An Update on Parkinson's Research in 2024 and beyond

Simon Stott
Director of Research
Cure Parkinson's

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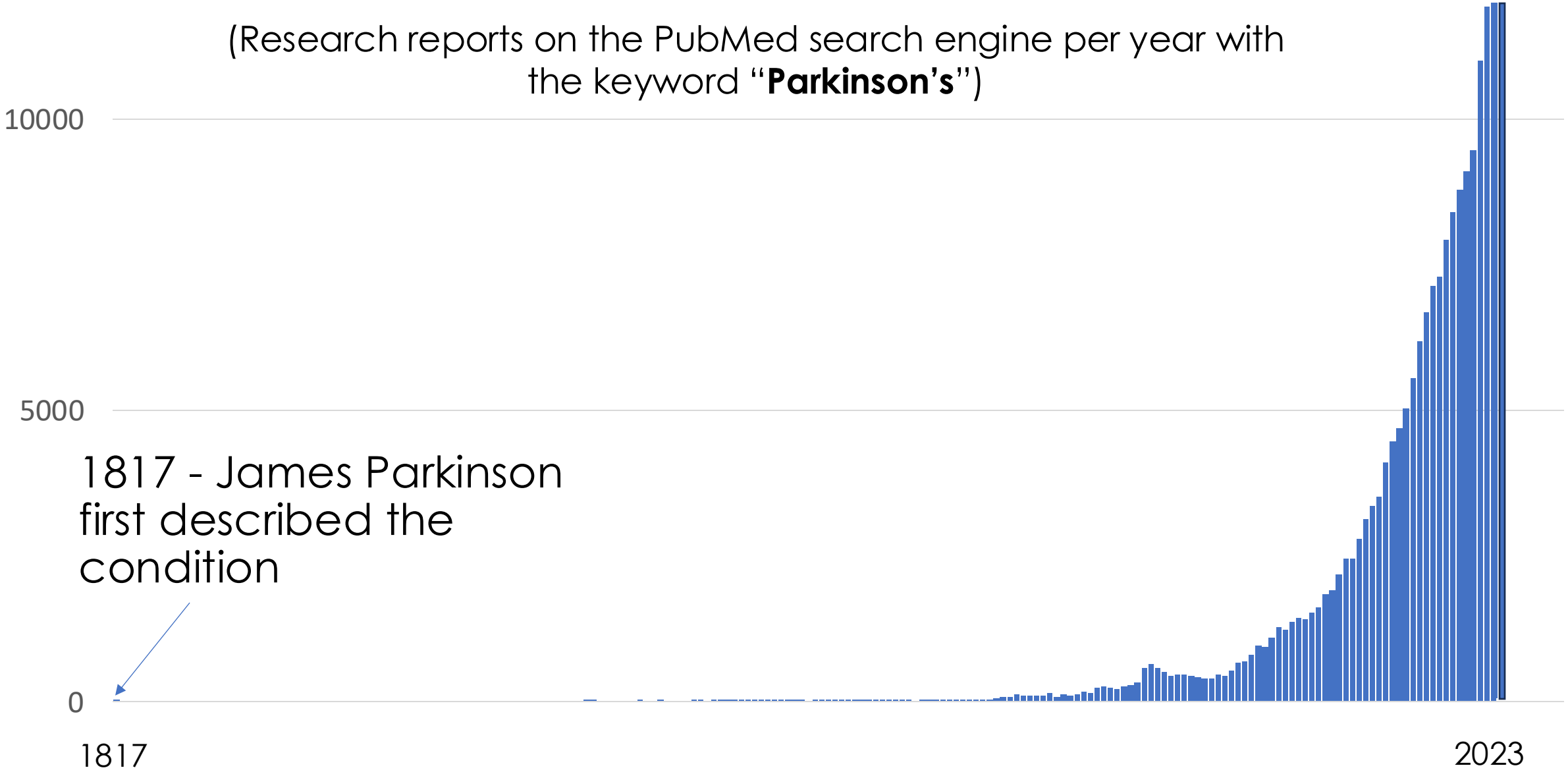
Employee of Cure Parkinson's

Founded in 2005, Cure Parkinson's is a medical research charity that is focused on **disease modification of Parkinson's**.

"The aim of Cure Parkinson's is to fund, facilitate and encourage research which leads to a cure for Parkinson's, with urgency for people currently living with Parkinson's"

Putting things into context…

(Research reports on the PubMed search engine per year with the keyword "**Parkinson's**")

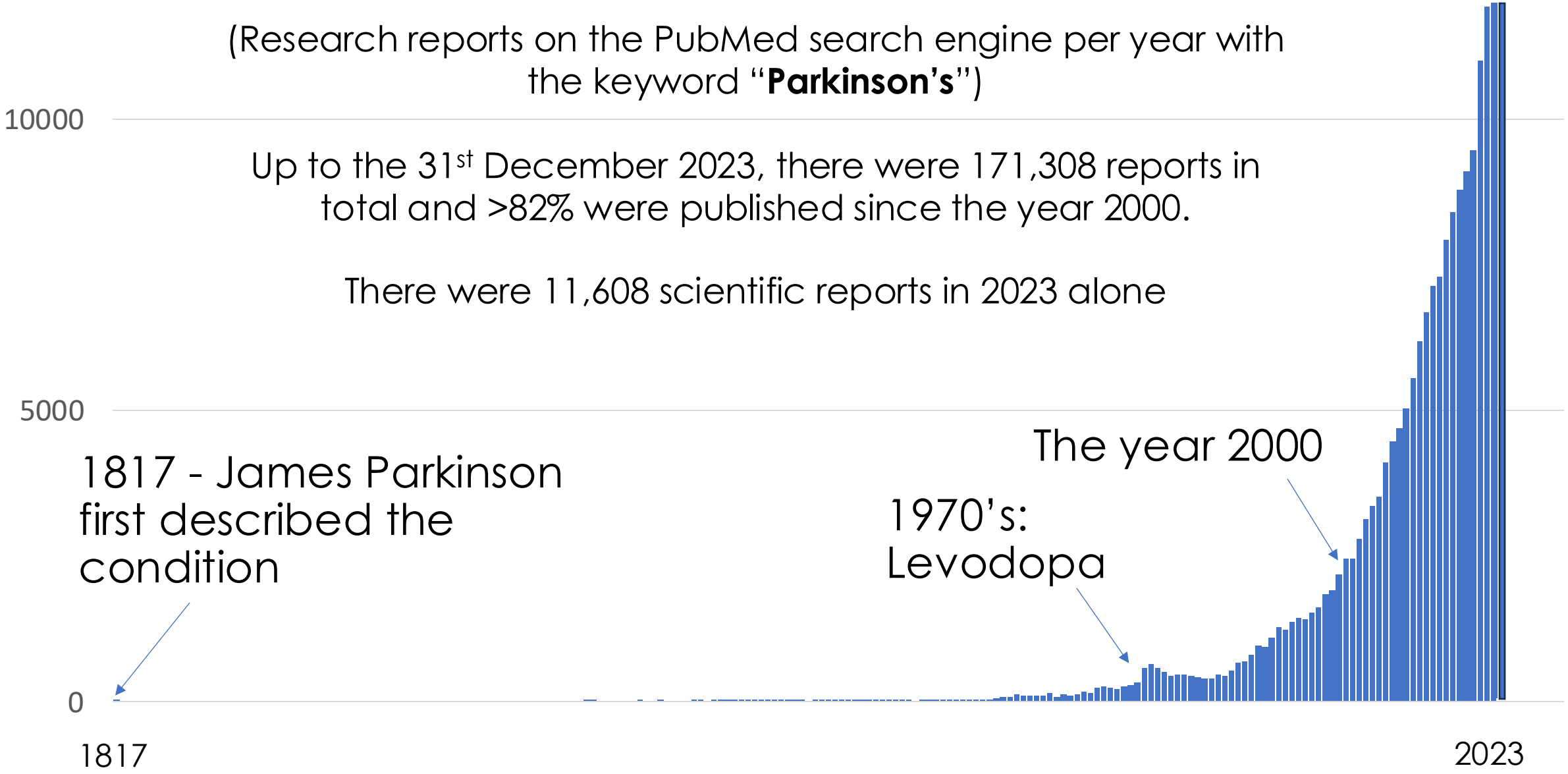


Putting things into context…

(Research reports on the PubMed search engine per year with the keyword "**Parkinson's**")

Up to the 31st December 2023, there were 171,308 reports in total and >82% were published since the year 2000.

There were 11,608 scientific reports in 2023 alone



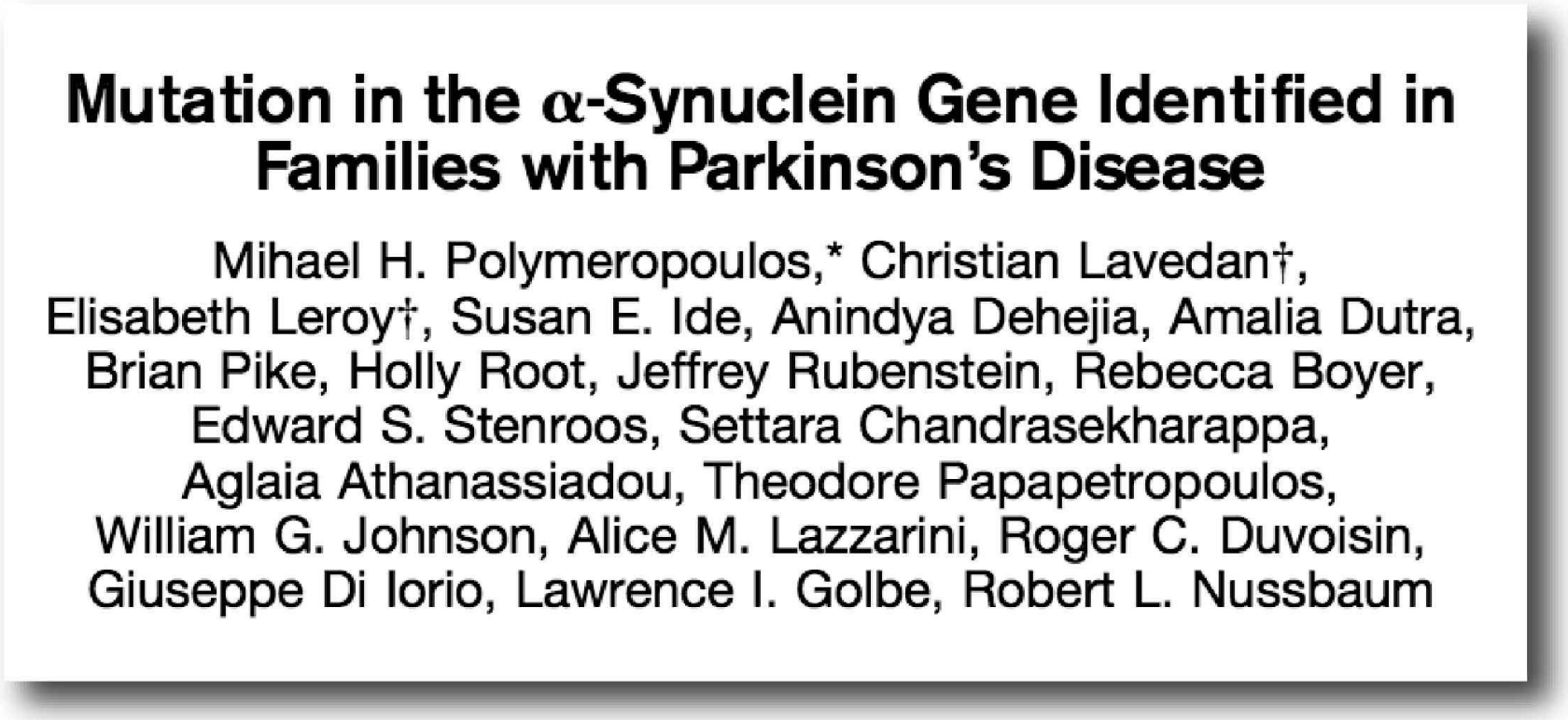
1997

(Dolly, Diana, DiCaprio & DNA)

In 1997, scientists reported on an Italian family, of which 61 of the 574 members of the extended family tree had developed Parkinson's.

The researchers found that genetic variations carried by these family members put them at a higher risk of developing Parkinson's.

The variations lay within the ***alpha synuclein*** gene.

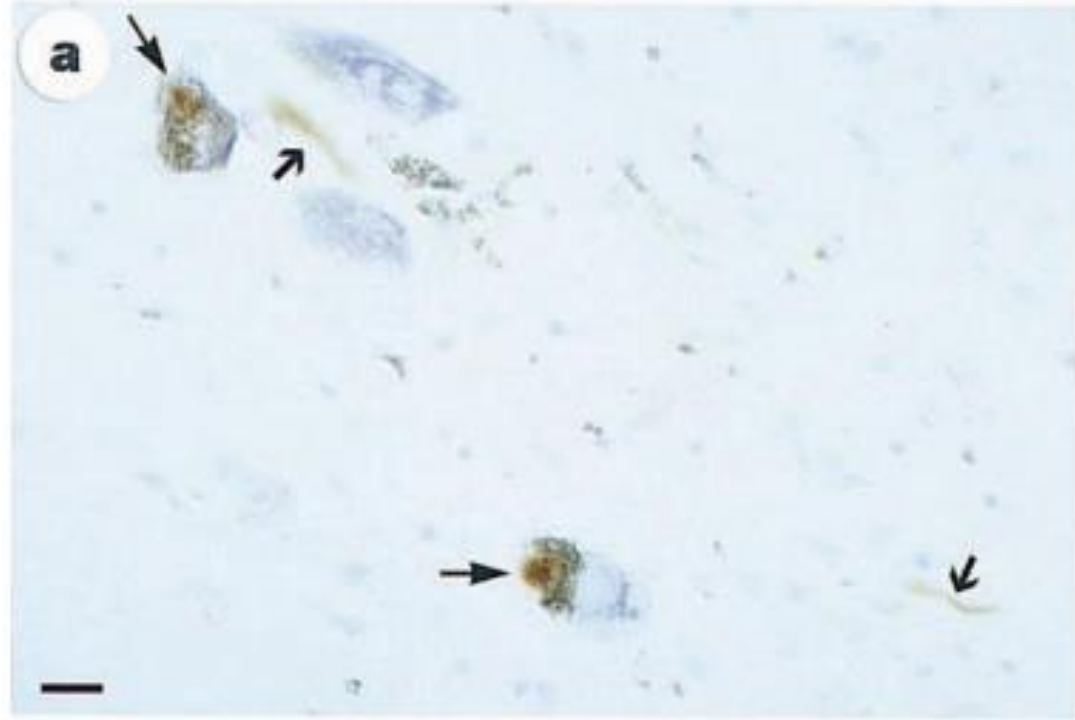


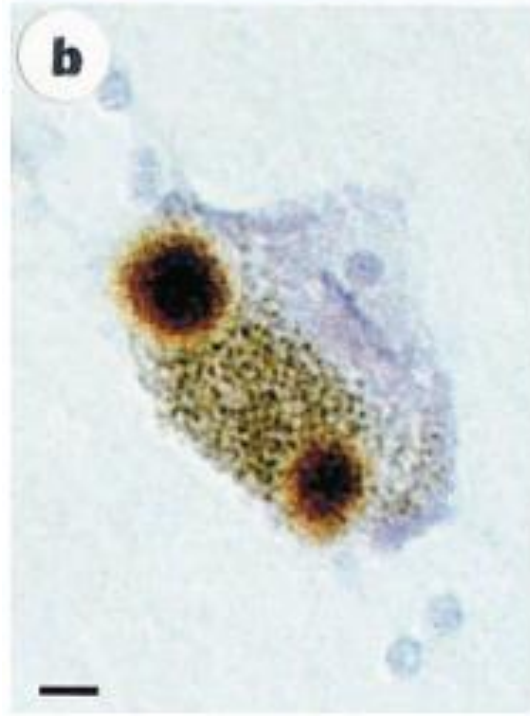
Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

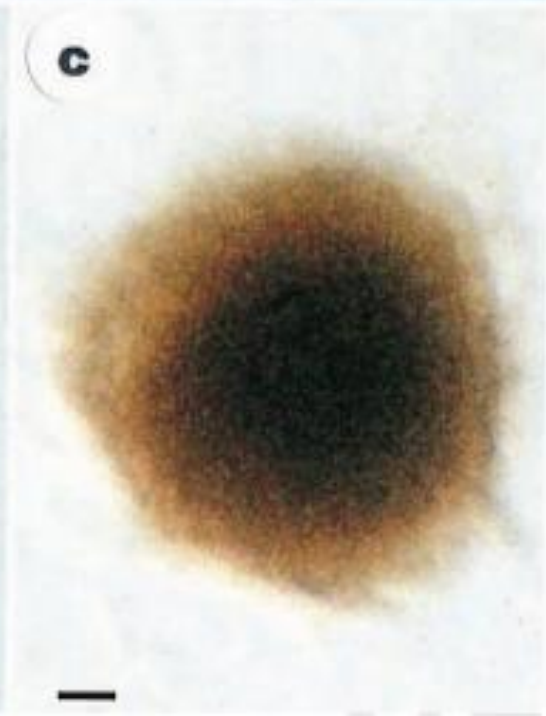
Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

α-Synuclein in Lewy bodies

Maria Grazia Spillantini
Medical Research Council Centre for Brain Repair and Department of Neurology, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK
Marie Luise Schmidt
Virginia M.-Y. Lee
John Q. Trojanowski
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-4283, USA
Ross Jakes, Michel Goedert
Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK







The early 2000s

The first decade of the new century was a gold rush of genetic sequencing:

1998 – **PARKIN**

2003 – **DJ-1**

2004 – **PINK1** & **LRRK2**

More than 80 genetic reggions associated with Parkinson's

The early 2000s was a very busy period of establishing the biology associated with these genetic risk factors.

