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Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Idiopathic pulmonary fibrosis is a progressive lung disease with a high mortality rate. Because the signaling pathways activated by several tyrosine kinase receptors have been shown to be involved in lung fibrosis, it has been suggested that the inhibition of these receptors may slow the progression of idiopathic pulmonary fibrosis.

METHODS

In a 12-month, phase 2 trial, we assessed the efficacy and safety of four different oral doses of the tyrosine kinase inhibitor BIBF 1120 as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Secondary end points included acute exacerbations, quality of life (measured with the St. George's Respiratory Questionnaire [SGRQ]), and total lung capacity.

RESULTS

A total of 432 patients underwent randomization to receive one of four doses of BIBF 1120 (50 mg once a day, 50 mg twice a day, 100 mg twice a day, or 150 mg twice a day) or placebo. In the group receiving 150 mg of BIBF 1120 twice a day, FVC declined by 0.06 liters per year, as compared with 0.19 liters per year in the placebo group, a 68.4% reduction in the rate of loss with BIBF 1120 ($P=0.06$ with the closed testing procedure for multiplicity correction; $P=0.01$ with the hierarchical testing procedure). This dose also resulted in a lower incidence of acute exacerbations, as compared with placebo (2.4 vs. 15.7 per 100 patient-years, $P=0.02$) and a small decrease in the SGRQ score (assessed on a scale of 0 to 100, with lower scores indicating better quality of life) as compared with an increase with placebo (–0.66 vs. 5.46, $P=0.007$). Gastrointestinal symptoms (which led to more discontinuations in the group receiving 150 mg twice a day than in the placebo group) and increases in levels of liver aminotransferases were more frequent in the group receiving 150 mg of BIBF 1120 twice daily than in the placebo group.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, BIBF 1120 at a dose of 150 mg twice daily, as compared with placebo, was associated with a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT00514683.)

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Idiopathic pulmonary fibrosis is a debilitating disease characterized by destruction of the gas-exchanging regions of the lung.[1] Its pathogenesis is thought to involve aberrant wound healing mediated by multiple signaling pathways, resulting in progressive lung injury and scarring.[1] Symptoms, including cough and dyspnea, limit physical activity and reduce the patient's quality of life and independence.[2] The course of the disease is difficult to predict, but it generally involves progressive deterioration, with a median survival time of 2.5 to 3.5 years after diagnosis.[3] Unpredictable acute exacerbations occur in some patients and are often fatal.[3,4]

BIBF 1120 is a potent intracellular inhibitor of tyrosine kinases that is in clinical development for the treatment of idiopathic pulmonary fibrosis and a number of types of cancer.[5] Its targets include platelet-derived growth factor receptors (PDGFR) α and β (half-maximal inhibitory concentration [IC_{50}], 59 and 65 nmol per liter, respectively), vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3 (IC_{50}, 34, 21, and 13 nmol per liter, respectively), and fibroblast growth factor receptors (FGFR) 1, 2, and 3 (IC_{50}, 69, 37, and 108 nmol per liter, respectively).[5] Because signaling pathways activated by these tyrosine kinase receptors have been shown to be involved in lung fibrosis,[6,7] inhibition of the receptors may slow the progression of idiopathic pulmonary fibrosis.[8-12] In a rat model, such inhibition was shown to prevent the development of bleomycin-induced lung fibrosis when a tyrosine kinase inhibitor was administered before or during the fibrotic phase of the disease.[9]

The aim of this 12-month, randomized, double-blind, placebo-controlled, phase 2 trial (To Improve Pulmonary Fibrosis with BIBF 1120 [TOMORROW]) was to evaluate the efficacy and safety of four different doses of BIBF 1120 in patients with idiopathic pulmonary fibrosis.

Methods

Patients

We recruited patients 40 years of age or older who had idiopathic pulmonary fibrosis that was consistent with the criteria published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[13] and who had received the diagnosis less than 5 years before screening. Eligible patients, who were recruited from 92 sites in 25 countries, had also undergone high-resolution computed tomography (HRCT) less than 1 year before randomization and had a forced vital capacity (FVC) that was 50% or more of their predicted value, a diffusing capacity of the lung for carbon monoxide (DL_{CO}) that was 30 to 79% of their predicted value, and a partial pressure of arterial oxygen (PaO_2) when breathing ambient air that was 55 mm Hg or greater at altitudes up to 1500 m or a PaO_2 of 50 mm Hg or greater at altitudes above 1500 m. (For exclusion criteria, see Section A in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Concomitant therapy with 15 mg or less of prednisone per day or the equivalent was permitted if the treatment dose had been stable for at least 8 weeks before screening.

