





# Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with progressive pulmonary fibrosis (FIBRONEER-ILD)

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## ABSTRACT

**Introduction** Progressive pulmonary fibrosis (PPF) includes any diagnosis of progressive fibrotic interstitial lung disease (ILD) other than idiopathic pulmonary fibrosis (IPF). However, disease progression appears comparable between PPF and IPF, suggesting a similar underlying pathology relating to pulmonary fibrosis. Following positive results in a phase II study in IPF, this phase III study will investigate the efficacy and safety of BI 1015550 in patients with PPF (FIBRONEER-ILD).

**Methods and analysis** In this phase III, double-blind, placebo-controlled trial, patients are being randomised 1:1:1 to receive BI 1015550 (9 mg or 18 mg) or placebo twice daily over at least 52 weeks, stratified by background nintedanib use. Patients must be diagnosed with pulmonary fibrosis other than IPF that is progressive, based on predefined criteria. Patients must have forced vital capacity (FVC)  $\geq 45\%$  predicted and haemoglobin-corrected diffusing capacity of the lung for carbon monoxide  $\geq 25\%$  predicted. Patients must be receiving nintedanib for at least 12 weeks, or not receiving nintedanib for at least 8 weeks, prior to screening. Patients on stable treatment with permitted immunosuppressives (eg, methotrexate, azathioprine) may continue their treatment throughout the trial. Patients with clinically significant airway obstruction or other pulmonary abnormalities, and those using immunosuppressives that may confound FVC results (cyclophosphamide, tocilizumab, mycophenolate, rituximab) or high-dose steroids will be excluded. The primary endpoint is absolute change from baseline in FVC (mL) at week 52. The key secondary endpoint is time to the first occurrence of any acute ILD exacerbation, hospitalisation for respiratory cause or death, over the duration of the trial.

**Ethics and dissemination** The trial is being carried out in accordance with the ethical principles of the Declaration of Helsinki, the International Council on Harmonisation Guideline for Good Clinical Practice and other local ethics committees. The study results will be disseminated at scientific congresses and in peer-reviewed publications.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment with BI 1015550 in a phase II study in idiopathic pulmonary fibrosis (IPF) preserved lung function and had an acceptable safety profile. Patients with progressive pulmonary fibrosis (PPF) experience comparable disease progression, lung function decline and mortality as patients with IPF, and therefore it is hypothesised that they share underlying pathobiology and may respond to the same treatments.

## WHAT THIS STUDY ADDS

⇒ The phase II trial of BI 1015550 was conducted in patients with IPF, and no data exist for patients with PPF. This article describes the study design of FIBRONEER-ILD, a phase III double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with PPF, either alone or with background nintedanib treatment.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will explore whether preferential inhibition of the phosphodiesterase 4B subtype, alone or in combination with background nintedanib, is an effective strategy for the treatment of PPF.

**Trial registration number** NCT05321082.

## INTRODUCTION

The term interstitial lung disease (ILD) incorporates over 200 separate disorders characterised by inflammation and/or fibrosis of the lung parenchyma.<sup>1–4</sup> Patients with certain ILD diagnoses other than idiopathic pulmonary fibrosis (IPF)—for example, fibrotic connective tissue disease-associated ILD, fibrotic hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia



and unclassifiable ILD—may develop a progressive phenotype.<sup>5,6</sup> This progressive phenotype is described by the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thorax Association clinical practice guidelines as progressive pulmonary fibrosis (PPF).<sup>6</sup> The disease progression, response to therapy and mortality of these patients are comparable to that observed in patients with IPF.<sup>1,4,7,8</sup> These similarities have led to the hypothesis that IPF and PPF may share common pathogenic mechanisms, and therefore may respond to the same treatments.<sup>7,9</sup>

Nintedanib is the only antifibrotic therapy approved for the treatment of PPF.<sup>6</sup> Nintedanib, a tyrosine kinase inhibitor first approved for the treatment of IPF based on the INPULSIS trials,<sup>10</sup> was subsequently approved for use in PPF based on the INBUILD trial<sup>11</sup> and for use in systemic sclerosis-associated ILD based on the SENSICIS trial.<sup>12</sup> Although nintedanib treatment can slow disease progression, it does not stop it. Therefore, there is an urgent need for novel treatments that can be used alone or with nintedanib for the treatment of PPF.