The 2010s

A better understanding of the biology associated with these genetic variants has pointed towards **pathophysiology associated with Parkinson's**, as well as opportunities for therapeutic intervention.

For example, genetic variations in the GBA1 gene are associated with reduced activity of the protein connected to this gene.

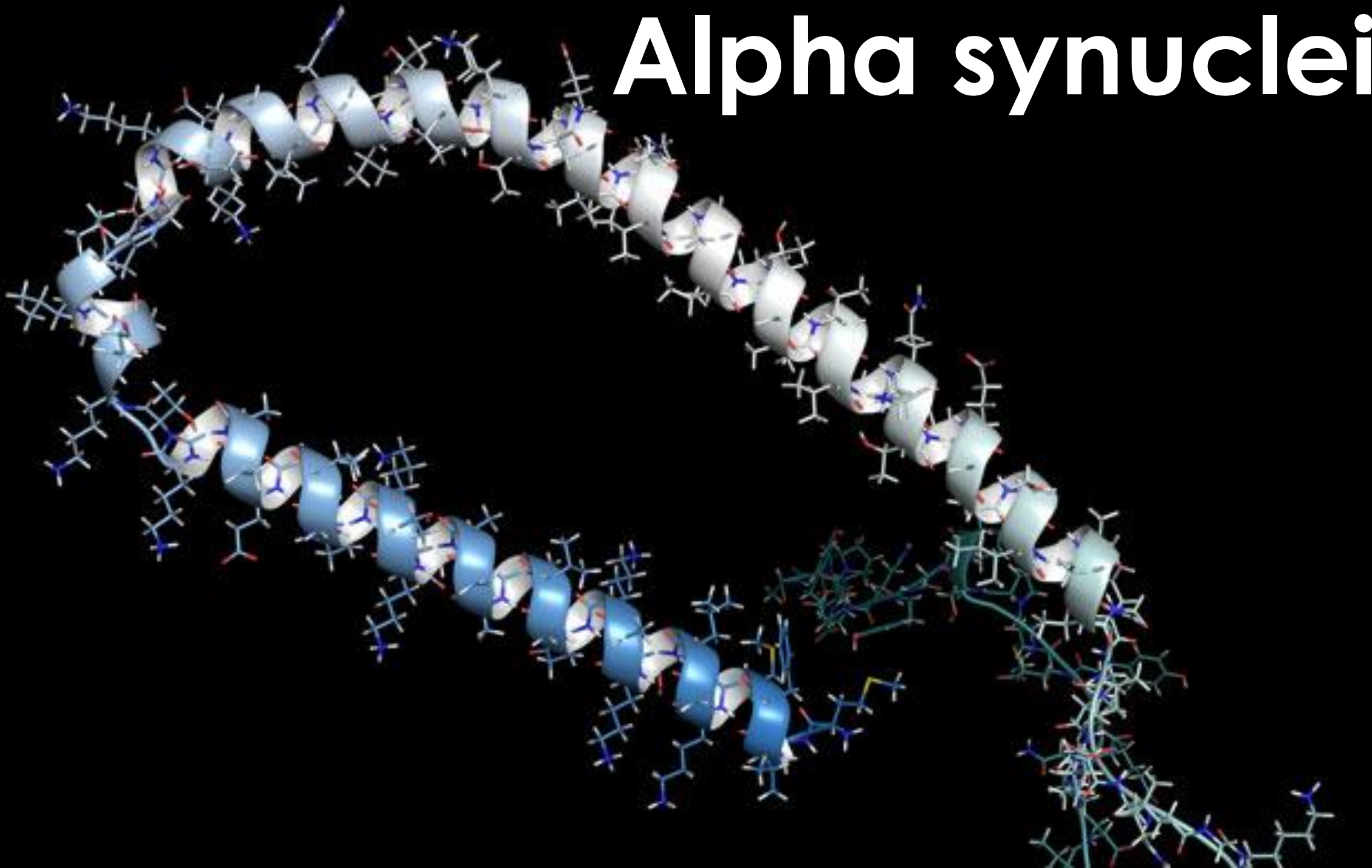
The 2010s was a period of drug screening and drug development based on the identified biological pathways.

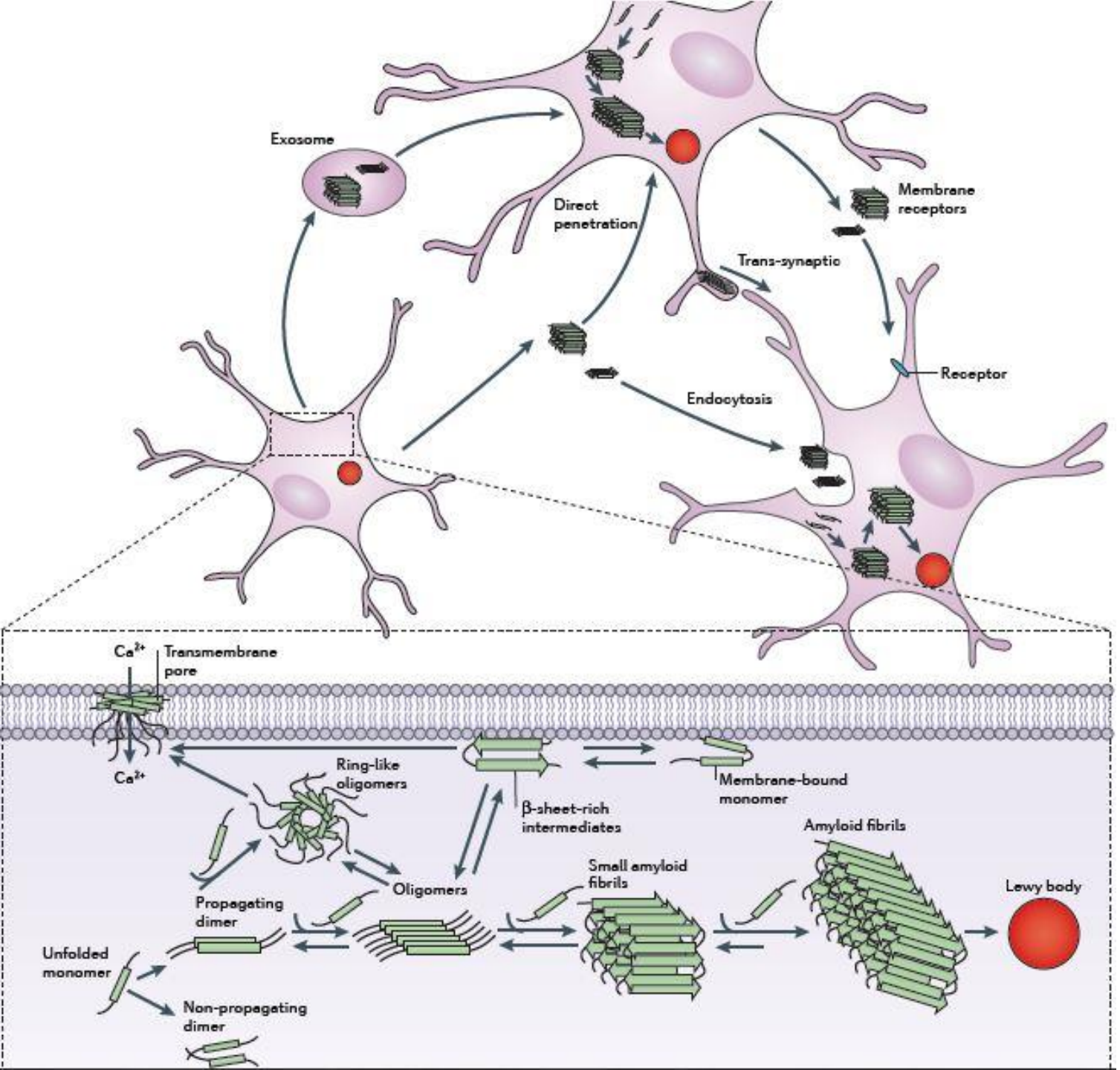
The 2020s

And now in the 2020s, researchers, biotech firms and pharmaceutical companies are lining up clinical trials based on these newly identified agents.

And hopefully these more targeted experimental drugs will provide better treatment options for the Parkinson's community in the future – ideally slowing the progression of Parkinson's.

Alpha synuclein





Alpha synuclein has lots of functions inside of cells, including aiding in the communication between neurons.

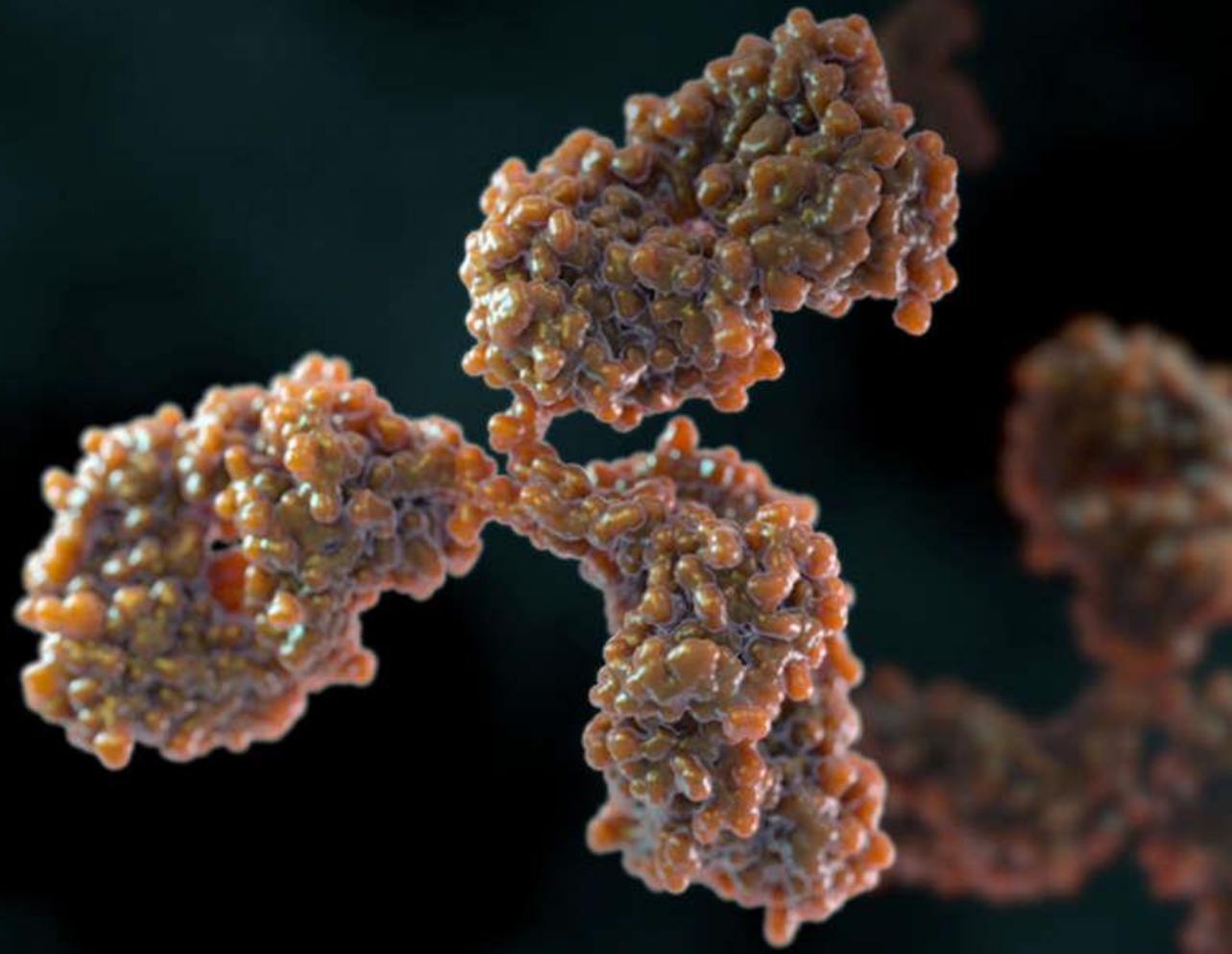
But in Parkinson's, the protein starts to clump (or aggregate) together for unknown reasons, and this is believed to put stress on cells.

Research has indicated that alpha synuclein aggregates may be passed between cells, providing a mechanism for disease progression.

If alpha synuclein is being passed between cells is a means of disease progression, researchers have proposed blocking this process as a therapeutic intervention.

One approach to doing this is using **antibodies.**

These are naturally occurring proteins and can be designed to target any protein.



So, the question was can antibodies grab alpha synuclein as it is being passed between cells? And would this slow down the progression of Parkinson's?

spark Biogen

PASADENA

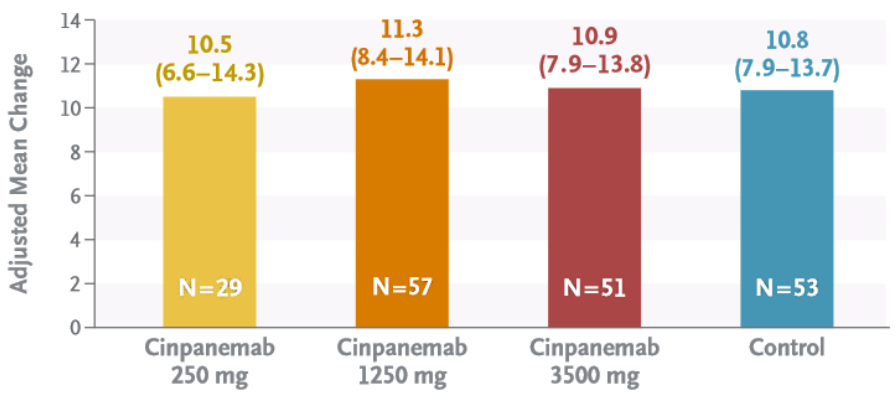
Roche

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Cinpanemab in Early Parkinson's Disease

Lang AE et al. DOI: 10.1056/NEJMoa2203395



CONCLUSIONS

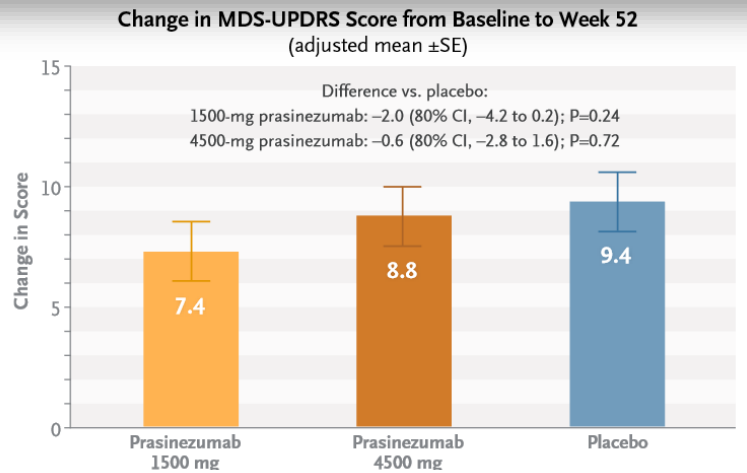
The monoclonal antibody cinpanemab, as compared with placebo, did not slow progression of Parkinson's disease in patients with early-stage disease.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Prasinezumab in Early-Stage Parkinson's Disease

Pagano G et al. DOI: 10.1056/NEJMoa2202867



CONCLUSIONS

The monoclonal antibody prasinezumab, as compared with placebo, did not slow disease progression in patients with early-stage Parkinson's disease over a 52-week treatment period.

spark Biogen

PASADENA

Roche

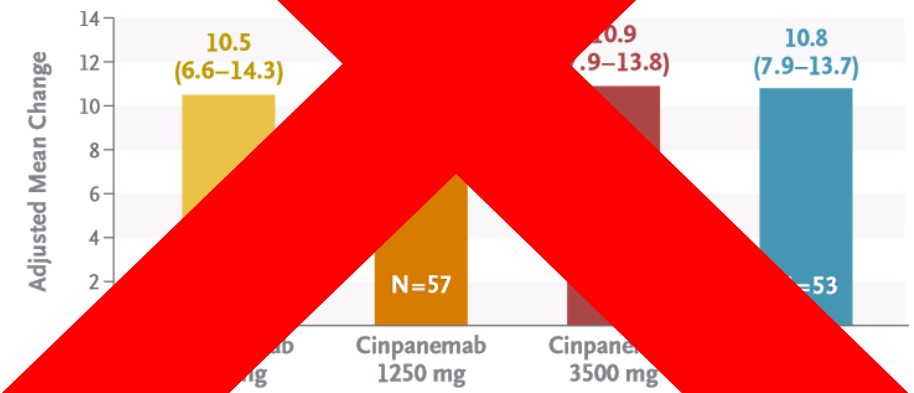
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

anemab in Early Parkins

E et al. DOI: 10.1056/NEJMoa22

Change Week 52



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The monoclonal antibody cinpanemab, as compared with placebo, did not slow progression of Parkinson's disease in patients with early-stage disease.

