Immunotherapy targeting α-synuclein: Hype or hope for Parkinson‘s Disease?

Werner Poewe
Emeritus Professor of Neurology
Dept of Neurology
Medical University Innsbruck
AUSTRIA

DISCLOSURES

Werner Poewe reports personal fees from AbbVie, Affiris, Allergan, AstraZeneca, BIAL, Boston Scientific, Britannia, Intec, Ipsen, Lundbeck, Merz, Neuroderm, Pharmaceuticals, Novartis, Orion Pharma, Prexton, Teva, UCB and Zambon (*consultancy and lecture fees in relation to clinical drug development programmes for PD).*

Royalties: Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press

Grant support: MJFF; EU FP7 & Horizon 2020

PRESENTATION OUTLINE

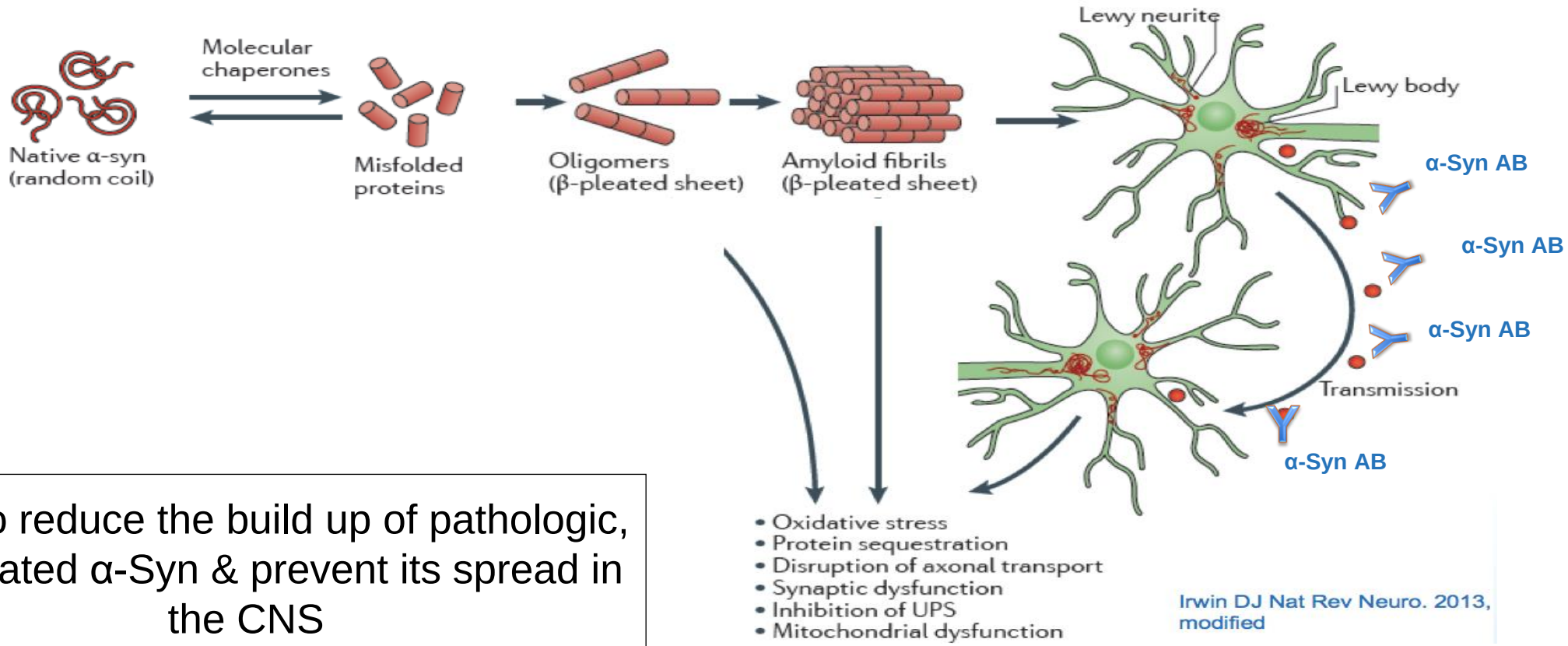
- Rationale for targeting α-synuclein in PD
- α-synuclein immunotherapy trials in PD
- α-synuclein immunotherapy trials in MSA
- Conclusions

Defining PD as a ‚Synucleinopathy‘

- Missense mutations in SNCA cause dominantly inherited PD
- Increase in SNCA wild-type gene dose (duplication; triplication) causes PD (or PDD)
- Sequence variations in regulatory region of SNCA associated with PD risk
- Lewy bodies and Lewy neurites in sporadic PD immunoreactive for α-synuclein

Polymeropoulos&al, Science 1197; Spillantini & al, Nature 1997; Chartier-Harlin,Lancet 2004; Blauwendraat&al, Lancet Neurol 2020

Targeting α-Syn with Immunotherapy



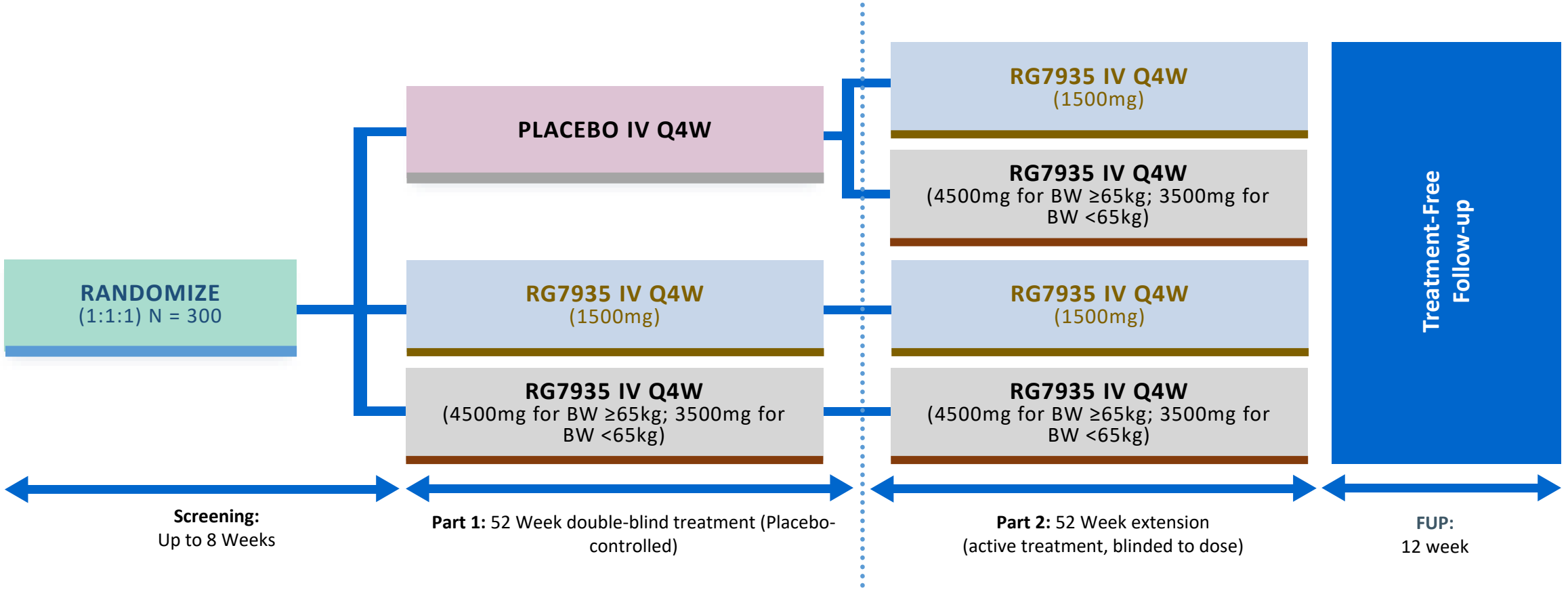
Goal: to reduce the build up of pathologic, aggregated α-Syn & prevent its spread in the CNS