BI 1015550 is an oral phosphodiesterase 4 (PDE4) inhibitor that preferentially inhibits the PDE4B subtype. PDE4 inhibitors produce anti-inflammatory effects by reducing the release of proinflammatory mediators and the recruitment of inflammatory cells.<sup>13</sup> The inhibition of PDE4 is also associated with attenuated fibrotic remodelling.<sup>14,15</sup> Preclinical studies have shown that BI 1015550 has anti-inflammatory and antifibrotic effects in *in vitro* and *in vivo* models of lung fibrosis, and demonstrated potential synergistic effects with nintedanib on fibroblast proliferation.<sup>16</sup>

PDE4 inhibitors have been associated with gastrointestinal side effects that limit their use, including nausea, emesis and diarrhoea.<sup>16</sup> There is evidence that these adverse events are linked to the inhibition of the PDE4D subtype<sup>17</sup>; preferential inhibition of the PDE4B subtype is expected to cause fewer side effects. BI 1015550 is roughly 10-fold more selective for the inhibition of PDE4B versus PDE4D.<sup>16</sup>

The efficacy and safety of treatment with BI 1015550 were investigated in a phase II study in patients with IPF.<sup>18</sup> Overall, BI 1015550 had an acceptable safety profile, with gastrointestinal disorders being reported most frequently and leading to discontinuation in 3.4% of patients. Treatment with BI 1015550 18mg two times per day (BID) prevented a decline in forced vital capacity (FVC) over 12 weeks. Following these encouraging results, it is anticipated that BI 1015550 may also be effective in patients with PPF, as was seen for nintedanib.<sup>10,11</sup>

This manuscript describes the study design of FIBRONEER-ILD, a phase III, double-blind, randomised, placebo-controlled trial investigating the efficacy and safety of BI 1015550 in adult patients with PPF, with or without background nintedanib treatment. Patients will be randomly assigned in a 1:1:1 ratio to receive BI 1015550 9mg or 18mg BID, or placebo. A sister

phase III trial, FIBRONEER-IPF, is being conducted in patients with IPF (NCT05321069) and will be described separately.