The diagnosis of idiopathic pulmonary fibrosis was confirmed before randomization by means of an independent review of HRCT scans of the chest in all patients by an expert chest radiologist and assessment of surgical lung-biopsy specimens (if available) by an expert lung pathologist. The population of patients included in this study was well defined and reflected the range of disease seen in clinical practice.

The trial was conducted in accordance with the principles laid down in the Declaration of Helsinki (1996 version) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and was approved by local authorities. Written informed consent was obtained from all participants.

Study Design

All authors designed the study and had access to the data, which were analyzed by statisticians at Boehringer Ingelheim, the sponsor of the study, and checked by an independent consultant. An employee of the sponsor vouches for the accuracy and completeness of the data and statistical analysis. The manuscript was drafted by medical writers from Fleishman-Hillard, with funding from Boehringer Ingelheim and in line with guidance from the first author, and was amended substantially, critically reviewed, and edited by all authors. The trial was carried out in compliance with the protocol and in accordance with the statistical analysis plan (both available at NEJM.org). The steering committee (see Section G in the Supplementary Appendix) made the decision to submit the manuscript for publication.

The diagnosis of idiopathic pulmonary fibrosis was confirmed at the screening visit, which took place 4 days or more before randomization. An interactive voice-response system was used to perform randomization. Patients, investigators, and the team from Boehringer Ingelheim were unaware of the treatment assignments throughout the study.

Patients were assigned to receive placebo capsules or one of the following doses of BIBF 1120: 50 mg once a day, 50 mg twice a day, 100 mg twice a day, or 150 mg twice a day. A stepwise increasing-dose approach was used (with concealment of the assigned active medication or placebo within each group), with each step reviewed by a data-monitoring committee before proceeding to the next step (for further information, see Sections D and G in the Supplementary Appendix). Additional patients underwent randomization to the previously established dose groups at later steps to maintain blinding between doses. The study medication was administered for 52 weeks.

The primary end point was the annual rate of decline in FVC. Spirometric results were centrally reviewed by an independent third party (VIASYS Healthcare [then CareFusion, now ERT], in Hoechberg, Germany) to meet ATS–ERS criteria.[14] Secondary end points included the changes from baseline in FVC and DL_{CO} as percentages of the predicted value; the changes in oxygen saturation levels (as measured by pulse oximetry [SpO_2]) and total lung capacity (as measured by body plethysmography); the distance achieved on the 6-minute walk test[15]; the total score on the St. George's Respiratory Questionnaire (SGRQ) (range, 0 to 100, with lower scores indicating a better quality of life; a minimum clinically important difference in the total score, 4 points)[16,17]; a decrease from baseline in FVC of more than 10% or more than 200 ml; an SpO_2 decrease of more than 4 percentage points; the incidence of acute exacerbations; survival at 52 weeks (with overall survival referring to all randomized patients and on-treatment survival based on the number of fatal adverse events that began during treatment or up to 14 days after treatment ended); and death from a respiratory cause (including all randomized patients). All deaths were adjudicated for cause of death by an independent committee (see Section G in the Supplementary Appendix) that was unaware of the treatment assignments. Data on vital status at the end of the planned treatment period (360 days) were available for 94.3% of patients in the placebo group and for 93.1%, 97.7%, 97.7%, and 97.7% of patients in the four treatment groups, respectively, in ascending order of doses.

STATISTICAL ANALYSIS

All efficacy analyses were based on the randomized set of 432 patients on an intention-to-treat basis. Only on-treatment measurements (data collected up to 1 day after the last dose was taken) were included in the primary efficacy analyses. Patients were assessed within the dose group to which they were randomly assigned at the start of the study.

To calculate the decrease in FVC over time, a linear decrease was modeled for every patient from the date on which the first dose of the assigned study drug was taken to the date of the last measurement obtained during the study, with all data taken into consideration. Analysis was performed with the use of a closed testing procedure for multiplicity correction and a hierarchical testing procedure; both were prespecified for assessment of the primary end point, although the closed testing procedure was prespecified for the primary analysis (Section E in the Supplementary Appendix).

Sample size was calculated to achieve 80% power to detect a difference of 0.1 liters in the annual decrease in FVC between patients receiving BIBF 1120 and those receiving placebo. The last-observation-carried-forward approach was used in the evaluation of secondary end points when data for the entire 52-week assessment period were not available.

