Early View

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Phase 2 clinical trial of PBI-4050 in patients with idiopathic pulmonary fibrosis

Nasreen Khalil¹, Helene Manganas², Christopher J. Ryerson³, Shane Shapera⁴, Andre M. Cantin⁵, Paul Hernandez⁶, Eric E. Turcotte⁷, Joseph M. Parker⁸, John E. Moran⁸, Gary R. Albert⁸, Renata Sawtell⁸, Aline Hagerimana⁸, Pierre Laurin⁸, Lyne Gagnon⁸, Frank Cesari⁸, Martin Kolb⁹

Affiliations:

1. Vancouver General Hospital - The Lung Centre, Vancouver, BC, Canada
2. Centre Hospitalier de l’Université de Montréal, Montréal, QC, Canada
3. Department of Medicine, University of British Columbia and Centre for Heart Lung Innovation, St. Paul’s Hospital, Vancouver, BC, Canada
4. University Health Network, University of Toronto, Toronto ON, Canada
5. Centre de Recherche Clinique du Centre Hospitalier Universitaire de Sherbrooke (CHUS-CRC), Sherbrooke, QC, Canada
6. Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada
7. Centre d'imagerie Moléculaire de Sherbrooke, Université de Sherbrooke, 3001, Sherbrooke, QC, Canada
8. Prometic Life Sciences Inc., Laval, QC, Canada
9. Firestone Institute for Respiratory Health St. Joseph’s Healthcare, Hamilton, ON, Canada

Correspondence:

Martin Kolb, Firestone Institute for Respiratory Health, St. Joseph’s Healthcare, Hamilton, ON, Canada. Email: kolbm@mcmaster.ca
ABSTRACT

PBI-4050, is a novel orally active small-molecule compound, with demonstrated anti-fibrotic activity in several models of fibrosis, including lung fibrosis. We present results from our first clinical study of PBI-4050 in patients with idiopathic pulmonary fibrosis (IPF).

This 12-week open-label study explored the safety, efficacy, and pharmacokinetics of daily oral doses of 800 mg PBI-4050 alone and in combination with nintedanib or pirfenidone in patients with predominantly mild or moderate IPF. Nine patients received PBI-4050 alone and, 16 patients each received PBI-4050/nintedanib and PBI-4050/pirfenidone.

PBI-4050 alone or in combination with nintedanib or pirfenidone were well tolerated. Pharmacokinetic profiles for PBI-4050 were similar in the PBI-4050 alone and PBI-4050/nintedanib groups but reduced in the PBI-4050/pirfenidone group, suggesting a drug-drug interaction. There were no significant changes in forced vital capacity (FVC), percent-predicted or mL, from baseline to Week 12 for PBI-4050 alone and PBI-4050/nintedanib. In contrast, a statistically significant reduction (p<0.024) in percent-predicted FVC was seen for PBI-4050/pirfenidone after 12 weeks.

There were no safety concerns with PBI-4050 alone and in combination with nintedanib or pirfenidone in IPF patients. The stability of FVC between baseline and Week 12 looked encouraging for PBI-4050 alone and in combination with nintedanib.
**Introduction**

Idiopathic pulmonary fibrosis (IPF) is a chronic, irreversible, progressive and usually fatal lung disease of unknown cause [1,2]. It is characterized by scarring of the lung parenchyma, progressive loss of lung function, dyspnoea and cough, eventually leading to respiratory failure [1]. IPF occurs primarily in older adults, with a median age at diagnosis of 66 years. Across Europe and North America, the incidence of IPF ranges from 3 to 9 cases per 100,000-person years [3] and appears to be rising. The prevalence has been reported as high as 45-199 per 100,000 in individuals 60-79 years old [4]. Median survival is 3 to 4 years after diagnosis [1,5,6].