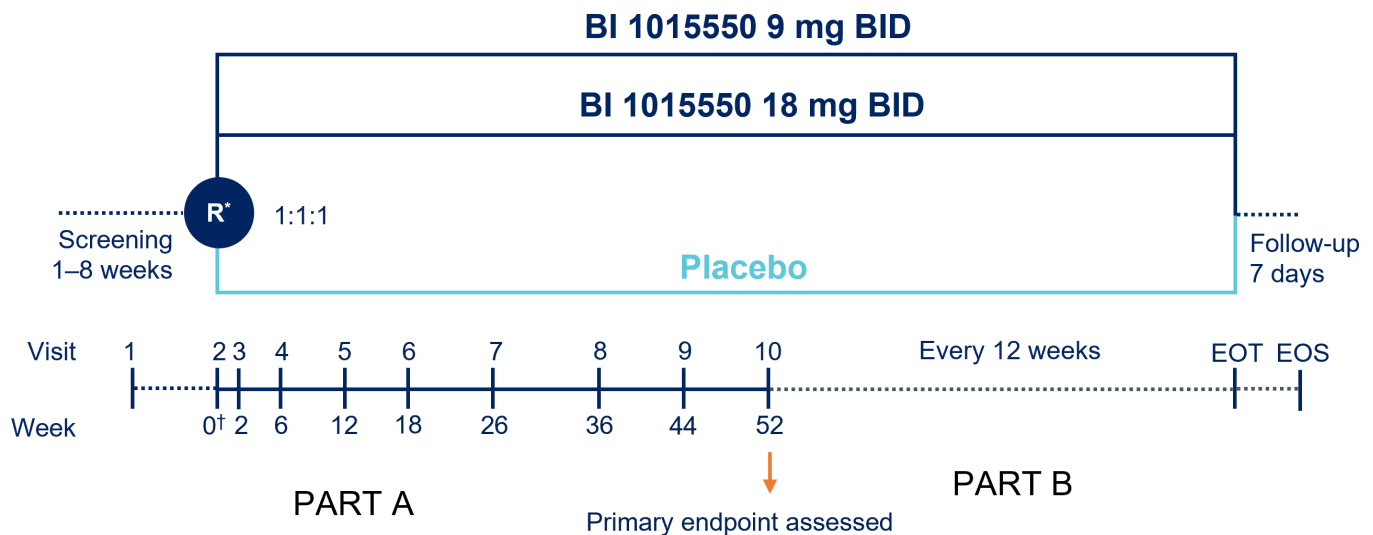
## METHODS AND ANALYSIS

### Trial design and interventions

The FIBRONEER-ILD trial is a phase III, double-blind, randomised, placebo-controlled trial (EudraCT: 1305-0023; ClinicalTrials.gov: NCT05321082) that is being conducted at over 400 sites in up to 45 countries across North, South and Central America, Europe, Africa, Australia and Asia (online supplemental figure 1). The trial began in October 2022 and is estimated to complete in November 2024. It is planned that 1041 patients will be randomised in a 1:1:1 ratio to BI 1015550 9mg or 18mg, or placebo BID for at least 52 weeks (figure 1). Patients will be enrolled at both urban and rural centres, ILD academic and expert centres, as well as community pulmonary centres. The 9mg dose is included to evaluate the benefit–risk profile of BI 1015550 at a lower dose, as well as to provide further dose-response and exposure-response data.

The trial consists of two parts. Part A consists of visits 2–10 over a 52-week treatment period. Following completion of the first 52 weeks, patients will remain in the study and continue blinded treatment in part B, over a variable period from visit 10 to the end of the trial, defined as the timepoint when the last patient randomised is expected to reach 52 weeks of treatment (ie, including data beyond 52 weeks). A follow-up visit will be performed 7 days after the end of treatment. Patients who discontinue early from their treatment will be asked to continue study visits. Temporary treatment interruption of BI 1015550 can be considered to manage adverse events. Dose reductions and treatment interruption for background nintedanib are allowed to manage adverse events as per prescribing information.<sup>19</sup>

Randomisation will be performed by BI, the sponsor of the study, with the use of an interactive voice-response system, and the randomisation list will be generated using a validated system, involving a pseudorandom number generator. Randomisation will be stratified by high-resolution CT (HRCT) imaging pattern (usual interstitial pneumonia-like vs other fibrotic patterns), similar to the INBUILD trial,<sup>11</sup> and presence of background treatment with nintedanib (nintedanib group vs non-nintedanib group). The nintedanib group includes patients who are on stable background therapy with nintedanib for at least 12 weeks and plan to continue this background treatment during the trial, whereas the non-nintedanib group includes patients not on treatment with nintedanib for at least 8 weeks. Patients, investigators, central reviewers and everyone involved in trial conduct will be blinded to the randomised treatment assignments.



**Figure 1** Trial design. \*Randomisation will be stratified by the presence of background nintedanib use (with or without nintedanib) and high-resolution CT imaging pattern (usual interstitial pneumonia pattern vs other fibrotic patterns). †Day 1. In part B, patients will continue treatment with blinded trial medication and have trial visits every 12 weeks, until the last randomised patient reaches 52 weeks of treatment. EOS is expected to be up to 130 weeks with an assumed recruitment period of 18 months. EOS, end of study; EOT, end of trial (ie, last randomised patient reaches 52 weeks of treatment); R, randomisation. Modified from Richeldi L *et al.*<sup>40</sup>

### Patient population

The main inclusion and exclusion criteria are shown in [box 1](#) and online supplemental table 1. Patients aged  $\geq 18$  years with any diagnosis of pulmonary fibrosis other than IPF (physician confirmed) are eligible, provided they meet the definition of progression. Patients can be enrolled into the trial without modification of their current nintedanib treatment; however, the number of patients with or without background nintedanib treatment will be monitored to ensure accurate representation of both groups. The definition of progressive ILD is based on the criteria used in the INBUILD trial.<sup>11</sup> Certain immunosuppressive agents (other than corticosteroids) will be permitted in the case of underlying systemic disease (eg, methotrexate, azathioprine), but these must be at a stable dose for at least 12 weeks prior to visit 1 and during the screening period. Similar to the INBUILD trial,<sup>20</sup> certain immunosuppressive agents (cyclophosphamide, tocilizumab, mycophenolate and rituximab) and high-dose steroids (prednisone  $>15$  mg/day or equivalent; online supplemental table 1) will not be allowed in this study. Although these agents are commonly used in real-world practice, they are not approved for the treatment of ILD in most countries and their benefit–risk profiles are not well established.<sup>20</sup> There is evidence that these agents may slow or prevent decline in FVC in some patients with connective tissue disease-related ILDs.<sup>21–25</sup> Thus, they may confound the assessment of the efficacy and safety of BI 1015550 in patients with PPF.