Safety analyses included all patients who received at least one dose of the study drug or placebo (428 patients), with data collected up to 14 days after administration of the last dose included in the analysis. Data on adverse events and laboratory results were analyzed with the use of descriptive statistics only.

RESULTS

PATIENTS

A total of 432 patients with idiopathic pulmonary fibrosis were randomly assigned to receive one of four doses of BIBF 1120 or placebo (Fig. S1 in the Supplementary Appendix). Four patients underwent randomization but did not participate in the study. Among the 428 patients who did participate,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=85)	BIBF 1120				Total (N=428)
		50 mg Once Daily (N=86)	50 mg Twice Daily (N=86)	100 mg Twice Daily (N=86)	150 mg Twice Daily (N=85)	
Male sex — no. (%)	63 (74.1)	65 (75.6)	62 (72.1)	65 (75.6)	65 (76.5)	320 (74.8)
Age — yr	64.8±8.6	65.3±9.4	64.9±8.5	65.1±8.6	65.4±7.8	65.1±8.6
Race — no. (%)†						
White	65 (76.5)	68 (79.1)	72 (83.7)	72 (83.7)	61 (71.8)	338 (79.0)
Asian	20 (23.5)	18 (20.9)	14 (16.3)	14 (16.3)	24 (28.2)	90 (21.0)
Weight — kg	77.3±13.3	78.8±13.4	79.0±16.2	76.0±14.5	74.9±14.6	77.2±14.5
Interval since diagnosis — yr	1.4±1.5	1.4±1.3	1.1±1.2	1.2±1.2	1.0±1.2	1.2±1.3
Surgical lung-biopsy specimen available — no. (%)	19 (22.4)	25 (29.1)	27 (31.4)	20 (23.3)	29 (34.1)	120 (28.0)
Diagnosis of idiopathic pulmonary fibrosis — no. (%)‡						
Definite	24 (28.2)	27 (31.4)	26 (30.2)	31 (36.0)	33 (38.8)	141 (32.9)
Probable	57 (67.1)	49 (57.0)	53 (61.6)	54 (62.8)	52 (61.2)	265 (61.9)
Possible	4 (4.7)	9 (10.5)	7 (8.1)	1 (1.2)	0	21 (4.9)
Definitely not	0	1 (1.2)	0	0	0	1 (0.2)
Median FVC						
% of predicted value	77.6	79.8	80.4	83.0	78.1	80.2
Liters	2.7	2.8	2.7	2.8	2.7	2.8
Median Spo_2 — %	96.0	96.0	96.0	96.0	96.0	96.0
Median DL_{CO} — mmol/min/kPa	3.7	3.5	3.6	3.7	3.5	3.6
Median Pao_2 — mm Hg	75.0	75.8	78.4	80.0	78.3	77.5
Concomitant therapy — no. (%)§						
Any glucocorticoid	43 (50.6)	47 (54.7)	42 (48.8)	45 (52.3)	33 (38.8)	210 (49.1)
Prednisone	21 (24.7)	19 (22.1)	14 (16.3)	17 (19.8)	18 (21.2)	89 (20.8)

* Plus–minus values are means ±SD. DL_{CO} denotes diffusing capacity of the lung for carbon monoxide, FVC forced vital capacity, Pao_2 partial pressure of arterial oxygen, and Spo_2 oxygen saturation as determined with the use of pulse oximetry while the patient was breathing ambient air.
† Race was self-reported.
‡ Although 21 patients (4.9%) with possible idiopathic pulmonary fibrosis underwent randomization and were included in the study groups early in the study period, no patients with possible idiopathic pulmonary fibrosis were included at later stages of the trial, and none were included in the group receiving 150 mg of BIBF 1120 twice daily. One patient who did not have idiopathic pulmonary fibrosis was erroneously enrolled in the study.
§ Concomitant therapy was administered at least once during the treatment period.

