Immunotherapy for Parkinson's disease

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disclosures:

- Dr. Quinn has received compensation from Prothena/Roche for serving as a site investigator for clinical trials of immunotherapy for Parkinson’s disease.

Frequently asked questions:

- Why passive (ie, monoclonal antibodies) rather than active (ie, vaccination) immunotherapy?
- Does a large molecule like an immunoglobulin get across the blood-brain barrier?
- Will the complications of immunotherapy seen in Alzheimer's disease be a problem in Parkinson's disease?
- What evidence is there that this approach will actually work?

outline

- Brief history of immunotherapy for neurodegenerative disease
- Review of published results of immunotherapy trials in Parkinson’s
- Review of trials currently under way

outline

- ***Brief history of immunotherapy for neurodegenerative disease***
- Review of published results of immunotherapy trials in Parkinson's
- Review of trials currently under way

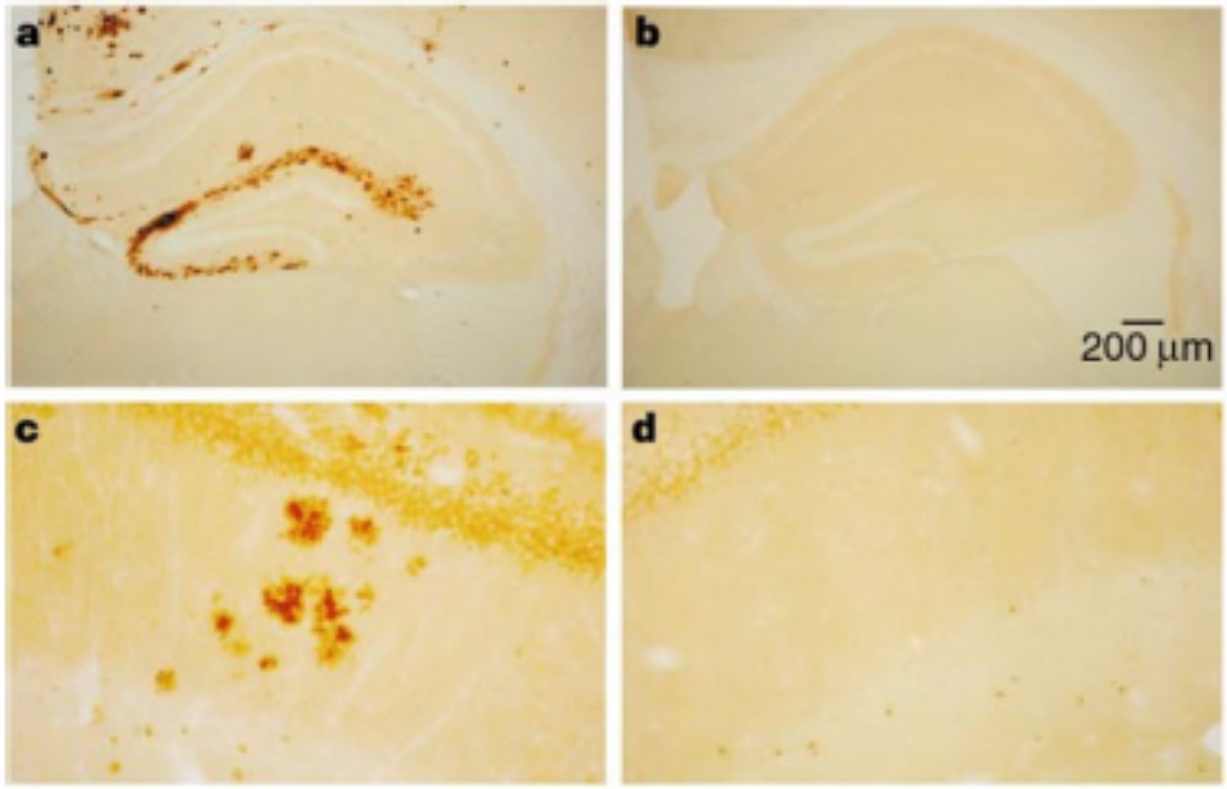
History of immunotherapy in neurodegeneration:

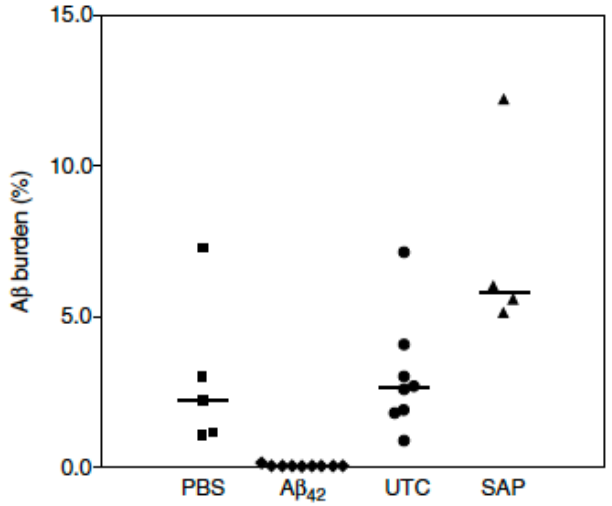
Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

NATURE | VOL 400 | 8 JULY 1999 | www.nature.com



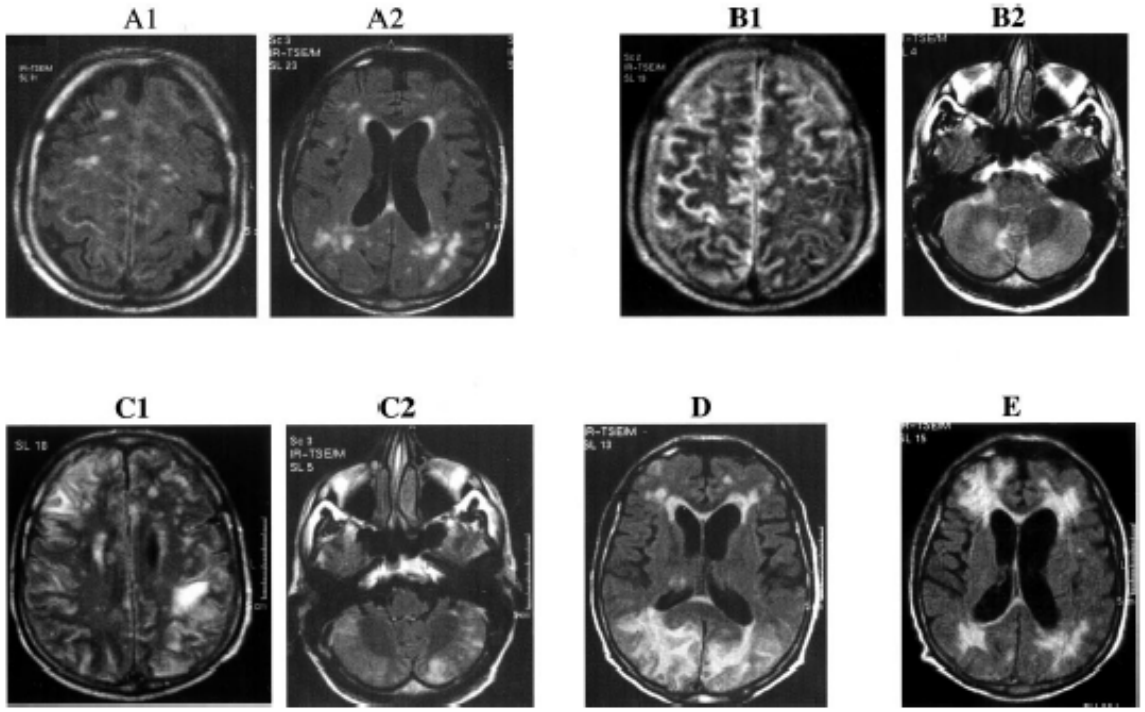


History of immunotherapy in neurodegeneration:

Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization

J.-M. Orgogozo, MD; S. Gilman, MD, FRCP; J.-F. Dartigues, MD, PhD; B. Laurent, MD; M. Puel, MD; L.C. Kirby, MD; P. Jouanny, MD, PhD; B. Dubois, MD; L. Eisner, MD; S. Flitman, MD; B.F. Michel, MD; M. Boada, MD; A. Frank, MD, PhD; and C. Hock, MD