Current clinical practice guidelines recommend the use of pirfenidone or nintedanib for the treatment of IPF [1,7]. However, both drugs have limitations in terms of efficacy and tolerability. Therefore, there is a need for additional therapies to treat this progressive and deadly disease [8].

Although inflammation may play a role in the initial injury to the lung in IPF, the primary process is an epithelial-dependent, fibroblast-activated progressive fibrotic process [2]. The trigger for IPF is thought to be the inability of the alveolar type II cells to self-renew and repair, leading to release of fibrotic factors [2,9,10,11]. This injury results in fibroblast recruitment, proliferation and differentiation into myofibroblasts, which lay down collagen and extracellular matrix (ECM) proteins resulting in scar formation [10,12,13].

PBI-4050, 3-pentylbenzeneacetic acid sodium salt, is a first-in-class orally active low molecular weight compound in clinical development for the treatment of patients with fibrotic diseases. It is a synthetic analogue of a medium-chain fatty acid that displays agonist and antagonist ligand affinity towards two G-protein coupled receptors, GPR40 and GPR84, respectively, leading to the reduction or reversal of fibrosis by regulating macrophages,
fibroblasts/myofibroblasts and epithelial cells [14]. By binding GPR40 and GPR84, PBI-4050 reduces fibrosis via the regulation of multiple anti-fibrotic pathways implicated in the pathogenesis of IPF [14]. PBI-4050 inhibits the differentiation of fibroblasts to myofibroblasts, as demonstrated by abrogation of alpha-smooth muscle actin expression in fibroblasts and subsequent accumulation of ECM protein deposition and fibrosis. PBI-4050 also reduces the expression of both pro-inflammatory markers (monocyte chemoattractant protein-1, interleukin [IL]-8 and IL-6) and profibrotic markers (connective tissue growth factor and IL-6). PBI-4050 also significantly attenuated fibrosis in kidney, liver, lung, heart, pancreas and skin fibrosis models including the murine model of bleomycin-induced lung fibrosis [14]. In the latter model, PBI-4050 showed a 47% reduction of histological lesions depicted as disrupted lung architecture, thickness of alveolar wall, and fibrosis [14]. These findings suggest that PBI-4050 may be clinically effective in fibrotic diseases, including IPF.

A series of phase 2 exploratory studies of PBI-4050 have been completed or are ongoing in patients with fibrotic diseases including IPF, type 2 diabetes with metabolic syndrome and Alström syndrome. Herein, we present data from a phase 2, open-label study evaluating the safety, efficacy, and pharmacokinetics (PK) of PBI-4050 in patients with IPF receiving nintedanib, pirfenidone or neither.

Methods

Study design

This was a 12-week, phase 2, single-arm, open-label study (NCT02538536) in adults with IPF conducted at six sites across Canada. Its primary purpose was to evaluate the safety and tolerability of PBI-4050 in this patient population. This study also explored the effect of PBI-4050 on pulmonary function. A subset of patients volunteered to take part in a PK sub-
study to evaluate the PK profile of PBI-4050. An open-label design was chosen due to the exploratory nature of the study.

The protocol was reviewed and approved by the institutional review board of each participating centre and the study was conducted in accordance with the Declaration of Helsinki and good clinical practices guidelines. All patients provided written informed consent prior to entering the study.

**Study population**

Patients were eligible if they were 40 years of age or older and had been diagnosed with IPF as determined by the investigators as per guidelines by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) [1]. High-resolution computed tomography (HRCT) scans of the thorax, were performed at screening or obtained within 12 months prior to the start of study drug treatment. HRCT scans performed at the site followed a standardised volumetric acquisition protocol that provided multi-planar reformations (coronal and sagittal) of the entire lung, improving the evaluation of abnormalities distribution and the extent of disease. Although all scans were sent to a central reader (Centre Hospitalier Universitaire de Sherbrooke, Quebec, Canada) for review, confirmation of IPF by a central reader was not factored into patient eligibility. There were no eligibility criteria based on pulmonary function tests. HRCT was also used to assess any intercurrent infection.

