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Published in:
American Journal of Respiratory and Critical Care Medicine

Publication status and date:
Published: 01/10/2024

DOI (link to publisher):
10.1164/rccm.202405-0977OC

Document Version
Publisher's PDF, also known as Version of record

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Citation for the published version (APA):
Corte, T. J., Behr, J., Cottin, V., Glassberg, M. K., Kreuter, M., Martinez, F. J., Ogura, T., Suda, T., Wijsenbeek, M., Berkowitz, E., Elpers, B., Kim, S., Watanabe, H., Fischer, A., & Maher, T. M. (2024). Efficacy and Safety of Admilparant, an LPA_1 Antagonist, in Pulmonary Fibrosis A Phase 2 Randomized Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*, *211*(2), 230-238. https://doi.org/10.1164/rccm.202405-0977OC

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ORIGINAL ARTICLE

Efficacy and Safety of Admilparant, an LPA_1 Antagonist, in Pulmonary Fibrosis

A Phase 2 Randomized Clinical Trial

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Abstract

Rationale: Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) have high morbidity and mortality; thus, novel treatments are needed.

Objectives: Assess efficacy and safety of admilparant (BMS-986278), an oral lysophosphatidic acid receptor 1 antagonist, in patients with IPF and PPF.

Methods: This phase 2, randomized, double-blind, placebo-controlled trial included parallel cohorts of patients with IPF ($n = 278$ randomized, $n = 276$ treated) or PPF ($n = 125$ randomized, $n = 123$ treated) who received 30 mg of admilparant, 60 mg of admilparant, or placebo (1:1:1) twice daily for 26 weeks. Background antifibrotics (both cohorts) and immunosuppressants (PPF only) were permitted.

Measurements and Main Results: Rates of change in percentage of predicted FVC over 26 weeks for IPF were −2.7% (placebo), −2.8% (30 mg), and −1.2% (60 mg) and for PPF were −4.3% (placebo), −2.9% (30 mg), and −1.1% (60 mg). Treatment differences between 60-mg admilparant and placebo were 1.4% (95% confidence interval, −0.1 to 3.0) for IPF and 3.2% (95% confidence interval, 0.7 to 5.7) for PPF. Treatment effect was observed with or without background antifibrotics in both cohorts. Diarrhea occurred at similar frequencies in admilparant arms versus placebo. Transient Day 1 postdose blood pressure reductions were observed in all arms in both cohorts but were greater with admilparant. Treatment discontinuations because of adverse events were similar across IPF arms and lower with admilparant (2.5% [30 mg]; 0% [60 mg]) versus placebo (17.1%) for PPF.

Conclusions: In this first phase 2 study to evaluate antifibrotic treatment in parallel IPF and PPF cohorts, 60-mg admilparant slowed lung function decline and was safe and well tolerated, supporting further evaluation in phase 3 trials.

Clinical trial registered with clinicaltrials.gov identifier (NCT04308681).

Keywords: idiopathic pulmonary fibrosis; lysophosphatidic acid receptor 1 antagonist; antifibrotic; admilparant (BMS-986278)

(Received in original form May 13, 2024; accepted in final form October 1, 2024)

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‡At the time of the analysis.

Supported by Bristol Myers Squibb.

Author Contributions: T.J.C., J.B., F.J.M., T.O., T.S., M.W., B.E., H.W., A.F., and T.M.M. contributed to the study design. All authors had access to the data, which were analyzed by S.K. The authors assume responsibility for data accuracy and completeness and affirm that the study was conducted according to the prespecified protocol and statistical analysis plan. All authors participated in drafting, reviewing, and editing the manuscript and provided approval for publication.

Am J Respir Crit Care Med Vol 211, Iss 2, pp 230–238, Feb 2025
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Originally Published in Press as DOI: 10.1164/rccm.202405-0977OC on October 11, 2024
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: This randomized phase 2 trial assessed the effect of admilparant (BMS-986278), an oral lysophosphatidic acid receptor 1 antagonist, on the rate of decline in percentage of predicted FVC compared with placebo in parallel idiopathic pulmonary fibrosis (IPF, $n = 276$) and progressive pulmonary fibrosis (PPF, $n = 123$) cohorts. Compared with placebo, 60-mg admilparant reduced the rate of decline in percent of predicted FVC by 1.4% in the IPF cohort and 3.2% in the PPF cohort.

What This Study Adds to the Field: These results support further evaluation of admilparant as a treatment option for patients with IPF and PPF in phase 3 trials.

Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are fibrotic interstitial lung diseases (ILDs) that are associated with irreversible loss of lung function and poor prognosis (1). Two antifibrotic treatments, pirfenidone and nintedanib, slow the decline of FVC in patients with IPF (2, 3); however, neither drug halts disease progression, and both are associated with adverse effects that limit treatment duration (4, 5). Similar safety and efficacy have been observed with nintedanib, and, although less conclusive, with pirfenidone, for treatment of patients with PPF (6, 7).

In pulmonary fibrosis, lysophosphatidic acid receptor 1 (LPA_1) activation is associated with fibroblast recruitment, activation/proliferation, and survival, as well as epithelial cell apoptosis, all of which drive lung fibrosis progression (8, 9). In patients with IPF, BMS-986020, a first-generation LPA_1 antagonist, significantly slowed FVC decline over 26 weeks compared with placebo (10); however, further clinical development was discontinued because of off-target hepatobiliary adverse events that were compound specific and unrelated to LPA_1 antagonism (11, 12).

