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

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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.

OBJECTIVE To evaluate the safety and tolerability of multiple intravenous infusions of PRX002 in patients with idiopathic PD.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled, multiple ascending-dose trial at 8 US study centers from July 2014 to September 2016. Eligible participants were aged 40 to 80 years with mild to moderate idiopathic PD (Hoehn and Yahr stages 1-3).

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.

MAIN OUTCOMES AND MEASURES Safety and tolerability assessments included physical and neurological examinations, laboratory tests, vital signs, and adverse events. Pharmacokinetic parameters included maximum PRX002 concentration, area under the curve, and half-life.

RESULTS Of the 80 participants, most were white (97.5%; n = 78) and male (80%; n = 64); median (SD) age was 58 (8.4) years. PRX002 was generally safe and well tolerated; no serious or severe PRX002-related treatment-emergent adverse events (TEAEs) were reported. The TEAEs experienced by at least 5% of patients receiving PRX002, irrespective of relatedness to study drug, were constipation (9.1%; n = 5), infusion reaction (7.3%; n = 4), diarrhea (5.5%; n = 3), headache (5.5%; n = 3), peripheral edema (5.5%; n = 3), post–lumbar puncture syndrome (5.5%; n = 3), and upper respiratory tract infection (5.5%; n = 3). No antidrug antibodies were detected. Serum PRX002 levels increased in an approximately dose-proportional manner; mean terminal elimination half-life was similar across all doses (10.2 days). Rapid dose- and time-dependent mean reductions from baseline vs placebo in free serum α-synuclein levels of up to 97% were seen after a single infusion at the highest dose ($F_{78,284} = 1.66$; $P = .002$), with similar reductions after 2 additional infusions. Mean cerebrospinal fluid PRX002 concentration increased with PRX002 dose and was approximately 0.3% relative to serum across all dose cohorts.

CONCLUSIONS AND RELEVANCE Single and multiple doses of PRX002 were generally safe and well tolerated and resulted in robust binding of peripheral α-synuclein and dose-dependent increases of PRX002 in cerebrospinal fluid, reaching cerebrospinal fluid concentrations that may be expected to engage extracellular aggregated α-synuclein in the brain. Findings support the design of an ongoing phase 2 clinical study (NCT03100149).

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02157714

JAMA Neurol. 2018;75(10):1206-1214. doi:10.1001/jamaneurol.2018.1487
Published online June 18, 2018.

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Supplemental content

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Parkinson disease (PD) is a chronic, progressive neurological disorder characterized by motor and nonmotor features.[1] Treatments primarily target symptoms but do not slow or halt the underlying neurodegeneration.[2] Eventually, debilitating adverse effects and treatment-resistant symptoms emerge. Therefore, there is a profound unmet need for disease-modifying therapies.

The cause of PD is not fully understood, but genetic, environmental, immune, and other causes contribute to its pathogenesis.[3] Pathologically, PD is typically associated with an accumulation of aggregated α-synuclein protein in the central nervous system (CNS) and the peripheral nervous system. Some forms of soluble aggregated α-synuclein have been proposed as a major extracellular neurotoxic species in the pathogenesis of PD.[4,5] Extracellular aggregated α-synuclein has been implicated in caudal-rostral propagation in the brain (Braak staging)[6] and in host-to-graft transfer of α-synuclein pathology into cells transplanted into the brains of patients with PD.[4,5,7]

Preclinical studies with transgenic mice have shown that overexpression of α-synuclein leads to the development of key PD features, including accumulation of intracellular α-synuclein pathology and motor and cognitive deficits.[8,9] Vaccination (active immunization) and monoclonal antibody (passive immunotherapy) studies in α-synuclein transgenic mice demonstrate that anti–α-synuclein antibodies with high relative affinity to the C-terminus protein region tempered neuronal pathology by decreasing intracellular accumulation of α-synuclein in cell bodies and synapses, protected against synaptic loss and gliosis, and ameliorated motor and cognitive behavior deficits.[9-12] Passive immunization with C-terminal α-synuclein antibodies reduced intracellular α-synuclein pathology, protected neurons, and improved behavior performance in lentiviral[13] and recombinant preformed fibril[14] α-synuclein-transmission models.

