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Original research article

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Phase I studies of BI 1015550, a preferential PDE4B inhibitor, in healthy males and patients with idiopathic pulmonary fibrosis

Toby M. Maher[1,2], Christina Schlecker[3], Doreen Luedtke[4], Sebastian Bossert[4], Donald F. Zoz[5], Armin Schultz[6]

[1]Inflammation, Repair, and Development Section, National Heart and Lung Institute, Imperial College London, London, UK; [2]Keck Medicine of USC, Los Angeles, CA, United States; [3]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [5]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, United States; [6]CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany.

Corresponding author: Toby Maher, MD

Address: Keck Medicine of USC, Los Angeles, CA, United States

Email: Toby.Maher@med.usc.edu

Contact telephone number: +1 650 278 0058

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Take-home message (254/256 characters) A preferential PDE4B inhibitor BI 1015550 is a candidate drug for the treatment of fibrotic interstitial lung disease. In Phase I studies, BI 1015550 had an acceptable safety profile in healthy males and patients with idiopathic pulmonary fibrosis.

Abstract (max 246/250 words)

Introduction: BI 1015550 is a phosphodiesterase 4 (PDE4) inhibitor that has antifibrotic properties. Phase I and Ic studies were conducted to investigate the safety, tolerability and pharmacokinetics of BI 1015550 in healthy males and patients with idiopathic pulmonary fibrosis (IPF).

Methods: In the Phase I study, 42 subjects were partially randomised to receive placebo or BI 1015550 in single rising doses of 36 mg and 48 mg, or multiple rising doses of 6 mg and 12 mg twice daily over 14 days. In the Phase Ic study, 15 patients with IPF were randomised to receive 18 mg BI 1015550 or placebo twice daily for up to 12 weeks. For both studies, the primary endpoint was the number of subjects with drug-related adverse events (AEs).

Results: In the Phase I study, drug-related AEs were reported for 50.0% of healthy males treated with a single dose of BI 1015550, compared with 16.7% receiving placebo. For those receiving multiple doses, drug-related AEs were reported for 37.5% of those treated with BI 1015550 and 12.5% receiving placebo. The most frequently reported AEs by organ class were nervous system disorders, which were largely driven by headache. In the Phase Ic study, drug-related AEs were reported in 90.0% of patients treated with BI 1015550, compared with 60.0% of those receiving placebo. The most frequent AEs by organ class were gastrointestinal AEs.

Conclusions: BI 1015550 had an acceptable safety profile in healthy males and patients with IPF, supporting further development in larger trials.

Keywords: (1-6 keywords): interstitial lung disease; phosphodiesterase 4B; phosphodiesterase 4 inhibitor; pulmonary fibrosis.

Clinical trial registrations: NCT03230487 (Phase I), NCT03422068 (Phase Ic)

Plain language summary

Idiopathic pulmonary fibrosis (IPF) is a disease that causes scarring of patients' lungs and cannot be cured. There is a need for new drugs to improve the care of patients with IPF. BI 1015550 was developed to help slow the lung damage in patients with IPF. Two clinical trials were performed; one in healthy volunteers and one in patients with IPF, and any medical problems the participants had during the trials were recorded. In the clinical trials, common medical problems were headache and effects on the digestive tract, but overall BI 1015550 seemed to be safe to use. This means BI 1015550 can be looked at in other clinical trials to see if it could be a useful treatment for IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare and fatal lung disease characterised by irreversible and progressive decline in lung function [1, 2]. There are two approved antifibrotic therapies for the treatment of IPF: nintedanib [3, 4] and pirfenidone [5, 6]. Nintedanib is approved for the treatment of IPF and other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, and for systemic sclerosis-associated ILD [3, 4]. Pirfenidone is approved for the treatment of IPF [5, 6]. These treatments can slow, but not stop or reverse, disease progression and are associated with side effects that can delay treatment initiation or lead to discontinuation [7]. This means there is an unmet need for new treatments for IPF and other forms of progressive pulmonary fibrosis that can be used alone or with standard of care [8].