α-Synuclein AB‘s in Clinical Development

Antibody	Specification	Company	Phase of development
PRX002/RG7935 (Prasinezumab)	humanized IgG1 monoclonal antibody	Roche	phase 2
BIIB054 (Cinpanemab)	fully human IgG1 monoclonal antibody	Biogen	phase 2
Lu AF82422	fully human IgG1 monoclonal antibody	Lundbeck	phase 1b
MEDI1341	fully human IgG1 monoclonal antibody	Astra Zeneca/Takeda	phase 1
ABBV-0805	fully human IgG1 monoclonal antibody	AbbVie	Phase 1

Adapted from: Poewe & al., Neuropharmacology 2020; 171:108085

PRASINEZUMAB PHASE 2 STUDY DESIGN (PASADENA)



https://clinicaltrials.gov/ct2/show/NCT03100149

Pagano & al; Front Neurol (in press)

PASADENA Phase II study in early PD: Endpoints

Primary endpoint

- Change from baseline at Week 52 in MDS-UPDRS Total score(sum of Parts I, II and III)

Key secondary endpoints

- Change from baseline at Week 52 in the following:
  - MDS-UPDRS Part I non-motor aspects
  - MDS-UPDRS Part II experiences of daily living (motor aspects)
  - MDS-UPDRS Part III motor examination and Part III sub-scores (bradykinesia, rigidity, tremor, axial signs)
  - MoCA total score
  - PGI-C, CGI-C and disability (SE-ADL)
  - Neurodegeneration of dopaminergic terminals (DaT-SPECT)

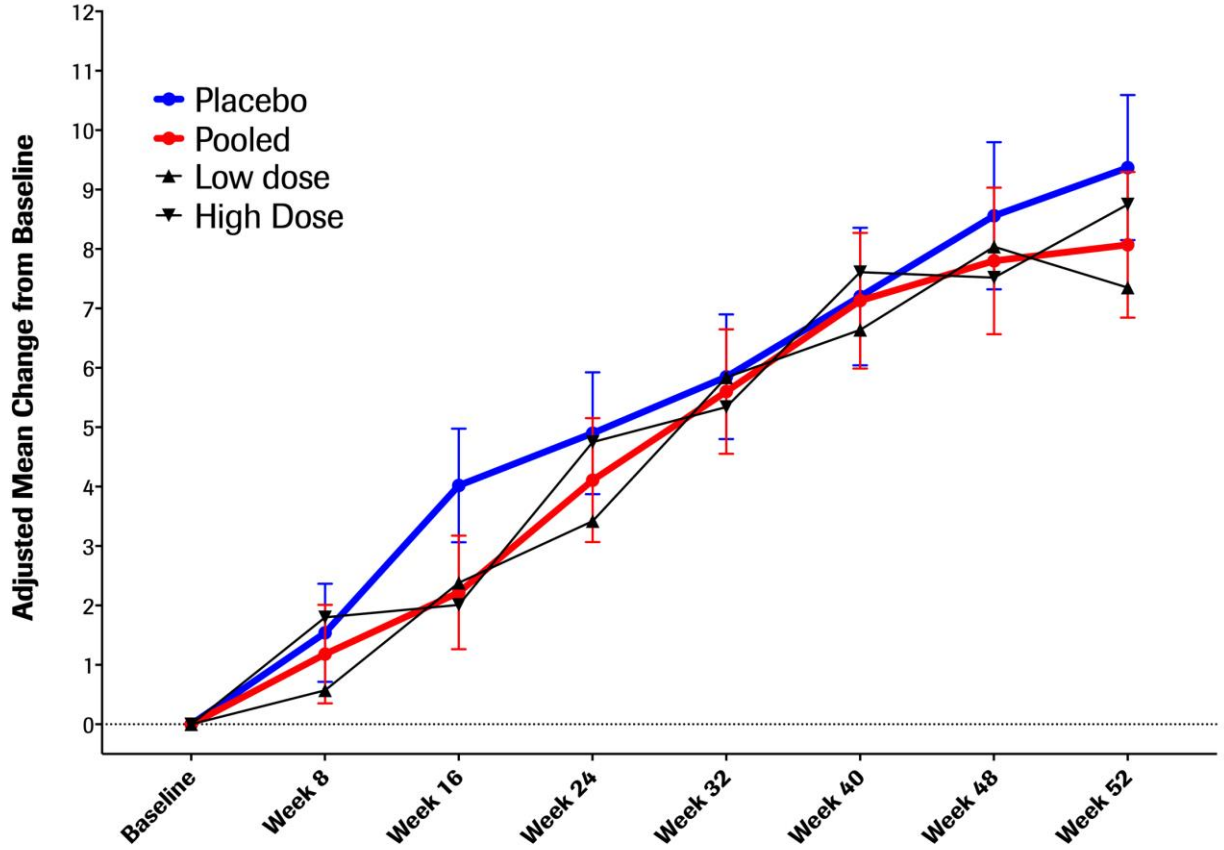
Key exploratory endpoints

- Digital PASADENA Motor Score
- ASL-MRI for cerebral blood flow
- Time to clinically meaningful worsening of motor function (+5 points MDS-UPDRS Part III)

