




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

Luca Richeldi ¹, Arata Azuma,^{2,3} Vincent Cottin,⁴ Michael Kreuter,^{5,6} Toby M Maher ^{7,8}, Fernando J Martinez,⁹ Justin M Oldham,¹⁰ Claudia Valenzuela ¹¹, Maud Gordat,¹² Yi Liu,¹³ Susanne Stowasser,¹⁴ Donald F Zoz,¹⁵ Marlies S Wijsenbeek¹⁶

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Introduction There is an unmet need for new treatments for idiopathic pulmonary fibrosis (IPF). The oral preferential phosphodiesterase 4B inhibitor, BI 1015550, prevented a decline in forced vital capacity (FVC) in a phase II study in patients with IPF. This study design describes the subsequent pivotal phase III study of BI 1015550 in patients with IPF (FIBRONEER-IPF).

Methods and analysis In this placebo-controlled, double-blind, phase III trial, patients are being randomised in a 1:1:1 ratio to receive 9 mg or 18 mg of BI 1015550 or placebo two times per day over at least 52 weeks, stratified by use of background antifibrotics (nintedanib/pirfenidone vs neither). The primary endpoint is the absolute change in FVC at week 52. The key secondary endpoint is a composite of time to first acute IPF exacerbation, hospitalisation due to respiratory cause or death over the duration of the trial.

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

Trial registration number NCT05321069.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrotic interstitial lung disease (ILD) of unknown cause that is characterised by progressive lung function decline, increased symptom burden and early mortality.^{1–3} Treatment options for IPF are currently limited to two antifibrotic treatments, nintedanib and pirfenidone, which have been shown to reduce the decline in forced vital capacity (FVC).^{4,5} Management of IPF may also include pulmonary rehabilitation, which has been shown to improve exercise capacity, dyspnoea and health-related quality of life (QoL).^{6,7} Lung transplantation

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease associated with a decline in lung function and early mortality. In a phase II trial, treatment with the oral preferential phosphodiesterase 4B inhibitor, BI 1015550, prevented a decline in lung function over 12 weeks and had an acceptable safety profile in patients with IPF, regardless of background use of antifibrotics, supporting phase III clinical development.

WHAT THIS STUDY ADDS

⇒ This article describes the study design of FIBRONEER-IPF, a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with IPF, either alone or in addition to background antifibrotic treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The FIBRONEER-IPF trial will provide further evidence on the efficacy and safety of BI 1015550 in patients with IPF, potentially leading to a new treatment for what remains a life-shortening disease.

has been shown to increase life expectancy and may be considered for selected patients.⁸

Nintedanib is a tyrosine kinase inhibitor that has been approved for the treatment of IPF, non-IPF progressive pulmonary fibrosis (PPF) and systemic sclerosis-associated ILD.^{9–11} Pirfenidone is a pyridine with an unknown mechanism of action and has been approved for the treatment of IPF.^{12–14} Although these antifibrotic treatments slow down the progressive decline in lung function over time, prognosis remains poor in most patients with IPF, as their lung function continues to decline, leading to premature death due to respiratory failure.¹⁵ In addition, nintedanib and pirfenidone are both associated with adverse events,



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For numbered affiliations see end of article.

Correspondence to

Professor Luca Richeldi; luca.richeldi@policlinicogemelli.it

which can result in treatment discontinuation.^{4 5 16–20} Therefore, there is an unmet need for more effective treatments with acceptable tolerability that can modify the disease course and preserve QoL in patients with IPF.

Phosphodiesterase 4 (PDE4) enzymes mediate the breakdown of the intracellular secondary messenger cyclic adenosine monophosphate, and are implicated in a range of inflammatory cell functions.²¹ There are four PDE4 subtypes (PDE4A, B, C, D) with varied roles and distributions in the body.^{22 23} PDE4 inhibition has been investigated as a treatment in inflammatory respiratory diseases, such as chronic obstructive pulmonary disease, and may also have potential therapeutic effects in pulmonary fibrosis through its regulation of inflammation and the modulation of immunocompetent cells.^{24–28}