Key exclusion criteria included a known diagnosis of a respiratory disorder other than IPF, extent of emphysema greater than the extent of fibrotic changes (honeycombing and reticular changes) on HRCT, and being an active smoker within 3 months prior to screening, as
smoking may worsen the progression of IPF and reduce the efficacy of background anti-fibrotic therapy [15,16,17].

**Treatment**

All patients received PBI-4050 at a dose of 800 mg once daily with a planned treatment duration of 12 weeks, administered orally as 4 × 200 mg gel capsules at least 1 hour before or more than 2 hours after a meal. This dose was based on the PK profile of PBI-4050 from phase 1 studies [18] that provided the same area under the concentration-time-curve as the effective dose of PBI-4050 (200 mg/kg) in the murine model of bleomycin-induced lung fibrosis [14]. This dose was also well tolerated in healthy volunteers and patients with stable renal impairment [18]. Nintedanib and pirfenidone were allowed during the study, as was the use of corticosteroids. Azathioprine and N-acetylcysteine were prohibited based on ATS/ERS/JRS/ALAT recommendations against these agents for the majority of IPF patients [1].

**Analysis**

The primary objective was safety and tolerability, which comprised the following endpoints: patient-reported adverse events, clinical laboratory tests, vital signs, electrocardiograms (ECGs) and physical examinations. Adverse events, defined as either new events emerging after study drug administration or previous events that increased in severity after study drug administration, were monitored throughout the treatment period until the follow-up visit (defined as 28 days after the last dose of study drug). Clinical laboratory tests and vital signs were measured at Weeks 1, 2, 6 and 12 and at follow-up; physical examinations and ECGs were measured at Weeks 1 and 12 and at follow-up. All safety endpoints were analysed descriptively.
The secondary objective was the assessment of clinical efficacy, which was measured by mean changes from baseline in pulmonary function tests (forced vital capacity [FVC] and haemoglobin-corrected diffusion capacity for carbon monoxide [DL\textsubscript{CO}]). FVC was measured at Weeks 1, 2, 6 and 12 and DL\textsubscript{CO} was measured at Weeks 1 and 12; both FVC and DL\textsubscript{CO} were measured by local laboratories using standard procedures, in accordance with ATS/ERS standards [19, 20]. All efficacy analyses were analysed descriptively.

The PK profile of PBI-4050 was also a secondary objective, which comprised individual and mean plasma concentration versus time curves at Week 12 as part of a separate sub-study. For this sub-study, blood samples were collected under fasting conditions at the following time points: pre-dose and at 0.5, 1, 2, 3, 4 and 5-6 hours post-dose. Descriptive statistics were used to describe the PK of PBI-4050. The PK of pirfenidone and nintedanib was not done in this study.

This study was exploratory in nature with a primary objective to test safety of PBI-4050; therefore, no power analysis or between-treatment group comparison was performed.

This study was designed as a single-arm trial, with all patients analysed as a single group for all primary analyses. A post hoc analysis was also conducted with patients grouped according to their background IPF pharmacotherapy (PBI-4050 alone, PBI-4050 + nintedanib, PBI-4050 + pirfenidone). As part of this analysis, exploratory hypothesis testing was performed within each treatment group to assess differences from baseline to Week 12 in FVC and DL\textsubscript{CO}. P-values (t-test) and 95% confidence intervals (CIs) were provided and are exploratory in nature. There were minimal missing data and imputation was not needed. Multiplicity testing was not applied across the efficacy endpoints.
Results

Between October 2015 and January 2017, 52 patients were screened, and 41 patients were enrolled (figure 1). All but one patient completed the study as planned (figure 1). The remaining patient (PBI-4050 + pirfenidone) withdrew early from the study due to an IPF exacerbation that occurred within 2 weeks of starting the study drug. A total of 9 patients received PBI-4050 with no background IPF pharmacotherapy (PBI-4050 alone), 16 patients received PBI-4050 with nintedanib (PBI-4050 + nintedanib), and 16 patients received PBI-4050 with pirfenidone (PBI-4050 + pirfenidone). A total of 9 patients (2, 4 and 3 patients, respectively) were included in the PK sub-study.

