ORIGINAL ARTICLE

Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Arata Azuma, M.D., Ph.D., Vincent Cottin, M.D., Ph.D., Christian Hesslinger, Ph.D., Susanne Stowasser, M.D., Claudia Valenzuela, M.D., Marlies S. Wijsenbeek, M.D., Ph.D., Donald F. Zoz, M.D., Florian Voss, Ph.D., and Toby M. Maher, M.D., Ph.D., for the 1305-0013 Trial Investigators*

ABSTRACT

BACKGROUND

Phosphodiesterase 4 (PDE4) inhibition is associated with antiinflammatory and antifibrotic effects that may be beneficial in patients with idiopathic pulmonary fibrosis.

METHODS

In this phase 2, double-blind, placebo-controlled trial, we investigated the efficacy and safety of BI 1015550, an oral preferential inhibitor of the PDE4B subtype, in patients with idiopathic pulmonary fibrosis. Patients were randomly assigned in a 2:1 ratio to receive BI 1015550 at a dose of 18 mg twice daily or placebo. The primary end point was the change from baseline in the forced vital capacity (FVC) at 12 weeks, which we analyzed with a Bayesian approach separately according to background nonuse or use of an antifibrotic agent.

RESULTS

A total of 147 patients were randomly assigned to receive BI 1015550 or placebo. Among patients without background antifibrotic use, the median change in the FVC was 5.7 ml (95% credible interval, −39.1 to 50.5) in the BI 1015550 group and −81.7 ml (95% credible interval, −133.5 to −44.8) in the placebo group (median difference, 88.4 ml; 95% credible interval, 29.5 to 154.2; probability that BI 1015550 was superior to placebo, 0.998). Among patients with background antifibrotic use, the median change in the FVC was 2.7 ml (95% credible interval, −32.8 to 38.2) in the BI 1015550 group and −59.2 ml (95% credible interval, −111.8 to −17.9) in the placebo group (median difference, 62.4 ml; 95% credible interval, 6.3 to 125.5; probability that BI 1015550 was superior to placebo, 0.986). A mixed model with repeated measures analysis provided results that were consistent with those of the Bayesian analysis. The most frequent adverse event was diarrhea. A total of 13 patients discontinued BI 1015550 treatment owing to adverse events. The percentages of patients with serious adverse events or severe adverse events were similar in the two trial groups.

CONCLUSIONS

In this placebo-controlled trial, treatment with BI 1015550, either alone or with background use of an antifibrotic agent, prevented a decrease in lung function in patients with idiopathic pulmonary fibrosis. (Funded by Boehringer Ingelheim; 1305-0013 ClinicalTrials.gov number, NCT04419506.)

The authors' affiliations are listed in the Appendix. Dr. Richeldi can be contacted at luca.richeldi@policlinicogemelli.it or at Unità Operativa Complessa di Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168 Rome, Italy.

*A list of the investigators in the 1305-0013 Trial is provided in the Supplementary Appendix, available at NEJM.org.

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Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible lung disease with high mortality.[1,2] Currently, there are two approved antifibrotic drugs — nintedanib and pirfenidone — that slow, but do not stop, the progression of fibrosis.[3-5] Therefore, there is a need for additional treatments that can be used alone or with existing antifibrotic therapies.[6]

Phosphodiesterase 4 (PDE4) inhibition is associated with antiinflammatory and antifibrotic properties.[7,8] Preferential inhibition of the PDE4B subtype may be beneficial in the treatment of IPF because it may harness these properties[9,10] and is also associated with a more acceptable safety profile than nonselective PDE4 inhibitors.[7,10]

IPF is a rare disease, which makes the recruitment of large numbers of patients in early-phase clinical trials a challenge. In this trial, we used Bayesian analysis[11,12] to incorporate informative historical data from phase 2–4 clinical trials of nintedanib for the control groups. Consistent decreases in the forced vital capacity (FVC) that have been observed in the placebo groups of these trials[3,4,13-16] make such an approach suitable for proof-of-concept studies of new drug candidates for the treatment of IPF. In this multicenter, randomized, double-blind, phase 2 trial, we investigated the efficacy and safety of BI 1015550, an oral preferential inhibitor of PDE4B,[17] in patients with IPF according to background nonuse or use of an antifibrotic agent.