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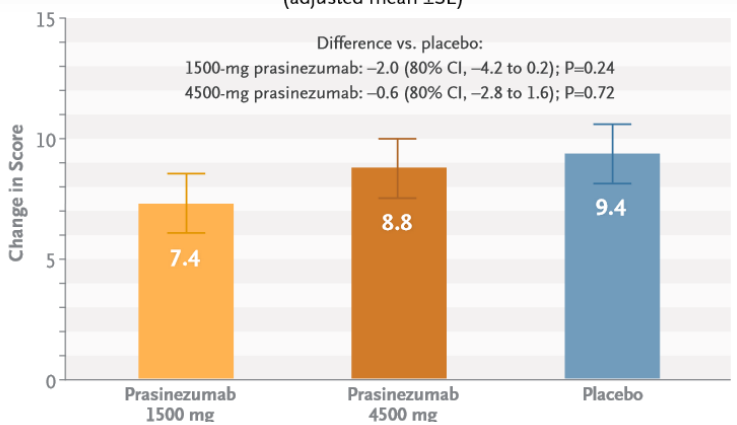
Trial of Prasinezumab in Early-Stage Parkinson's Disease

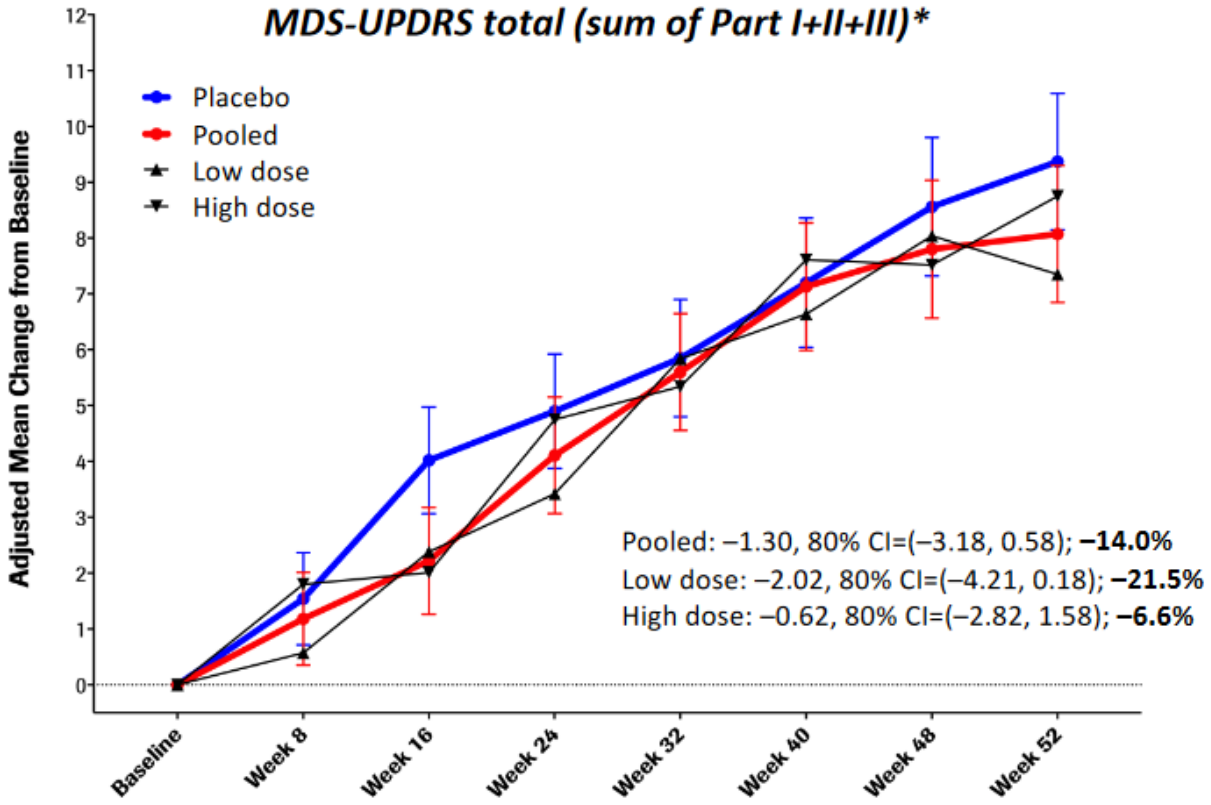
Pagano G et al. DOI: 10.1056/NEJMoa2202867

Change in MDS-UPDRS Score from Baseline to Week 52
(adjusted mean ±SE)

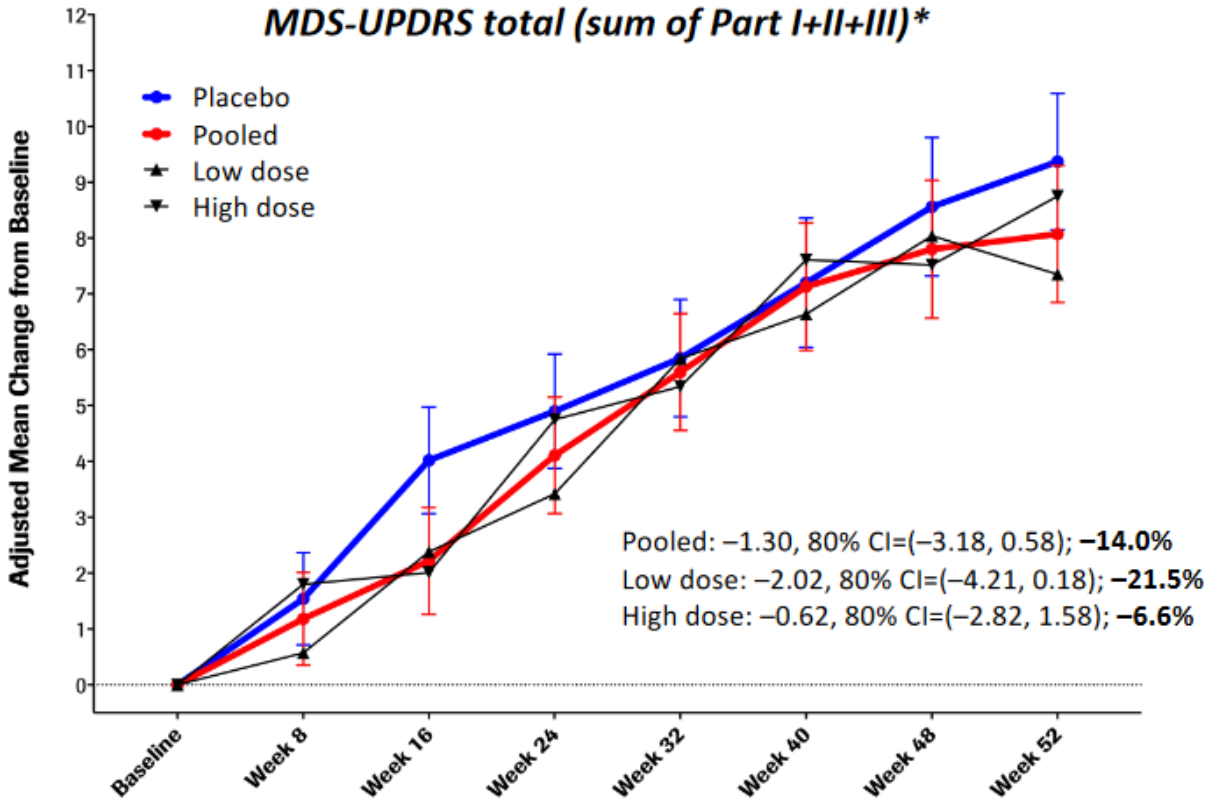


CONCLUSIONS

The monoclonal antibody prasinezumab, as compared with placebo did not slow disease progression in patients with early-stage Parkinson's disease over a 52-week treatment period.

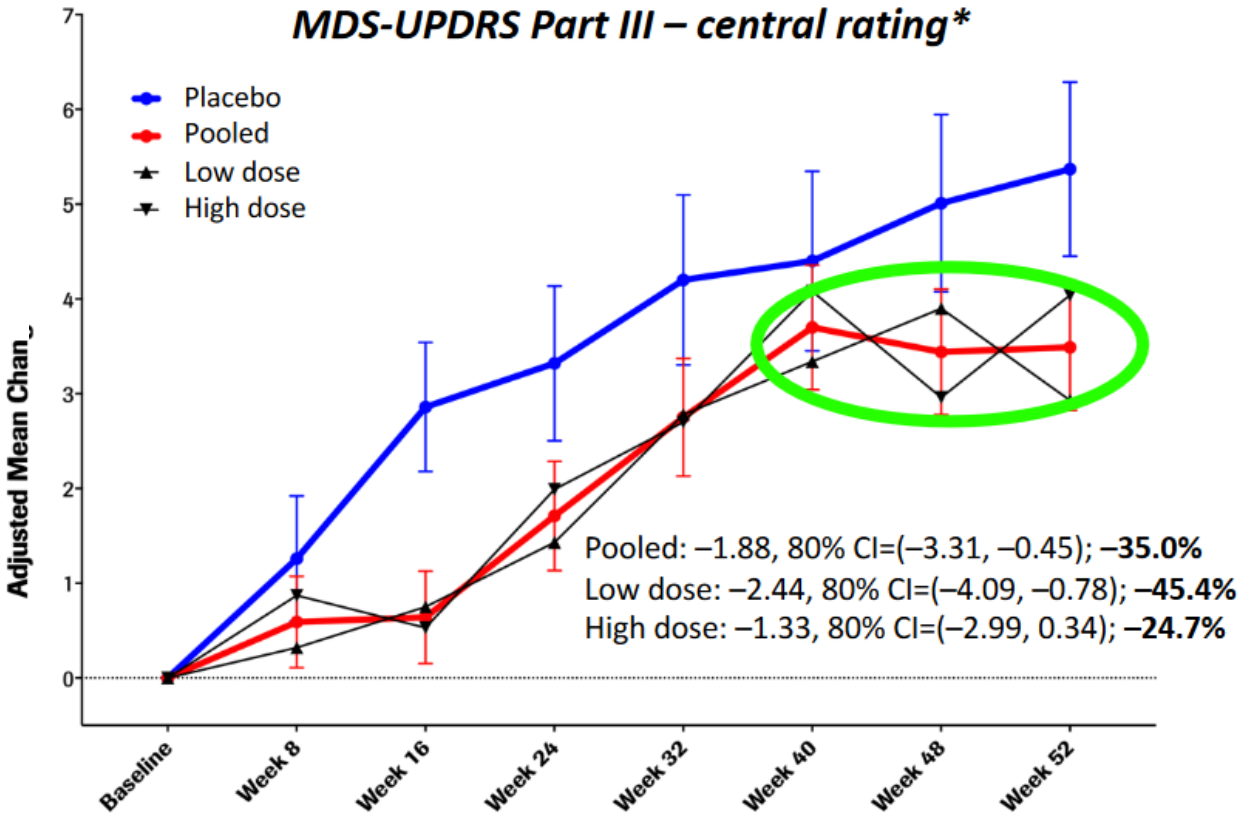


The researchers at Roche found no difference between their 3 study groups when assessing UPDRS parts I, II, & III…

