# Perspectives of Disease Modification in Parkinson‘s Disease


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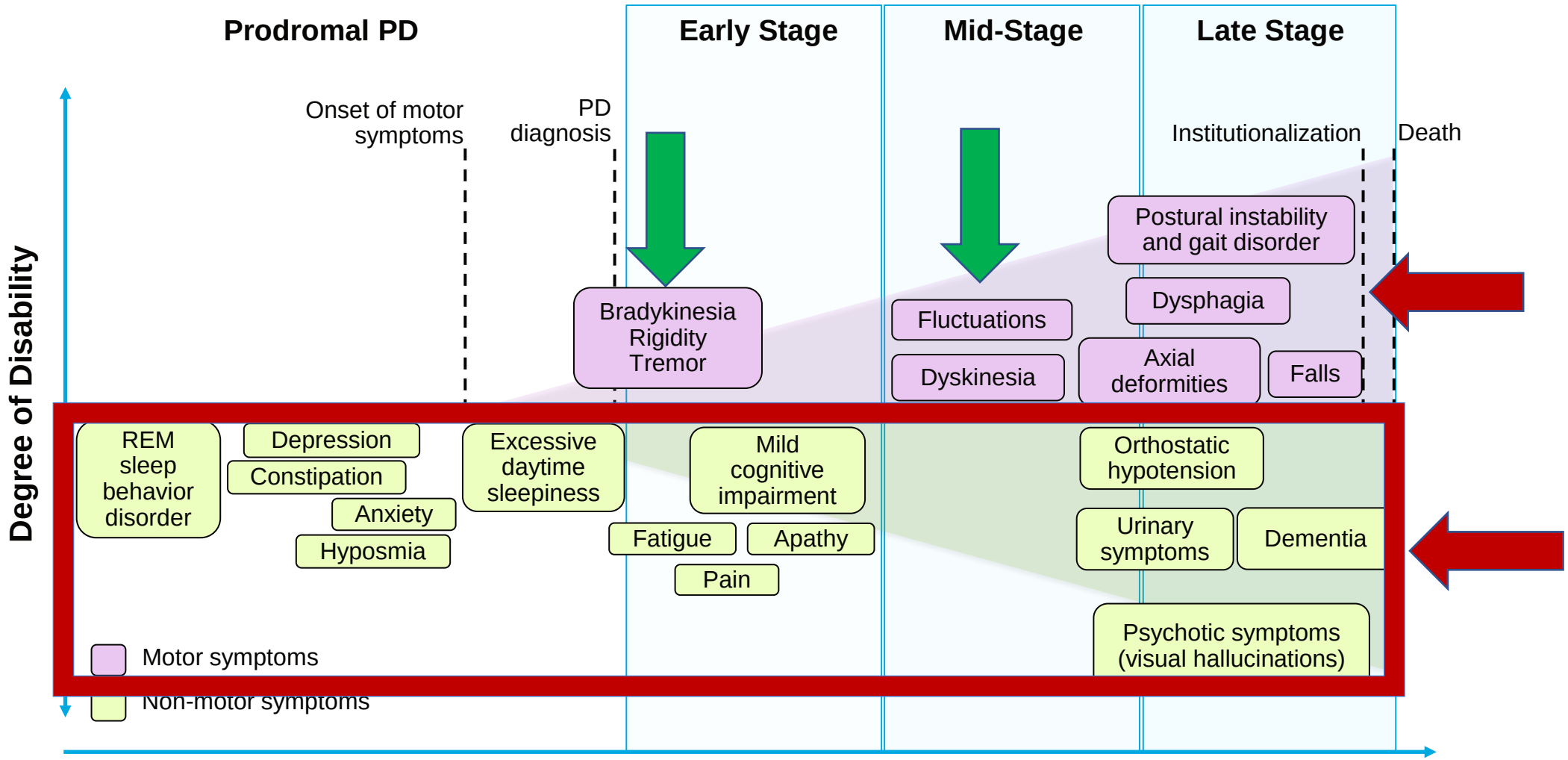
# Disclosures

| | |
|---|---|
| **Consultancy** | AbbVie, Affiriris, AC Immune, Alterity, BIAL, Biogen, Britannia, Lilly, Lundbeck, MSD, NeuroDerm, Neurocrine, Roche, Sanofi, Stada, Takeda, Teva, UCB |
| **Grants** | MJFF; EU FP7 & Horizon 2020 |
| **Lecture fees** | AbbVie, AC Immune, BIAL, Britannia, Boehringer, Eisai, Lundbeck, Merz, Stada, Zambon |

# OUTLINE

- DM in PD – the Holy Grail
- α-Synuclein as a target for DM in PD
- ‘Biological‘ PD Definition: Implications for DM trials

# Progression of Parkinson's Disease




Poewe W, *et al*. (2017) Nat Rev Dis Primers, 3:17013.

# Disease Modification Trials in PD – A History of Failure?

**Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study**

(Whone et al. Ann Neurol. 2003)

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease

(Olanow, Rascol et al. N Engl J Med 2009)

**Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial**

(Schapira et al. Lancet Neurol. 2013)

**A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit**

Parkinson Study Group QE3 Investigators; JAMA Neurol. 2014)

Effect of Creatine Monohydrate on Clinical Progression in Patients With Parkinson Disease
A Randomized Clinical Trial

Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators JAMA. 2015)

Caffeine as symptomatic treatment for Parkinson disease (Café-PD)
A randomized trial

(Postuma et al. Neurology® 2017)

**Isradipine Versus Placebo in Early Parkinson Disease A Randomized Trial**

The Parkinson Study Group STEADY-PD III Investigators*

(Ann Intern Med. 2020)

JAMA Neurology | Original Investigation

Efficacy of Nilotinib in Patients With Moderately Advanced Parkinson Disease
A Randomized Clinical Trial

(Simuni et alo. JAMA Neurol. 2021)

JAMA | Original Investigation

Effect of Urate-Elevating Inosine on Early Parkinson Disease Progression
The SURE-PD3 Randomized Clinical Trial

The Parkinson Study Group SURE-PD3 Investigators JAMA. 2021)

JAMA Neurology | Original Investigation

Evaluation of Simvastatin as a Disease-Modifying Treatment for Patients With Parkinson Disease
A Randomized Clinical Trial

(Stevens et al. JAMA Neurol. 2022)

Trial of Deferiprone in Parkinson's Disease

(Devos et al. N Engl J Med 2022)

# PD Clinical Trial Pipeline 2024*

- $N_{tot}$ = 136
  - Symptomatic therapies : 76 (56%)
  - Disease-modifying ther.: 60 (44%)

- DM Trials by Phase
  - Phase 1 : 37%
  - Phase 2 : 58%
  - Phase 3 : 5%

- DM Trials by Target
  - α-synuclein : 15%
  - GBA : 12%
  - Kinase-Inhibitors (incl. LRRK2) : 11%
  - Anti-inflammatory : 10%
  - GLP-1 agonist : 8%
  - Mitochondria : 7%
  - Neurotrophic : 7%
  - Other : 15%

*based on ClinicalTrials.gov online registry

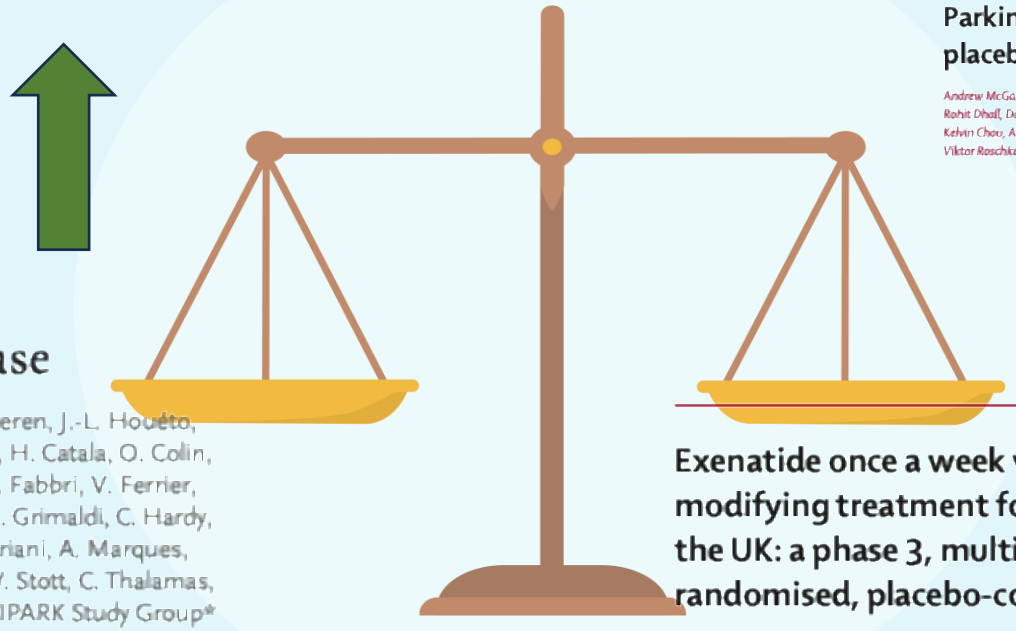
McFarthing et al. JPD 2024; 14: 899-912

# GLP-1 Receptor agonists to slow Progression in PD: the Jury is still out

**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*

*Lancet* 2017; 390: 1664–75



**Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial**

*Andrew McGarry, Shane Rosanbalm, Mika Leinonen, C Warren Olanow, Dennis To, Adam Bell, Daniel Lee, Jamie Chang, Jordan Dubow, Rohit Dhall, Daniel Burdick, Sotirios Parashos, Jeanne Feuerstein, Joseph Quinn, Rajesh Pahwa, Mitra Afshan, Aldolfo Ramirez-Zamora, Kelvin Chou, Arjun Tarakad, Cornelio Luca, Kevin Klos, Yvette Bordelon, Marie-Helene St Hilaire, David Shprecher, Seulki Lee, Ted M Dawson, Viktor Roschke, Karl Kieburtz*

**Lancet Neurol 2024; 23: 37–45**

**Trial of Lixisenatide in Early Parkinson's Disease**

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houeto, 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*

N ENGL J MED 390;13 NEJM.ORG APRIL 4, 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 McCormish, 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*

www.thelancet.com **Published online February 4, 2025** https://doi.org/10.1016/S0140-6736(24)02808-3

# Targets for Disease-Modification in Genetic PD

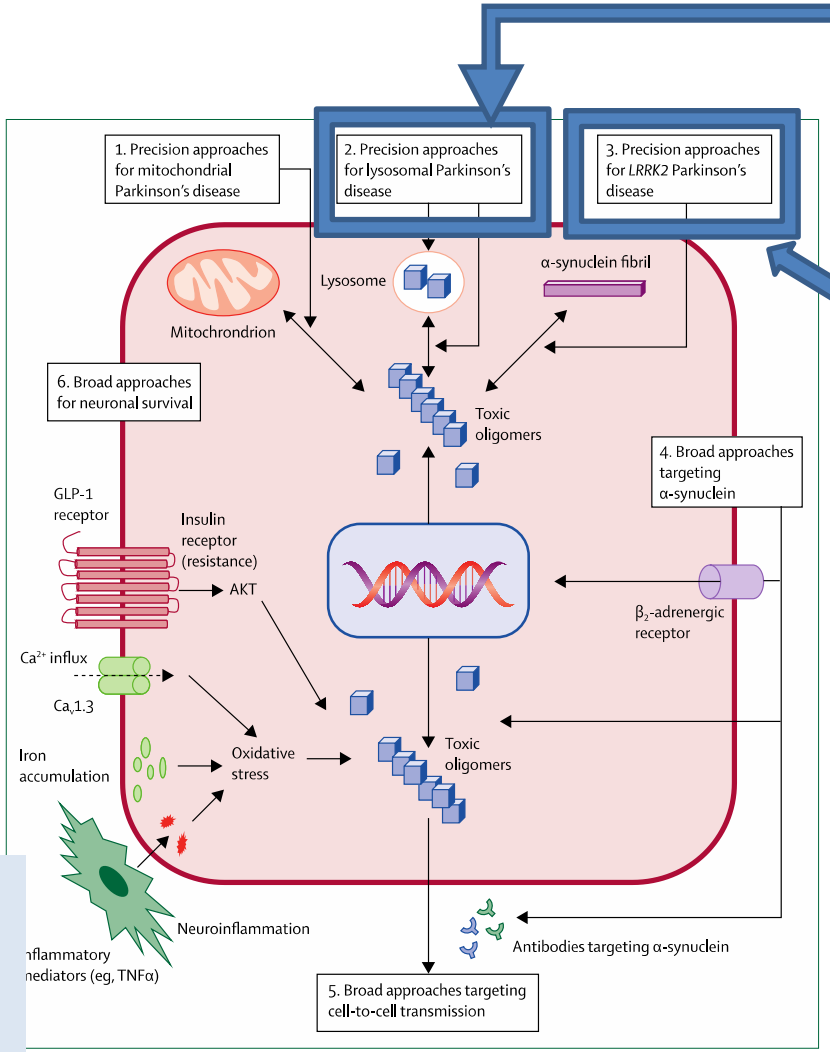
Pioglitazon: neg ph 2
Inosin: neg. ph 3
Kreatin: neg RCT‘s
CoQ10: neg RCT‘s

Exenatide
Liragluitde
Lixisenatide
Semaglutide

Isradipine: negative ph 3

Deferiprone: neg ph 2

Minocyclin: neg ph 2
Verdiperstat: neg MSA trial
Simvastatin: neg ph 2
NLRP3 inhibitors: ongoing ph1/ph 2



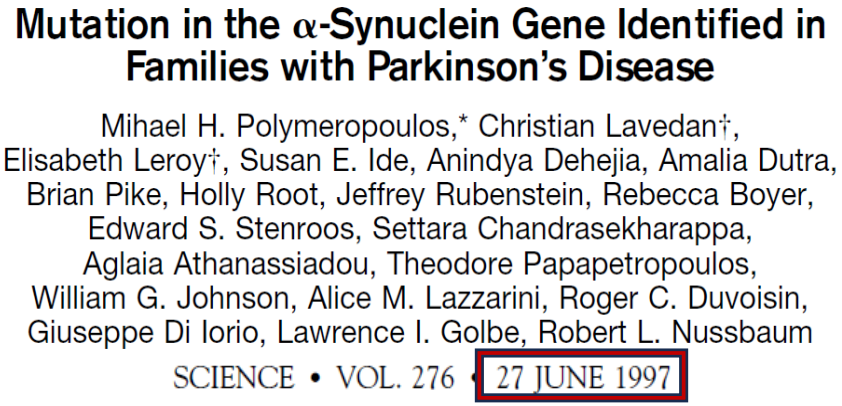

**Ambroxol: ph 2 ongoing**
**LTI-291/BIA-28: ph 2ongoing**
**PR001: ongoing ph 1**

**BIIB 122/DNL 151: ongoing ph 2**
**BIIB094 : ongoing ph 2**

*Nirosen Vijiaratnam, Tanya Simuni, Oliver Bandmann, Huw R Morris, Thomas Foltynie* *Lancet Neurol* 2021; 20: 559–72

# Defining PD as a ‚Synucleinopathy‘

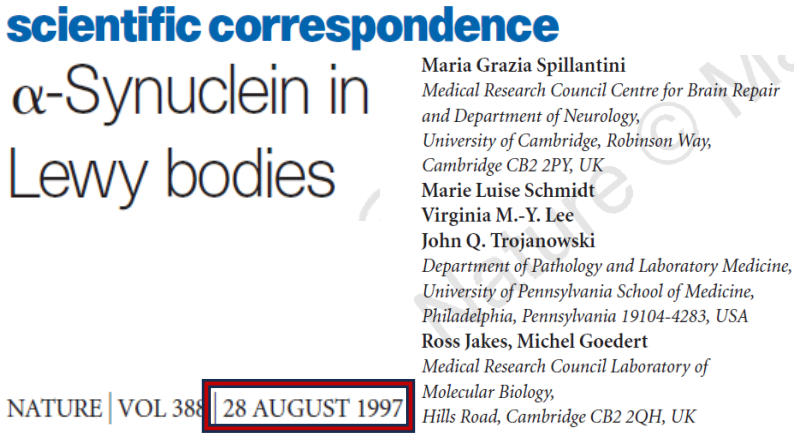
- **Missense mutations in SNCA sufficient to cause dominantly inherited PD** [1,3]
- Increase in SNCA wild-type gene dose (duplication; triplication) causes PD (or PDD) [4]
- Sequence variations in regulatory region of SNCA associated with PD risk [5]
- **Lewy bodies and Lewy neurites in sporadic PD immunoreactive for α-synuclein** [2]



**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

SCIENCE • VOL. 276 • 27 JUNE 1997



**scientific correspondence**

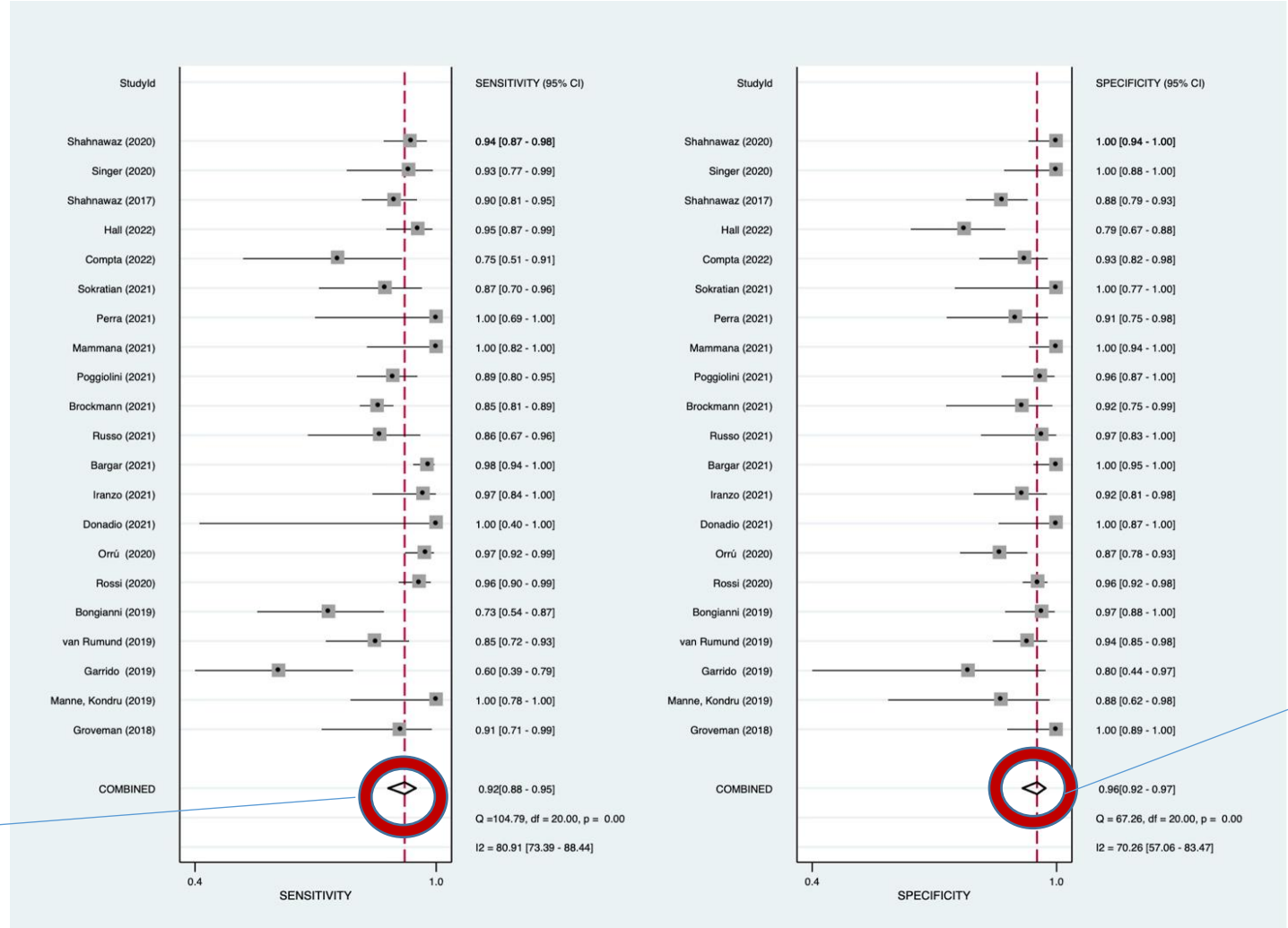
**α-Synuclein in Lewy bodies**


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*


NATURE | VOL 388 | 28 AUGUST 1997


1.Polymeropoulos &al.,Science. 1997 Jun 27;276(5321):2045-7; 2.Spillantini &al.,Nature. 1997 Aug 28;388(6645):839-40. 3.Krüger &al.,Nat Genet. 1998 Feb;18(2):106-8; 4.Singleton &al., Science. 2003 Oct 31;302(5646):841; 5.Blauwendraat &al., Lancet Neurol. 2020 Feb;19(2):170-178.

# Diagnostic Performance of CSF α-Synuclein SAA (PD/DLB vs. Ctrls.)




**sensitivity : 92%**

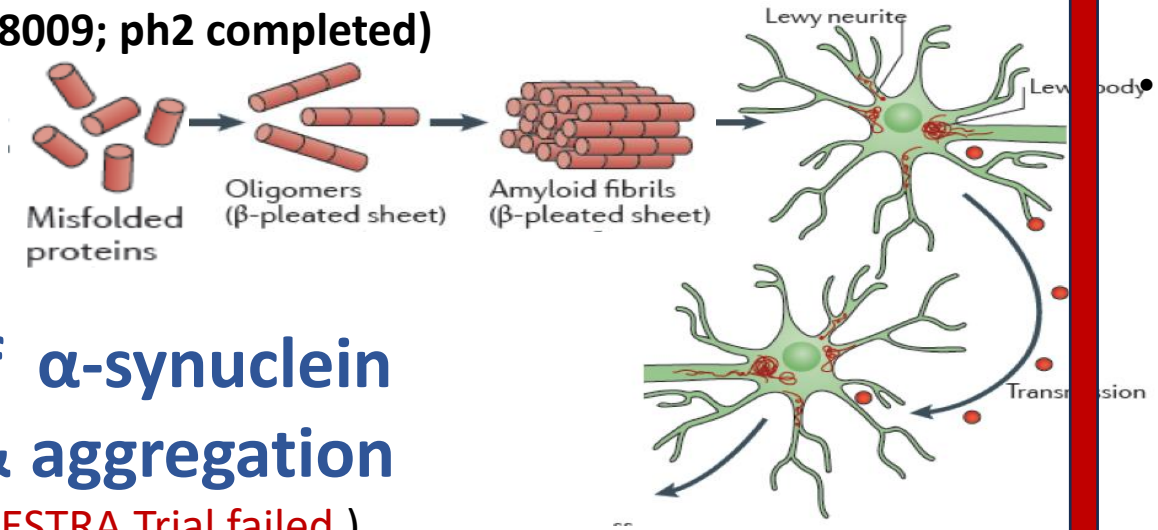
**specificity : 96%**

Grossauer et al; Mov Dis Clin Pract , 2023

# DM Trials in PD:Targeting α-Synuclein

## Clearance of intracellular α-synuclein aggregates (c-ABL1 inhibition)

- **Nilotinib: neg trials**
- **Vodobatinib,K0706 (ph.2 neg. )**
- **Radotinib** (ph2 recruiting)
- **Risvodetinib (IkT 148009; ph2 completed)**




Irwin DJ & al., Nat Rev Neuroscience 2013; 14: 62 636

## Inhibition of α-synuclein misfolding & aggregation

- **UCB0599** (ORCHESTRA Trial failed )
- **ANLE 138B** phase 3 in MSA ongoing
- **ATH 434 ,** phase 2 in MSA completed

## Passive Immunotherapy

- **Cinpanemab** (SPARK trial neg**)**
- **Prazinesumab** (PASADENA&PADOVA: +ve efficacy signals **)**
- **Lu AF82422**: (AMULET Trial in MSA +ve efficacy signals )

## Active Immunotherapy

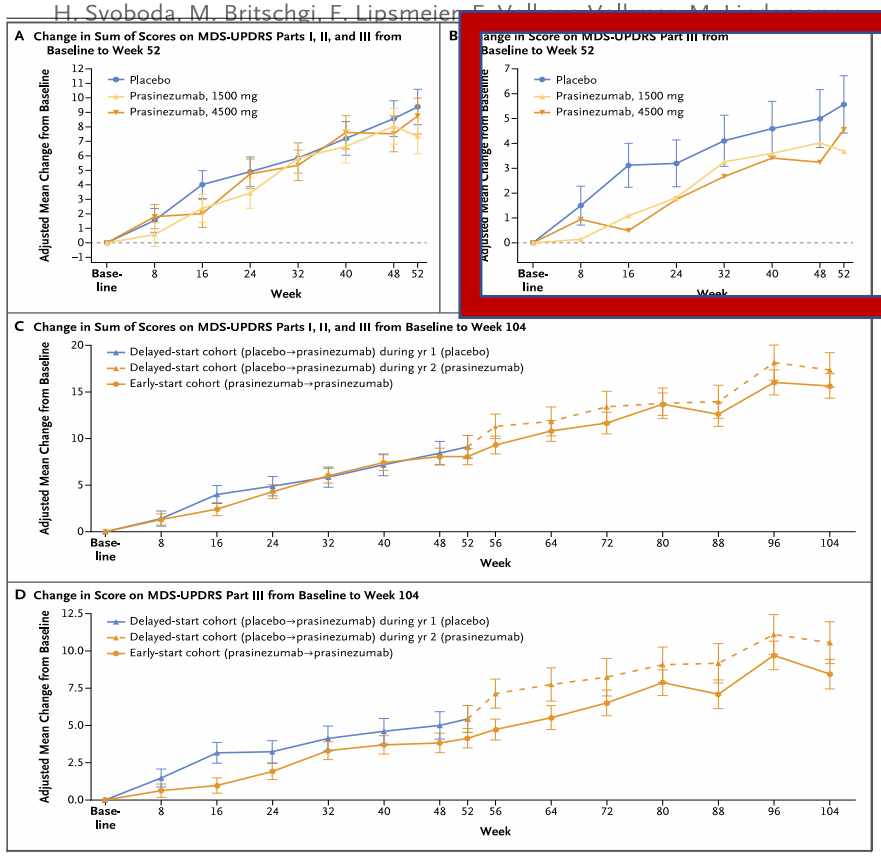
- **PD03A** Phase 2a pos safety&immunogenicity
- **UB-312** Phase 2a pos safety&immunogenicity
- **ACI-7104: phase 2 ongoing**