There are four phosphodiesterase 4 (PDE4) enzymes (PDE4A, B, C and D), which hydrolyse cyclic adenosine monophosphate to 5'adenosine monophosphate [9]. PDE4 is widely expressed in immune system cells and inhibition of PDE4 reduces the release of pro-inflammatory mediators and the recruitment of inflammatory cells [10]. PDE4 inhibitors are associated with anti-inflammatory and antifibrotic effects and have the potential to reduce pulmonary inflammation and fibrotic remodelling in lung diseases [8, 11]. However, the use of oral PDE4 inhibitors is limited due to their systemic adverse events (AEs), which include gastrointestinal AEs, headaches, weight loss and psychiatric symptoms [9, 12, 13].

BI 1015550 is an oral PDE4 inhibitor that preferentially inhibits PDE4B and is a candidate drug for the treatment of IPF and other progressive fibrosing interstitial lung diseases. Preclinical studies have demonstrated that BI 1015550 has anti-inflammatory and antifibrotic properties in *in vitro* and *in vivo* models of lung fibrosis [14]. *In vitro* findings include inhibition of human lung fibroblast proliferation and myofibroblast transformation, suggesting that BI 1015550 may have activity in patients with progressive fibrosing interstitial lung diseases [14].

We describe the results from two early phase clinical studies of BI 1015550. The first was a Phase I study that aimed to investigate the safety, tolerability and pharmacokinetics of BI 1015550 in healthy males. Based on the results from this study, a Phase Ic study aimed to investigate the safety, tolerability and pharmacokinetics of BI 1015550 in patients with IPF.

Materials and methods

Phase I study in healthy males

Study design

This Phase I study (NCT03230487) was conducted between 15 August 2017 (first informed consent) and 16 January 2018 (study completion date of last subject) at the CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany. The independent ethics committee and competent authority approved the study. Written informed consent was obtained from all subjects prior to admission to the study.

Healthy males aged 18–45 years with a body mass index of 18.5–29.9 kg/m^2 were enrolled. Full inclusion and exclusion criteria are detailed in the Supplementary Methods.

Subjects received oral BI 1015550 or matching placebo in single rising doses (SRDs) of 36 mg and 48 mg, or multiple rising doses (MRDs) of 6 mg and 12 mg twice daily (BID) over 14 days. Both the SRD and MRD parts had a partially randomised, parallel-group design where the first block of each dose group was treated in a fixed sequence, whereas the other block was randomised in a 2:1 ratio. In the MRD part, subjects and investigators were both blinded to treatment allocation, whereas in the SRD part, only patients were blinded.

The SRD part was conducted under fasted conditions and the MRD part under fed conditions. In the MRD part, subjects were treated over 14 days and received a single morning dose on Day 1, followed by 11 days of treatment (i.e. 6 mg BID, 12 mg BID or

matching placebo on Days 3 to 13), and a single morning dose on Day 14. No treatments were administered on Day 2 to allow 34-hour pharmacokinetic sampling after a single dose.

Details of randomisation and blinding, subject allocation and sample size determination can be found in the Supplementary Methods.

Assessment endpoints

The primary endpoint was the number of subjects with drug-related AEs, with AEs graded as 'mild' (awareness of signs or symptoms that were easily tolerated), 'moderate' (sufficient discomfort to cause interference with usual activity), or 'severe' (incapacitating or causing inability to work or to perform usual activities).

Pharmacokinetic parameters were analysed as secondary endpoints and are described in detail in the Supplementary Methods. Briefly, these included the peak plasma concentration (C_{max}), the area under the concentration−time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$; SRD part) and accumulation ratios. In the MRD part, alongside C_{max}, AUC was evaluated over a uniform dosing interval τ after the first dose ($AUC_{\tau,1}$) and over the dosing interval τ at steady state after the last dose ($C_{max,ss}$, $AUC_{\tau,ss}$).

Secondary safety endpoints included electrocardiography (ECG), laboratory investigations and, in the MRD part, suicidality assessment; further details can be found in the Supplementary Methods. Descriptive statistics were calculated for all endpoints. No formal interim analysis was planned or performed.

Phase Ic study in patients with IPF

Study design

This Phase Ic study (NCT03422068) was conducted between 23 April 2018 (first informed consent) and 10 July 2019 (last patient visit) at 11 sites in 7 European countries (Supplementary Table 1). Independent ethics committee approval from the participating

centres was obtained prior to study initiation. Written informed consent was obtained from all patients prior to study admission.