141 patients met the criteria for definite idiopathic pulmonary fibrosis, 265 met the criteria for probable idiopathic pulmonary fibrosis, 21 patients had possible idiopathic pulmonary fibrosis, and 1 patient did not have idiopathic pulmonary fibrosis (Tables S1 and S2 in the Supplementary Appendix). The first patient was screened on September 14, 2007, and the last patient completed the study on June 10, 2010. A total of 112 patients discontinued the study medication prematurely: 24 of the 86 patients in the group receiving 50 mg once a day (27.9%), 18 of the 86 receiving 50 mg twice a day (20.9%), 14 of the 86 receiving 100 mg twice a day (16.3%), 32 of the 85 receiving 150 mg twice a day (37.6%), and 24 of the 85 receiving placebo (28.2%) (Fig. S2 in the Supplementary Appendix). Ninety-six of the 112 discontinuations (85.7%) were due to adverse events. Of the 32 patients receiving 150 mg of the study drug twice a day who discontinued the study drug early, 11 patients had previously had their dose reduced. The dose was reduced by one dose level in 5, 7, 11, and 20 patients in the four active-treatment groups, in ascending order

of doses, and was reduced by one level in 7 patients receiving placebo. No significant differences in baseline characteristics were observed among the groups (Table 1).

PRIMARY END POINT

The predefined, multiplicity-corrected primary end point did not differ significantly between the group of patients receiving the highest BIBF 1120 dose and the placebo group, although the difference approached the threshold for significance. The annual rate of decline in FVC in the group receiving 150 mg of BIBF 1120 twice a day was 0.06 liters (95% confidence interval [CI], −0.14 to 0.02), as compared with 0.19 liters in the placebo group (95% CI, −0.26 to −0.12) (P=0.06 with the closed testing procedure for multiplicity; P=0.01 with hierarchical testing) (Fig. 1, and Table S4 in the Supplementary Appendix). This difference corresponds to a reduction of 68.4% in the annual rate of decline in FVC in the group receiving 150 mg of BIBF 1120 twice a day as compared with the placebo group. The highest-dose group also had a significant absolute change in FVC from baseline over time, as compared with the placebo group (Fig. 2).

Although there was a higher number of discontinuations in the group receiving the highest dose of BIBF 1120 than in the placebo group, at week 52, the number of patients for whom FVC measurements were recorded, including patients who discontinued the study medication, did not differ significantly between the two groups (57 patients in the highest-dose group vs. 61 in the placebo group) (Fig. 2). The results of a sensitivity analysis that included all visits (the baseline visit and all follow-up visits, including visits after discontinuation) were similar to the results of the primary analysis, with an annual rate of decline in FVC of 0.10 liters in the group receiving 150 mg twice a day, as compared with 0.22 liters in the placebo group (P=0.02 [P=0.18 with the closed testing procedure for multiplicity]) (Table S4 in the Supplementary Appendix). In the highest-dose group, 20 patients (23.3%) underwent a dose reduction during the trial, as compared with 7 patients in the placebo group (8.0%); however, when the data were analyzed according to the final dose rather than the randomly assigned dose, the annual rates of decline in FVC were similar to those calculated in the primary analysis (0.04 liters in the group receiving 150 mg of BIBF 1120 twice a day vs. 0.19 liters in the placebo group) (Table S4 in the Supplementary Appendix).

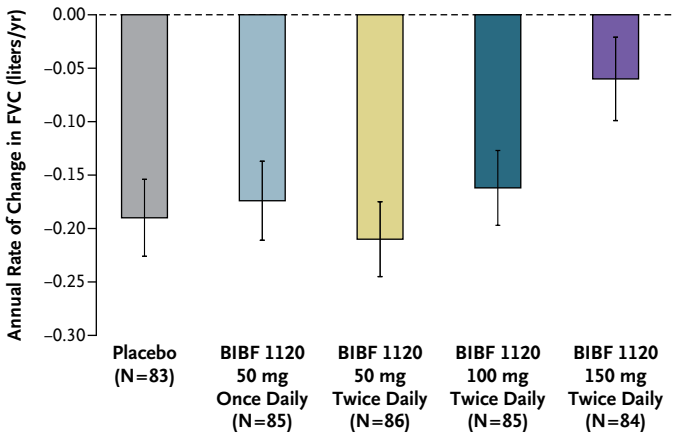
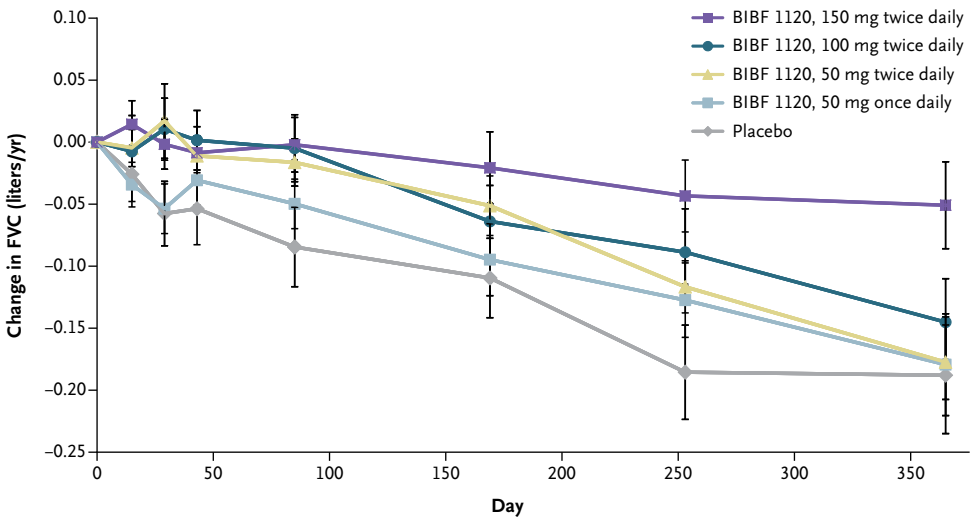