ORIGINAL ARTICLE

# Trial of Prasinezumab in Early-Stage Parkinson's Disease

G. Pagano, K.I. Taylor, J. Anzures-Cabrera, M. Marchesi, T. Simuni, K. Marek, R.B. Postuma, N. Pavese, F. Stocchi, J.-P. Azulay, B. Mollenhauer, L. López-Manzanares, D.S. Russell, J.T. Boyd, A.P. Nicholas, M.R. Luquin, R.A. Hauser, T. Gasser, W. Poewe, B. Ricci, A. Boulay, A. Vogt, F.G. Boess, J. Dukart, G. D'Urso, R. Finch, S. Zanigni, A. Monnet, N. Pross, A. Hahn, H. Svoboda, M. Britschgi, F. Lipsmeier

Engl J Med 2022;387:421-32.
DOI: 10.1056/NEJMoa2202867



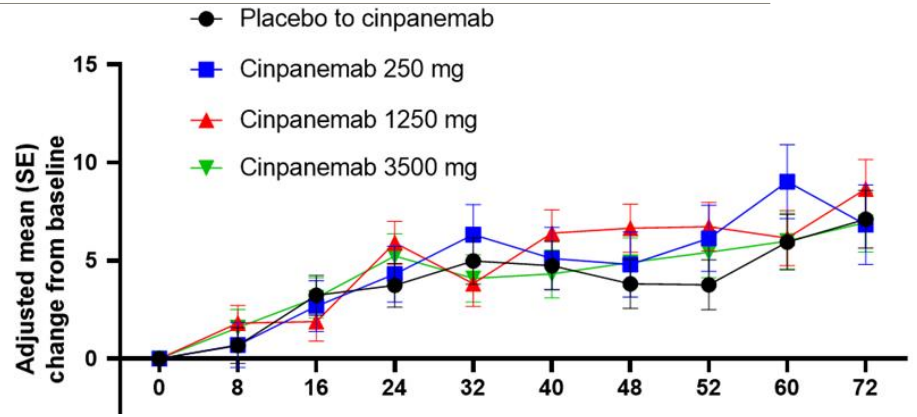


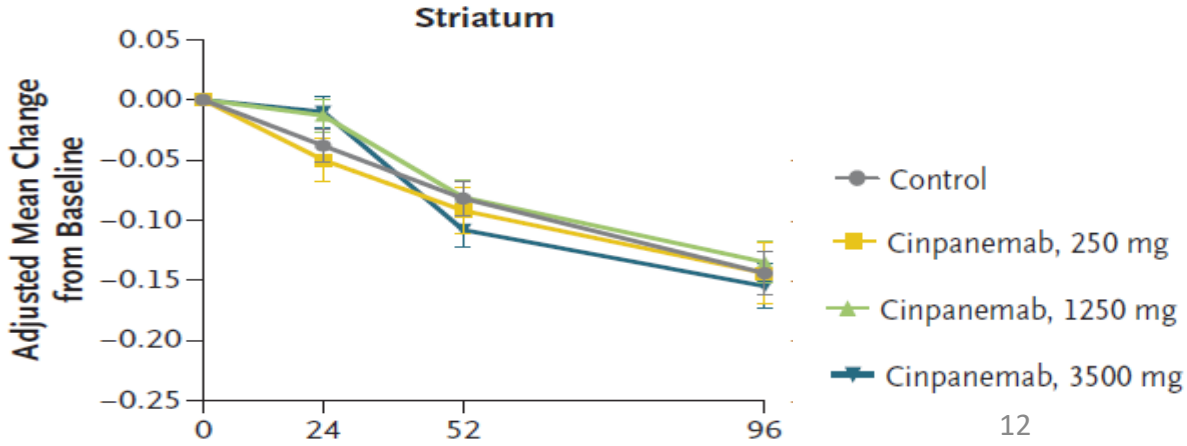

ORIGINAL ARTICLE

# Trial of Cinpanemab in Early Parkinson's Disease

A.E. Lang, A.D. Siderowf, E.A. Macklin, W. Poewe, D.J. Brooks, H.H. Fernandez, O. Rascol, N. Giladi, F. Stocchi, C.M. Tanner, R.B. Postuma, D.K. Simon, E. Tolosa, B. Mollenhauer, J.M. Cedarbaum, K. Fraser, J. Xiao, K.C. Evans, D.L. Graham, I. Sapir, J. Inra, R.M. Hutchison, M. Yang, T. Fox, S. Budd Haeberlein, and T. Dam, for the SPARK Investigators*

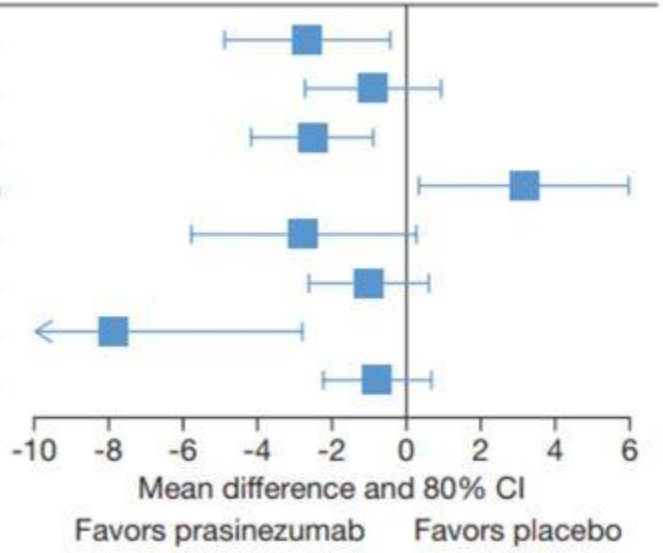
N Engl J Med 2022;387:408-20.
DOI: 10.1056/NEJMoa2203395

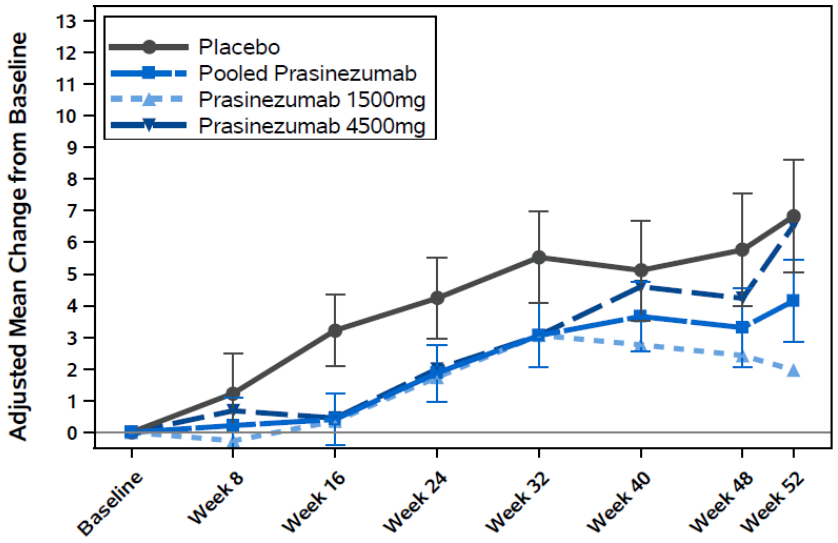


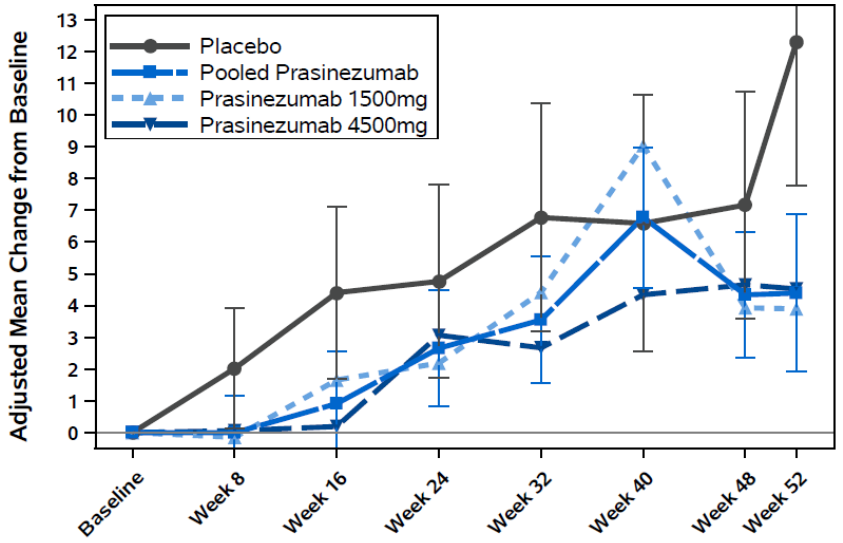
# PASADENA: Subgroup-Analysis

| Category | Subgroup | Total n | Placebo adj. mean | Prasinezumab pool adj. mean | Adj. mean difference | 80% CI | Relative difference |
|---|---|---|---|---|---|---|---|
| MAO-B inhibitor | Yes | 115 | 6.82 | 4.15 | -2.66 | (-4.87, -0.45) | -39.0% |
| | No | 201 | 5.04 | 4.18 | -0.87 | (-2.69, 0.94) | -17.3% |
| Hoehn & Yahr stage | 2 | 238 | 6.34 | 3.76 | -2.55 | (-4.19, -0.90) | -40.2% |
| | 1 | 78 | 2.17 | 5.23 | 3.14 | (0.32, 5.95) | 144.7% |
| RBDSQ | ≥5 | 85 | 7.76 | 5.00 | -2.76 | (-5.78, 0.25) | -35.6% |
| | <5 | 230 | 4.98 | 3.95 | -1.03 | (-2.63, 0.57) | -20.7% |
| Data-driven subphenotype | Diffuse malignant | 59 | 12.29 | 4.39 | -7.86 | (-12.90, -2.82) | -64.0% |
| | Non-diffuse malignant | 257 | 4.76 | 3.99 | -0.77 | (-2.20, 0.66) | -16.2% |




*MAO-B inhibitor treated (n=115)*




*Diffuse malignant (n=59)*


nature medicine

Article

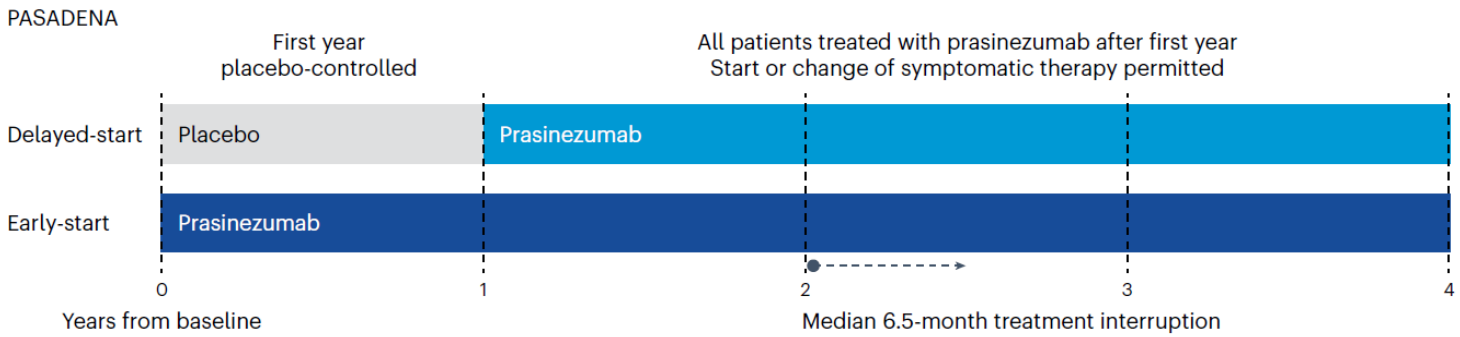
https://doi.org/10.1038/s41591-024-02886-y

**Prasinezumab slows motor progression in rapidly progressing early-stage Parkinson's disease**

Pagano et al; Nature Medicine 2024

# PASADENA Trial Open-Label Extension

- 5-year OL study following washout after week 104 of RCT
- 271/316 participants entered OL (86%)
- OL infusions of 1500mg of prasinezumab every 4 weeks
- PPMI dataset used as historical control (propensity score matching to balance baseline characteristics&modelling)
- Exploratory analysis of MDS-UPDRS progression PASADENA vs PPMI cohort over 4 years




PPMI — No intervention (start of symptomatic treatment permitted after 6 months)

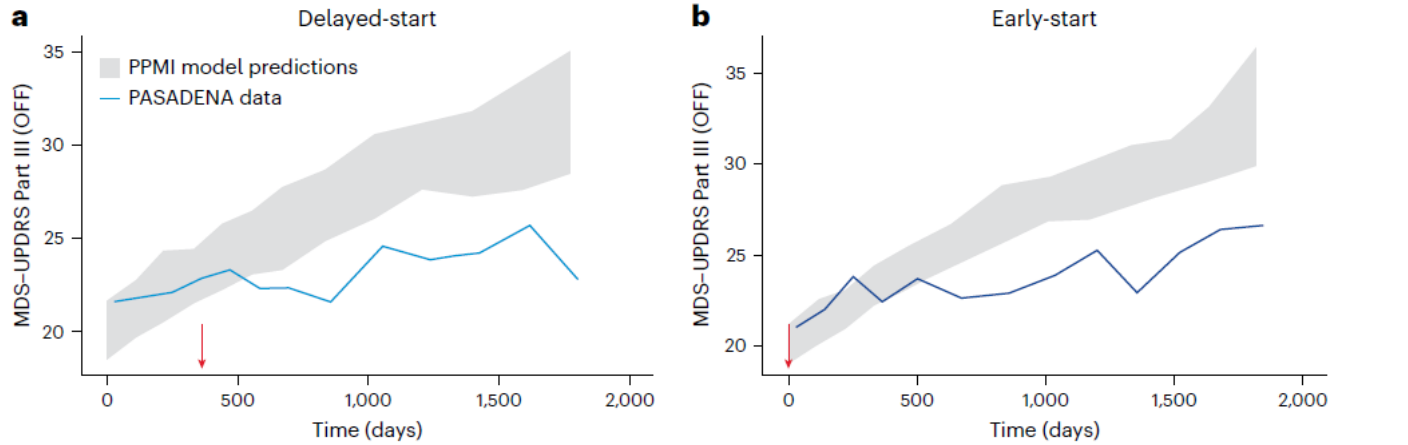
| Characteristic | After weighting | | |
|---|---|---|---|
| | PASADENA, *n*=271 | EC PPMI, *n*=270 | SMD |
| Age (years), mean (s.d.) | 59.98 (9.00) | 61.20 (9.28) | 0.133 |
| Male sex, *n* (%) | 188.0 (69.4) | 189.3 (70.1) | 0.017 |
| MDS–UPDRS Part III, mean (s.d.) | 21.15 (8.96) | 21.13 (9.71) | 0.001 |
| H&Y 2, *n* (%) | 201.0 (74.2) | 205.7 (76.2) | 0.047 |
| PD diagnosis (months), mean (s.d.) | 9.89 (6.34) | 9.20 (5.61) | 0.115 |
| Years of education ≥12, *n* (%) | 244.0 (90.0) | 236.2 (87.5) | 0.080 |
| Montreal Cognitive Assessment, mean (s.d.) | 28.17 (1.79) | 28.02 (1.89) | 0.082 |
| DaT–SPECT putamen bilateral, mean (s.d.) | 0.92 (0.26) | 0.92 (0.31) | 0.018 |

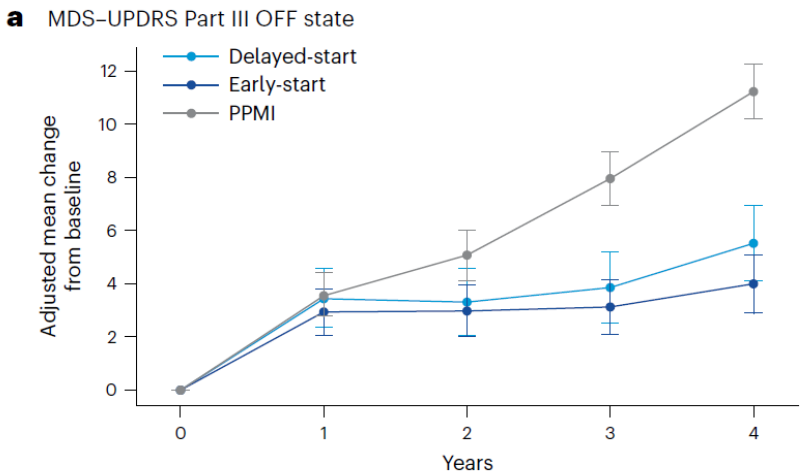
Pagano&al. Nature Medicine | Volume 30 | December 2024 | 3669–3675

nature medicine

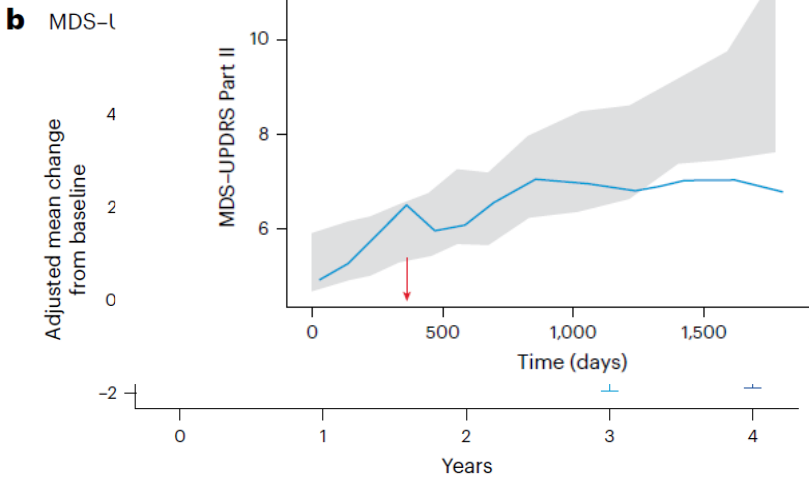
Article

# Sustained effect of prasinezu
# Parkinson's disease motor pr
# open-label extension of the P

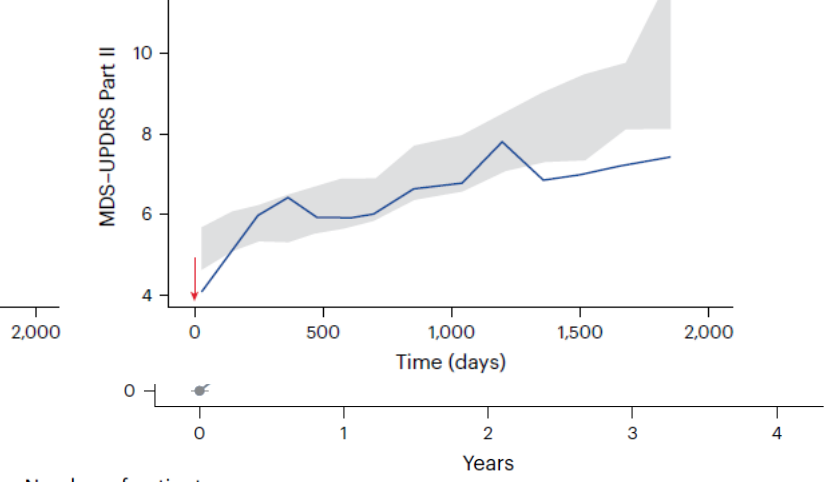



| Number of patients | | | | | |
|---|---|---|---|---|---|
| Delayed-start | 94 | 93 | 83 | 83 | 75 |
| Early-start | 177 | 175 | 149 | 147 | 143 |
| PPMI | 303 | 215 | 185 | 182 | 180 |

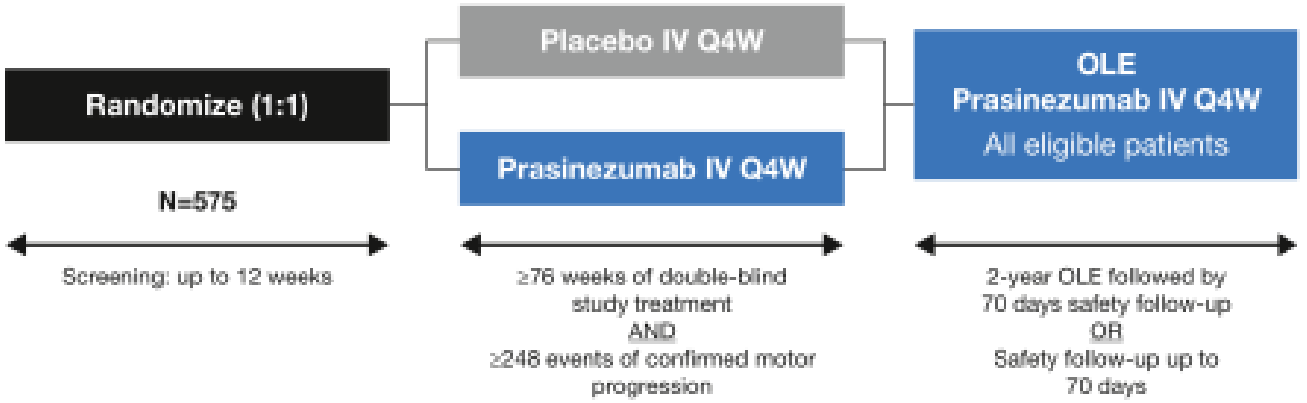



| Number of patients | | | | | |
|---|---|---|---|---|---|
| Delayed-start | 94 | 94 | 91 | 91 | 88 |
| Early-start | 177 | 177 | 167 | 167 | 165 |
| PPMI | 303 | 263 | 249 | 249 | 232 |




| Number of patients | | | | | |
|---|---|---|---|---|---|
| Delayed-start | 94 | 94 | 93 | 91 | 90 |
| Early-start | 177 | 177 | 174 | 167 | 166 |
| PPMI | 303 | 268 | 262 | 265 | 248 |

# PADOVA Trial: Efficacy and Safety of Prasinezumab in Patients with Early PD:




- **Phase 2b** (**NCT04777331**)
- **n =** 575 PD patients ≤ 2 yrs from dx

**ROCHE press Release Dec. 2024:**
**HR of 0.84 [0.69-1-01] for time to confirmed motor progression (p=0.065)**
**More pronounced effect in LD-treated subgroup : HR 0.79 [0.63-0.99]**
**Positive trends across multiple secondary endpoints**

- *-time to motor complications (MDS-UPDRS IV)*
- *time to ≥ 3-pt worsening MDS-UPDRS II*
- *time to worsening CGI-P*

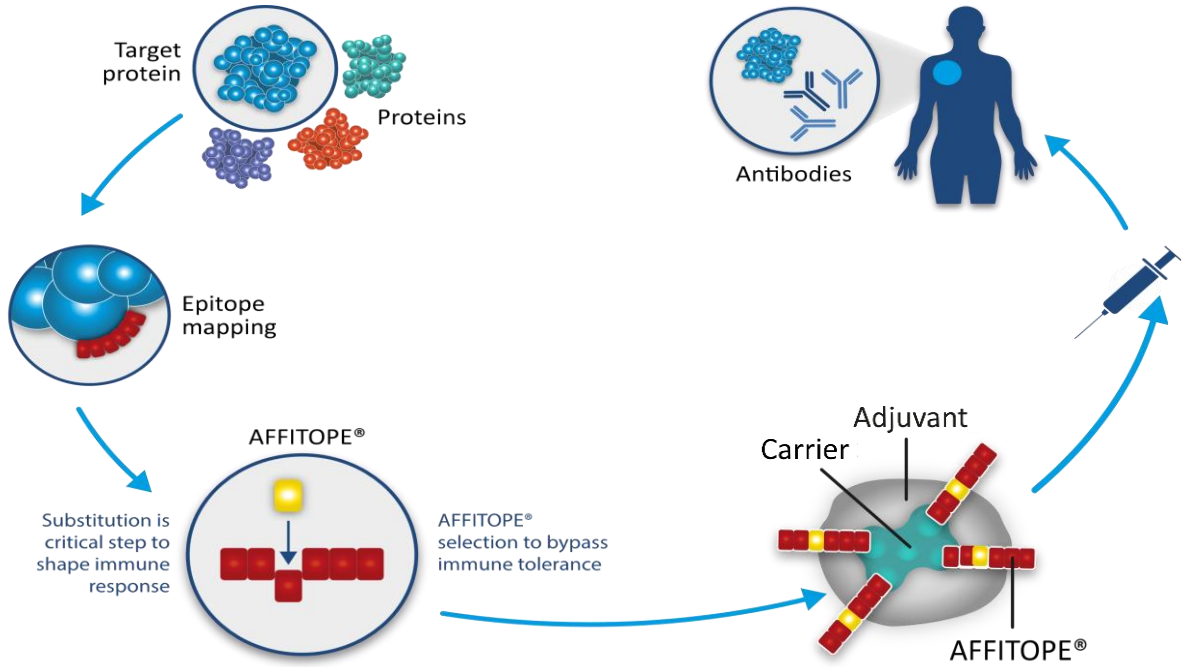
| | | | |
|---|---|---|---|
| MDS-UPDRS Part II score, mean (SD) | 5.0 (3.8) | 5.2 (4.0) | 4.5 (3.4) |
| MDS-UPDRS Part III score, mean (SD) | 24.5 (10.4) | 25.1 (10.4) | 22.5 (10.1) |

Nikolcheva&al. Park Rel Dis 132 (2025) 107257

# Active Immunisation: Advantages and Challenges

- **Advantages vs passive Immuno-Tx:**
  - long-lasting immune response
  - large interdose intervals
  - sc/im dosing
  - may address > one target protein

