

JAMA | Preliminary Communication

Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis

A Randomized Clinical Trial

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IMPORTANCE Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease with poor prognosis. Approved therapies do not halt disease progression.

OBJECTIVE To determine the effect of recombinant human pentraxin 2 vs placebo on change from baseline to week 28 in mean forced vital capacity (FVC) percentage of predicted value.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, randomized, double-blind, placebo-controlled trial conducted at 18 sites in 7 countries of eligible patients with IPF (N = 117; aged 40-80 years; FVC \geq 50% and \leq 90% predicted; ratio of forced expiratory volume in the first second/FVC $>$ 0.70; diffusing capacity for carbon monoxide [DLCO] \geq 25% and \leq 90% predicted; and distance of \geq 150 m on the 6-minute walk test). Study period was August 2015-May 2017.

INTERVENTIONS Patients were randomized to receive either recombinant human pentraxin 2 (10 mg/kg intravenous every 4 weeks, n = 77) or placebo (n = 39) for 24 weeks, and stratified by concurrent IPF treatment status.

MAIN OUTCOMES AND MEASURES The primary end point was the least-squares mean change in FVC percentage of predicted value from baseline to week 28 (minimal clinically important difference, decline of 2%-6%). Secondary end points included mean change in lung volumes (total, normal, and interstitial lung abnormalities) on high-resolution computed tomography (HRCT) and 6-minute walk distance (minimal clinically important difference, 24-45 m).

RESULTS Of 117 randomized patients, 116 received at least 1 dose of study drug (mean age, 68.6 years; 81.0% men; mean time since IPF diagnosis, 3.8 years), and 111 (95.7%) completed the study. The least-squares mean change in FVC percentage of predicted value from baseline to week 28 in patients treated with recombinant human pentraxin 2 was -2.5 vs -4.8 for those in the placebo group (difference, $+2.3$ [90% CI, 1.1 to 3.5]; P = .001). No significant treatment differences were observed in total lung volume (difference, 93.5 mL [90% CI, -27.7 to 214.7]), quantitative parenchymal features on HRCT (normal lung volume difference, -1.2% [90% CI, -4.4 to 1.9]; interstitial lung abnormalities difference, 1.1% [90% CI, -2.2 to 4.3]), or measurement of DLCO (difference, -0.4 [90% CI, -2.6 to 1.7]). The change in 6-minute walk distance was -0.5 m for patients treated with recombinant human pentraxin 2 vs -31.8 m for those in the placebo group (difference, $+31.3$ m [90% CI, 17.4 to 45.1]; P < .001). The most common adverse events in the recombinant human pentraxin 2 vs placebo group were cough (18% vs 5%), fatigue (17% vs 10%), and nasopharyngitis (16% vs 23%).

CONCLUSIONS AND RELEVANCE In this preliminary study, recombinant human pentraxin 2 vs placebo resulted in a slower decline in lung function over 28 weeks for patients with idiopathic pulmonary fibrosis. Further research should more fully assess efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02550873

JAMA. 2018;319(22):2299-2307. doi:10.1001/jama.2018.6129
Published online May 20, 2018.

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➕ Supplemental content

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Idiopathic pulmonary fibrosis (IPF), a progressive disease that leads to an irreversible loss of lung function, has a 5-year survival rate between 20% and 40%.¹ In 2015, the incidence of IPF in North America and Europe was estimated at 3 to 9 cases per 100 000 person-years, with lower incidence in Asia and South America.² IPF disproportionately affects older men.³ Pirfenidone⁴ and nintedanib⁵ are currently the only therapies approved for the treatment of IPF. Although the rate of decline in forced vital capacity (FVC) is slower in patients treated with pirfenidone and nintedanib, neither treatment halts disease progression or improves any objective measurements of disease status. Thus, a need for additional novel treatment approaches remains.

Evidence suggests that epithelial damage and abnormal wound repair contribute to the pathogenesis of IPF.⁶ Fibrocytes, usually inactive fibroblast-like cells derived from peripheral blood monocytes, have been implicated in this process.⁷ Purified serum amyloid P, also known as pentraxin 2, inhibits monocyte differentiation into profibrotic fibrocytes.^{8,9} Pentraxin 2 is also a potent inhibitor of monocyte differentiation into proinflammatory macrophages¹⁰ and production of transforming growth factor (TGF)- β 1, which is a key mediator of pulmonary fibrosis.¹¹ Plasma pentraxin 2 concentrations are reduced in patients with IPF and correlate with disease severity, further supporting its role in modulating fibrosis.¹¹

A recombinant human pentraxin 2 protein decreased lung fibrosis in preclinical models of TGF- β 1 overexpression and bleomycin-induced lung fibrosis; the effect lasted for as long as 30 days after dosing.¹¹⁻¹³ In a phase 1 study in healthy participants and patients with pulmonary fibrosis, administration of recombinant human pentraxin 2 increased circulating pentraxin 2 concentrations 6- to 13-fold.¹⁴ An additional phase 1 study in patients with IPF showed improvements in predicted percentage of FVC value and 6-minute walk distance following treatment with recombinant human pentraxin 2.¹⁵ This placebo-controlled phase 2 trial (PRM-151-202) was conducted to assess the efficacy and adverse events of recombinant human pentraxin 2 in patients with IPF.

Methods

The trial protocol and statistical analysis plan are available in [Supplement 1](#).

Study Oversight

The trial was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and was approved by local ethical review boards. The clinical protocol was approved by an independent ethics committee or institutional review board at each participating center. All patients provided written informed consent prior to enrollment. An independent data and safety monitoring board provided oversight.

