Supplementary Online Content

Jankovic J, Goodman I, Safirstein B, et al. 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. *JAMA Neurol*. Published online June 18, 2018. doi:10.1001/jamaneurol.2018.1487

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary Methods

Blinding

Study participants, investigators, sponsor, and all staff involved in the conduct of the study were blinded to treatment assignment. The only nonblinded personnel were the pharmacist and the bioanalyst/pharmacokineticist, who were not involved in the clinical assessment of participants. Randomization codes were maintained in a secure location to which only the nonblinded pharmacist had access.

Procedures

Serum PRX002 concentrations for the first and third infusions were assessed before infusion; 30 minutes after the start of infusion; immediately after the end of infusion (EOI); 0.25, 0.5, 1, 2, and 4 hours after EOI; 1 day after EOI (first infusion only); 2 and 3 weeks after EOI; and 4 weeks after EOI. Serum PRX002 concentrations for the second infusion were assessed before infusion, 30 minutes after start of infusion, and 1 hour and 4 hours after EOI. Cerebrospinal fluid (CSF) PRX002 concentrations were determined at screening and 2-9 days after the third infusion.

Outcomes

Pharmacokinetics were assessed in all 55 participants who received PRX002. Immunogenicity, pharmacodynamics, and clinical efficacy were assessed in all 80 participants. Serum PRX002 pharmacokinetic parameters were generated using noncompartmental analysis (Phoenix WinNonlin® version 6.4; Certara, Princeton, NJ). Serum and CSF PRX002 pharmacokinetic variables included maximum concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}) for the first dose, area under the concentration-time curve from the start of dosing until the end of the dosing interval (AUC_{tau}), observed terminal rate constant (λ_z), terminal half-life ($t_{½}$), total body clearance (CL), and volume of distribution at steady state (V_{ss}) and during the terminal elimination phase (V_z).

Supplementary eTable 1. Serum Pharmacokinetic Parameters After Infusions of PRX002

Measure, geometric mean (CV%)	PRX002 Dose Level					
	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**
C_{max}, ng/mL						
Infusion 1	5970 (17.5)	20,600 (20.9)	69,000 (23.5)	201,000 (22.1)	548,000 (14.2)	1,210,000 (49.4)
Infusion 3	6850 (16.9)	22,200 (14.1)	83,100 (37.7)	203,000 (22.4)	631000 (12.2)	1,110,000 (34.3)
AUC_{tau}, h·µg/mL						
Infusion 1	634 (26.5)	2390 (14.1)	7320 (30.4)	23,600 (22.9)	70,500 (16.4)	130,000 (17.6)
Infusion 3	844 (34.3)	3060 (23.9)	10,100 (29.1)	32,200 (25.7)	103,000 (19.4)	164,000 (24.6)
AUC_{inf}, h·µg/mL						
Infusion 1	699 (28.8)	2730 (15)	8050 (30.2)	28,600 (25.9)	77,800 (18)	152,000 (17.7)
Terminal $t_{½}$, h						
Infusion 1	216 (21.7)	212 (33.4)	265 (9.73)	260 (29.5)	206 (21.5)	250 (24.9)
Infusion 3	243 (16.2)	272 (18.5)	270 (23.2)	282 (5.09)	212 (26.5)	250 (25.7)
CL, L/h						
Infusion 1	0.0361 (30.9)	0.0225 (34.4)	0.0259 (30.0)	0.0289 (22.9)	0.0257 (25)	0.0286 (25.2)
Infusion 3	0.0391 (14.1)	0.02 (45.5)	0.024 (24.9)	0.0261 (22.8)	0.0185 (33.9)	0.0302 (25.1)
V_z, L						
Infusion 1	11.7 (50.7)	7.3 (52.7)	9.92 (23.1)	10.8 (38.9)	7.63 (32.5)	10.3 (30.6)
V_{ss}, L						
Infusion 3	10.5 (39.5)	7.37 (47.7)	7.81 (45.2)	11.4 (41.3)	6.12 (39.8)	9.72 (16.6)

AUC_{inf}, area under the serum concentration-time curve from time 0 hours to infinity (calculated for first infusion); AUC_{tau}, area under the serum concentration-time curve from time 0 hours to the end of the dosing interval (4 weeks); CL, total body clearance; C_{max}, maximum concentration; CV, coefficient of variation; h, hour; $t_{½}$, elimination half-life; V_{ss}, volume of distribution at steady state; V_z, volume of distribution during terminal elimination phase.

