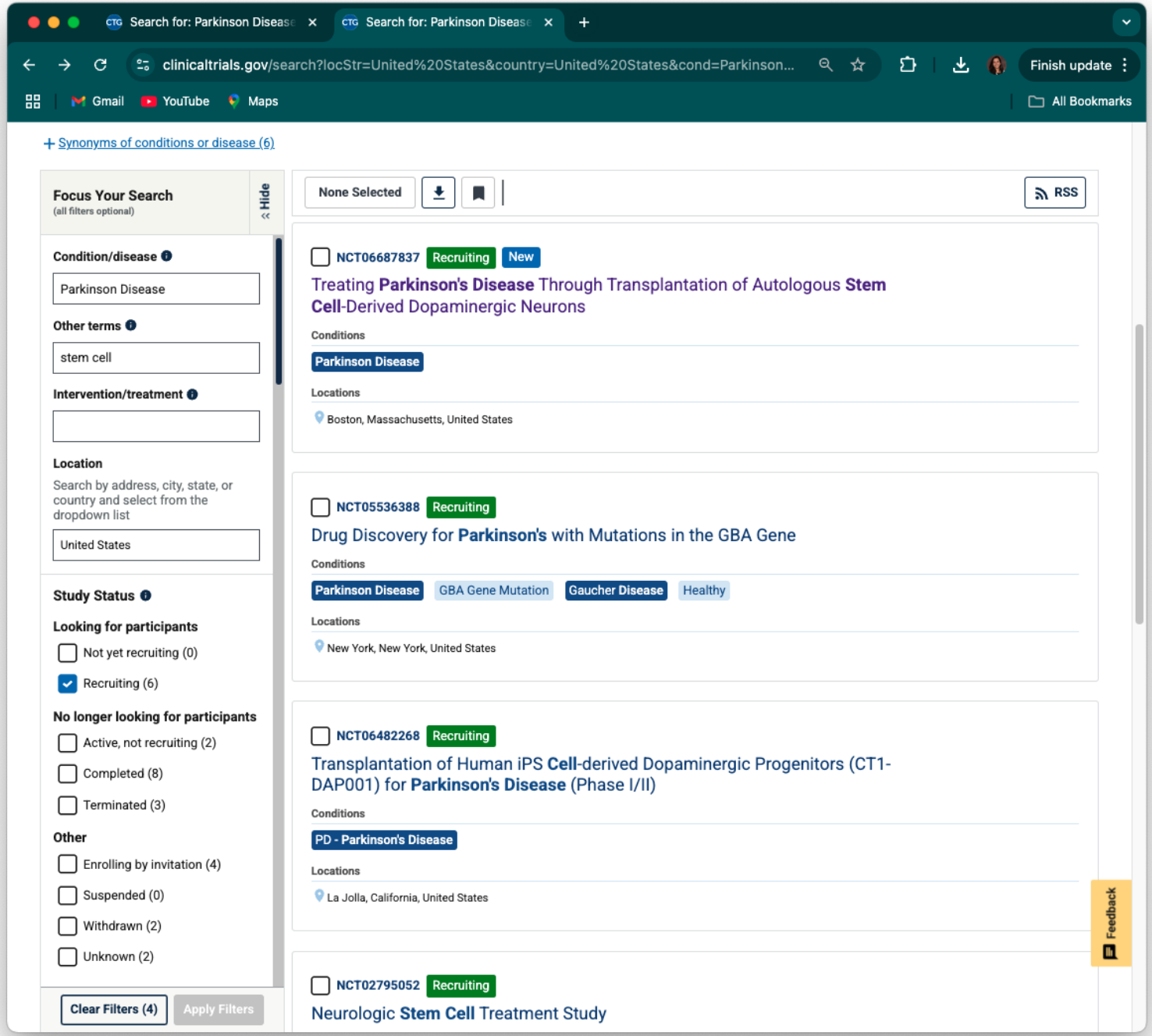
- Originally developed as treatment for diabetes
- Stimulates insulin release in high blood sugar states
- May also promote neuron survival and growth
- Reduces risk of PD in people with diabetes