This study was conducted according to a randomised, double-blind, placebo-controlled, within-dose-groups design. Male and female patients with a diagnosis of IPF based on international guidelines [15], aged ≥40 years, who had not been treated with nintedanib or pirfenidone within 30 days of Visit 1 and were not planning to be initiated on nintedanib or pirfenidone for the duration of the study, were eligible. Full inclusion and exclusion criteria are detailed in the Supplementary Methods.

Two sequential doses were planned to be tested: 18 mg BID and 24 mg BID, however dose escalation was stopped after the 18 mg BID dose because exposure predictions for the 24 mg BID dose group exceeded the pre-defined exposure threshold (Supplementary Methods). Due to challenges in recruitment, the duration of treatment was reduced from 12 weeks to 4 weeks, with patients recruited before this amendment treated up to a maximum of 12 weeks (Figure 1).

Further details on the randomisation, blinding and allocation, determination of sample size and modifications to the study design can be found in the Supplementary Methods.

Assessment endpoints

The primary endpoint was the number of patients with drug-related AEs, with the severity grading the same as for the Phase I study in healthy males. Pharmacokinetic parameters of BI 1015550 were evaluated as secondary endpoints after the first dose on Day 1 ($AUC_{\tau,1}$ and C_{max}) and after the morning dose on Day 14 ($AUC_{\tau,ss}$ and $C_{max,ss}$). Secondary safety endpoints included ECG, laboratory investigations and suicidality assessment; further details are provided in the Supplementary Methods. Exploratory lung function efficacy endpoints were changes in forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide and forced expiratory volume in 1 second. Descriptive statistics were calculated for all endpoints. No formal interim analysis was performed.

Results

Phase I study in healthy males

Subjects

The flow of subjects is shown in Figure 1 and subject demographics in Supplementary Table 2. Demographic and baseline characteristics were similar between the treatment groups.

Safety

A summary of AEs is shown in Table 1, all AEs are shown in Supplementary Table 3, and salient laboratory parameters are shown in Supplementary Table 4.

AEs were reported more frequently for patients treated with BI 1015550 versus placebo in the SRD part (66.7% vs 16.7%), and with similar frequencies in the MRD part (43.8% vs 37.5%).

In the SRD part, the most common AEs by organ class were nervous system disorders (headache and dizziness), reported for 41.7% of patients receiving BI 1015550 and 16.7% of patients treated with placebo. This was largely driven by headache as there was only one case of dizziness (36 mg SRD part) in the whole study. The second most common AEs by organ class were gastrointestinal disorders (abdominal distension, upper abdominal pain, constipation, diarrhoea and nausea), reported for 25.0% of patients receiving BI 1015550 and 16.7% of patients receiving placebo.

In the MRD part, the most common AEs by organ class were nervous system disorders (headache), reported for 31.3% of patients receiving BI 1015550 and 12.5% of patients treated with placebo. The second most common AEs by organ class were gastrointestinal disorders (abdominal distension, diarrhoea, nausea and oral hypoesthesia), reported for 18.8% of patients receiving BI 1015550 and 12.5% of patients receiving placebo.

All AEs were mild or moderate in intensity and resolved before the end of the study.

One subject in the 48 mg treatment group prematurely discontinued study participation after a single dose due to an AE (ligament sprain) that was not considered drug related.

There were no reported deaths, severe AEs, serious AEs, protocol-specified AEs of special interest or other significant AEs (according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E3), and no clinically relevant findings with respect to ECG recordings or vital signs. The only clinically relevant laboratory finding was an increase in blood triglycerides in one subject in the 12 mg BID treatment group, which was considered drug related. No incidence of suicidal ideation or behaviour were detected using the Columbia Suicide Severity Rating Scale (C-SSRS).

Body weight was measured in the MRD part, where there was a trend for a decrease in weight in the BI 1015550 treatment groups only. In the 6 mg and 12 mg BID treatment groups, the mean changes from baseline were –1.21 kg (SD 0.43) and –1.34 kg (SD 1.61), respectively. In the placebo MRD group, the mean change from baseline was 0.21 kg (SD 1.06).