Supplementary eTable 2. Schedule of Exploratory Clinical Assessments

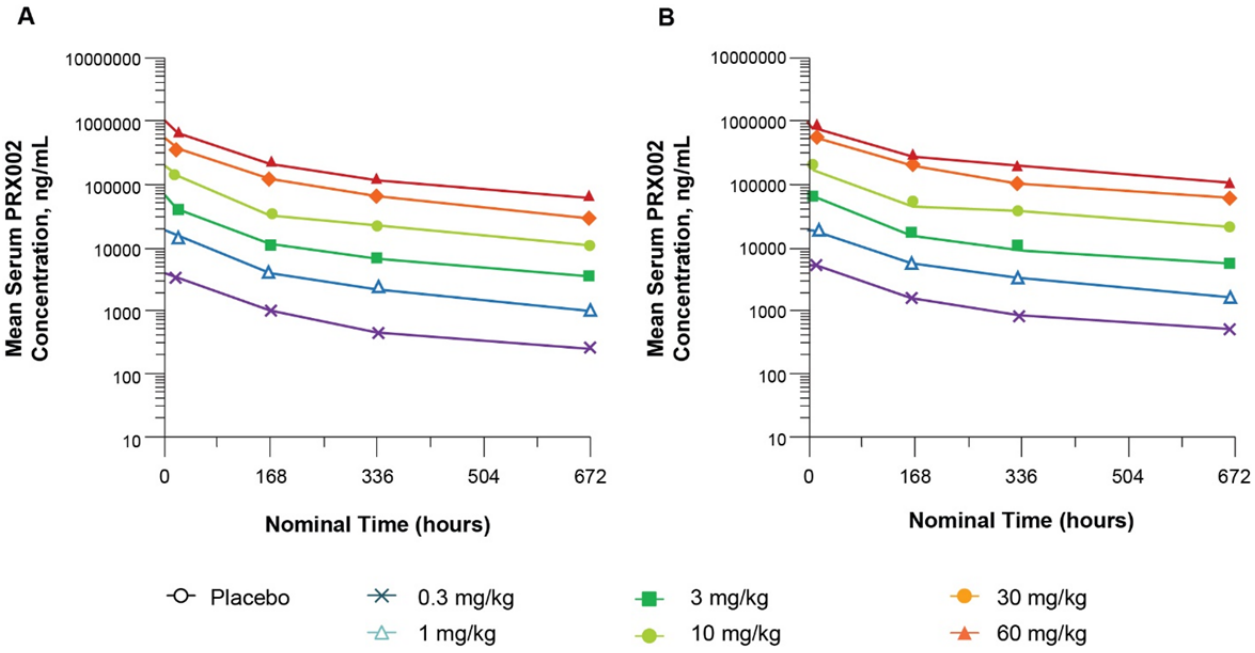
	Screening Days –56 to –1	Randomization and Dosing Day 1	Day 2	Day 8	Week 2 Day 15	Week 4 Day 29	Week 6 Day 43	Week 8 Day 57	Week 9 Day 64	Week 10 Day 71	Week 12 Day 85 or Early Termination	Week 24 Day 169
MDS-UPDRS[1]	X[3]			X					X			
CGIC[2]	X[3]			X					X			
Daily Bowel Movement Record[1]	X	X	X	X	X	X	X	X	X	X	X	X
PAC-SYM[1]	X				X				X			
UPSIT	X				X				X			
PDQ-39[1]	X									X		
DaTscan (Cohorts 4 to 6)[1]	X[3]									X		

1. Changes from baseline to each timepoint were analyzed using an ANCOVA model with fixed effects for treatment group (7 levels: 0, 0.3, 1, 3, 10, and 60 mg/kg) and covariates for the baseline value and age.
2. PRX002 and placebo distributes were compared using Fisher's exact test.
3. Screening DaTscan and MDS-UPDRS/CGIC were performed within 30 days before baseline.