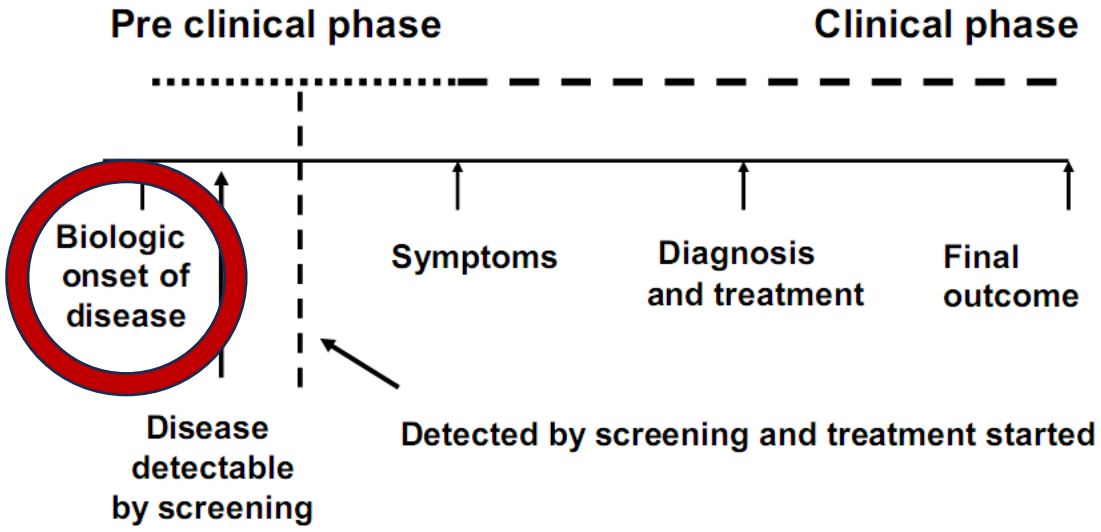
- **Challenges:**
  - Overcome immune tolerance
  - Robust immune response
  - Avoid T-cell mediated toxicity



# DM Trials In PD – Why do they Fail?

- Wrong  Target
  - Pathophysiological heterogeneity
  - Monotherapy = one size fits all
- Wrong  Dose
- Trial Design Issues
  - Insensitive  outcome measures
  - Lack of progression biomarkers
  - Insufficient trial duration

- **Wrong target population**
  - **Lack of stratification for PD subtypes**
  - **‚early PD‘ may be too late**



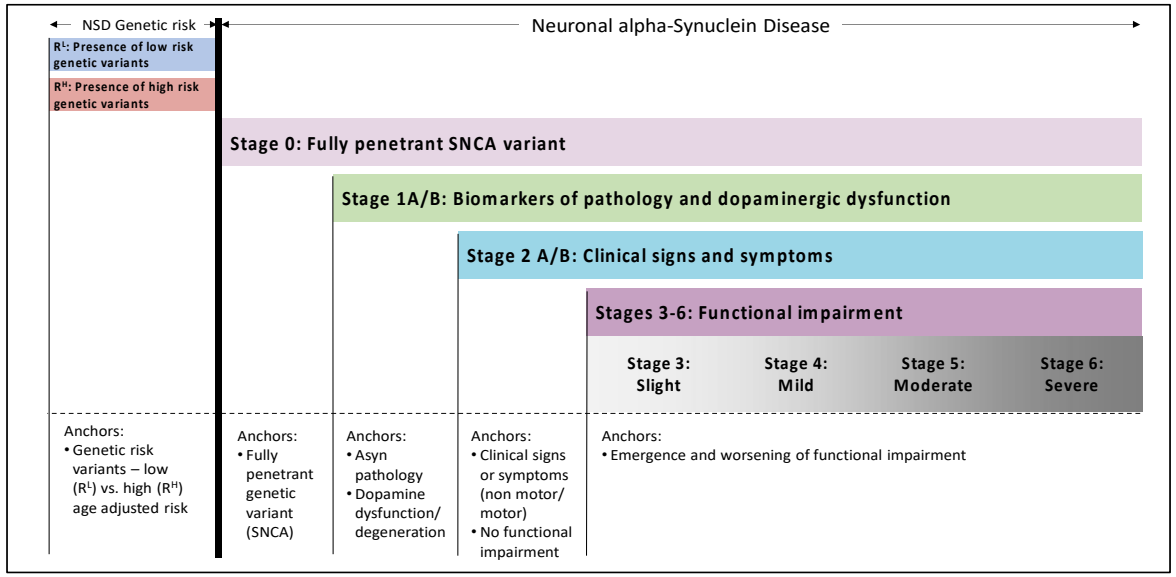
# A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria

Günter U Höglinger, Charles H Adler, Daniela Berg, Christine Klein, Tiago F Outeiro, Werner Poewe, Ronald Postuma, A Jon Stoessl, Anthony E Lang

With the hope that disease-modifying treatments could target the molecular basis of Parkinson's disease, even before the onset of symptoms, we propose a biologically based classification. Our classification acknowledges the complexity and heterogeneity of the disease by use of a three-component system (SynNeurGe): presence or absence of pathological α-synuclein (S) in tissues or CSF; evidence of underlying neurodegeneration (N) defined by neuroimaging procedures; and documentation of pathogenic gene variants (G) that cause or strongly predispose to Parkinson's disease. These three components are linked to a clinical component (C), defined either by a single high-specificity clinical feature or by multiple lower-specificity clinical features. The use of a biological classification will enable advances in both basic and clinical research, and move the field closer to the precision medicine required to develop disease-modifying therapies. We emphasise the initial application of these criteria exclusively for research. We acknowledge its ethical implications, its limitations, and the need for prospective validation in future studies.

*Lancet Neurol* 2024; 23: 191–204
See Comment pages 130 and 133

Department of Neurology, University Hospital, Ludwig-Maximilians-University (LMU) and German Center for Neurodegenerative Diseases, Munich, Germany (Prof G U Höglinger MD); Munich Cluster for Systems Neurology (SyNergy), Munich Germany (Prof G U Höglinger);




# A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research

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*Lancet Neurol* 2024; 23: 178–90

Parkinson's disease and dementia with Lewy bodies are currently defined by their clinical features, with α-synuclein

## Commonalities :

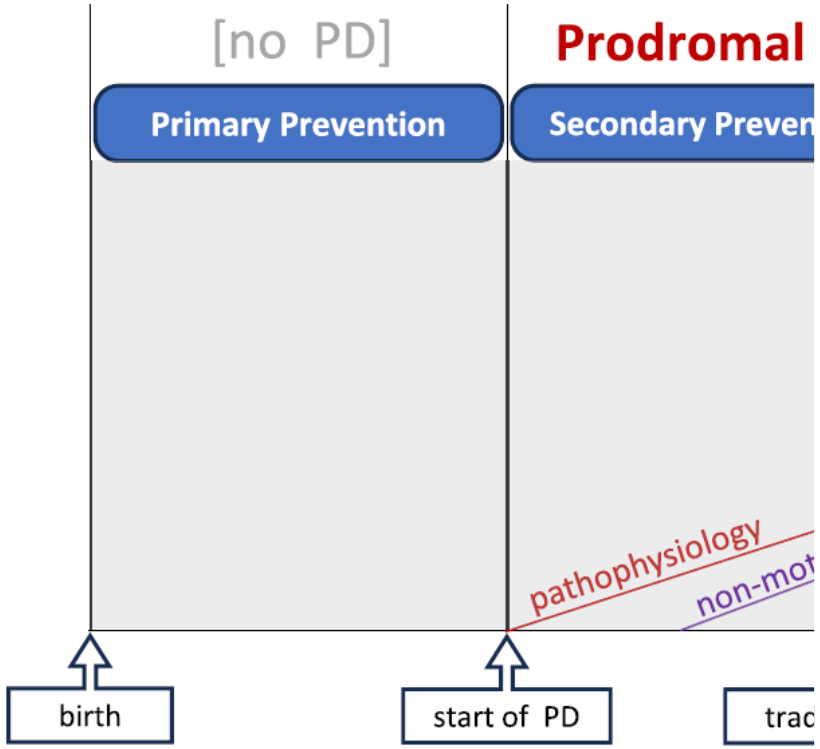
- define PD based on biomarkers
  - α-syn seeding activity
  - genetic variants
  - Imaging evidence for DAergic denervation

## Differences:

- Nosologic classification (NSD vs PD)
- Staging only part of NSD-ISS
- Use of ‚disease' label for SAA+ asymptomatic subjects in NSD-ISS
- Inclusion of SAA- genetic PD (SynNeurGe)

Höglinger GU, et al. Lancet Neurology 2024; Simuni T et al. Lancet Neurology 2024.

# Moving from Disease Modification to Prevention Trials




| Key design question \ Disease stage | | 'Prodromal' Parkinson's Disease | | |
|---|---|---|---|---|
| | | Pre-clinical | Clinical: Non-motor | Clinical: Early motor |
| 1) Whom to enroll? | a) | e.g., αSyn-SAA+ | | |
| | b) | genetically (*LRRK2+*, *GBA+*) at-risk | | |
| | c) | | RBD* | |
| | d) | | RBD/hyposmia ± motor**,*** | |
| | e) | | | early motor |
| 2) What intervention? | a) | lifestyle & low-risk, repurposed $R_x$*,** | | |
| | b) | | mod - high risk $R_x$*** | |
| | c) | | | invasive $R_x$ |
| 3) How to measure progression? | a) | ? quant. αSyn biomarker | | |
| | b) | composite prodromal load** | | |
| | c) | | DAT neuro-imaging*,*** | |
| | d) | | motor/cognitive*,**,*** | |
| | e) | | phenoconversion* | |

*G.F. Crotty et al.* Journal of Parkinson's Disease 14 (2024) S381–S393

* EITRS**Slow-SPEED-NL *** P2P Programme

# SUMMARY

- Disease modification remains the single most important unmet need in PD
- A plethora of past DM trials have not met their primary outcomes
- Promising novel targets have evolved through enhanced understanding of pathogenetic pathways
- Immunotherapy trials targeting α-synuclein have provided signals for efficacy
- Biomarker-based diagnostic frameworks will pave the way towards PD ‚prevention' trials


# Targeting alpha-synuclein in early Parkinson's disease: ACI-7104.056 in the Phase 2 trial

VacSYn

Günther Staffler, PhD | ADPD 2025 | April 2025

AC Immune

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# Disclosures

*Günther Staffler is employed by AC Immune and is entitled to stock options.*

# Parkinson’s disease

- Pathological deposition of alpha-synuclein

**Most common neurodegenerative movement disorder**
Affects ~1% of the population over 65 years

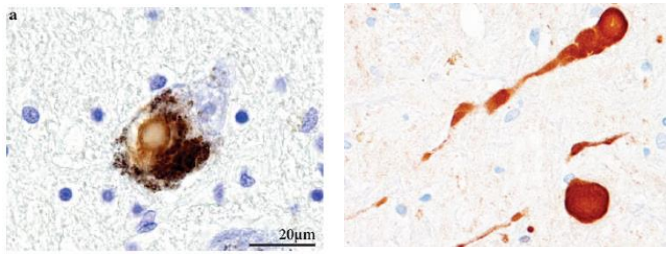
**Etiology**
5-10% genetic, 90-95% idiopathic, unknown cause

**Cardinal motor symptoms**
Tremor, rigidity, bradykinesia

**Common non-motor symptoms**
Sleep disorder, depression, cognitive impairment

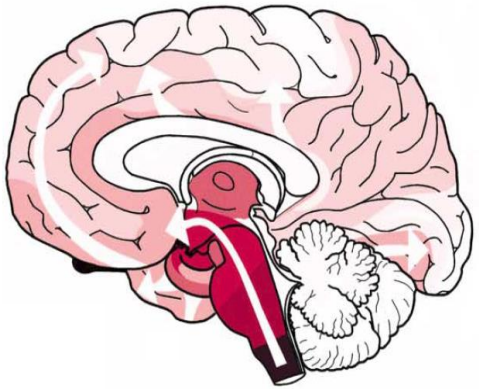
**Pathological hallmarks**
Neuron loss, alpha-synuclein aggregates – Lewy bodies

**Main component of Lewy bodies: Alpha-synuclein**



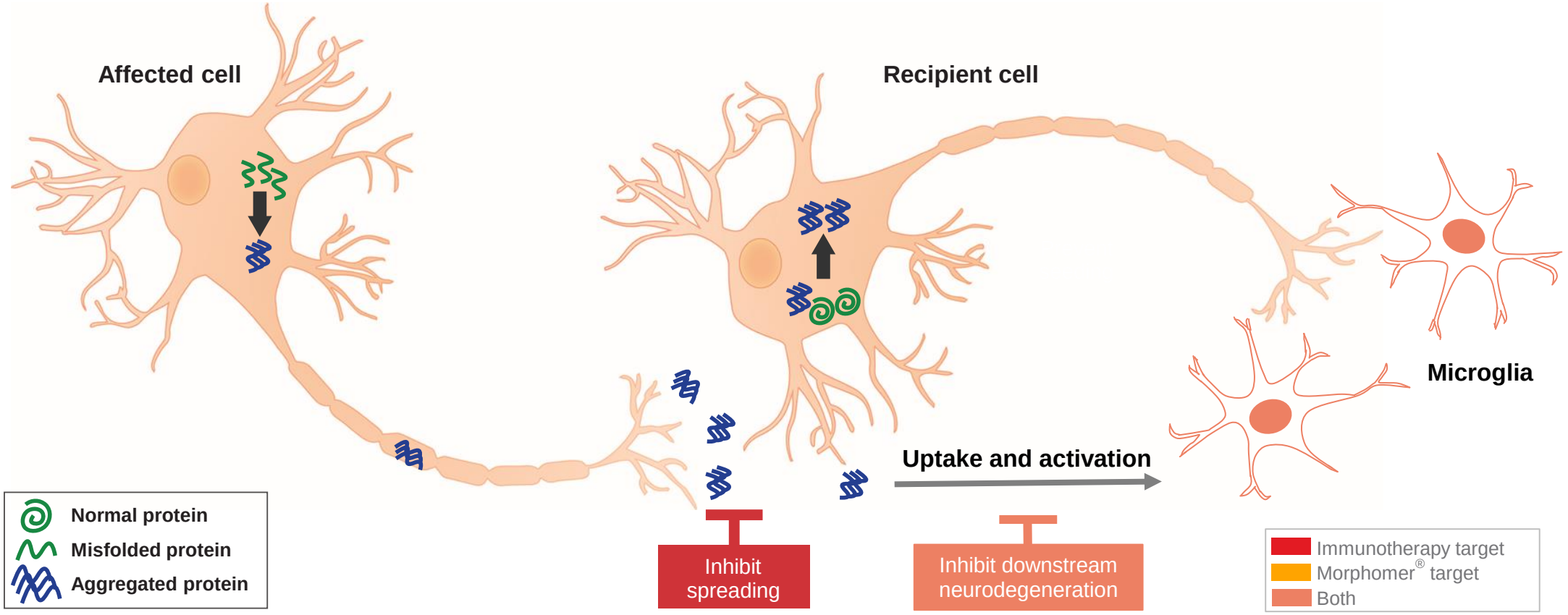

Halliday *et al.* 2011

**Progression of pathology**



Braak *et al.* 2003

# Pathological oligomeric a-syn[1] is causally linked to PD[2] and other NDD[3]



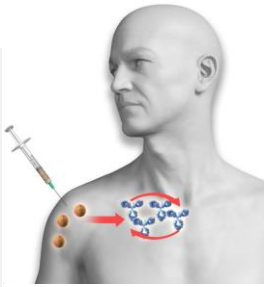

- A-syn misfolding and aggregation are the molecular basis for a-synucleinopathies, e.g. PD, DLB[4] and MSA[5]
- Seeding and spreading of a-syn are potential drivers of disease progression

(1) Alpha-synuclein; (2) Parkinson's disease; (3) Neurodegenerative diseases; (4) Dementia with Lewy bodies; (5) Multiple system atrophy

# Major advantages for long-term use

## Provides global opportunity to treat and prevent neurodegenerative diseases

- Long-lasting specific immunity for pathological target, consistent, boostable, durable
- Limited annual dosing (once or twice) after priming year
- Safety profile well suited to long-term use
- Cost-effective (attractive healthcare economics across global populations)
- Improved access (ease of administration, simple logistics)

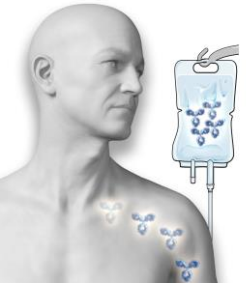


**Active immunotherapy**

Vaccines stimulate the patient's immune system to produce antibodies

**Passive immunotherapy**

Externally generated monoclonal antibodies require administration every two to four weeks



- Active immunotherapy is potentially the only option for global prevention of NDDs[1]

(1) Neurodegenerative diseases

# Immunological potential of ACI-7104

## The optimized a-syn peptide-conjugate formulation

ACTIVE Immune Therapy

Generates target-specific antibody response

Safely engages target-unrelated T-cells to enhance & maintain response

### Key outcomes

| | |
|---|---|
| Immunogenicity | ✓ |
| Target specificity | ✓ |
| Selective for aggregated α-syn | ✓ |
| Sustained antibody response | ✓ |
| Boosting | ✓ |
| Evidence of memory B cells | ✓ |
| Preclude activation of T cells specific for α-syn | ✓ |

- ACI-7104: optimized formulation delivers the clinical validated PD01A peptide[1] which provided:
  - Robust a-syn immunogenicity with a well tolerated profile in PD patients
  - Long lasting antibody responses supporting a disease prevention approach

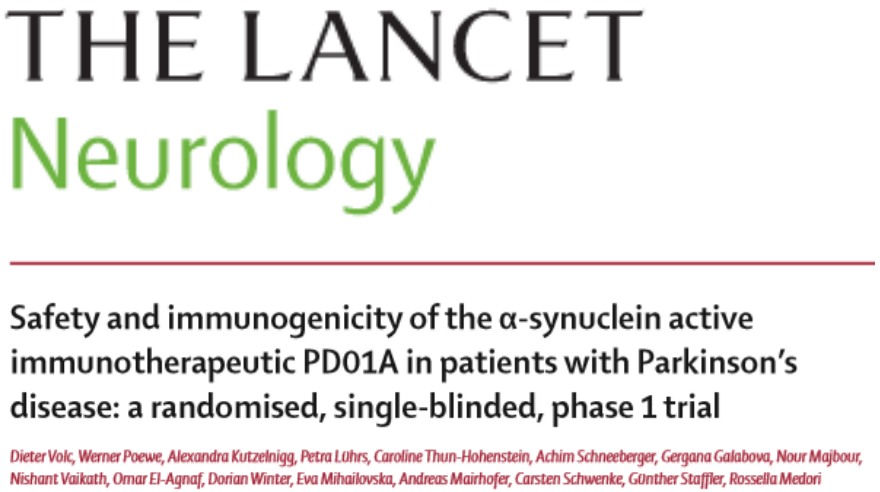
(1) Volc et al., Lancet Neurol. 2020;

# Clinically validated anti-a-syn

ACTIVE Immune Therapy

Phase 1 results published in *The Lancet Neurology*[1] support best-in-class profile

1. Safe and well tolerated with no safety concerns noted in PD[2] patients followed for more than 3.5 years
2. Induced strong and boostable antibody responses
3. Evidence of target engagement: 50% reduction in pathological (oligomeric) α-syn[3] in the CSF[4]
4. UPDRS III[5] scores correlated with reductions in oligomeric α-syn


THE LANCET
Neurology

Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial

Dieter Volc, Werner Poewe, Alexandra Kutzelnigg, Petra Lührs, Caroline Thun-Hohenstein, Achim Schneeberger, Gergana Galabova, Nour Majbour, Nishant Vaikath, Omar El-Agnaf, Dorian Winter, Eva Mihailovska, Andreas Mairhofer, Carsten Schwenke, Günther Staffler, Rossella Medori

(1) Volc *et al.*, Lancet Neurol. 2020; (2) Parkinson's disease; (3) alpha-synuclein; (4) Cerebrospinal fluid; (5) Unified Parkinson's Disease Rating Scale




AC Immune

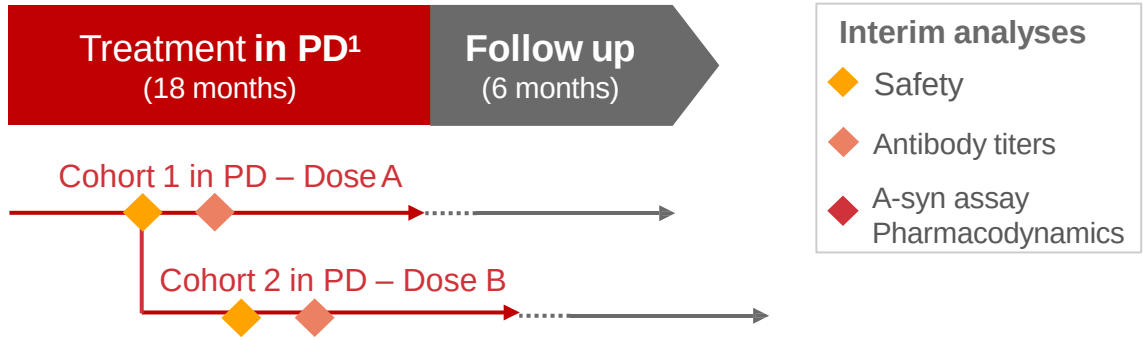
# VacSYn: Adaptive biomarker-based Phase 2 study of ACI-7104 in early PD

## Placebo-controlled Phase 2 Study Overview

- Seamless transition
  - All participants from Part 1 will contribute to final analysis
- Biomarker based interim analyses
  - Early immunogenicity to tailor dose and/or dose regimen
  - Apply disease-relevant biomarkers for early transition to filing

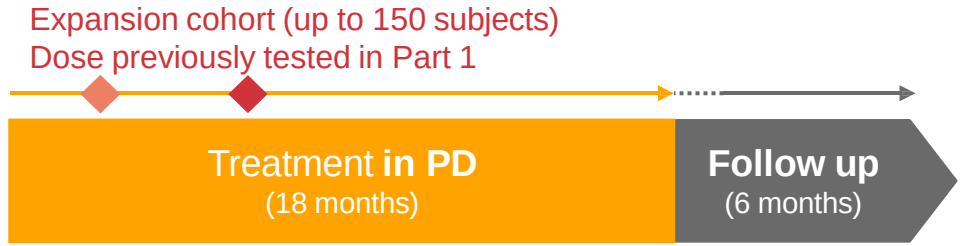
## Part 1: Safety & Immunogenicity

- Key immunogenicity measures
- Measures of pathological a-syn (a-syn oligomers and aggregates)




## Part 2: Proof of Concept in Early PD

- Motor and Non-Motor Functioning (UPDRS[2] based)
- Degeneration of dopaminergic terminals (DaT SPECT[3] imaging)
- Advanced MRI (including ASL[4] and DTI[5])
- Digital biomarkers of motor and non-motor function
- Functional and patient reported outcomes




(1) Participants must have idiopathic PD and be stable on up to 300 mg of L-Dopa treatment and dopaminergic deficit determined by Dopamine Transporter Single Photon Emission Computed Tomography; (2) Unified Parkinson's disease rating scale; (3) Dopamine Transporter Single Photon Emission Computed Tomography; (4) Arterial spin labeling; (5) Diffusion tensor imaging

# VacSYn an adaptive biomarker-based Phase 2 study of ACI-7104 in early PD[1]

## Key Inclusion and Exclusion Criteria

### Key Inclusion Criteria

- Aged ≥40 to ≤75 years
- Diagnosis of clinically established early PD[1] (confirmed by DaT-SPECT[2])
- ≤ 2 years from time of onset motor symptoms
- H&Y[3] Stage I to II
- Monotherapy treatment with L-Dopa[4] at 300 mg per day or treatment naïve

### Key Exclusion Criteria

- Carriers of certain familial PD[1] gene mutations
- Parkinsonian syndrome other than idiopathic PD[1]
- Significant CNS[5] disease[6]

- Enrolment status: 34 patient randomized

(1) Parkinson's disease; (2) Dopamine Transporter Single Photon Emission Computed Tomography; (3) Hoehn & Yahr scale; (4) Levodopa; (5) Central Nervous System; (6) Parkinsonian syndrome other than idiopathic PD, including but not limited to, progressive supranuclear palsy, multiple system atrophy, drug induced parkinsonism, essential tremor, vascular parkinsonism, primary dystonia.