Baseline patient demographics and disease characteristics

Demographic and baseline characteristic data are summarised in table 1. In general, the overall study population was consistent with an underlying disease of IPF, with all but two patients (95%) having a definite UIP pattern on HRCT (the remaining patients had a possible UIP pattern). Patients ranged in age from 46 to 83 years, and most patients were male and Caucasian. Other baseline characteristics were more variable across the treatment groups. Mean/median weight was higher in the PBI-4050 + pirfenidone group than in the other two treatment groups, but these differences did not reach statistical significance and appeared to be associated with a few outliers. Patients in the PBI-4050 + pirfenidone group were generally more recently diagnosed and had a higher proportion of moderate or severe disease than the other two treatment groups. Mean/median percent-predicted FVC was similar between the two combination groups but highest in the PBI-4050 alone group.
**Safety and tolerability**

All patients who received at least one dose of PBI-4050 were included in the safety analysis. Most patients (~83%) had at least one adverse event as summarised in table 2. The majority of events were mild or moderate in severity and not serious. Three patients experienced severe adverse events, which included diarrhoea (PBI-4050 + nintedanib), dyspnoea and IPF exacerbation (PBI-4050 + pirfenidone) and gastrointestinal disorder (PBI-4050 + pirfenidone); none of these events were related to PBI-4050. No patient died, and one patient in the PBI-4050 + nintedanib group had a serious adverse event (pneumonia) that was not related to PBI-4050. In addition, one patient in the PBI-4050 + pirfenidone group discontinued treatment due to an AE (IPF exacerbation) related to their underlying disease. The most frequent adverse events were diarrhoea, nausea and headache. There were no clinically significant changes in clinical laboratory tests, vital signs, physical examinations, or ECG.

**Pharmacokinetics**

The average PK profiles for PBI-4050 alone and PBI-4050 + nintedanib groups appeared similar (figure 2). The PK profile of the PBI-4050 + pirfenidone group, however, demonstrated a reduced absorption rate or lower maximum observed plasma concentration and a faster metabolism (shorter half-life) compared with the other treatment groups, suggesting a drug-drug interaction between PBI-4050 and pirfenidone.

**Efficacy**

Pulmonary function test results are shown in table 3. Only patients who received all 12 weeks of treatment were included in the efficacy analysis. No statistically significant changes were observed in mean FVC (percent-predicted and mL) from baseline to Week 12 in the PBI-4050 + nintedanib group (0.06% [p = 0.9513] and 1.87 mL [p = 0.9539]) and in the PBI-4050
alone group (-1.11% [p = 0.4759] and -12.2 mL [p = 0.7959]) as shown in table 3. For the PBI-4050 + pirfenidone group, there was a statistically significant mean decrease in FVC (percent predicted and mL) from baseline to Week 12 (-2.69% [p = 0.0240] and -102 mL [p = 0.0124]). The mean changes in mean percent-predicted DL\textsubscript{CO} from baseline to Week 12 were not statistically significant in all treatment groups (-4.00 [p = 0.1427] in the PBI-4050 alone group; -1.50 [p = 0.1073] in the PBI-4050 + nintedanib group; and -2.54 [p = 0.1390] in the PBI-4050 + pirfenidone group (table 3). These results are also shown graphically in figures 3a and 3b.