Figure 1. Annual Rate of Change in Forced Vital Capacity (FVC).
The mean (±SE) adjusted rate of change in FVC for the primary analysis is shown according to study group. The rate of change was calculated for the randomized study population with the use of both a closed testing procedure for multiplicity and hierarchical testing (P=0.06 and P=0.01, respectively, for the comparison of 150 mg of BIBF 1120 twice a day with placebo). Adjustments were based on a repeated-measures, mixed-effects linear-regression model with terms for study group, time, sex, height, and patient.

PRESPECIFIED SECONDARY END POINTS

Analyses of secondary end points supported the efficacy of BIBF 1120 at a dose of 150 mg twice a day (Table S4 in the Supplementary Appendix). The number of patients who had a decrease in FVC of more than 10% or more than 200 ml, was smaller in the highest-dose group than in the placebo group (20 patients [23.8%] vs. 37 patients [44.0%], P=0.004). The adjusted mean absolute change from baseline in total lung capacity was higher with placebo than with 150 mg of BIBF 1120 twice a day (−0.24 liters vs. 0.12 liters, P<0.001). The adjusted mean absolute change from baseline in resting Spo_2 was an increase of 0.1% with 100 mg of BIBF 1120 twice a day and a decrease of 0.2% with 150 mg twice a day, as compared with a 1.3% decrease with placebo (P=0.005 and P=0.02, respectively, for the comparison with placebo). The proportion of patients with more than a 4% decrease from baseline in resting Spo_2 was smaller in the group receiving 150 mg twice a day than in the placebo group (3.6% vs. 11.0%, P=0.03). There were no significant differences in DL_{CO} or distance achieved in the 6-minute walk test between any of the groups receiving BIBF 1120 and the placebo group (data not shown).

An analysis of the change from baseline in the SGRQ score showed that there was a small re-



	0	15	29	43	85	169	253	365
No. of Patients								
Total	432	419	416	415	398	385	372	317
Placebo	87	81	82	82	80	79	74	61
50 mg once daily	87	85	82	80	78	72	71	61
50 mg twice daily	86	85	86	86	82	81	80	71
100 mg twice daily	86	84	84	84	80	82	79	67
150 mg twice daily	86	84	82	83	78	71	68	57

Figure 2. Change in Forced Vital Capacity (FVC) over Time.

The mean (±SE) values for FVC after study discontinuation were included if available, but last observations were not carried forward in the case of missing values. The data included are from visits at planned time points only.

duction (indicating an improved quality of life) in the group receiving 150 mg of BIBF 1120 twice a day, as compared with an increase in the placebo group (adjusted mean absolute change from baseline, −0.66 points vs. 5.46 points; P=0.007). There were improvements in two domains of the SGRQ — symptoms and activity — in the group receiving 150 mg of BIBF 1120 twice a day as compared with the placebo group (change from baseline, −3.14 points vs. 6.45 points [P=0.003] and 0.32 points vs. 7.48 points [P=0.004], respectively), and there was a dose-dependent trend toward an improvement in the impact domain, which is a broad measure of the impact of respiratory disease on the patient (Table S5 in the Supplementary Appendix). At the time the study was conducted, the minimum clinically important difference in the SGRQ score was defined as 4 points,[17] but the difference has recently been estimated as 5 to 8 points in patients with idiopathic pulmonary fibrosis.[18] The proportion of patients who had an improvement in the SGRQ score of 4 points or more was higher in the group receiving 100 mg of the study drug twice a day (32.6%) and the group receiving 150 mg twice a day (29.1%) than in the placebo group (16.1%; P=0.007 and P=0.03, respectively) (see Fig. S3 in the Supplementary Appendix).