PRX002/RG7935 (PRX002) is a humanized IgG 1 monoclonal antibody designed to target the C-terminus of neurotoxic (aggregated) forms of α-synuclein. Preclinical efficacy of the PRX002 murine homologue (9E4) has been demonstrated using multiple in vivo and in vitro α-synucleinopathy models; specifically, 9E4 blocked cell-to-cell transmission of α-synuclein, reduced intracellular α-synuclein pathology, protected against synaptic loss and gliosis, and ameliorated cognitive and motor behavior deficits.[9,11,12,15,16] Sequestration, neutralization, and clearance of toxic α-synuclein species by PRX002 is thought to halt the spreading of pathogenic α-synuclein between neurons, resulting in neuronal protection and potentially slowing disease progression.[15] PRX002 has a substantially higher affinity/avidity for aggregated than monomeric forms of α-synuclein (kinetic affinity constant [K_D], 0.048 nM vs 20 nM, respectively); this attribute, besides targeting an epitope in the C-terminus of α-synuclein, was designed to support antibody efficacy.[15,17]

In a single ascending-dose phase 1 study in healthy volunteers, PRX002 was safe and well tolerated up to the highest tested dose (30 mg/kg) and resulted in dose-dependent reductions in free serum α-synuclein.[18] We report the results of a multiple ascending-dose phase 1b study designed to evaluate the safety and tolerability of PRX002 at doses up to 60 mg/kg in 80 participants with mild to moderate PD. Secondary and exploratory objectives included assessments of the pharmacokinetics, immunogenicity, pharmacodynamics, and clinical efficacy of multiple intravenous infusions of PRX002.

Key Points

Question Is repeated administration of a monoclonal antibody against α-synuclein (PRX002/RG7935) safe and well tolerated in patients with Parkinson disease?

Findings In this randomized clinical trial of 80 patients with Parkinson disease treated with multiple ascending doses of PRX002/RG7935 or placebo, repeated PRX002/RG7935 treatment was generally safe and well tolerated and induced marked reductions in free serum α-synuclein.

Meaning The results of this phase 1b trial provided important safety, pharmacokinetic, and pharmacodynamic information needed to design the ongoing phase 2 trial to assess whether PRX002/RG7935 shows evidence of a treatment benefit during 52 weeks in patients with Parkinson disease.

Methods

Experimental Design

This was a multicenter, randomized, double-blind, placebo-controlled, multiple ascending-dose, phase 1b study in patients with mild to moderate PD at 8 US study centers. The formal trial protocol is available in Supplement 1. Participants were enrolled sequentially into 1 of 6 escalating-dose cohorts and were to receive a total of 3 intravenous infusions of 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, administered approximately once every 28 days. Participants returned for pharmacokinetic and pharmacodynamic assessments until 4 weeks after final dosing and for clinical efficacy and safety assessments until 16 weeks after final dosing (24 weeks total). The sample size of 56 active participants was based on detecting an adverse event (AE) of interest occurring at a true rate of 0.04 with a probability of 89.8% and detecting an AE of interest occurring at a true rate of 0.20 with a probability of at least 99%. The study protocol was approved by appropriately constituted institutional review boards. All participants provided written informed consent. The study was conducted according to International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Participants

Key enrollment criteria included mild to moderate idiopathic PD (Hoehn and Yahr stage 1-3) with bradykinesia plus another cardinal PD sign (resting tremor or rigidity); receiving stable (≥90 days) doses of anti-PD medication at baseline if being treated for PD; age 40 to 80 years; body weight 45 to 110 kg; body mass index (calculated as weight in kilograms divided by height in meters squared) 18 to 34; postmenopausal, surgically sterile, or using adequate contraception; and

no history of significant cardiac disorders or abnormal magnetic resonance imaging results.

Randomization

Participants in cohorts 1 through 4 were randomly assigned in blocks of 3, each in a 2 to 1 ratio of PRX002 and placebo (PRX002, n = 8; placebo, n = 4). Participants in cohorts 5 and 6 were randomly assigned in blocks of 4, each in a 3 to 1 ratio of PRX002 and placebo (PRX002, n = 12; placebo, n = 4). Within each cohort, the first block served as a sentinel group (cohorts 1-4, n = 3; cohorts 5-6, n = 4) to assess safety and tolerability before the remaining participants were randomly assigned. Details of blinding procedures are provided in the eMethods in Supplement 2.