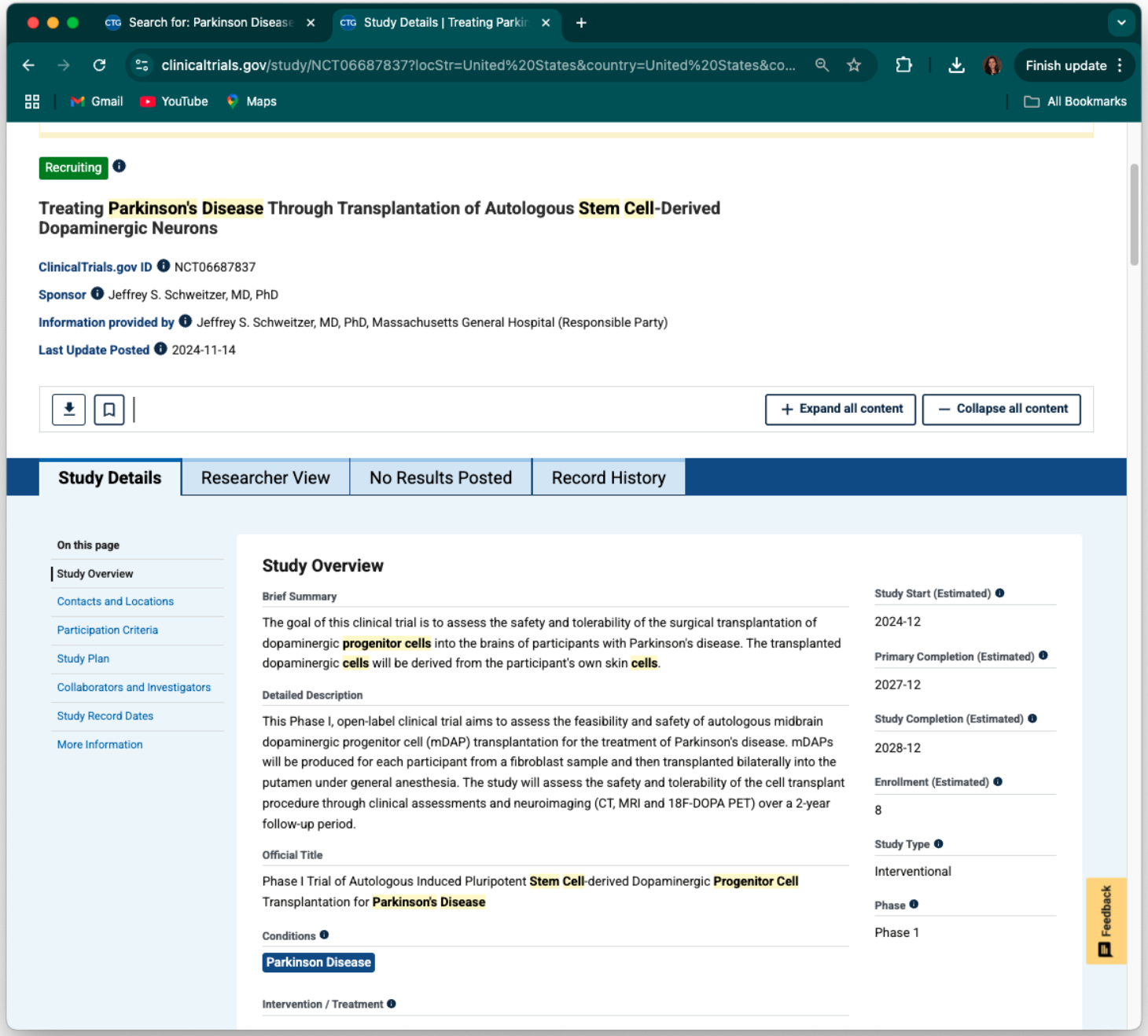
- Study on lixisenatide vs placebo in participants with PD showed motor improvement
- Recent study on exenatide vs placebo in participants with PD found no benefit
  - Largest and longest study to date of a GLP-1 receptor agonist