The incidence of acute exacerbations was lower in the group receiving 150 mg of BIBF 1120 twice a day than in the placebo group (2.4 vs. 15.7 per 100 patient-years, P=0.02). There was a trend toward a dose response with increasing doses of BIBF 1120 as compared with placebo (Fig. 3).

There was a trend toward fewer deaths from respiratory causes in the group receiving 150 mg of BIBF 1120 twice a day and the group receiving 100 mg twice a day as compared with the placebo group (number of deaths, 9, 3, 2, and 2 in the four active-treatment groups, in ascending order of doses, vs. 8 in the placebo group; P=0.04 for 100 mg twice a day and P=0.06 for 150 mg twice a day). There were no significant differences in death from any cause between any of the groups,

with 11, 3, 4, and 7 deaths in the active-treatment groups, in ascending order of doses, and 9 deaths in the placebo group.

ADVERSE EVENTS

The overall incidence of adverse events was similar in all groups, as was the number of patients with adverse events that were serious (defined as fatal, life-threatening, disabling, incapacitating, requiring hospitalization, or medically significant) or severe (defined as incapacitating or causing inability to work or perform usual activities) and adverse events that required hospitalization, although the proportion of patients with serious adverse events was lower in the group receiving 150 mg of BIBF 1120 twice a day than in the placebo group (27.1% vs. 30.6%) (Table 2). The highest proportion of patients who discontinued the study medication because of adverse events was in the group receiving 150 mg of BIBF 1120 twice a day (30.6%, vs. 25.9% in the placebo group), and the lowest proportion was in the group receiving 100 mg twice a day (14.0%). The adverse events most frequently leading to discontinuation were diarrhea, nausea, and vomiting (in the group receiving 150 mg twice a day as compared with those receiving placebo, the respective rates were 11.8% vs. 0%, 4.7% vs. 0%, and 2.4% vs. 1.2%). Among the 85 patients in the group receiving 150 mg of the study drug twice a day, 4 (4.7%) had serious gastrointestinal events and 5 (5.9%) had severe gastrointestinal events, especially diarrhea, as compared with no patients in the placebo group.

There was a decrease in the number of fatal adverse events (which included deaths after the end of treatment resulting from adverse events that began during the study period) with increasing doses of BIBF 1120: in ascending order of doses, the numbers of patients in the active-treatment groups who died were 10, 4, 5, and 1, respectively; 12 patients in the placebo group died (Table 2).

Clinically significant elevations in liver enzyme levels (at least three times the upper limit of the normal range for aspartate aminotransferase or alanine aminotransferase at any time after baseline) were observed in 6 patients in the group receiving 150 mg of BIBF 1120 twice a day (7.1%), 1 each in the group receiving 100 mg twice a day and the group receiving 50 mg twice a day, and none in the group receiving 50 mg once a day or the placebo group (Section G in the Supplementary Appendix). All aminotransferase levels normalized or decreased from elevated levels with continued treatment (in 3 patients receiving 150 mg twice a day and 1 patient receiving 100 mg twice a day), with a dose reduction (from 150 mg twice a day to 100 mg twice a day in 1 patient), or with withdrawal of the drug (in 2 patients receiving 150 mg twice a day and 1 patient receiving 50 mg twice a day). Only 2 patients discontinued the study medication because of abnormal results on liver-function tests (1 patient receiving 50 mg twice a day and 1 patient receiving 150 mg twice a day).

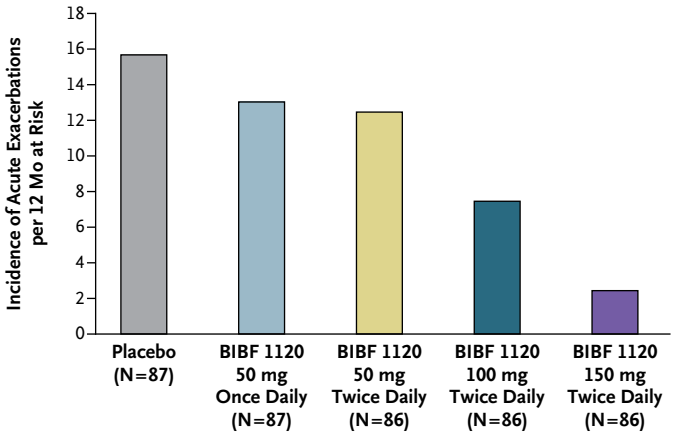


Figure 3. Incidence of Acute Exacerbations over 12 Months.