Procedures

Lyophilized PRX002 was reconstituted with sterile water for injection and prepared by a nonblinded study pharmacist in normal saline for intravenous infusion for a mean (SD) of 60 (10) minutes for all participants in cohorts 1 through 5 and either 60 (10) minutes or 120 (10) minutes for participants in cohort 6. Premedication was not required. Normal saline was used as placebo. Dose escalation for subsequent cohorts occurred after all participants in the preceding cohort had received at least 1 dose and after review of 6 weeks' safety data from 75% of participants from the preceding cohort. Immunogenicity was assessed before and 4 weeks after each infusion. Serum PRX002 concentrations were assessed at various times before, during, and after each infusion (eMethods in Supplement 2). Free (unbound to PRX002) and total (free plus bound to PRX002) serum α-synuclein concentrations were assessed before and 1 and 4 hours after each of the 3 infusions; 1 and 2 weeks after the first and third infusions; and 4 weeks after the third infusion. Free and total cerebrospinal fluid (CSF) α-synuclein and CSF PRX002 concentrations were determined at screening and 2 to 9 days after the third infusion.

Outcomes

Primary study objectives were to evaluate the safety and tolerability of multiple intravenous infusions of PRX002, and secondary objectives were to assess the pharmacokinetics and immunogenicity of single and multiple infusions of PRX002 in participants with PD. Exploratory objectives were to assess relevant biomarkers and clinical PD progression.

Safety and tolerability were assessed in all patients who received study drug (PRX002 or placebo) and included AEs, laboratory tests, vital signs, electrocardiography, and physical and neurological examinations. Serum and CSF PRX002 were measured using a Prothena-developed quantitative sandwich electrochemiluminescence (ECL) assay.[18] Serum PRX002 pharmacokinetic parameters were generated using noncompartmental analysis; pharmacokinetic variables are described in the eMethods in Supplement 2. Immunogenicity was assessed by measuring anti-PRX002 antibodies using a qualitative dilution-based bridging ECL assay. Total and free α-synuclein were measured in serum and CSF using quantitative sandwich ECL (Intertek Pharmaceutical Services), with free serum α-synuclein values normalized to percentage of total α-synuclein; samples with hemoglobin levels greater than 0.06 g/dL were excluded from analysis because of potential peripheral α-synuclein contamination by lysed red blood cells (to convert to grams per liter, multiply by 10). Total β-amyloid (Aβ) and Aβ42 were measured in CSF using quantitative sandwich ECL. DJ-1 was measured in CSF using enzyme-linked immunosorbent assay.

Exploratory clinical assessments included the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (days 8 and 64), 39-item Parkinson's Disease Questionnaire (day 71), posttreatment Clinical Global Impression of Change (days 8 and 64), 40-item University of Pennsylvania Smell Identification Test (days 15 and 64), 12-item Patient Assessment of Constipation Symptoms (days 15 and 64), bowel movement frequency diaries (days 1, 2, 8, 15, 29, 43, 57, 64, 71, 85, and 169), and DaTscan (cohorts 4-6; day 71). Details of exploratory clinical assessments are listed in eTable 1 in Supplement 2.

Statistical Analysis

Baseline and demographic characteristics, safety, and pharmacokinetic data were summarized using descriptive statistics. All tests were 2-sided, with significance level of .05. No adjustments for multiple comparisons were made. Maximum concentration (C_{max}), area under the concentration-time curve from time-zero extrapolated to infinity for the first infusion, and C_{max} and area under the concentration-time curve from zero to tau for the third infusion were compared across each dose level to assess change in systemic exposure with change in PRX002 dose. Total α-synuclein and free serum α-synuclein percentage changes from baseline were summarized using linear mixed models for repeated measurements. The statistical significance of CSF α-synuclein change from baseline was determined by analysis of covariance.