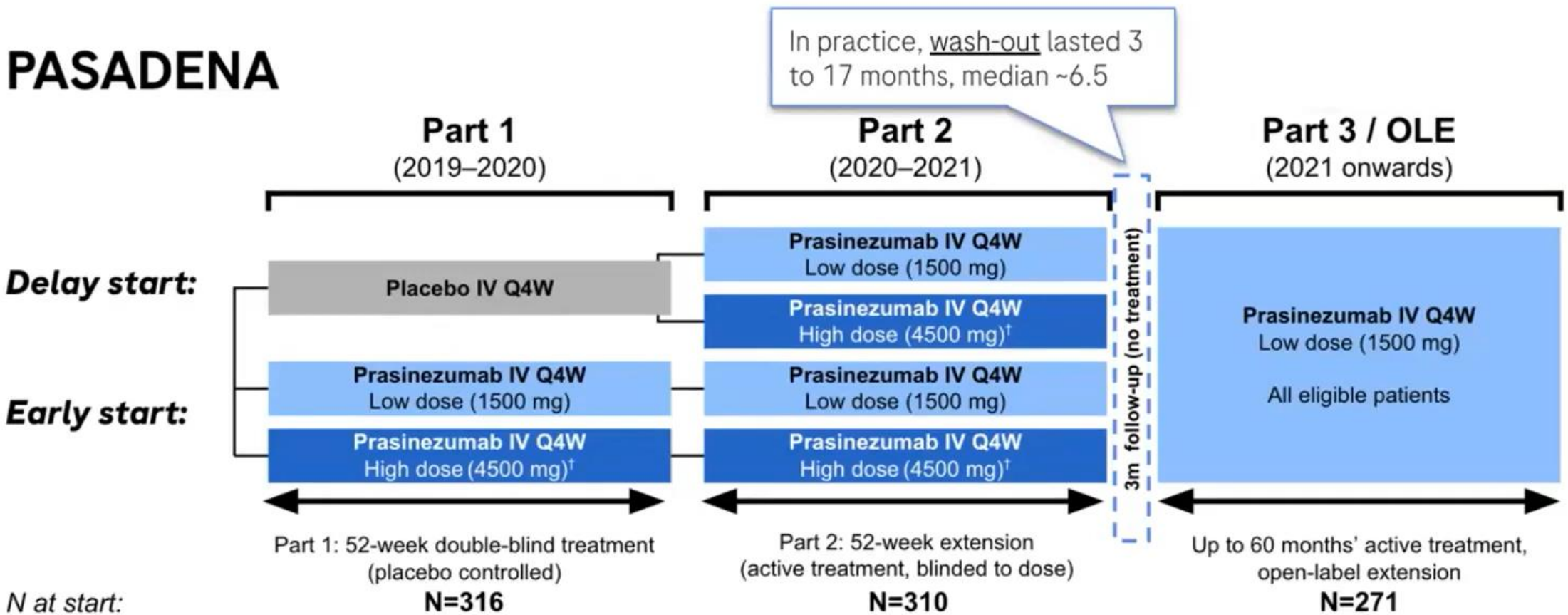


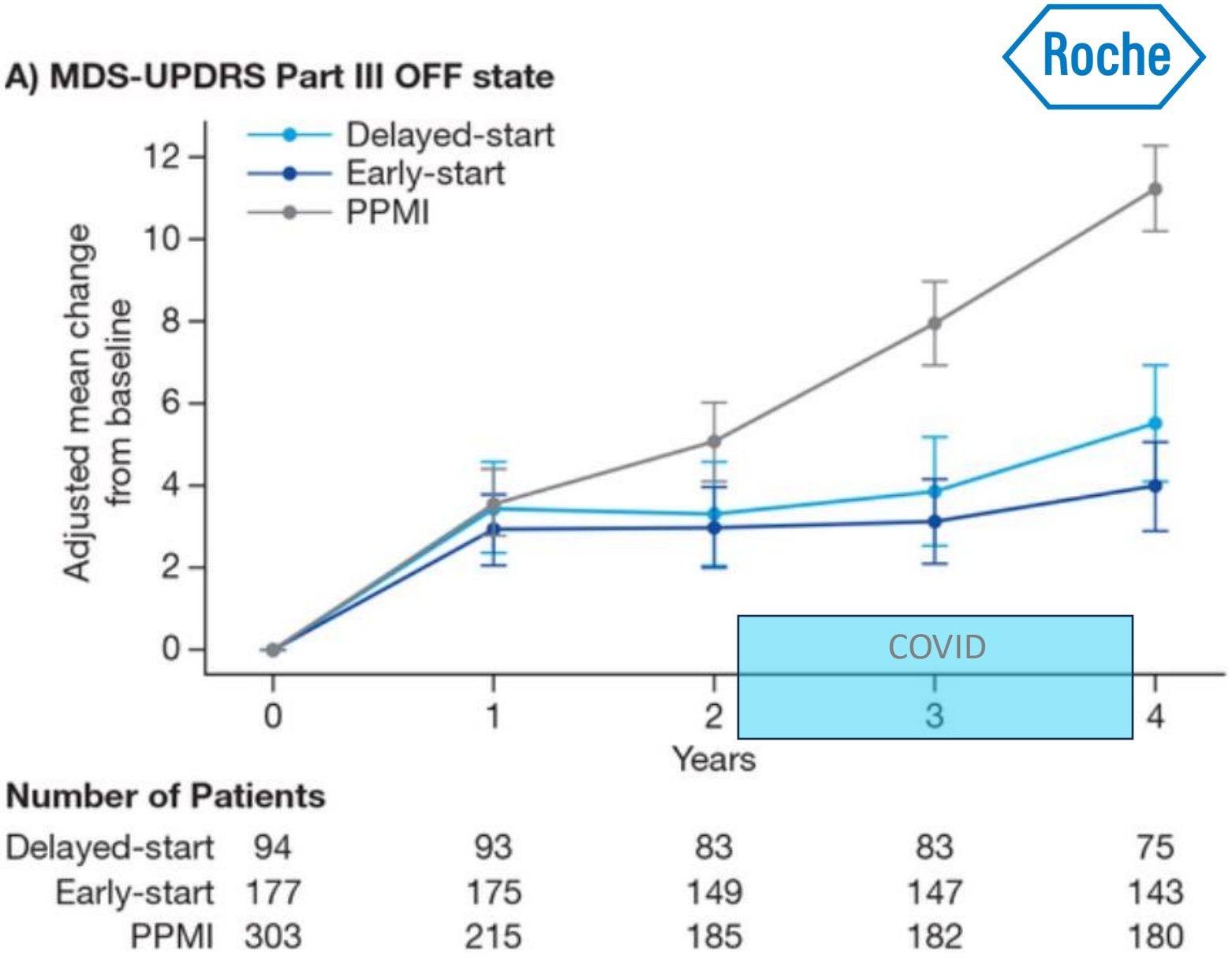
The researchers at Roche found no difference between their 3 study groups when assessing UPDRS parts I, II, & III…

BUT, when they focused on just the motor component of UPDRS, they found that both treatment groups performed better than the placebo arm of the study.



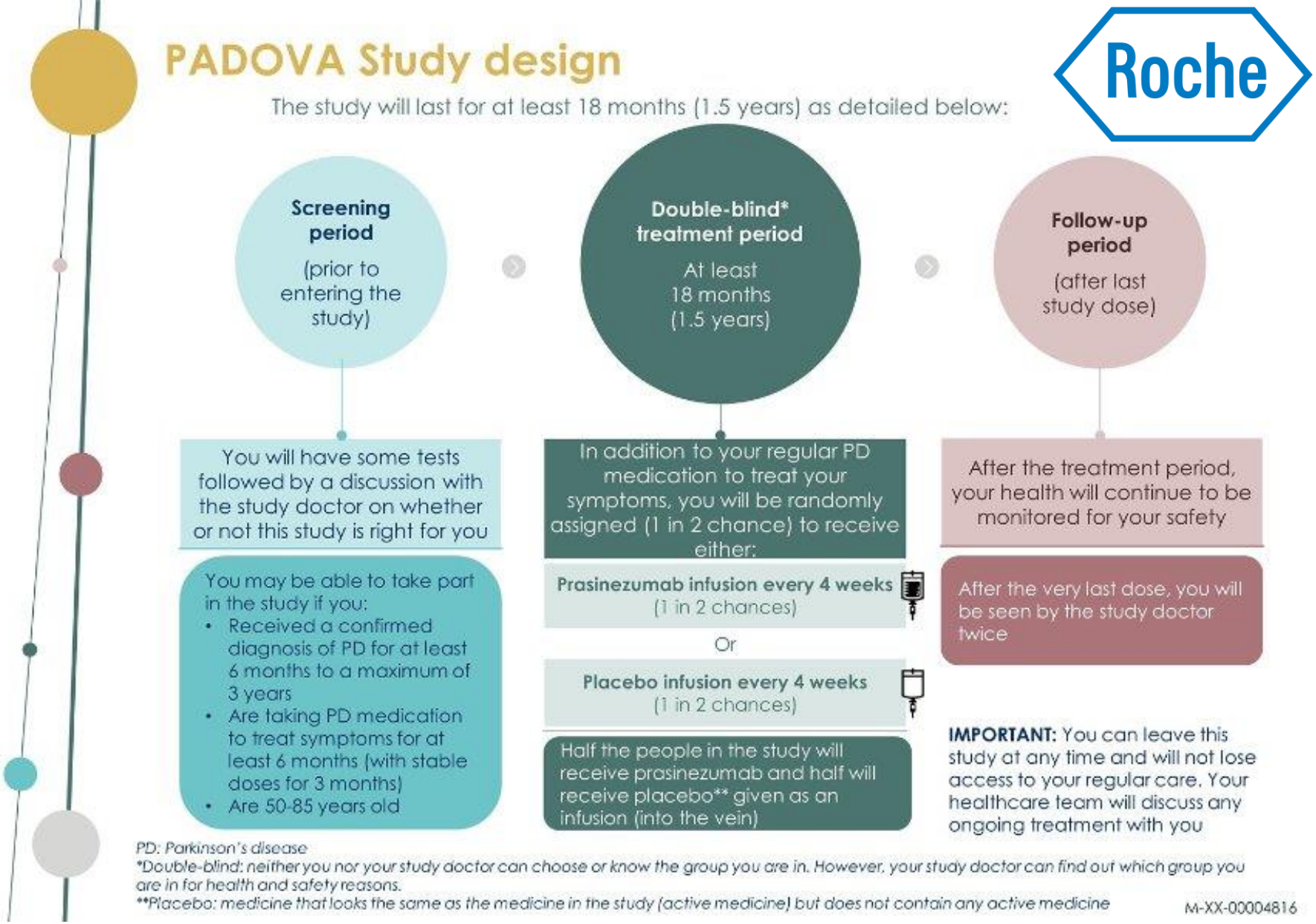
PASADENA Open Label Extension





https://www.researchsquare.com/article/rs-4232431/v1

The long-term extension study found stabilization of the motor component and patient reported outcomes parts of UPDRS, over 3 years of monthly treatment (with low drop-out rates).



Roche is very quick to point out that much of this analysis is 'post-hoc' and the extension study doesn't involve a proper control arm.

They also have another clinical trial (the PADOVA study – 18-months plus follow up of 586 participants).

Completion date is Sept 2024.

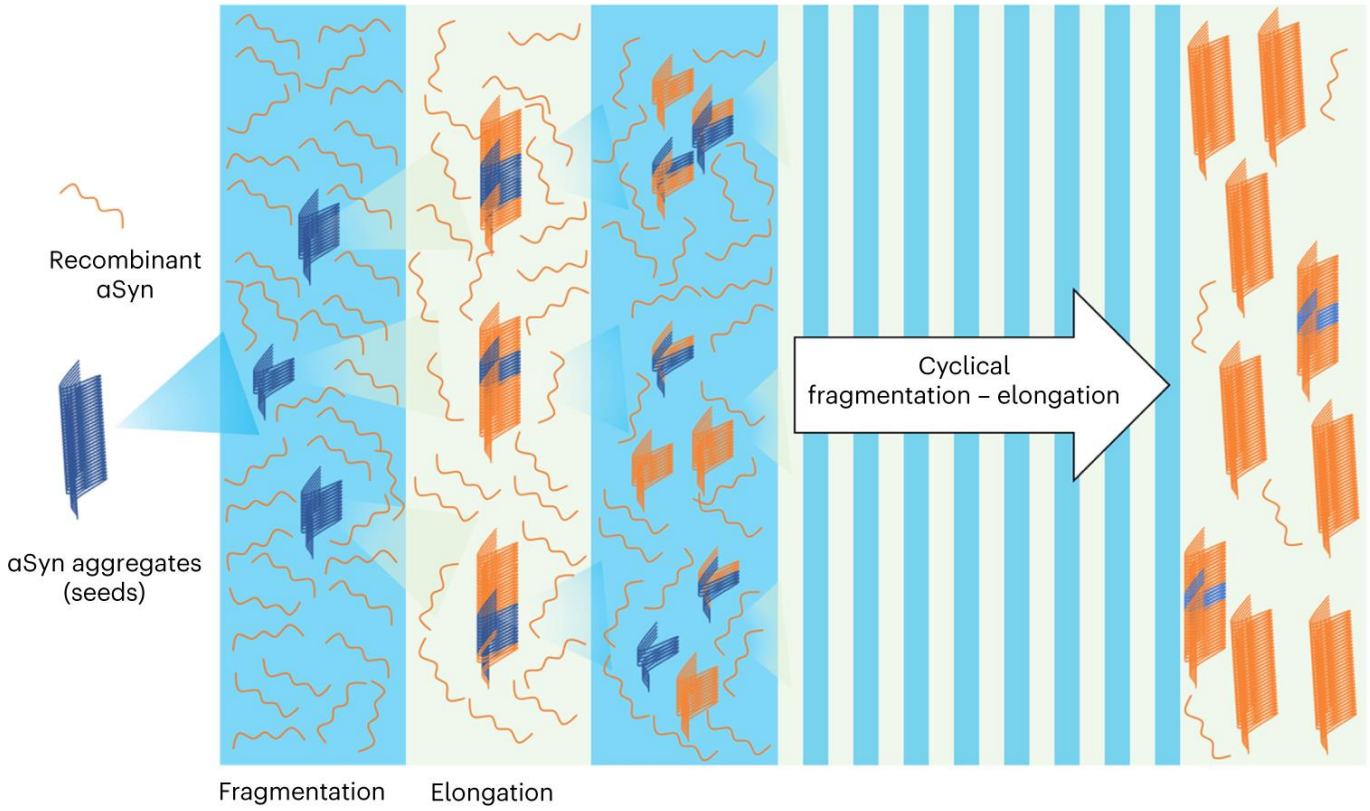
If you are interested in learning more about all of this research watch this video: https://www.youtube.com/watch?v=sPh1KG9J4S0

In 2023, we also had the publication of more data on the **alpha synuclein seeding assay** – offering the potential for a biomarker test for Parkinson's (and associated conditions) which may aid the diagnostic process and help with future clinical trials.

Articles

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*



Small molecule inhibitors

Antibodies have a hard time getting into the brain, let alone into cells, so scientists have been designing small molecule approaches that can get inside of cells and prevent the aggregation of alpha synuclein.

UCB have been conducting an 18-month study to evaluate the efficacy and safety of a high and low dose of oral **Minzasolmin (UCB0599)** in 450 participants with early-stage Parkinson's (NCT04658186). The primary completion date for the study is April this year.

Primary study:
NCT04658186;
Extension arm:
NCT05543252

β-Glucocerebrosidase

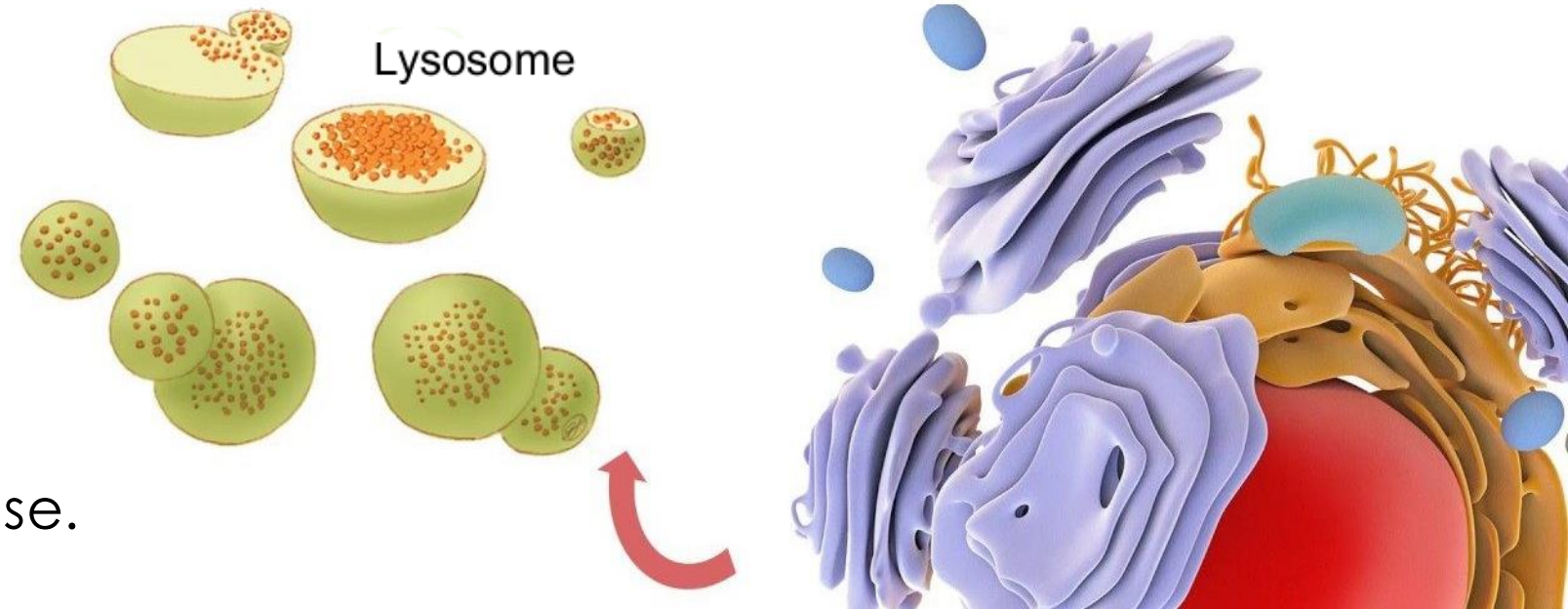
GGase & GBA1-associated PD

About 5-10% of people with Parkinson's have a genetic variant in their GBA1 gene, which results in reduced levels of activity for a protein called GCase.

GCase is a lysosomal enzyme that is involved with waste disposal inside of cells.

Many people with iPD have reduced levels of GCase activity.

So, researchers have been looking for activators of GCase.