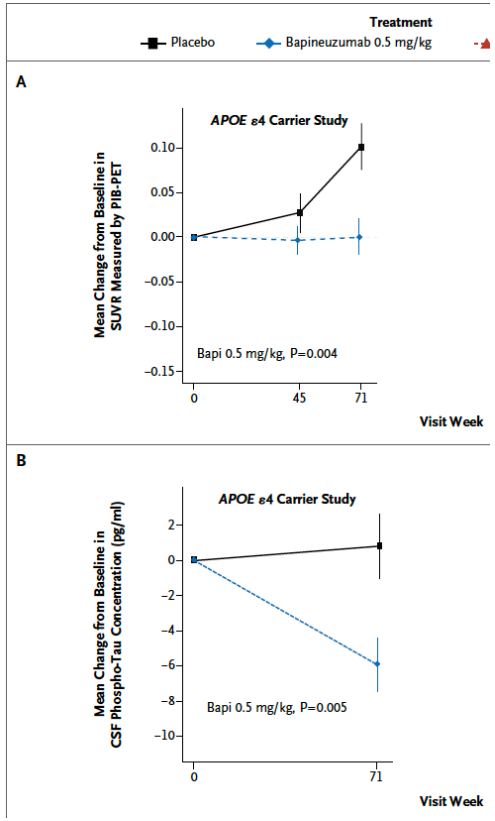
NEUROLOGY 2003;61:46–54

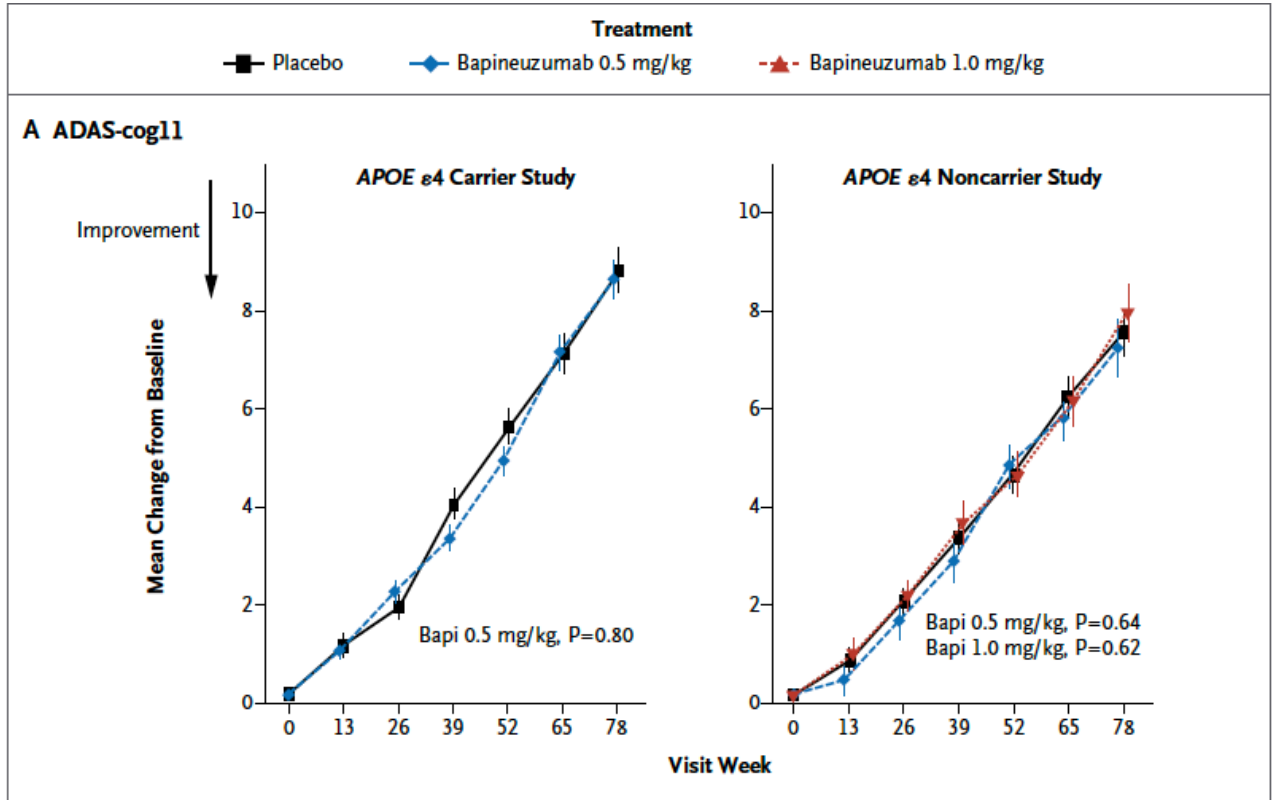


Early studies in AD: effects on biomarkers but not on clinical outcomes:

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

N ENGL J MED 370;4 NEJM.ORG JANUARY 23, 2014





Passive immunotherapy also carries risks:

Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup

Reisa A. Sperling[a,b,*], Clifford R. Jack, Jr.,[c], Sandra E. Black[d], Matthew P. Frosch[e], Steven M. Greenberg[f], Bradley T. Hyman[g], Philip Scheltens[h], Maria C. Carrillo[i], William Thies[i], Martin M. Bednar[j], Ronald S. Black[k], H. Robert Brashear[l], Michael Grundman[m], Eric R. Siemers[n], Howard H. Feldman[o,p], Rachel J. Schindler[q]

Alzheimer's & Dementia 7 (2011) 367–385

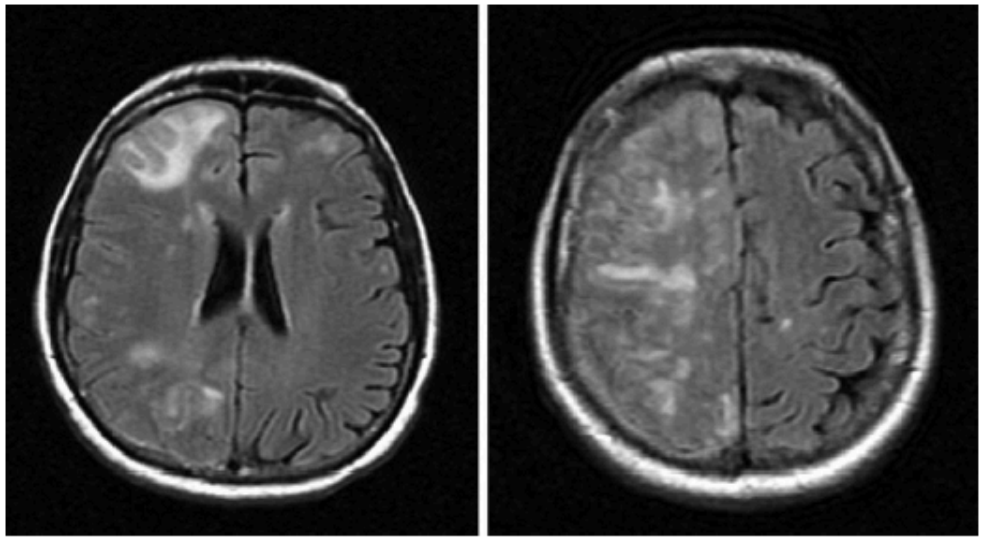


Fig. 1. ARIA-E which occurred during a monoclonal antibody trial, as seen on fluid attenuation inversion recovery (FLAIR) magnetic resonance images d onstrating increased signal in multiple regions of the right hemisphere affecting both gray and white matter.

Edema

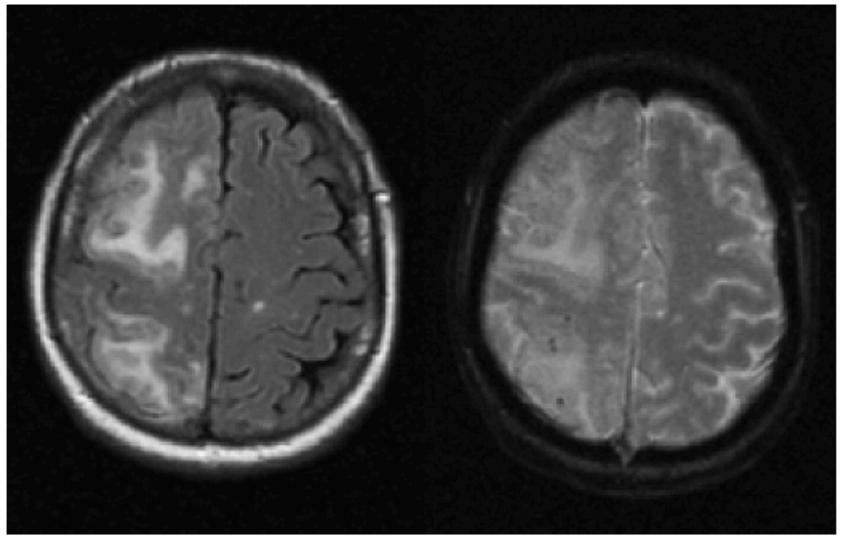


Fig. 5. Relationship between ARIA-E and ARIA-H. Left, FLAIR image demonstrating ARIA-E with increased signal in white and gray matter and sulcal effacement in right frontal and parietal regions. Right, GRE image showing mH (ARIA-H) in right parietal region only.

edema plus hemorrhage

These complications are thought to be related to antibody effects on vascular Abeta.
Most are not associated with clinical signs or symptoms