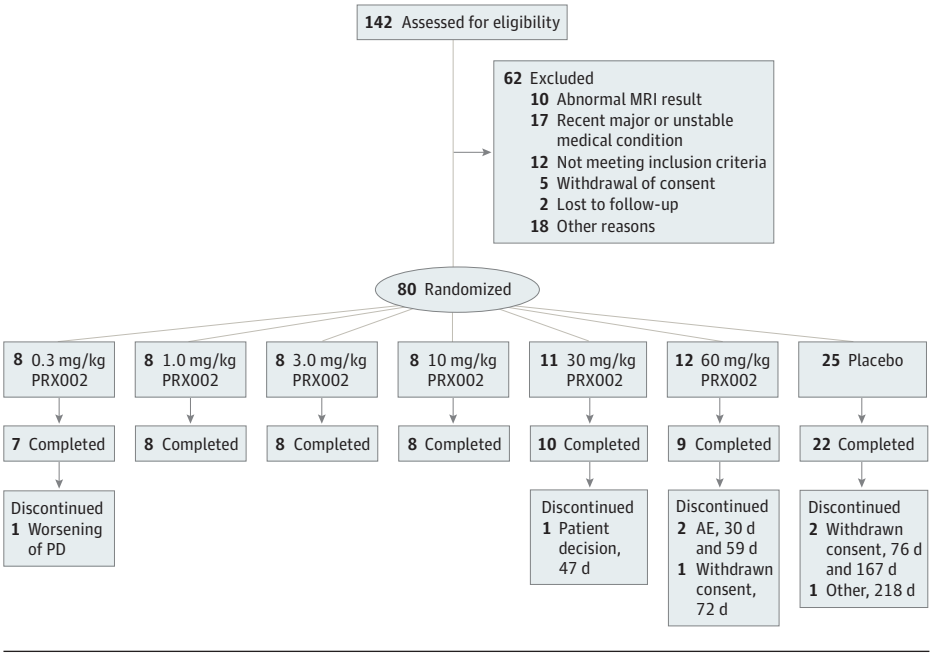
Results

Study Population

Eighty patients with PD were randomly assigned to receive placebo or PRX002 from July 2014 to September 2016 (**Figure 1**). Demographics and baseline characteristics appeared similar across cohorts (**Table 1**). Median patient age was 58 years. Most participants had Hoehn and Yahr stage 2 (72.0% placebo vs 70.9% PRX002); mean total MDS-UPDRS scores were 48.5 (placebo) vs 47.3 (PRX002). Medical and treatment histories were also similar; most participants across all cohorts used dopaminergic medications before baseline (96.0% placebo vs 80.0% PRX002), did not have a family history of PD (84.0% placebo vs 78.2% PRX002), and did not have a history of rapid eye movement sleep behavioral disorder (88.0% placebo vs 72.7% PRX002).

No significant protocol deviations occurred. One additional patient in cohort 5 was enrolled to replace a patient who was randomly assigned but not treated. All 80 participants (25 placebo and 55 PRX002) were included in the intent-to-treat, pharmacodynamic, and safety analyses; all 55 participants who received PRX002 were included in the pharmacokinetic analysis.

Figure 1. CONSORT Flowchart



Eligibility exclusions were counted more than once for the inclusion/exclusion criteria they did not meet. AE indicates adverse event; MRI, magnetic resonance imaging; PD, Parkinson disease.

Safety and Immunogenicity

Multiple intravenous infusions of PRX002 (range, 0.3-60 mg/kg) were generally safe and well tolerated; no serious or severe treatment-emergent AEs (TEAEs) were reported in PRX002-treated participants. No deaths occurred during the study. Two patients in the 60-mg/kg PRX002 group had AEs leading to study discontinuation (days 30 and 59; both infusion-related reactions [IRRs]).

Fifty-four participants (67.5%) reported TEAEs, most of which were mild. Common TEAEs more frequent in the PRX002 group vs placebo group, irrespective of study drug relatedness, were constipation, IRR, diarrhea, peripheral edema, and post-lumbar puncture syndrome (**Table 2**). The only PRX002-related TEAE experienced by at least 1 participant in any cohort was IRR, reported in 4 participants in the 60-mg/kg PRX002 cohort. Two participants reported moderate IRR. One occurred after the first infusion (acute allergic reaction [skin rash and tongue numbness]) and the other after the second infusion (skin rash); both events resolved with medication, and study drug was discontinued. A third participant reported moderate IRR following the first and second infusions (skin rash) that resolved with medication. This participant was premedicated for the third infusion, which was increased to 120 minutes and was uneventful. A fourth participant reported mild IRRs (dysgeusia and pruritus) with the first infusion that spontaneously resolved; the second and third infusions (no premedication) were uneventful.