Methods

Patient Population

We enrolled patients 40 years of age or older who had a diagnosis of IPF that was based on current international guidelines.[18] Patients with a usual interstitial pneumonia or a pattern of probable usual interstitial pneumonia on high-resolution computed tomography of the chest, as confirmed by central review, were eligible.[19] Patients also had an FVC of at least 45% of the predicted value and a diffusing capacity of the lungs for carbon monoxide (DLCO), corrected for the hemoglobin level, that was between 25% and less than 80% of the predicted value. Patients were permitted to continue antifibrotic therapy (nintedanib or pirfenidone) if they had been receiving a stable dose for at least 8 weeks before screening. Patients with airway obstruction, recent respiratory tract infection, an acute IPF exacerbation within the past 4 months, receipt of more than 15 mg per day of prednisone, or a history of suicidal behavior in the past 2 years were excluded. Other exclusion criteria are listed in the Supplementary Appendix, which is available with the full text of this article at NEJM.org.

Trial Design and Oversight

We conducted this double-blind, placebo-controlled, parallel-design, phase 2 trial at 90 sites in 22 countries. Patients were randomly assigned in a 2:1 ratio to receive either BI 1015550 at a dose of 18 mg twice daily or matching placebo, administered orally, for 12 weeks. Randomization was performed with the use of an interactive voice-response system and stratified according to background use of an antifibrotic agent (no or yes) at baseline. We aimed to enroll at least 60 patients per trial group and up to 150 patients overall. After the completion of the 12-week treatment period, patients entered a 1-week follow-up period. Patients who prematurely discontinued the trial regimen were asked to attend all trial visits as originally planned in order to minimize missing data. Patients, investigators, central reviewers, and those involved in the trial conduct and analysis were unaware of the trial-group assignments.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Council for Harmonisation and was approved by local authorities. The clinical protocol, which is available at NEJM.org, was approved by an independent ethics committee or institutional review board at each participating center. All the patients provided written informed consent before trial entry.

Six of the authors designed the trial. All the authors had access to the data, which were analyzed by statisticians at Boehringer Ingelheim, the sponsor of the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors were involved in drafting the manuscript. Medical writing assistance, funded by the sponsor, was provided by MediTech Media U.K., in line with guidance from all the authors. The sponsor was given the opportunity to review the manuscript for medical and scientific accuracy as well as for intellectual property considerations. The members of the steering committee (listed in

the Supplementary Appendix) made the decision to submit the manuscript for publication.

END POINTS

The primary end point was the change from baseline in the FVC at 12 weeks. Spirometric results, assessed with the use of spirometers (ERT SpiroSphere) provided by the sponsor, were centrally reviewed to meet American Thoracic Society–European Respiratory Society criteria.[20] The secondary end point was the percentage of patients with adverse events during the treatment period (including the 1-week follow-up period). The change from baseline in the percentage of the predicted value of the DLCO, corrected for the hemoglobin level, was assessed as a further lung-function efficacy end point; the assessment was conducted with the equipment at each trial site and was carried out according to international guidelines.[21] Additional end points included the change from baseline to week 12 in quality of life, which was assessed with the use of the Living with Pulmonary Fibrosis (L-PF) questionnaire.[22] Other end points that were collected but not described here are shown in the Supplementary Appendix.

An independent data and safety monitoring committee evaluated the safety data throughout the trial (see the Supplementary Appendix). Prospective suicidality monitoring was applied throughout the trial with the use of the Columbia Suicide Severity Rating Scale because of the risk that has been described for marketed PDE4 inhibitors.[23-27]

STATISTICAL ANALYSIS

The primary end point was evaluated separately according to background nonuse or use of an antifibrotic agent at baseline and included all the data that had been collected while patients were receiving BI 1015550 or placebo. The primary analysis was based on a Bayesian approach to incorporate historical data for the placebo groups by means of meta-analytic predictive (MAP) priors that were made robust against prior-data conflicts.[11] A vaguely informative prior was used for the BI 1015550 groups. This approach discounts historical data to account for between-trial heterogeneity and leads to dynamic borrowing; that is, the weight given to the historical information depends on the similarity to the current controls. The priors were chosen to reflect an effective sample size that corresponded to approximately 20 historical patients who had received placebo. A sensitivity analysis for the choice of the weight for the informative component of the prior was performed (see the Supplementary Appendix).