This phase 2 study evaluated the efficacy and safety of admilparant (BMS-986278), a second-generation, oral LPA_1 antagonist, in parallel arms of patients with either IPF or PPF, including those concurrently receiving background antifibrotic treatment. Some of the results of this study have been previously reported in the form of abstracts (13, 14).

Methods

Study Design

This was a phase 2, randomized, double-blind, placebo-controlled study with parallel IPF and PPF cohorts conducted at 79 sites in 17 countries (clinicaltrials.gov identifier: NCT04308681) (15). Randomized patients (1:1:1) received 30 mg or 60 mg of admilparant or placebo twice daily orally for 26 weeks. Centralized randomization with a computer-generated permuted block schedule was managed by interactive response technology. Patients, study staff, and the sponsor were blinded to treatment assignment until after the Week 26 database lock for each cohort. Randomization stratification factors for IPF were country (Japan vs. non-Japan) and background use of antifibrotic treatment (pirfenidone vs. nintedanib vs. none) and for PPF were presence of usual interstitial pneumonia (UIP) pattern (present vs. absent) and background therapy category (antifibrotics ± ILD-targeted immunosuppressants vs. ILD-targeted immunosuppressants vs. none).

As a phase 1 study showed that some healthy volunteers who received placebo or admilparant had reversible and generally asymptomatic blood pressure reductions (16), this study included monitoring for blood pressure changes and for orthostatic signs and symptoms per standard guidelines (17). If prespecified blood pressure criteria (*see* online supplement) were met, additional blood pressure monitoring was implemented, and patients were to receive a dose reduction to 10 mg admilparant or matching placebo twice daily.

The primary endpoint was the rate of change in percentage of predicted FVC (ppFVC) from baseline to Week 26 in patients with IPF. Secondary endpoints included rate of change in ppFVC from baseline to Week 26 in patients with PPF, absolute change in FVC (milliliters) from baseline to Week 26 in each cohort, acute exacerbations of lung fibrosis (18), and safety. Centrally reviewed spirometry evaluations were required to meet acceptability and repeatability criteria (19).

Patients

Patients with IPF (age $\geq$ 40 yr; diagnosis of IPF within 7 yr) or PPF (age $\geq$ 21 yr with high-resolution computed tomography [HRCT] obtained at screening that demonstrates evidence of $>$10% parenchymal fibrosis within the whole lung and evidence of progression within 2 years [i.e., relative decline of $\geq$10% in ppFVC, relative decline in ppFVC $\geq$5% to $<$10% and increased extent of fibrosis on HRCT, or symptoms associated with ILD progression and increased extent of fibrosis on HRCT]) were recruited for the study. Patients with connective tissue disease ILD, other than ILD associated with rheumatoid arthritis, were excluded from the PPF cohort. Additional criteria included ppFVC $\geq$ 40%, FEV_1/FVC $\geq$ 0.7, and percentage of predicted diffusing lung capacity of carbon monoxide $\geq$ 25%, corrected for hemoglobin. Background antifibrotic treatment (nintedanib or pirfenidone) was allowed in both cohorts if dosing was stable for $\geq$3 months before randomization. Background ILD-targeted immunosuppressants (mycophenolate mofetil, mycophenolic acid, azathioprine, and/or tacrolimus) were allowed in the PPF cohort if dosing was stable for $\geq$6 months before randomization.

Statistical Analysis

This phase 2 study was designed under an estimation-based approach and was not powered to claim statistical significance. The

Data sharing: Bristol Myers Squibb is committed to sharing data while maintaining the privacy of patients. View the policy on data sharing and submit a request for data at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

IPF cohort sample size was determined by considering earlier IPF trials (2, 3, 10, 20) and assumed an SD of 6.5%. A sample size of 80 patients per arm was chosen, allowing for sufficient precision such that the lower bound of the 95% confidence interval (CI) of the true difference in rate of change in ppFVC between an admilparant arm and the placebo arm would exclude 0 if a difference of 2.5% was observed. No statistical considerations were used to determine the PPF cohort size.

All randomized patients who received one or more study treatment doses were included in efficacy analyses and analyzed according to treatment assignment at randomization. Rate of change in ppFVC was evaluated using a linear mixed-effects model that included random coefficients for intercept and slope for time and treatment, time since randomization, interaction of treatment and time, and baseline stratification factors as covariates in the model. The unstructured covariance was used for the distribution of random coefficients defined. A prespecified two-estimand framework was used to estimate the treatment effect under different conditions, namely with or without dose reduction when blood pressure criteria were met. The following strategies were defined in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 (R1) Statistical Principles for Clinical Trials addendum on estimands and sensitivity analysis in clinical trials in collaboration with regulatory authorities (21, 22). The "treatment policy strategy," similar to an intent-to-treat analysis, included all observed data regardless of dose reduction to provide an estimate of the treatment effect under conditions in which dose reduction may have occurred. The "while-on-treatment strategy" included all observed data before dose reduction to provide an estimate of the treatment effect without dose reduction. Results are reported for the treatment policy strategy, except where indicated. To support the primary analysis in the IPF cohort, a Bayesian approach was used to provide the probability (percentage) of a positive treatment difference for admilparant compared with placebo; the prior distribution was constructed based on historical trials (2, 3, 20). The association of treatment group with the proportion of patients with ⩾10% absolute decline from baseline in ppFVC during the main study period was summarized using the common odds ratio adjusted for cohort-specific stratification factors; patients without baseline ppFVC data were not included in the analysis. A prespecified subgroup analysis compared patients in both cohorts according to background antifibrotic use; in the PPF cohort, an additional subgroup analysis compared patients based on presence/absence of UIP pattern. Absolute change in FVC (milliliters) from baseline to Week 26 was evaluated using a mixed model for repeated measures. No imputations for missing data or adjustments for multiple comparisons were performed. Safety endpoints were evaluated for all patients who received one or more doses of study treatment, analyzed as treated. Prespecified asymptomatic and symptomatic blood pressure criteria were assessed. Treatment-emergent adverse events (TEAEs), serious TEAEs, discontinuations, and deaths were summarized using frequency distribution tables.