All other PRX002-related TEAEs (mild headache, moderate worsening of insomnia, mild nausea, mild diarrhea, mild dizziness, and mild fatigue) occurred in 1 patient each and resolved without treatment. No clinically relevant or treatment-related trends emerged from clinical laboratory data, physical examinations, neurological examinations, vital signs, or electrocardiography after dosing. Exploratory clinical assessments showed no clinically meaningful or dose-dependent PRX002-related treatment differences within any treatment cohort. DaTscan showed statistically significant ($F_{3,31} = 2.3$; $P < .05$) increases in DaTscan tracer uptake from baseline to day 71, relative to placebo, but these were not considered clinically meaningful because they occurred only for the 10 mg/kg dose group. No antidrug antibodies were detected.

Pharmacokinetics

Serum mean C_{max} and mean area under the curve increased in an approximately dose-proportional manner across the 6 dose cohorts (eTable 2 in Supplement 2). The mean terminal elimination half-life was similar across all dose cohorts and was approximately 10.2 days (245 hours; range, 206-282; eFigure 1 in Supplement 2). Clearance was similar across dose cohorts and not different between the first and last (third) infusions, with mean clearance at steady state ranging from 0.0185 to 0.0391 L/h. Volume of distribution at steady state was approximately consistent across dose groups, with means ranging from 6.12 to 11.4 L after the third infusion. Accumulation ratios, as measured by C_{max} and area under the concentration-time curve from zero to tau, suggested minimal accumulation of less than 1.5-fold on systemic exposure following the third infusion. Mean CSF PRX002 exposure measured at approximately week 9 increased with PRX002 dose; on average, the concentration of PRX002 in CSF relative to serum was approximately 0.3% across all dose cohorts (**Figure 2**).

Pharmacodynamics

Infusions of PRX002 resulted in statistically significant dose- and time-dependent reductions from baseline in free (unbound) serum α-synuclein (**Figure 3**). The greatest reductions after the first infusion were in the 60-mg/kg dose cohort (96.7%) and were similar after the first, second, and third infusions.

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.

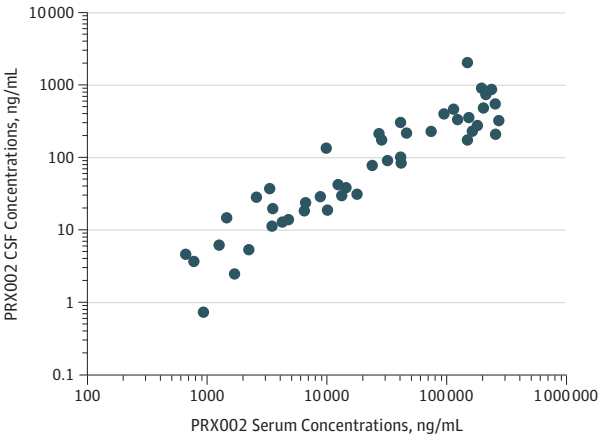
[c] Moderate PRX002-related AEs in 3 participants resulted in the discontinuation of 2 participants from the study.

Statistically significant reductions from baseline vs placebo after the first infusion were seen at 1 and 4 hours for all dose groups, at days 8 and 15 for the 3- to 60-mg/kg PRX002 groups, and at day 29 for the 3-mg/kg, and the 10- to 60-mg/kg PRX002 groups. Statistically significant reductions after the third infusion were seen at 1 and 4 hours for all dose groups, at day 64 for the 1- to 60-mg/kg PRX002 groups, at day 71 for the 1-mg/kg and the 3- to 60-mg/kg PRX002 groups, and at day 85 for the 3- to 60-mg/kg PRX002 groups. Reductions were maintained for longer durations after higher PRX002 doses.