### Outcomes

The primary endpoint is absolute change from baseline in FVC (mL) at week 52. Other endpoints are shown in [box 2](#).

Patient-reported outcome measures will include the Living with Pulmonary Fibrosis Symptoms and Impact questionnaire total scores, EuroQol 5-Dimensional Quality of Life questionnaire total scores and the Patient's Global Impression of Severity for Cough, Shortness of Breath and Fatigue. Pharmacokinetic endpoints include predose plasma concentrations of BI 1015550. Exploratory biomarkers of inflammation, epithelial injury, tissue degradation and fibrosis will be assessed in blood over time (online supplemental table 3).

### Safety

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities. An independent data monitoring committee (DMC) that is unblinded to the treatment allocation will monitor the safety and progress of the trial. Safety monitoring and analyses will include physical examination, vital signs, safety laboratory parameters, ECG, review of adverse events reporting, Columbia-Suicide Severity Rating Scale and Hospital Anxiety and Depression Scale. Adverse events of special interest, which include potential severe drug-induced liver injury, vasculitis, severe infections, new onset of severe depression or new onset of severe anxiety, will be monitored.

### Statistical analysis

The primary endpoint of absolute change from baseline in FVC (mL) at week 52 will be estimated using a mixed-effect model for repeated measures analysis. This model will include discrete fixed effects for treatment at each visit, baseline intake of nintedanib therapy at each visit, HRCT pattern at each visit and continuous fixed

### Box 1 Main inclusion and exclusion criteria

#### Inclusion criteria

- ⇒ ≥18 years old.
- ⇒ Presence of fibrotic lung disease with disease extent >10% on HRCT performed within 12 months of visit 1 as confirmed by central review.
- ⇒ Patients with pulmonary fibrosis other than IPF who manifest progression according to at least one of the following predefined criteria within 24 months of visit 1:
  - ⇒ Relative decline in FVC% predicted of ≥10%.
  - ⇒ Decline in FVC% of ≥5% to <10% with worsening of respiratory symptoms.
  - ⇒ Decline in FVC% predicted of ≥5% to <10% with increasing extent of fibrotic changes on chest imaging.
  - ⇒ Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging.
- ⇒ FVC ≥45% of predicted.
- ⇒ DLco ≥25% of predicted normal corrected for haemoglobin.
- ⇒ Patients are either on stable treatment\* with nintedanib therapy for at least 12 weeks and plan to stay on this background treatment after randomisation, or not on treatment with nintedanib for at least 8 weeks (eg, either antifibrotic treatment naïve or previously discontinued) and do not plan to start or restart antifibrotic treatment.
- ⇒ Patients treated with permitted immunosuppressive agents (other than corticosteroids) for an underlying systemic disease (eg, methotrexate, azathioprine) need to be on a stable treatment for at least 12 weeks prior to visit 1 and during the screening period.

#### Exclusion criteria

- ⇒ Patients treated with the following medications prior to visit 1:
  - ⇒ Oral corticosteroids >15 mg/day within 4 weeks.
  - ⇒ Cyclophosphamide, tocilizumab or mycophenolate within 8 weeks.
  - ⇒ Rituximab within 6 months.
- ⇒ Prebronchodilator FEV<sub>1</sub>/FVC <0.7 at visit 1.
- ⇒ Patients with an acute ILD exacerbation within 3 months and/or during the screening period.
- ⇒ Active, unstable or uncontrolled vasculitis within 8 weeks.
- ⇒ Any suicidal behaviour (past 2 years) or suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (past 3 months).

\*Stable therapy is defined as a tolerated regimen of nintedanib (no dose change) for at least 12 weeks.

DLco, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

effects for baseline FVC (mL) value at each visit. The key secondary endpoint will be analysed using a Cox proportional hazards model with data from the whole trial (ie, including data beyond 52 weeks). The model will include treatment, HRCT pattern, background nintedanib treatment, age, FVC% predicted and diffusing capacity of the lung for carbon monoxide % predicted (corrected for haemoglobin) at baseline as covariates. To account for multiplicity introduced by testing two doses of BI 1015550 vs placebo for the primary and key secondary endpoints, the graphical testing procedure as depicted in online supplemental figure 2 will be used to maintain the family-wise type I error rate at a two-sided alpha level of 0.05.