Trial Oversight

This study was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, Good Clinical Practice, the International Council for Harmonisation, and applicable local requirements. The protocol and documentation provided to patients were reviewed and approved by independent review boards and independent ethics committees before study initiation. All patients provided written informed consent before all study procedures.

Results

Between July 2020 and February 2023, 403 patients were randomized (278 in the IPF cohort and 125 in the PPF cohort), and 399 received one or more doses of study treatment (276 in the IPF cohort and 123 in the PPF cohort; *see* Figure E1 in the online supplement). Across arms, 18 patients with IPF and 12 patients with PPF had study drug dose reductions after meeting prespecified blood pressure criteria.

Patient demographics and clinical characteristics were generally balanced across arms in each cohort (Table 1). The mean baseline ppFVC was 76.5% and 66.8% for the IPF and PPF cohorts, respectively. Background antifibrotics were used by 67% of patients with IPF and 37% of patients with PPF. Background ILD-targeted immunosuppressants with or without antifibrotics were used by 15% (placebo), 13% (30 mg), and 12% (60 mg) of patients with PPF (Table E1). In addition, UIP pattern was present in 52% of the PPF cohort, and the range of disease subtypes included unclassifiable ILD (27%), chronic hypersensitivity pneumonitis (17%), rheumatoid arthritis–associated ILD (16%), idiopathic fibrotic nonspecific interstitial pneumonia (13%), and interstitial pneumonia with autoimmune features (10%). Seventeen percent had other forms of PPF.

Efficacy

The primary endpoint was evaluated by two prespecified estimands. Using the treatment policy strategy, which included all data, the rate of change in ppFVC over 26 weeks in patients with IPF was −2.7% for placebo versus −2.8% and −1.2% for the 30-mg and 60-mg admilparant arms, respectively. The treatment difference between the 60-mg arm versus placebo was 1.4% (95% CI, −0.1 to 3.0), a relative reduction of 54% (Figure 1A). Using the while-on-treatment strategy, which included all data before dose reduction, the rate of change in ppFVC was −2.8% for placebo versus −3.2% and −1.1% for the 30-mg and 60-mg admilparant arms, respectively. The treatment difference between the 60-mg admilparant arm versus placebo was 1.8% (95% CI, 0.2 to 3.4), a 62% relative reduction (Figure 1B). In the Bayesian analysis, the posterior probability of a positive treatment difference for 60-mg admilparant versus placebo was >95% under both estimand strategies.

The rate of change in ppFVC over 26 weeks in patients with PPF was −4.3% for placebo versus −2.9% and −1.1% for the 30-mg and 60-mg admilparant arms, respectively, per the treatment policy strategy. The treatment difference for 60-mg admilparant versus placebo was 3.2% (95% CI, 0.7–5.7), a relative reduction of 74% (Figure 1C). Using the while-on-treatment strategy, the rate of change in ppFVC was −4.2% for placebo versus −2.7% and −1.3% for the 30-mg and 60-mg arms, respectively. The treatment difference between 60-mg admilparant versus placebo was 3.0% (95% CI, 0.4–5.6), a relative reduction of 70% (Figure 1D).

In the IPF cohort, fewer patients who received 30 mg or 60 mg of admilparant had a ⩾10% absolute decline from baseline in ppFVC over 26 weeks compared with placebo (16 [17%], 9 [10%], and 6 [7%] in the placebo, 30-mg, and 60-mg arms,