**Discussion**

Positive results from a murine model of bleomycin-induced lung fibrosis [14] provided the impetus for the first clinical study of PBI-4050 in patients with IPF. The aim of this study was to evaluate the safety and tolerability of PBI-4050 after 12 weeks of treatment and to assess its PK and efficacy in this patient population. This study was exploratory in nature and not pivotal. An open-label design was chosen to maximise exposure to PBI-4050 and concomitant therapy with nintedanib or pirfenidone was allowed. Daily oral administration of PBI-4050 at a dose of 800 mg/day over a 12-week period appeared well tolerated in IPF patients when given alone or in combination with nintedanib or pirfenidone. No patients died, and the only serious AE (pneumonia) was considered to be due to the underlying disease. AEs were generally mild or moderate in severity, and treatment was not stopped for any PBI-4050-related adverse event. The most frequent adverse events were diarrhoea, nausea and headache. The PK profiles were similar among patients receiving PBI-4050 alone or in combination with nintedanib but were different in the combination with pirfenidone. The PK profile of PBI-4050 when added to pirfenidone showed reduced absorption and lower maximum observed plasma concentration of PBI-4050 and a faster
metabolism (shorter half-life) compared with the other treatment groups, suggesting a drug-
drug interaction between PBI-4050 and pirfenidone.
Decline in lung function as measured by FVC has long been used to monitor disease
progression in IPF and has been identified as an independent predictor of mortality in IPF
[21, 22, 23, 24]. A reduction in the annual rate of decline in percent-predicted FVC, as
determined by spirometry, is therefore a suitable primary endpoint for therapeutic studies in
IPF. Current clinical practice guidelines recommend the use of one of the two available anti-
fibrotic drugs, pirfenidone or nintedanib, for the treatment of IPF [1, 7]. Both drugs slowed
the progression of lung function decline by approximately 50% as compared to placebo in
large Phase 3 clinical studies [25, 26]. Although pirfenidone and nintedanib represent a
significant improvement in the treatment of IPF, they do not represent a cure and both drugs
have significant and sometimes intolerable side effects. Therefore, clinical research continues
to focus on new therapies for the treatment of this progressive and often fatal disease.

A post-hoc analysis of the three treatment groups showed no statistically significant changes
in FVC (percent-predicted and mL) after 12 weeks of treatment in patients receiving PBI-
4050 alone and in combination with nintedanib (p > 0.40). In contract, this analysis showed a
statistically significant decline in FVC during the same time period for patients in the
PBI-4050 + pirfenidone group (FVC percent-predicted [p = 0.024] and FVC mL [p =
0.0124]). This latter finding was not impacted by the disparity in baseline weight, as there
appeared to be no correlation between FVC (percent-predicted and mL) reduction and
individual weight in this group: 7% and 220 mL (62 kg), 10% and 280 mL (69 kg), 6% and
250 mL (78 kg), 5% and 220 mL (113 kg), 5% and 200 mL (88 kg) and 6% and 250 mL (84
kg). Rather, the FVC findings are supported by the PK data, where a reduced absorption rate
or lower maximum observed plasma concentration and a faster metabolism (shorter half-life) of PBI-4050 were seen in the pirfenidone group but not in the other two treatment groups. Drug-drug interactions with pirfenidone have been reported in clinical IPF studies, similar to the results observed in the PBI-4050 IPF study [27, 28]. Reduced efficacy of pirfenidone was observed with the combination of N-acetylcysteine in a 24-week randomised, double-blind, placebo-controlled study in IPF patients (PANORAMA study). This combination significantly reduced the adjusted rate of FVC decline compared to placebo and pirfenidone (125.6 mL/6 months vs 34.3 mL/6 months, respectively; p = 0.031), with safety largely unchanged [27]. Reduced exposure was also observed with the combination of nintedanib and pirfenidone in a 28-day randomised, double-blind, dose-escalation study in Japanese IPF patients [28]. Area under the concentration-time curve and maximum plasma concentration of nintedanib and its metabolites were reduced in patients receiving pirfenidone, but there were no changes in the PK profile for pirfenidone [28].