Ambroxol

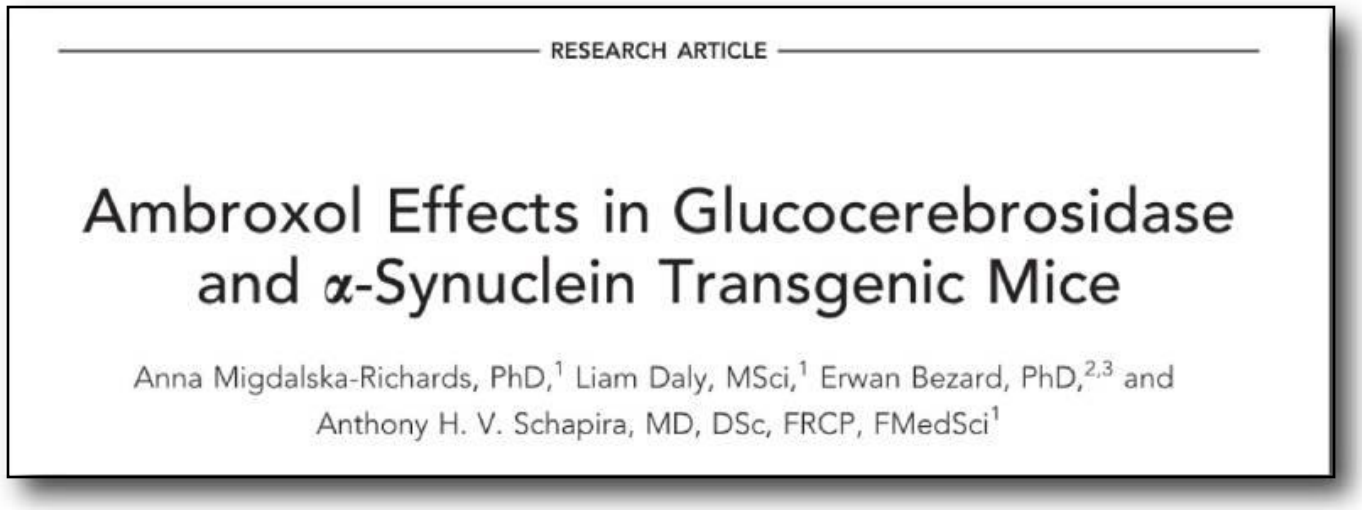
A respiratory treatment being repurposed for Parkinson's because it has been identified as an agent that can increase levels of GCase in cells.

VAN ANDEL INSTITUTE®

PARKINSON'S UK

The John Black Charitable Foundation

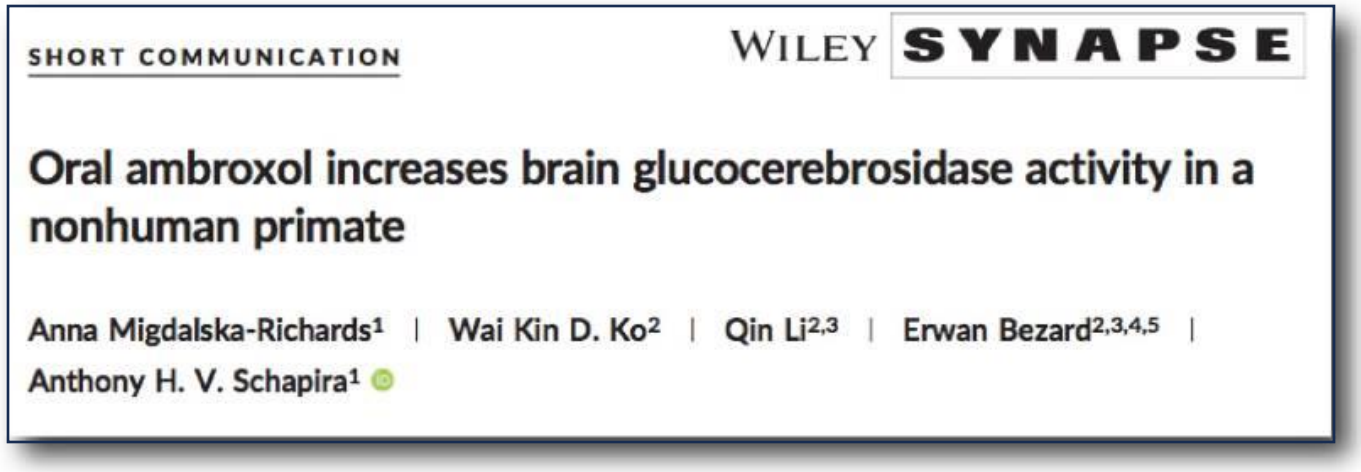
CURE PARKINSON'S



RESEARCH ARTICLE

Ambroxol Effects in Glucocerebrosidase and α-Synuclein Transgenic Mice

Anna Migdalska-Richards, PhD,[1] Liam Daly, MSci,[1] Erwan Bezard, PhD,[2,3] and Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci[1]



SHORT COMMUNICATION

WILEY SYNAPSE

Oral ambroxol increases brain glucocerebrosidase activity in a nonhuman primate

Anna Migdalska-Richards[1] | Wai Kin D. Ko[2] | Qin Li[2,3] | Erwan Bezard[2,3,4,5] | Anthony H. V. Schapira[1]

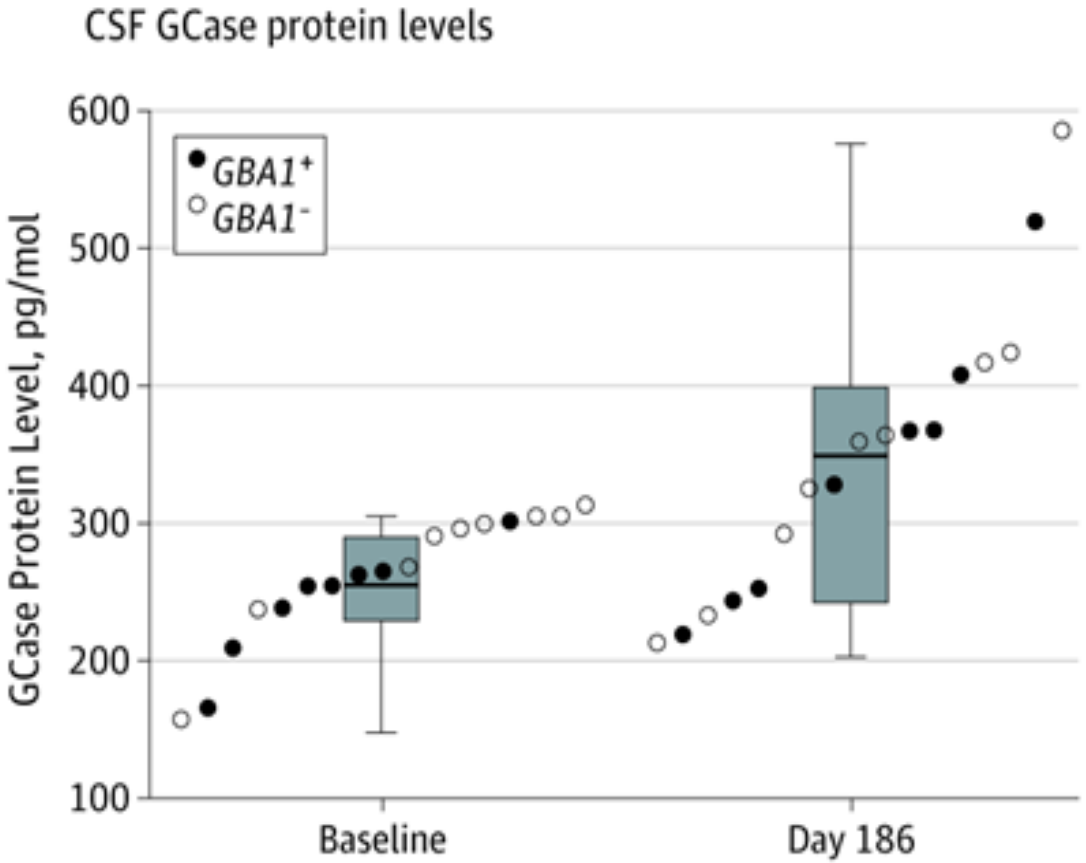
Drug screening experiments highlighted ambroxol as a GCase activator.

Ambroxol has also been shown to rescue models of Parkinson's.

This led to a Phase II clinical trial funded by Cure Parkinson's, the Van Andel Institute, and John Black Charitable Foundation.

The "Ambroxol in Disease Modification in Parkinson Disease" (AiM-PD) study involved 18 participants, who were treated for six months with ambroxol (NCT02941822).

The treatment (1200mg) was well tolerated, and elevated levels of Gcase in the brain.



Mullin et al 2020 JAMA Neurol

Ambroxol to Slow the Progression of Parkinson's Disease: ASPro-PD

CURE PARKINSON'S

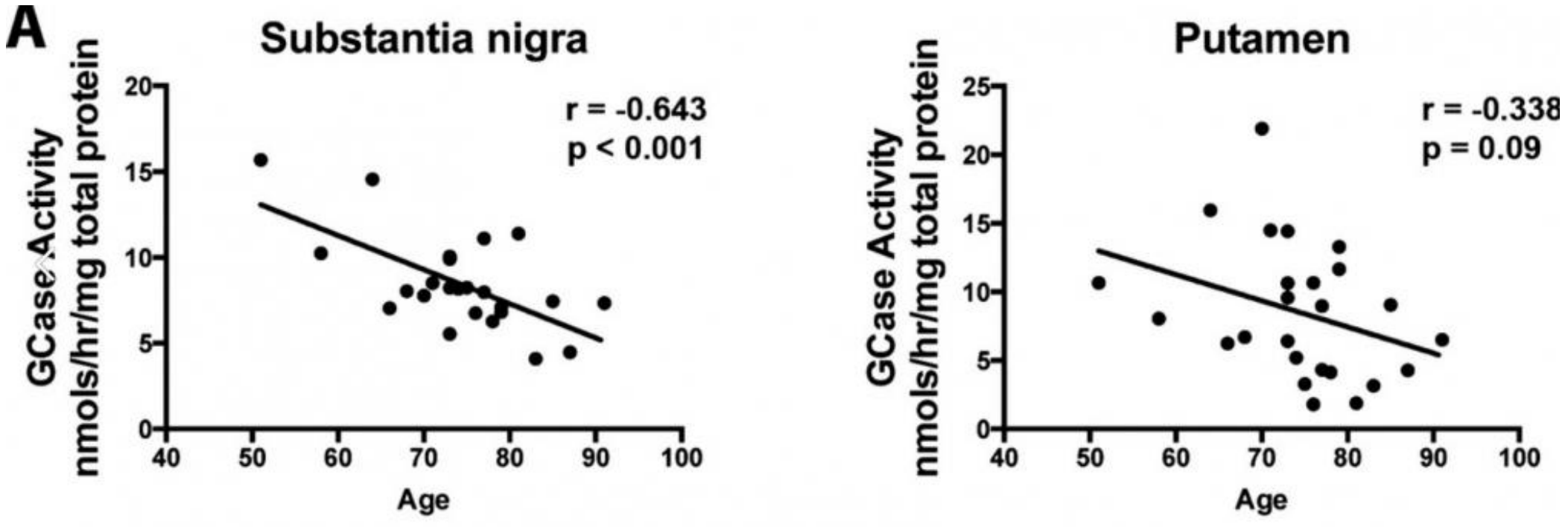
- Led by Professor Antony Schapira at UCL, this UK-based trial will determine whether ambroxol can slow the progression of Parkinson's.

- This is a Phase 3, 2-year trial in 330 people with Parkinson's, half of whom will have GBA Parkinson's.

- Primary outcome is to demonstrate an improvement on MDS-UPDRS I-III.

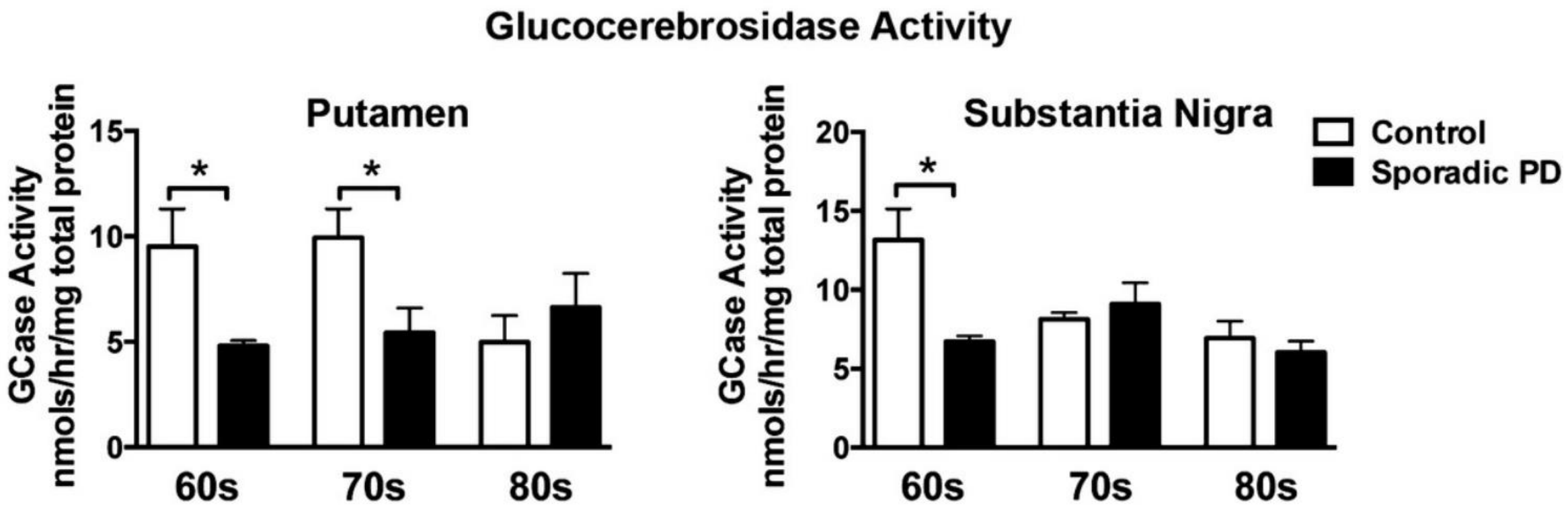
GCase enhancers for iPD?

Research has indicated that there is a reduction in GCase activity in the brain in normal aging.



GCase enhancers for iPD?

Curiously individuals with idiopathic Parkinson's have more reduced levels of GCase activity in particular areas of the brain.



Other GCase activator programs

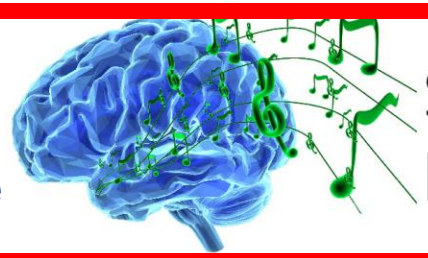
There are a large number of biotech companies developing GCase activators for Parkinson's:

ARKUDA THERAPEUTICS

VANQUA BIO

DENALI THERAPEUTICS

AVROBIO
Freedom from a lifetime of disease



Sinfonia Biotherapeutics

Neumora

Bial BIOTECH

Lilly

Prevail THERAPEUTICS

coave THERAPEUTICS

FREELINE

Amicus Therapeutics

GAIN THERAPEUTICS

oxyrane

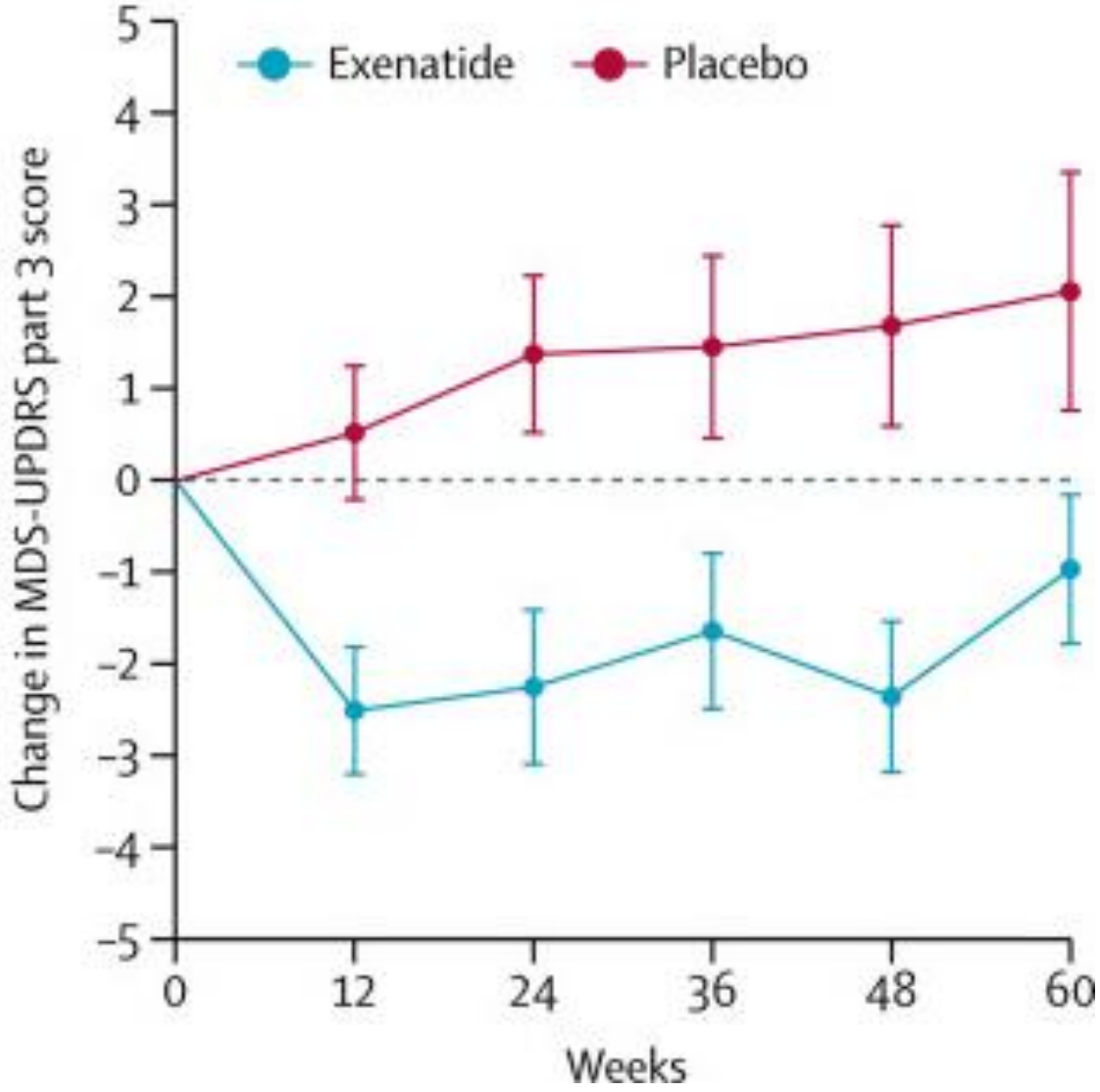
GLP-1 receptor agonists

The second interesting insight of 2023

Exenatide

The diabetes drug exenatide has already provided interesting clinical trial results.