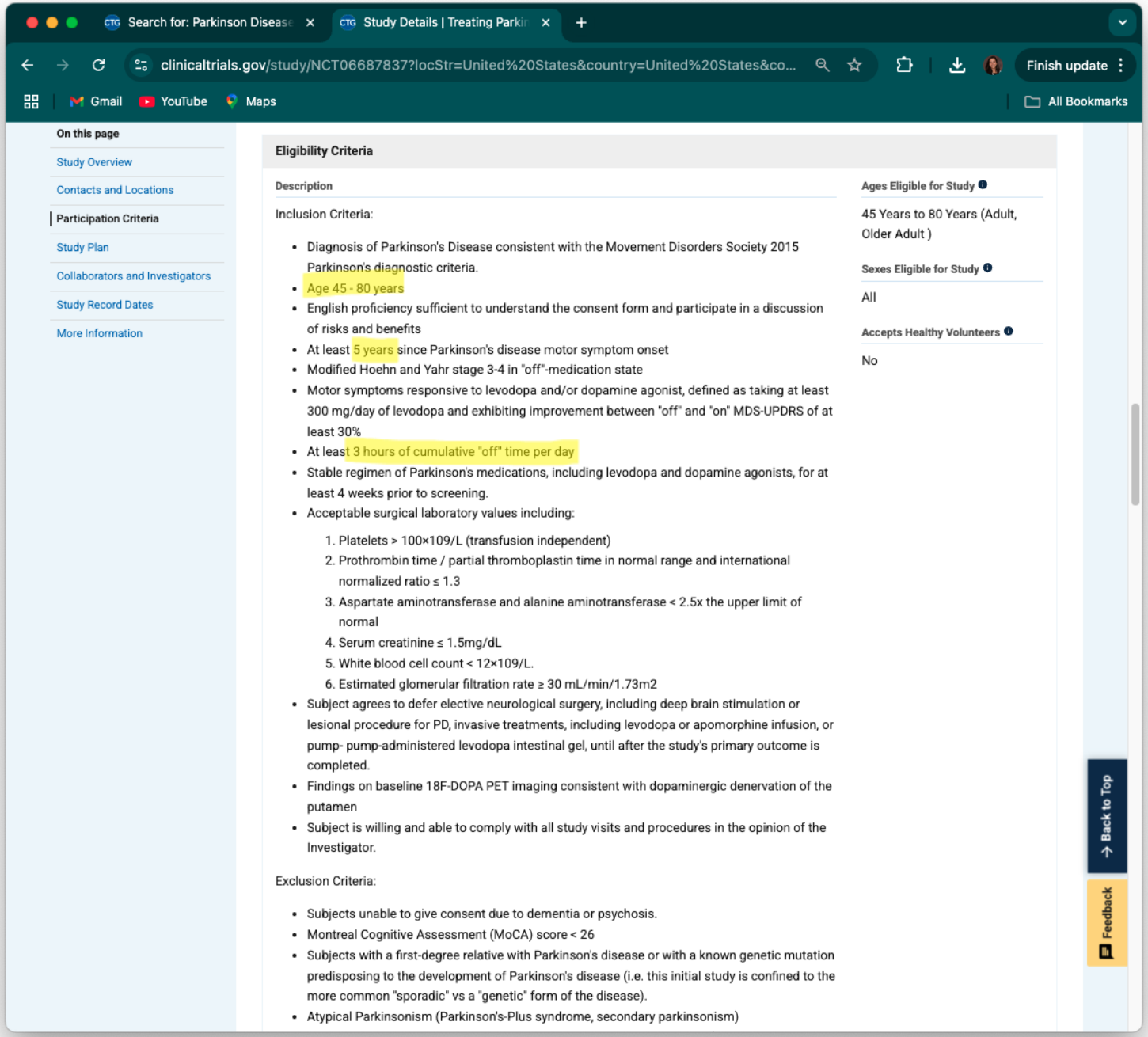
Stem cells

- Embryonic stem cells = cell in an embryo that can become any other type of cell in the body
- Induced pluripotent stem cells = cells that are programmed to become a different kind of cell
  - i.e. skin cell becomes a liver cell
- Can we use stem cells to replace lost dopamine neurons in PD?
  - To treat symptoms, not disease modifying
- Clinical trials are in *early* stages to test safety and efficacy