Study Sites and Patients

This study was conducted at 18 sites in 7 countries (United States, Germany, Italy, Czech Republic, the Netherlands, Spain,

Key Points

Question What is the effect of intravenous recombinant human pentraxin 2 on change in forced vital capacity (FVC) for patients with idiopathic pulmonary fibrosis?

Findings In this randomized clinical trial that included 117 patients with IPF, treatment with recombinant human pentraxin 2 every 4 weeks for 24 weeks resulted in a change in FVC percentage of predicted value of -2.5% compared with -4.8% with placebo, a difference that was statistically significant. Recombinant human pentraxin 2 infusions were well tolerated.

Meaning These preliminary findings suggest that recombinant human pentraxin 2 may reduce the decline in lung function in patients with idiopathic pulmonary fibrosis, but more definitive research is required.

and Switzerland); all sites were interstitial lung disease specialty centers. Eligible patients were between the ages of 40 and 80 years with a diagnosis of IPF (established at the study sites in accordance with the inclusion criteria; eAppendix [Complete Patient Inclusion Criteria] in [Supplement 2](#)),¹⁶ FVC of 50% or greater and of 90% or less predicted, diffusing capacity for carbon monoxide (DLCO) of 25% or greater and of 90% or less predicted, distance of at least 150 m on the 6-minute walk test,¹⁷ and ratio of forced expiratory volume in the first second (FEV₁)/FVC greater than 0.70. Concurrent therapy with pirfenidone or nintedanib was permitted if the dosage was stable for at least 3 months; patients not receiving concurrent pirfenidone or nintedanib must have stopped treatment for at least 4 weeks prior to baseline. Patients with emphysema (\geq 50% on chest high-resolution computed tomography [HRCT]) or greater extent of emphysema than fibrosis (see eAppendix [Complete Patient Exclusion Criteria] in [Supplement 2](#) for further methodological details), cigarette smoking within the previous 3 months, or oxygen saturation by pulse oximetry less than 89% on room air or supplemental oxygen at rest were excluded. A comprehensive list of inclusion and exclusion criteria is provided in the eAppendix (Complete Patient Inclusion Criteria; Complete Patient Exclusion Criteria; in [Supplement 2](#)).

Study Design

This phase 2, randomized, double-blind, placebo-controlled trial included a 4-week screening period, a 24-week randomized treatment period, and a 4-week follow-up visit (week 28). Patient groups were assigned using a software-generated randomization list (Proc plan; SAS version 9.4) composed of a block of 3, balanced at a ratio of 2:1 in favor of recombinant human pentraxin 2 over placebo. Randomization was stratified according to concomitant IPF treatments (patients receiving pirfenidone or nintedanib; patients not receiving concurrent pirfenidone or nintedanib for IPF). Patients received either recombinant human pentraxin 2 (10 mg/kg intravenous [IV] every 4 weeks) or placebo (see eAppendix [Randomization] in [Supplement 2](#)) with a loading regimen of 3 doses at the start of treatment (days 1, 3, and 5). Patients who completed the trial were eligible to participate in an open-label treatment extension period.

Efficacy and Tolerability End Points

Researchers and the site study teams were blinded to study group assignment, as was the study sponsor; therefore, outcomes assessments were blinded.

The primary efficacy end point of the trial was the least-squares mean change in FVC percentage of predicted value from baseline to week 28 (a decline of 2% to 6% represents a clinically important difference in an IPF population).¹⁸ Secondary end points included least-squares mean change from baseline to week 28 in FVC percentage of predicted value analyzed by concomitant therapy status (patients receiving concomitant pirfenidone or nintedanib or patients without concurrent IPF therapy), mean change from baseline to week 28 in total lung volume and volume of parenchymal features (in mL [not reported in this article] and percentage of total lung volume) on HRCT using quantitative imaging software (Lung Texture Analysis, Imbio; clinically important difference in an IPF population is not defined), the percentage of patients with categorical change in FVC ($\geq 5\%$ or $\geq 10\%$ absolute change in percentage of the predicted value, $< 5\%$ change, and ≥ 100 mL or ≥ 200 mL change), hemoglobin-corrected DLCO (clinically important difference in an IPF population is not defined; however, a change of 10% to 15% in predicted values is used clinically), and 6-minute walk distance (a difference of 24 to 45 m in the 6-minute walk test has been reported to be clinically important in the IPF population).¹⁹ All pulmonary function test readings were centralized. The correlation of the least-squares mean change of FVC percentage (predicted values) and measures of quantitative imaging (a secondary end point) is not reported in this article.

Adverse events and tolerability were assessed by means of scheduled physical examinations, vital signs evaluation, 12-lead electrocardiogram, clinical laboratory test results, any incidental testing, and recording of adverse events, including serious adverse events. The frequency and severity of adverse events were documented according to the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0). Tolerability analyses were descriptive.

Additional adverse events of interest included respiratory decline events (any unscheduled visits to a health care professional or urgent care for deterioration in respiratory status, or hospitalization due to a worsening of respiratory symptoms; see eAppendix [Respiratory Decline Events] in Supplement 2). Drug-induced liver injury was assessed post hoc via evaluation of drug-induced serious hepatotoxicity (eDISH) plot. Serum levels of antibodies to human pentraxin 2 were measured to assess potential immune response to study drug every 4 weeks. All patients were observed for symptoms of infusion reaction, including allergic reactions or hypersensitivity.