In 2017, the results of a Phase 2 study found that motor symptom progression appeared to stablise over the 48-week period of treatment of this diabetes drug (vs placebo).



Athauda et al 2017

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

The Liraglutide Trial

CURE PARKINSON'S

In 2022, we learnt the results of the liraglutide study, which reported **significant improvements in non-motor symptoms** – adding to a body of research suggesting that this class of diabetes treatment could have beneficial effects as a treatment for some people with Parkinson's.

Phase 2 trial results of lixisenatide published

3 weeks ago NEWS Research news Diabetes and Parkinson's

Share

Lixisenatide

The study involved 156 people, each within 3 years of their PD diagnosis, randomized 1:1 to 12 months of Lixisenatide or placebo.

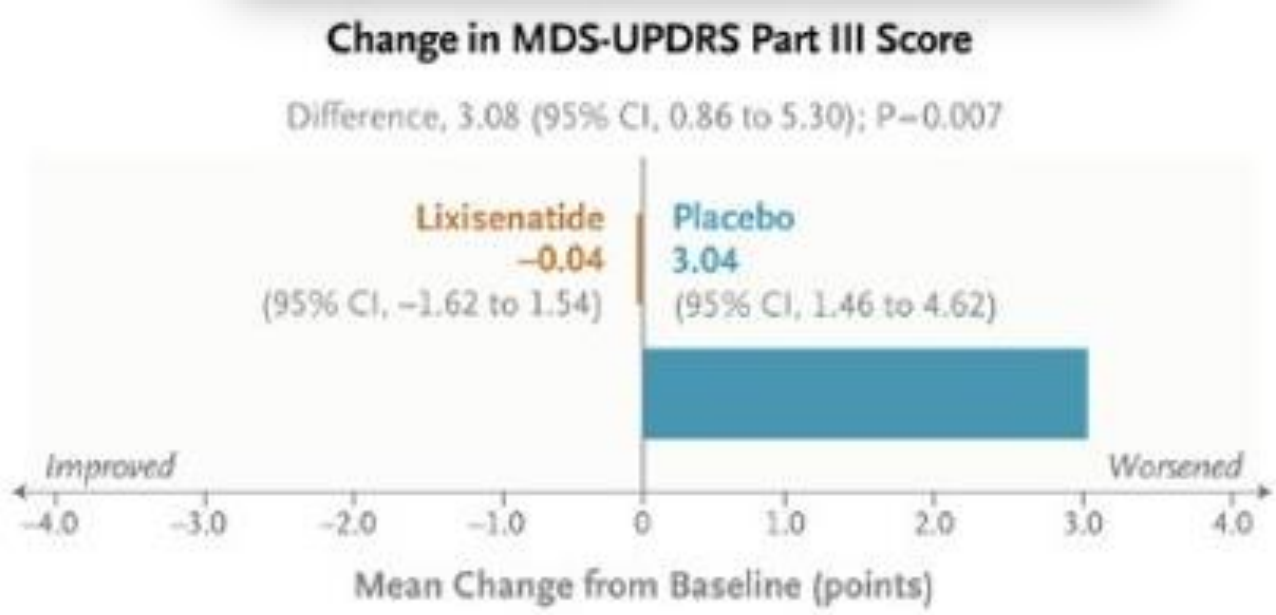
The results show that the participants on Lixisenatide did not progress beyond their baseline UPDRS III motor scores, while the control group worsened by 3 points.

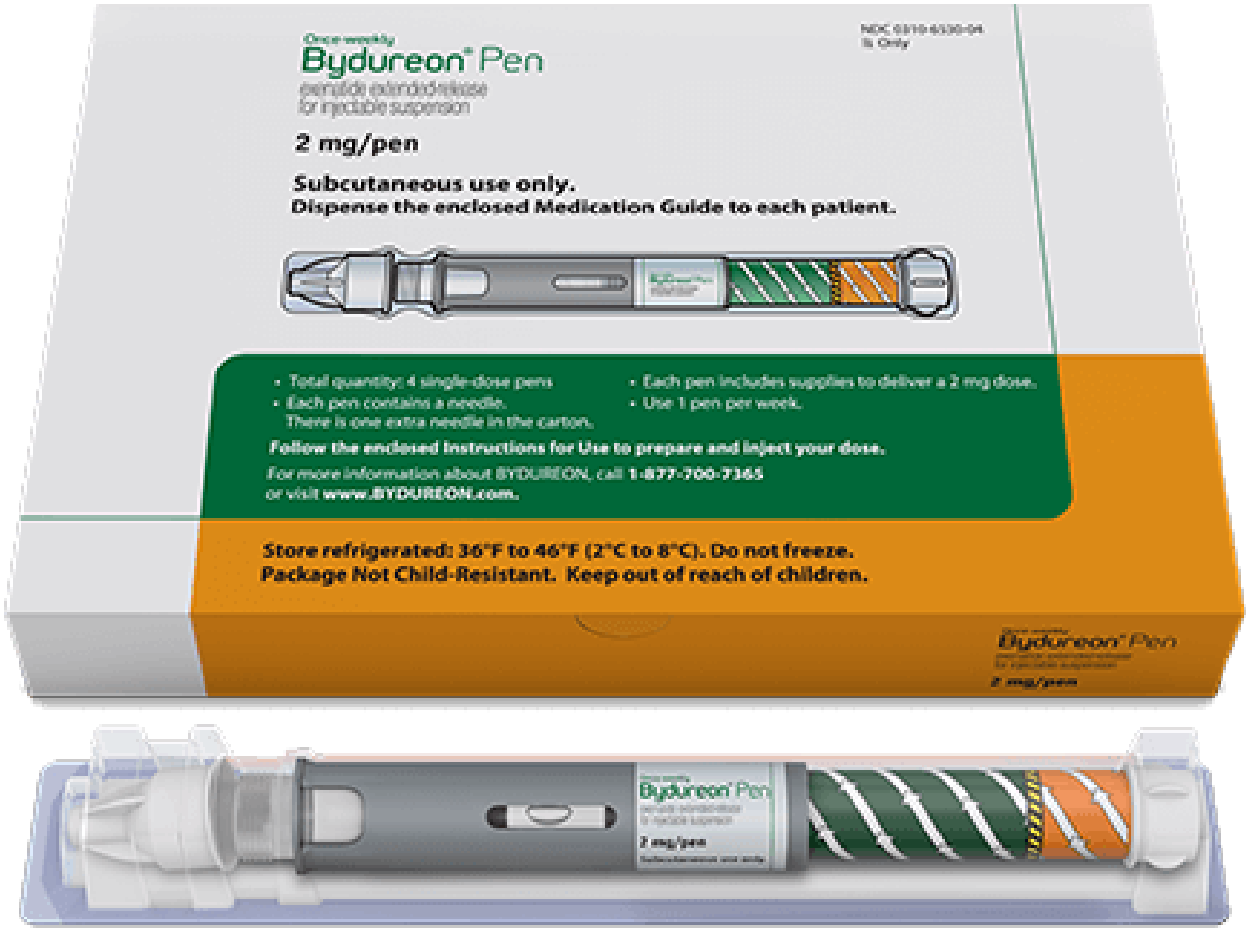
CURE PARKINSON'S

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, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, 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*





We are expecting the results of a Phase 3 clinical study of exenatide that has been conducted in the UK.

It was a 2-year study involving 200 people with Parkinson's taking place in six sites around the UK.

The results of this trial should be available in mid-late 2024.

There has also been a Phase 2 study in Stockholm, which has involved 60 participants who were treated for 12 months with exenatide (or placebo). The study included brain imaging analyses, and we are expecting the results in mid-2024.

Additional research of interest

GDNF

AskBio announced that their Phase Ib clinical trial of **AB-1005** (GDNF gene therapy) in 11 patients with Parkinson's disease meets primary endpoint (safety at 18 months).

Planning is underway for a Phase II trial to be initiated in the first half of 2024.

BAYER

AskBio

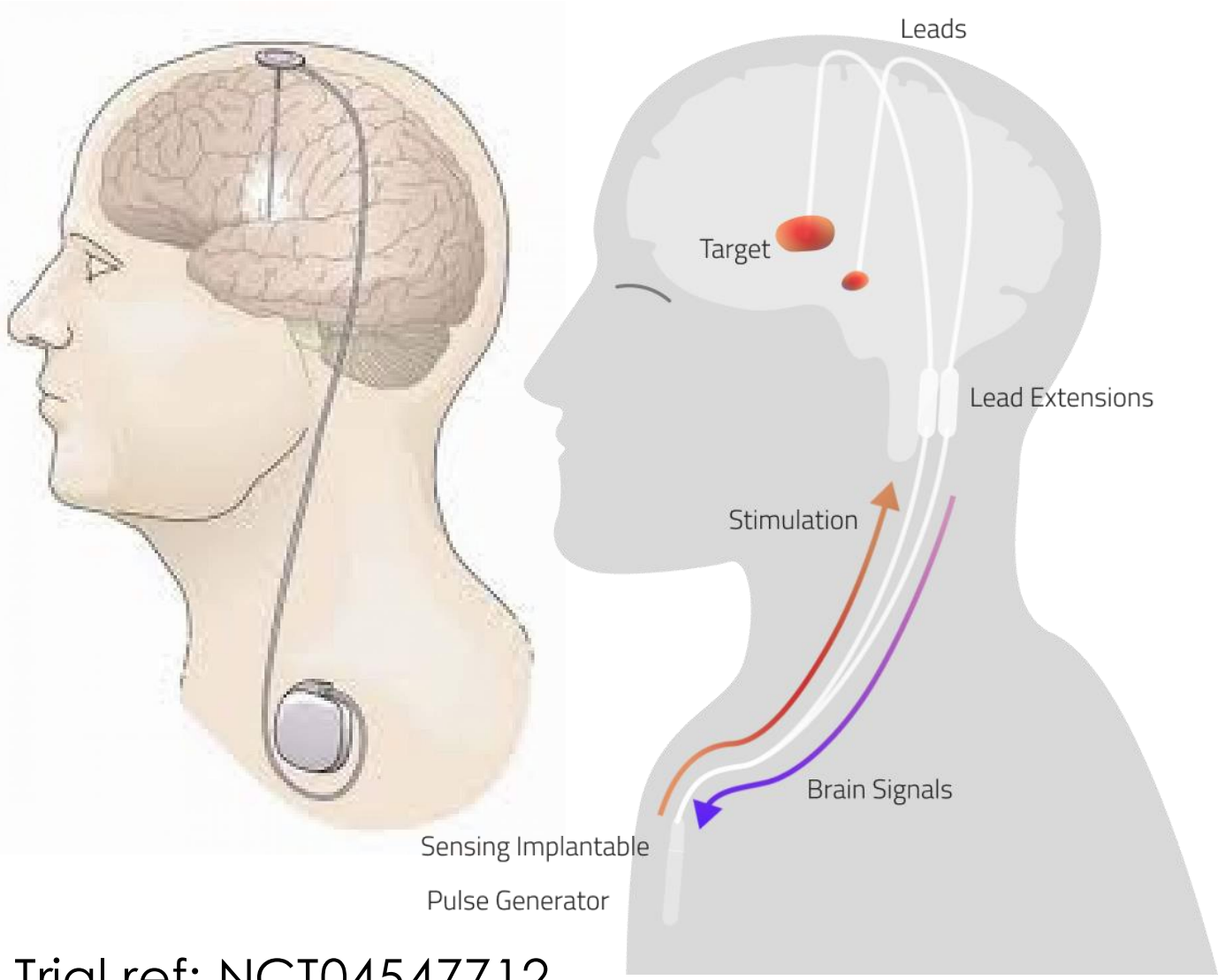
Adaptive DBS

Deep brain stimulation (DBS) is a well characterized advanced treatment for Parkinson's. It involves stimulation of particular areas of the brain.

Medtronics has been developing adaptive DBS which involves recording brain activity and stimulating according to needs.

They have conducted a single-blind, randomized crossover study of in 85 individuals with Parkinson's. We are expecting to see results from this study in 2024.