The analysis of the primary end point was conducted in a two-step procedure. First, the data from the current trial were analyzed with a restricted maximum likelihood–based approach with the use of a mixed model with repeated measures (MMRM). On the basis of this model, the adjusted mean changes from baseline in the FVC at 12 weeks (and the related standard error) were calculated for the BI 1015550 group and the placebo group according to background nonuse or use of an antifibrotic agent. Second, the adjusted means in the placebo groups were combined with the MAP priors, which were derived on the basis of clinical trials in the clinical development program of nintedanib for the treatment of IPF (see the statistical analysis plan, which is available with the protocol). To evaluate the treatment effects in each trial cohort, the posterior distribution for the difference between the BI 1015550 group and the placebo group with respect to the primary end point was used. The median of the posterior distribution for the difference (and 95% credible interval) was calculated in the primary analysis, and posterior probabilities that the difference was higher than various boundaries were reported.

All the patients who received BI 1015550 or placebo were included in the safety population. The safety analysis was descriptive in nature and was based on adverse events that occurred during the treatment period (including the 1-week follow-up period).

Missing data for the primary analysis (continuous end point) were not imputed. The MMRM analysis allows for missing data, under the assumption that they are missing at random. Sensitivity analyses were conducted to investigate the potential effect of missing data as well as early discontinuation by means of a treatment policy strategy (i.e., including all data regardless of treatment discontinuation[28]), and a pooled analysis was conducted that combined data from all the patients regardless of background treatment with an antifibrotic agent.

Because this was an exploratory trial, no confirmatory testing or adjustment for multiplicity was planned. Therefore, we do not report

any P values but only point estimates together with 95% credible intervals or confidence intervals, depending on the analysis. We aimed to enroll at least 60 patients per trial group and up to 150 patients overall. The sample size was chosen on the basis of the evaluations of posterior probabilities for the change from baseline in the FVC at week 12, with an assumed standard deviation of 200 ml and a difference of 70 ml among patients without background antifibrotic use and of 20 ml among those with background antifibrotic use. With these assumptions, the probability that the median treatment difference was at least 50 ml among patients without background antifibrotic use, or at least 35 ml among those without background antifibrotic use and at least 30 ml among those with background antifibrotic use, was 0.75, whereas the probability was 0.11 under an assumption of no treatment effect (see the Supplementary Appendix).

Quality of life, as assessed with the use of the L-PF questionnaire total score, was analyzed by means of an MMRM approach. Descriptive statistics were planned for the change from baseline in the DLCO at week 12. The DLCO analysis that was based on the same MMRM as defined for the primary end point was conducted post hoc.

RESULTS

PATIENTS

The first patient underwent screening on August 12, 2020, and the last patient completed the trial on October 15, 2021. A total of 147 patients underwent randomization and received either BI 1015550 or placebo (Fig. 1).

The demographic and clinical characteristics of the patients at baseline are shown in Table 1, and the representativeness of the trial population is shown in Table S1 in the Supplementary Appendix. The characteristics of the patients were similar in the two trial groups, although the patients with background antifibrotic use tended to have a longer time since diagnosis and lower