# VacSYn: Patient baseline characteristics and interim safety/tolerability findings

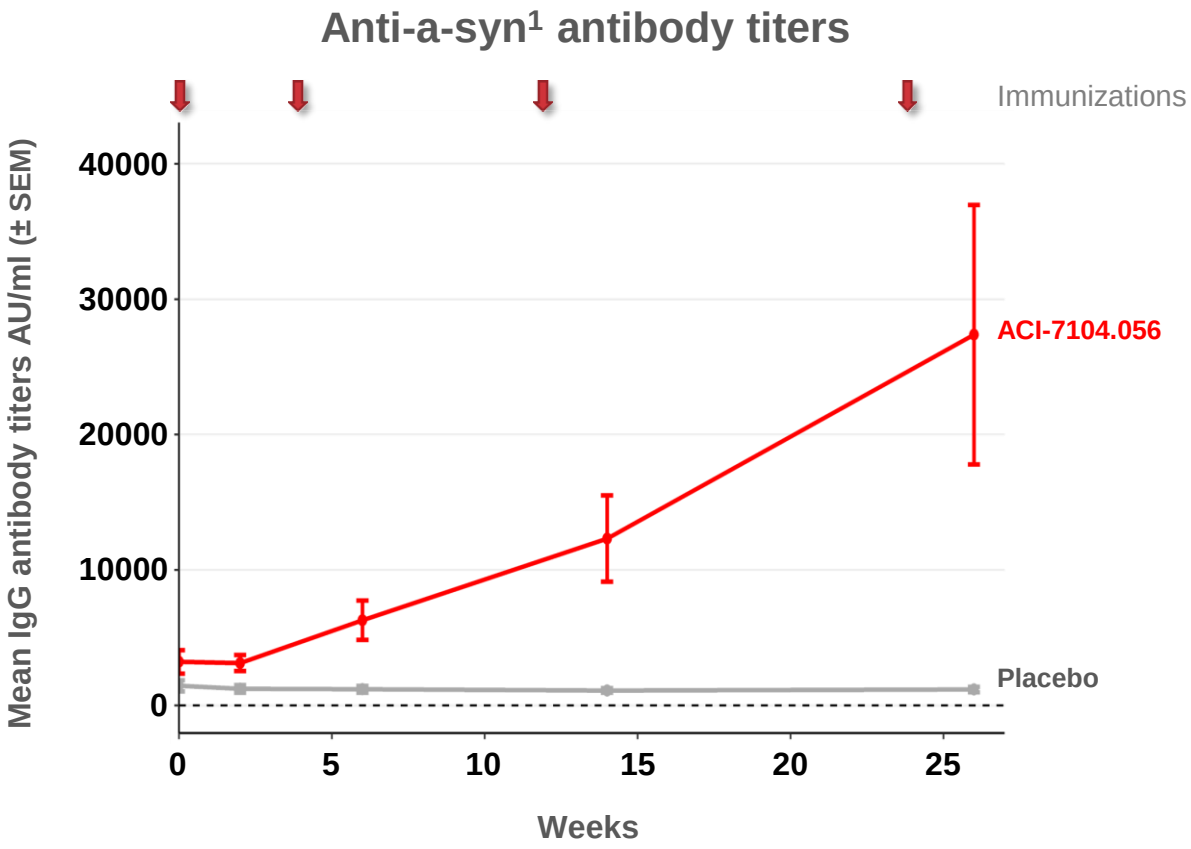
## Placebo-controlled Ph 2 Study: No safety concerns raised by DSMB[4]

| Baseline profile | Unit | Total[1] |
|---|---|---|
| **Total number of patients** | n | 34 |
| **Age** | Years mean (std) | 62.1 (6.7) |
| **Sex** | | |
| Male | n (%) | 22 (65%) |
| Female | n (%) | 12 (35%) |
| **Hoehn and Yahr stage** | | |
| Stage I | n (%) | 16 (47%) |
| Stage II | n (%) | 18 (53%) |
| **MDS-UPDRS scores** | | |
| Part 1: Non-motor experiences of daily living | mean (std) | 4.09 (3.1) |
| Part 2: Non-motor experiences of daily living | mean (std) | 4.09 (3.2) |
| Part 3: Motor examination | mean (std) | 21.09 (9.8) |
| **PD Treatment** | | |
| treatment-naïve | n (%) | 11 (32%) |
| L-Dopa 300mg/day | n (%) | 23 (68%) |

1. **Overall good safety/tolerability to date**
2. **No death or severe adverse event observed to date; no serious adverse event considered related to the study drug**
3. **One AE[5] leading to discontinuation from the study[2] considered unrelated to study drug**
4. **Most common AEs are transient and generally of mild severity: Injection Site Reactions (50%) and headaches (14.7%)[3]**
5. **No significant MRI[6], lab, ECG[7] abnormalities**

(1) cut-off date November 08, 2024; (2) Worsening of preexisting generalized anxiety disorder unrelated to study drug; (3) incidence in the pooled active and placebo subjects; (4) Data Safety Monitoring Board; (5) Adverse Event; (6) Magnetic Resonance Imaging; (7) Electrocardiogram

# ACI-7104.056 VacSYn Ph 2 trial: Interim results (week 26)




**Strong and boostable anti-a-syn antibody response**
(after four immunizations)

## Key results

- Anti-a-syn antibody titers evident after **2 injections**
- ACI-7104.056 induces anti-a-syn antibody levels on average **over 20-fold higher**[2] than placebo after 4 immunizations
- Repeated immunizations showed **boostability** and potential for **further amplification of the response**
- No anti-a-syn antibody responses were observed in placebo-treated subjects
- To date, no clinically relevant safety issue reported

(1) alpha-synuclein (peptide aa 115-121); (2) assay background level defined by signal in the placebo group

# Summary

| | |
|---|---|
| **Clinical trial** | ▪ Phase 2 study in early PD subjects based on innovative two-part trial design |
| **Adaptive Design** | ▪ Designed for early de-risking and simultaneously allowing acceleration with rapid entry into a pivotal clinical phase |
| **Patient selection** | ▪ Targeting early PD population |
| **Safety and Immunogenicity** | ▪ Good safety and tolerability profile with no safety concerns identified to date<br>▪ Strong IgG response induced<br>  ▪ Significant titers post 3rd dose and further boosting post the 4th dose |
| **Status** | ▪ Completed Part 1 randomization; Initiation of Part 2 expected in Q4 2025 |

Anke Post
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Jonathan Wagg
Nicolas Fournier
Tanja Touilloux
Erika Borcel
Olivier Sol
Valérie Hliva
Marija Vukicevic
Emma Fiorini
Rakel Carpintero
Francesca Capotosti
Marie Kosco-Vilbois
Andrea Pfeifer

We want to thank the study participants, their families for their participation and commitment, as well as all Investigators and Site personnel for their active participation and support.

# Precision Prevention of Alzheimer's Disease

Prof. dr Philip Scheltens, FAAN, FEAN

EQT Life Sciences Amsterdam

Alzheimer Center Amsterdam

April 2025

# Disclosures

Dr Scheltens is co-chair of the steering committee of the EVOKE studies of Novo Nordisk.

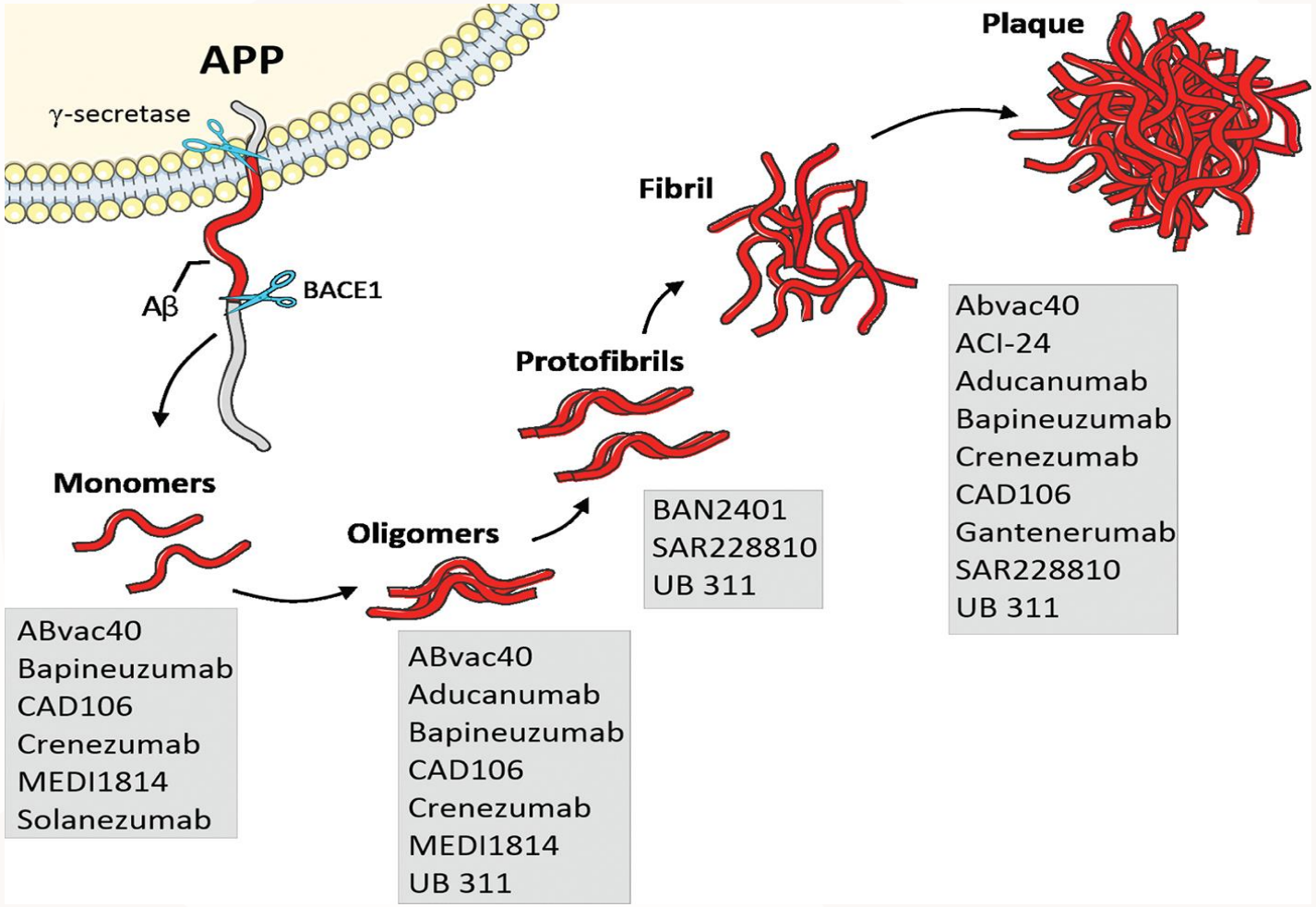
He is a member of the DSMB of the Retain and IBC-01-01 studies

He is fulltime employee of EQT Life Sciences.

# Contents

- Disease-modifying immunotherapies (DMTs) targeting Abeta and Tau in AD
- Importance of early intervention, and ultimately prevention
- Enabling AD prevention:
    - Early diagnosis using biofluid (blood-based) and imaging biomarkers
    - Large-scale identification of at-risk individuals based on biomarker profile and genetics
    - Safe and effective disease-modifying immunotherapies to prevent before symptoms appear
- Precision prevention: preserving brain health

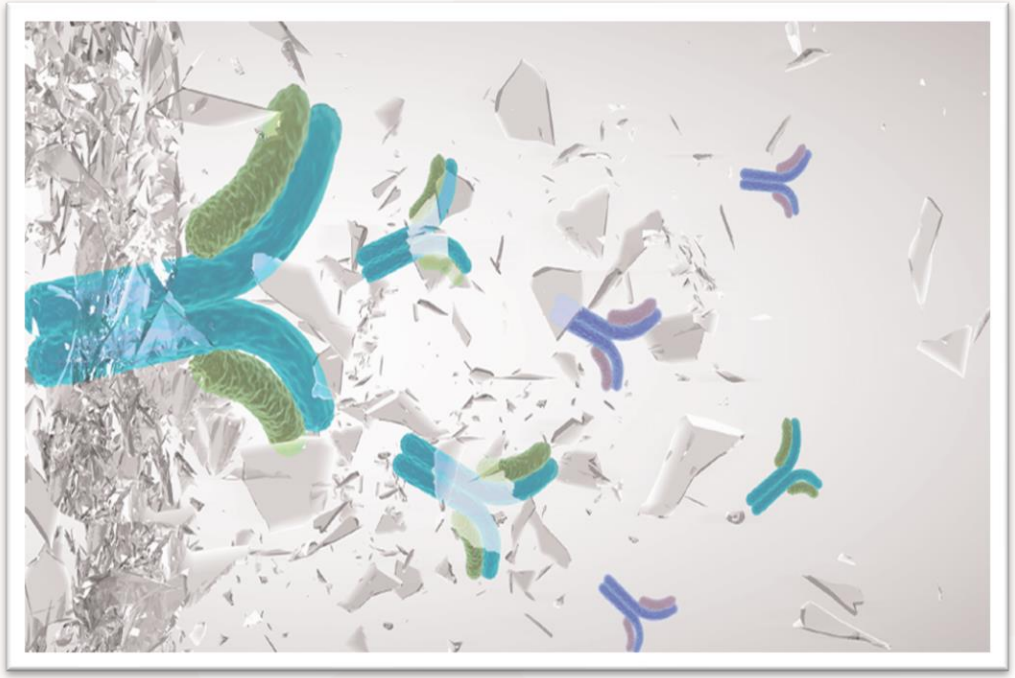
# Amyloid targeting immunotherapy approaches



# Making progress

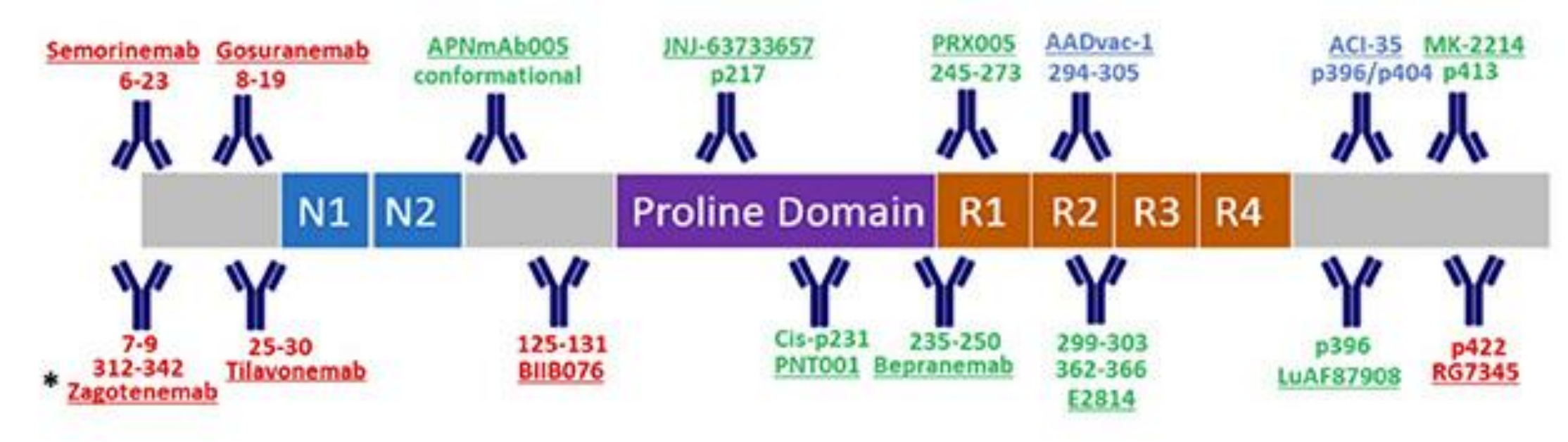
**Up to 2025**

## Anti-amyloid monoclonal antibodies

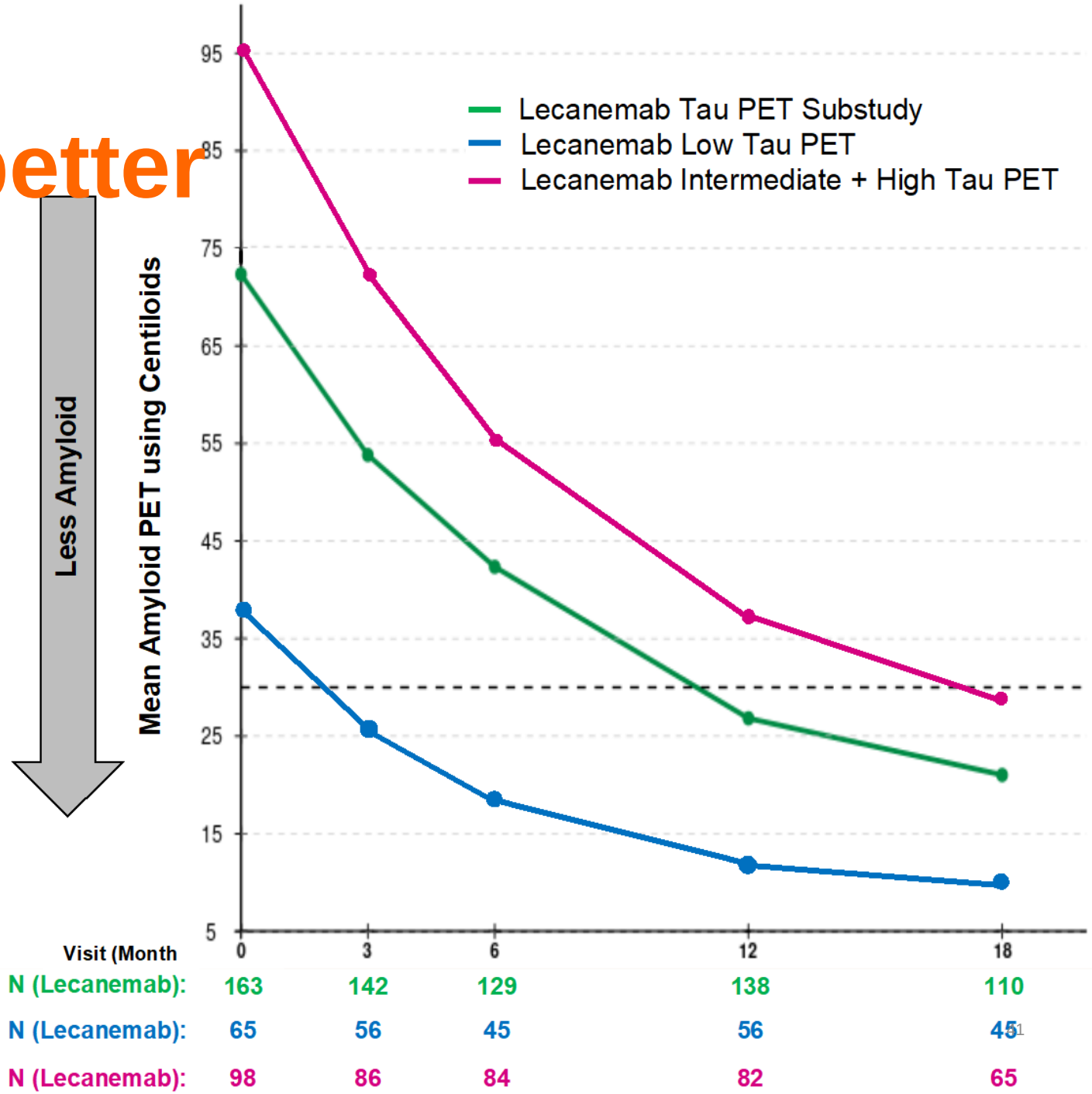


- Aducanumab – accelerated approval by FDA in 2021 . No CMS coverage and no EMA approval; withdrawn by Biogen
- Lecanemab – Phase 2 plaque lowering and and robust evidence of slowing of cognitive decline; phase 3 successful; FDA, Japan, China, EMA, UK approvals
- Donanemab – Phase 2 plaque lowering and slowing of cognitive decline; Phase 3 hits on all endpoints; FDA, UK approved
- Gantenerumab – Phase 3 Graduate I and II: failed

# Tau targeting immunotherapy approaches



# The earlier the better



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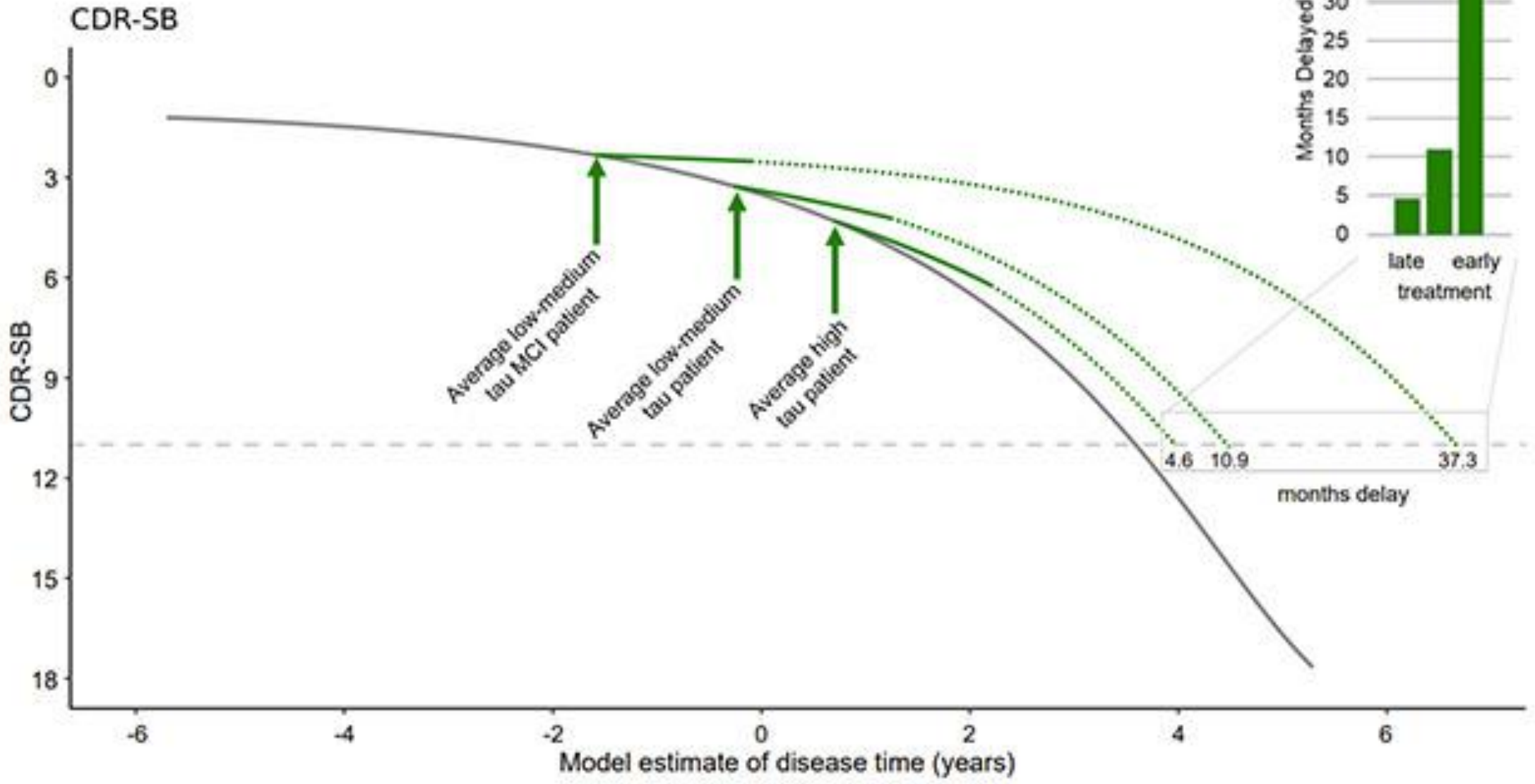
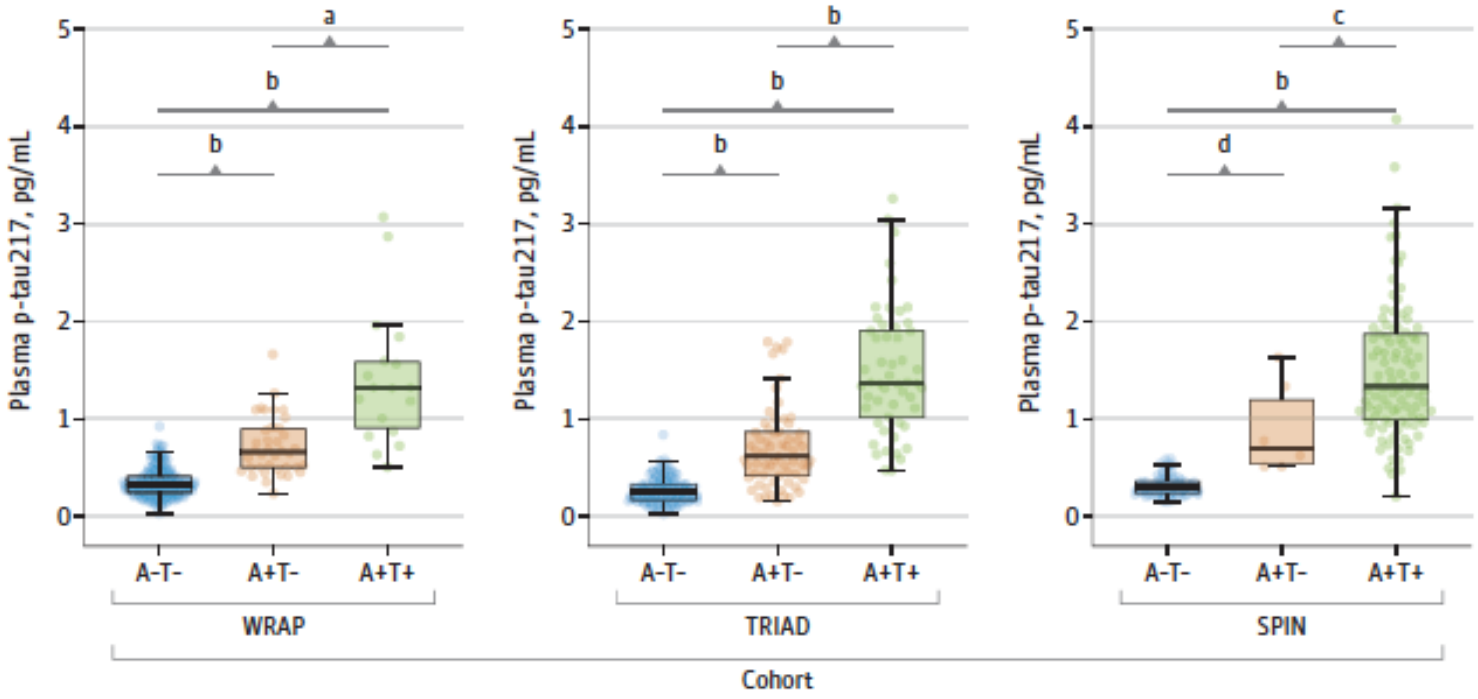


JAMA Neurology | Original Investigation

# Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology

Nicholas J. Ashton, PhD; Wagner S. Brum; Guglielmo Di Molfetta, MSc; Andrea L. Benedet, PhD; Burak Arslan, MD; Erin Jonaitis, PhD; Rebecca E. Langhough, PhD; Karly Cody, PhD; Rachael Wilson, PhD; Cynthia M. Carlsson, PhD; Eugeen Vanmechelen, PhD; Laia Montoliu-Gaya, PhD; Juan Lantero-Rodriguez, PhD; Nesrine Rahmouni, MSc; Cecile Tissot, PhD; Jenna Stevenson, PhD; Stijn Servaes, PhD; Joseph Therriault, PhD; Tharick Pascoal, MD, PhD; Alberto Lleó, MD, PhD; Daniel Alcolea, MD, PhD; Juan Fortea, MD, PhD; Pedro Rosa-Neto, MD, PhD; Sterling Johnson, MD, PhD; Andreas Jeromin, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD

**Figure 1. Plasma Phosphorylated Tau 217 (p-Tau217) Levels According to Amyloid β (A) and Tau (T) Profiles**




A+= Amyloid PET

T+ = TAU PET / CSF p-tau in SPIN

*JAMA Neurol*. doi:10.1001/jamaneurol.2023.5319
Published online January 22, 2024.