In summary, there were no safety concerns with PBI-4050 alone and in combination with nintedanib or pirfenidone after 12 weeks of treatment in patients with predominantly mild or moderate IPF. PK profiles for PBI-4050 alone and in combination with nintedanib were similar but reduced with pirfenidone, suggesting a drug-drug interaction. FVC results were encouraging for PBI-4050 alone and in combination with nintedanib, despite limitations in sample size and study design.

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| Characteristic | PBI-4050 Alone (n = 9) | PBI-4050 + Nintedanib (n = 16) | PBI-4050 + Pirfenidone (n = 16) |
|---------------|----------------------|-------------------------------|-------------------------------|
| Age, yr       |                      |                               |                               |
| Mean          | 71.6                 | 69.4                          | 66.1                          |
| Median        | 69.0                 | 72.0                          | 65.5                          |
| Range         | 65.0 - 84.0          | 46.0 - 83.0                   | 58.0 - 80.0                   |
| Sex, n (%)    |                      |                               |                               |
| Male          | 6 (66.7)             | 12 (75.0)                     | 13 (81.3)                     |
| Female        | 3 (33.3)             | 4 (25.0)                      | 3 (18.8)                      |
| Race, n (%)   |                      |                               |                               |
| White         | 9 (100.0)            | 15 (93.8)                     | 16 (100.0)                    |
| Other         | 0                    | 1 (6.3)                       | 0                             |
| Height, cm    |                      |                               |                               |
| Mean          | 168.0                | 170.8                         | 171.5                         |
| Median        | 172.0                | 171.0                         | 170.5                         |
| Range         | 151.0 - 178.0        | 157.0 - 186.0                 | 153.0 - 193.0                 |
| Weight, kg    |                      |                               |                               |
| Mean          | 76.8                 | 76.3                          | 89.0                          |
| Median        | 78.8                 | 74.5                          | 86.2                          |
| Range         | 61.5 - 87.0          | 57.5 - 97.0                   | 62.1 - 130.4                  |
| Body mass index, kg/m² | | | |
| Mean          | 27.3                 | 26.1                          | 30.4                          |
| Median        | 26.6                 | 25.7                          | 28.4                          |
| Range         | 23.4 - 35.1          | 23.3 - 31.0                   | 23.8 - 55.7                   |
| Duration of IPF disease (yr) | | | |
| Mean          | 2.80                 | 1.84                          | 1.24                          |
| Median        | 2.1                  | 1.7                           | 0.9                           |
| Range         | 0.8 - 5.4            | 0.0 - 5.9                     | 0.1 - 5.7                     |
| Stage of IPF disease as determined by the investigator, n (%) | | | |
| Mild          | 5 (55.6)             | 9 (56.3)                      | 6 (37.5)                      |
| Moderate      | 4 (44.4)             | 6 (37.5)                      | 8 (50.0)                      |
| Severe        | 0                    | 1 (6.3)                       | 2 (12.5)                      |
| Characteristic | PBI-4050 Alone (n = 9) | PBI-4050 + Nintedanib (n = 16) | PBI-4050 + Pirfenidone (n = 16) |
|---------------|------------------------|---------------------------------|---------------------------------|
| **HRCT**      |                        |                                 |                                 |
| Compatible with UIP pattern, n (%) |            |                                 |                                 |
| Definite      | 9 (100.0)              | 15 (93.8)                       | 14 (93.3)                       |
| Possible      | 0                      | 1 (6.3)                         | 1 (6.7)                         |
| **Percent-predicted FVC** |        |                                 |                                 |
| Mean          | 83.1                   | 71.3                            | 70.8                            |
| Median        | 79.0                   | 69.0                            | 68.0                            |
| Range         | 58.0 - 109.0           | 45.0 - 107.0                    | 45.0 - 100.0                    |
| **FVC**, mL   |                        |                                 |                                 |
| Mean          | 2884                   | 2761                            | 2849                            |
| Median        | 2650                   | 2735                            | 2930                            |
| Range         | 1750 - 4380            | 1290 - 3480                     | 1580 - 4280                     |
| **Percent-predicted DLCO** |       |                                 |                                 |
| Mean          | 45.2                   | 50.8                            | 49.1                            |
| Median        | 47.0                   | 53.0                            | 45.0                            |
| Range         | 27.0 - 64.0            | 24.0 - 70.0                     | 23.0 - 83.0                     |