Safety, tolerability, pharmacokinetics and immunogenicity

Pagano & al; Front Neurol (in press)

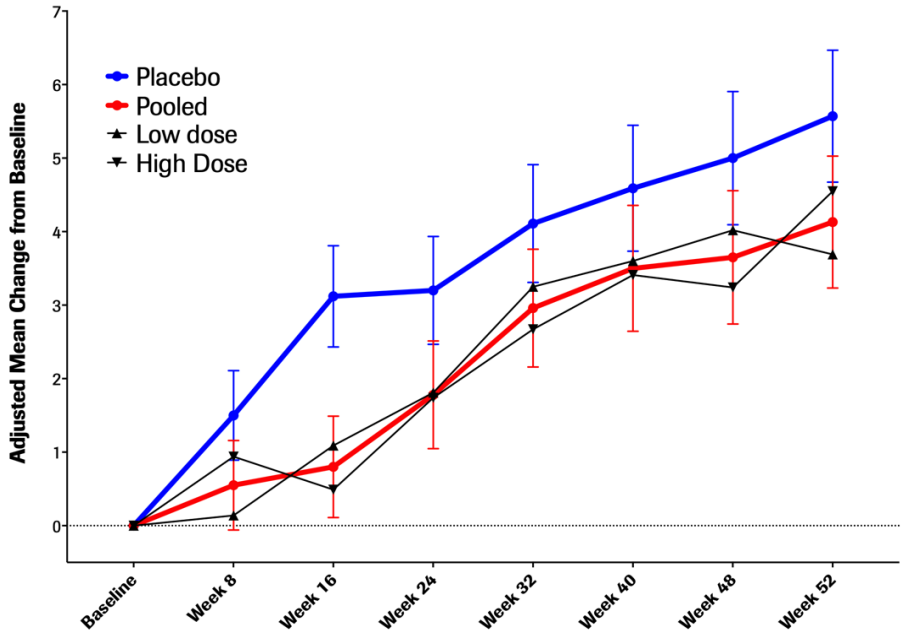
PASADENA: 52 weeks results

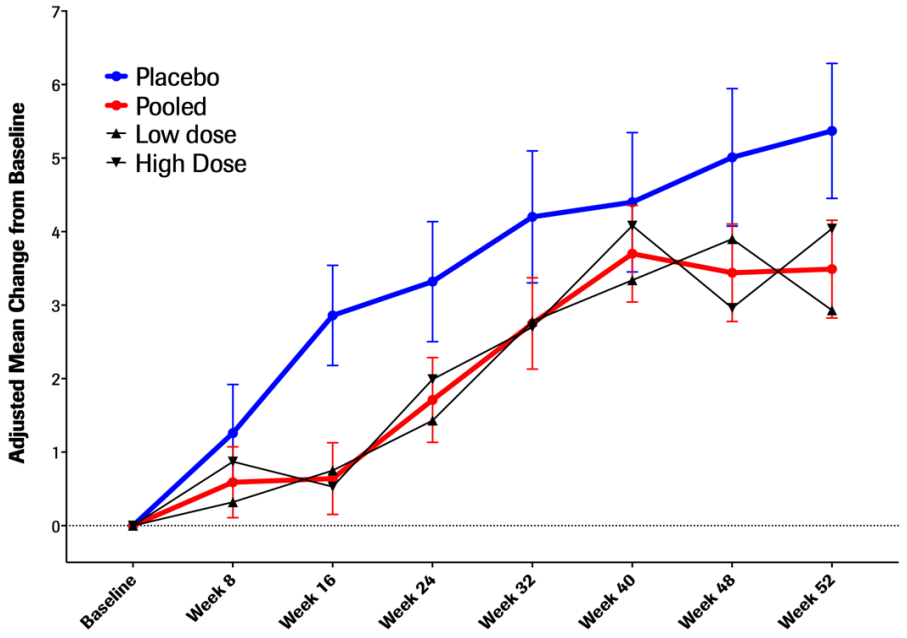


Primary endpoint not met

Pagano &al, MDS Virtual Congress 2020

PASADENA: 52 weeks results





Treatment with prasinezumab reduced clinical decline in MDS-UPDRS Part III Score, confirmed by central rating

Pagano &al, MDS Virtual Congress 2020

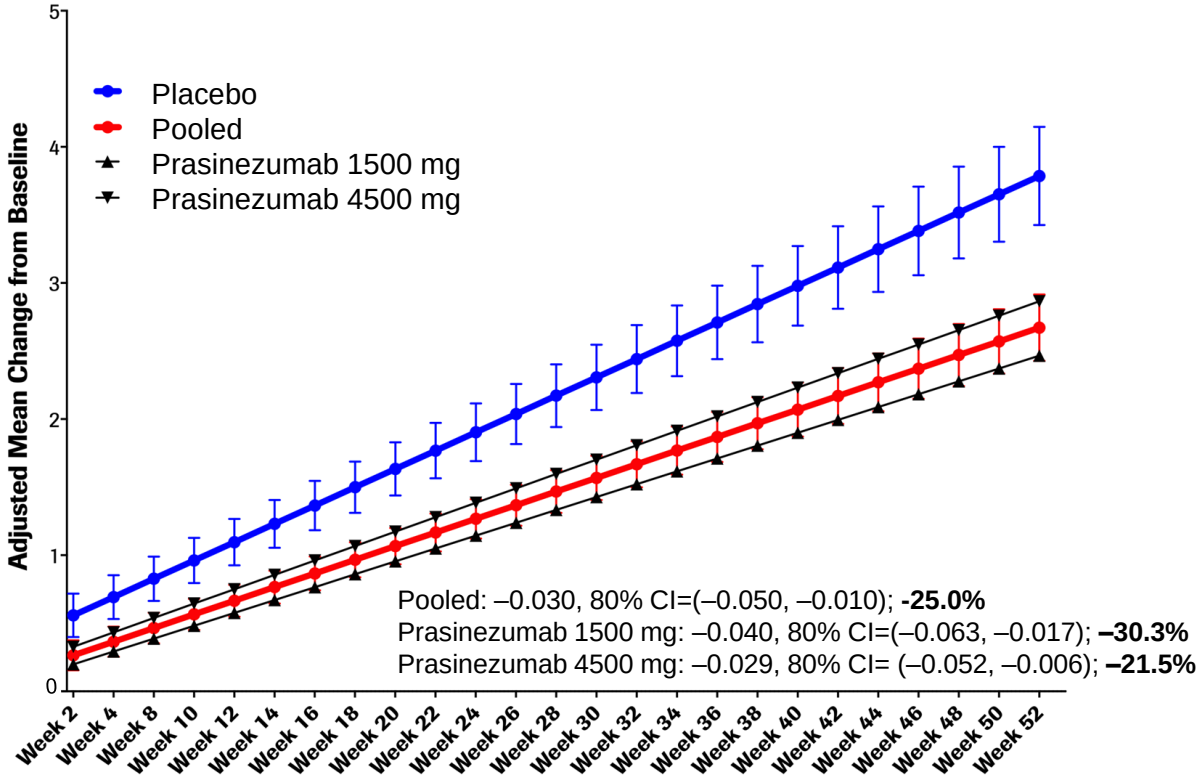
Reduced clinical decline confirmed by digital measures of progression (slope analysis)