JAMA Neurology | Original Investigation

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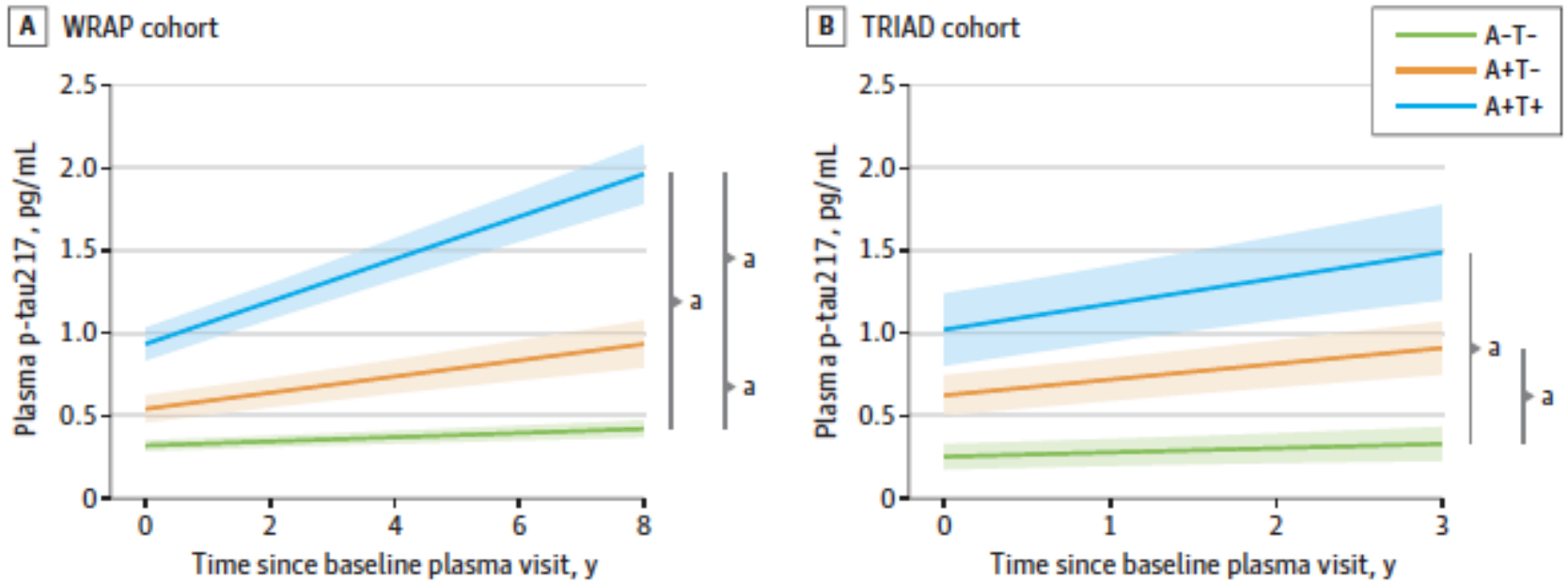
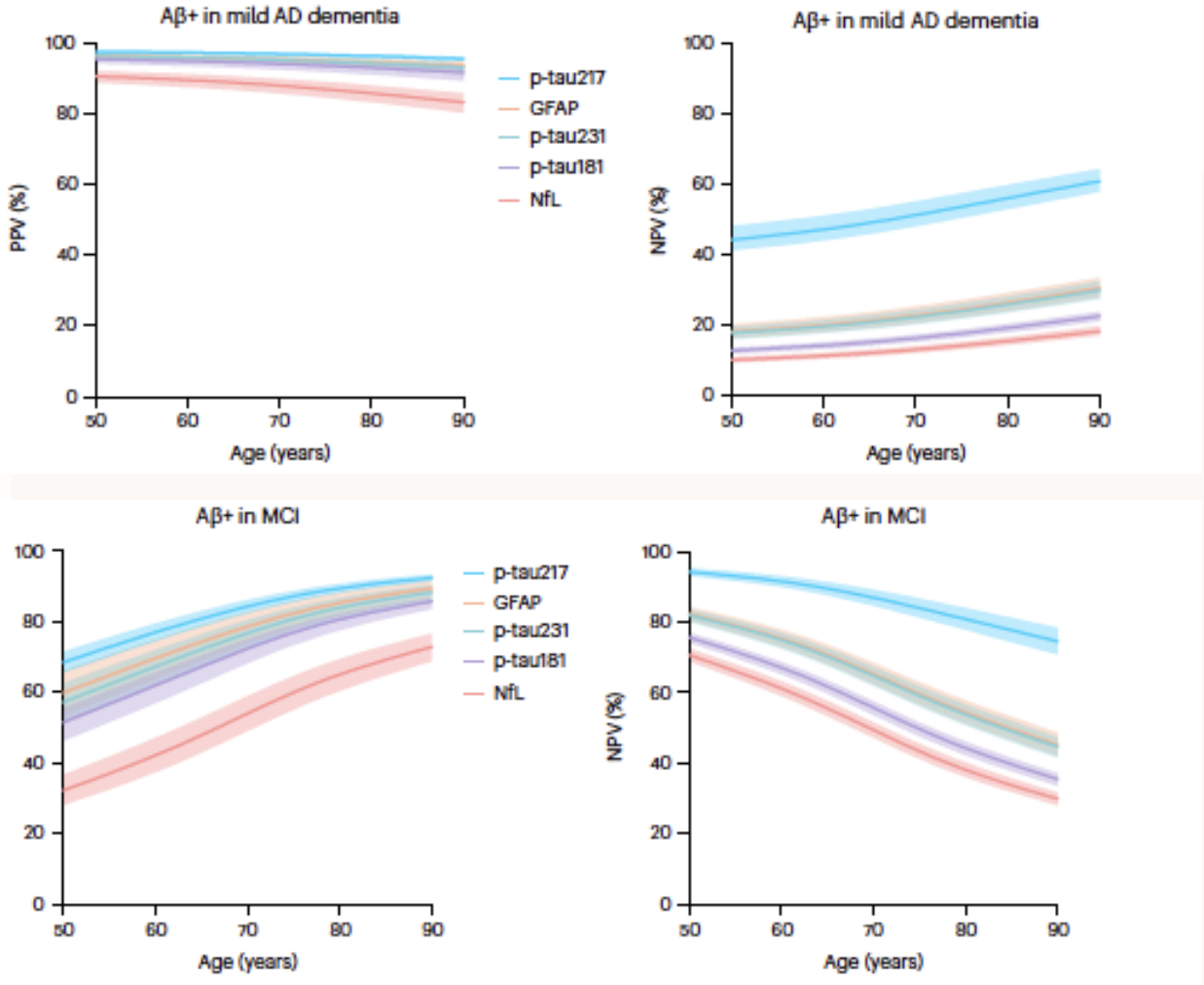
**Figure 3. Longitudinal Trajectories of Plasma Phosphorylated Tau 217 (p-Tau217) Values According to Amyloid β (A) and Tau (T) Status by Positron Emission Tomography (PET)**




*JAMA Neurol*. doi:10.1001/jamaneurol.2023.5319
Published online January 22, 2024.

Letter https://doi.org/10.1038/s43587-024-00731-y

# Diagnosis of Alzheimer's disease using plasma biomarkers adjusted to clinical probability



https://doi.org/10.1093/braincomms/fcad024 BRAIN COMMUNICATIONS 2023: Page 1 of 10 | 1

BRAIN COMMUNICATIONS

# Plasma biomarkers predict amyloid pathology in cognitively normal monozygotic twins after 10 years

Anouk den Braber,[1,2,3] Inge M. W. Verberk,[2,4] Jori Tomassen,[1,2] Ben den Dulk,[2,4] Erik Stoops,[5] Jeffrey L. Dage,[6] Lyduine E. Collij,[7,8] Frederik Barkhof,[7,8,9] Gonneke Willemsen,[3] Michel G. Nivard,[3] Bart N. M. van Berckel,[7,8] Philip Scheltens,[1,2] Pieter Jelle Visser,[1,2,10,11] Eco J. C. de Geus[3] and Charlotte E. Teunissen[2,4]

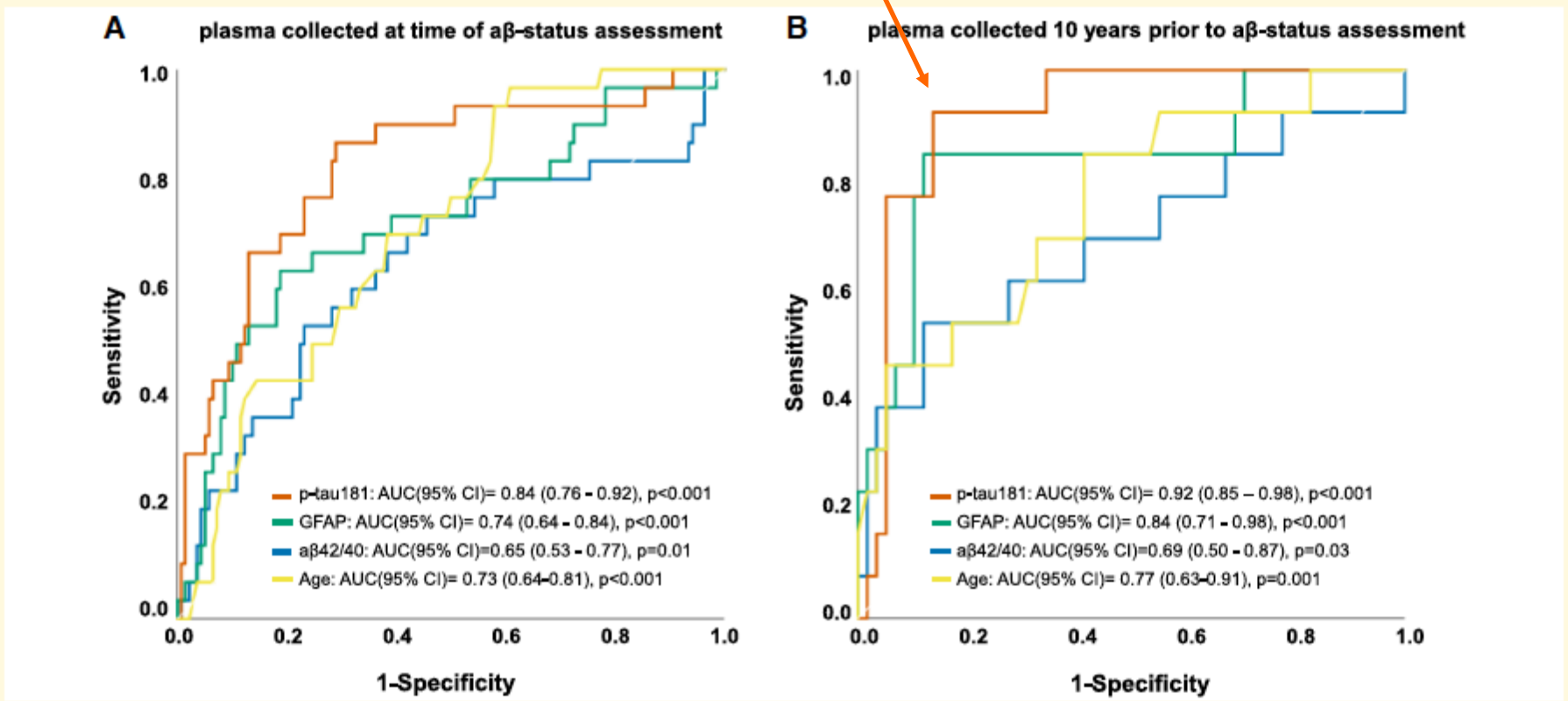


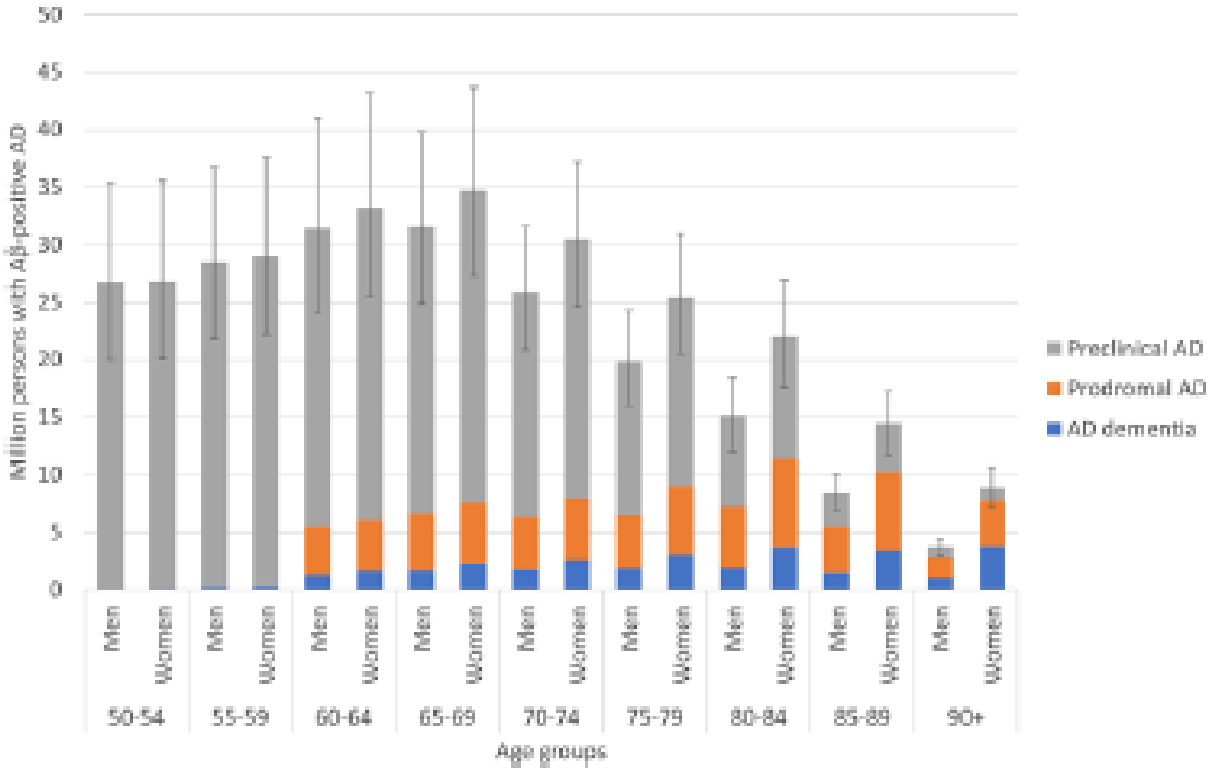

**Figure 1 Receiver operating characteristic curve analyses.** Receiver operating characteristic area under the curve analyses predicting amyloid pathology using plasma amyloid-$\beta_{1\text{-}42/1\text{-}40}$ ($n = 181$), p-tau181 ($n = 186$) and GFAP ($n = 200$) levels obtained at the time of amyloid-β status assessment (**A**) or plasma amyloid-β1-42/1-40 ($n = 73$), p-tau181 ($n = 78$) and GFAP ($n = 80$) levels obtained 10 years prior to amyloid-β status assessment (**B**). AUC: area under the curve; CI: confidence interval.

# Global estimates on the number of persons across the Alzheimer's disease continuum

Anders Gustavsson[1] | Nicholas Norton[2] | Thomas Fast[2] | Lutz Frölich[3] | Jean Georges[4] | Drew Holzapfel[5] | Tunahan Kirabali[6] | Pierre Krolak-Salmon[7] | Paolo M. Rossini[8] | Maria Teresa Ferretti[9] | Lydia Lanman[10] | Antonella Santuccione Chadha[6] | Wiesje M. van der Flier[11]

Project Alzheimer's Value (PAVE), 2021

In conclusion, when taking into account predementia stages, the number of persons with AD is much larger than what is conveyed in available literature and the public discourse, which typically focuses on the prevalence of dementia. The vast majority of persons on the AD continuum do not have dementia but are in the predementia stages of disease, providing a window of opportunity for prevention. Policy makers




Prevention is key!

# Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

Lancet Neurol 2014; 13: 788–94

| | Relative risk (95% CI)* | Communality (%)† |
|---|---|---|
| Diabetes mellitus | 1·46 (1·20–1·77) | 50·9% |
| Midlife hypertension | 1·61 (1·16–2·24) | 65·0% |
| Midlife obesity | 1·60 (1·34–1·92) | 43·7% |
| Physical inactivity | 1·82 (1·19–2·78) | 49·0% |
| Depression | 1·65 (1·42–1·92) | 37·4% |
| Smoking | 1·59 (1·15–2·20) | 58·1% |
| Low educational attainment | 1·59 (1·35–1·86) | 45·6% |

*Sources are provided in the appendix. †The proportion of the variance in each risk factor shared with the other risk factors, estimated using the Health Survey for England 2006.[17]

**Table 1: Relative risks for Alzheimer's disease and shared variance between risk factors**

30% AD worldwide related to the big 7

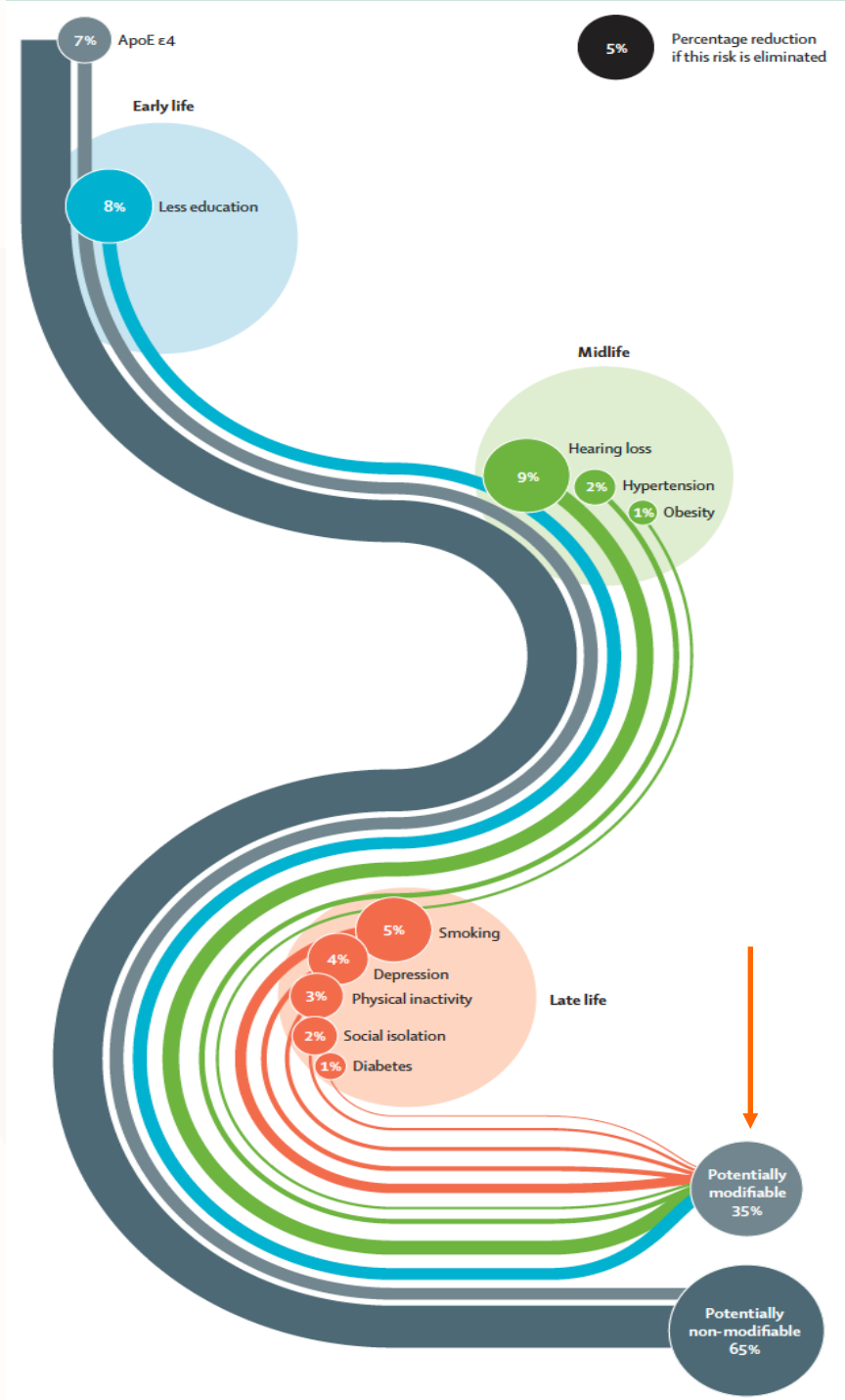
## Dementia prevention, intervention, and care

*Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam*

# From 7 to 10 risk factors

Added:
Social isolation
Hearing loss
ApoE4

Removed: Alzheimer's




Livingston et al. Lancet 2020

# Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

*Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad*, Naaheed Mukadam**

# From 10 to 14 risk factors

Added:
Excessive alcohol
Visual loss
Air polution
High LDL
Traumatic Brain Injury

Removed:
APOE 4

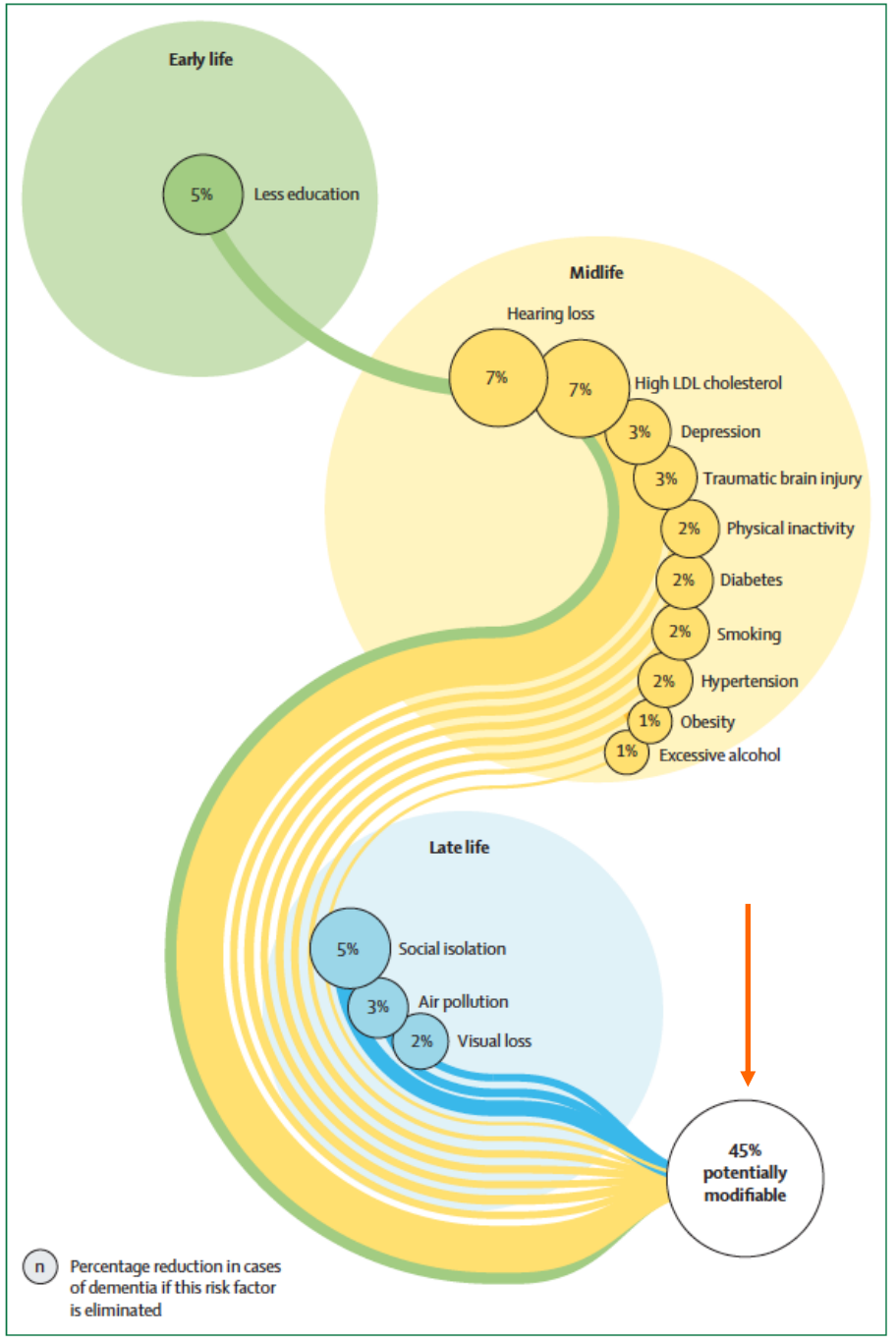



*Figure 9:* **Population attributable fraction of potentially modifiable risk factors for dementia**

# Another Prevention strategy: active immunotherapy

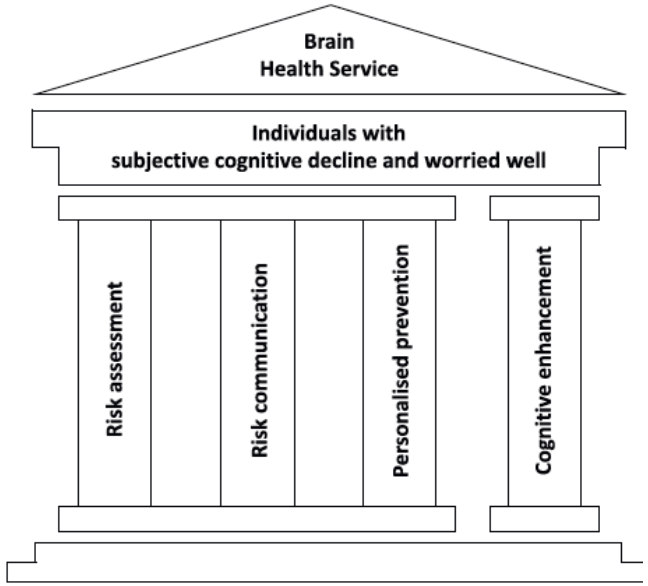
- Long-lasting specific immunity for pathological target, consistent, boostable, durable
- Limited annual dosing (once or twice) after priming year
- No observed ARIA-E to date (safety profile well suited to long-term use)
- Cost-effective (attractive healthcare economics across global populations)
- Improved access (ease of administration, simple logistics)