### Box 2 Endpoints

#### Primary endpoint

- ⇒ Absolute change from baseline in FVC (mL) at week 52.

#### Key secondary endpoint

- ⇒ Time to first acute ILD exacerbation, first respiratory hospitalisation or death (whichever occurs first) over the duration of the trial.

#### Other secondary endpoints

- ⇒ Time to first acute ILD exacerbation or death over the duration of the trial.
- ⇒ Time to hospitalisation for respiratory cause or death over the duration of the trial.
- ⇒ Time to absolute decline in FVC% predicted of >10% from baseline or death over the duration of the trial.
- ⇒ Time to absolute decline in DLco% predicted of >15% from baseline or death over the duration of the trial.
- ⇒ Time to death over the duration of the trial.
- ⇒ Absolute change from baseline in L-PF Symptoms dyspnoea domain score at week 52.
- ⇒ Absolute change from baseline in L-PF Symptoms cough domain score at week 52.
- ⇒ Absolute change from baseline in L-PF Symptoms fatigue domain score at week 52.
- ⇒ Absolute change from baseline in FVC% predicted at week 52.
- ⇒ Absolute change from baseline in DLco% predicted at week 52.

DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; L-PF, living with pulmonary fibrosis.

The trial plans to randomise 1041 patients so that 347 patients are included in each study arm. Approximately 30% of patients are expected to be on background nintedanib treatment. This corresponds to the current treatment/prescription practices across the participating countries. This sample size will provide approximately 90% power to detect a treatment effect of 71 mL in change from baseline in FVC at week 52 for at least one dose group with an overall type I error of 0.05. For the primary endpoint, statistical significance will be declared if the analyses in either dose group are statistically significant at the designated alpha level according to online supplemental figure 2. The assumed treatment effect of 71 mL was derived based on the assumed FVC decline at week 52 in the placebo arm taking into account the expected number of patients with background nintedanib use, different HRCT patterns (usual interstitial pneumonia-like vs other fibrotic patterns) and FVC changes observed in INPULSIS and INBUILD.

Intercurrent events (except for death and lung transplant) will be handled via a treatment policy strategy. Missing data will not be imputed except for death, where a poor outcome will be assigned. Lung transplant will be handled via a hypothetical strategy. Data measured after a patient's lung transplantation will be censored. The mixed-effect model will handle missing data based on a likelihood method under the 'missing at random assumption'. A tipping point analysis is planned as sensitivity analysis to assess the robustness of the primary analysis against deviations from the missing at random

assumption. The effect of missing data on the primary endpoint will be further investigated using other multiple imputation techniques. Sensitivity analyses, including different covariates in the primary analysis model, will also be performed. Appropriate sample and data management system for clinical data and samples is in place, and patient identification numbers will be used to ensure confidentiality. The investigator or institution will allow site trial-related monitoring, audits, institutional review boards/independent ethics committees review and regulatory inspections.

### Trial governance and oversight

An independent DMC that is unblinded to the treatment allocation will primarily evaluate safety data and limited efficacy data on a regular basis. An interim analysis to assess the futility of the 9 mg BID dose will be performed by the independent DMC when approximately 300 patients in the trial (100 patients per arm) have completed 12 weeks of treatment. The independent DMC will make a recommendation to the sponsor on the continuation or stoppage of the 9 mg BID dose arm. The same independent DMC will review the sister trial in IPF (FIBRONEER-IPF) to ensure the broadest possible evaluation of safety in the programme.

An independent adjudication committee composed of cardiologists and neurologists will review all fatal cases for the primary cause of death and all adverse events categorised as major adverse cardiovascular events. A separate independent adjudication committee composed of rheumatologists/vasculitis experts will review all events of suspected or possible vasculitis.

A contingency plan has been developed for this trial in case patients are not able to perform an on-site visit due to their health status or COVID-19, which includes the direct shipment of investigational products to patients, remote check-ups and home spirometry.