Digital measures included in the Roche Parkinson's Disease Mobile Application v2

PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Arm Swing & Tremor	Mobility & Sociability
Daily	Daily	Daily

ACTIVE TESTS									
Bradykinesia			*Tremor/ Bradykinesia*	*Tremor*			*Rigidity/ Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

Digital PASADENA motor score



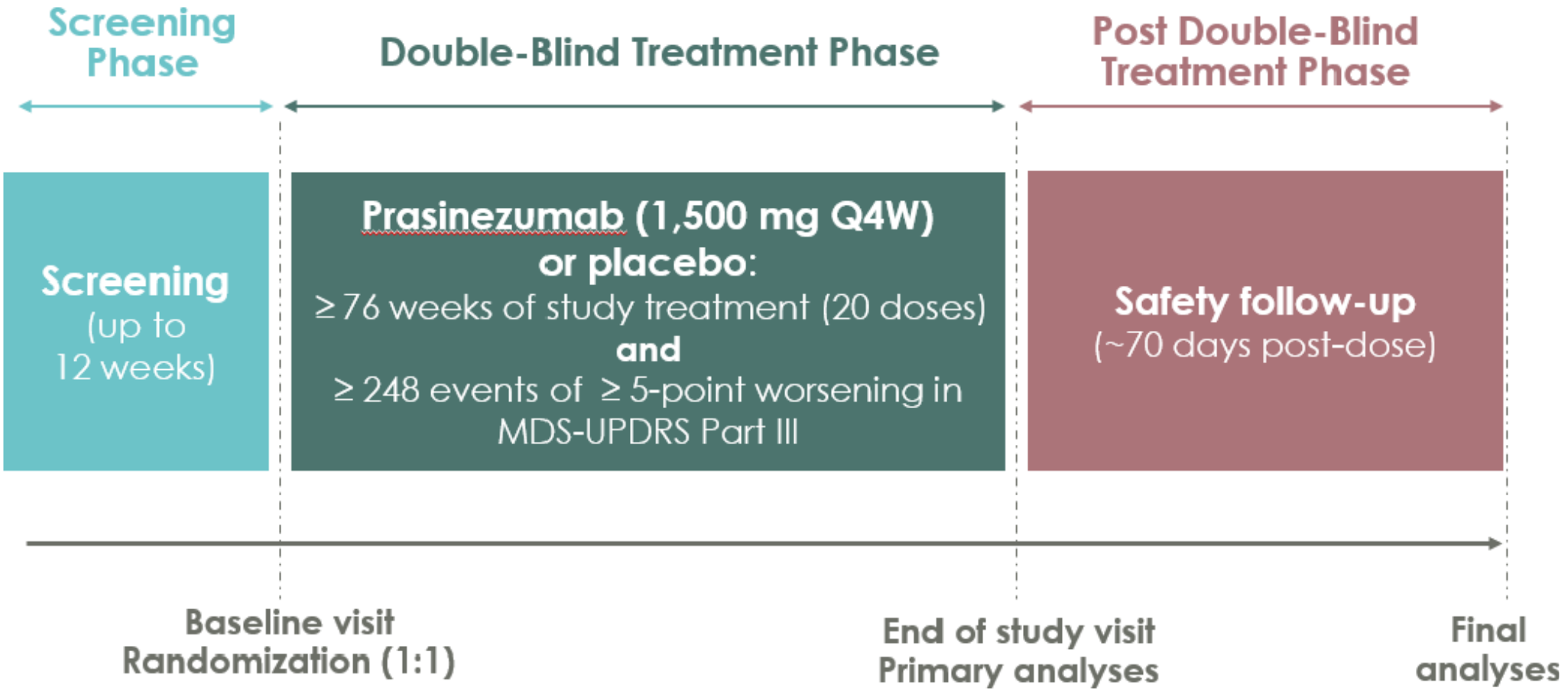
Pooled dose analysis is a prespecified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg.
The digital PASADENA motor score was built from 80% bradykinesia features and 20% resting tremor features using blinded data from 150 PASADENA patients prior to unblinding.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