Incidence was calculated as the number of patients with one or more acute exacerbations divided by the total number of years at risk. The risk ratios for the four BIBF 1120 doses as compared with placebo were as follows: 50 mg once a day, 0.83 (95% confidence interval [CI], 0.36 to 1.93); 50 mg twice a day, 0.80 (95% CI, 0.34 to 1.84); 100 mg twice a day, 0.48 (95% CI, 0.18 to 1.27); and 150 mg twice a day, 0.16 (95% CI, 0.03 to 0.70).

DISCUSSION

This phase 2 trial comparing an oral tyrosine kinase inhibitor with placebo in patients with idiopathic pulmonary fibrosis failed, by a small margin, to show a significant difference in the predefined, multiplicity-corrected end point (closed testing procedure), the rate of loss of FVC over a 12-month period. The closed testing procedure is a conservative method of testing multiple hypotheses (in this case, four groups, each receiving a different dose) simultaneously. As compared with placebo, the dose of 150 mg of BIBF 1120 twice a day reduced the annual decline in FVC by two thirds. Treatment with BIBF 1120 was associated with improvements in many of the secondary out-

Table 2. Adverse Events.

Event	Placebo (N=85)	BIBF 1120				Total (N=428)
		50 mg Once Daily (N=86)	50 mg Twice Daily (N=86)	100 mg Twice Daily (N=86)	150 mg Twice Daily (N=85)	
		number of patients (percent)				
Any adverse event	77 (90.6)	78 (90.7)	78 (90.7)	82 (95.3)	80 (94.1)	395 (92.3)
Most frequent adverse events*						
Diarrhea	13 (15.3)	9 (10.5)	17 (19.8)	32 (37.2)	47 (55.3)	118 (27.6)
Cough	17 (20.0)	11 (12.8)	17 (19.8)	20 (23.3)	8 (9.4)	73 (17.1)
Nausea	8 (9.4)	9 (10.5)	8 (9.3)	17 (19.8)	20 (23.5)	62 (14.5)
Bronchitis	11 (12.9)	11 (12.8)	16 (18.6)	7 (8.1)	9 (10.6)	54 (12.6)
Dyspnea	11 (12.9)	7 (8.1)	14 (16.3)	13 (15.1)	6 (7.1)	51 (11.9)
Progression of idiopathic pulmonary fibrosis	11 (12.9)	11 (12.8)	7 (8.1)	9 (10.5)	4 (4.7)	42 (9.8)
Vomiting	4 (4.7)	1 (1.2)	6 (7.0)	11 (12.8)	11 (12.9)	33 (7.7)
Upper abdominal pain	3 (3.5)	6 (7.0)	10 (11.6)	2 (2.3)	10 (11.8)	31 (7.2)
Severe adverse events	20 (23.5)	21 (24.4)	17 (19.8)	19 (22.1)	19 (22.4)	96 (22.4)
Serious adverse events	26 (30.6)	26 (30.2)	23 (26.7)	18 (20.9)	23 (27.1)	116 (27.1)
Fatal adverse events	12 (14.1)	10 (11.6)	4 (4.7)	5 (5.8)	1 (1.2)	32 (7.5)
Adverse events requiring hospitalization	22 (25.9)	22 (25.6)	18 (20.9)	15 (17.4)	23 (27.1)	100 (23.4)
Adverse events leading to study discontinuation	22 (25.9)	20 (23.3)	14 (16.3)	12 (14.0)	26 (30.6)	94 (22.0)
Respiratory, thoracic, and mediastinal disorders	10 (11.8)	8 (9.3)	2 (2.3)	3 (3.5)	4 (4.7)	27 (6.3)
Gastrointestinal disorders	2 (2.4)	2 (2.3)	2 (2.3)	2 (2.3)	14 (16.5)	22 (5.1)
Infections and infestations	6 (7.1)	2 (2.3)	3 (3.5)	2 (2.3)	0	13 (3.0)
Cardiac disorders	6 (7.1)	2 (2.3)	2 (2.3)	1 (1.2)	0	11 (2.6)

* Adverse events defined as most frequent were those having an incidence of more than 10% in any study group.

comes, suggesting that this agent is a promising treatment for idiopathic pulmonary fibrosis, a serious medical condition for which there are few therapeutic options.