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

50 | NATURE | VOL 537 | 1 SEPTEMBER 2016

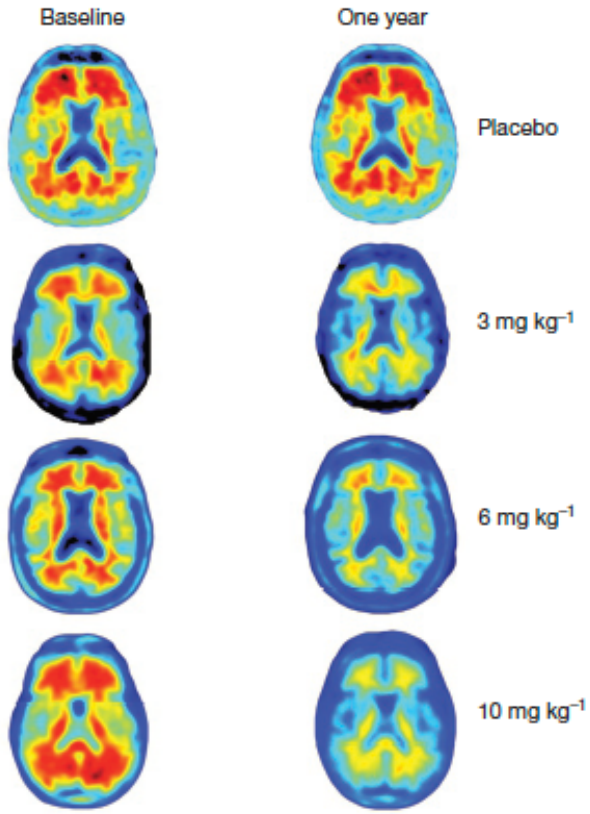
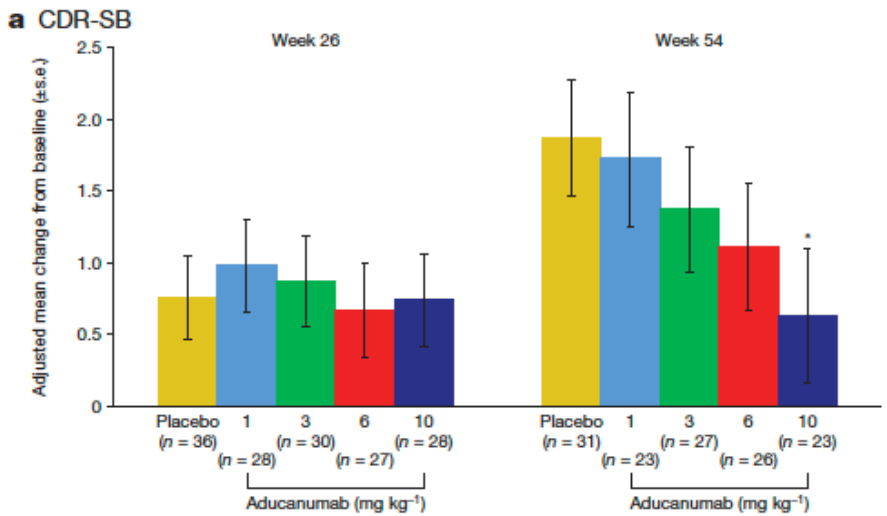


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chos



How is aducanumab different?

- Epitope? Trial design? Trial execution?
- Dose:
  - prior antibody studies: 0.5-1 mg/kg
  - aducanumab: 1-10 mg/kg
- Also dose –dependent toxicity:

Table 2 | Summary of adverse events and most common adverse events

		Aducanumab			
Adverse event (*n* (%))	Placebo ($n=40$)	1 mg kg^{-1} ($n=31$)	3 mg kg^{-1} ($n=32$)	6 mg kg^{-1} ($n=30$)	10 mg kg^{-1} ($n=32$)
Any adverse event	39 (98)	28 (90)	27 (84)	28 (93)	29 (91)
Serious event	15 (38)	3 (10)	4 (13)	4 (13)	12 (38)
Discontinuing treatment due to an adverse event	4 (10)	3 (10)	2 (6)	3 (10)	10 (31)
Common adverse events					
ARIA	2 (5)	2 (6)	4 (13)	11 (37)	15 (47)

History of immunotherapy in AD

- 1999- animal study demonstrating efficacy of vaccination
- 2002- clinical trial complication of auto-immune encephalitis described
- 2005-2018-monoclonal antibody trials
  - BBB penetration (about 0.1% of blood levels)
  - Effects on biomarkers
  - Reversible complication of ARIA
  - No clinical benefit
- 2016-aducanumab shows clinical efficacy in phase 2
- 2019-aducanumab shows clinical efficacy in Phase 3
- 2020- Biogen plans to file with the FDA in latter half of 2020

outline

- Brief history of immunotherapy for neurodegenerative disease
- ***Review of published results of immunotherapy trials in Parkinson's***
- Review of trials currently under way

JAMA Neurology | Original Investigation

Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti–α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease

A Randomized Clinical Trial

Joseph Jankovic, MD; Ira Goodman, MD; Beth Safirstein, MD; Tonya K. Marmon, DrPH; Dale B. Schenk, PhD; Martin Koller, MD, MPH; Wagner Zago, PhD; Daniel K. Ness, DVM, PhD; Sue G. Griffith, MD, PhD, MRCP; Michael Grundman, MD, MPH; Jay Soto, BS; Susanne Ostrowitzki, MD, PhD; Frank G. Boess, PhD; Meret Martin-Facklam, PhD; Joseph F. Quinn, MD; Stuart H. Isaacson, MD; Omid Omidvar, MD; Aaron Ellenbogen, DO; Gene G. Kinney, PhD

JAMA Neurol. 2018;75(10):1206-1214.

IMPORTANCE Aggregated α-synuclein is believed to be central to the pathogenesis of Parkinson disease (PD). PRX002/RG7935 (PRX002) is a humanized monoclonal antibody designed to target aggregated forms of α-synuclein, thereby inhibiting neuron-to-neuron transfer of presumed pathogenic forms of α-synuclein, potentially resulting in neuronal protection and slowing disease progression.

INTERVENTIONS Participants were enrolled into 6 ascending-dose cohorts and randomly assigned to receive PRX002 (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg) or placebo. Participants received 3 intravenous infusions every 4 weeks of PRX002 or placebo and were monitored during a 24-week observational period.