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

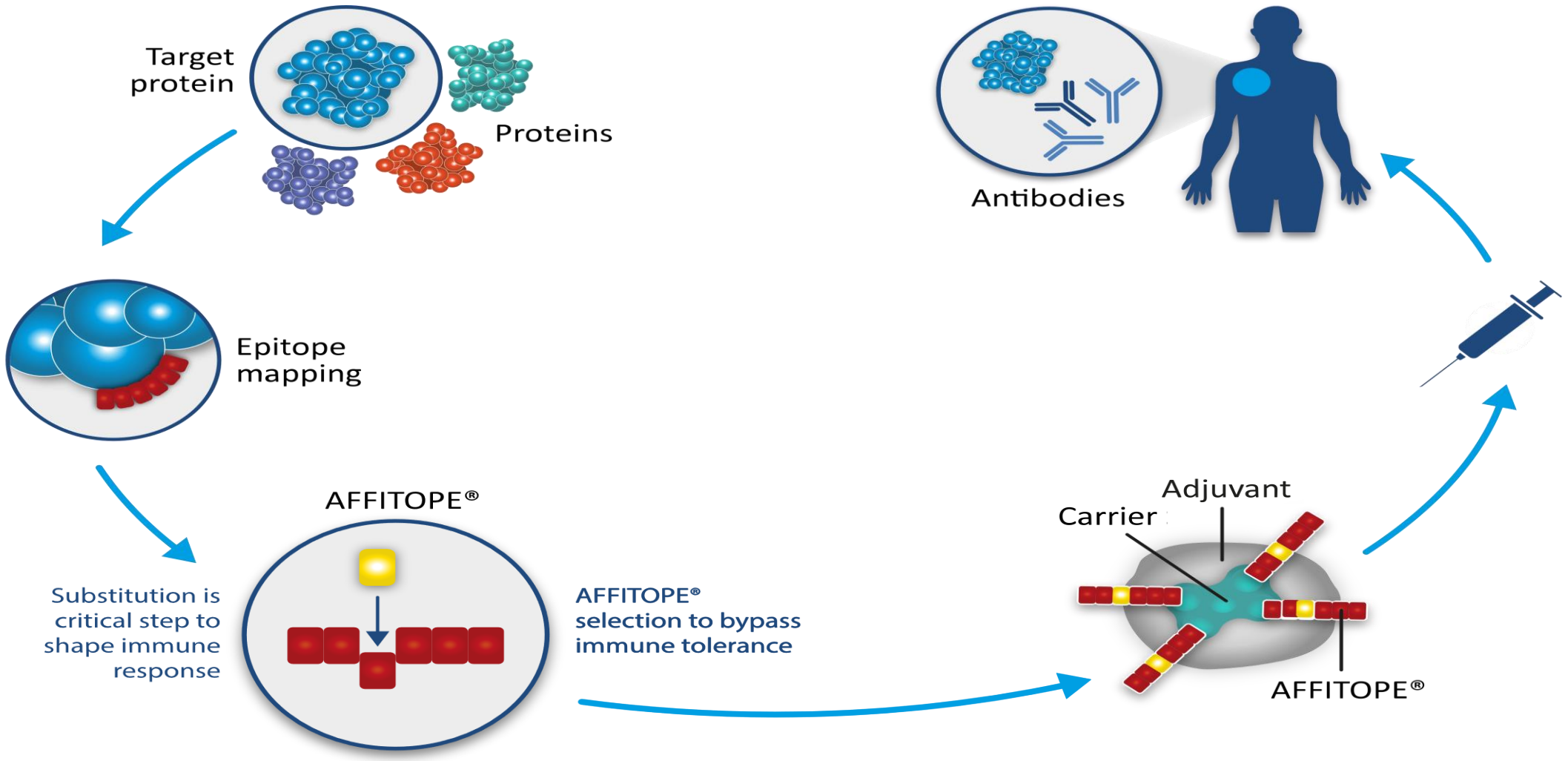
ClinicalTrials.gov Identifier: NCT04777331

Recruitment Status : Recruiting
First Posted : March 2, 2021
Last Update Posted : September 20, 2021