Table 1. Baseline Demographics and Clinical Characteristics

Parameter	IPF Cohort			PPF Cohort		
	Placebo (*n* = 92)	30 mg Admilparant (*n* = 91)	60 mg Admilparant (*n* = 93)	Placebo (*n* = 41)	30 mg Admilparant (*n* = 40)	60 mg Admilparant (*n* = 42)
Demographics						
Age, yr	69.0 ± 6.7	69.5 ± 7.3	68.8 ± 7.9	68.8 ± 8.1	71.4 ± 7.9	67.9 ± 8.4
Male sex	76 (82.6)	77 (84.6)	69 (74.2)	20 (48.8)	23 (57.5)	22 (52.4)
Race						
White	65 (70.7)	64 (70.3)	64 (68.8)	31 (75.6)	27 (67.5)	32 (76.2)
Asian	25 (27.2)	25 (27.5)	27 (29.0)	8 (19.5)	9 (22.5)	6 (14.3)
Other	2 (2.2)	2 (2.2)	2 (2.2)	2 (4.9)	4 (10.0)	4 (9.5)
Clinical characteristics						
Weight, kg	76.5 ± 15.0	76.5 ± 14.1	75.8 ± 15.6	71.9 ± 16.2	73.5 ± 17.3	74.9 ± 19.4
BMI, kg/m^2	27.2 ± 4.1	26.9 ± 4.0	27.1 ± 4.5	26.9 ± 4.7	26.3 ± 5.0	27.0 ± 4.8
Cigarette smoking history						
Never	32 (34.8)	30 (33.0)	31 (33.3)	19 (46.3)	19 (47.5)	24 (57.1)
Current	1 (1.1)	1 (1.1)	2 (2.2)	0	0	0
Former	59 (64.1)	60 (65.9)	60 (64.5)	22 (53.7)	21 (52.5)	18 (42.9)
Concurrent background antifibrotic treatment*						
Pirfenidone	26 (28.3)	26 (28.6)	25 (26.9)	3 (7.3)	4 (10.0)	6 (14.3)
Nintedanib	36 (39.1)	36 (39.6)	37 (39.8)	12 (29.3)	11 (27.5)	9 (21.4)
None†	30 (32.6)	29 (31.9)	31 (33.3)	26 (63.4)	25 (62.5)	27 (64.3)
Time since diagnosis, yr	2.7 ± 1.7	2.8 ± 1.6	2.8 ± 1.7	2.8 ± 2.6	3.1 ± 2.7	3.9 ± 2.7
No.	89	82	84	39	36	39
FVC, ml	2,741 ± 810	2,768 ± 770	2,641 ± 768	2,126 ± 616	2,246 ± 728	2,113 ± 723
FVC, percentage of predicted	77 ± 19	77 ± 19	76 ± 17	68 ± 18	67 ± 16	65 ± 17
No.	92	91	93	41	40	42
D_{LCO}, percentage of predicted, hemoglobin corrected	51.1 ± 17.4	50.9 ± 16.2	50.8 ± 18.0	48.0 ± 16.0	48.7 ± 18.7	46.1 ± 12.4
No.	80	81	82	41	40	42
6MWT, m	380.5 ± 112.1	391.6 ± 108.8	396.2 ± 116.1	339.6 ± 108.8	326.6 ± 108.0	340.2 ± 107.5
No.	89	88	90	39	39	42
Quantitative lung fibrosis (HRCT), %	17.3 ± 11.0	17.3 ± 10.8	17.2 ± 10.4	18.1 ± 11.1	19.1 ± 11.9	23.9 ± 12.4

Definition of abbreviations: 6MWT = 6-minute-walk test; BMI = body mass index; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.
Data are presented as mean ± SD or *n* (%).
*Patients with PPF were permitted to remain on background antifibrotics ± ILD-targeted immunosuppressants (Table E1).
†In the PPF cohort, this includes patients with immunosuppression alone.

respectively; odds ratio [95% CI] versus placebo: 0.54 [0.29–1.01] for 30 mg and 0.49 [0.26–0.91] for 60 mg). In the PPF cohort, five patients (14%) and one patient (3%) who received 30 mg or 60 mg of admilparant, respectively, had a ⩾10% absolute decline from baseline in ppFVC over 26 weeks compared with five patients (13%) in the placebo arm (odds ratio [95% CI] vs. placebo: 0.97 [0.24–3.87] for 30 mg and 0.19 [0.02–1.61] for 60 mg). Rate of change in FVC (milliliters) for both cohorts is shown in Figure E2. The adjusted mean treatment differences in absolute change in FVC (milliliters) between the 60-mg admilparant and placebo arms at Week 26 were 45.5 ml for the IPF cohort and 87.4 ml for the PPF cohort (Figure 2). The treatment differences in rates of change in ppFVC were consistent with or without background antifibrotic use in both the IPF (Figures 3A and 3B) and PPF cohorts (Figures 3C and 3D). Similarly, treatment differences were seen in the PPF cohort independent of UIP pattern presence or absence (Figure E3). Acute exacerbations of lung fibrosis were observed in six patients (2%) with IPF (placebo: *n* = 2; 30 mg: *n* = 3; 60 mg: *n* = 1) and in four patients (3%) with PPF (placebo: *n* = 3; 60 mg: *n* = 1).

Safety

TEAEs were reported in 80% (placebo), 76% (30 mg), and 74% (60 mg) in the IPF cohort and in 78% (placebo), 83% (30 mg), and 67% (60 mg) in the PPF cohort (Table 2). Serious TEAEs were reported in 17% of the placebo arm versus 11% of each admilparant arm in the IPF cohort and in 32% of the placebo arm versus 10% (30 mg) and 14% (60 mg) in the PPF cohort. Nine deaths due to TEAEs were evenly distributed across IPF cohort arms; three deaths occurred in the PPF cohort, all in the placebo arm. In the IPF cohort, treatment discontinuations due to TEAEs occurred in 10% (placebo), 10% (30 mg), and 7% (60 mg); in the PPF cohort, discontinuations occurred in 17% (placebo), 3% (30 mg), and 0% (60 mg). No clinically meaningful laboratory or physical examination findings were observed.