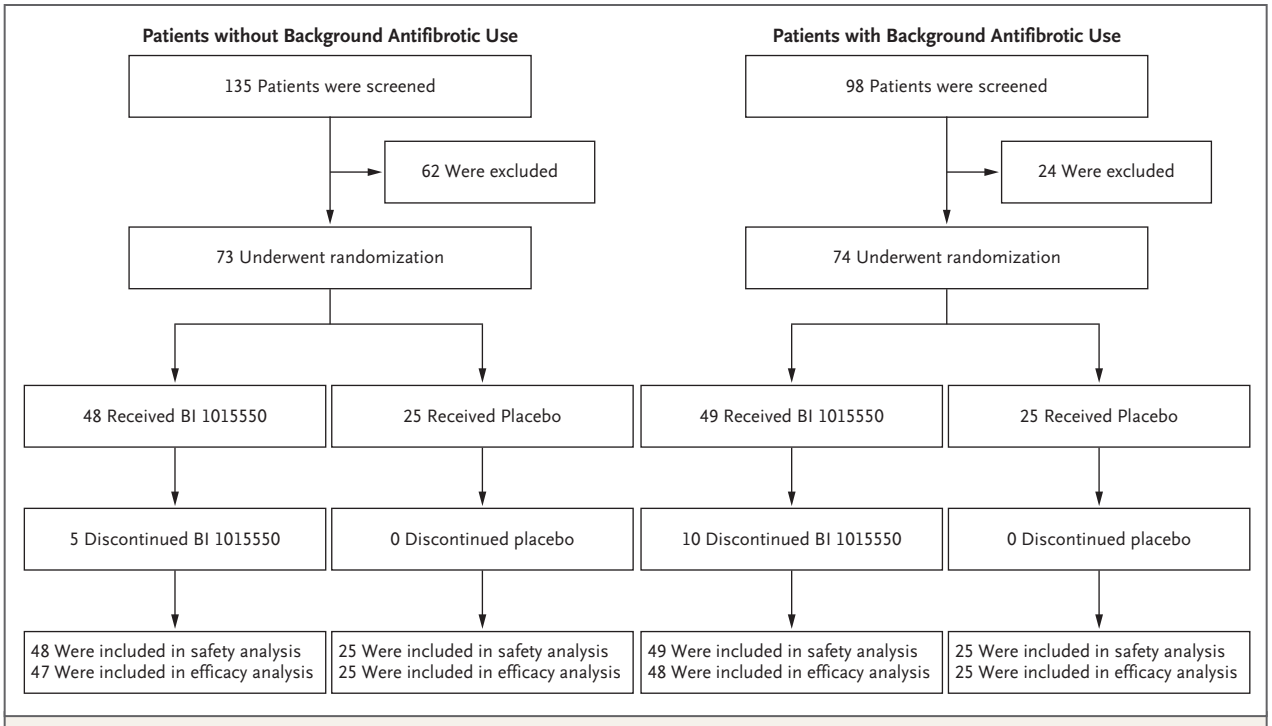

Figure 1. Randomization and Follow-up of the Patients.

Among patients without background antifibrotic use, reasons for premature discontinuation of BI 1015550 included adverse events (in three patients), withdrawal from the trial (in one), and other reason (in one). Among patients with background antifibrotic use, all those who prematurely discontinued BI 1015550 did so because of adverse events. Two patients (one in each cohort) were not included in the efficacy analysis because they did not have postbaseline data on lung function.

Table 1. Characteristics of the Patients at Baseline, According to Cohort.*

Characteristic	Patients without Background Antifibrotic Use		Patients with Background Antifibrotic Use	
	BI 1015550 (N=48)	Placebo (N=25)	BI 1015550 (N=49)	Placebo (N=25)
Male sex — no. (%)	34 (71)	17 (68)	44 (90)	18 (72)
Age — yr	69.9±8.3	71.8±9.3	69.3±6.6	67.5±10.7
Race — no. (%)†				
White	36 (75)	21 (84)	37 (76)	21 (84)
Asian	12 (25)	4 (16)	12 (24)	4 (16)
Weight — kg	75.9±15.2	78.2±16.3	77.4±12.8	81.0±16.8
Body-mass index‡	27.4±5.0	27.6±4.8	26.2±3.0	27.9±5.3
Smoking history — no. (%)				
Never smoked	19 (40)	9 (36)	14 (29)	5 (20)
Former smoker	26 (54)	15 (60)	33 (67)	20 (80)
Current smoker	3 (6)	1 (4)	2 (4)	0
Time since diagnosis of idiopathic pulmonary fibrosis — yr	2.7±2.4	2.2±2.6	4.6±3.7	3.9±3.3
Antifibrotic treatment — no. (%)				
Nintedanib	0	0	26 (53)	17 (68)
Pirfenidone	0	0	23 (47)	8 (32)
Supplemental-oxygen therapy — no. (%)	2 (4)	0	7 (14)	2 (8)
Immunosuppressant therapy — no. (%)				
Oral glucocorticoid	1 (2)	2 (8)	1 (2)	1 (4)
Cyclosporine	1 (2)	0	0	2 (8)
Hydroxychloroquine	1 (2)	0	0	0
Mycophenolate sodium	0	1 (4)	0	0
Tocilizumab	0	0	1 (2)	0
FVC				
Mean — ml	2782.9±835.1	2864.9±1015.1	2875.6±752.8	2690.0±890.0
Median — ml	2646	2835	2869	2411
Percent of predicted value	80.4±16.0	82.1±17.7	75.8±17.9	71.7±12.3
Percent of predicted DLCO, corrected for the hemoglobin level	52.0±16.7	48.3±12.1	49.0±18.3	47.2±14.8
L-PF questionnaire total score§	33.9±18.3	32.4±16.1	25.8±16.7	26.1±15.7