Statistical Analysis

Assuming that it would not be possible to evaluate data for 15% of patients, the sample size was calculated as 117 patients (78 patients in the recombinant human pentraxin 2 group and 39 patients in the placebo group) to provide 80% power to demonstrate superiority with a 2-sided type I error rate of .10. The study was powered to detect a difference of 2.63 in FVC percentage (predicted value) favoring the recombinant human

pentraxin 2 group, based on the following assumptions: (1) 75% of patients were receiving concurrent IPF therapy; (2) a decline of 3% in patients not receiving concurrent IPF therapy in the placebo group; and (3) a decline of 1.5% in patients receiving concurrent IPF therapy in the placebo group (resulting in an average decline of 1.88% in the placebo group) compared with an increase of 0.75% in the recombinant human pentraxin 2 group (with or without concurrent IPF treatment). The goal of the stratified randomization was to provide a similar proportion of patients in both treatment groups receiving concomitant pirfenidone or nintedanib, and patients not receiving concurrent IPF therapy.

The primary efficacy end point as well as secondary end points collected at each visit were analyzed using linear mixed models for repeated measures with the end point from week 4 to week 28 as a dependent variable, and time (days since first dose), treatment group, and the treatment \times time interaction as explanatory variables. Post hoc analyses were performed to assess the potential effects of site (random model effect) and sex (fixed model effect) on the results. The statistical model was used without imputation of missing values and is valid under the assumption of missing at random. Multiple imputations technique (jump to reference method)²⁰ was used to assess the robustness of the primary efficacy analysis.

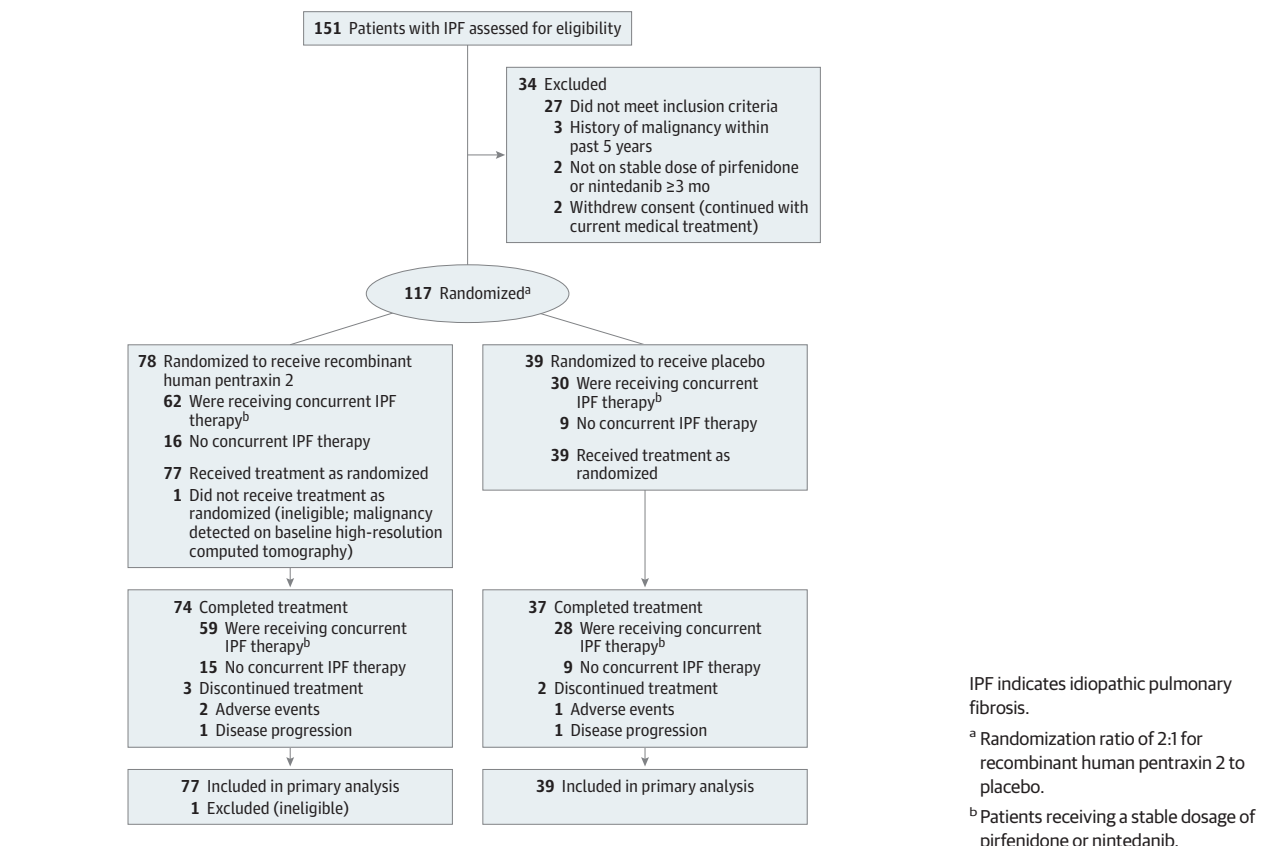
To analyze data collected only at baseline and week 28, a linear model was fitted with the observed change from baseline to week 28 as the response variable and treatment group as the explanatory variable. Both models were adjusted for concurrent treatment status and corresponding baseline score. The comparison of recombinant human pentraxin 2 vs placebo was conducted by computing the difference in the estimated change from baseline at week 28, the corresponding 90% CI, and the *P* value of the difference estimate vs 0. Statistical significance was determined using a 2-sided type I error rate of .10. Given the multiplicity of secondary end points and risk of type I error, some end points may be considered exploratory in nature. Interaction tests were conducted to assess if background therapy status influenced the primary efficacy end point. All analyses were performed on all randomized patients having received at least 1 dose of the study medication. SAS version 9.4 was used for the statistical analyses.