Increases from baseline of total (unbound plus PRX002 bound) serum α-synuclein were also dose and time dependent (eFigure 2 in Supplement 2). The greatest increase was seen 1 week after the third infusion in the 60-mg/kg cohort (least squares mean, 86 µg/mL; increase, 458%). Increases were statistically significant 1 week after the first infusion for the 30- and 60-mg/kg cohorts and 4 weeks after the first infusion for the 10-mg/kg cohort. Increases for the 30- and 60-mg/kg cohorts remained significant until the last sampling (4 weeks after the third infusion) except at 1 hour after the third infusion for the 30-mg/kg cohort, with an upward trend in total serum α-synuclein levels across the 3 infusions.

No statistically significant CSF changes from baseline vs placebo were seen for free α-synuclein, total α-synuclein (except cohort 5 [30 mg/kg PRX002]), total Aβ, Aβ42, or DJ-1 (except cohort 3 [3 mg/kg PRX002]) across the PRX002 dose cohorts, and no dose-dependent trends were observed.

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.

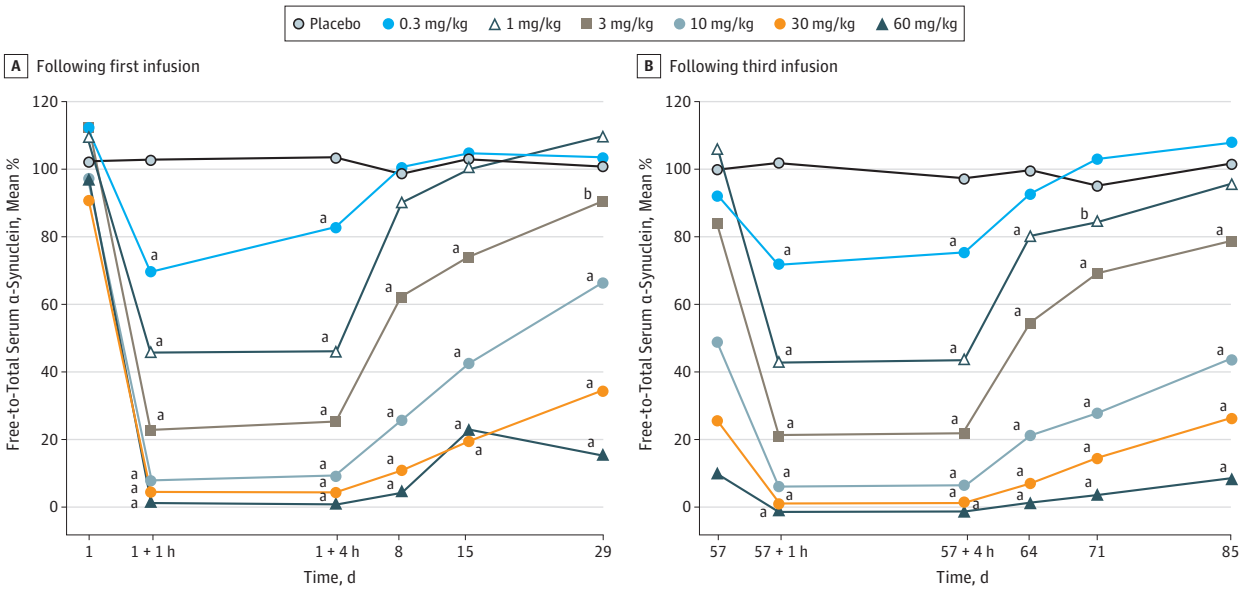
Discussion

This study demonstrated that PRX002, an immunotherapy designed to preferentially target aggregated α-synuclein, was capable of engaging peripheral α-synuclein in patients with PD. Multiple intravenous infusions of PRX002 were generally safe and well tolerated at all dose levels up to and including 60 mg/kg intravenously every 4 weeks. No deaths, serious AEs, or anti-PRX002 antibodies were noted. Marked reductions in free serum α-synuclein levels were seen within 1 hour of PRX002 administration after each of the 3 infusions. Dose-dependent increases in PRX002 levels were demonstrated in serum and in CSF.