* Plus–minus values are means ±SD. DLCO denotes diffusing capacity of the lung for carbon monoxide, and FVC forced vital capacity.
† Race was noted in the electronic case-report form by the trial site staff. There were no explicit instructions regarding patient report or investigator determination of race.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44-item questionnaire with two modules: Symptoms and Impacts.[22] Scores in the Symptoms and Impacts modules are summed to yield a total L-PF score. Summary scores range from 0 to 100, with higher scores indicating greater impairment.

baseline percentages of predicted values for the FVC than patients without background antifibrotic use.

In the overall population, 132 patients (90%) completed the planned treatment period. A total of 15 patients prematurely discontinued BI 1015550; no patients discontinued placebo. The primary reason for premature discontinuation of BI 1015550

was adverse events (in 3 patients without background antifibrotic use and in 10 with background antifibrotic use). Among patients without background antifibrotic use, the mean (±SD) duration of BI 1015550 use was 81.4±12.3 days and the mean duration of placebo use was 85.6±3.8 days; among patients with background antifibrotic use, these values were 74.6±23.0 days and 84.7±1.5 days, respectively.

EFFICACY

On the basis of the Bayesian analysis, the median change in the FVC was 5.7 ml (95% credible interval, −39.1 to 50.5) in the BI 1015550 group and −81.7 ml (95% credible interval, −133.5 to −44.8) in the placebo group among patients without background antifibrotic use (median difference, 88.4 ml; 95% credible interval, 29.5 to 154.2; probability that BI 1015550 was superior to placebo, 0.998). Among patients with background antifibrotic use, the respective FVC changes were 2.7 ml (95% credible interval, −32.8 to 38.2) and −59.2 ml (95% credible interval, −111.8 to −17.9) (median difference, 62.4 ml; 95% credible interval, 6.3 to 125.5; probability that BI 1015550 was superior to placebo, 0.986) (Fig. 2 and Table S2).

Consistent effects of BI 1015550 treatment on the FVC were shown in the prespecified MMRM analysis, which was based on observed values only (Figs. 2, 3, and S5 and Table S2). The treatment effect that was estimated from the MMRM analysis was similar regardless of background antifibrotic use, with an overall between-group difference of 88.4 ml (95% confidence interval [CI], 40.7 to 136.0). In the MMRM analysis involving patients without background antifibrotic use, the mean change in the FVC from baseline to week 12 was 6.1 ml (95% CI, −39.7 to 51.9) in the BI 1015550 group and −95.6 ml (95% CI, −157.1 to −34.1) in the placebo group (difference, 101.7 ml; 95% CI, 25.0 to 178.4). Among patients with background antifibrotic use, the mean change in FVC from baseline to week 12 was 2.7 ml (95% CI, −33.5 to 38.9) in the BI 1015550 group and −77.7 ml (95% CI, −124.9 to −30.5) in the placebo group (difference, 80.4 ml; 95% CI, 20.9 to 140.0).