Search for: Parkinson Disease
Home | ClinicalTrials.gov
clinicaltrials.gov
Finish update
Gmail
YouTube
Maps
All Bookmarks
An official website of the United States government Here's how you know
National Library of Medicine
National Center for Biotechnology Information
PRS Login
ClinicalTrials.gov
Find Studies
Study Basics
Submit Studies
Data and API
Policy
About
My Saved Studies (0)
ClinicalTrials.gov is a place to learn about clinical studies from around the world.
The U.S. government does not review or approve the safety and science of all studies listed on this website.
Read our full disclaimer for details.
Focus Your Search (all filters optional)
Expert Search
Condition/disease
Parkinson Disease
Other terms
stem cell
Intervention/treatment
Location
Search by address, city, state, or country and select from the dropdown list
United States
Location selected
Study Status
All studies
Recruiting and not yet recruiting studies
More Filters
Search
Feedback


Search for: Parkinson Disease
Search for: Parkinson Disease
clinicaltrials.gov/search?locStr=United%20States&country=United%20States&cond=Parkinson...
Finish update
Gmail
YouTube
Maps
All Bookmarks
+ Synonyms of conditions or disease (6)
Focus Your Search
(all filters optional)
Hide
Condition/disease
Parkinson Disease
Other terms
stem cell
Intervention/treatment
Location
Search by address, city, state, or country and select from the dropdown list
United States
Study Status
Looking for participants
Not yet recruiting (0)
Recruiting (6)
No longer looking for participants
Active, not recruiting (2)
Completed (8)
Terminated (3)
Other
Enrolling by invitation (4)
Suspended (0)
Withdrawn (2)
Unknown (2)
Clear Filters (4)
Apply Filters
None Selected
RSS
NCT06687837 Recruiting New
Treating Parkinson's Disease Through Transplantation of Autologous Stem Cell-Derived Dopaminergic Neurons
Conditions
Parkinson Disease
Locations
Boston, Massachusetts, United States
NCT05536388 Recruiting
Drug Discovery for Parkinson's with Mutations in the GBA Gene
Conditions
Parkinson Disease
GBA Gene Mutation
Gaucher Disease
Healthy
Locations
New York, New York, United States
NCT06482268 Recruiting
Transplantation of Human iPS Cell-derived Dopaminergic Progenitors (CT1-DAP001) for Parkinson's Disease (Phase I/II)
Conditions
PD - Parkinson's Disease
Locations
La Jolla, California, United States
NCT02795052 Recruiting
Neurologic Stem Cell Treatment Study
Feedback


Search for: Parkinson Disease
Study Details | Treating Parkin
clinicaltrials.gov/study/NCT06687837?locStr=United%20States&country=United%20States&co...
Finish update
Gmail
YouTube
Maps
All Bookmarks
Recruiting
Treating Parkinson's Disease Through Transplantation of Autologous Stem Cell-Derived Dopaminergic Neurons
ClinicalTrials.gov ID NCT06687837
Sponsor Jeffrey S. Schweitzer, MD, PhD
Information provided by Jeffrey S. Schweitzer, MD, PhD, Massachusetts General Hospital (Responsible Party)
Last Update Posted 2024-11-14
+ Expand all content
— Collapse all content
Study Details
Researcher View
No Results Posted
Record History
On this page
Study Overview
Contacts and Locations
Participation Criteria
Study Plan
Collaborators and Investigators
Study Record Dates
More Information
Study Overview
Brief Summary
The goal of this clinical trial is to assess the safety and tolerability of the surgical transplantation of dopaminergic progenitor cells into the brains of participants with Parkinson's disease. The transplanted dopaminergic cells will be derived from the participant's own skin cells.
Detailed Description
This Phase I, open-label clinical trial aims to assess the feasibility and safety of autologous midbrain dopaminergic progenitor cell (mDAP) transplantation for the treatment of Parkinson's disease. mDAPs will be produced for each participant from a fibroblast sample and then transplanted bilaterally into the putamen under general anesthesia. The study will assess the safety and tolerability of the cell transplant procedure through clinical assessments and neuroimaging (CT, MRI and 18F-DOPA PET) over a 2-year follow-up period.
Official Title
Phase I Trial of Autologous Induced Pluripotent Stem Cell-derived Dopaminergic Progenitor Cell Transplantation for Parkinson's Disease
Conditions
Parkinson Disease
Intervention / Treatment
Study Start (Estimated)
2024-12
Primary Completion (Estimated)
2027-12
Study Completion (Estimated)
2028-12
Enrollment (Estimated)
8
Study Type
Interventional
Phase
Phase 1
Feedback