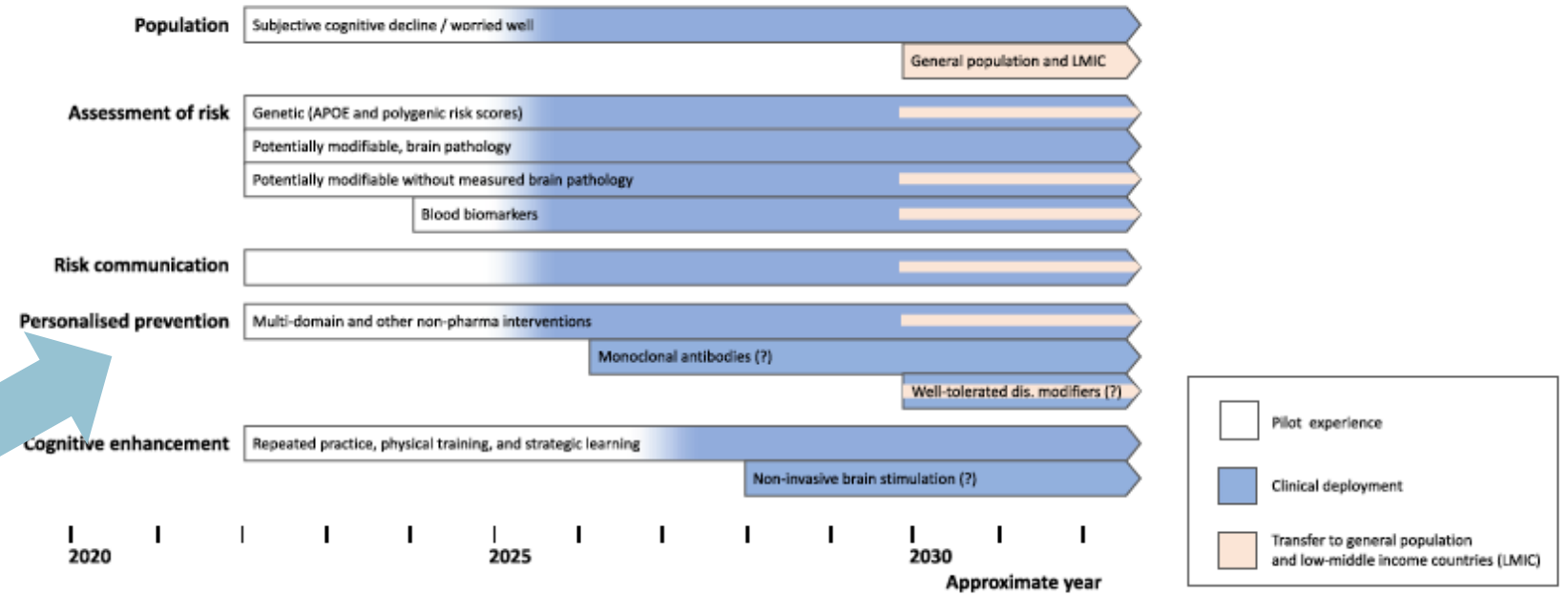
# Active immunotherapy in AD

| Anti-Abeta active immunotherapies | | | | |
|---|---|---|---|---|
| **Immunotherapy** | **Developer** | **Type** | **Binding profile** | **Clin. Dev. Stage** |
| **ACI-24.060** | AC Immune / Takeda | Liposomal vaccine | Oligomers, pyroGlu-Abeta | Phase 1b/2 |
| **UB-311** | Vaxxinity | Peptide vaccine | Aggregated Abeta | Phase 2a |
| **ALZ-101** | Alzinova | Hexameric conformationally restricted Abeta1-42 | Oligomeric Abeta | Phase 1b |
| **AV-1959D** | Nuravax | DNA vaccine | n/a | Phase 1 |
| **ABvac40** | Araclon Biotech/Grifols | Peptide vaccine | Monomeric, oligomeric and Abeta plaques | Phase 2 |
| **ALZN-002** | Alzamend Neuro | Patient derived dendritic cells | Monomeric and oligomeric Abeta | Phase 1/2a |
| **Anti-Tau active immunotherapies** | | | | |
| **Immunotherapy** | **Developer** | **Type** | **Binding profile** | **Clin. Dev. Stage** |
| ***ACI-35.030 JNJ-2056*** | *AC Immune / Janssen* | *Liposomal vaccine* | *phosphoTau and ePHF* | *Phase 2b* |
| **AADvac1** | Axon Neuroscience | Conjugate vaccine | misfolded Tau | Phase 2 |
| **AV-1980R** | Nuravax | Peptide vaccine | Monomeric Tau, multiple smaller and larger Tau species | Preclinical |
| **PRX123** | Prothena | Conjugated linear peptide | Aβ plaques and tau neurofibrillary tangles | Preclinical |
| **VXX-301** | Vaxxinity | Peptide vaccine | Potential combo with other proteins | Preclinical |

# Dementia prevention in memory clinics: recommendations from the European task force for brain health services

Giovanni B. Frisoni,[a,*] Daniele Altomare,[a] Federica Ribaldi,[a] Nicolas Villain,[b,c] Carol Brayne,[d] Naaheed Mukadam,[e] Marc Abramowicz,[f] Frederik Barkhof,[g,h] Marcelo Berthier,[i] Melanie Bieler-Aeschlimann,[j,k] Kaj Blennow,[l] Andrea Brioschi Guevara,[j,m] Emmanuel Carrera,[n] Gaël Chételat,[o] Chantal Csajka,[p] Jean-François Demonet,[j,q] Alessandra Dodich,[r] Valentina Garibotto,[s] Jean Georges,[t] Samia Hurst,[u] Frank Jessen,[v,w,x] Miia Kivipelto,[y,z,aa,ab] David J. Llewellyn,[ac,ad] Laura McWhirter,[ae] Richard Milne,[d,af] Carolina Minguillón,[ag,ah,ai] Carlo Miniussi,[r,aj] José Luis Molinuevo,[ag,ak] Peter M. Nilsson,[al,am] Alastair Noyce,[an] Janice M. Ranson,[ac] Oriol Grau-Rivera,[ag] Jonathan M. Schott,[ao] Alina Solomon,[ap,aq,ab] Ruth Stephen,[ap] Wiesje van der Flier,[ar,as,at] Cornelia van Duijn,[au,av] Bruno Vellas,[aw] Leonie N. C. Visser,[y,ax] Jeffrey L. Cummings,[ay] Philip Scheltens,[ar,az] Craig Ritchie,[ba] and Bruno Dubois[b,c]



# The first active immunotherapy being investigated for AD prevention: ACI-35.030/JNJ2056 in the Phase 2b Retain study

Lennert Steukers DVM, PhD – on behalf of the Tau Active team
Clinical Leader

**AFFILIATIONS:**
Johnson & Johnson – Belgium

**DISCLOSURES:**
LS is a full-time employee and shareholder of Johnson & Johnson.



Presented by L. Steukers at AD/PD, 2025; Vienna, Austria

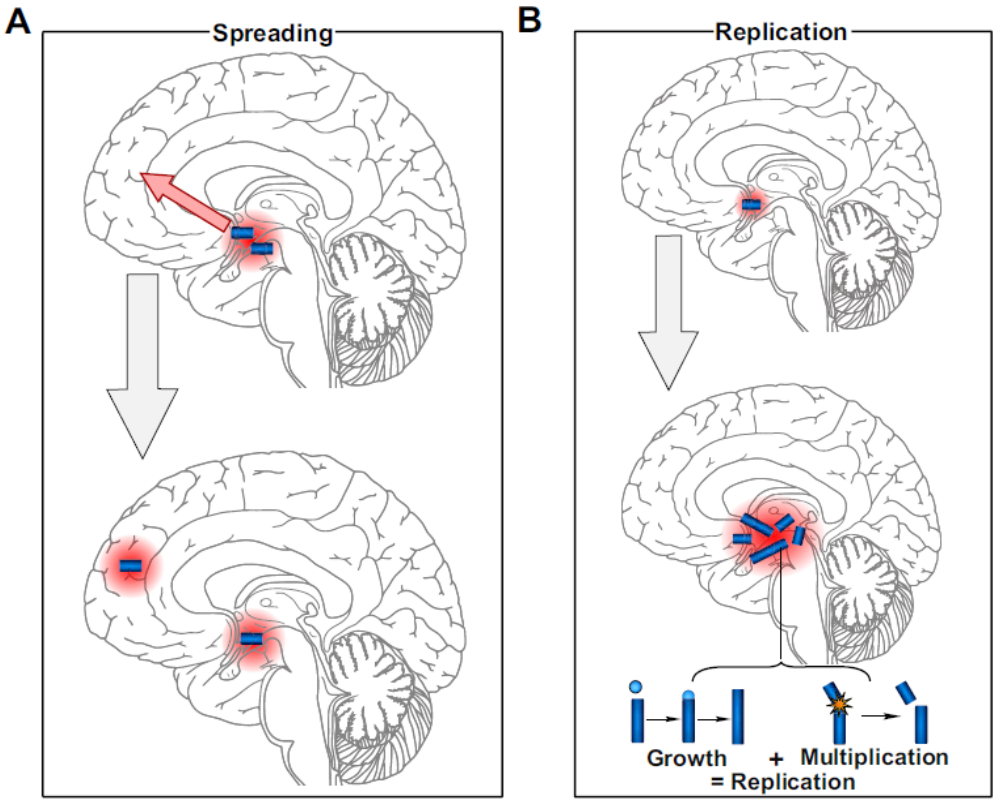
# Targeting ptau & mechanism-of-action (MoA)

# Why target ptau and why engage early in the tau propagation process?

- **Tau pathology (ptau)** is closely **associated with neurodegeneration** and **cognitive decline**

- **Tau pathology stereotypical pattern** with drivers being:
  - **A.** **Spreading** refers to the **transfers of seeds between brain regions**
  - **B.** **replication** refers to **local cell-to-cell transfer, growth, and/or multiplication**

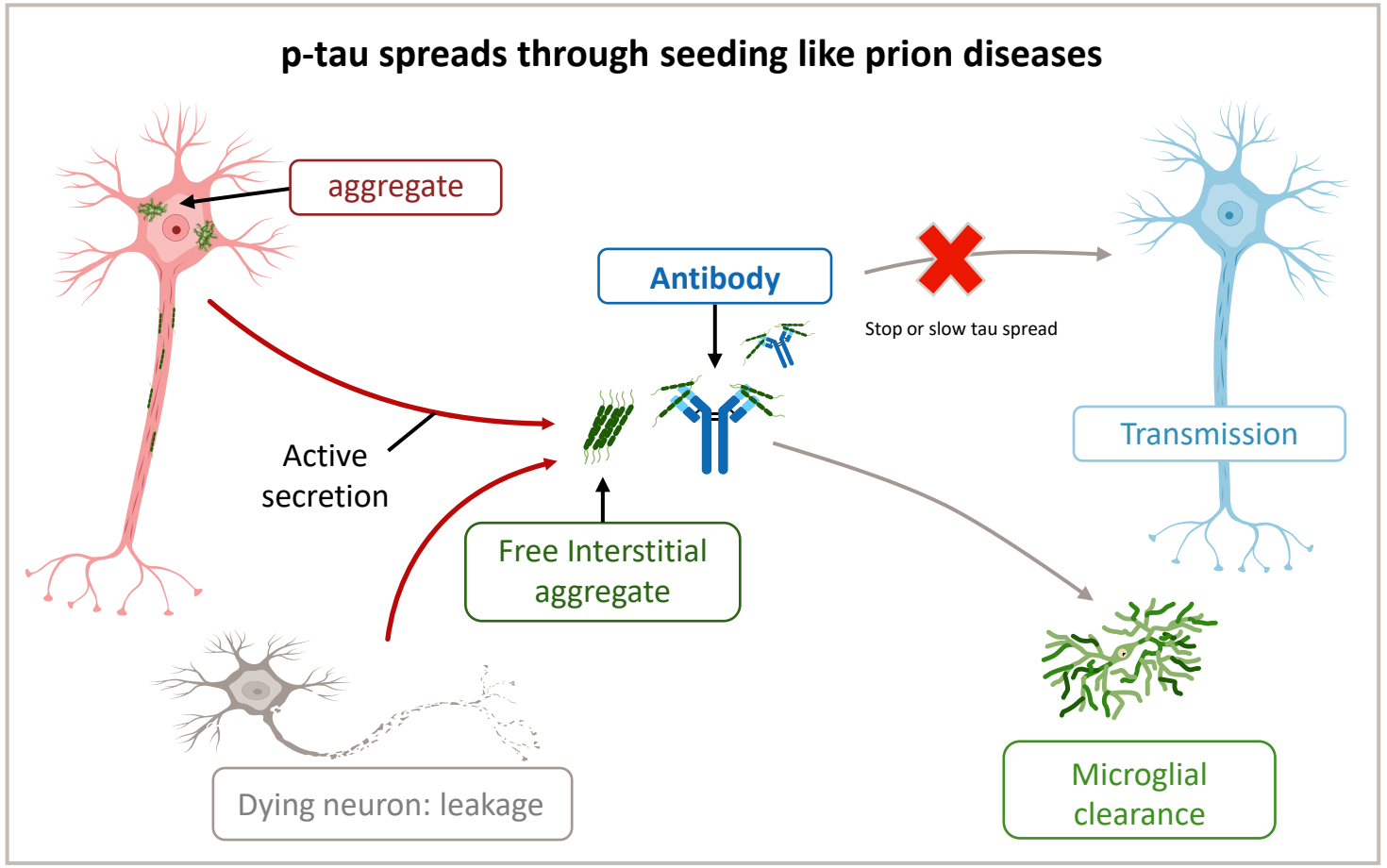
- **Spreading from one brain region to another** has been hypothesized to be a **key factor** in the **disease progression**




From Meisl et al., 2021

# Antibodies targeting phosphorylated tau as therapeutic target for Alzheimer's disease

- Immunotherapy aims to have adequate presence of ptau binding antibodies that prevent the propagation of neurofibrillary lesions and tau toxicity in unaffected neurons to slow neurodegeneration and preserve cognition in AD.
- UCB's Bepranemab, a monoclonal IgG4 antibody, slowed tau pathology as measured by tau PET. This is the first tau-directed antibody to do so and supports the hypothesis that targeting (the mid-domain of) tau will slow tau spread (M. Barton CTAD 2024).



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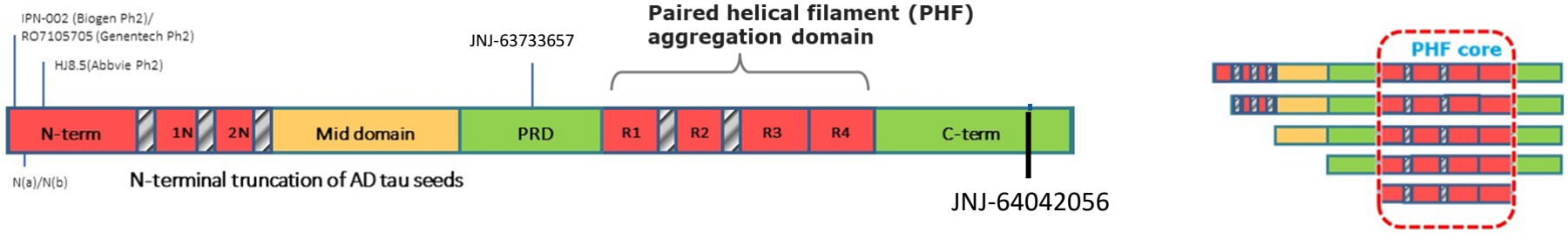
# Tau Active (JNJ-64042056), an active immunotherapy being developed for the treatment of preclinical AD

# JNJ-64042056 liposomal drug product is designed for high specificity for pTau and robust immuno-response



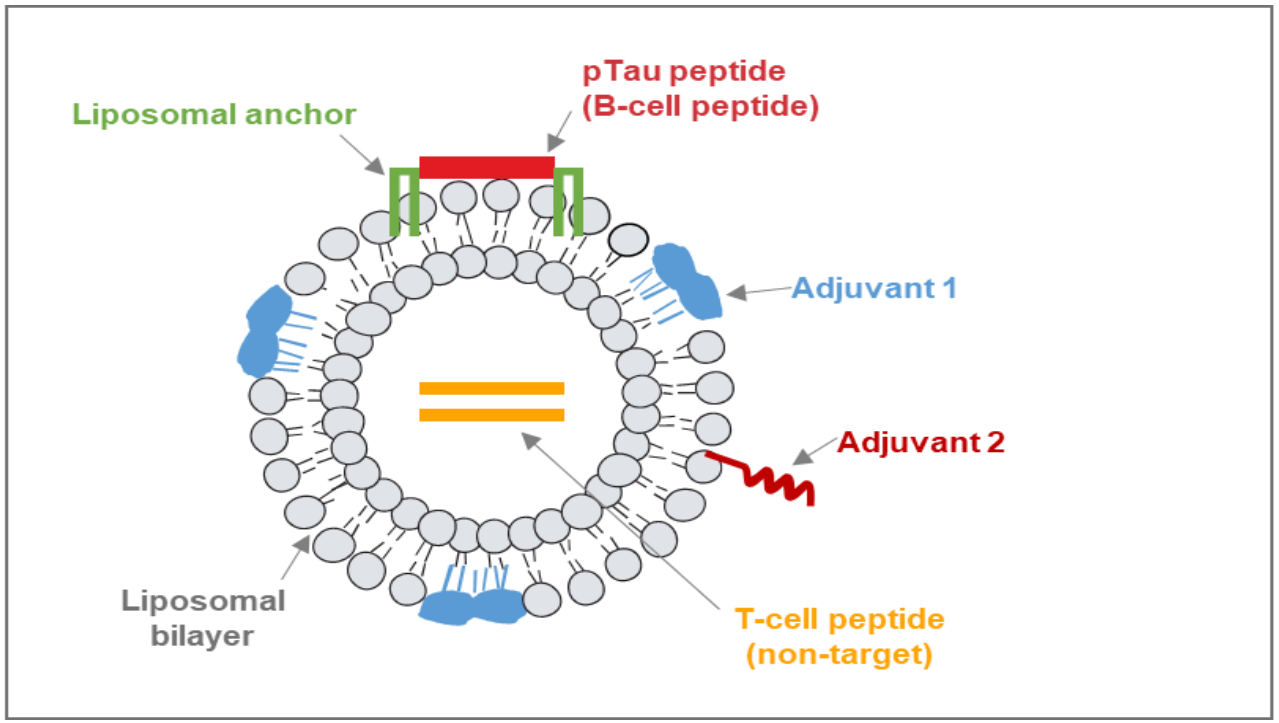




Image courtesy of AC Immune

- Human phospho-Tau T3 synthetic peptide as antigen anchored via 4 palmitoyl acid chains to induce and stabilize conformation
- Liposome to carry peptide and adjuvants consists of lipid bilayer of cholesterol & other lipid components
- Universal T cell Peptide to induce T cell help
- 2 adjuvants to enhance immunogenicity



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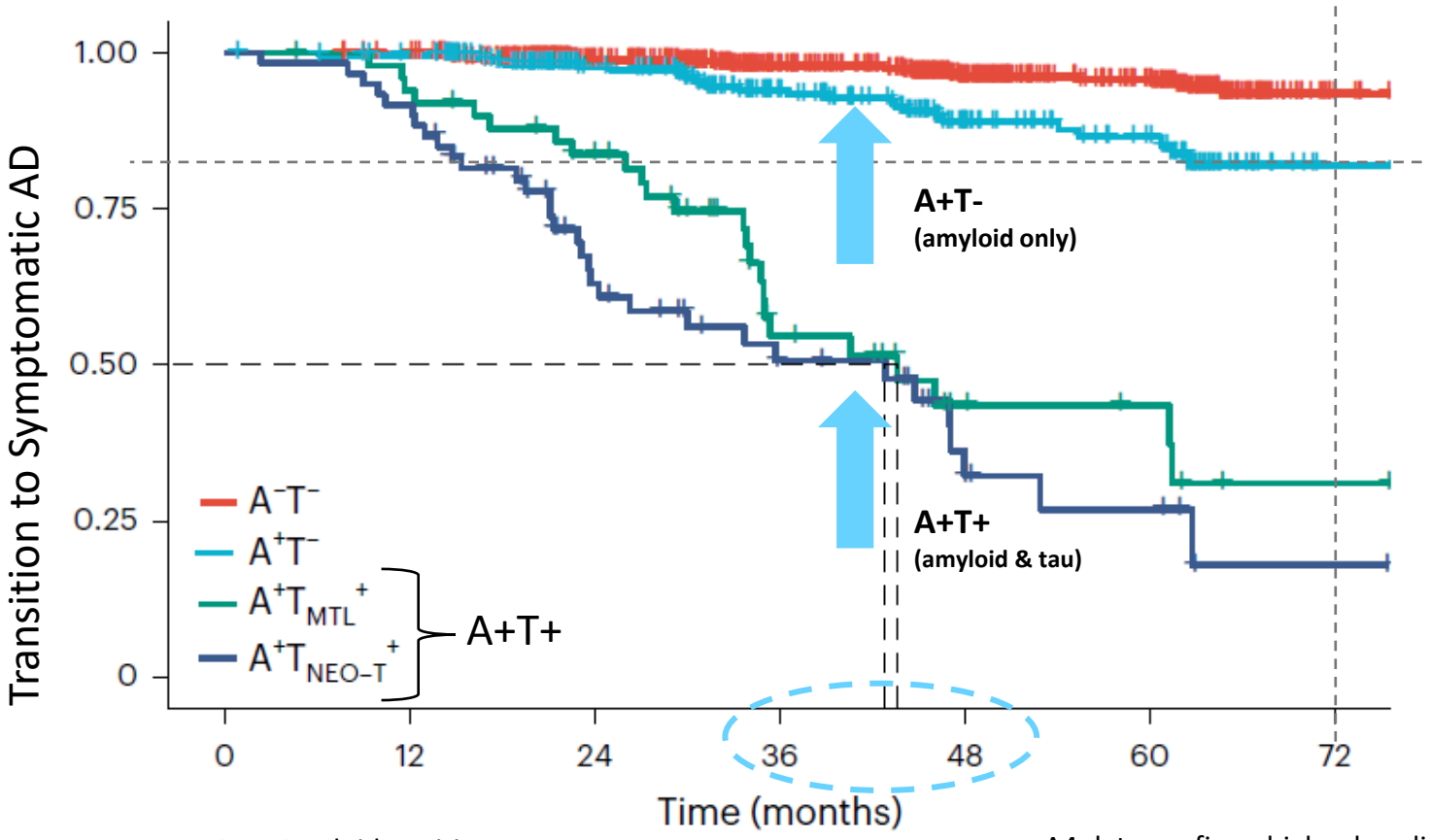
# Why target ptau in preclinical AD?

**Because it is an optimal window for disease modification, prior to substantial neuronal loss but close to symptom onset.**

**~50% of A+T+** preclinical AD individuals transitioned to mild cognitive impairment (MCI) within 3-½ years (vs. **only ~4-10% of A+T-**)




| Years to Transition to MCI | % of Preclinical AD | |
|---|---|---|
| | A+T- | A+T+ |
| 1 | ~1% | ~2-10% |
| 2 | ~2% | ~20-40% |
| **3** | **~4%** | **~48-50%** |
| **4** | **~10%** | **~55-65%** |
| 5 | ~12% | ~55-68% |
| 6 | ~20% | ~72-80% |

Ossenkoppele et al., Nat Med 2022

A+ = Amyloid-positive
T+ = Tau-positive

A4 data confirms higher baseline levels of amyloid and tau markers (specifically ptau217 and tau PET positivity) were found to be associated with increased rates of cognitive decline and progression to functional impairment (Sperling 2024).