Across cohorts, diarrhea was the most common TEAE (Table 2) and was predominantly seen in patients receiving background antifibrotic therapy. In the IPF cohort, rates of diarrhea were 16% (10/62; placebo), 13% (8/62; 30 mg), and 13% (8/62; 60 mg) in patients receiving background

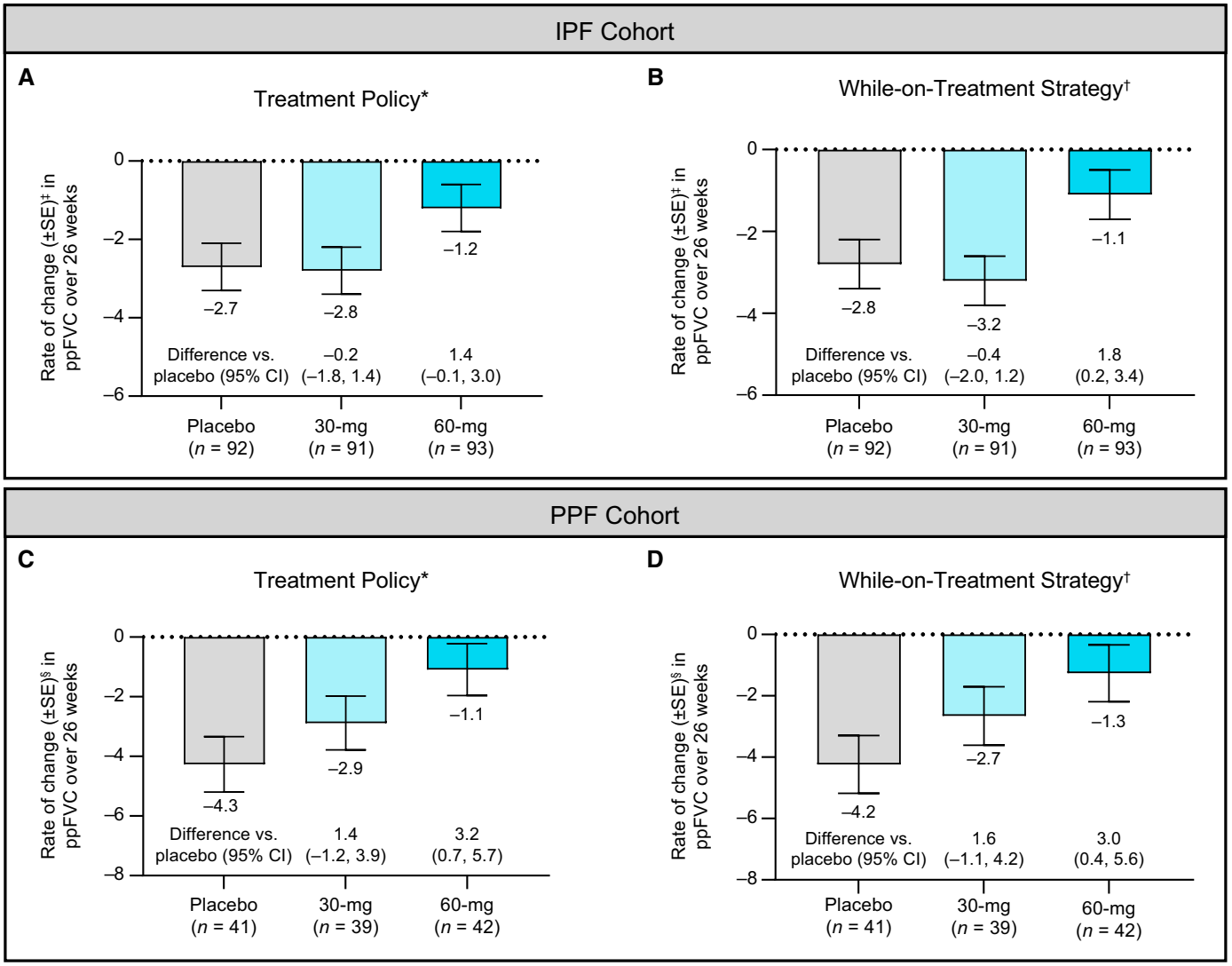


Figure 1. Rate of change in percentage of predicted FVC (ppFVC) over 26 weeks in the IPF cohort for treatment policy (*A*) and while-on-treatment strategy (*B*), and in the PPF cohort for treatment policy (*C*) and while-on-treatment strategy (*D*). *All observed data, regardless of dose reduction, were included and analyzed as randomized. †All observed data before dose reduction were included and analyzed as randomized. Thus, data on and after dose reduction were excluded. ‡Linear mixed model (IPF): ppFVC (%) = treatment + time + treatment × time + antifibrotic drug type + region. §Linear mixed model (PPF): ppFVC (%) = treatment + time + treatment × time + exposure to antifibrotics + usual interstitial pneumonia pattern. The difference in rate of change in ppFVC for each admilparant arm compared with placebo is shown (together with corresponding 95% CIs) in each graph. CI = confidence interval; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

antifibrotics and were 3% (1/30; placebo), 7% (2/29; 30 mg), and 7% (2/31; 60 mg) in patients without background antifibrotics. In the PPF cohort, diarrhea occurred in 40% (6/15; placebo), 13% (2/15; 30 mg), and 13% (2/15; 60 mg) of patients on background antifibrotics and in 0% (0/26; placebo), 16% (4/25; 30 mg), and 4% (1/27; 60 mg) of patients without background antifibrotics. One treatment discontinuation was due to diarrhea in a patient with IPF in the placebo arm.