Data are presented as n, mean or n (%). IPF: idiopathic pulmonary fibrosis; HRCT: high-resolution computed tomography; FVC: forced vital capacity; DLCO: haemoglobin-corrected diffusion capacity for carbon monoxide; *: Data based on efficacy population.
| Parameter                                                      | PBI-4050 Alone | PBI-4050 + Nintedanib | PBI-4050 + Pirfenidone |
|---------------------------------------------------------------|----------------|-----------------------|------------------------|
| Number of patients                                           | 9              | 16                    | 16                     |
| Number of patients with at least one AE                       | 8 (88.9)       | 12 (75.0)             | 14 (87.5)              |
| Number of patients with at least one severe AE                | 0              | 1 (6.3)               | 2 (12.5)               |
| Number of patients with at least one serious AE               | 0              | 1 (6.3)               | 0                      |
| Death                                                         | 0              | 0                     | 0                      |
| AE leading to permanent discontinuation of study drug          | 0              | 0                     | 1 (6.3)                |
| AEs in > 2 patients, by preferred term*                        |                |                       |                        |
| Diarrhoea                                                     | 3 (33.3)       | 7 (43.8)              | 6 (37.5)               |
| Nausea                                                        | 0              | 0                     | 4 (25.0)               |
| Headache                                                      | 2 (22.2)       | 1 (6.3)               | 1 (6.3)                |
| Fatigue                                                       | 0              | 1 (6.3)               | 2 (12.5)               |
| Non-cardiac chest pain                                       | 1 (11.1)       | 0                     | 2 (12.5)               |
| Cough                                                         | 0              | 0                     | 3 (18.8)               |
| Dyspnoea                                                      | 0              | 0                     | 3 (18.8)               |