Parkinson disease treatments are aimed chiefly toward attenuating motor symptoms, typically through modulating dopamine pathways,[2] but they do not address the underlying degeneration. Several disease-modifying treatments are being investigated in clinical trials and include but are not limited to growth factors, gene therapy, antiapoptotic agents, immune modulation, stem cell–based neuron replacement therapy, and targeting aggregated protein.[19-21]

The protein α-synuclein performs multiple functions in the body and may be best described as a regulator of vesicular

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] $P < .05$.

transport and neurotransmitter release in the synaptic terminals of neurons.[22] Multiplications and certain point mutations in *SNCA*, the gene encoding α-synuclein, lead to familial PD, and genome-wide association studies place *SNCA* as the top genetic risk factor for the sporadic form of the disease.[1] In addition, evidence to support targeting α-synuclein as a potential disease-modifying strategy in PD is derived from α-synuclein aggregates in Lewy bodies and neurites in affected brain regions and in nerves innervating peripheral organs in patients with PD and prodromal PD patients.[23-29] Furthermore, neuropathologic staging of PD, as proposed by Braak, points to a neuron-to-neuron propagation of α-synuclein pathology between nervous system regions in patients with PD.[6] Similarly, host-to-graft propagation of α-synuclein pathology was observed post mortem in some nigral transplants.[4,5] Injection of recombinant preformed α-synuclein fibrils into specified brain regions in mice leads to intraneuronal aggregation of α-synuclein and propagation of the pathology, similar to what is observed in PD, indicating that an extracellular form of aggregated α-synuclein may be involved in this pathomechanism.[30-35]

In preclinical studies, the murine homologue of PRX002 reduced intracellular α-synuclein pathology, protected neurons, and ameliorated cognitive and motor behavior deficits in multiple mouse models of α-synucleinopathy.[9,11,12,15,16] Targeting toxic proteins with monoclonal antibodies is also being evaluated as a potential therapeutic strategy in other neurodegenerative diseases.[36-38]

This study demonstrated a favorable safety and tolerability profile and a marked reduction of free (unbound) serum α-synuclein after multiple doses of PRX002. Notably, rapid and robust reductions in free serum α-synuclein levels were achieved without seriously affecting safety, consistent with a previous healthy volunteer PRX002 study.[18] The one PRX002-related TEAE of note in this study was mild to moderate IRR in 4 participants in the highest dose group, which led to study discontinuation in 2 participants; symptoms were rash, pruritus, dysgeusia, and tongue numbness. Infusion-related reactions are the most commonly reported AEs associated with the administration of monoclonal antibodies.[39] In studies with other antibodies, IRR effects have been mitigated by dose fractionation, lower infusion rates, and/or premedication with antihistamines, acetaminophen, or corticosteroids.[40] Premedication of participants for potential IRRs was not required in this study.

Pharmacokinetic profiles were mostly similar to those in an earlier report of single PRX002 infusions in 30 healthy volunteers, with serum concentrations increasing proportionally with PRX002 dose.[18] The terminal half-life in this study was somewhat shorter than that in the single-dose study in healthy volunteers (approximately 10 days vs approximately 18 days, respectively), possibly because of the more prolonged assessment in the single-dose study. Population pharmacokinetic analyses further confirmed a lack of difference in clearance between healthy participants[18] and participants with PD. Data from this study continue to support monthly dosing for further clinical development. In addition, the CSF/serum antibody ratio of 0.3% in this study was in the high range among studies of monoclonal antibodies targeting β-amyloidor α-synuclein in the CNS.[41,42]

Reductions in free serum α-synuclein were rapid, dose dependent, prolonged, and comparable in magnitude and duration after the first and last doses. These findings, along with in vitro data demonstrating a substantially higher

avidity/affinity of PRX002 for aggregated (K_D, 0.048 nM) vs monomeric (K_D, 20 nM) α-synuclein (determined by surface plasmon resonance in kinetic mode; eFigure 3 in Supplement 2)[17] and CSF penetration of PRX002, suggest that target engagement of aggregated α-synuclein in the CNS may be achieved.

Limitations

Limitations of this study were the small number of patients exposed, the short exposure duration, the relatively low demographic diversity, and the possibility that some patients might later be found to have a disorder other than PD. No adjustments were made for multiple comparisons of exploratory efficacy assessments. Further limitations were the lack of validated assay to directly measure aggregated α-synuclein CSF levels and unavailability of imaging methods to monitor intracellular α-synuclein pathology in the brains of patients with PD. Nonetheless, the substantially higher affinity/avidity of PRX002 for aggregated α-synuclein forms,[15,17] along with the high relative CSF concentrations observed in this study (0.3% of blood), indicate that the antibody has the potential to fully engage extracellular aggregated forms of α-synuclein in the CNS within the doses tested in this study.