Pharmacokinetics

Pharmacokinetic parameters are shown in Table 2 and Table 3. The geometric mean (gMean) plasma concentration-time profiles after single and multiple doses are shown in Figure 3. Plasma concentrations increased quickly. They reached a peak concentration of the analyte in plasma with a median time from last dosing to the maximum measured concentration (t_{max}) of 1.25 hours to 1.52 hours after single and multiple oral administration, and then declined with terminal half-lives of 16 hours to 27 hours.

Linear pharmacokinetics with a dose-proportional increase in AUC of the analyte in plasma were observed for the dose ranges tested (from 36 mg to 48 mg single dose and from 6 mg to 12 mg BID BI 1015550). Steady state was reached by Day 6, with a slight accumulation after multiple BID administrations. gMean accumulation ratios based on C_{max} were 1.60 and

1.52 for 6 mg BID and 12 mg BID, respectively. gMean accumulation ratios based on $AUC_{\tau,1}$ were 1.85 and 1.68 for 6 mg BID and 12 mg BID, respectively.

Phase Ic study in patients with IPF

Patients

The flow of patients with IPF is shown in Figure 2 and patient demographics in Supplementary Table 4. Ten patients were treated with BI 1015550 and five patients with placebo for a median duration of 53.5 and 84.0 days, respectively. Baseline lung function was comparable between the treatment groups.

Safety

A summary of AEs is shown in Table 4, all AEs are shown in Supplementary Table 6, and salient laboratory parameters are shown in Supplementary Table 7.

The most frequently reported AEs by organ class were gastrointestinal disorders, reported in 8 (80.0%) patients treated with BI 1015550 and 2 (40.0%) patients receiving placebo, followed by infections and infestations, reported in 5 (50.0%) of patients treated with BI 1015550 and 2 (40.0%) of patients receiving placebo. The most frequent infection was nasopharyngitis reported in 4 (40%) of patients treated with BI 1015550. The most frequent gastrointestinal events were diarrhoea, which affected 4 (40.0%) patients receiving BI 1015550 and placebo. All patients with diarrhoea had recovered by the end of the trial.

There was one severe AE of insomnia in a patient treated with BI 1015550, which was considered drug related and stopped when the patient discontinued BI 1015550 treatment. This was the only severe AE in the study, and the only AE leading to discontinuation. All other AEs were mild or moderate in intensity, and most were resolved by the end of the study. There were no reported deaths, and no cases of suicidal ideation or behaviour were detected using the C-SSRS.

One patient in the BI 1015550 group experienced two serious AEs (SAEs) (anal fistula and anal incontinence) that were mild in intensity. This patient had a long history of anal fistula and was scheduled for an elective surgical treatment of anal fistula and secondary anal incontinence. Anal fistula and anal incontinence were categorised as SAEs due to hospitalisation but were not considered drug related.

There were no clinically relevant findings with respect to 12-lead ECG or vital signs. Laboratory tests also revealed no clinically relevant findings except for a slight increase in C-reactive protein in the BI 1015550 group.

Overall, there was no notable difference between the two treatment groups with respect to body weight. Mean observed weight loss in patients treated for up to 12 weeks was –1.18 kg in the placebo group and –1.74 kg in the BI 1015550 group, and this small numerical difference was not consistent over time.

Pharmacokinetics

A summary of the pharmacokinetic parameter results is shown in Table 5. gMean plasma concentration-time profiles after single and multiple doses of BI 1015550 18 mg BID are shown in Figure 3. The gMeans for C_{max} and $AUC_{\tau,1}$ were higher after multiple administrations than after administration of a single dose. The gMean for accumulation ratios based on C_{max} and AUC_{τ} was 1.66 and 1.87, respectively. Inter-individual variability was generally low to moderate after administration of a single dose, and moderate to high after multiple administrations. After approximately five administrations of BI 101555018 mg BID, 95% of the steady-state concentration was reached.

Exploratory efficacy endpoints

Lung function parameter data were highly variable between patients and no clear effect of BI 1015550 treatment on lung function parameters could be observed over the course of the trial. There was a trend towards a slight reduction in FVC over time in the placebo group; this trend was not observed in the BI 1015550 group (data not shown).