Figure 1. CONSORT Flowchart

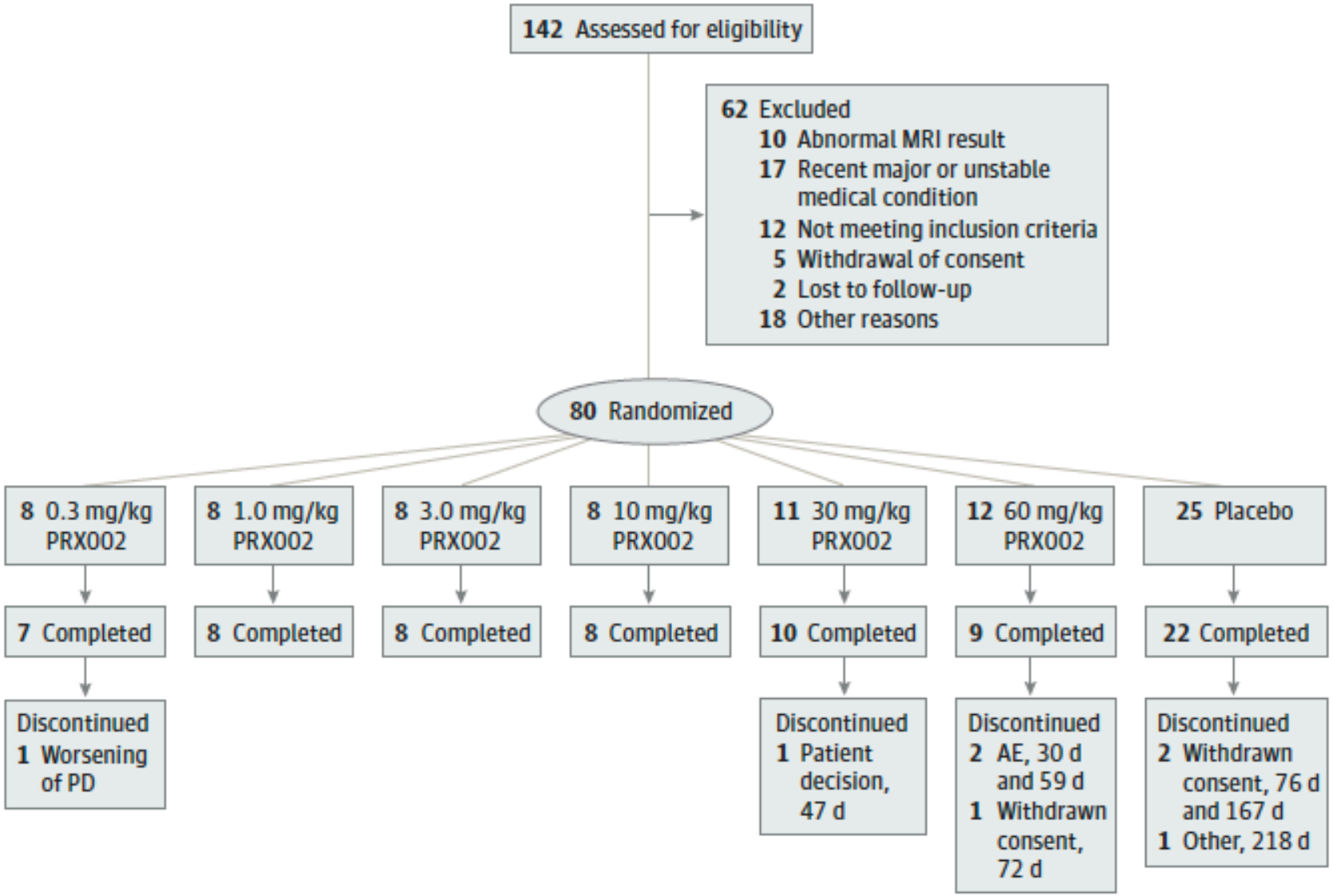


Table 1. Baseline Characteristics of Participants With Parkinson Disease

Characteristic	No. (%)								
		PRX002 Dose Level							
	Placebo (n = 25)	0.3 mg/kg (n = 8)	1 mg/kg (n = 8)	3 mg/kg (n = 8)	10 mg/kg (n = 8)	30 mg/kg (n = 11)	60 mg/kg (n = 12)	Total (n = 55)	All Participants (n = 80)
Age, median (range), y	58.0 (47-77)	56.0 (43-78)	64.0 (48-74)	58.0 (43-73)	59.5 (51-65)	53.0 (43-73)	55.0 (46-73)	57.0 (43-78)	58.0 (43-78)
Sex									
Male	24 (96.0)	6 (75.0)	5 (62.5)	6 (75.0)	7 (87.5)	7 (63.6)	9 (75.0)	40 (72.7)	64 (80.0)
Female	1 (4.0)	2 (25.0)	3 (37.5)	2 (25.0)	1 (12.5)	4 (36.4)	3 (25.0)	15 (27.3)	16 (20.0)
Race									
White	24 (96.0)	7 (87.5)	8 (100)	8 (100)	8 (100)	11 (100)	12 (100)	54 (98.2)	78 (97.5)
Asian	1 (4.0)	0	0	0	0	0	0	0	1 (1.3)
Black or African American	0	1 (12.5)	0	0	0	0	0	1 (1.8)	1 (1.3)
Body weight, median (range), kg	79.4 (59-117)	82.3 (65-96)	70.3 (46-87)	74.7 (63-100)	84.8 (65-106)	73.9 (52-99)	79.5 (59-106)	75.3 (46-106)	78.7 (46-117)
Time since onset of symptoms, median (range), y	7.1 (1-24)	4.2 (2-10)	5.4 (3-18)	4.7 (3-13)	5.0 (2-9)	3.0 (2-8)	4.2 (2-17)	4.2 (2-18)	4.6 (1-24)
Time since diagnosis of PD, median (range), y	3.9 (1-15)	2.8 (0-8)	2.5 (0-12)	2.5 (1-13)	3.5 (0-9)	2.2 (1-6)	3.1 (1-15)	3.0 (0-15)	3.2 (0-15)
Hoehn and Yahr stage									
Stage 1	3 (12.0)	0	1 (12.5)	1 (12.5)	1 (12.5)	3 (27.3)	1 (8.3)	7 (12.7)	10 (12.5)
Stage 2	18 (72.0)	6 (75.0)	3 (37.5)	6 (75.0)	6 (75.0)	7 (63.6)	11 (91.7)	39 (70.9)	57 (71.3)
Stage 3	4 (16.0)	2 (25.0)	4 (50.0)	1 (12.5)	1 (12.5)	1 (9.1)	0	9 (16.4)	13 (16.3)
Total MDS-UPDRS score, mean (range)	48.5 (19-98)	55.8 (41-71)	43.9 (15-71)	52.4 (22-87)	41.5 (11-59)	40.5 (14-57)	50.6 (24-75)	47.3 (11-87)	47.7 (11-98)
Previous use of dopaminergic medications	24 (96.0)	7 (87.5)	5 (62.5)	8 (100)	5 (62.5)	9 (81.8)	10 (83.3)	44 (80.0)	68 (85.0)

Abbreviations: MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PD, Parkinson disease.

Table 2. Treatment-Emergent Adverse Events Occurring in at Least 5% of Participants

Adverse Event	No. (%)							
		PRX002 Dose Level						
	Placebo (n = 25)	0.3 mg/kg (n = 8)	1 mg/kg (n = 8))	3 mg/kg (n = 8)	10 mg/kg (n = 8)	30 mg/kg (n = 11)	60 mg/kg (n = 12)	Total (n = 55)
AEs[a]	17 (68.0)	4 (50.0)	5 (62.5)	5 (62.5)	4 (50.0)	10 (90.9)	9 (75.0)	37 (67.3)
Treatment-related AEs	3 (12.0)	1 (12.5)	0	1 (12.5)	1 (12.5)	0	4 (33.3)	7 (12.7)
TEAEs								
Constipation	0	0	0	1 (12.5)	2 (25.0)	2 (18.2)	0	5 (9.1)
Infusion-related reaction	0	0	0	0	0	0	4 (33.3)[b,c]	4 (7.3)
Diarrhea	0	0	2 (25.0)	1 (12.5)[b]	0	0	0	3 (5.5)
Headache	2 (8.0)	1 (12.5)[b]	1 (12.5)	0	1 (12.5)	0	0	3 (5.5)
Peripheral edema	0	0	0	0	1 (12.5)	0	2 (16.7)	3 (5.5)
Postlumbar puncture syndrome	0	0	0	1 (12.5)	0	1 (9.1)	1 (8.3)	3 (5.5)
Upper respiratory tract infection	3 (12.0)	0	0	0	0	2 (18.2)	1 (8.3)	3 (5.5)

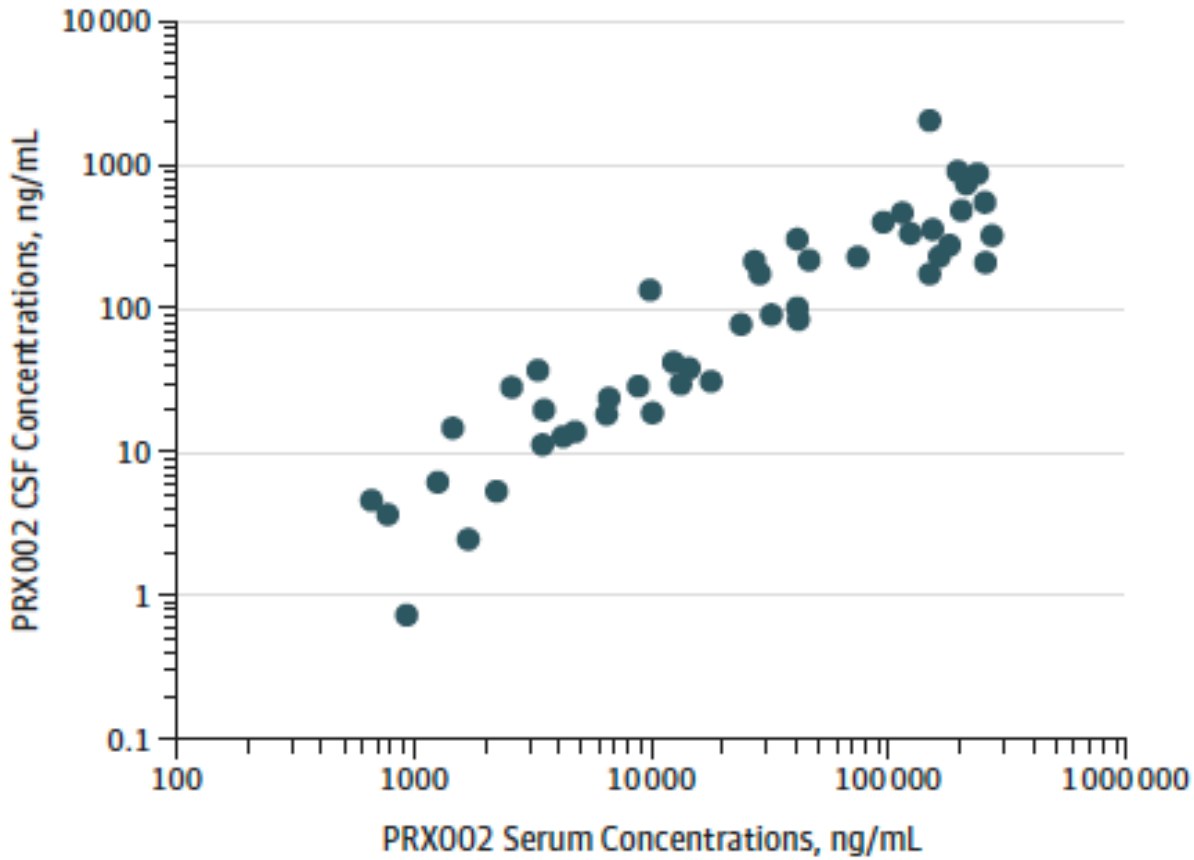
Abbreviations: AE, adverse events; TEAEs, treatment-emergent adverse events.

[a] Unless indicated, all adverse events were mild and were unrelated to study drug.

[b] Considered related to study drug.