Common adverse events associated with marketed oral pan-PDE4 inhibitors include diarrhoea, nausea and headache,²⁶ with other adverse events including depression, suicidal ideation and behaviour.^{29 30} PDE4 inhibitors have also been associated with vasculitis in preclinical toxicology studies.³¹ The emetic side effects associated with pan-PDE4 inhibition may be linked to the inhibition of the PDE4D subtype.³² It has been suggested that preferential inhibition of the PDE4B subtype may lead to anti-inflammatory and antifibrotic effects but with a reduced risk of side effects,^{25 33} making it a potential promising target for treating pulmonary fibrosis.²³

BI 1015550 is an oral preferential PDE4B inhibitor with approximately 10-fold selectivity for inhibition of PDE4B compared with PDE4D.³³ In preclinical studies, BI 1015550 was associated with anti-inflammatory and antifibrotic effects in *in vitro* and *in vivo* models of pulmonary fibrosis, and demonstrated potential synergistic effects with nintedanib on fibroblast proliferation.³³ In phase I trials, treatment with BI 1015550 showed acceptable safety and tolerability in healthy male adults and in

male and female patients with IPF.³⁴ In a phase II trial, the efficacy and safety of BI 1015550 were investigated in 147 patients with IPF stratified by use of background antifibrotics (nintedanib/pirfenidone vs neither).³⁵ Treatment with BI 1015550 18 mg two times per day prevented a decline in FVC over 12 weeks and had an acceptable safety profile both as a monotherapy and in addition to background antifibrotic treatment.³⁵

This manuscript describes the design of the subsequent study, FIBRONEER-IPF, a randomised, placebo-controlled, pivotal phase III trial investigating the safety and efficacy of BI 1015550 9 mg and 18 mg two times per day compared with placebo in adult patients with IPF.

METHODS AND ANALYSIS

Trial design

This multicentre, double-blind, randomised, placebo-controlled trial is investigating the efficacy and safety of BI 1015550 in patients with IPF stratified by use of background antifibrotics over at least 52 weeks (EudraCT: 1305-0014; ClinicalTrials.gov: NCT05321069). The trial began in September 2022 and is estimated to complete in November 2024. Patients are being recruited globally from approximately 400 sites in 45 countries across the Americas, Europe, Africa, Australia and Asia (online supplemental figure 1). Patients will be enrolled at both urban and rural centres, ILD academic and expert centres, as well as community pulmonary centres, all with pulmonologists as principal investigators. It is planned that 963 patients will be randomised in a 1:1:1 ratio to receive 9 mg or 18 mg of BI 1015550 or placebo two times per day. Randomisation will be performed with the use of an interactive voice-response system and stratified according to background use of an antifibrotic treatment at screening. The trial is composed of

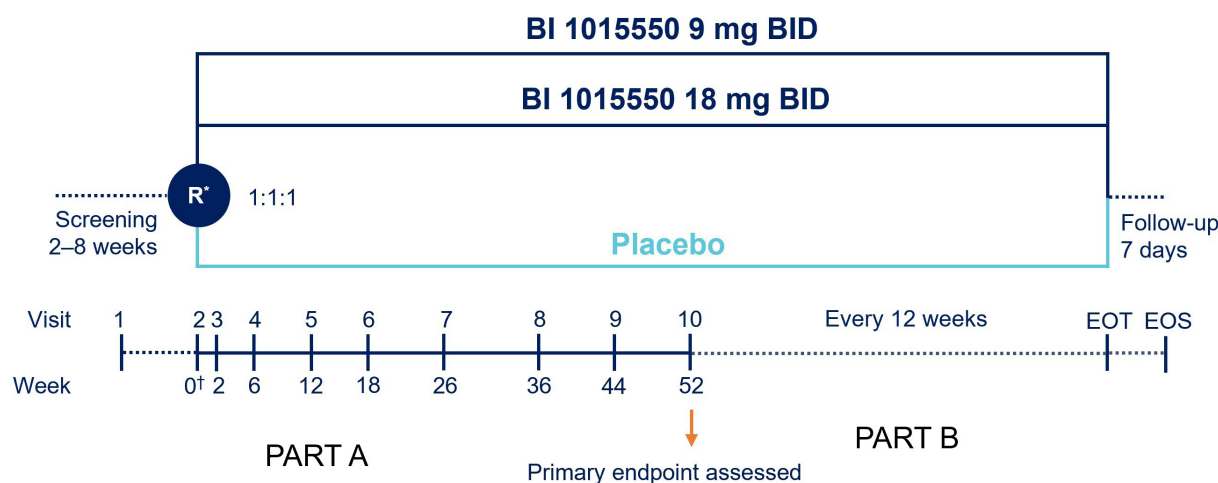


Figure 1 FIBRONEER-IPF trial design. *Randomisation will be stratified by use of background antifibrotic (nintedanib/pirfenidone vs neither). †Day 1. Part B will begin from visit 10 to EOT over a variable period; patients will continue treatment with blinded trial medication and have trial visits every 12 weeks. EOS is expected to be up to 130 weeks with an assumed recruitment period of 18 months. BID, two times per day; EOS, end of study; EOT, end of trial (ie, last randomised patient reaches 52 weeks of treatment); R, randomisation.