Among patients without background antifibrotic use, the change in the percentage of the predicted value for DLCO was similar in the two trial groups, with an adjusted mean difference of 0.8 percentage points (95% CI, −3.5 to 5.0) at 12 weeks. Among patients with background antifibrotic use, the adjusted mean difference between

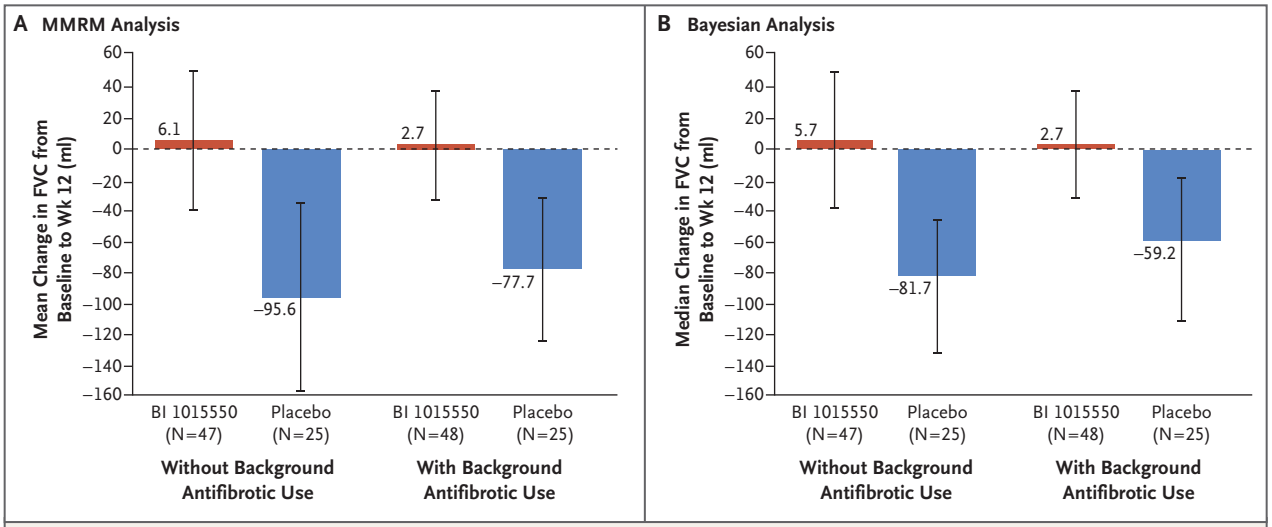

Figure 2. Changes in the Forced Vital Capacity (FVC) at Week 12, According to Background Antifibrotic Nonuse or Use, in MMRM and Bayesian Analyses.

In the mixed model with repeated measures (MMRM) analysis (Panel A), the mean between-group difference in the FVC was 101.7 ml (95% confidence interval [CI], 25.0 to 178.4) among patients without background antifibrotic use and 80.4 ml (95% CI, 20.9 to 140.0) among patients with background antifibrotic use. I bars in Panel A indicate the 95% confidence interval. In the Bayesian analysis (Panel B), the posterior median between-group difference in the FVC was 88.4 ml (95% credible interval, 29.5 to 154.2) among patients without background antifibrotic use and 62.4 ml (95% credible interval, 6.3 to 125.5) among patients with background antifibrotic use. I bars in Panel B indicate the 95% credible interval.

the trial groups was 2.8 percentage points (95% CI, −0.4 to 5.9). Details are provided in Tables S3 and S4 and Figures S6 and S7. The adjusted mean changes in the L-PF total score from baseline to week 12 were similar across the trial groups, regardless of background antifibrotic use (Table S5).

SAFETY

Adverse events during the treatment period (including the 1-week follow-up period) are shown in Tables 2 and S6 through S8. The percentage of patients with any adverse event was higher in the BI 1015550 group than in the placebo group regardless of background antifibrotic use. Adverse events that led to discontinuation were reported only in the BI 1015550 group.

The most common adverse events according to organ class were gastrointestinal disorders. Among patients without background antifibrotic use, gastrointestinal disorders were reported in 27% of those who received BI 1015550 and in 16% of those who received placebo; among patients with background antifibrotic use, the corresponding percentages were 37% and 32%. The most common adverse event, according to preferred term, was diarrhea, which was also the most frequent adverse event leading to the discontinuation of BI 1015550 (in 3 patients). The percentage of patients with diarrhea was higher in the BI 1015550 group than in the placebo group regardless of background antifibrotic use. Most cases of diarrhea were reported as being mild.