Results

Patients

During the study period (August 2015 and May 2017), 151 patients were screened, 117 underwent randomization, and 116 received at least 1 dose of the study drug. A total of 111 patients completed the study and 5 patients discontinued from the study (Figure 1). The baseline characteristics of recombinant human pentraxin 2 and placebo-treated patients were similar (Table 1). Participants were predominantly male (81.0%). Patients' mean age was 68.6 years and their mean time since IPF diagnosis was 3.8 years. A total of 91 patients (78.4%) were receiving concurrent therapy (pirfenidone or nintedanib) at baseline. Men were more likely to be receiving concurrent IPF therapy compared with women (36.0% vs 14.3%).

Figure 1. Participant Flow in a Trial of Recombinant Human Pentraxin 2 vs Placebo for Idiopathic Pulmonary Fibrosis



A total of 15 patients (12.9%) noted not having received IPF treatment in the past.

Overall, the mean (SD) baseline plasma pentraxin 2 concentration was 30 626 ng/mL (12 463 ng/mL) and was similar between treatment groups. No patients had antidrug antibodies at baseline. Almost all randomized patients received the 9 planned infusions (73 patients [94.8%]) in the recombinant human pentraxin 2 group and 37 patients [94.9%] in the placebo group. The volume of study drug administered vs intended administration volume was above 96%.

Primary End Point

The between-group difference in least-squares mean change in FVC percentage of predicted value from baseline to week 28 in patients treated with recombinant human pentraxin 2 (−2.5) compared with placebo (−4.8) was 2.3 (90% CI, 1.1 to 3.5; $P = .001$; Figure 2A). This effect was independent of concurrent IPF therapy status ($P = .65$). In separate subgroup analyses, the between-group difference in least-squares mean change of FVC percentage of predicted value in patients treated with recombinant human pentraxin 2 (0.1) compared with placebo (−1.9) without concurrent IPF therapy was 2.0 (90% CI, −0.2 to 4.1; $P = .13$), and the between-group difference in least-squares mean change of FVC percentage of predicted value in patients treated with recombinant human pentraxin 2 (−3.1) compared with placebo (−5.7) in the subgroup who received

concomitant pirfenidone or nintedanib was 2.6 (90% CI, 1.3 to 4.0; $P = .002$; Figure 2A). Patients treated with recombinant human pentraxin 2 had less decline in observed mean change in FVC percentage of predicted value over time compared with patients treated with placebo (Figure 2B). Additional analyses showing the distribution in observed change in FVC percentage of predicted value were performed and are shown in eFigure 1 in Supplement 2.

There was no indication of a sex or site effect when added to the model because a post hoc analysis showed a significant treatment effect for recombinant human pentraxin 2 vs placebo on FVC percentage of predicted value ($P < .01$). Imputation of missing data using a conservative method (jump to reference method)²⁰ still provided a significant treatment × time interaction for FVC percentage of predicted ($P = .02$).

Secondary End Points

In the quantitative HRCT analysis, no significant differences in least-squares mean changes were observed in the recombinant human pentraxin 2 group compared with the placebo group from baseline to week 28 for total lung volume (93.5 mL [90% CI, −27.7 to 214.7]; $P = .20$), percentage of normal lung volume (−1.2% [90% CI, −4.4% to 1.9%]; $P = .52$), or percentage of interstitial lung abnormalities (1.1% [90% CI, −2.2% to 4.3%]; $P = .58$) (see eFigure 2 in Supplement 2 for data by background therapy status, as well as additional

analyses showing the distribution of the observed changes). Categorical changes in FVC are presented in eTable 1 (Supplement 2). Increases of 5% or greater in FVC percentage of predicted value were observed in 2 patients (3.0%) treated with recombinant human pentraxin 2 and none in the placebo group ($P = .29$); 7 patients (10.4%) in the recombinant human pentraxin 2 group and none in the placebo group experienced an increase of 100 mL or greater in FVC ($P = .05$). A total of 20 patients (29.9%) in the recombinant human pentraxin 2 group and 13 patients (37.1%) in the placebo group experienced a 5% or greater decrease in FVC percentage of predicted value ($P = .42$). Thirty-seven patients (55.2%) in the recombinant human pentraxin 2 group and 18 patients (51.4%) in the placebo group experienced a decrease of 100 mL or greater in FVC ($P = .78$).

The difference in least-squares mean change in DLCO between patients in the recombinant human pentraxin 2 group and the placebo group from baseline to week 28 was -0.4 (90% CI, -2.6 to 1.7 ; $P = .74$) (see eFigure 3 in Supplement 2 for data by background therapy status, as well as an additional analysis showing the distribution of the observed changes). In the 6-minute walk test, the difference between patients treated with recombinant human pentraxin 2 (-0.5 m) and placebo (-31.8 m) in least-squares mean change from baseline to week 28 was 31.3 m (90% CI, 17.4 to 45.1 ; $P < .001$; Figure 3A). This effect was dependent on concurrent IPF therapy status ($P = .002$). The between-group difference in least-squares mean change from baseline to week 28 in the 6-minute walk test distance in patients treated with recombinant human pentraxin 2 (33.7 m) compared with placebo (-43.6 m) in the subgroup without concurrent IPF therapy was 77.2 m (90% CI, 25.2 to 129.3 ; $P = .02$ Figure 3A); the between-group difference in patients treated with recombinant human pentraxin 2 (-8.9 m) compared with placebo (-30.5 m) in the subgroup that received concurrent pirfenidone or nintedanib was 21.6 m (90% CI, -1.2 to 44.4 ; $P = .12$; Figure 3A). Patients treated with recombinant human pentraxin 2 experienced stabilization in the observed mean change in the 6-minute walk test over time, whereas patients treated with placebo experienced a decline (Figure 3B). Additional analyses showing the distribution of observed change in the 6-minute walk test were performed and are shown in eFigure 4 in Supplement 2.