Discussion

The results of the Phase I study show that BI 1015550 has an acceptable safety and tolerability profile in healthy males. Overall, the total exposure to BI 1015550 appeared to increase proportionally with dose over the range tested. In the Phase Ic study, only the 18 mg BID dose was investigated because the pharmacokinetic exposure prediction for the 24 mg BID exceeded the predefined exposure threshold. In the Phase Ic study, BI 1015550 at 18 mg BID had acceptable safety and tolerability in patients with IPF who had not received background antifibrotic treatment. After approximately five administrations at 18 mg BID, 95% of the steady-state concentration was reached. There was no difference in pharmacokinetic parameters between healthy volunteers and patients with IPF.

The use of oral PDE4 inhibitors is currently limited due to their association with AEs such as gastrointestinal AEs and headache [9]. An alternative therapeutic strategy to reduce the AEs associated with oral PDE4 inhibitors is to preferentially inhibit PDE4B, potentially leading to anti-inflammatory and antifibrotic effects whilst circumventing many of the AEs associated with more general PDE4 inhibitors [9, 16, 17].

In the Phase Ic and Phase I studies, gastrointestinal disorders were the first and second mostly commonly reported adverse events by organ class, respectively. In the Phase I, the most common AEs by system organ class was nervous system disorders, driven by headache. Both gastrointestinal disorders and headache are known class effects of other non-selective PDE4 inhibitors [9]. In both trials, suicidal ideation and behaviour and weight loss were monitored because they are listed as side effects associated with marketed oral PDE4 inhibitors [12]. No suicidal ideation or behaviour was reported in either of our studies. In the Phase I trial in healthy volunteers, there was a slight trend for a decrease in weight in subjects treated with BI 1015550 but there were no notable differences between treatment groups in the Phase Ic trial in patients with IPF.

BI 1015550, an oral preferential inhibitor of PDE4B, is the first PDE4 inhibitor to be investigated in patients with IPF. Preclinical data have shown that BI 1015550 has anti-inflammatory and antifibrotic effects [14]. BI 1015550 also appears to have a complementary mode of action with nintedanib on fibroblast transformation and synergistic effects on fibroblast proliferation [14]. A limitation of the Phase Ic study is that recruitment was restricted to patients who were not receiving background antifibrotic treatment. This precluded investigation of potential additive effects on the efficacy and/or safety of BI 1015550 in combination with background antifibrotic standard of care. Such effects are, however, being investigated in a Phase II study of BI 1015550 in patients with IPF with and without background antifibrotic treatment, which has recently completed (NCT04419506) [18].

Further limitations of both studies include the small sample size, lack of diversity among study participants, and short study duration. Potential effects of sex, race and/or ethnicity on bioavailability and clearance of BI 1015550 will be examined in future studies in more diverse populations. In the Phase I study there was possible observer bias of dose-dependent and time-dependent effects. In the Phase Ic study, patients with IPF had relatively preserved lung function (mean FVC% predicted: 91.7%); therefore, the effects in patients with more severe disease are unknown.

In conclusion, the results of these studies suggest that BI 1015550 has an acceptable safety and tolerability profile in healthy males and in patients with IPF within the dose range tested and for up to 12 weeks. There were no obvious differences in pharmacokinetic parameters between healthy volunteers and patients with IPF. These data support further clinical studies to investigate the safety and efficacy of BI 1015550 18 mg BID in larger and more diverse populations of patients with IPF.

Disclosures

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of the manuscript. Claire Scott, PhD, and Hanne Stotesbury, PhD, of Meditech Media (UK) provided writing, editorial support and formatting assistance, which was contracted and funded by Boehringer Ingelheim International GmbH (BI). BI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. The Phase I and Phase Ic trials were supported and funded by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss and Boehringer Ingelheim (Canada) Ltd/Ltée, Burlington, Ontario, Canada, respectively.

Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim **grants all external authors access** to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. **Clinical study documents and participant clinical study data are available to be shared on request** after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (see https://www.mystudywindow.com/msw/datasharing). Bonafide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Table 1. Phase I study in healthy males: summary of AEs

	SRD				MRD			
	Placebo n (%)	**BI 1015550 36 mg n (%)**	**BI 1015550 48 mg n (%)**	**BI 1015550 Total n (%)**	**Placebo n (%)**	**BI 1015550 6 mg BID n (%)**	**BI 1015550 12 mg BID n (%)**	**BI 1015550 Total n (%)**
Number of subjects	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	16 (100.0)
Subjects with any AE	1 (16.7)	4 (66.7)	4 (66.7)	8 (66.7)	3 (37.5)	2 (25.0)	5 (62.5)	7 (43.8)
Subjects with investigator defined drug-related AEs	1 (16.7)	2 (33.3)	4 (66.7)	6 (50.0)	1 (12.5)	2 (25.0)	4 (50.0)	6 (37.5)

AE, adverse event; BID, twice daily; MRD, multiple-rising-dose; SRD, single-rising-dose.