Among patients without background antifibrotic use, severe adverse events were reported in 4% of those who received BI 1015550 and in 4% of those who received placebo; among patients with background antifibrotic use, the percentage was also 4% in each group. Among patients without background antifibrotic use, serious adverse events were reported in 6% of those in the BI 1015550 group and in 20% of those in the placebo group; among patients with antifibrotic use, 6% of those in the BI 1015550 group had a serious adverse event, and no patients in the placebo group did so.

Two patients in the BI 1015550 group had fatal adverse events: pneumonia related to coronavirus disease 2019 (Covid-19) (in one patient without background antifibrotic use) and suspected vasculitis and suspected IPF exacerbation (in one patient with background antifibrotic use; the vasculitis was not confirmed by an independent data monitoring committee). No patients reported any adverse events related to depression, suicidal behavior, or suicidal ideation. However, there was one report of suicidal ideation type 1 ("wish to be dead") that occurred 9 days after the completion of BI 1015550 treatment.

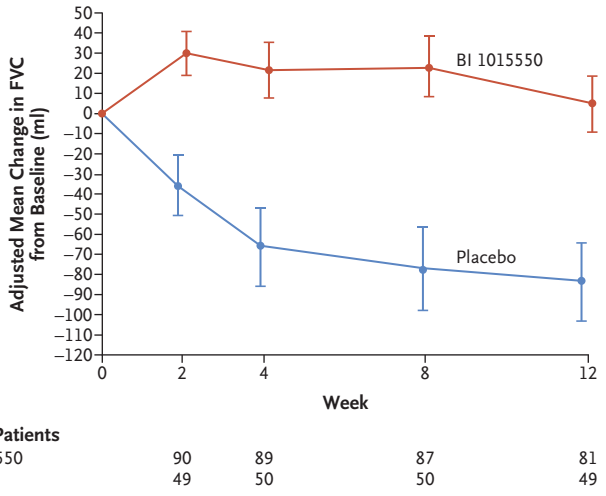

Figure 3. Change in the FVC over Time in All Patients (MMRM Analysis).
I bars indicate the standard error.

DISCUSSION

Treatment with BI 1015550 appeared to stabilize lung function regardless of whether patients were receiving a background antifibrotic agent, in contrast to the placebo group, in which there was a marked decrease in the FVC. The difference between groups was supported by both Bayesian and MMRM analyses.

This trial used a Bayesian approach that allowed more patients to be randomly assigned to active treatment; because of the use of historical data, this approach reduced the number of patients who were assigned to the placebo group for the 12-week duration of the trial.[11,12] This strategy may also have facilitated the recruitment and conduct of the trial, in particular during the Covid-19 pandemic.

The Bayesian approach led to smaller and more conservative estimates of the treatment effect than the MMRM analysis, which used only observed data. However, the Bayesian analysis still led to a 0.998 posterior probability of a positive treatment effect of BI 1015550 among patients

Table 2. Adverse Events during Treatment, Including the 1-Week Follow-up Period, According to Cohort.*

Event	Patients without Background Antifibrotic Use		Patients with Background Antifibrotic Use	
	BI 1015550 (N=48)	Placebo (N=25)	BI 1015550 (N=49)	Placebo (N=25)
	number of patients (percent)			
Any adverse event	31 (65)	13 (52)	36 (73)	17 (68)
Most frequent adverse events†				
Diarrhea	8 (17)	2 (8)	15 (31)	4 (16)
Fatigue	2 (4)	1 (4)	1 (2)	3 (12)
Severe adverse event	2 (4)	1 (4)	2 (4)	1 (4)
Adverse event considered by the investigator to be related to BI 1015550 or placebo	9 (19)	5 (20)	18 (37)	5 (20)
Adverse event leading to discontinuation of trial regimen	3 (6)	0	10 (20)	0
Most frequent adverse event leading to discontinuation of trial regimen: diarrhea‡	0	0	3 (6)	0
Prespecified adverse event of special interest§	0	0	1 (2)	0
Serious adverse event¶				
Any serious adverse event	3 (6)	5 (20)	3 (6)	0
Serious adverse event resulting in death	1 (2)	0	1 (2)	0
Serious adverse event that led to or prolonged hospitalization	2 (4)	3 (12)	3 (6)	0
Other important medical event‖	1 (2)	2 (8)	0	0