Adverse Events

Of 108 patients (93.1%) who experienced an adverse event during the trial, 107 patients (92.2%) experienced an event after receiving treatment (Table 2). Most events were mild or moderate in intensity. Cough was the most frequently reported adverse event (18% in the recombinant human pentraxin 2 group and 5% in the placebo group). Serious adverse events occurred in 6 patients (7.8%) in the recombinant human pentraxin 2 group and 4 patients (10.3%) in the placebo group. None of the serious adverse events were considered related to the study treatment. Three patients (2.6%) experienced adverse events that led to discontinuation from the study drug (2 patients in the recombinant human pentraxin 2 group and 1 patient in the placebo group). One patient in the placebo group died from pneumonia.

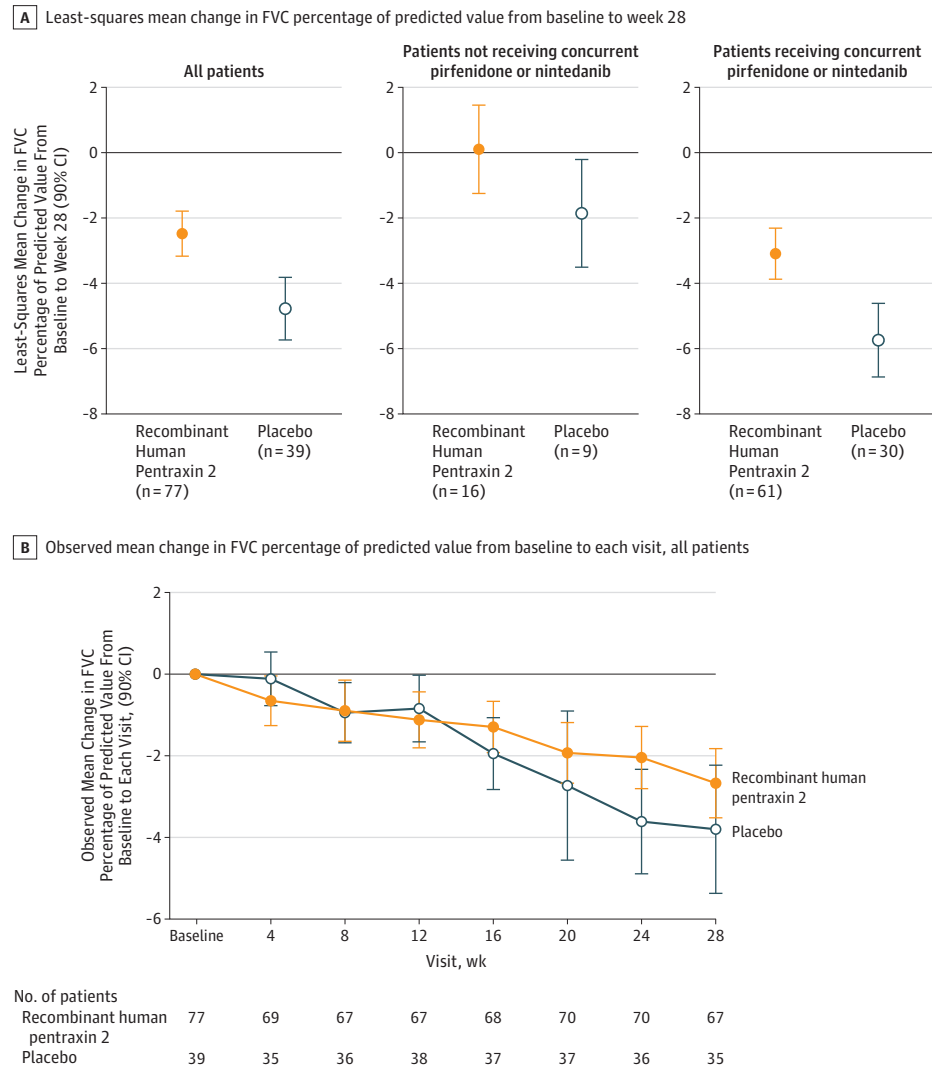
Table 1. Baseline Characteristics of Patients

Characteristics	Recombinant Human Pentraxin 2 (n = 77)	Placebo (n = 39)
Male sex, No. (%)	65 (84)	29 (74)
Age, mean (SD), y	69.0 (6.3)	67.6 (7.1)
Weight, mean (SD), kg	86.1 (15.2)	87.5 (13.4)
Time since diagnosis of IPF		
Mean (SD), y	3.7 (2.2)	3.9 (2.6)
Median (IQR), y	3.0 (2.0-5.0)	3.0 (2.0-4.0)
FVC		
Mean (SD), mL	2733 (630)	2763 (654)
Median (IQR), mL	2700 (2320-3140)	2610 (2290-3250)
Percentage of predicted value, mean (SD)	67.7 (10.9)	67.4 (11.4)
FEV ₁ /FVC, mean (SD), %	81.2 (5.1)	81.6 (4.7)
Hemoglobin-corrected DLco, % of predicted values, mean (SD)	40.1 (9.14)	43.2 (10.5)
6-min walk test distance		
Mean (SD), m	434.8 (92.5)	457.7 (117.7)
Median (IQR), m	436.0 (368.0-494.0)	450.0 (370.0-535.0)
Sp _{O₂} at rest, mean (SD), %	95.6 (2.1)	95.5 (1.8)
Patients with Sp _{O₂} at rest <95%, No. (%)	20 (26)	9 (23)
IPF therapy status at baseline, No. (%)		
Concurrent IPF therapy	61 (79)	30 (77)
Pirfenidone	39 (64)	22 (73)
Nintedanib	22 (36)	8 (27)
No concurrent IPF therapy	16 (21)	9 (23)
IPF therapy naive	8 (10)	7 (18)
Baseline pentraxin 2 concentrations		
Mean (SD), ng/mL	30 456 (13 567)	30 962 (10 090)
Median (IQR), ng/mL	29 500 (23 500-38 750)	29 500 (26 250-33 500)
Comorbid conditions		
GERD	47 (61)	16 (41)
Hypertension	38 (49)	14 (35)
Cardiac disorders	29 (38)	7 (18)
Coronary artery disorders	15 (19)	4 (10)
Emphysema	2 (3)	0
Pulmonary hypertension	1 (1)	3 (8)

Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; Sp_{O₂}, oxygen saturation of peripheral blood.

Four infusion-related reactions (IRRs) occurred in 3 patients. One patient in the recombinant human pentraxin 2 group experienced dizziness and another experienced a hypertensive crisis event; 1 patient in the placebo group experienced 2 hypertensive crisis events. None of the IRR events were deemed serious. There were no IRR events among the 7 patients with antidrug antibodies (6 patients in the recombinant human pentraxin 2 group; 1 patient in the placebo group) by week 28.

Figure 2. Least-Squares Mean Change (Primary End Point) and Observed Mean Change in Forced Vital Capacity Percentage of Predicted Value From Baseline to Week 28



Of the 17 adverse events coded as IPF, 3 were IPF exacerbation events (1 event in 1 patient [1.3%] in the recombinant human pentraxin 2 group and 2 events in 1 patient [2.6%] in the placebo group that led to hospitalization). The remaining 14 events corresponded to IPF progression (10 patients in the recombinant human pentraxin 2 group [13.0%] and 4 patients in the placebo group [10.3%]); 1 patient in the placebo group (1.3%) required hospitalization. Four patients (10.3%) in the placebo group experienced a total of 8 respiratory decline events; 7 events were deemed serious. In the recombinant human pentraxin 2 group, 11 patients (14.3%) experienced a total of 14 respiratory decline events, of which 4 events were deemed serious.

Clinically significant elevations were observed for aspartate aminotransferase (2 patients in the recombinant human pentraxin 2 group [2.6%]) and liver function test (3 patients in the placebo group [7.7%]), as determined by an eDISH plot. Few abnormal findings from physical examinations or vital

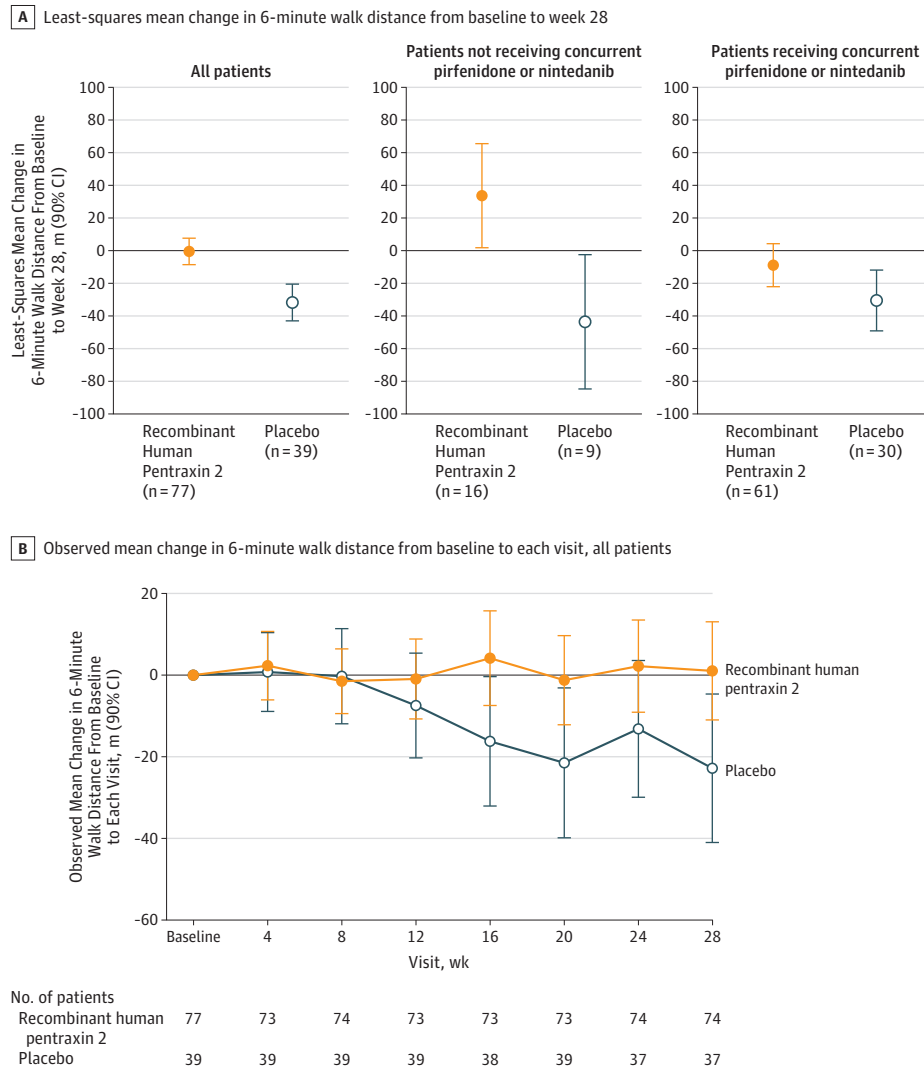
signs were observed. Heart rate, blood pressure, respiratory rate, and oxygen saturation did not change appreciably over the course of the study.