Although the higher number of discontinuations and dose reductions in the group of patients receiving 150 mg twice a day could have introduced bias in the estimates of treatment effect, the results of sensitivity analyses for the decline in FVC, with discontinuations and dose reductions taken into consideration, were similar to the results of the primary analysis. These observations suggest that the early withdrawal of patients in the group receiving 150 mg of BIBF 1120 twice a day and for whom no follow-up data on FVC were available did not skew our observed outcomes.

The results of secondary end-point analyses provide consistent support for the dose of 150 mg of BIBF 1120 twice a day, and for some end points, the data are strengthened by similar results for the dose of 100 mg twice a day. The incidence of acute exacerbations was significantly lower in the group receiving 150 mg twice a day than in the placebo group. This result is clinically important, since acute exacerbations are associated with rapid disease progression, a severe and abrupt decline in FVC, and high mortality.[19,20] The reduction in acute exacerbations in patients receiving 100 mg twice a day or 150 mg twice a day may have contributed to the more stable quality of life seen in these groups as compared with the other groups, which had higher incidences of exacerbations. The larger numbers of patients with a clinically meaningful improvement in the SGRQ score in the group receiving 100 mg twice a day and the group receiving 150 mg twice a day suggest that treatment with BIBF 1120 provided a benefit with respect to the health-related quality of life, an im-

portant consideration for patients with idiopathic pulmonary fibrosis.[21]

No significant differences in DL_{CO} or distance walked in 6 minutes were observed between the groups receiving BIBF 1120 and the group receiving placebo, but it is unclear whether this was the result of methodologic problems or a true lack of effect on these end points. One possible methodologic reason for this outcome was the lack of central control for the procedures involved in the measurement of DL_{CO} or the 6-minute walk test.[22]

Gastrointestinal side effects were common in the group receiving the highest dose of BIBF 1120, but the majority of these effects were of mild or moderate intensity. Severe adverse events occurred with similar frequency in the placebo group and the four active-treatment groups.

In conclusion, the results of this phase 2 study showed an acceptable safety profile and potential clinical benefits of treatment with 150 mg of BIBF 1120 twice a day in patients with idiopathic pulmonary fibrosis. These results warrant the investigation of BIBF 1120 in phase 3 clinical studies.

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REFERENCES

1. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 2001;134:136-51.
2. De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. Eur Respir J 2001;17:954-61.
3. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183:431-40.
4. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636-43.
5. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774-82.
6. Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. Ther Adv Respir Dis 2010;4:367-88.
7. Allen JT, Spiteri MA. Growth factors in idiopathic pulmonary fibrosis: relative roles. Respir Res 2002;3:13.
8. Grimminger F, Schermuly RT, Ghofrani HA. Targeting non-malignant disorders with tyrosine kinase inhibitors. Nat Rev Drug Discov 2010;9:956-70.
9. Chaudhary NI, Roth GJ, Hilberg F, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J 2007;29:976-85.
10. Abdollahi A, Li M, Ping G, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. J Exp Med 2005;201:925-35.
11. Yu C, Wang F, Jin C, et al. Role of fibroblast growth factor type 1 and 2 in carbon tetrachloride-induced hepatic injury and fibrogenesis. Am J Pathol 2003;163:1653-62.
12. Hamada N, Kuwano K, Yamada M, et al. Anti-vascular endothelial growth factor gene therapy attenuates lung injury and fibrosis in mice. J Immunol 2005;175:1224-31.
13. American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med 2000;161:646-64.
14. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
15. du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med 2011;183:1231-7.
16. Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. Respir Med 1991;85:Suppl B:25-31.
17. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2:75-9.
18. Swigris JJ, Brown KK, Behr J, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respir Med 2010;104:296-304.
19. Hyzy R, Huang S, Myers J, Flaherty K, Martinez F. Acute exacerbation of idiopathic pulmonary fibrosis. Chest 2007;132:1652-8.
20. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005;142:963-7.
21. Swigris JJ, Gould MK, Wilson SR. Health-related quality of life among patients with idiopathic pulmonary fibrosis. Chest 2005;127:284-94.
22. Wells AU, Behr J, Silver R. Outcome measures in the lung. Rheumatology (Oxford) 2008;47:Suppl 5:v48-v50.