### Patients and public involvement

During the planning of the FIBRONEER trials, feedback on the trial designs was obtained from a trial simulation involving patients, caregivers and healthcare professionals and during advisory board meetings with members of patient organisations and ILD experts. Participants provided their insights on the trial design, trial assessments, trial visit schedule and duration, and participant support. Patient-focused adaptations were then made to the trial protocols and conduct.

### Ethics and dissemination

The trial is being conducted in compliance with the ethical principles of the Declaration of Helsinki, in accordance with the International Council on Harmonisation Guideline for Good Clinical Practice, the EU directive 2001/20/EC and the Japanese Good Clinical Practice regulations (Ministry of Health and Welfare Ordinance

No. 28, 27 March 1997). Written informed consent will be obtained from each patient before entry into the study. Collection of blood samples for DNA banking is optional and not a prerequisite for participation (only for patients who have signed a separate informed consent form). Samples may be analysed retrospectively. The study results will be disseminated at scientific congresses and in peer-reviewed publications.

### DISCUSSION

The FIBRONEER-ILD trial is evaluating the efficacy, safety and tolerability of BI 1015550 compared with placebo in patients with PPF in addition to patient's standard of care over at least 52 weeks. A sister phase III study, FIBRONEER-IPF, is being conducted in parallel in patients with IPF. Together, these studies aim to address the need for new treatments for pulmonary fibrosis.

#### Selection of patients with PPF

The phase II trial of BI 1015550 was conducted in patients with IPF, and no data exist for patients with PPF. However, in patients with PPF, the natural history appears to follow a course similar to IPF, with worsening of respiratory symptoms, lung function decline, reduced quality of life and early mortality.<sup>1 6–8</sup> Nintedanib is approved for both IPF and PPF based on similar clinical outcomes and consistent effects in both diseases.<sup>10 11</sup> Together, this suggests shared underlying pathobiological mechanisms in patients with IPF and PPF. Given the positive efficacy and tolerability results in the phase II trial in IPF, it is hypothesised that similar treatment effects may be seen in patients with PPF.<sup>3 18</sup>

Furthermore, due to the rare nature of many ILD diagnoses, the grouping of patients with different ILDs that demonstrate PPF behaviour provides an opportunity to conduct an appropriately powered clinical study that is reflective of a real-world population.<sup>20 26</sup> This grouping is similar to that used in the INBUILD trial, and is justified based on their clinical and biological similarities.<sup>7</sup>

#### Targeting inflammation and fibrosis

ILDs incorporate a wide range of lung disorders, characterised by parenchymal damage mediated by inflammation and fibrosis.<sup>2</sup> PDE4 inhibition is being used in inflammatory diseases such as chronic obstructive pulmonary disease and psoriasis.<sup>27</sup> Many lung diseases that manifest PPF also have an inflammatory component, including fibrotic connective tissue disease-associated ILD, fibrotic hypersensitivity pneumonitis and idiopathic non-specific interstitial pneumonia.<sup>5 6 27</sup> PDE4 inhibition produces anti-inflammatory effects by reducing the release of proinflammatory mediators and reducing the recruitment of inflammatory cells.<sup>13</sup> Preclinical evidence has also shown that PDE4 inhibitors are associated with antifibrotic effects and may reduce fibrotic remodelling in lung disease.<sup>14 15</sup> In preclinical studies, BI 1015550 has

demonstrated anti-inflammatory and antifibrotic effects in *in vitro* and *in vivo* models of lung fibrosis.<sup>16</sup>

### Rationale for including patients with and without background nintedanib

In preclinical studies, the combination of nintedanib and BI 1015550 demonstrated potentially synergistic effects on the inhibition of fibroblast proliferation in primary lung fibroblasts in patients with IPF.<sup>16</sup> In the phase II trial, treatment with BI 1015550 at 18 mg BID preserved lung function in patients with IPF over the 12-week study period in patients either receiving or not receiving antifibrotic therapy,<sup>18</sup> with suggestion of an additive effect with nintedanib.<sup>28</sup>

Predose and postdose concentration levels of BI 1015550 were similar between patients treated with nintedanib and those not treated with any antifibrotics, indicating that nintedanib use did not impact the exposure of BI 1015550.<sup>29</sup> Thus, the efficacy and safety of BI 1015550 will be assessed in patients with PPF with or without background nintedanib treatment.