See **Contacts and Locations**



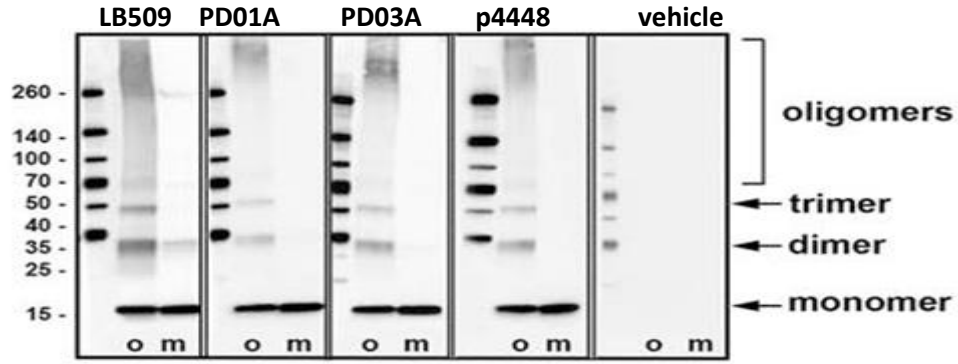
AFFITOPE® Immunisation Technology



Courtesy AFFiRiS

PD01A and PD03A-induced antibodies cross-react with α-Syn species

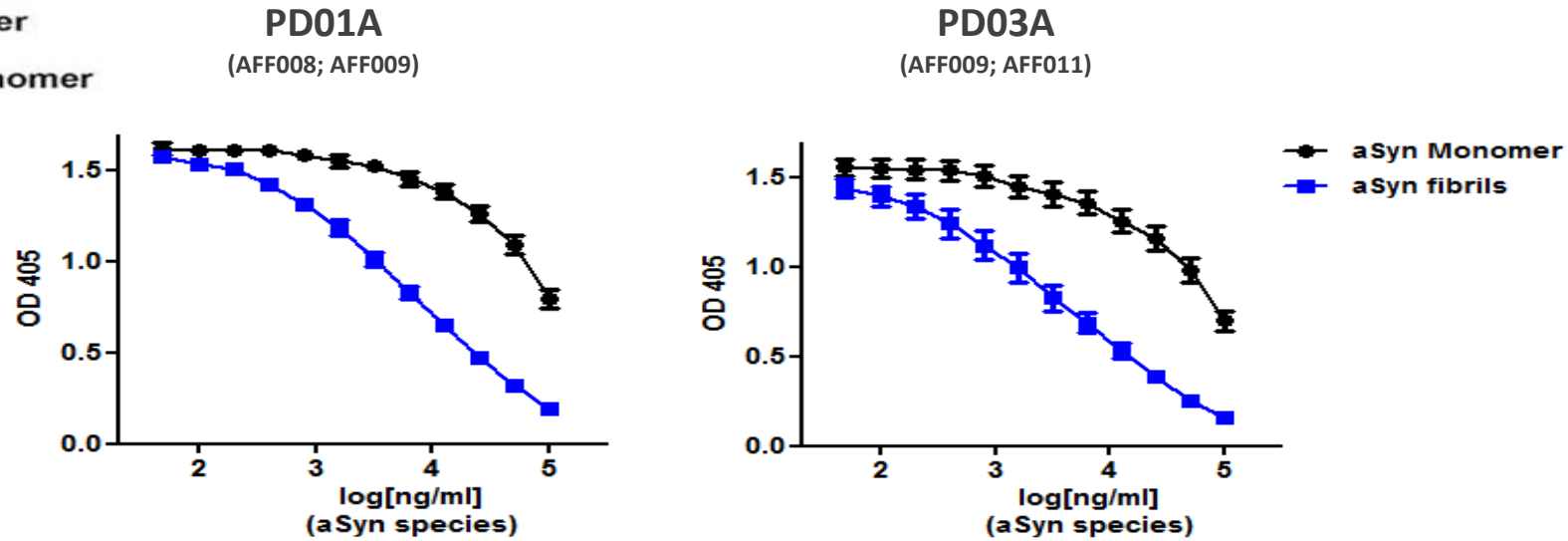
Abs reactivity assessed by WB analysis



p4448: αSyn original epitope

Mandler et al. Acta Neuropath 2014

Preferential binding of AFFITOPE-induced Abs



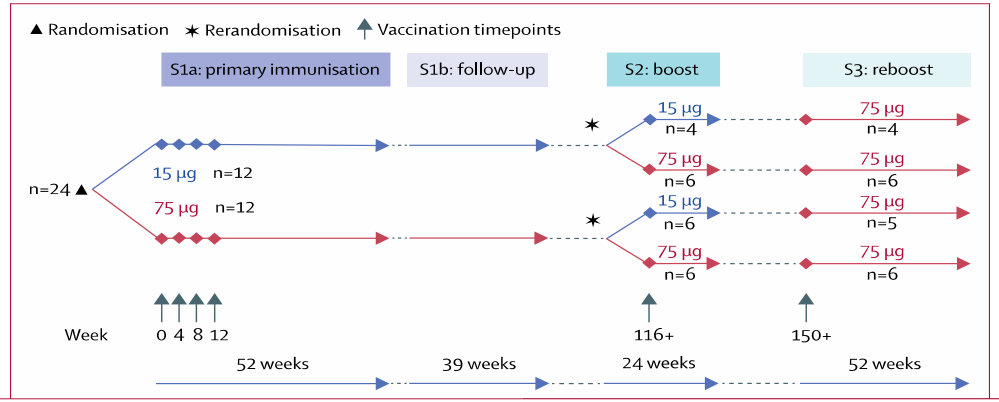
Sabine Schmidhuber & Dorian Winter

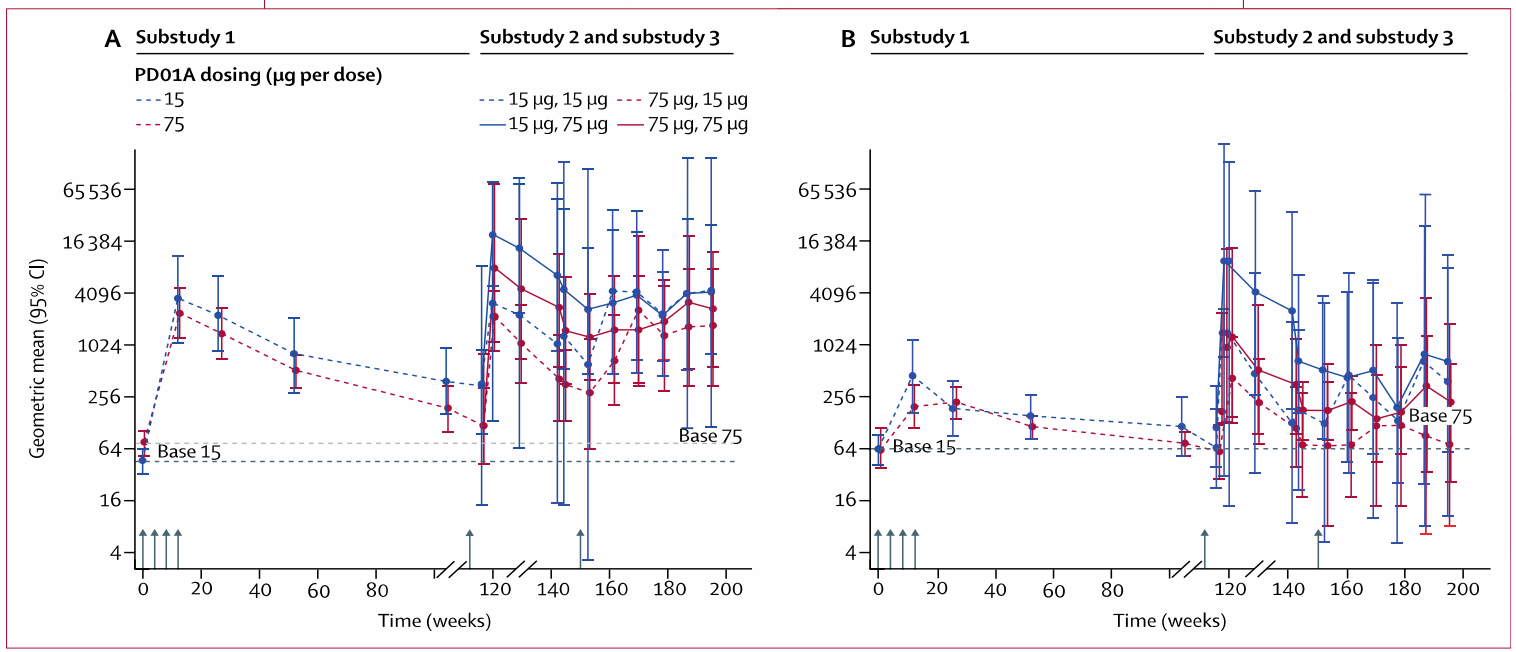
PD01A- and PD03A-induced Abs bind preferentially to aggregates/fibrils over the monomeric form of α-Syn