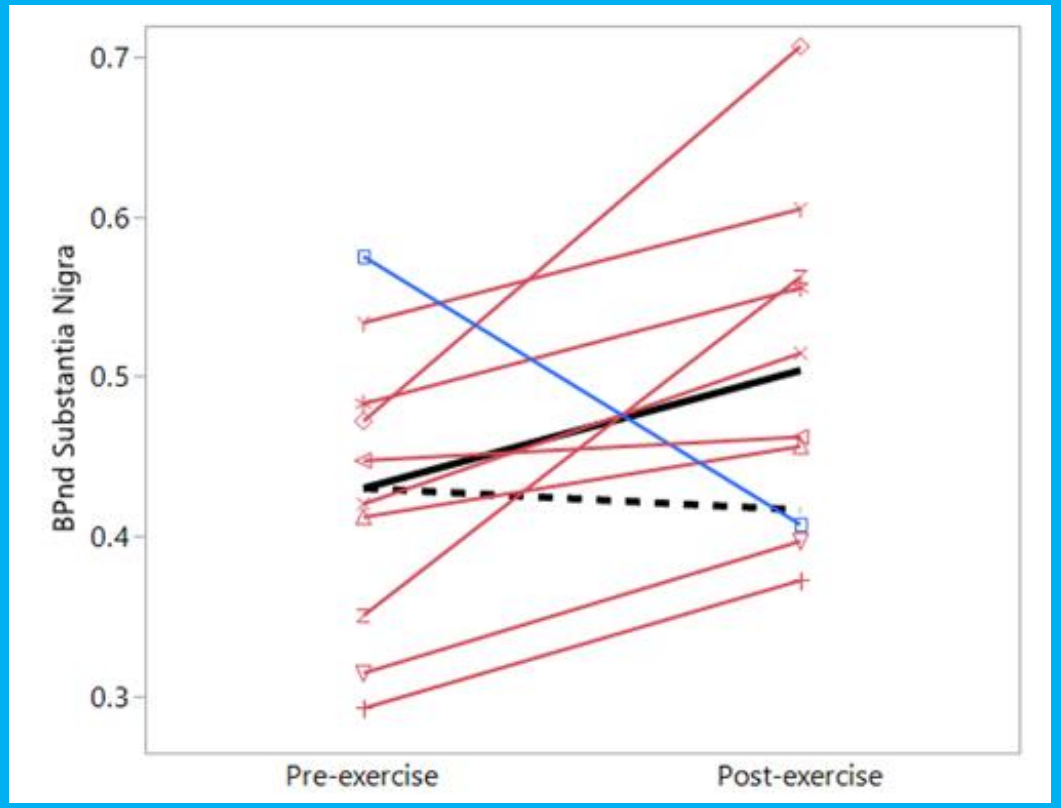
Medtronic



Trial ref: NCT04547712

Exercise

A recent clinical study assessed high-intensity interval training classes three times a week over 6 months & found positive benefits in brain imaging outcomes.



npj | parkinson's disease

www.nature.com/npjparkd

ARTICLE OPEN

Intense exercise increases dopamine transporter and neuromelanin concentrations in the substantia nigra in Parkinson's disease

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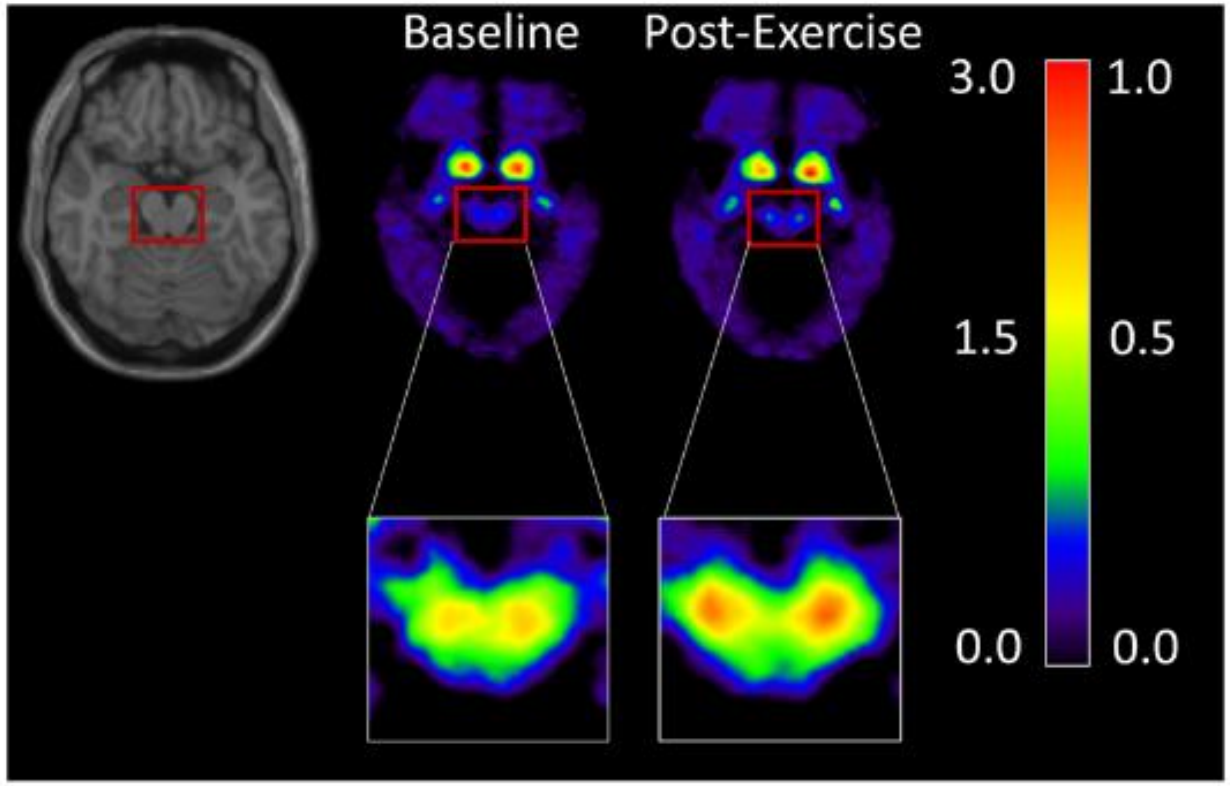

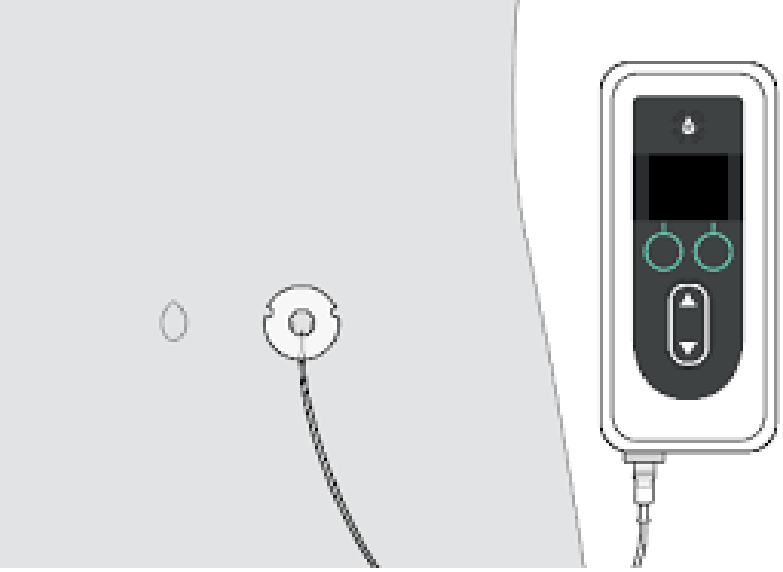

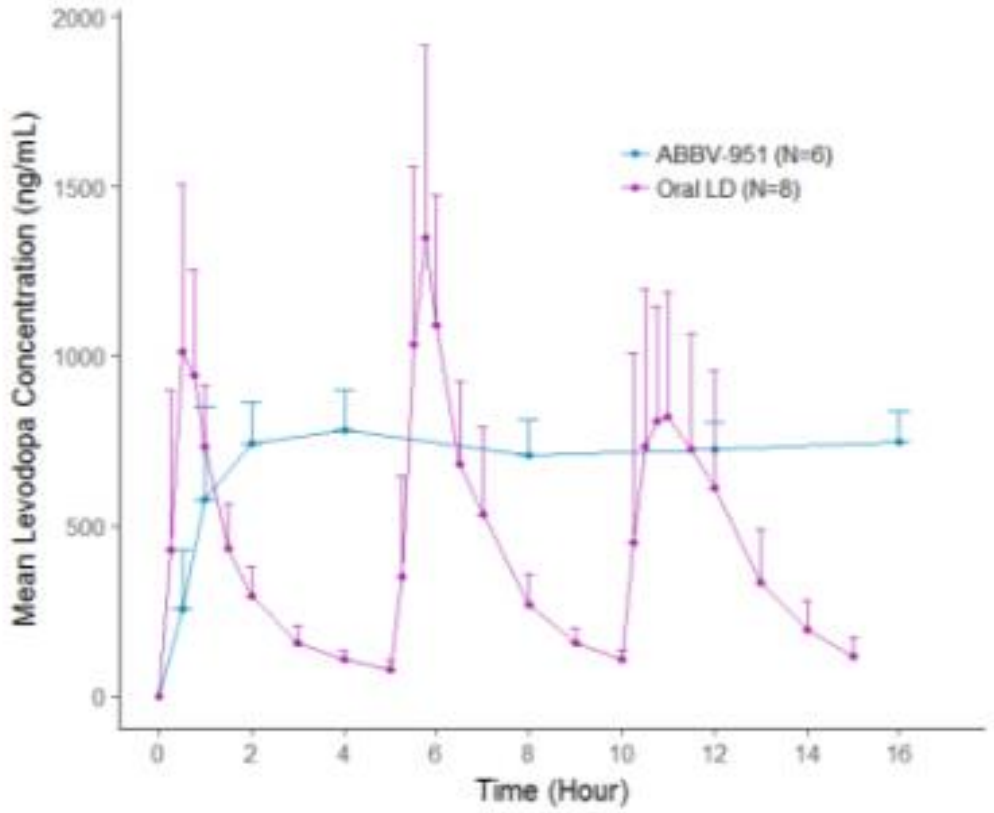

Foslevodopa

The NIHR recently approved the use of Abbvie's 24-hour infusion of levodopa-based therapy for Parkinson's.

It acts as a pump to steadily releasing levodopa into the bloodstream, providing a continuous supply of dopamine to the brain, and avoiding the 'peaks and troughs' of oral pills.

abbvie


One more thing...

EJS ACT-PD

Accelerating Clinical Trials in Parkinson's

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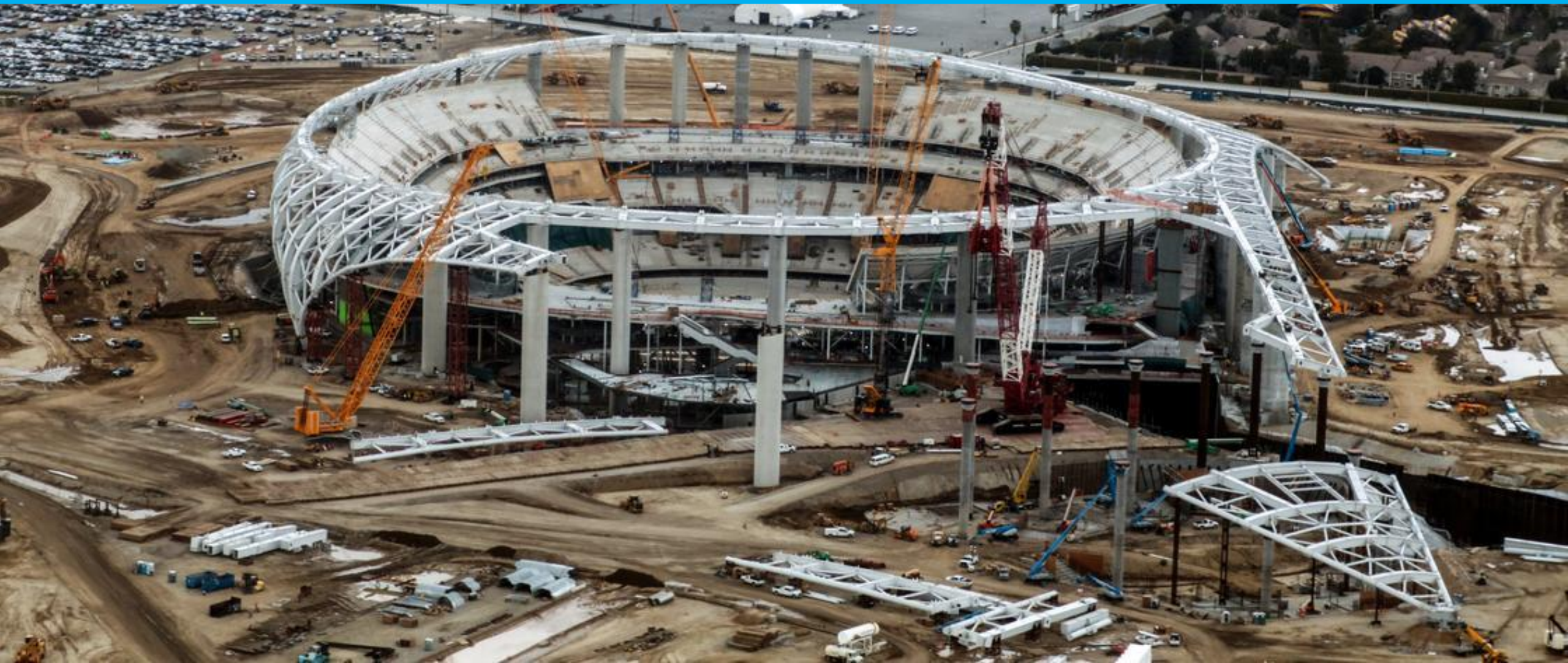
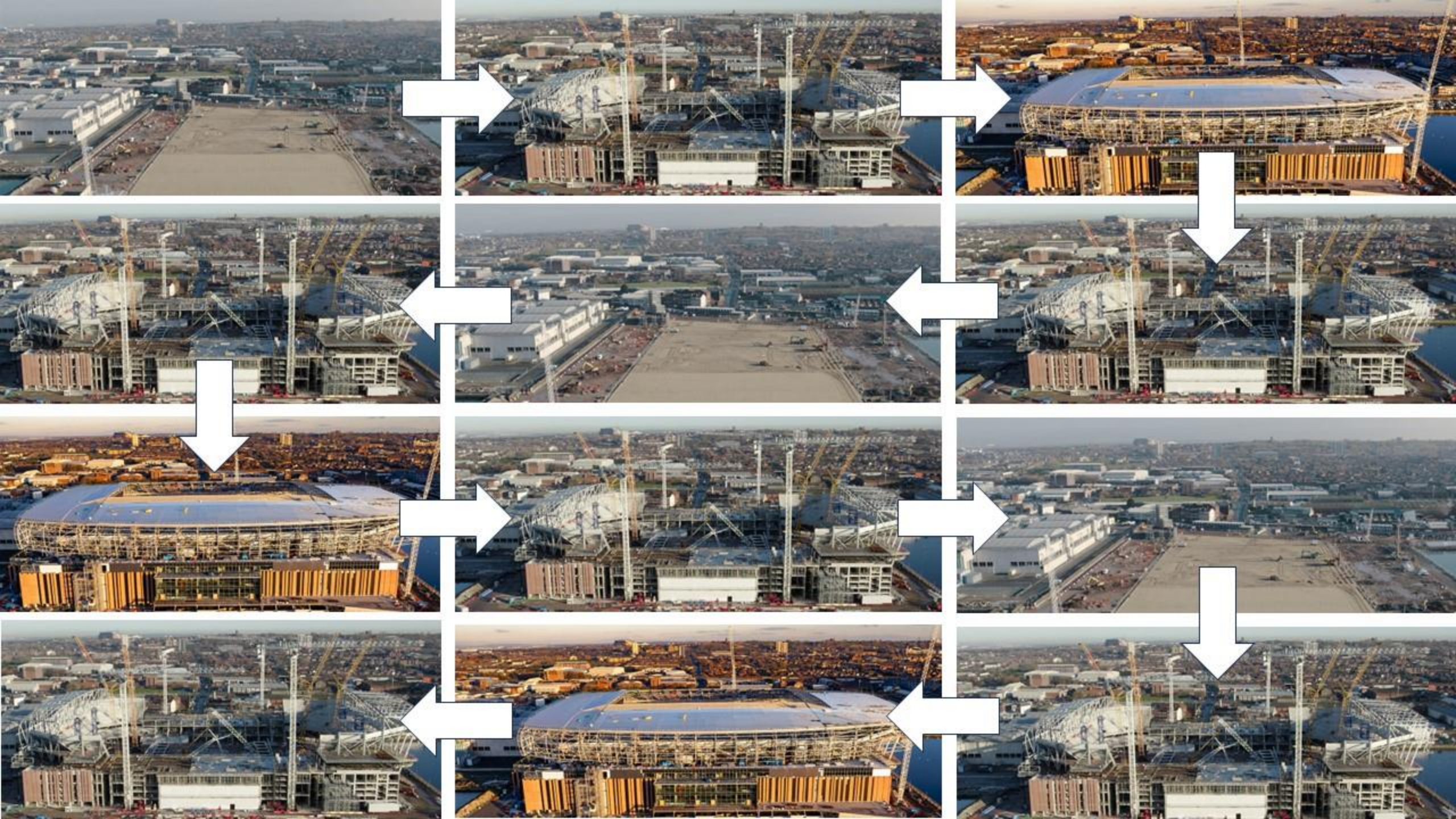
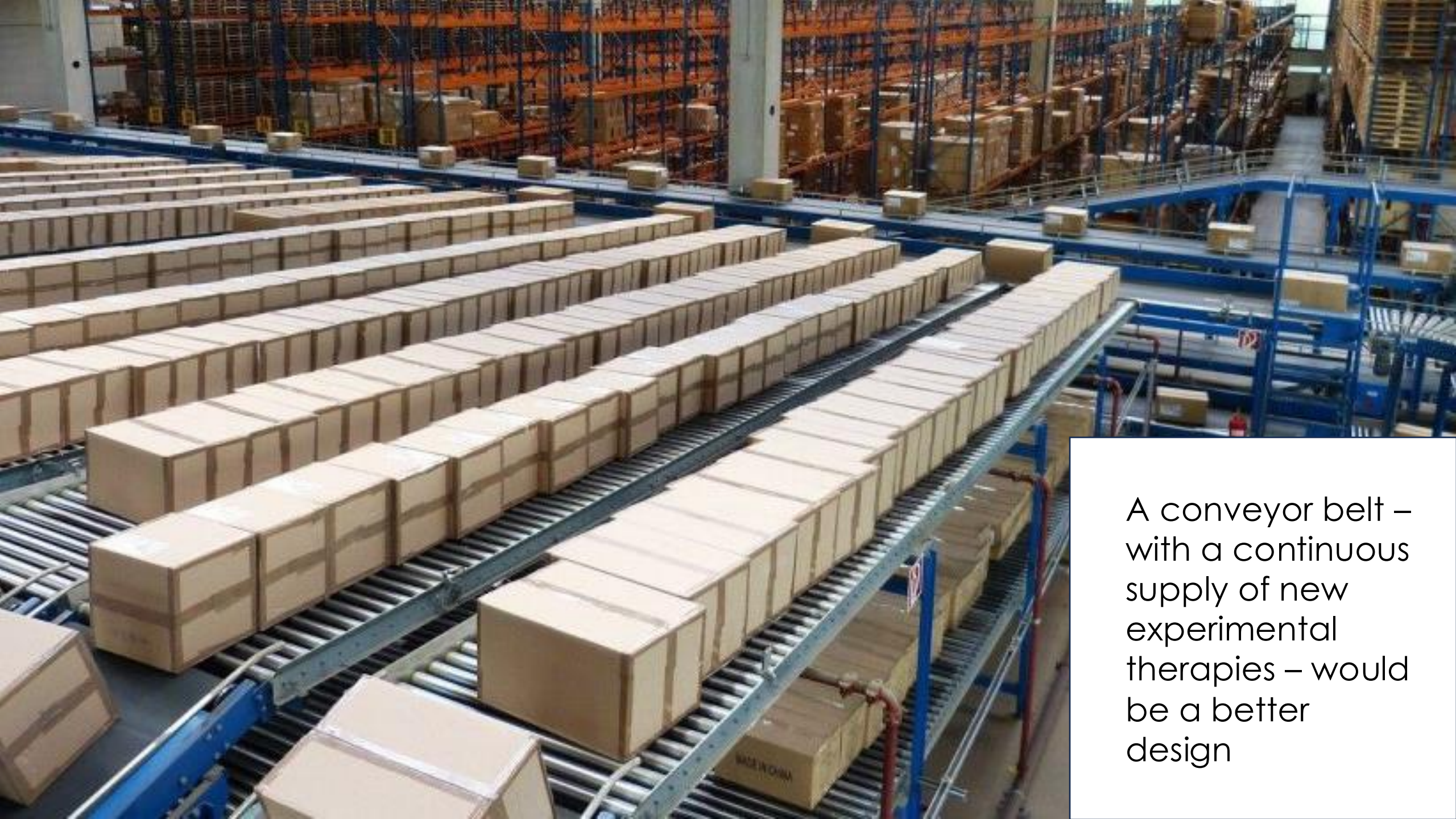
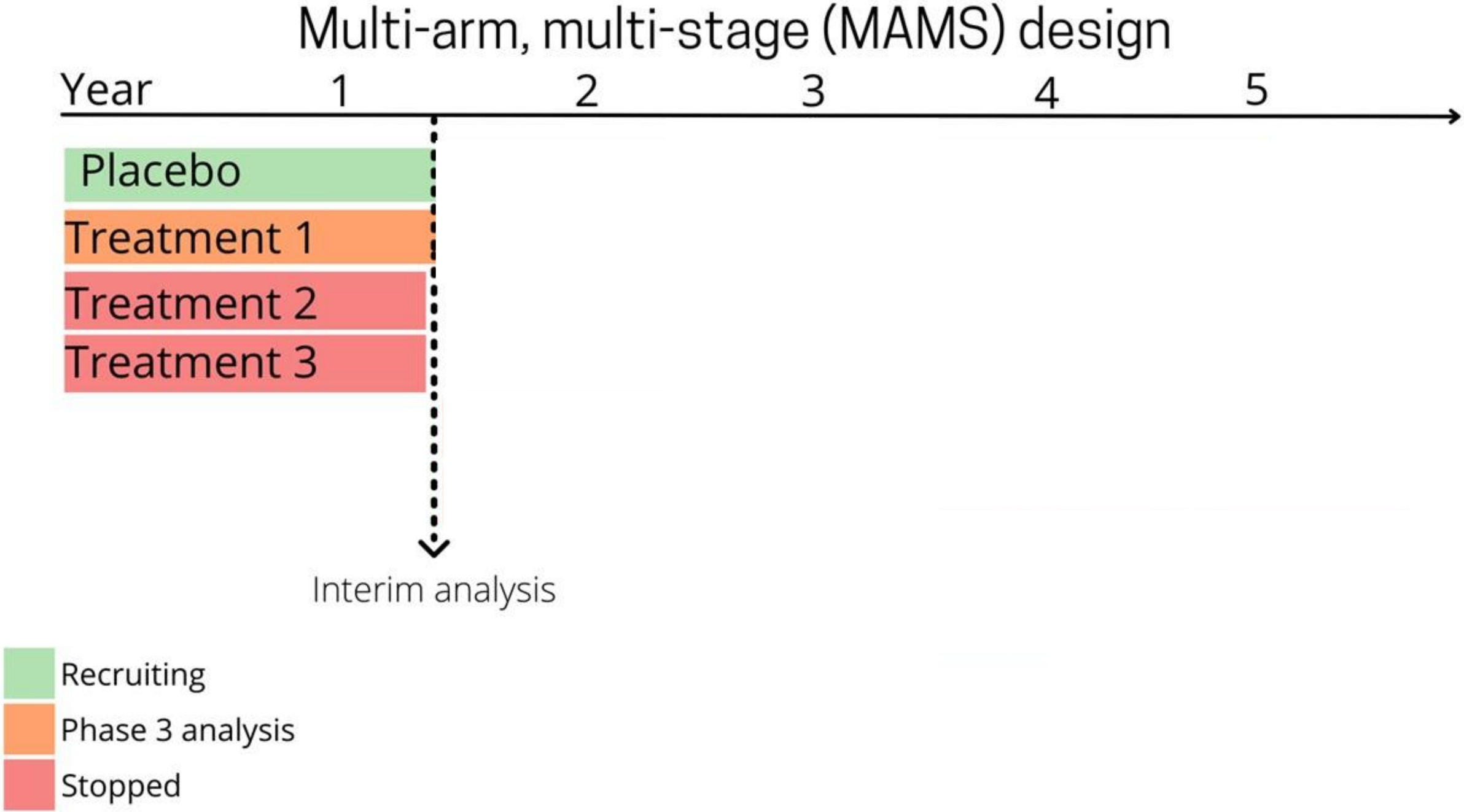
Currently, conducting a clinical trial is building a football stadium, playing one game and then deconstructing the stadium.