two parts (see [figure 1](#)). In part A, patients will attend study visits over a 52-week treatment period. This will be followed by part B, during which patients will remain in the study and continue treatment with blinded trial medication over a variable period until the end of the trial, which will be defined as the point when the last patient randomised is expected to reach 52 weeks of treatment. 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 will be considered to manage adverse events, and reintroduction of treatment will be encouraged if considered safe by the investigator. Dose reductions and treatment interruption of background antifibrotics are allowed to manage adverse events, as per the prescribing information for each drug.^{9 13}

Patient population

Eligible patients are aged ≥ 40 years, have received a diagnosis of IPF, and have an FVC $\geq 45\%$ of predicted and a diffusing capacity of the lung for carbon monoxide (DLco) $\geq 25\%$ and $< 90\%$ of predicted. A diagnosis of IPF is based on: (1) 2022 international guidelines,³ as confirmed by the investigator based on a chest high-resolution CT (HRCT) scan taken within 12 months of visit 1; and (2) usual interstitial pneumonia (UIP) or probable UIP at HRCT, as confirmed by central review before randomisation. Patients with an HRCT finding indeterminate for UIP are eligible if a clinical diagnosis of IPF can be confirmed locally, based on historical surgical lung biopsy or cryobiopsy demonstrating a histopathology pattern consistent with UIP or probable UIP.

As patients are stratified by background antifibrotic use, patients with background antifibrotic treatment are defined as patients on stable treatment with an approved antifibrotic drug (nintedanib or pirfenidone) for at least 12 weeks prior to study entry and planning to continue this background treatment during the trial. Patients without background antifibrotic treatment must not have been on approved antifibrotic treatment for at least 8 weeks before and throughout the duration of the trial, but antifibrotic treatment may be used as rescue medication after the first 12 weeks as deemed appropriate by the investigator.

Patients who have relevant acute or chronic infections, an acute IPF exacerbation 3 months before visit 1 and/or during the screening period, active vasculitis within the past 8 weeks, suicidal behaviour in the past 2 years or suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) (past 3 months) are excluded. Patients who are taking immunosuppressants other than prednisone ≤ 15 mg/day or equivalent for respiratory or pulmonary indications are excluded. The main inclusion and exclusion criteria are shown in [box 1](#) and online supplemental table 1.

Box 1 Main inclusion and exclusion criteria

Inclusion criteria

- ⇒ An IPF diagnosis based on 2022 international guidelines.³
- ⇒ Chest HRCT scans must be performed within 12 months of visit 1 and confirmed by central review prior to visit 2.
- ⇒ Patients on stable treatment with background antifibrotic treatment need to have received antifibrotic treatment for at least 12 weeks prior to visit 1 and during screening, and plan to stay on this background treatment after randomisation. A combination of nintedanib plus pirfenidone is not allowed. Patients not on stable treatment with background antifibrotics need to have not received antifibrotic treatment for at least 8 weeks prior to visit 1 and during the screening period (eg, either antifibrotic treatment naïve or previously discontinued), and must not be planning to start or restart antifibrotic treatment.*
- ⇒ To meet the following criteria at visit 1:
 - ⇒ FVC $\geq 45\%$ predicted.
 - ⇒ DLco corrected for Hb $\geq 25\%$ and $< 90\%$ predicted.