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

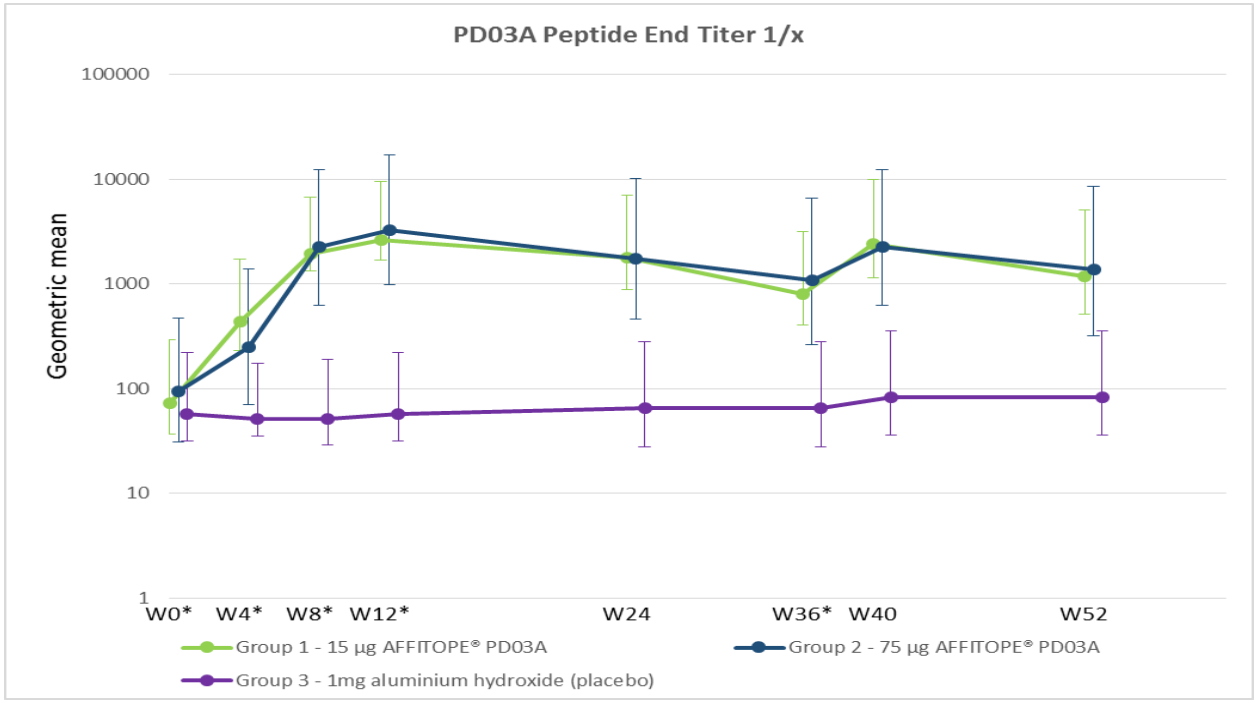
Lancet Neurol 2020; 19: 591–600

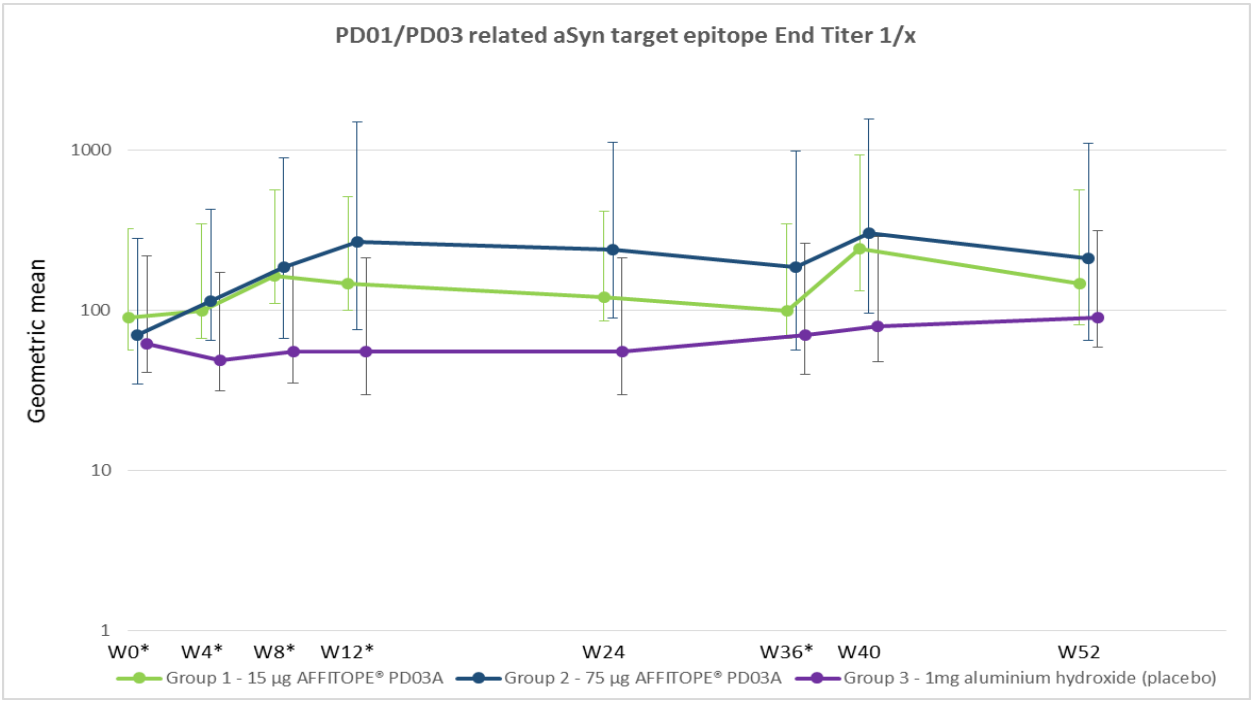
Dieter Volc, Werner Poewe, Alexandra Kutzelnigg, Petra Lührs, Caroline Thun-Hohenstein, Achim Schneeberger, Gergana Galabova, Nour Majbour, Nishant Vaikath, Omar El-Agnaf, Dorian Winter, Eva Mihailovska, Andreas Mairhofer, Carsten Schwenke, Günther Staffler, Rossella Medori





AFF 011 Trial: Immunological Response





- **PD03A is immunogenic and boostable in early PD patients**
- **Cross-reactivity against original aSYN epitope is higher in the 75µg group**