On this page
Study Overview
Contacts and Locations
Participation Criteria
Study Plan
Collaborators and Investigators
Study Record Dates
More Information

Eligibility Criteria

Description

Inclusion Criteria:

- Diagnosis of Parkinson's Disease consistent with the Movement Disorders Society 2015 Parkinson's diagnostic criteria.
- Age 45 - 80 years
- English proficiency sufficient to understand the consent form and participate in a discussion of risks and benefits
- At least 5 years since Parkinson's disease motor symptom onset
- Modified Hoehn and Yahr stage 3-4 in "off"-medication state
- Motor symptoms responsive to levodopa and/or dopamine agonist, defined as taking at least 300 mg/day of levodopa and exhibiting improvement between "off" and "on" MDS-UPDRS of at least 30%
- At least 3 hours of cumulative "off" time per day
- Stable regimen of Parkinson's medications, including levodopa and dopamine agonists, for at least 4 weeks prior to screening.
- Acceptable surgical laboratory values including:
    1. Platelets > 100×109/L (transfusion independent)
    2. Prothrombin time / partial thromboplastin time in normal range and international normalized ratio ≤ 1.3
    3. Aspartate aminotransferase and alanine aminotransferase < 2.5x the upper limit of normal
    4. Serum creatinine ≤ 1.5mg/dL
    5. White blood cell count < 12×109/L.
    6. Estimated glomerular filtration rate ≥ 30 mL/min/1.73m2
- Subject agrees to defer elective neurological surgery, including deep brain stimulation or lesional procedure for PD, invasive treatments, including levodopa or apomorphine infusion, or pump- pump-administered levodopa intestinal gel, until after the study's primary outcome is completed.
- Findings on baseline 18F-DOPA PET imaging consistent with dopaminergic denervation of the putamen
- Subject is willing and able to comply with all study visits and procedures in the opinion of the Investigator.

Exclusion Criteria:

- Subjects unable to give consent due to dementia or psychosis.
- Montreal Cognitive Assessment (MoCA) score < 26
- Subjects with a first-degree relative with Parkinson's disease or with a known genetic mutation predisposing to the development of Parkinson's disease (i.e. this initial study is confined to the more common "sporadic" vs a "genetic" form of the disease).
- Atypical Parkinsonism (Parkinson's-Plus syndrome, secondary parkinsonism)