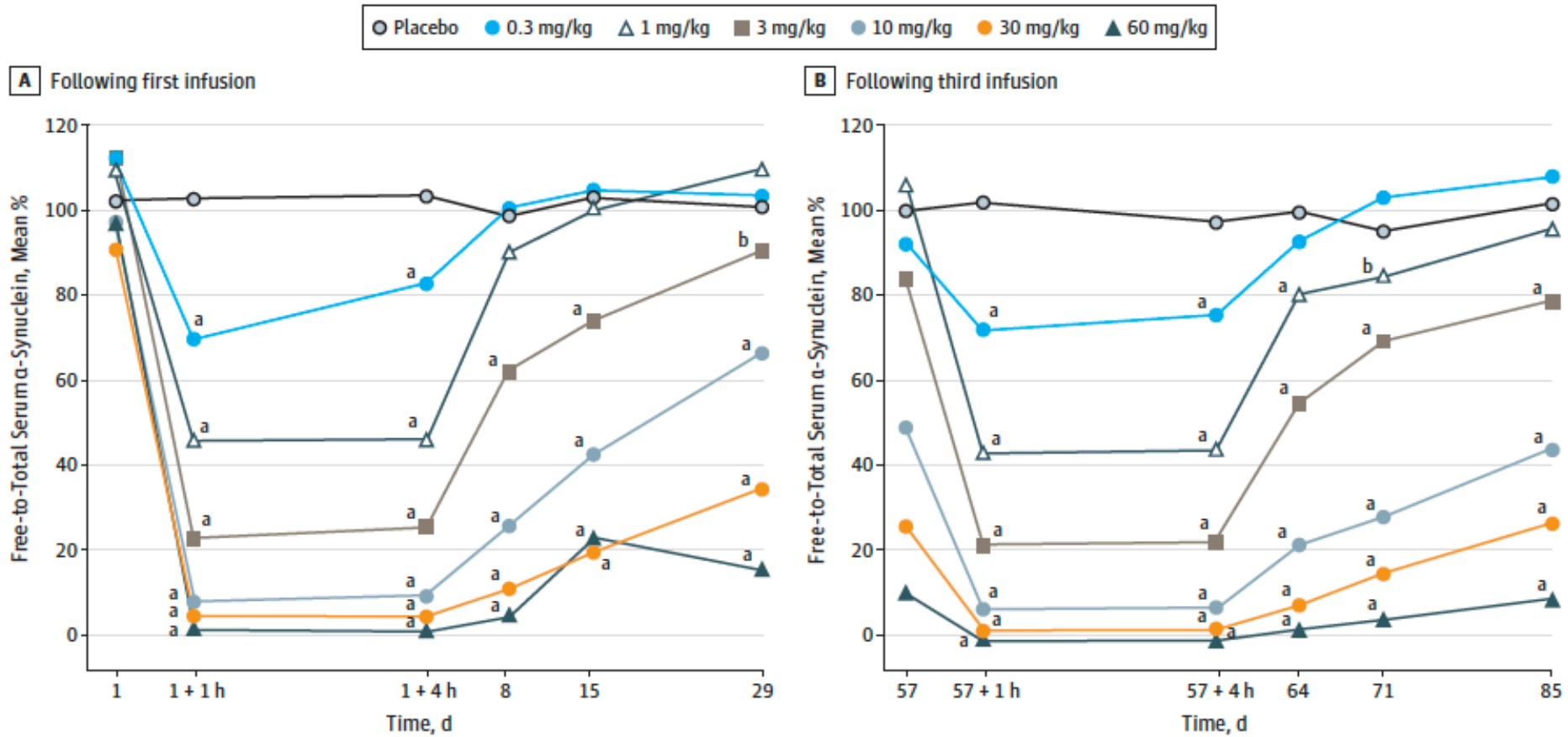
[c] Moderate PRX002-related AEs in 3 participants resulted in the discontinuation of 2 participants from the study.

Figure 2. Cerebrospinal Fluid (CSF) and Serum PRX002 Concentrations Approximately 9 Weeks After the First Infusion



Study drug was administered at baseline, week 4, and week 8. The ratio of CSF to serum concentrations was approximately the same across all dose levels.

Figure 3. Pharmacodynamics of Free-to-Total Serum α-Synuclein



Pharmacodynamics after the first (A) and third (B) infusions of PRX002. Data represent free serum α-synuclein levels normalized to total α-synuclein. *P* values represent statistical significance compared with placebo.

[a] $P < .001$.

[b] $P < .05$.

Randomized Phase I Clinical Trial of Anti–α-Synuclein Antibody BIIB054

Miroslaw Brys, MD, PhD,[1*] Laura Fanning, MD,[1] Serena Hung, MD,[1] Aaron Ellenbogen, MD,[2,3] Natalia Penner, PhD,[1] Minhua Yang, MS,[1] Mackenzie Welch,[1] Erica Koenig, PhD,[1] Eric David,[1] Tara Fox, MS,[4] Shavy Makh, MS,[4] Jason Aldred, MD,[5] Ira Goodman, MD,[6] Blake Pepinsky, PhD,[1] YuTing Liu, MD,[1] Danielle Graham, PhD,[1] Andreas Weihofen, PhD,[1] and Jesse M. Cedarbaum, MD[1]

Movement Disorders, Vol. 34, No. 8, 2019

Methods: A total of 48 healthy volunteers (age 40–65, 19 women) and 18 Parkinson's disease participants (age 47–75, 5 women, Hoehn and Yahr stage ≤2.5) were in the study. Volunteers were enrolled into 6 single-dose cohorts of BIIB054 (range 1–135 mg/kg) or placebo, administered intravenously; Parkinson's disease participants received a single dose of BIIB054 (15 or 45 mg/kg) or placebo. All participants

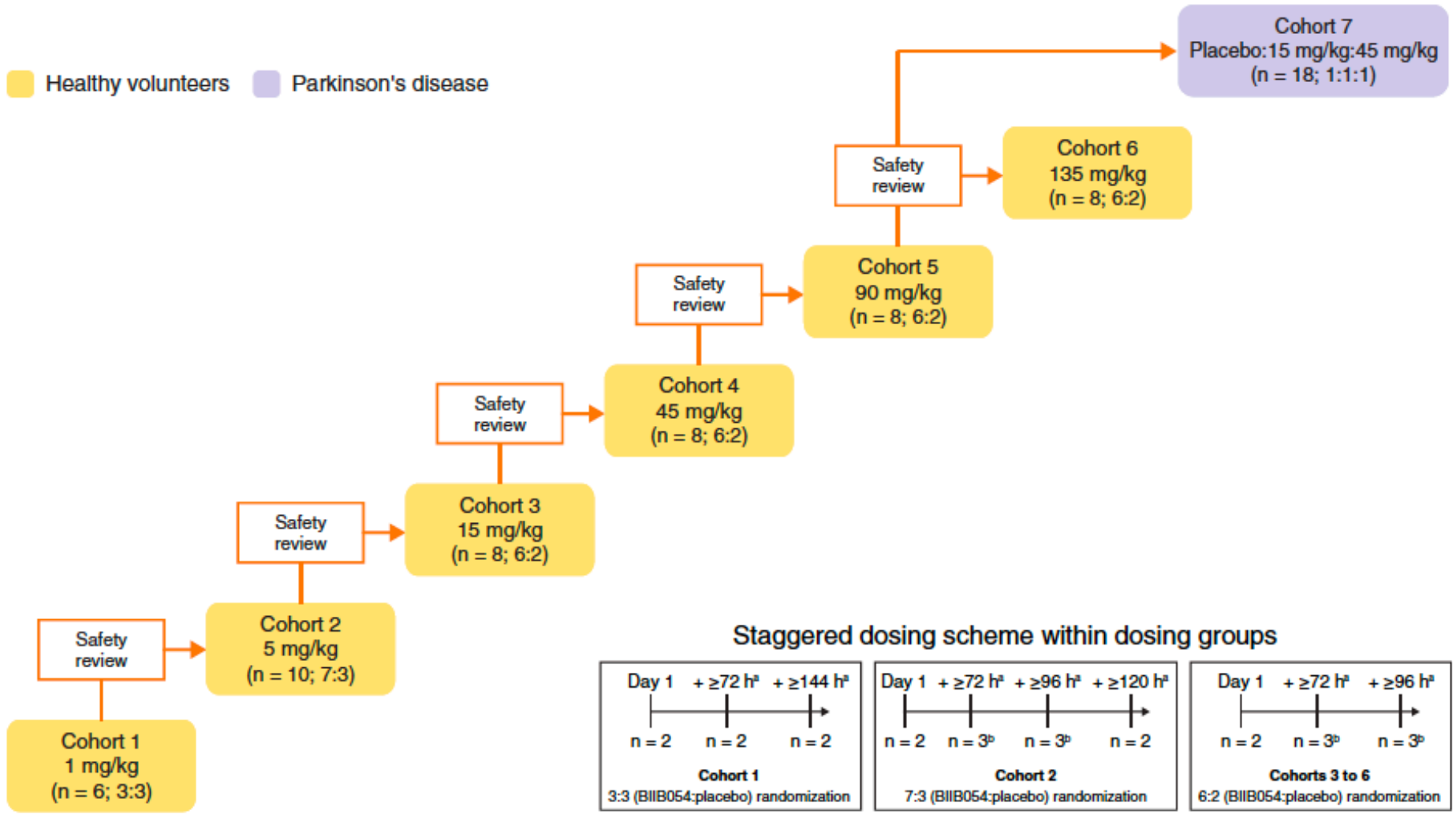


FIG. 1. Study design. Staggered dosing was not used in cohort 7. [a]Time from completion of dosing of first participant within same cohort. [b]Up to 3 participants.