# REτAIN – A Secondary Prevention study

**A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Study, to Assess Efficacy, Safety and Immunogenicity of JNJ-64042056 in Participants with Preclinical AD.**

**This study aims to provide proof-of-concept that JNJ-64042056 slows the spread of ptau and slows cognitive decline over 48 months compared to placebo in 498 people with preclinical AD.**

**Primary endpoint**

- Change from baseline in PACC-5 at 48 months vs placebo

**Key secondary endpoint**

- Change from baseline in the spread of tau pathology, as measured by tau PET vs placebo

**Secondary endpoints**

- Change from baseline in CDR-GS (time-to-event), CDR-SB, MBI-C, ADCS-ADL-PI, QOL-AD, volumetric MRI, and CSF/plasma biomarkers vs placebo

**Exploratory endpoint**

- Change in multimodal digital biomarker measuring cognitive and motoric functions during daily life activities vs placebo



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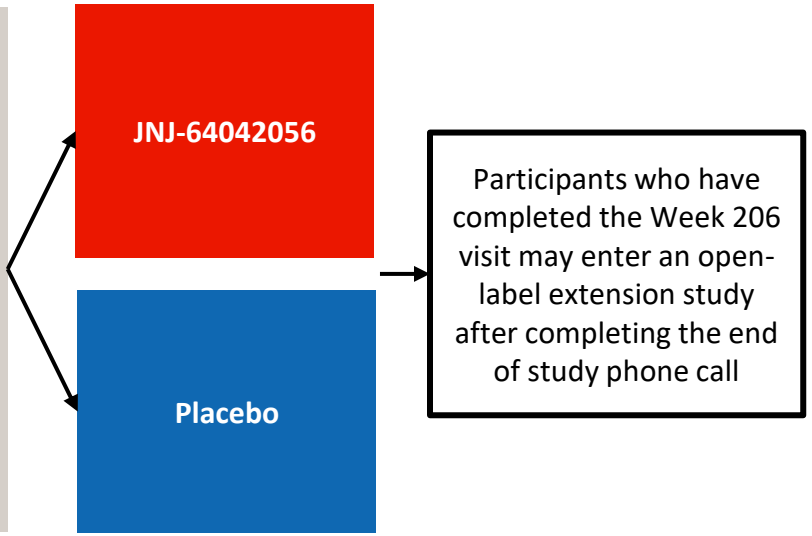
# Study Design

## Retain Phase 2b

| 4 weeks | 13 weeks | 206 weeks | 2 weeks |
|---|---|---|---|
| **Prescreening** | **Screening** | **Treatment period*** | **Follow-up** |

- Pre-screening ICF
- Pre-screening eligibility criteria
- Blood sample collection for p217+tau
- Exploratory speech-based assessment for cognition
- Participants meeting pre-specified plasma p217+tau criteria can be screened for participation in study

- Disclosure of positive p217+ results
- Screening ICF
- Assessment of IN/EX criteria, medical history, demographics, psychiatric and safety evaluations
- Study partner needs to accompany to sign ICF and complete clinical scales
- CDR and PACC-5
- MRI and tau PET scan




***Treatment period:**

- Eligible participants will be randomized in a 1:1 ratio to JNJ-64042056 or placebo. The randomization will be balanced and stratified by geographical region and baseline tau burden.
- 3 immunizations during the first 6 months followed by Q6M immunizations
- Assessments include safety/tolerability, immunogenicity, Tau PET, Fluid AD biomarkers, PACC-5, CDR-GS, CDR-SB, ADCS-ADL-PI, MBI-C, EQ-5D, QoL-AD, RUD-lite & a digital measure of neurocognitive function



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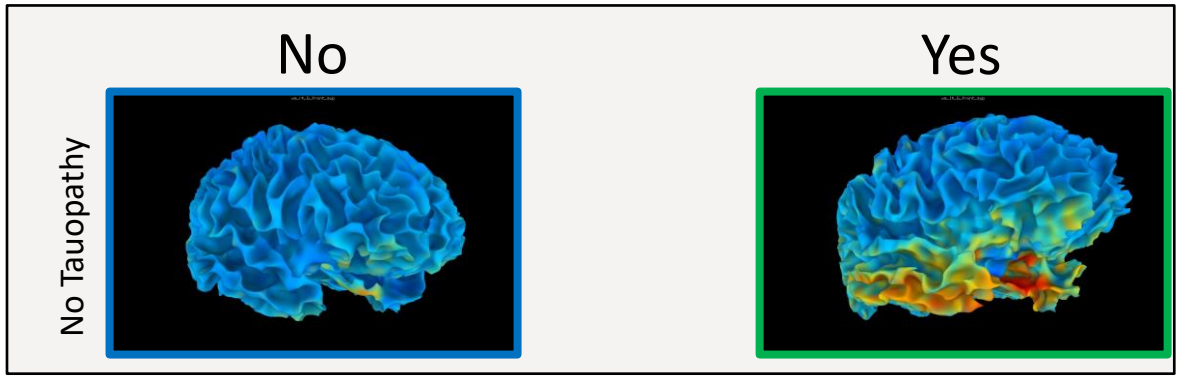
# Study Population

## Key Inclusion Criteria

- 55-75 years of age, inclusive, at randomization visit
- **Elevated brain tau pathology on a screening tau PET scan**, reviewed centrally by a qualified reader




- **Global CDR score of 0** at screening and baseline
- **MMSE ≥27** (with educational adjustment)
- Able to read and write and with a minimum 5 years of formal education as reported by participant and study partner at screening.
- Must have a designated study partner

## Key Exclusion Criteria

- Fulfils diagnostic criteria for Alzheimer's Dementia or non-Alzheimer's Dementia, or has a history consistent with or known autosomal dominant AD
- Diagnosis of Mild Cognitive Impairment
- Participant has any known amyloid-related imaging abnormalities due to administered anti-amyloid antibodies. Received anti-amyloid or anti-tau therapy.
- Abnormal function of the immune system
- ANA positive titer at dilution of 1:160 or greater at screening in participants without clinical symptoms of auto-immune disease



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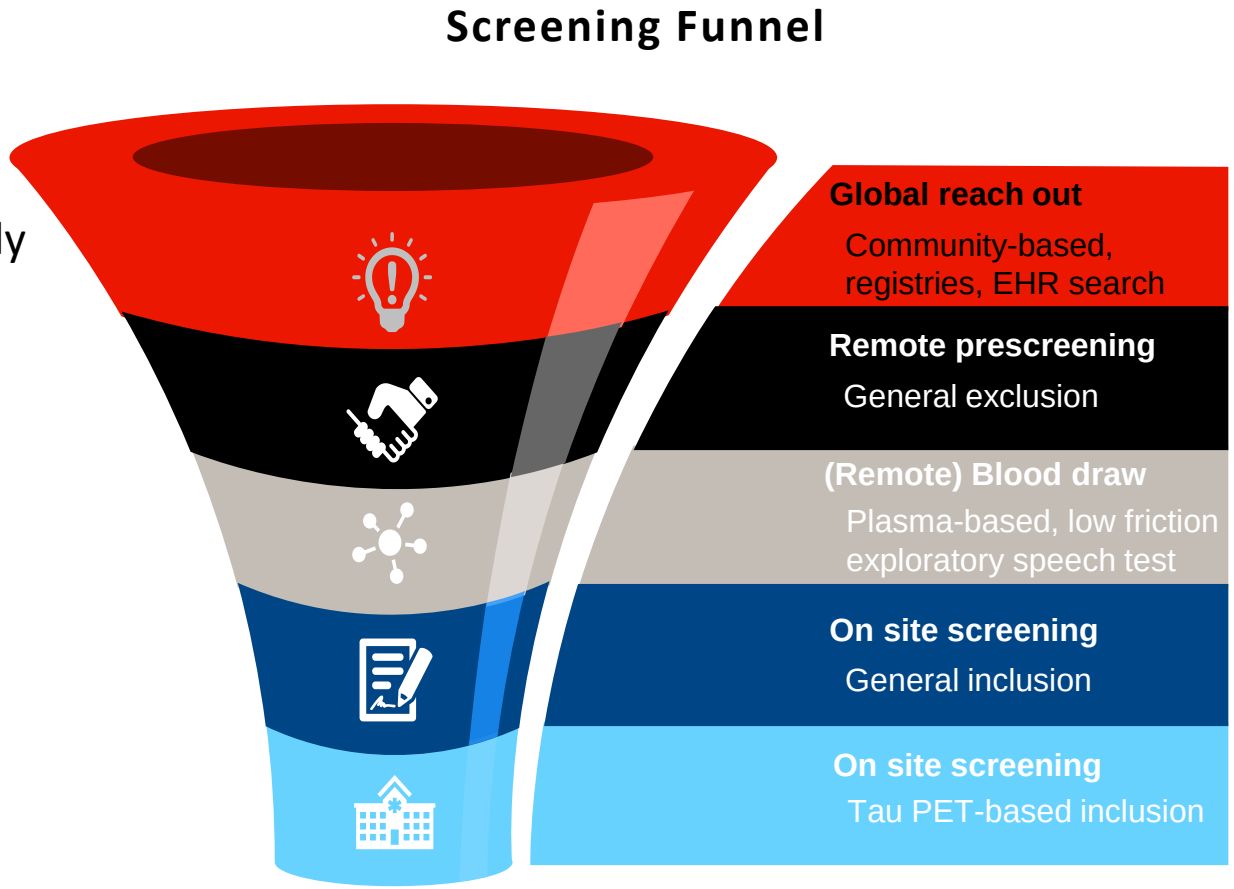
# Participant identification

To most efficiently identify the study population and avoid unnecessary radiation exposure, **a two-step biomarker precision strategy is applied:**

1. a **plasma p217+tau assay** is used to prescreen cognitively unimpaired individuals for evidence suggestive of elevated brain amyloid & tau (A+T+ status)
2. Only individuals meeting the p217+tau criteria, will undergo a **tau PET scan** to confirm tau pathology.

The use of this blood-based biomarker is expected to result in at least a 3 to 3.5-fold reduction in the number of screening PET scans thereby reducing overall study burden, time & cost.



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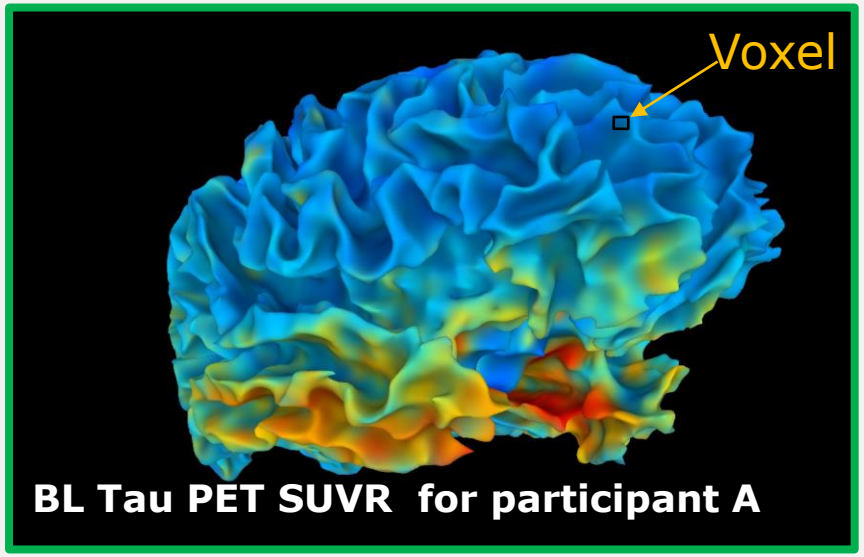
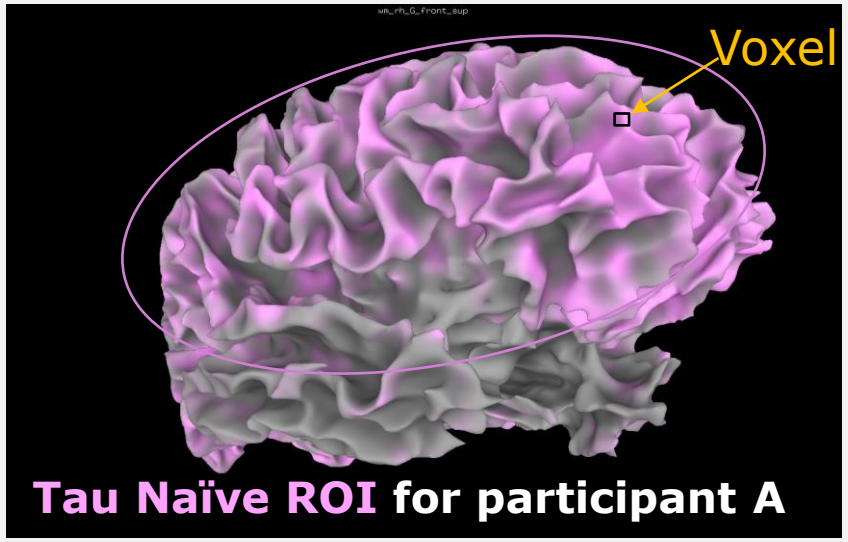
# If tau is spatially heterogenous, how do we capture treatment effect?

It depends. In anti-tau trials targeting tau seed spreading: Treatment effect *not expected* where tangles are established, treatment effect may be largest in Tau Naïve regions* at BL

**We developed *spread* measures to *complement* measures of *aggregation***




1- Start with a participant's BL tau PET scan




2- Mark a voxel as being tau naïve if its BL tau PET is within +/- 1 sd of tau PET at that location in control group of amyloid free cohort.

* where BL NFT levels are within 1 SD from controls

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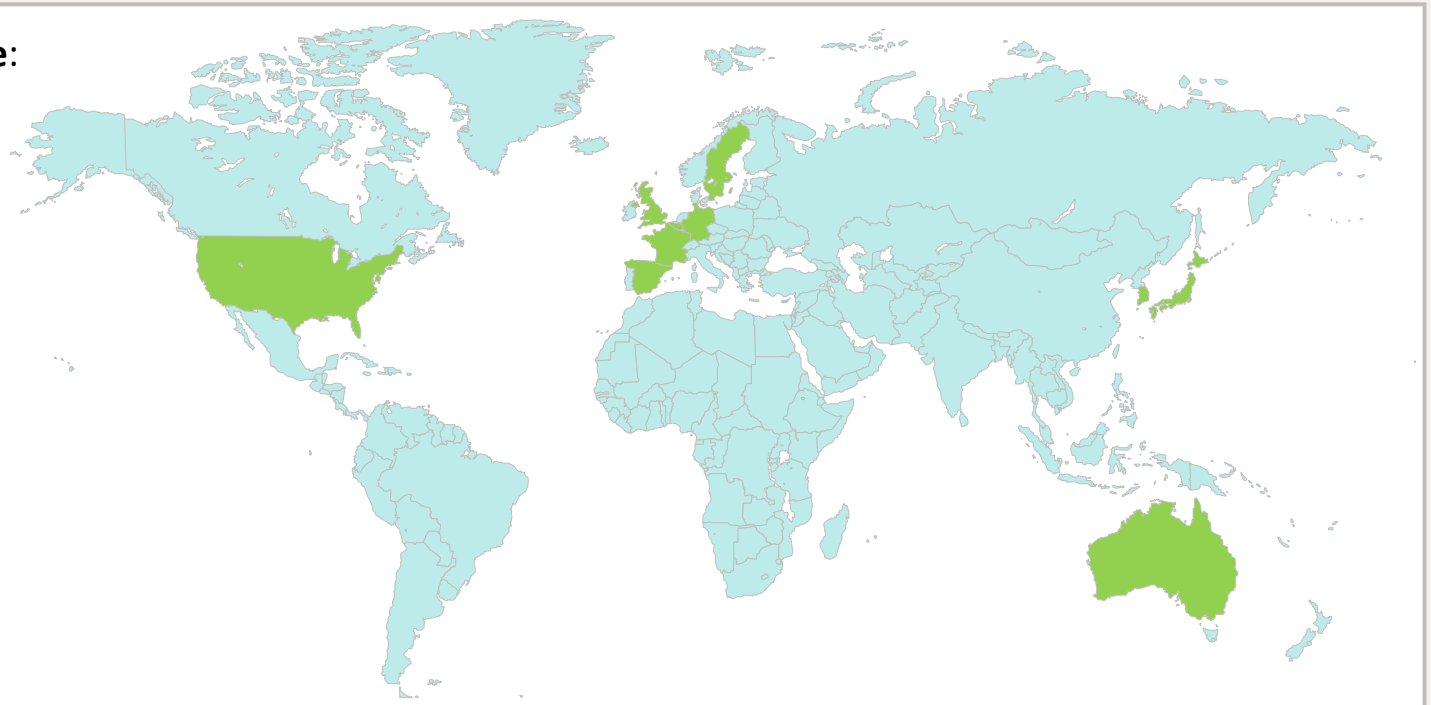
# Study Status

REτAIN initiated prescreening in April 2024 and is currently enrolling in 69 sites in 7 countries. Study is ongoing.

**Enrolling countries will include**:

Australia
Belgium
Germany
France
Japan
Spain
Sweden
United States
United Kingdom
South Korea





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# Key Takeaways

# Precision Neuroscience approach – first anti-tau treatment being tested in sporadic preclinical AD in REτAIN study

- Treatment interventions for AD must be associated with demonstrable benefit to patients, which outweigh the potential risks. REτAIN is designed **to demonstrate impact on disease progression and/or clinical improvement using precision approaches.**

- **Use of innovative J&J blood-based assay Quanterix Lucent AD® followed by tau PET in screening:**

Select those likely to progress & most likely to benefit

**Precision in patient selection**

- **Use of precision measures:**
  - ➢ Demonstrate treatment-related slowing in the spread of tangles using tau PET measures designed to measure spread rather than aggregation
  - ➢ Use of sensitive cognitive measure supplemented with measures of function and behavior
  - ➢ Evaluate multimodal digital biomarker will measure cognitive and motoric functions during daily life.

**Precision in endpoint strategy**



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# Acknowledgements

We want to thank our research participants, their study partners as well as all our investigators and site staff to embark on this clinical research journey together. Without their commitment, we would not be where we are today. We also want to recognize the tremendous work our J&J teams globally are doing to make this clinical trial a success! Finally, we want to thank our collaborator AC Immune for their continued support.

The image depicted contains models and is being used for illustrative purposes only.

# Anti-Abeta active immunotherapy in early AD and DSAD: ACI-24.060 in the Phase 1b/2 ABATE study

Anke Post, MD, PhD | ADPD 2025 | April 2025

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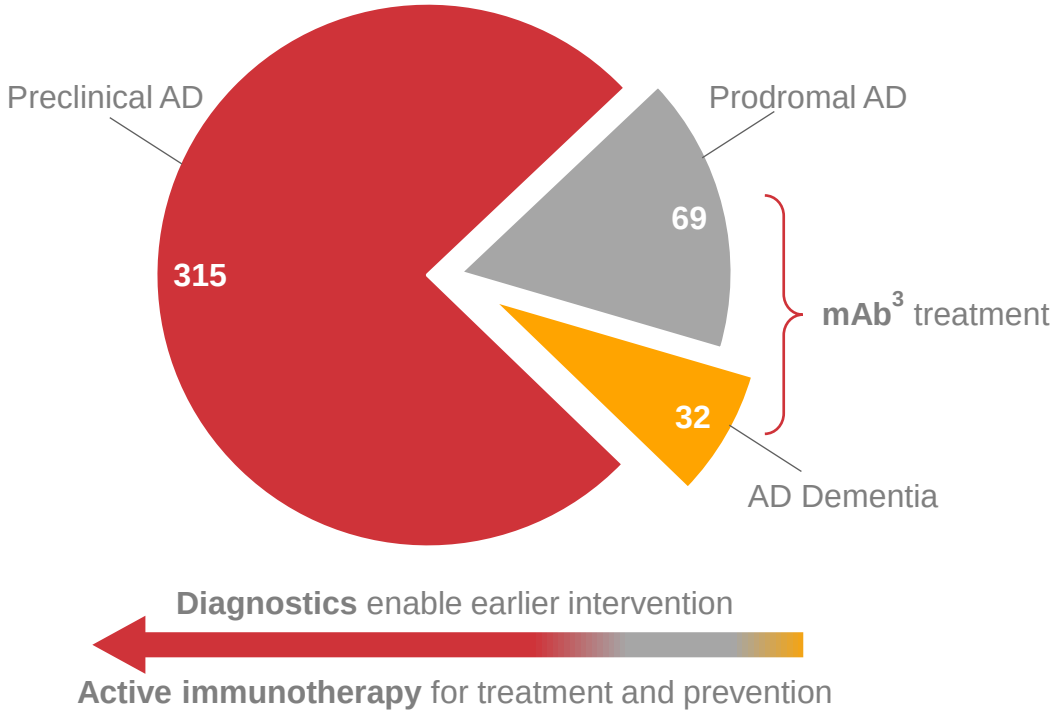
## Conflict of interest disclosure

*Anke Post is an employee and shareholder of AC Immune and participates in the stock incentive plan.*

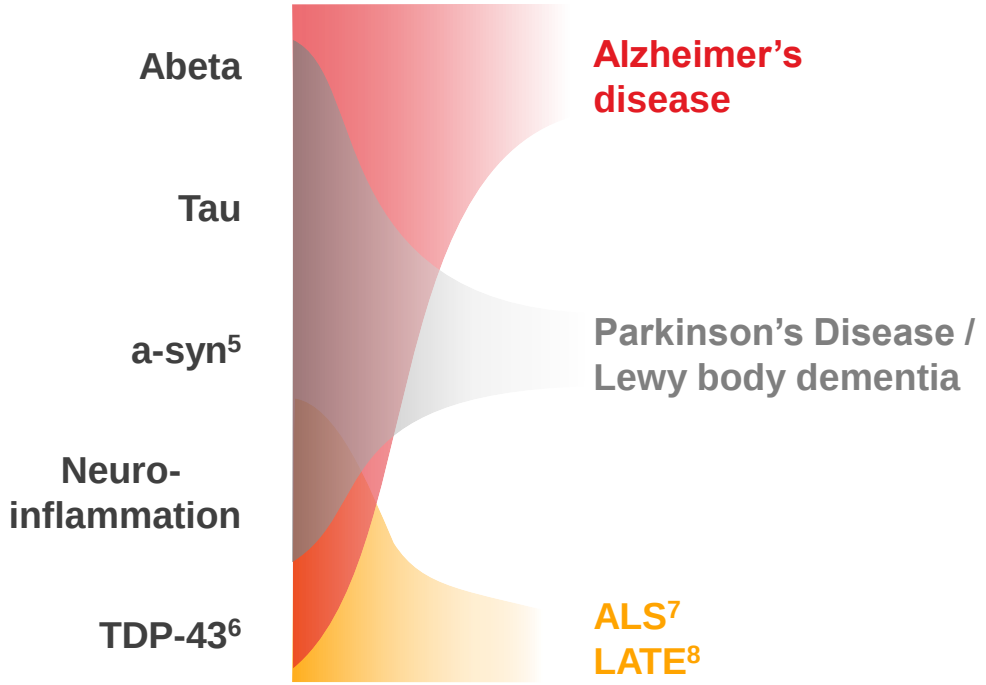
# Precision medicine to address the complexity of Alzheimer`s disease

## Prevention as the best approach to long-term preservation of brain health

**Global Prevalence of AD[1] stages[2] (million)**



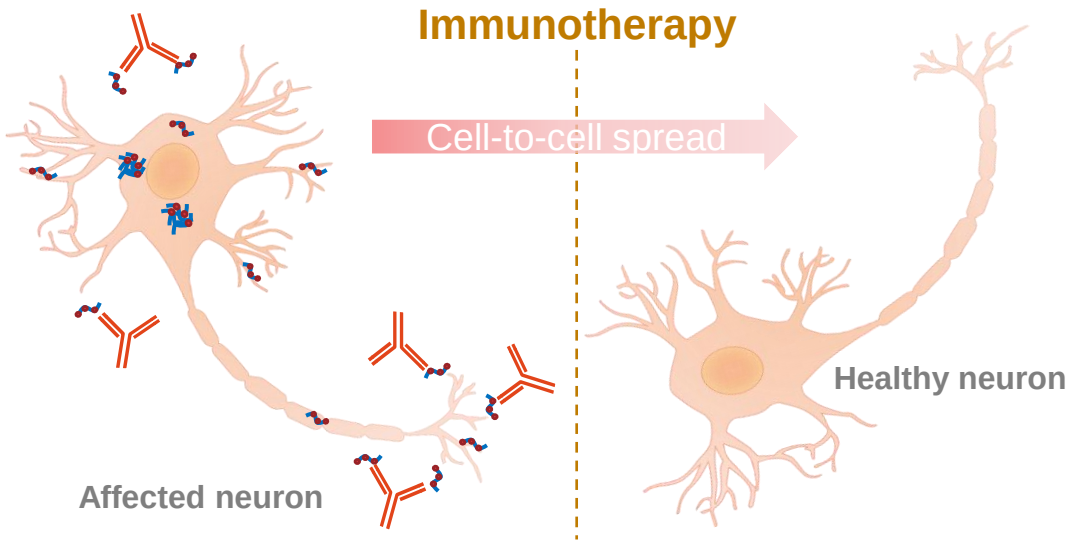

**Co-pathologies in NDD[4]**




- Precision prevention for AD through early risk detection and active immunotherapy

(1) Alzheimer's disease; (2) Gustavsson et al. Alzheimer's and Dement. 2023 19:658-670. https://doi.org/10.1002/alz.12694; (3) Monoclonal antibody; (4) Neurodegenerative disease; (5) alpha-synuclein; (6) TAR DNA-binding protein 43; (7) Amyotrophic lateral sclerosis; (8) Limbic-predominant age-related TDP-43 encephalopathy

# Clinical pipeline of active immunotherapies in neurodegenerative diseases

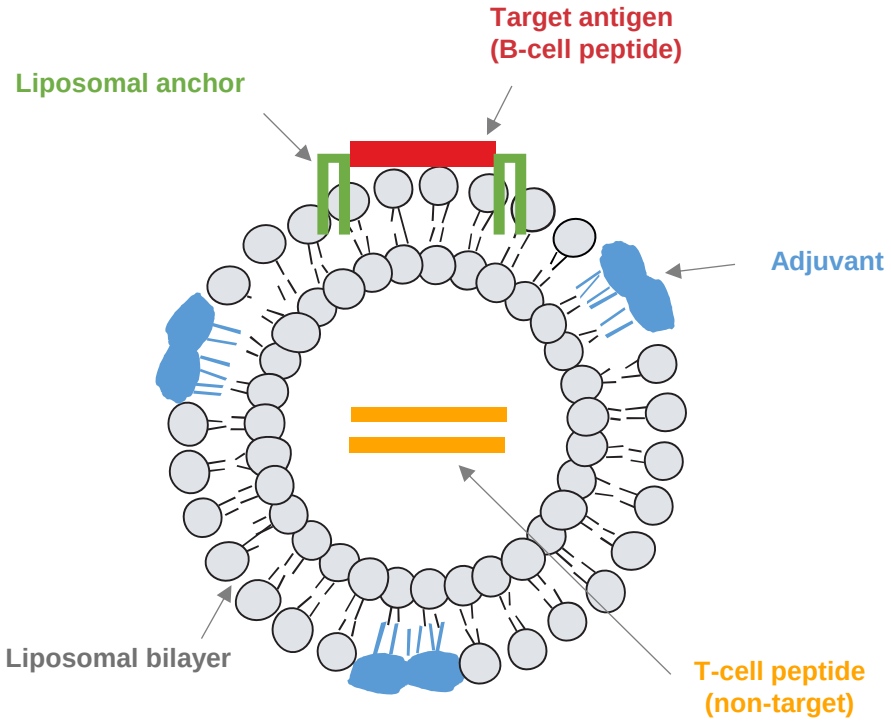



| CANDIDATE | PARTNER | INDICATION | DISCOVERY | PRECLINICAL | PHASE 1 | PHASE 2 | PHASE 3 |
|---|---|---|---|---|---|---|---|
| **ACI-24.060** *(anti-Abeta active immunotherapy)* | Takeda | AD treatment | | | | | |
| | | AD treatment (*Down syndrome*[2]) | | | | FDA Fast Track | |
| **ACI-35.030 (JNJ-2056)** *(anti-pTau active immunotherapy)* | janssen | AD[1] prevention | | | | FDA Fast Track | |
| **ACI-7104.056** *(anti-a-syn*[3] *active immunotherapy)* | | PD[4], a-synucleinopathies | | | | | |

(1) Alzheimer's disease; (2) Down syndrome-related Alzheimer's disease; (3) Alpha-synuclein; (4) Parkinson's disease

# ACI-24.060: anti-Abeta active immunotherapy

## Induces antibodies against pathological species to fight Alzheimer's Disease (AD)




Generates a target-specific antibody response

Safely engages Abeta-unrelated T-cells to enhance & maintain immune responses

| | |
|---|---|
| Immunogenicity | ++++ |
| Target specificity | ++++[1] |
| Conformation specificity | +++ |
| Avidity increase over time | +++ |
| Sustainability of response | +++ |
| Boosting | +++ |

- ACI-24.060 Abeta active immunotherapy is safe and immunogenic in non-human primates (NHPs)