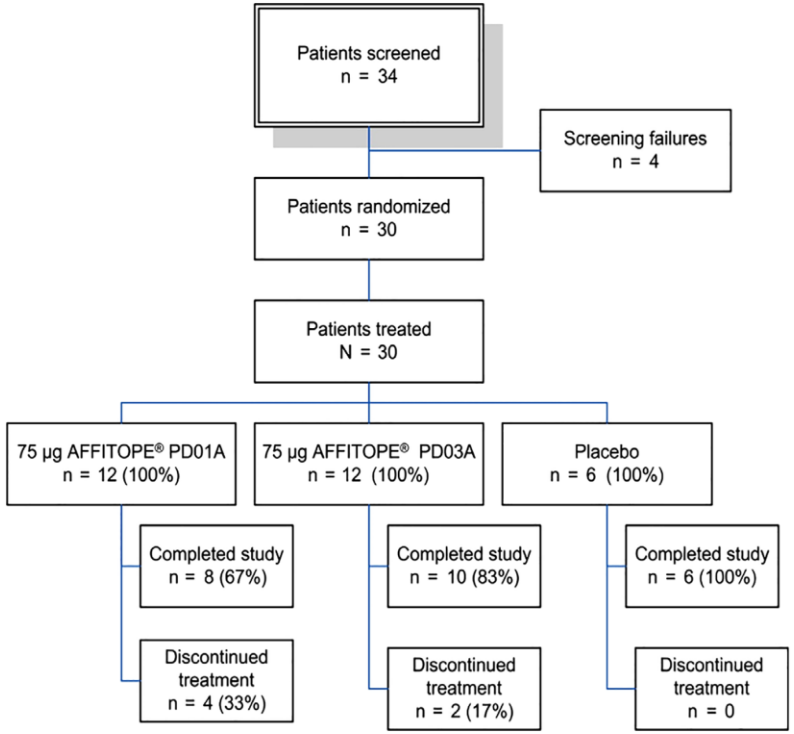
Poewe & al; J Park Dis 2021

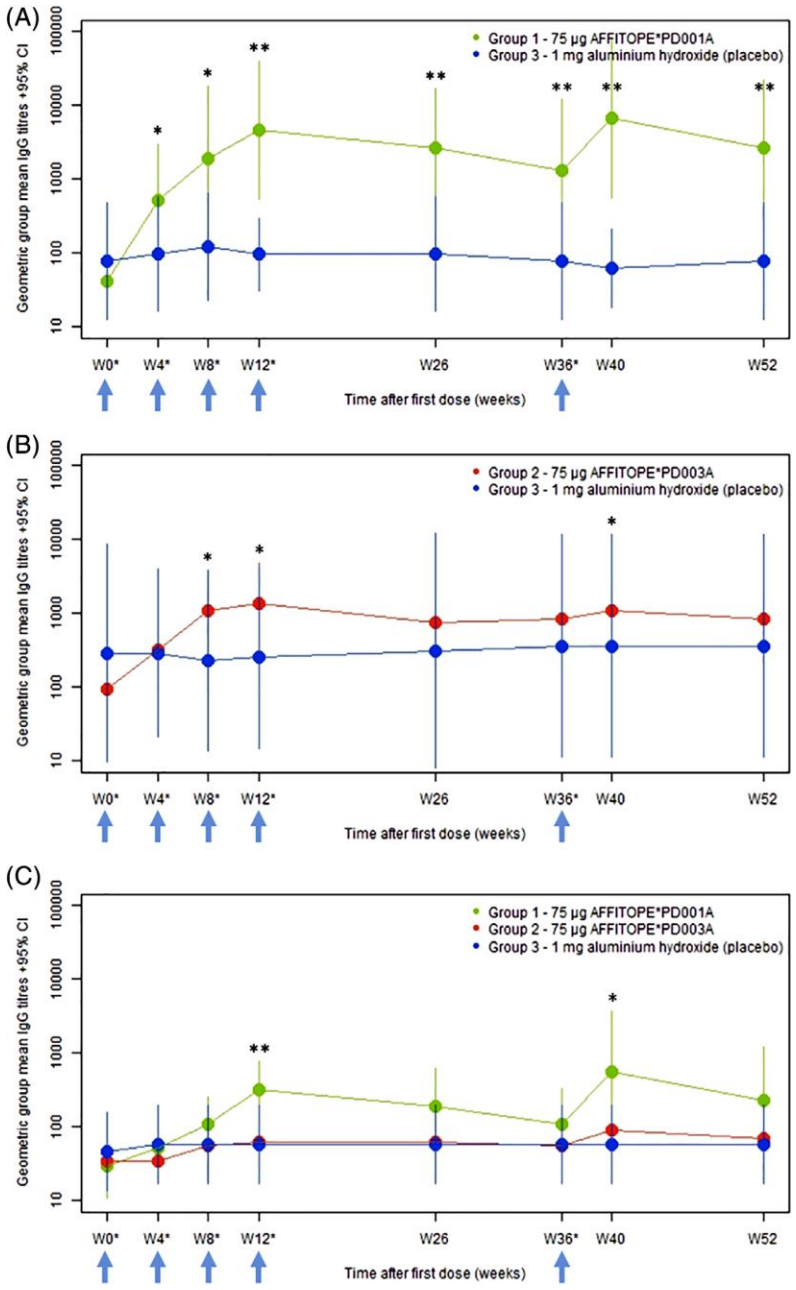
RESEARCH ARTICLE

A Phase 1 Randomized Trial of Specific Active α-Synuclein Immunotherapies PD01A and PD03A in Multiple System Atrophy

Wassilios G. Meissner, MD, PhD,[1,2,3,4*] Anne Pavy-Le Traon, MD, PhD,[5] Alexandra Foubert-Samier, MD, PhD,[1,6] Gergana Galabova, PhD,[7†] Monique Galitzky, MD,[8] Alexandra Kutzelnigg, MD,[7] Brice Laurens, MD,[1] Petra Lührs, PhD,[7] Rossella Medori, MD,[7] Patrice Péran, PhD,[9] Umberto Sabatini, MD,[10] Sylvain Vergnet, MD,[1] Dieter Volc, MD,[11] Werner Poewe, MD,[12] Achim Schneeberger, MD,[7‡] Günther Staffler, PhD,[7] and Olivier Rascol, MD, PhD,[13] on behalf of the AFF009 Study Investigators

Movement Disorders, Vol. 35, No. 11, 2020





SUMMARY

- α-synuclein proteostasis is a key target for DMT‘s in PD
- Immunotherapy able to target polymeric (aggregated) α-synuclein
  - reduces α-syn-burden, cell-to cell-transmission and motor deficits in experimental models
- Two phase 2b RCT‘s with monoclonal α-syn-AB‘s in early PD show
  - satisfactory safety
  - disappointing efficacy results (negative on primary outcomes, efficacy signals on secondary motor outcomes in PASADENA)
- Phase 1 active anti-α-syn-immunization studies in PD and MSA show safety and proof of principle
- Persistent uncertainty ref target population (prodromal, early or advanced PD) and outcome measures

AFF 011 Trial: Safety

- Most common AEs were local reactions (89% of subjects, no difference between active and placebo), mostly mild to moderate
- 8 SAEs in 5 patients (15µg: 4; 75µg: 0; Placebo: 4), none related to IMP
- No severe systemic reaction
- No Suspected Unexpected Serious Adverse Reaction (SUSAR)
- No safety signal in laboratory results
- No signs of encephalitic response (clinic & radiology)

Poewe & al; J Park Dis 2021