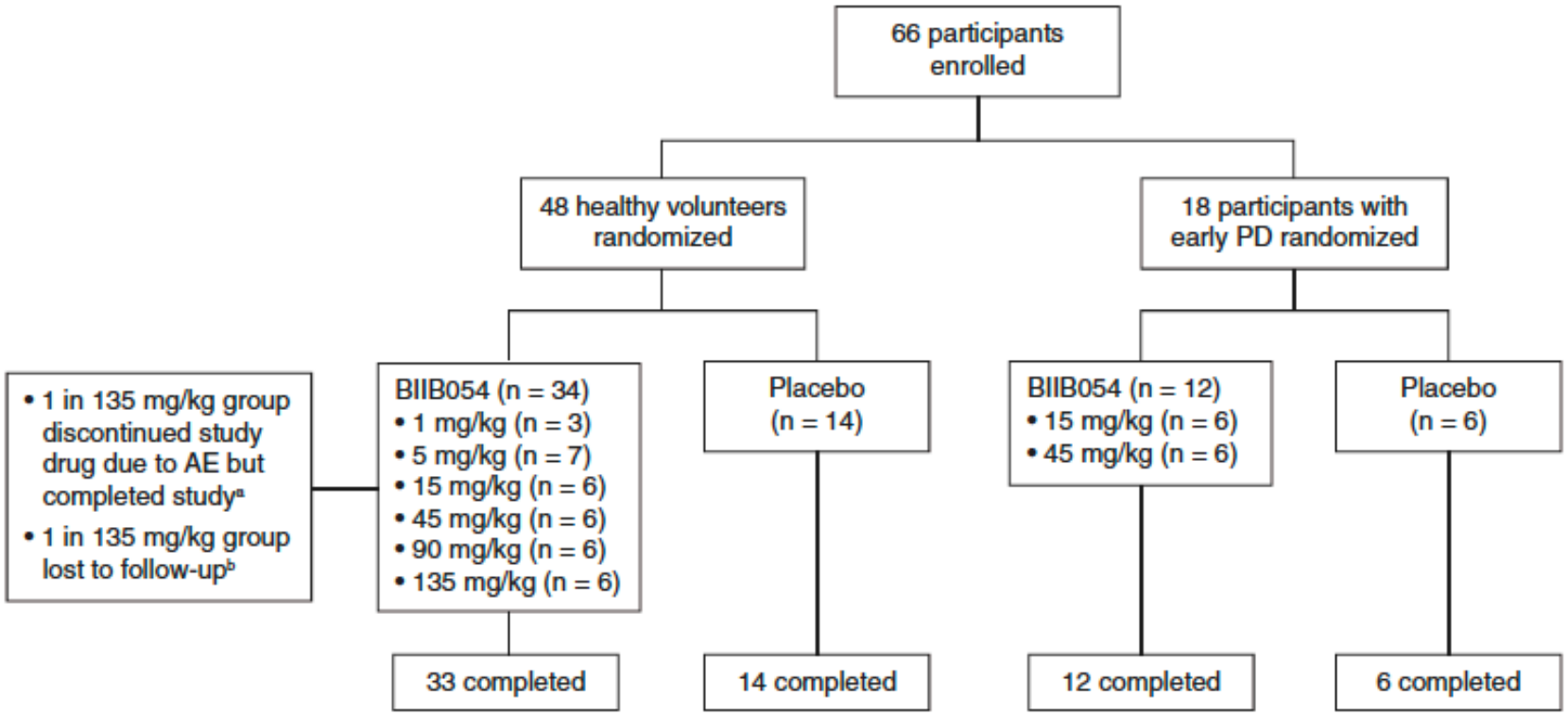


FIG. 2. Patient disposition. [a]Participant received 32% of BIIB054 dose because of grade 1 hypersensitivity reaction but completed study. [b]Participant could not be contacted after the week 3 visit despite multiple phone calls and certified letters, was listed as lost to follow-up, and did not complete the study. AE, adverse event; PD, Parkinson's disease.

TABLE 1. Baseline characteristics

Characteristic	Healthy volunteers							Participants with PD		
		BIIB054							BIIB054	
	Placebo, n = 14	1 mg/kg, n = 3	5 mg/kg, n = 7	15 mg/kg, n = 6	45 mg/kg, n = 6	90 mg/kg, n = 6	135 mg/kg, n = 6	Placebo, n = 6	15 mg/kg, n = 6	45 mg/kg, n = 6
Age, y, mean (range)	53.5 (40–65)	51.0 (46–59)	50.6 (43–61)	45.0 (41–52)	53.0 (48–63)	48.2 (40–60)	51.2 (43–59)	66.2 (51–75)	63.7 (51–72)	57.7 (47–69)
Male, n (%)	8 (57)	1 (33)	3 (43)	4 (67)	4 (67)	4 (67)	5 (83)	4 (67)	4 (67)	5 (83)
Race, n (%)										
White	10 (71)	1 (33)	4 (57)	5 (83)	6 (100)	4 (67)	6 (100)	6 (100)	6 (100)	6 (100)
Black/African American	4 (29)	2 (67)	3 (43)	1 (17)	0	2 (33)	0	0	0	0
Weight, kg, mean	79.74	79.97	74.37	78.32	78.88	78.23	70.43	82.42	84.75	80.53
BMI, kg/m^2, mean (range)	26.57 (22.7–30.2)	26.92 (25.7–27.6)	25.67 (20.5–30.9)	26.57 (22.6–28.8)	27.17 (26.2–28.3)	27.06 (22.9–29.7)	24.44 (21.5–29.6)	26.75 (23.8–30.0)	27.39 (24.4–29.5)	25.83 (21.2–31.8)
H&Y score, n (%)										
1	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (17)	2 (33)
2	NA	NA	NA	NA	NA	NA	NA	6 (100)	5 (83)	4 (67)
MDS-UPDRS, mean/median (range)										
I	NA	NA	NA	NA	NA	NA	NA	4.7/2.5 (1–14)	5.7/5.0 (2–12)	6.3/5.5 (0–16)
II	NA	NA	NA	NA	NA	NA	NA	7.8/7.5 (2–14)	3.8/4.0 (1–6)	6.7/6.0 (1–17)
III	NA	NA	NA	NA	NA	NA	NA	27.5/29.5 (12–39)	24.2/24.0 (14–33)	20.2/19.0 (9–37)
IV	NA	NA	NA	NA	NA	NA	NA	1.3/0.0 (0–6)	0.5/0.0 (0–3)	0.5/0.0 (0–3)
Symptomatic treatment, n (%)	NA	NA	NA	NA	NA	NA	NA	4 (67)	3 (50)	2 (33)
Carbidopa/levodopa								2	2	0
Rasagiline								1	1	1
Both								1	0	1

BMI, body mass index; H&Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorders Society–Unified Parkinson's Disease Rating Scale; NA, not available; PD, Parkinson's disease.

TABLE 2. Adverse events

	Healthy volunteers								Participants with PD			
		BIIB054								BIIB054		
AE, n (%)	Placebo, n = 14	All, n = 34	1 mg/kg, n = 3	5 mg/kg, n = 7	15 mg/kg, n = 6	45 mg/kg, n = 6	90 mg/kg, n = 6	135 mg/kg, n = 6	Placebo, n = 6	All, n = 12	15 mg/kg, n = 6	45 mg/kg, n = 6
Any AE	7 (50)	19 (56)	1 (33)	4 (57)	2 (33)	2 (33)	5 (83)	5 (83)	6 (100)	9 (75)	5 (83)	4 (67)
AEs in ≥10% in placebo or all BIIB054												
Headache	4 (29)	8 (24)	1 (33)	2 (29)	0	1 (17)	3 (50)	1 (17)	2 (33)	4 (33)	2 (33)	2 (33)
Dizziness	2 (14)	5 (15)	1 (33)	1 (14)	0	1 (17)	1 (17)	1 (17)	0	0	0	0
Procedural pain	1 (7)	4 (12)	0	1 (14)	0	1 (17)	1 (17)	1 (17)	0	0	0	0
Back pain	1 (7)	2 (6)	0	0	0	0	1 (17)	0	0	2 (17)	1 (17)	1 (17)
Post–LP syndrome	0	0	0	0	0	0	0	0	0	2 (17)	1 (17)	1 (17)
Upper respiratory tract infection	0	0	0	0	0	0	0	0	0	2 (17)	1 (17)	1 (17)
CTCAE grade												
2	1 (7)[a]	5 (15)[b]	1 (33)[b]	0	1 (17)	0	3 (50)[b]	0	2 (33)[c]	4 (33)[d]	2 (33)[d]	2 (33)[d]
3	0	1 (3)[e]	0	0	0	0	0	1 (17)[e]	1 (17)[f]	0	0	0
AEs related to study treatment	2 (14)	4 (12)[g]	0	0	1 (17)	0	1 (17)	2 (33)[g]	1 (17)[f]	1 (8)	0	1 (17)
Serious AEs	0	1 (3)[e]	0	0	0	0	0	1 (17)[e]	1 (17)[f]	0	0	0