Exclusion criteria

- ⇒ Relevant airways obstruction (prebronchodilator FEV₁/FVC ratio < 0.7) at visit 1.
- ⇒ Experienced an acute IPF exacerbation within 3 months and/or during the screening period.
- ⇒ Confirmed infection with SARS-CoV-2 and not fully recovered according to investigator judgement within the 4 weeks prior to randomisation.
- ⇒ AST or ALT $> 2.5 \times$ ULN or total bilirubin $> 1.5 \times$ ULN at visit 1.
- ⇒ eGFR ≤ 30 mL/min/1.73 m² at visit 1 (CKD-EPI formula or Japanese version of CKD-EPI for Japanese patients).
- ⇒ Active, unstable or uncontrolled vasculitis within the past 8 weeks prior to visit 1 or during the screening period.
- ⇒ Any suicidal behaviour (past 2 years) or any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months.
- ⇒ Acute or chronic severe depression defined as HADS subscore > 14 at visit 1 and/or visit 2.
- ⇒ Patients treated with PDE1, PDE3, PDE4 or PDE10 inhibitors, or non-selective PDE inhibitors, within 30 days before visit 1.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; C-SSRS, Columbia-Suicide Severity Rating Scale; DLco, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; HADS, Hospital Anxiety and Depression Scale; Hb, haemoglobin; HRCT, high-resolution computed tomography; PDE, phosphodiesterase; SARS, severe acute respiratory syndrome; ULN, upper limit of normal.

*Stable therapy is defined as the individually and generally tolerated regimen of either nintedanib or pirfenidone (no dose changes) for at least 12 weeks.

Endpoints

The primary endpoint is absolute change from baseline in FVC (mL) at week 52. This will be assessed using spirometry according to American Thoracic Society/European Respiratory Society 2019 guidelines.³⁶ The key secondary endpoint is a composite of the time to first acute IPF exacerbation, first hospitalisation for respiratory cause or death (whichever occurs first) over the duration of the trial. Other endpoints include change in QoL, as measured by the patient-reported outcome measure (PROM), the Living with Pulmonary Fibrosis

**Box 2** Endpoints to be assessed**Primary endpoint**

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

Key secondary endpoint

⇒ Time to first IPF acute exacerbation, first hospitalisation for respiratory cause or death, over the duration of the trial.

Other secondary endpoints

- ⇒ Time to first acute IPF 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 from baseline in FVC% predicted >10% from baseline or death over the duration of the trial.
- ⇒ Time to absolute decline in DLco% predicted >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; IPF, idiopathic pulmonary fibrosis; L-PF, living with pulmonary fibrosis.

Questionnaire (L-PF).³⁷ Time-to-event endpoints will also be assessed separately over the duration of the trial, including time to first acute IPF exacerbation or death, and time to first hospitalisation due to respiratory cause or death. Absolute change from baseline in DLco% predicted and FVC% predicted will also be assessed at week 52 (box 2 and online supplemental table 2).

Pharmacokinetic endpoints include predose plasma concentrations of BI 1015550. Exploratory blood biomarkers of inflammation, epithelial injury, tissue degradation and fibrosis will be assessed in blood over time, including protein biomarkers. 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.

Safety

For safety analyses, physical examination, vital signs, safety laboratory parameters and ECG will be performed. Depression, suicidal ideation and behaviour are listed as side effects associated with marketed oral pan-PDE4 inhibitors.^{38–42} Suicide risk monitoring is required during the clinical development of PDE4 inhibitors, and this will be assessed using the C-SSRS in this study. Depression and anxiety will be measured using the Hospital Anxiety and Depression Scale (HADS).

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities. 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 throughout the study.

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, including treatment at each visit, baseline background antifibrotic treatment and continuous fixed effects for baseline FVC (mL) at each visit as covariates. The key secondary endpoint of time to first acute IPF exacerbation, first hospitalisation for respiratory cause or death will be analysed using a Cox proportional hazards model using data over the whole trial (ie, including data beyond 52 weeks). The model will include treatment, background antifibrotic treatment, age and FVC% predicted and DLco% predicted (corrected for haemoglobin) at baseline as covariates. Kaplan-Meier plots will be presented for each treatment arm. The percentage of patients with an event at week 52 will be presented descriptively and by Kaplan-Meier estimates.

To account for multiple testing associated with two doses of BI 1015550 being compared with placebo for both the primary and key secondary endpoints, a graphical testing procedure⁴³ will be applied, with a focus on the 18 mg dose and primary endpoint. A sample size of 321 patients per group will yield 90% power to detect an effect of a 74 mL change in FVC at week 52 for a BI 1015550 dose group over placebo, with an overall type I error rate 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 the graphical testing procedure (online supplemental figure 2).