Table 2. Phase I study in healthy males: summary of pharmacokinetic parameters of BI 1015550 in the SRD part

Parameter (unit)	BI 1015550 36 mg (fasted) n=6		BI 1015550 48 mg (fasted) n=6	
	gMean	gCV (%)	gMean	gCV (%)
C_{max} (nmol/L)	710	20.7	955	15.5
$AUC_{0-\infty}$ (nmol·h/L)	5910	21.2	8700[#]	17.2
fe_{0-120} (%)	12.5[#]	45.2	12.1[¶]	13.4
$CL_{R,0-120}$ (mL/min)	30.5[¶]	21.5	25.2[¶]	20.6

[#]n=5; [¶]n=4. AUC, area under the concentration−time curve; $AUC_{0-\infty}$, AUC of the analyte in plasma over the time interval from 0 extrapolated to infinity; $CL_{R,0-120}$, renal clearance of the analyte in plasma over the time interval (0 to 120 h after first drug administration); C_{max}, maximum measured concentration of the analyte in plasma; fe_{0-120} fraction of administered drug excreted unchanged in urine over the time interval (0-120 h after drug administration); gCV, geometric coefficient of variation; gMean, geometric mean; SRD, single-rising-dose.

Table 3. Phase I study in healthy males: summary of pharmacokinetic parameters of BI 1015550 in the MRD part

Parameter (unit)	BI 1015550 6 mg BID (fed) n=8		BI 1015550 12 mg BID (fed) n=8	
	gMean	gCV (%)	gMean	gCV (%)
C_{max} (nmol/L)	103	28.2	229	29.9
$AUC_{\tau,1}$ (nmol·h/L)	564	24.8	1370	15.9
$C_{max,ss}$ (nmol/L)	164	21.3	348	14.1
$AUC_{\tau,ss}$ (nmol·h/L)	1050	25.7	2300	15.8
$R_{A,Cmax}$	1.60	35.0	1.52	23.6
$R_{A,AUC}$	1.85	9.91	1.68	14.8

AUC, area under the concentration−time curve; $AUC_{\tau,1,}$ AUC of the analyte in plasma over a uniform dosing interval τ after the first dose; $AUC_{\tau,ss,}$ AUC of the analyte in plasma over the dosing interval τ at steady state; BID, twice daily; C_{max}, maximum measured concentration of the analyte in plasma; $C_{max,ss}$, C_{max} at steady state over a uniform dosing interval τ; gCV, geometric coefficient of variation; gMean, geometric mean; MRD, multiple-rising-dose; $R_{A,AUC}$, accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ, expressed as ratio of AUC at steady state and after single dose; $R_{A,Cmax}$, accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ, expressed as ratio of C_{max} at steady state and after single dose.

Table 4. Phase Ic study in patients with IPF: summary of AEs

	Placebo n (%)	**BI 1015550 18 mg BID n (%)**	**Total on treatment n (%)**
Patients treated	5 (100.0)	10 (100.0)	15 (100.0)
Any AE	5 (100.0)	10 (100.0)	15 (100.0)
Severe AEs	0 (0.0)	1 (10.0)	1 (6.7)
Investigator-defined drug-related AE	3 (60.0)	9 (90.0)	12 (80.0)
AE leading to discontinuation of study drug	0 (0.0)	1 (10.0)	1 (6.7)
Patients with AESI[#]	0 (0.0)	0 (0.0)	0 (0.0)
Patients with other significant AEs according to ICH E3	0 (0.0)	1 (10.0)	1 (6.7)
Patients with SAEs	0 (0.0)	1 (10.0)	1 (6.7)
Patients requiring or prolonging hospitalisation	0 (0.0)	1 (10.0)	1 (6.7)

[#]Hepatic injury was defined as an AESI. AE, adverse event; AESI, AE of special interest; BID, twice daily; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event.