Data are presented as n or n (%). Patients may be counted in more than one category. AE: adverse event; *: Medical Dictionary for Regulatory Activities, version 18.0, https://www.meddra.org/sites/default/files/guidance/file/intguide_18_0_english.pdf.
| Pulmonary Function Test | PBI-4050 Alone (n = 9) | PBI-4050 + Nintedanib (n = 16) | PBI-4050 + Pirfenidone (n = 15) |
|-------------------------|------------------------|---------------------------------|-------------------------------|
| **Percent-predicted FVC** |                        |                                 |                               |
| Baseline                |                        |                                 |                               |
| Mean (±SD)              | 83.11 (17.37)          | 71.31 (17.05)                   | 70.80 (14.82)                 |
| Median                  | 79.0                   | 69.0                            | 68.0                          |
| Range                   | 58.0 - 109.0           | 45.0 - 107.0                    | 45.0 - 100.0                  |
| Week 12                 |                        |                                 |                               |
| Mean (±SD)              | 82.00 (16.57)          | 71.38 (15.98)                   | 68.11 (15.79)                 |
| Median                  | 74.0                   | 69.5                            | 64.0                          |
| Range                   | 56.0 - 105.0           | 51.0 - 98.0                     | 39.0 - 101.0                  |
| Change from baseline at week 12 |                |                                 |                               |
| Mean change (± SD)      | -1.11 (4.46)           | 0.06 (4.02)                     | -2.69 (4.11)                  |
| Median                  | -1.0                   | 1.0                             | -4.0                          |
| 95% confidence interval | -4.5, 2.3              | -2.1, 2.2                       | -5.00, -0.4                   |
| P-value*                | 0.4759                 | 0.9513                          | 0.0240                        |
| **FVC (mL)**            |                        |                                 |                               |
| Baseline                |                        |                                 |                               |
| Mean (± SD)             | 2884 (759.59)          | 2761 (530.03)                   | 2849 (745.62)                 |
| Median                  | 2650                   | 2735                            | 2930                          |
| Range                   | 1750 - 4380            | 1290 - 3480                     | 1580 - 4280                   |
| Week 12                 |                        |                                 |                               |
| Mean (± SD)             | 2872 (811.82)          | 2763 (520.70)                   | 2747 (813.67)                 |
| Median                  | 2770                   | 2775                            | 2720                          |
| Range                   | 1640 - 4330            | 1430 - 3440                     | 1470 - 4360                   |
| Change from baseline at week 12 |                |                                 |                               |
| Mean change (± SD)      | -12.2 (137.1)          | 1.9 (127.6)                     | -102 (137.8)                  |
| Median                  | -50.0                  | 25.0                            | -140                          |
| 95% confidence interval | -117.6, 93.2           | -66.1, 69.9                     | -178.3, -25.7                 |
| P-value*                | 0.7959                 | 0.9539                          | 0.0124                        |
| **Percent predicted DLco** |                        |                                 |                               |
| Baseline                |                        |                                 |                               |
| Mean (± SD)             | 45.22 (11.62)          | 50.75 (14.81)                   | 49.07 (16.33)                 |
| Pulmonary Function Test | PBI-4050 Alone (n = 9) | PBI-4050 + Nintedanib (n = 16) | PBI-4050 + Pirfenidone (n = 15) |
|-------------------------|------------------------|-------------------------------|-------------------------------|
| Median                  | 47.0                   | 53.0                          | 45.0                          |
| Range                   | 27.0 - 64.0            | 24.0 - 70.0                   | 23.0 - 83.0                   |
| **Week 12**             |                        |                               |                               |
| Mean (± SD)             | 41.22 (11.20)          | 49.25 (14.03)                 | 46.53 (18.10)                 |
| Median                  | 41.0                   | 49.5                          | 45.0                          |
| Range                   | 26.0 - 56.0            | 22.0 - 72.0                   | 18.0 - 83.0                   |
| **Change from baseline at week 12** |                       |                               |                               |
| Mean change (± SD)      | -4.00 (7.4)            | -1.50 (3.5)                   | -2.54 (6.3)                   |
| Median                  | -3.0                   | -3.0                          | 0.0                           |
| 95% confidence interval | -9.7, 1.7              | -3.4, 0.37                    | -6.0, 0.9                     |
| P-value*                | 0.1427                 | 0.1073                        | 0.1390                        |

FVC: forced vital capacity; SD: standard deviation; DL\textsubscript{CO}: haemoglobin-corrected diffusion capacity for carbon monoxide; * P-value based on paired t-test.
FIGURE 1 Patient disposition
FIGURE 2 Pharmacokinetic profile of PBI-4050 alone (n = 2) or in combination with nintedanib (n = 4) or pirfenidone (n = 3) at week 12. Data are presented as mean ± SD. SD: standard deviation; W12: Week 12; PIRF: pirfenidone; NINT: nintedanib; HC: healthy controls; *: This data is from a different study.
FIGURE 3a Absolute mean change from baseline in percent-predicted FVC following 12 weeks of treatment with PBI-4050 alone or in combination with either nintedanib or pirfenidone.

FVC: forced vital capacity; SD: standard deviation.
**FIGURE 3b** Absolute mean change from baseline in FVC (mL) and DL\textsubscript{CO} (%) following 12 weeks of treatment with PBI-4050 alone or in combination with either nintedanib or pirfenidone.

DL\textsubscript{CO}: haemoglobin-corrected diffusion capacity for carbon monoxide; FVC: forced vital capacity; SD: standard deviation.