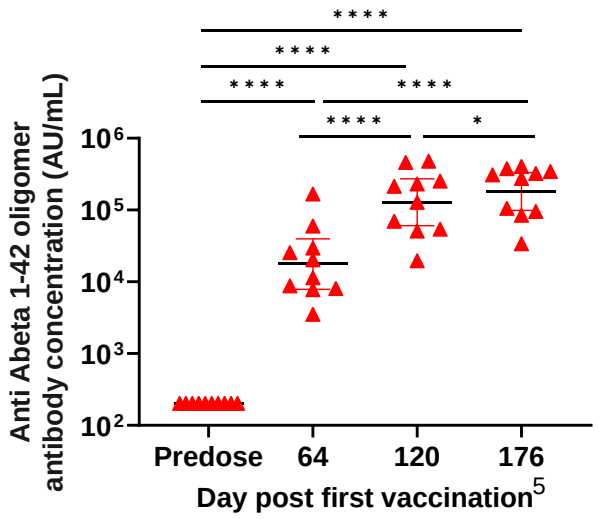
(1) Increases over time

# ACI-24.060: Potent immune response against pathological Abeta species

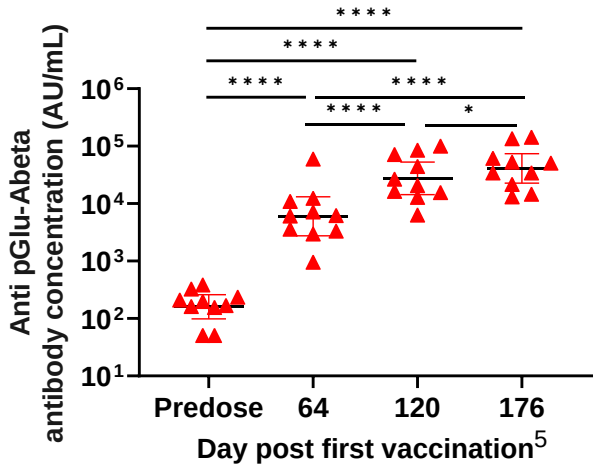
## Strong antibody response against Abeta 1-42 oligomers and pyroglutamate Abeta 3-42 in NHPs[1]

**ACI-24.060 in NHPs**

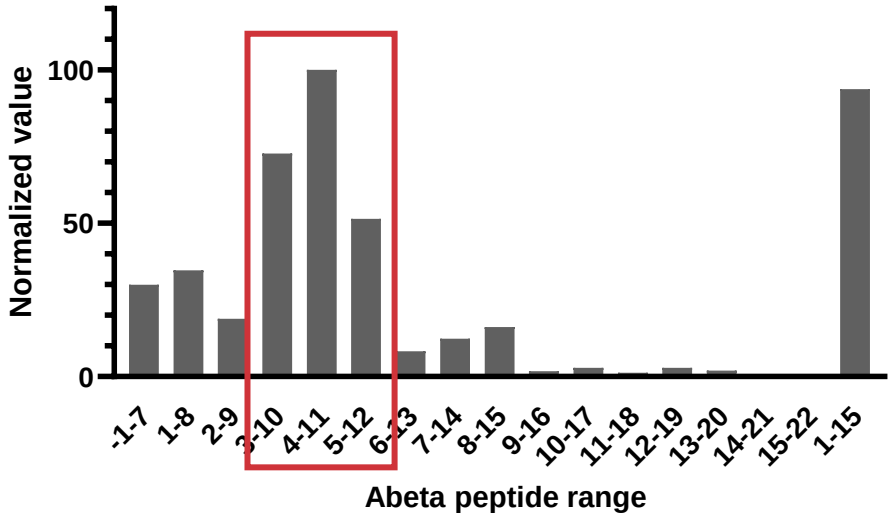
Anti Abeta1-42 oligomer IgG




Anti-pGlu[2]3-42 IgG




**Epitope mapping (on day 113)**




Fiorini, AAIC 2024

* p<0.05 **** p<0.0001

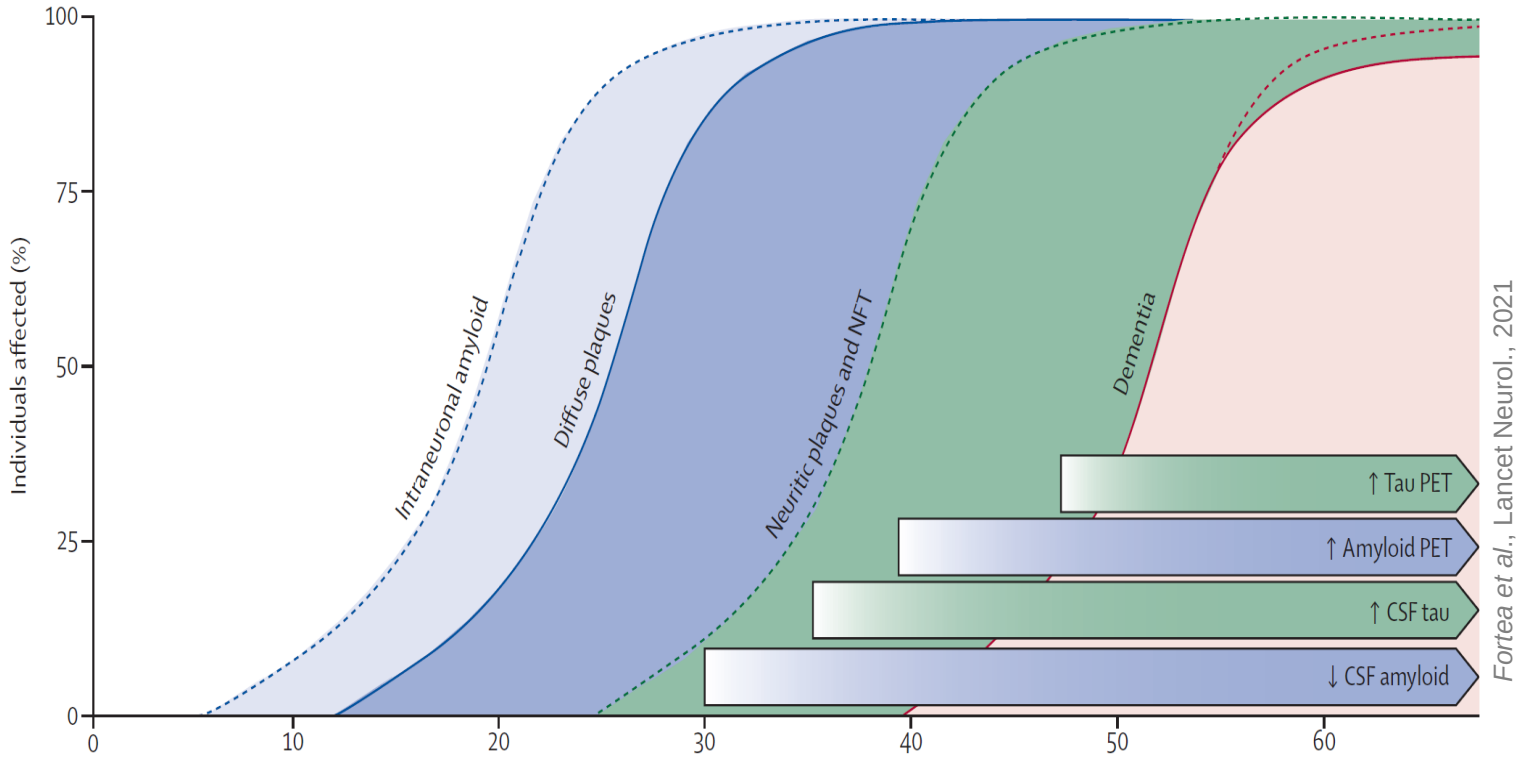
- Preclinically, sustained, boostable IgG titers against Abeta oligomers[3] and pGlu[4] Abeta 3-42
- In NHPs, induced antibodies bind epitopes present in Abeta oligomers and pGlu 3-42 pathological species

(1) Non-human primates; (2) pyroglutamate Abeta3-42; (3) Target of lecanemab; (4) Target of donanemab; (5) Injections on days: 0, 29, 57, 85, 113, 141, 169;

# AD[1] associated with Down Syndrome: a genetic form of dementia

## AD biomarker patterns in people with DS[2] closely resemble patterns of sporadic AD and ADAD[3]

- AD associated with DS is a genetic form of dementia
  - 85-100% of subjects with DS have dementia-like symptoms in those older than 65 years
  - Neuropathologic hallmarks of AD are present in adults with DS by the age of 40 years
  - Similar pathophysiology and biomarkers as compared to autosomal dominant AD
- Predictive, age-associated biomarker pattern supports prevention studies




*Fortea et al.*, Lancet Neurol., 2021

(1) Alzheimer's disease; (2) Down syndrome; (3) Autosomal dominant AD; (4) A; Amyloid biomarker; T; Tau biomarker; N; Neurodegeneration biomarker; CSF; Cerebro Spinal Fluid; (5) Positron emission tomography (6) Food and Drug Administration

# Aβate Biomarker-based Phase 1b/2 study of ACI-24.060 in AD[1] and DS[2]

## Placebo-controlled Phase 1b/2 Study Overview

### Adaptive Study Design

**Both**
- Interim analyses of safety/tolerability & immunogenicity
- Biomarker analyses including Abeta-PET[3]

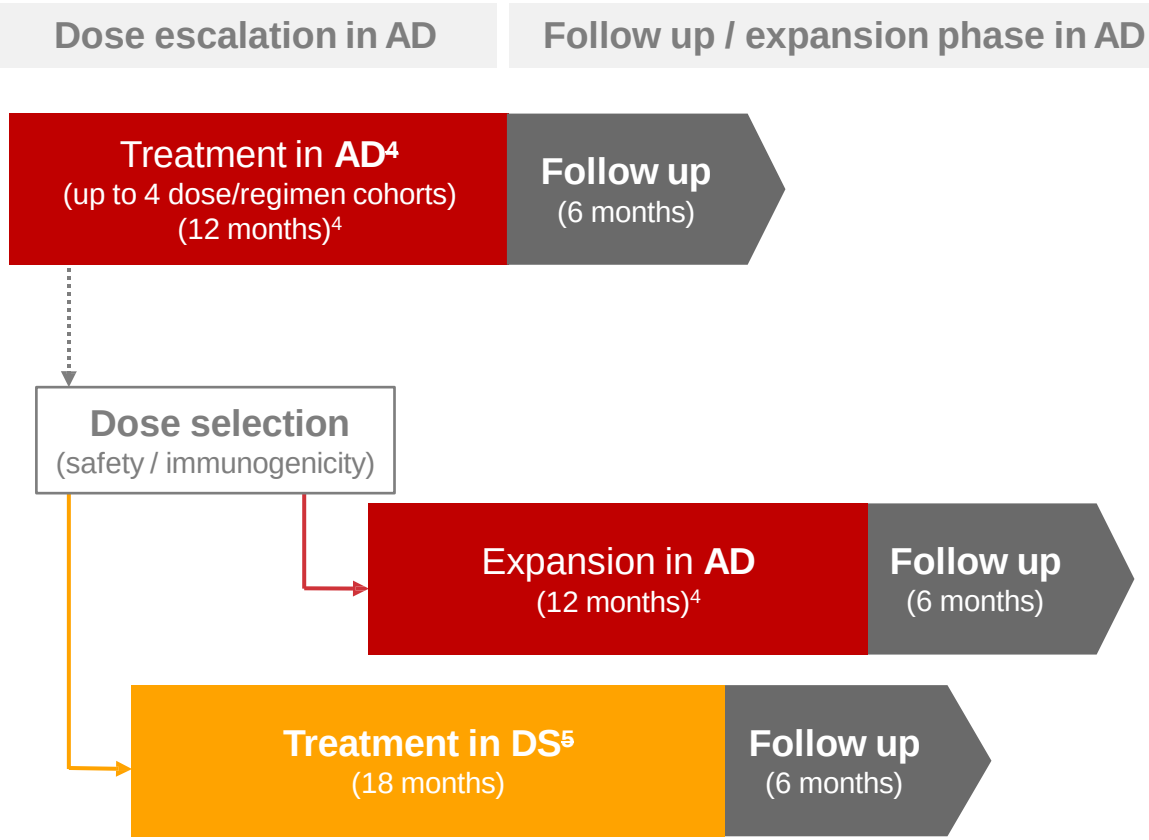
**AD**
- Up to 4 different doses and/or dose regimens
- Expansion of one cohort to assess effect on Abeta-PET

**DS**
- Initiation using selected dose identified in AD (based on safety/tolerability and immunogenicity)

### Outcome measures

**Both**
- Safety/tolerability
- Immunogenicity assessments
- Abeta-PET imaging
- Exploratory biomarkers and clinical endpoints

## Trial Schematic




(1) Alzheimer's disease; (2) Down syndrome-related AD; (3) Positron emission tomography; (4) Treatment duration for cohorts AD1, AD2 and AD3

# Biomarker-based Phase 1b/2 study of ACI-24.060 in AD[1] and DS[2]

## Key Inclusion Criteria

**in AD and DS:**

- PET[3] scan consistent with the presence of amyloid pathology

**in AD:**

- 50-85 years old
- MCI due to AD according to NIA-AA criteria (prodromal AD), CDR global score = 0.5

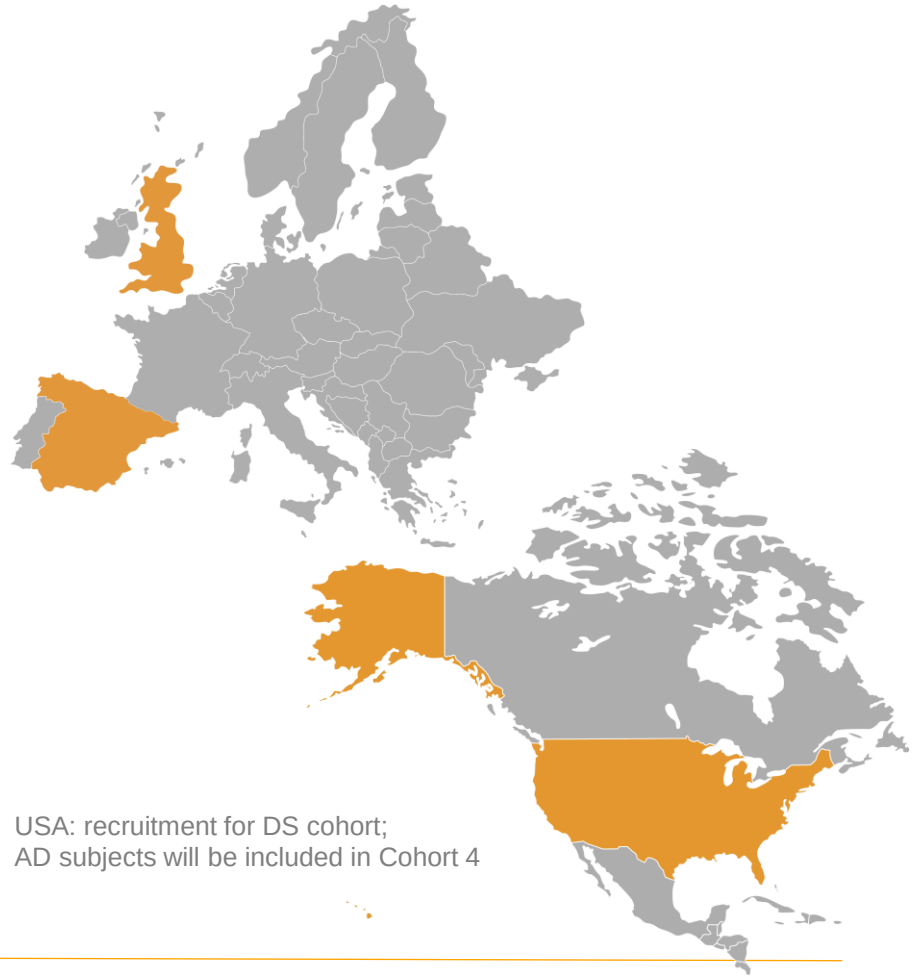
**in DS:**

- 35-50 years old
- cytogenetic diagnosis of trisomy 21

## Key Exclusion Criteria

**in AD and DS:**

- Unstable and/or clinically significant medical condition
- History of clinically relevant CNS disorders
- Cerebrovascular abnormalities (MRI[4]) of relevance or any structural evidence of other brain pathologies

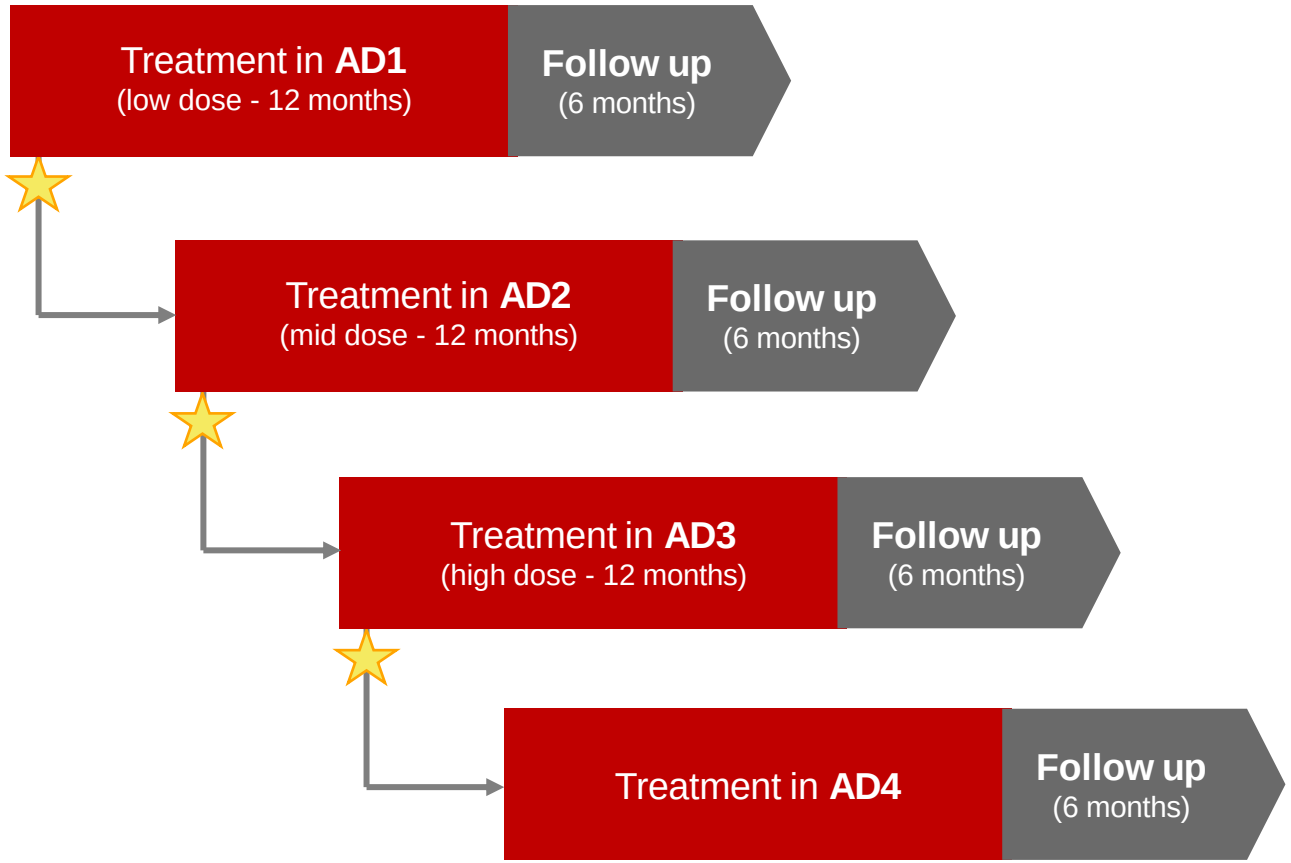


USA: recruitment for DS cohort;
AD subjects will be included in Cohort 4

- Enrolment status: >90 subjects enrolled across AD and DS cohorts

(1) Alzheimer's disease; (2) Down syndrome-related AD; (3) Positron emission tomography; (4) vasogenic edema, siderosis, macro-hemorrhage, >4 microhemorrhages, >2 lacunar infarcts, or a single infarct >1 cm on magnetic resonance imaging

# Enrolment status of Part 1 in prodromal AD[1] participants




Cohort AD1: Recruitment complete ✓
**ACI-24.060 low dose or Placebo, 3:1 ratio**
**8 subjects** randomized

Cohort AD2: Recruitment complete ✓
**ACI-24.060 mid dose or Placebo, 2:1 ratio**
**29 subjects** randomized

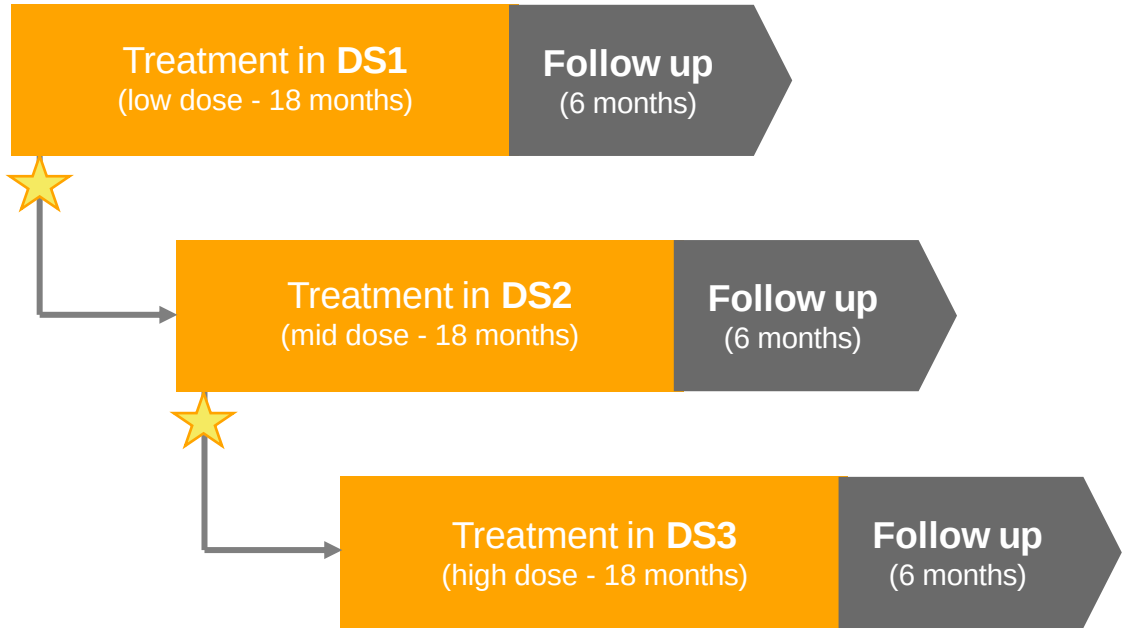
Cohort AD3: Recruitment complete ✓
**ACI-24.060 high dose or Placebo, 2:1 ratio**
**37 subjects** randomized

Cohort AD4: **Recruitment start planned in H2 2025**
**Cohort structure and dosing regimen in preparation**

- Total number of patients randomized across all AD1, AD2 and AD3 cohorts: 74 subjects

Interim analysis considered from week 6 onwards for each cohort; (1) Alzheimer's disease

# Enrolment status of Part 2 in non-demented DS[1] participants




Cohort DS1: Recruitment complete ✓
**ACI-24.060 low dose or Placebo, 3:1 ratio**
**8 subjects** randomized

Cohort DS2: Recruitment complete ✓
**ACI-24.060 mid dose or Placebo, 3:1 ratio**
**8 subjects** randomized

Cohort DS3: Recruitment ongoing
**ACI-24.060 high dose or Placebo, 3:1 ratio**
**Target: 8 subjects randomized**

- Total number of individuals to be randomized across all DS cohorts: 24 subjects

Interim analysis considered from week 6 onwards for each cohort; (1) Down syndrome

# Patient baseline characteristics and interim safety/tolerability findings

## Placebo-controlled Phase 1b/2 study: no safety concerns to date

| Baseline profile[1] | Unit | Part 1: AD | Part 2: DS |
|---|---|---|---|
| **Number of patients** | n | 74 | 15 |
| **Age** | | | |
| Years | mean | 70.7 | 45.0 |
| | std | 6.14 | 3.95 |
| **Sex** | | | |
| Male | n (%) | 34 (45.9%) | 6 (40.0%) |
| Female | n (%) | 40 (54.1%) | 9 (60.0%) |
| **Race** | | | |
| White | n (%) | 71 (95.9%) | 15 (100%) |
| Black / African American | n (%) | 2 (2.7%) | 0 |
| Asian | n (%) | 1 (1.4%) | 0 |
| **Cognitive performance** | | | |
| MMSE [2] | mean (std) | 24.5 (3.6) | - |
| ADAS-Cog-13 [3] | mean (std) | 25.3 (9.0) | - |
| KBIT-2 [4] | mean (std) | - | 53.8 (10.6) |

1. **Overall good safety and tolerability in both, AD and DS, study populations**

2. **To date, no death; one serious adverse event related to study treatment** (vomiting and headache in AD)

3. **Most frequent TEAEs[5] are injection site reactions of mild or moderate intensity**

4. 
   - **No ARIA-E**
   - **No evidence of CNS inflammation**

5. 
   - **No ARIA-H in subjects with DS**
   - **In AD, all events were asymptomatic and their frequency in line with expected placebo incidence**

(1) Data cut-off date: 23 Jan. 2025; (2) Mini-mental state examination, interim data; (3) Alzheimer's Disease Assessment Scale, Cognitive part, interim data; (4) Kaufman Brief Intelligence Test Second Edition, interim data based on 14 out of 15 subjects with DS; (5) Treatment Emergent Adverse Events

# Preliminary insights from blinded cohorts AD1, AD2 and AD3

## ACI-24.060 exhibits a dose-dependent immune response against toxic species of Abeta

1. **Immunogenicity observed in AD subjects at all tested doses**
2. **Trend towards increase in the magnitude of anti-Abeta$_{1-42}$ IgG titers with increasing dose**
3. **Increase in the responder rate with increasing dose and repeated immunizations**
4. **Boosting effect for all dose levels observed after repeated immunizations with ACI-24.060**
5. **More durable and sustained immune response were observed in cohorts AD2 and AD3**

- 12-month treatment time point for AD1, AD2 and AD3 reached in late 2025

# Conclusions

| | |
|---|---|
| **Safety / tolerability** | ▪ Good safety and tolerability profile with no safety concerns related to study drug identified to date |
| **Immunogenicity** | ▪ Early blinded interim data has shown that ACI-24.060 generates anti-Abeta antibody titers at all tested doses |
| **Future developments** | ▪ AD Cohort 4 is currently in preparation<br>▪ Recruitment of AD4 is expected to start in H2 2025 |
| **Part 1: AD status** | ▪ 12-month treatment time point for AD1, AD2 and AD3 reached in late 2025 |
| **Part 2: DS status** | ▪ DS1 (12 months) and DS2 (6 months) time points reached in H2 2025<br>▪ DS3 recruitment is ongoing |

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