* Adverse events were assessed with the use of the *Medical Dictionary for Regulatory Activities*, version 24.1.
† The most frequent adverse events were defined as those with an incidence of more than 10% in any trial group.
‡ The most frequent adverse event leading to the discontinuation of the trial regimen and occurring in more than 5% of the patients in any trial group was diarrhea. No other adverse event met these criteria.
§ Adverse events of special interest were vasculitis and hepatic injury.
¶ There were no reported cases of immediate life-threatening, persistent, or clinically significant disability or incapacity or of congenital anomaly or birth defect.
‖ These adverse events were judged by the investigator to represent a clinically significant hazard.

without background antifibrotic use and a 0.986 posterior probability among those with background antifibrotic use. These findings support the robustness of the results and increase confidence in their validity. Although this trial was only 12 weeks long, it appeared to show the stabilization of FVC with BI 1015550 therapy, which was replicated in patients regardless of background antifibrotic use and thus provides a proof of concept for longer-term phase 3 trials. This conclusion is supported by a recent meta-analysis of clinical trials involving patients with IPF that also showed that differences between active treatment and placebo with regard to FVC can be identified over a period of 12 weeks.[29]

In this trial, patients with IPF who had been receiving a background antifibrotic agent and had been randomly assigned to receive placebo had a greater decrease in the FVC than patients in previous trials.[3-5] The reason for this discrepancy could be because the patients enrolled in this trial may have had more progressive disease than the patients in the other trials.

Overall, the safety profile of BI 1015550 seemed to be acceptable, although the adverse events leading to discontinuation were all reported in pa-

tients treated with BI 1015550; of these 13 patients, 10 were receiving background antifibrotic therapy. The most common adverse events were gastrointestinal disorders; such events led to treatment discontinuation in 5 patients. Although the combination with approved antifibrotic agents seems to be feasible despite an overlap in the gastrointestinal side-effect profile, a comprehensive characterization of the safety profile of BI 1015550 as monotherapy or as combined therapy in a larger patient population over a longer duration in a phase 3 trial is warranted. The percentages of patients with serious or severe adverse events were similar in the BI 1015550 groups and the placebo groups. In preclinical toxicologic studies, PDE4 inhibitors have been linked to vasculitis.[30] In this trial, there was one unconfirmed case that was reported as "suspected IPF exacerbation and suspected vasculitis." It will be important to evaluate vasculitis as an adverse event of special interest in phase 3 trials of BI 1015550.

Limitations of this trial include the 12-week duration and relatively small sample size. Although the size and duration of the trial were sufficient for the determination of changes in the FVC, these factors did not permit the meaningful collection of data relating to clinically important events, including acute exacerbations or death, or the determination of changes in patients' quality-of-life measures. A phase 3 trial will be necessary to evaluate these preliminary findings and assess additional outcomes that are relevant to patients with IPF.

In this placebo-controlled, phase 2 trial, treatment with BI 1015550 at a dose of 18 mg twice daily prevented a decrease in lung function in patients with IPF over a period of 12 weeks, regardless of whether patients were receiving a background antifibrotic agent. The safety profile of BI 1015550, in combination with the observed effects on the FVC, warrants further research as a treatment for IPF and other forms of progressive pulmonary fibrosis.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: Unità Operativa Complessa di Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome (L.R.); Nippon Medical School, Tokyo (A.A.); Hôpital Louis Pradel, Centre National de Référence des Maladies Pulmonaires Rares, Hospices Civils de Lyon, Unité Mixte de Recherche 754 Institut National de la Recherche Agronomique and Université Claude Bernard Lyon 1, ERN-LUNG (European Reference Network on Rare Respiratory Diseases), RespiFil, OrphaLung, Lyon, France (V.C.); Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim International, Biberach (C.H.), and TA Inflammation Medicine (S.S.), Boehringer Ingelheim Pharma (F.V.), Ingelheim am Rhein — both in Germany; the Interstitial Lung Disease Unit, Department of Pulmonology, Hospital Universitario de la Princesa, University Autonoma de Madrid, Madrid (C.V.); the Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands (M.S.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.F.Z.); Keck School of Medicine, University of Southern California, Los Angeles (T.M.M.); and the National Heart and Lung Institute, Imperial College London, London (T.M.M.).

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