In the primary analysis, intercurrent events except for death will be handled via a treatment policy strategy. Missing data will not be imputed except for death, for which a poor outcome will be assigned. The intercurrent event of lung transplantation will be treated with a hypothetical strategy approach (which considers the effect of what would have happened if the intercurrent event did not occur) with the data set as missing and handled by the model via the missing at random (MAR) assumption (primary endpoint) or censoring (key secondary endpoint). The mixed-effect model will handle missing data based on a likelihood method under the 'MAR' assumption. A tipping-point analysis is planned as a sensitivity analysis to assess how robust the primary analysis is against deviations from the MAR assumption. The effect of missing data on the primary endpoint will be further investigated using other multiple imputation techniques. In addition, sensitivity analysis including additional covariates in the primary analysis model will be performed.

Trial governance and oversight

An independent data monitoring committee (DMC) that may be unblinded to the treatment allocation will evaluate safety data on a regular basis. An interim analysis to assess the potential futility of the BI 1015550 9 mg two times per day arm will be conducted by the independent DMC after approximately 300 patients (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 BI 1015550 9 mg two times per day dose arm.

Two independent adjudication committees will conduct regular reviews of the trial safety data. An independent adjudication committee involving cardiologists and neurologists will review all fatal cases for the primary cause of death and will review all adverse events categorised as major adverse cardiovascular events. A separate independent adjudication committee of rheumatologists and 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.

Patient and public involvement

Feedback on the trial design was obtained from a trial simulation involving patients, caregivers and healthcare professionals, and from advisory board meetings with members of patient organisations and expert investigators.

DISCUSSION

Rationale for conducting the study

Real-world data from registries suggest that antifibrotics improve survival in patients with IPF; however, these treatments do not stop disease progression and are associated with adverse events, such as diarrhoea and nausea, leading to a proportion of patients discontinuing treatment.^{18–20} Therefore, there is a need for additional treatments that can be used as monotherapy or in addition to existing antifibrotic treatments. Preferential PDE4B inhibition demonstrates anti-inflammatory and antifibrotic effects, suggesting that it may have potential as a treatment for patients with IPF and other forms of PPF.³³ A phase II trial of BI 1015550 in patients with IPF showed promising results in preventing a decline in lung function combined with an acceptable safety profile, with the most frequently reported adverse event being diarrhoea.³⁵ However, this proof-of-concept study was limited by its 12-week duration and relatively small sample size.³⁵

BI 1015550 is the first oral preferential PDE4B inhibitor advancing to phase III clinical development in IPF. The FIBRONEER-IPF trial is investigating the efficacy and safety of BI 1015550, alone or in combination with background antifibrotic use, in patients with IPF. As

IPF and PPF may share common pathobiological pathways for pulmonary fibrosis,^{44 45} a sister trial is underway that is evaluating the efficacy and safety of BI 1015550 in patients with PPF (FIBRONEER-ILD; NCT05321082). Collectively, these studies add to the body of evidence for the safety and efficacy of BI 1015550 in pulmonary fibrosis.

FIBRONEER-IPF is also investigating BI 1015550 as an add-on therapy to background antifibrotics, which are the standard of care in IPF.⁴⁶ Preclinical data show that BI 1015550 has complementary activity to nintedanib on human myofibroblast transformation and a synergistic effect in combination with nintedanib on fibroblast proliferation.³³ A post hoc analysis of the phase II trial also suggests that BI 1015550 may have an additive effect with nintedanib.⁴⁷ Given that there are multiple fibrotic pathways involved in IPF^{48 49} and preclinical evidence suggesting synergistic effects with nintedanib,³³ data from this trial on the use of BI 1015550 in patients receiving background antifibrotics may lead to a new frontier for IPF combination treatments.

Rationale for trial design

The age and lung function inclusion criteria of this study are inclusive of a broader population of patients compared with previous IPF clinical trials.^{4 5} There is no upper limit for age or FVC, and patients will be included if they have FVC% predicted $\geq 45\%$, which may be more representative of patients with IPF in the real world.

Due to the COVID-19 pandemic, there may be unprecedented challenges involved with setting up a multicentre and international phase III trial.⁵⁰ Several contingency measures will be implemented if required to mitigate potential disruptions from COVID-19 when initiating and conducting the trial or if a patient with a poor health status cannot attend on-site visits.