Transient postdose reductions in blood pressure were observed in each admilparant dose arm and the placebo arm on Day 1 of the study in both the IPF and PPF cohorts and were greater in active treatment arms. In patients with IPF, the nadir postdose reductions from baseline on Day 1 in mean seated systolic blood pressure were −2.1 mm Hg, −10.8 mm Hg, and −14.1 mm Hg for the placebo, 30-mg, and 60-mg admilparant arms, respectively. In patients with PPF, the nadir postdose reductions from baseline on Day 1 in mean seated systolic blood pressure were −4.2 mm Hg, −10.7 mm Hg, and −12.7 mm Hg for the placebo, 30-mg, and 60-mg admilparant arms, respectively. Prespecified blood pressure criteria were met by similar proportions of patients across IPF cohort arms, but the proportions of patients meeting these criteria increased in a dose-dependent manner across PPF cohort arms (Table E2).

Discussion

This phase 2 trial is the first reported study to evaluate antifibrotic treatment in parallel

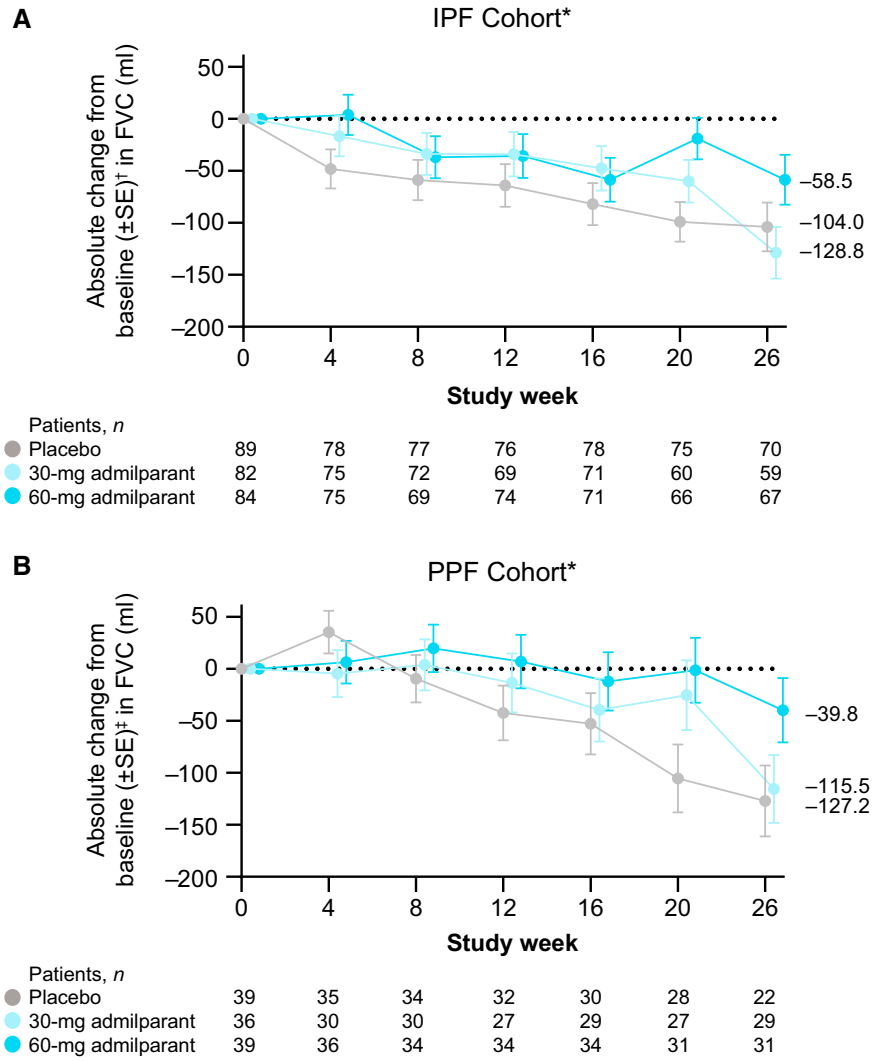


Figure 2. Absolute change in FVC (ml) over 26 weeks in the IPF cohort (*A*) and PPF cohort (*B*). *All observed data regardless of dose reduction were included and analyzed as randomized. †Mixed effect model for repeated measures (IPF): change from baseline in FVC (ml) = treatment + visit + treatment × visit + antifibrotic drug type + region + age + sex + height + baseline FVC (ml). ‡Mixed effect model for repeated measures (PPF): change from baseline in FVC (ml) = treatment + visit + treatment × visit + exposure to antifibrotics + usual interstitial pneumonia pattern + age + sex + height + baseline FVC (ml). IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

cohorts of patients with IPF and PPF. Over 26 weeks of treatment, 60 mg of admilparant, an oral LPA_1 antagonist, reduced the rate of ppFVC decline compared with placebo in both patient populations. Based on the treatment policy and while-on-treatment estimand strategies, the corresponding relative reductions in ppFVC decline were 54% and 62%, respectively, for IPF and 74% and 70%, respectively, for PPF. The treatment effect of 60 mg of admilparant was consistent in subgroups of patients with and without background antifibrotic use in both cohorts and in the presence and absence of UIP pattern in the PPF cohort. This observed treatment benefit among patients with IPF and PPF provides confidence in the validity of the antifibrotic effect of admilparant. Further studies are needed to understand why 30-mg admilparant had a treatment effect in the PPF cohort but not in the IPF cohort. Recognizing the heterogeneity of PPF, possible explanations for the findings could be differences in drug exposure due to variations in baseline characteristics between the two cohorts or a result of the underlying pathophysiology. Indeed, PPF may have more inflammatory drivers, so the antiinflammatory activity of LPA_1 antagonism may provide additive effects. LPA_1 is known to be involved in inflammatory responses of vascular endothelium and fibroblast recruitment, and LPA_1 deficiency attenuated fibroblast recruitment in a murine model of lung fibrosis (8).