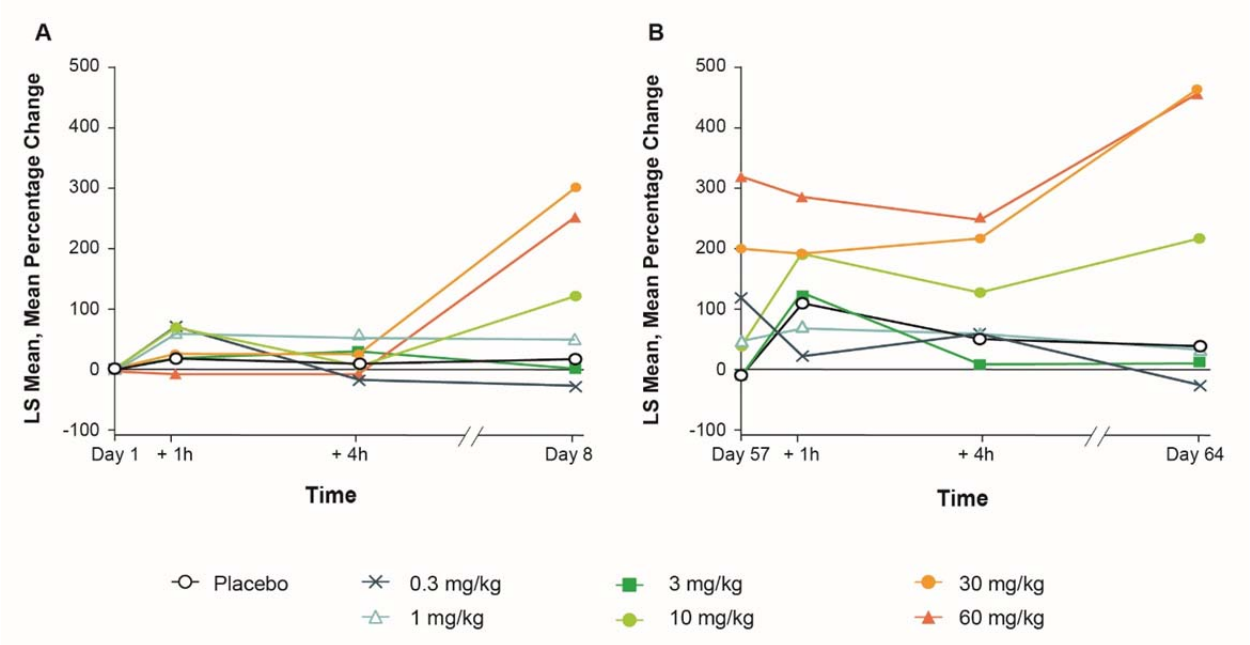
ANCOVA, analysis of covariance; CGIC, Clinical Global Impression of Change; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PAC-SYM, 12-Item Patient Assessment of Constipation Symptoms; PDQ-39, 39-Item Parkinson's Disease Questionnaire; UPSIT, 40-Item University of Pennsylvania Smell Identification Test.

SUPPLEMENTARY FIGURES

Supplementary eFigure 1. Serum pharmacokinetics profiles after the (A) first and (B) third infusions of PRX002.



Supplementary eFigure 2. Pharmacodynamics of total serum α-synuclein concentrations after the (A) first and (B) third infusions of PRX002. LS, least squares.



Supplementary eFigure 3. PRX002 binding to aggregated versus monomeric forms of α-synuclein. Curves were estimated based on dissociation constants for PRX002, determined by surface plasmon resonance in kinetic mode, of an apparent K_D of 0.048 nM (avidity/affinity) for aggregated α-synuclein and a K_D of 20 nM (affinity) for monomeric α-synuclein.[18] CSF and serum PRX002 concentrations represent the typical concentrations achieved in patients infused with PRX002. CSF, cerebrospinal fluid.