Rationale for dose selection

The selection of the BI 1015550 18 mg two times per day dose is supported by the results from the phase II study, in which treatment with this dose was associated with preserving lung function in patients with IPF.³⁵ In this phase III trial, we have an additional 9 mg two times per day 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 analysis is planned to assess the efficacy and safety profile of the 9 mg two times per day 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 endpoints

Change in FVC is a commonly used primary endpoint in IPF trials and has been associated with mortality.^{51 52} Patients in this study have a treatment period of at least 52 weeks and remain on blinded treatment for a variable period beyond week 52 depending on the recruitment rate. This will allow

more time to assess time-to-event efficacy endpoints, since changes in these clinically meaningful outcomes may vary in occurrence and may only become apparent over a longer time period than 52 weeks.⁵³ In addition, for the assessment of the key secondary endpoint (time to first exacerbation, hospitalisation due to respiratory cause or death), a longer follow-up should allow more events to be captured and consequently increase the power of the analysis. An issue in IPF clinical trials is determining appropriate PROMs with good sensitivity to capture change in QoL over time.⁵⁴ The L-PF questionnaire is a validated PROM that can be used in patients with IPF^{35,37} and was found to best capture the signs/symptoms and impacts on patients in a consensus study on PROMs for IPF and PPF.⁵⁵

Depression, suicidal ideation and behaviour have also been reported in previous studies of pan-PDE4 inhibitors.^{38,56–59} New onset of severe depression, defined as HADS subscore >14, and new onset of severe anxiety, defined as HADS subscore >14, are investigated as adverse events of special interest as part of the safety assessment in this trial. In preclinical toxicology studies, vasculitis has been associated with PDE4 inhibitor treatment.³¹ In the phase I trials with BI 1015550, there were no confirmed adverse events of vasculitis, depression or suicidal ideation or behaviour.³⁴ In the phase II study, there was one patient with suspected vasculitis, which was not confirmed by the independent DMC, and one report of suicidal ideation type 1 that had occurred after the residual effect period of BI 1015550, 9 days after the completion of treatment.³⁵ Patients are monitored for vasculitis during this trial and suspected cases will be assessed by independent adjudication and DMCs.

CONCLUSIONS

FIBRONEER-IPF is the first phase III trial of a preferential PDE4B inhibitor in patients with IPF. The results of this trial will increase our understanding of the safety and efficacy of BI 1015550 as a monotherapy or in combination with current antifibrotic standard of care in a larger and broader population of patients with IPF. These data will help to address an unmet need for new treatments for patients with IPF and potentially provide evidence for combination treatment in IPF.

Author affiliations

¹Unità Operativa Complessa di Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

²Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan

³Respiratory Medicine and Clinical Research Centre, Meisei Hospital, Saitama, Japan

⁴Hôpital Louis Pradel, Centre Coordonnateur National de référence des Maladies Pulmonaires Rares, Hospices Civils de Lyon, UMR754, INRAE, Université Claude Bernard Lyon 1, Member of ERN-LUNG, Lyon, France

⁵Centre for Interstitial and Rare Lung Diseases, Department of Pneumology, Thoraxklinik, University of Heidelberg, German Center for Lung Research, Heidelberg, Germany

⁶Department of Pneumology, RKH Clinic Ludwigsburg, Ludwigsburg, Germany

⁷Department of Pulmonary, Critical Care and Sleep Medicine, USC Keck School of Medicine, Los Angeles, California, USA

⁸Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London, London, UK

⁹Department of Medicine, Cornell University, New York City, New York, USA

¹⁰Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan, USA

¹¹ILD Unit, Pulmonology Department, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain

¹²Clinical Development & Operation Department, Boehringer Ingelheim, Reims, France

¹³Department of Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut, USA

¹⁴TA Inflammation Med, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

¹⁵Global Clinical Development and Medical Affairs, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut, USA

¹⁶Centre for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The trial is being carried out 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 was obtained from each patient before entry into the study. The results of the study will be disseminated at scientific congresses and in peer-reviewed publications.

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Data availability statement Data are available on reasonable request. To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on <https://vivli.org/>, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit <https://www.mystudywindow.com/msw/datasaring> for further information.

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ORCID iDs

Luca Richeldi <http://orcid.org/0000-0003-0506-9966>
 Toby M Maher <http://orcid.org/0000-0001-7192-9149>
 Claudia Valenzuela <http://orcid.org/0000-0002-0856-6290>

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