Low rates of serious TEAEs and TEAEs leading to discontinuation were observed in each admilparant arm and were comparable to placebo. These findings are noteworthy, particularly because current antifibrotic therapies, which were used as background treatment in 67% and 37% of the IPF and PPF cohorts in this study, respectively, are associated with gastrointestinal adverse effects (2, 3), which can limit treatment persistence and/or require dose adjustments (4, 5). In both cohorts in this study, diarrhea was the

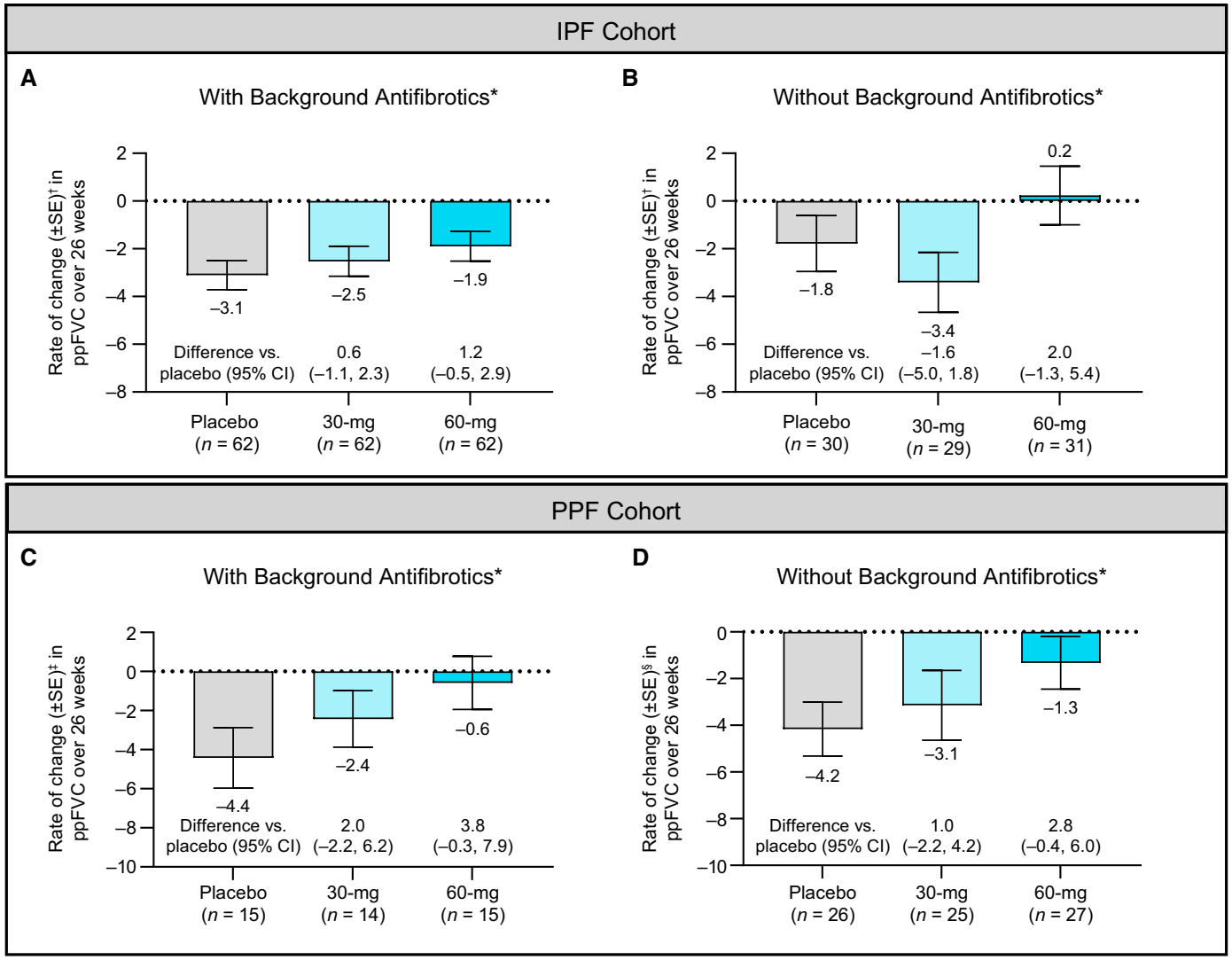


Figure 3. Rate of change in percentage of predicted FVC (ppFVC) over 26 weeks in the IPF cohort for patients with (*A*) and without (*B*) background antifibrotics, and in the PPF cohort for patients with (*C*) and without (*D*) background antifibrotics. *All observed data regardless of dose reduction were included and analyzed as randomized. †Linear mixed model (IPF): ppFVC (%) = treatment + time + treatment × time + region. ‡Linear mixed model (PPF): ppFVC (%) = treatment + time + treatment × time + usual interstitial pneumonia pattern. CI = confidence interval; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

most common TEAE; however, rates were low (ranging from 7% to 15% across arms), and events were mostly observed in the subgroups of patients receiving background antifibrotic therapy. Only one treatment discontinuation was due to diarrhea in a patient with IPF in the placebo arm. Postdose reductions in blood pressure on Day 1 were dose dependent and observed in the IPF and PPF cohorts in all study arms but were most pronounced in active treatment arms; these events were transient and mostly asymptomatic.