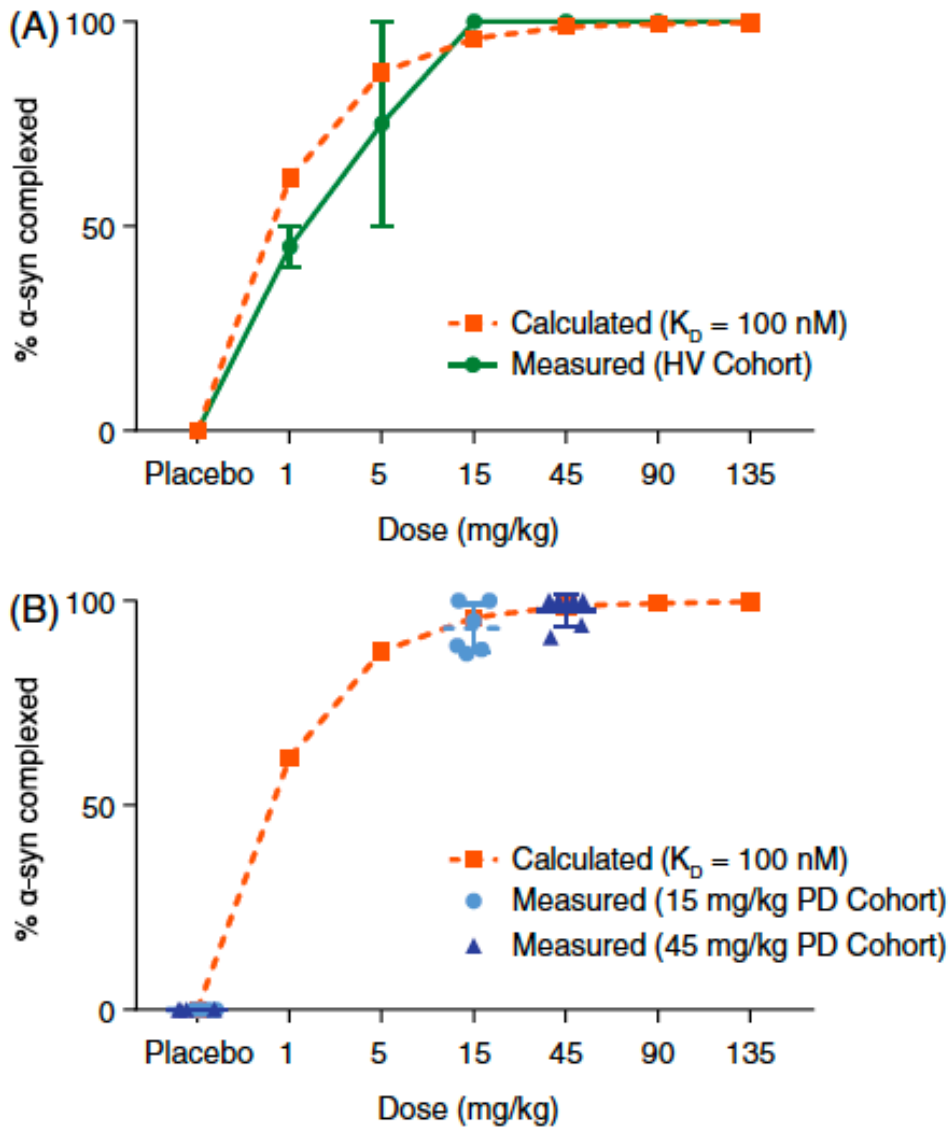


FIG. 3. Percent of total α-syn bound to BIIB054 in plasma at 48 hours postinfusion in (**A**) healthy volunteers and (**B**) participants with Parkinson's disease (PD). α-syn, α-synuclein.

Phase 1 antibody studies-conclusions :

- Encouraging safety profile, especially in light of complications seen with anti-amyloid immunotherapies
- High doses also tolerated—likely important for efficacy as suggested by anti-amyloid immunotherapies

- Maybe active immunization could be safe?

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

Lancet Neurol 2020; 19: 591–600

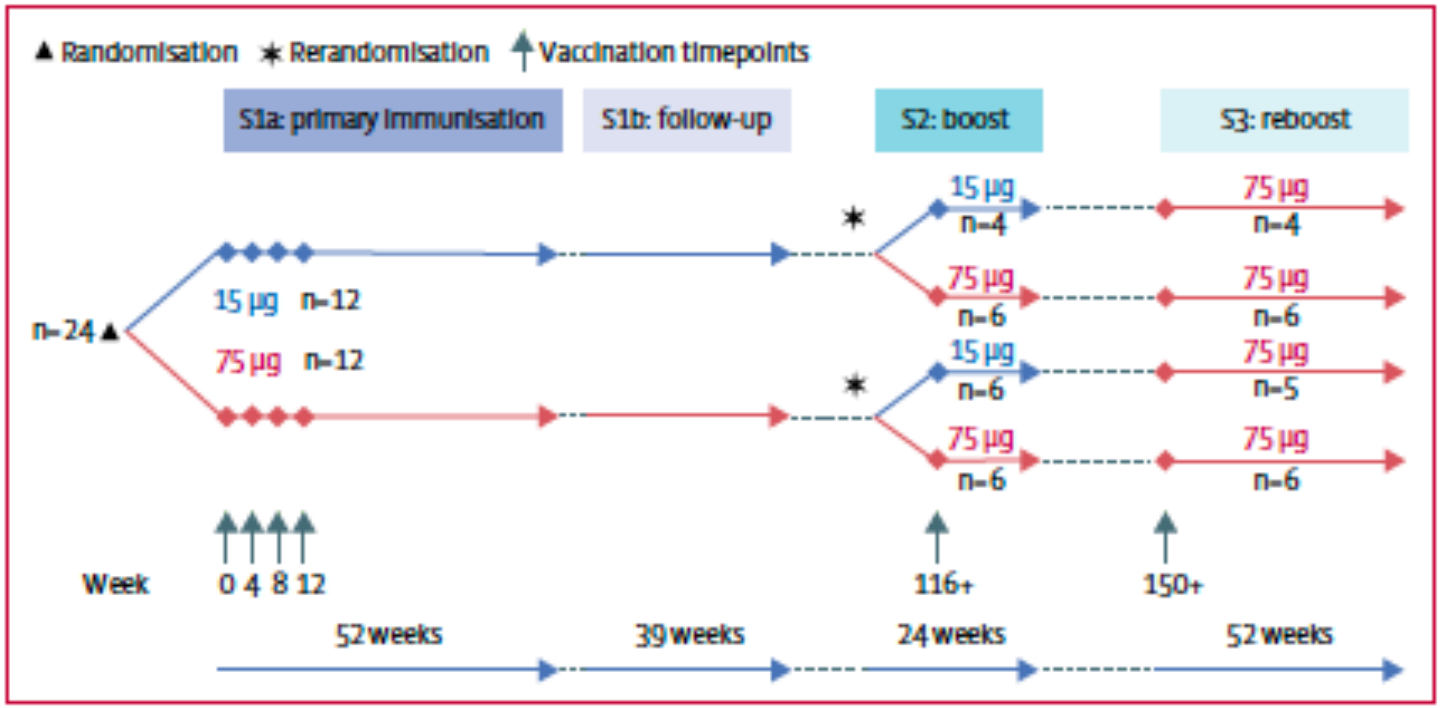
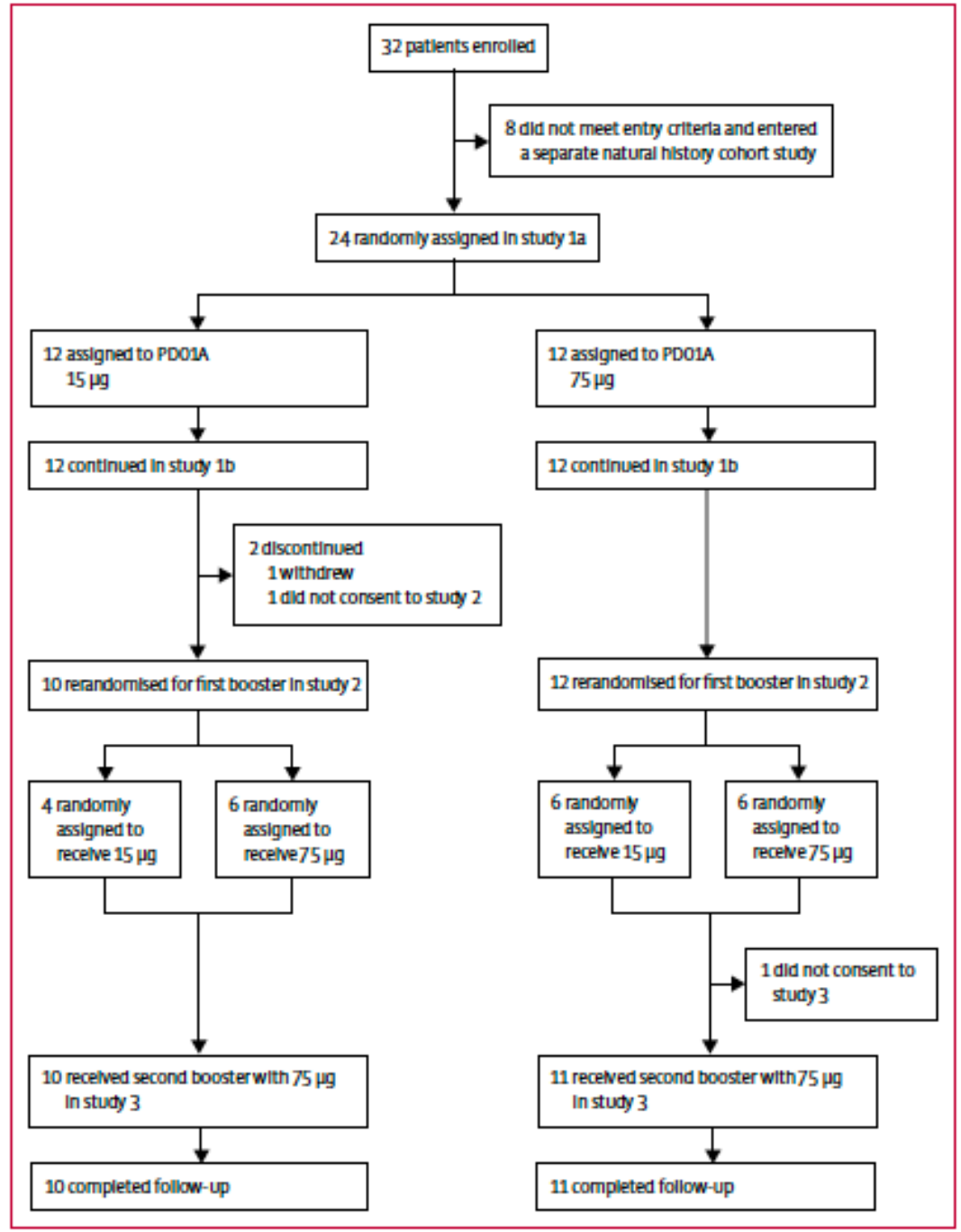


Figure 1: PD01A phase 1 study series schematic

Schematic is not drawn to scale. Blood sampling occurred at screening and weeks 0, 2, 4, 8, 12, 26, 40, and 52 of S1a; at weeks 0, 13, 26 and 39 of S1b; at screening and weeks 0, 2, 4, 12, and 24 of S2; at screening and months 0, 2, 4, 6, 8, 10, and 12 of S3. S1a=substudy 1a. S1b=substudy 1b. S2=substudy 2. S3=substudy 3.