Discussion

In this trial, a significant treatment effect for recombinant human pentraxin 2 vs placebo on the primary end point, least-squares mean change in FVC percentage of predicted value, was observed; the effect was independent of patients receiving concurrent pirfenidone or nintedanib, or no concurrent therapy for IPF. The effect was robust to statistical modeling assumptions and aligned with values considered to be clinically important.¹⁸

The subset of patients who received placebo and concurrent IPF therapy experienced considerable decline in FVC during the trial compared with patients receiving IPF therapy in

Figure 3. Least-Squares Mean Change (Secondary End Point) and Observed Mean Change in 6-Minute Walk Distance From Baseline to Week 28



earlier studies. However, in contrast to patients enrolled in most other IPF clinical trials, the duration since IPF diagnosis prior to enrollment in the recombinant human pentraxin 2 trial was longer. Use of standard-of-care treatments (pirfenidone or nintedanib), reported in 87% of patients in this trial, as well as perceived response to these drugs over time, may have contributed to the time point when patients elected to enroll in this study. This observation curtails the direct comparability of these data to those of earlier IPF trials.

There was no appreciable decline from baseline to week 28 in the mean 6-minute walking distance for patients in the recombinant human pentraxin 2 group. However, there was a statistically significant mean decline of 32 m in patients in the placebo group. For context, results from a pivotal study of pirfenidone showed that all patients experienced a decline in the 6-minute walk test, with less decline experienced by patients who were treated using pirfenidone compared with those who received placebo.⁴ Furthermore, results from a phase 2

study of nintedanib compared with placebo showed that there was no significant difference in decline between treatment groups in the 6-minute walk test.²¹

Although the 6-minute walk findings should be interpreted as exploratory, the lack of decline in the treatment group may suggest a potential benefit for overall functional decline. This difference was also noteworthy because a difference of 24 to 45 m in the 6-minute walk test has been reported to be clinically important in the IPF population.¹⁹ Furthermore, a decline of more than 25 m has been independently associated with 1-year all-cause mortality in IPF,²² which suggests that the 6-minute walk distance may serve as an important measure of prognosis. The literature suggests that the 6-minute walk distance correlates weakly with FVC, DLCO, and dyspnea in patients with IPF.¹⁹

There was no notable difference in rate of adverse events between treatment groups. The most frequently reported adverse event was cough. The types of adverse events reported

Table 2. Adverse Events^a

Events	No. (%) of Patients With Event	
	Recombinant Human Pentraxin 2 (n = 77)	Placebo (n = 39)
Any adverse event	71 (92)	36 (92)
Most frequent adverse events ^b		
Cough	14 (18)	2 (5)
Fatigue	13 (17)	4 (10)
Nasopharyngitis	12 (16)	9 (23)
Headache	11 (14)	3 (8)
Idiopathic pulmonary fibrosis	11 (14)	5 (13)
Diarrhea	9 (12)	2 (5)
Bronchitis	8 (10)	5 (13)
Dyspnea	7 (9)	4 (10)
Upper respiratory tract infection	7 (9)	5 (13)
Back pain	3 (4)	4 (10)
Severe adverse events ^c	7 (9)	2 (5)
Serious adverse events ^d	6 (8)	4 (10)
Fatal adverse events	0	1 (3)
Adverse events leading to discontinuation	2 (3)	1 (3)
Pneumonia	0	1 (3)
Lung carcinoma cell type unspecified stage II	1 (1)	0
Idiopathic pulmonary fibrosis	1 (1)	0

^a Events occurring after the patient received treatment.

^b The most frequent adverse events were defined as those with an incidence greater than 10% in any study group ordered by frequency of occurrence in the recombinant human pentraxin 2 group. eTable 2 in Supplement 2 shows adverse events with an incidence greater than 5%.

^c Adverse events were graded as follows: grade 1 (mild) asymptomatic or mild symptoms and clinical or diagnostic observations only; grade 2 (moderate) minimal, local, or noninvasive intervention indicated; grade 3 (severe) medically significant but not immediately life threatening; grade 4 (life threatening) life threatening consequences with urgent intervention indicated; and grade 5 (fatal), death related to adverse event.

^d A serious adverse event was defined as any adverse event that resulted in death, was immediately life threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.

in this trial are consistent with symptoms common in patients with IPF. The percentage of patients in both treatment groups who experienced disease progression and respiratory decline were similar. Although approximately 9% of patients experienced serious adverse events, none were related to study medication. Infusion-related reactions were infrequent and none were serious.

Limitations

This study had several limitations. First, the sample size used to demonstrate superiority of recombinant human pentraxin 2 treatment over placebo was not appropriate to explore additional hypotheses beyond the prespecified primary analyses; secondary end points should be considered exploratory in nature. Second, the diagnosis of IPF was made in accordance with current guidelines, but allowing for “possible usual interstitial pneumonia,” which has been reported to be a radiologic subtype present in substantial fraction of patients with IPF.²³ Third, the HRCT was not centrally read, which may introduce heterogeneity in the patient population. Fourth, while the quantitative HRCT findings did not show a statistically significant treatment effect, the imaging techniques are susceptible to potential artifacts from inspiratory effort and the expected change over a short trial period is small, which can limit interpretability. Fifth, although the distance walked in 6 minutes has prognostic value and potentially indicated real-world functional status, these data align with earlier studies that suggest this test has weak correlation to other quantifiable parameters. This signal in early data for the small trial is an opportunity for further refinement in the 6-minute walk testing of future trials and determination of correlation with other indicators of disease severity and functional status.