No effect was seen on free α-synuclein in CSF, which may best be explained by PRX002 concentrations in the CSF, which, in contrast to the periphery, are not sufficiently high to engage the monomeric species (eFigure 3 in Supplement 2). In addition, how much of the toxic protein must be removed to modify disease progression is unknown. This phase 1b safety, tolerability, and pharmacokinetic study involved 3 infusions in a small number of participants and a short duration of observation, limiting clinical assessment of potential treatment effects. Clinical assessments helped rule out any significant untoward investigational drug effects. Despite the limitations, safety and pharmacokinetics findings from this phase 1b trial provide support for further evaluation of doses up to 60 mg/kg in the ongoing phase 2 efficacy study of PRX002. A dose of 60 mg/kg or less is predicted to effectively engage α-synuclein in the brain and is supported by preclinical efficacy models. The absence of serious safety concerns in this study, the accumulating scientific data in support of this approach, and the clear unmet medical need for disease-modifying therapeutics in PD underscore the importance of future trials.

Conclusions

Single and multiple doses of PRX002 resulted in robust binding of peripheral α-synuclein and in dose-dependent increases of PRX002 in CSF and reached CSF concentrations that may be expected to engage extracellular aggregated α-synuclein in the brain. All tested dose levels of PRX002 had acceptable safety and tolerability profiles, supporting the design of an ongoing phase 2 clinical trial, PASADENA (NCT03100149).

ARTICLE INFORMATION

Accepted for Publication: March 8, 2018.

Published Online: June 18, 2018. doi:10.1001/jamaneurol.2018.1487

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Author Contributions: Drs Kinney and Koller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Schenk, Kinney.
Administrative, technical, or material support: Koller, Ness, Griffith, Grundman, Quinn, Isaacson, Ellenbogen, Kinney.
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Conflict of Interest Disclosures: Dr Jankovic has served as a consultant to Prothena Biosciences Limited and Prothena Biosciences Inc and has received funding from the Parkinson's Foundation to support the Baylor College of Medicine Center of Excellence. Dr Goodman is an employee of Bioclinica. Drs Marmon and Ness and Mr Soto are employees of Prothena Biosciences Inc and shareholders of Prothena Corporation plc. Dr Grundman is a consultant to Prothena Biosciences Limited and a shareholder of Prothena Corporation plc. Dr Schenk was an employee of Prothena Biosciences Inc and an officer and shareholder of Prothena Corporation plc. Dr Koller was an employee of and is a consultant to Prothena Biosciences Inc and was an officer and a shareholder of Prothena Corporation plc. Dr Zago is an employee of Prothena Biosciences Inc and an officer and shareholder of Prothena Corporation plc. Dr Griffith is a consultant to Prothena Biosciences Inc. Dr Ostrowitzki is an employee and stock owner of Genentech Inc, a member of the Roche group. Dr Boess is an employee and stock owner of F. Hoffmann-La Roche Ltd. Dr Martin-Facklam is an employee of F. Hoffmann-La Roche Ltd. Dr Quinn received compensation for serving on a data and safety monitoring board for vTv Therapeutics. Dr Ellenbogen is an employee of the QUEST Research Institute. Dr Kinney is an employee of Prothena Biosciences Inc and an officer and a shareholder of Prothena Corporation plc. No other disclosures were reported.

Funding Support: This study was sponsored by Prothena Biosciences Limited (Dun Laoghaire, Ireland) and F. Hoffmann-La Roche Ltd (Basel, Switzerland).

Role of the Funder/Sponsor: In collaboration with the authors, the study sponsors (Prothena Biosciences Limited and F. Hoffmann-La Roche Ltd) participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; review and approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: Medical writing and editorial assistance was provided by ApotheCom

(San Francisco, California) and was funded by Prothena Biosciences Inc and F. Hoffmann-La Roche Ltd.

Additional Information: Dale B. Schenk, PhD, passed away in September 2016.

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