### Rationale for dose selection

The selection of the BI 1015550 18 mg BID dose is supported by the results from the phase II study, where BI 1015550 treatment preserved lung function in patients with IPF.<sup>18</sup> In this phase III trial, we have an additional 9 mg BID dose to evaluate the benefit–risk profile at a lower dose, as well as to provide further dose–response and exposure–response data. An interim futility analysis is planned to assess the efficacy and safety profile of the 9 mg BID dose, ensuring patients are exposed to the lower dose for the shortest period possible in case of a non-favourable benefit–risk profile.

### Rationale for the choice of inclusion and exclusion criteria

This study opted for similar criteria to the INBUILD trial, given its successful use in a large sample of patients with fibrosing lung disease.<sup>7</sup> The study protocol was developed prior to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thorax Association 2022 guidelines on definition of PPF.<sup>6</sup> Although there are minor differences between this definition and the INBUILD criteria, the inclusion criteria used in this trial are inclusive of a broad population of patients with PPF. There is no upper limit for age or FVC, and patients will be included if they have FVC% predicted of  $\geq 45\%$ , which may be more representative of patients with PPF in the real world. Certain immunosuppressive agents that may impact FVC (eg, cyclophosphamide, tocilizumab, mycophenolate, rituximab) will not be allowed in this study, to avoid the potential confounding impact of these drugs on the assessment of the efficacy and safety of BI 1015550 in PPF.

### Rationale for trial endpoints

The study endpoints are consistent with previous trials and reflect clinically meaningful outcomes. In this study, the primary endpoint is absolute change from baseline in FVC (mL) at week 52. This differs from the primary endpoint of annual rate of decline in FVC (mL/year) used in the INBUILD trial due to findings from the phase II study of BI 1015550 in patients with IPF; the phase II study showed an early increase in FVC in the treated group, suggesting a non-linear course. In contrast, a continuous decline was observed with nintedanib in INBUILD.<sup>18</sup> Thus, change from baseline FVC (mL) may be a more suitable endpoint for this phase III study.

The short duration of the phase II study and its small sample size limit the conclusions that can be drawn regarding the treatment effect of 18 mg BID.<sup>18</sup> In this phase III trial, the minimum treatment period of 52 weeks has been selected according to the guidance from American and European clinician organisations (2015 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thorax Association guidelines) to confirm these treatment effects on FVC over a longer time period and in a larger sample of patients.<sup>30</sup> This study also includes a variable period in which patients will continue treatment with BI 1015550 or placebo beyond week 52. Patients with PPF may have different underlying pathophysiology to those with IPF. Thus, there may be heterogeneity in rates of progression and response to treatment throughout the trial. This time scale will also allow more time and longer follow-up, to record more events for the assessment of the key secondary endpoint (time to first exacerbation, hospitalisation due to respiratory cause or death), thus increasing the power of the trial. In addition, specific efficacy and safety endpoints and changes in clinically significant outcomes may vary in occurrence and may only become apparent beyond 52 weeks.

### Safety assessments

Depression and suicidal ideation or behaviour are listed as side effects associated with marketed oral pan-PDE4 inhibitors, and therefore, will be monitored as part of the safety assessments in this trial.<sup>31–35</sup> In preclinical toxicology studies, PDE4 inhibitors have been associated with vasculitis.<sup>36–39</sup> In the phase II study, there was one patient with suspected vasculitis and IPF exacerbation, but vasculitis was not confirmed by the independent DMC.<sup>18</sup> Patients will be monitored for vasculitis during this trial and suspected cases will be assessed by the independent adjudication committee and independent DMC.

### Limitations

While some immunosuppressive agents (eg, methotrexate, azathioprine) will be permitted, cyclophosphamide, tocilizumab, mycophenolate, rituximab and high-dose steroids will not be allowed in this study, to avoid

the potential confounding impact of these drugs on the assessment of the efficacy and safety of BI 1015550 in PPF. This is a limitation of the trial, as many patients with PPF may use these immunosuppressive agents and biologics in real-world practice.

## CONCLUSIONS

The FIBRONEER-ILD trial is investigating the efficacy, safety and tolerability of oral BI 1015550 in patients with PPF, over a long-term period, in patients with or without nintedanib. The study commenced in October 2022. Following the positive results of the BI 1015550 phase II trial in patients with IPF and the similarities in disease course between IPF and PPF, it is anticipated that treatment effects may also be seen in patients with PPF.

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