Ages Eligible for Study

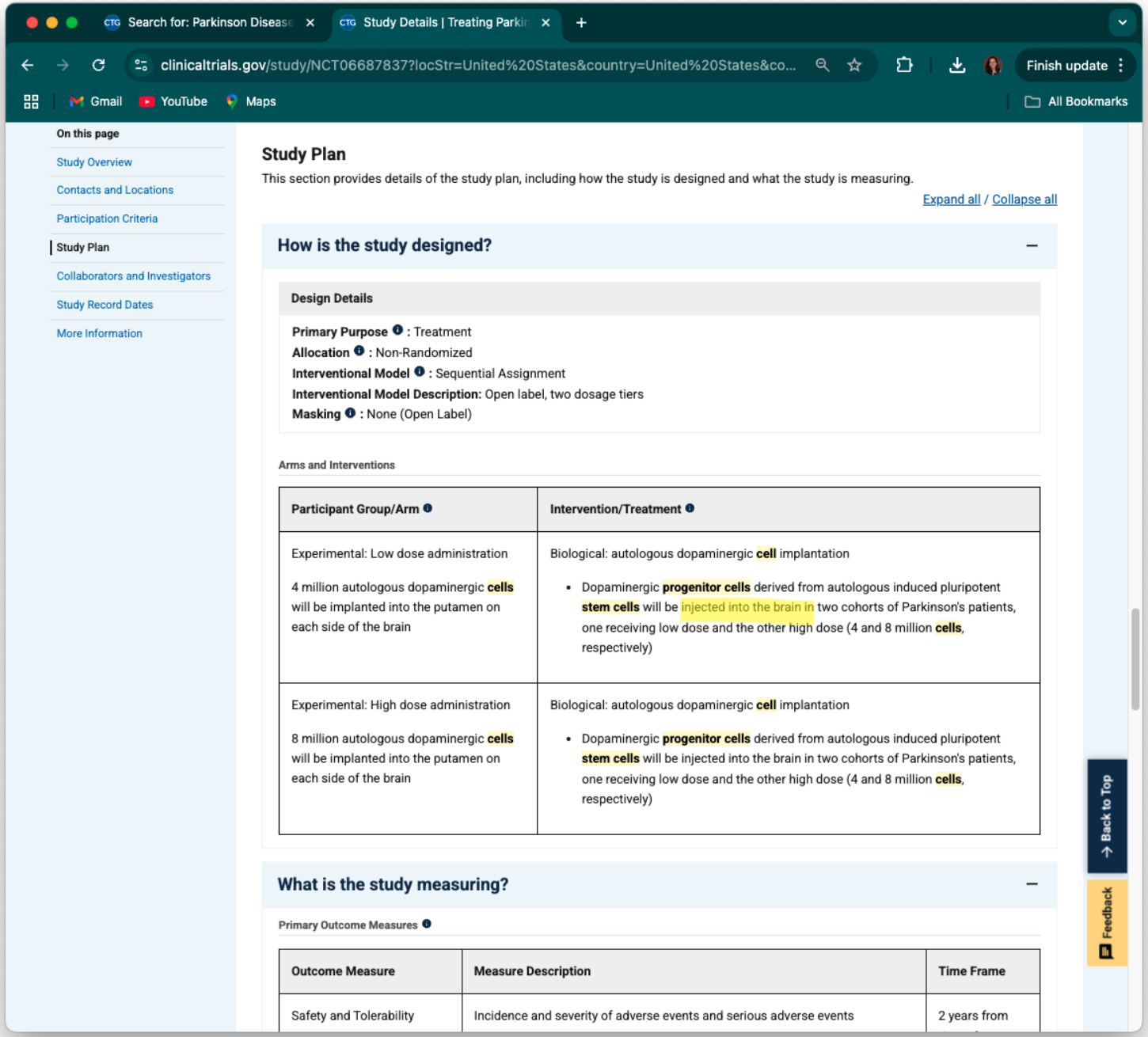
45 Years to 80 Years (Adult, Older Adult)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

No



On this page
Study Overview
Contacts and Locations
Participation Criteria
Study Plan
Collaborators and Investigators
Study Record Dates
More Information

Study Plan

This section provides details of the study plan, including how the study is designed and what the study is measuring.

Expand all / Collapse all

How is the study designed?

Design Details

Primary Purpose : Treatment
Allocation : Non-Randomized
Interventional Model : Sequential Assignment
Interventional Model Description: Open label, two dosage tiers
Masking : None (Open Label)

Arms and Interventions

Participant Group/Arm	Intervention/Treatment
Experimental: Low dose administration 4 million autologous dopaminergic **cells** will be implanted into the putamen on each side of the brain	Biological: autologous dopaminergic **cell** implantation • Dopaminergic **progenitor cells** derived from autologous induced pluripotent **stem cells** will be injected into the brain in two cohorts of Parkinson's patients, one receiving low dose and the other high dose (4 and 8 million **cells**, respectively)
Experimental: High dose administration 8 million autologous dopaminergic **cells** will be implanted into the putamen on each side of the brain	Biological: autologous dopaminergic **cell** implantation • Dopaminergic **progenitor cells** derived from autologous induced pluripotent **stem cells** will be injected into the brain in two cohorts of Parkinson's patients, one receiving low dose and the other high dose (4 and 8 million **cells**, respectively)

What is the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Safety and Tolerability	Incidence and severity of adverse events and serious adverse events	2 years from

Back to Top
Feedback

Thank you!

Questions?