Conclusions

In this preliminary study, infusions of recombinant human pentraxin 2 vs placebo resulted in a slower decline in lung function over 28 weeks for patients with idiopathic pulmonary fibrosis. Further research should more fully assess efficacy and tolerability.

ARTICLE INFORMATION

Accepted for Publication: April 23, 2018.

Published Online: May 20, 2018.

doi:10.1001/jama.2018.6129

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Obtained funding: Golden.

Administrative, technical, or material support: van den Blink, Hamblin, Wijsenbeek, Kreuter, Mulder, Bartholmai.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Dr Raghu reports receipt of grant support to his institution for study costs for the clinical trial and personal fees for consulting during the conduct of the study; and for consulting outside the submitted work: receipt of personal fees and other from Boehringer Ingelheim and Sanofi; personal fees from Promedior, Fibrogen, Patara, and Veracety; and other from Gilead Sciences, Roche-Genentech, Bristol-Myers Squibb, Bellorophon, and Nitto. Dr Hamblin reports receipt of research grant support from Promedior during the conduct of the study; and outside the submitted work: a clinical trial research grant and a medical education grant from Boehringer Ingelheim, and clinical trial research grants from Genentech, Biogen, Fibrogen, and Global Blood Therapeutics; and personal fees from Boehringer Ingelheim and Genentech for serving as a contracted speaker. Dr Brown reports receipt of grants and personal fees from Promedior during the conduct of the study; and receipt of personal fees from Genentech (advisory board), Theravance Biopharma (consulting fees), and Pilot for IPF (honorarium for curriculum development for CME programs) outside the submitted work. Dr Golden reports receipt of a research support grant from Promedior. Dr Ho has reports receipt of personal fees from Genentech and Boehringer Ingelheim for serving on an advisory board. Dr Wijsenbeek reports receipt of research grants to her institution from Boehringer Ingelheim and Intermune/Hoffman la Roche, personal fees and other from Boehringer Ingelheim and Intermune/Hoffman la Roche; and other from Galapagos. Dr Antin-Ozerkis reports receipt of grants to her institution from Promedior during the conduct of the study and grants from Genentech, Fibrogen, and Boehringer Ingelheim outside the submitted work. Dr Meyer reports receipt of research grants from the National Institutes of Health (NIH), Genentech/Roche, InterMune, Parion, Nivalis, Promedior; and personal fees for speaking engagements from the University of Nebraska and Practice Point Communications and National Jewish Health. Dr Kreuter's institution has received research support from Roche and Boehringer Ingelheim. Dr Kreuter reports receipt of independent grants to his institution and personal fees from Roche and form Boehringer Ingelheim and personal fees for consulting work from AstraZeneca, GlaxoSmithKline, Galapagos, and Chiesi. Dr Santin-Janin reports receipt of other from Venn Life Sciences, the contractor that provided statistical analysis for this study. Dr Mulder reports being a nonexecutive director on the board of Promedior. Dr Bartholmai reports receipt of personal fees from Promedior for serving as a scientific advisor during the conduct of the study; personal fees from Imbio outside the submitted work; and a pending patent (licensee, Mayo Clinic) for systems and methods for analyzing in vivo tissue volumes using medical imaging. Dr Richeldi reports receipt of research grants from InterMune; and personal fees from InterMune, Roche, Fibrogen, and Promedior (advisory board member), Sanofi, ImmuneWorks, Celgene, Nitto, and Bristol-Myers Squibb (consulting), Shionogi (speaker), Boehringer Ingelheim (steering committee), and DynaMed (editorial activity). No other disclosures were reported.

Funding/Support: The study was funded by Promedior.

Role of the Funder/Sponsor: Promedior, the study sponsor, took part in the design and conduct of the

study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr Raghu, the lead investigator, had the final decision to submit the manuscript for publication.

Meeting Presentation: Presented, in part, at the American Thoracic Society international conference on May 20, 2018; San Diego, California.

Additional Contributions: We thank the patients for their time and participation in the trial; Donna Moran, Promedior, Lexington, Massachusetts, for clinical project management, and Brigitte Mahner, MD, for medical monitoring, and Francois Aubin, MD, Medical and Methodology Department, Venn Life Sciences, Paris, France; Apurva H. Davé, PhD, Medical Expressions, Chicago, Illinois, for preparing the first draft of the manuscript (under the direction of the first and last authors; compensated by Promedior); Kevin Anstrom, PhD, biostatistician at Duke University Clinical Research Institute, for helpful comments and careful review of the manuscript (consulting fees were paid to his institution); and the following contributors for serving as clinical investigators in the study: Andreas Günther, MD, Univeritätsklinikum Geissen, Geissen, Germany; Maria Molina, MD, PhD, University Hospital of Bellvitge, Barcelona, Spain; Carlo Vancheri, MD, PhD, University of Catania, Catania, Italy; Romain Lazor, MD, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Tristan Huie, MD, National Jewish Health and University of Colorado, Denver; Corey Dean Kershaw, MD, University of Texas Southwestern Medical Center, Dallas; Rafael Perez, MD, University of Louisville, Louisville, Kentucky; and Leo Ginns, MD, Massachusetts General Hospital, Boston (all of whom received research support for their role in the study).

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