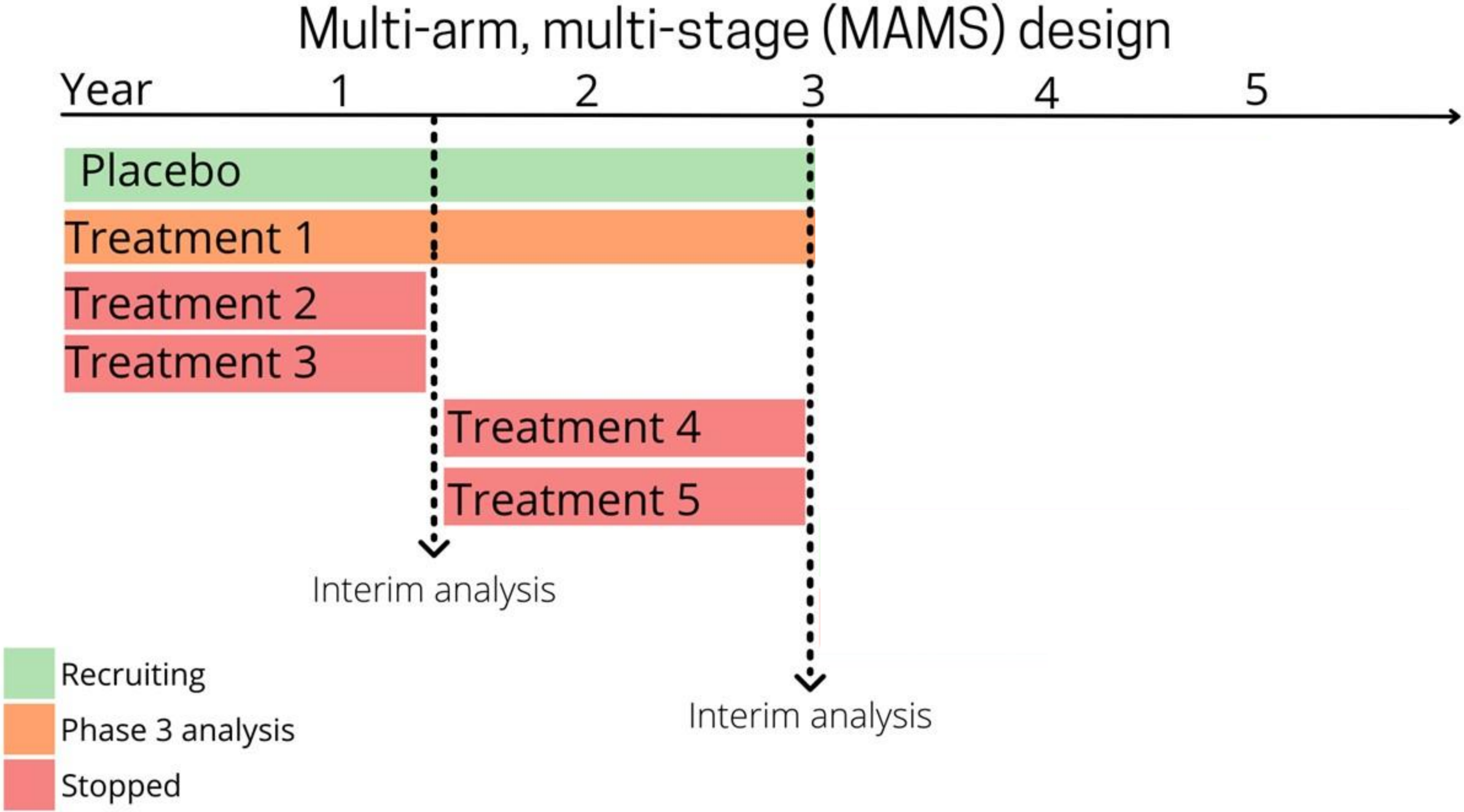






A conveyor belt – with a continuous supply of new experimental therapies – would be a better design


Multi-arm, multi-stage (MAMS) design
Year
1
2
3
4
5
Placebo
Treatment 1
Treatment 2
Treatment 3
Interim analysis
Recruiting
Phase 3 analysis
Stopped


Multi-arm, multi-stage (MAMS) design
Year
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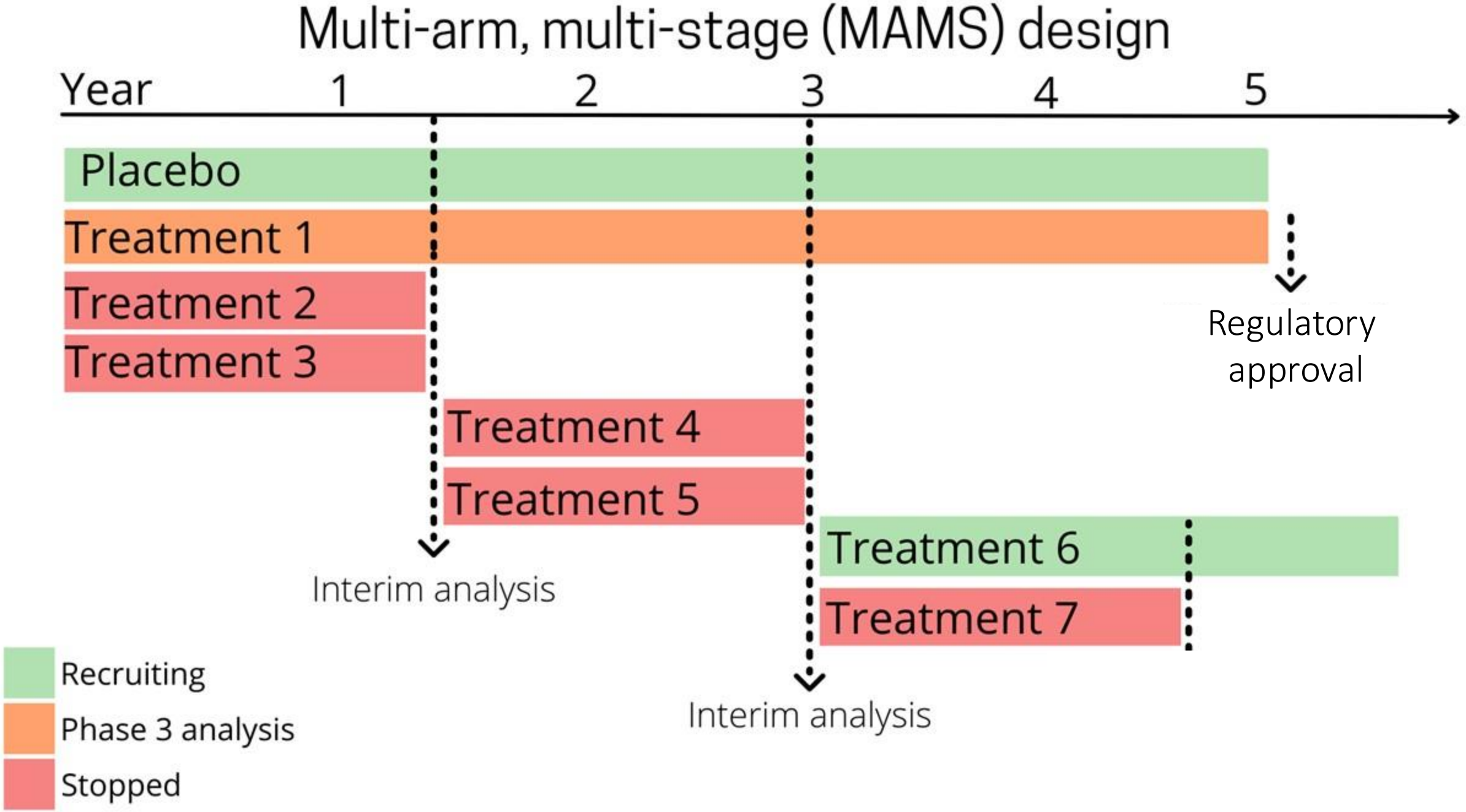
Placebo
Treatment 1
Treatment 2
Treatment 3
Treatment 4
Treatment 5
Interim analysis
Interim analysis
Recruiting
Phase 3 analysis
Stopped


Multi-arm, multi-stage (MAMS) design
Year
1
2
3
4
5
Placebo
Treatment 1
Treatment 2
Treatment 3
Treatment 4
Treatment 5
Treatment 6
Treatment 7
Regulatory approval
Interim analysis
Interim analysis
Recruiting
Phase 3 analysis
Stopped

EJS ACT-PD

Accelerating Clinical Trials in Parkinson's

The consortium of Parkinson's researchers, PwPs, care partners and other stakeholders are now collaborating in large working groups, planning out how to get this project started.

Treatment candidates have been selected, and now efforts are being made to secure funding.

Summary

- Encouraging clinical trial results from studies targeting different kinds of biology associated with Parkinson's (such as **alpha synuclein**).
- A **cough medicine (ambroxol)** shows promise in elevating a PD enzyme
- **Diabetes drugs** are being repurposed for Parkinson's with encouraging results.
- New **GDNF gene therapy** clinical trial
- **Adaptive deep brain stimulation** study results are expected.
- Evidence that **exercise** has an impact.
- The Edmund J Safra Accelerating Clinical Treatments for Parkinson's Disease (EJS-ACT PD) **multi-arm, multi-stage platform** is being constructed to speed up identification of disease modifying therapies for Parkinson's.

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Registered with FUNDRAISING REGULATOR

Thank you!

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