The inclusion of a parallel cohort of patients with PPF was a novel aspect of this trial, as most clinical trials for ILD have traditionally been targeted at the IPF population. By including a parallel cohort for patients with PPF in this study, patients who may have otherwise been excluded from the trial for not meeting IPF eligibility criteria had the opportunity to participate in the trial. Therefore, the parallel-cohort trial design provided the advantage of broadening the heterogeneity of disease subtypes included in the trial and enhancing the real-world applicability of these results.

The study findings should be considered in the context of several limitations. Although this is one of the largest phase 2 studies in patients with pulmonary fibrosis, the efficacy and safety findings warrant confirmation in larger trials with longer treatment duration. The 26-week treatment duration of this study was not sufficient to conclusively determine whether the effect of admilparant on FVC would translate to a meaningful effect on long-term patient outcomes. Therefore, the effect of a longer treatment duration of admilparant on measures such as quality of life and hospitalizations will be important to evaluate in future IPF and PPF studies. In addition, the small number of patients who were not on background antifibrotics limited firm conclusions being drawn from the subgroup

Table 2. Safety Summary

Patients	IPF Cohort			PPF Cohort		
	Placebo (*n* = 92)	30 mg Admilparant (*n* = 91)	60 mg Admilparant (*n* = 93)	Placebo (*n* = 41)	30 mg Admilparant (*n* = 40)	60 mg Admilparant (*n* = 42)
⩾1 TEAE	74 (80.4)	69 (75.8)	69 (74.2)	32 (78.0)	33 (82.5)	28 (66.7)
⩾1 TEAE related to study drug	20 (21.7)	23 (25.3)	25 (26.9)	7 (17.1)	8 (20.0)	11 (26.2)
⩾1 Serious TEAE	16 (17.4)	10 (11.0)	10 (10.8)	13 (31.7)	4 (10.0)	6 (14.3)
Discontinuations due to TEAEs	9 (9.8)	9 (9.9)	6 (6.5)	7 (17.1)	1 (2.5)	0
Deaths due to TEAEs	2 (2.2)	3 (3.3)	4 (4.3)	3 (7.3)	0	0
TEAEs in ⩾7.5% of patients in any arm across cohorts						
Diarrhea	11 (12.0)	10 (11.0)	10 (10.8)	6 (14.6)	6 (15.0)	3 (7.1)
Cough	5 (5.4)	7 (7.7)	10 (10.8)	4 (9.8)	3 (7.5)	5 (11.9)
COVID-19	6 (6.5)	3 (3.3)	8 (8.6)	2 (4.9)	6 (15.0)	6 (14.3)
Orthostatic hypotension	9 (9.8)	7 (7.7)	5 (5.4)	1 (2.4)	2 (5.0)	4 (9.5)
Dyspnea	8 (8.7)	6 (6.6)	5 (5.4)	6 (14.6)	2 (5.0)	0
Nausea	2 (2.2)	5 (5.5)	4 (4.3)	3 (7.3)	4 (10.0)	1 (2.4)
Dizziness	3 (3.3)	3 (3.3)	2 (2.2)	4 (9.8)	0	4 (9.5)
Hypotension	1 (1.1)	2 (2.2)	4 (4.3)	0	4 (10.0)	3 (7.1)
Hypertension	1 (1.1)	3 (3.3)	7 (7.5)	0	0	1 (2.4)
Vomiting	4 (4.3)	0	2 (2.2)	1 (2.4)	3 (7.5)	0
Rash	1 (1.1)	2 (2.2)	2 (2.2)	0	3 (7.5)	0

Definition of abbreviations: COVID-19 = coronavirus disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis; TEAE = treatment-emergent adverse event.
Data are presented as *n* (%).

analyses. Patients with connective tissue disease ILD, other than rheumatoid arthritis–associated ILD, were excluded from enrollment in the PPF cohort, so the study findings need to be further evaluated in patients with other immune-mediated diseases.

In summary, in this phase 2 study, treatment with 60 mg of admilparant twice daily was associated with reduced lung function decline over 26 weeks compared with placebo, an effect seen with or without background antifibrotic treatment and across IPF and PPF cohorts. Admilparant was generally safe and well tolerated, with low rates of TEAEs and discontinuations due to TEAEs. Together, these findings support further evaluation of admilparant as a therapeutic option for patients with IPF and PPF in phase 3 trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the study staff and investigators, as well as the patients and their families, for their participation in this study. They also thank Edgar Charles, M.D., for protocol development and guidance with conducting the study, Ashfaq Parkar, Ph.D., and Joel Myers, M.Pharm., for critical review and guidance in data interpretation, Steve Greenberg, M.D., for data interpretation, and Giridhar S. Tirucherai, Ph.D., for data analysis and interpretation, all of whom are current or former employees of Bristol Myers Squibb. Medical writing support was provided by Amanda Martin, Ph.D., of Medical Expressions (Chicago, IL), in alignment with guidance from all authors, and editorial support was provided by Parexel International and was funded by Bristol Myers Squibb.

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