32 patients enrolled
8 did not meet entry criteria and entered a separate natural history cohort study
24 randomly assigned in study 1a
12 assigned to PD01A 15 µg
12 assigned to PD01A 75 µg
12 continued in study 1b
12 continued in study 1b
2 discontinued
1 withdrew
1 did not consent to study 2
10 rerandomised for first booster in study 2
12 rerandomised for first booster in study 2
4 randomly assigned to receive 15 µg
6 randomly assigned to receive 75 µg
6 randomly assigned to receive 15 µg
6 randomly assigned to receive 75 µg
1 did not consent to study 3
10 received second booster with 75 µg in study 3
11 received second booster with 75 µg in study 3
10 completed follow-up
11 completed follow-up

	PD01A 15 µg (n=12)	PD01A 75 µg (n=12)
Age, years	55·4 (7·5)	53·9 (7·3)
Sex		
Male	8 (67%)	4 (33%)
Female	4 (33%)	8 (67%)
Weight, kg	86·9 (12·2)	75·0 (17·3)
Time since symptom onset, months	31·4 (15·4)	32·8 (16·6)
Hoehn and Yahr stage		
1·0 (unilateral disease)	9 (75%)	12 (100%)
1·5 (unilateral disease plus axial involvement)	3 (25%)	0
MDS-UPDRS scores		
Part 1a	0	0
Part 2	5·8 (1·0–16·0)	4·2 (0·0–11·0)
Part 3	11·9 (2·0–24·0)	12·3 (2·0–26·0)
Levodopa use	9 (75%)	7 (58%)
Months on treatment	13·6 (2·0–38·0)	11·7 (1·0–39·0)
Dopamine agonist use	9 (75%)	9 (75%)
Months on treatment	20·9 (1·0–57·0)	17·2 (2·0–59·0)
MAO-B inhibitor use	2 (17%)	1 (8%)
Months on treatment	17·5 (6·0–29·0)	6·0 (6·0–6·0)
Levodopa dose equivalent	432 (264)	344 (248)

Data are mean (SD), n (%), or mean (range). MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. MAO-B=monoamine oxidase B.

Table 1: **Baseline characteristics of all randomly assigned patients**

	15 µg PD01A (n=12)	75 µg PD01A (n=12)
Overall adverse event frequency	12 (100%)	12 (100%)
Treatment-related adverse events	11 (92%)	11 (100%)
Treatment-related severe adverse event	5 (42%)	3 (25%)
Serious adverse event	5 (42%)	2 (17%)
Treatment-related serious adverse event	0	0
Adverse event leading to withdrawal	0	0

Data are n (%). Pooled data are presented for the full follow-up (ie, across all substudies). Pooled treatment groups (pooled 15 µg and 75 µg) are presented based on the study dose given in substudy 1a, irrespective of their first booster dose in substudy 2.

Table 2: **Adverse events**

No MRI abnormalities emerged post baseline, with the exception of one microhaemorrhage in the 15 µg group, which was not considered related to the study drug. None of the patients developed meningoencephalitis and none of the immunisations resulted in a clinically detectable type 1 allergic reaction. DAT-SPECT examinations did not

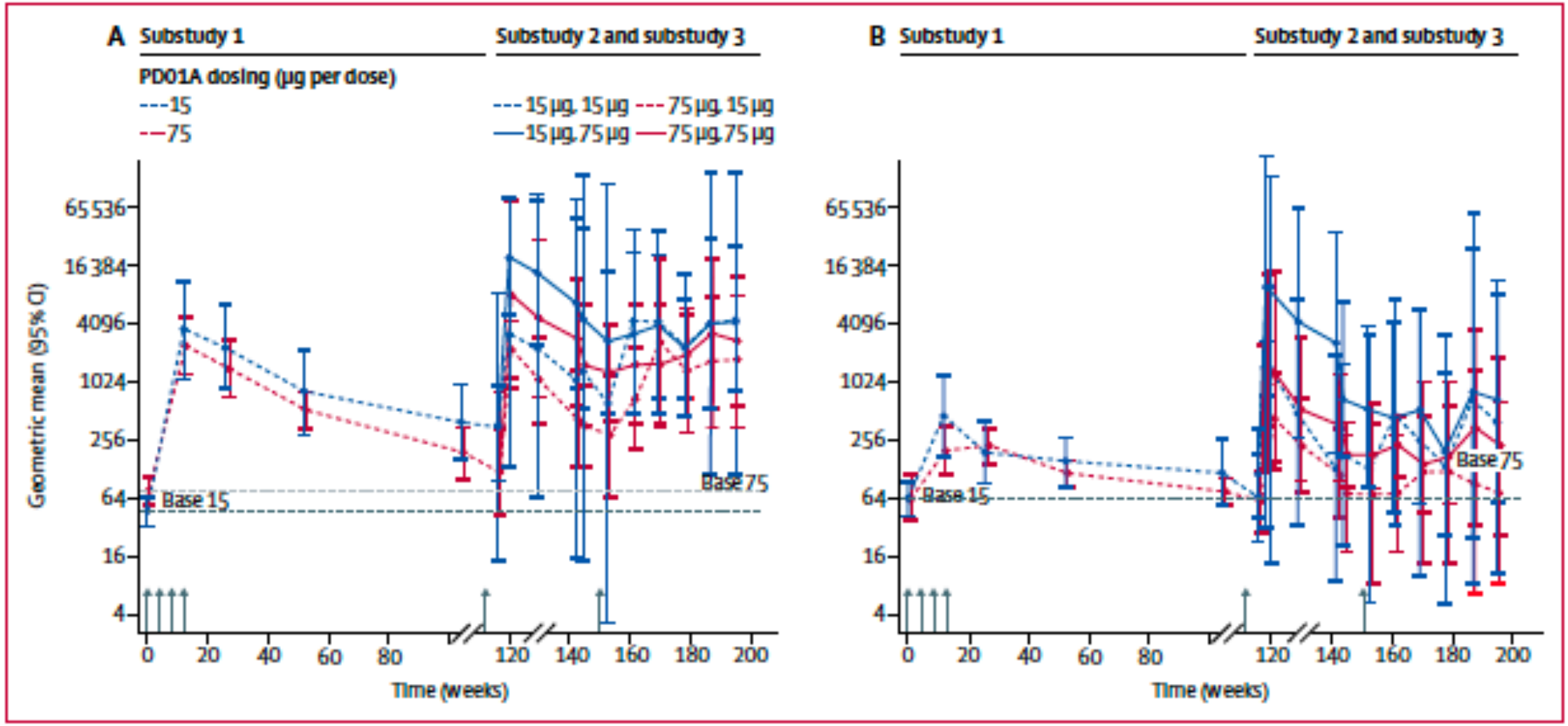


Figure 3: Geometric mean antibody titres over time for PD01 peptide (A) and for native target sequence on α-synuclein (B)

Hints of efficacy?

UPDRS:

Mean MDS-UPDRS part 3 scores in the pooled 15 µg group were 11·9 (SD 8·2) at baseline and 12·5 (14·8) at the last visit. In the pooled 75 µg group, MDS-UPDRS part 3 scores were 12·3 (7·2) at baseline and 8·6 (7·7) at the last visit. Levodopa dose equivalents increased from 355 mg at baseline to 587 mg at the final visit.

CSF synuclein:

Independent of the dose group, the concentration of total α-synuclein in CSF did not change after immunisation. However, post-hoc analysis of week 26 samples revealed a mean reduction of 51% in CSF oligomeric α-synuclein in patients immunised with the 75 µg dose. Treatment with the 15 µg dose also led to a slight decrease in the oligomeric α-synuclein (appendix p 5). Further

outline

- Brief history of immunotherapy for neurodegenerative disease
- Review of published results of immunotherapy trials in Parkinson's
- ***Review of trials currently under way***

According to www.clinicaltrials.gov:

	sponsor	drug	study
Passive immunotherapy (monoclonal antibody)	Roche (Prothena)	PRX002 prasinezumab	NCT03100149 Phase 2 “active, not recruiting”
“	Biogen	BIIB054	NCT03318523 “active, not recruiting”
“	Astra Zeneca	MEDI 1341	NCT03272165 Phase 1 “recruiting”
Active immunotherapy (vaccine)	AFFiRiS	Affitope PD01A	Multiple “completed”
“	AFFiRiS	Affitope PD03A	NCT02267434 “completed”
“	Center for Human Drug Research	UB312	NCT04075318 “recruiting” (healthy and PD)

Back to the FAQ's:

- Why passive?
  - Because of the adverse effects of active immunization in AD
- Does Ig get across BBB?
  - Yes, CSF reaches 0.1-0.3% of peripheral blood levels
- What about complications in AD?
  - Largely due to vascular Abeta, may not be relevant to PD
- Will it actually work?
  - Absence of significant morbidity in preliminary studies encouraging.
  - Aggressive dosing may increase chances of efficacy
  - Aducanumab "success" suggests that it can work in PD
  - Multiple companies are betting on the possibility.

Thank you for your attention…