Table 5. Phase Ic study in patients with IPF: pharmacokinetic parameters of BI 1015550 18 mg BID

Parameter (unit)	gMean n=10	gCV (%)
Day 1 (after the first dose)		
C_{max} (nmol/L)	277	23.1
$AUC_{\tau,1}$ (nmol·h/L)	1990	18.2
Day 14 (at steady state)		
$C_{max,ss}$ (nmol/L)	460	41.7
$AUC_{\tau,ss}$ (nmol·h/L)	3720	49.5

AUC, area under the concentration−time curve; $AUC_{\tau,ss}$, AUC of the analyte in plasma at steady state over a uniform dosing interval τ at steady state; $AUC_{\tau,1}$, AUC of the analyte in plasma over a uniform dosing interval τ after administration of the first dose; BID, twice daily; C_{max}, maximum measured concentration of the analyte in plasma; $C_{max,ss}$, C_{max} at steady state over a uniform dosing interval τ; gCV, geometric coefficient of variation; gMean, geometric mean; IPF, idiopathic pulmonary fibrosis.

Figures and tables

Figure 1. Phase I study in healthy males: subject flow

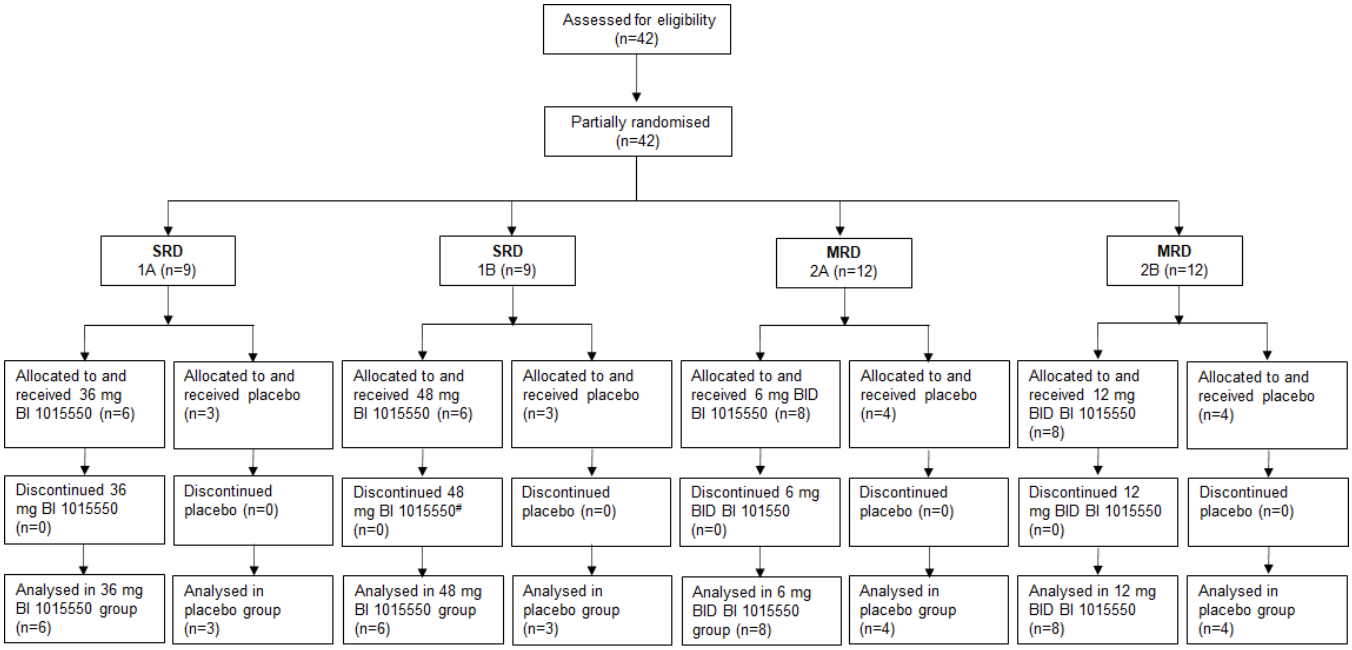
[#]One patient prematurely discontinued the study after taking 48 mg BI 1015550 due to an AE not considered drug related (ligament sprain). AE, adverse event; BID, twice daily; MRD, multiple-rising-dose; SRD, single-rising-dose.

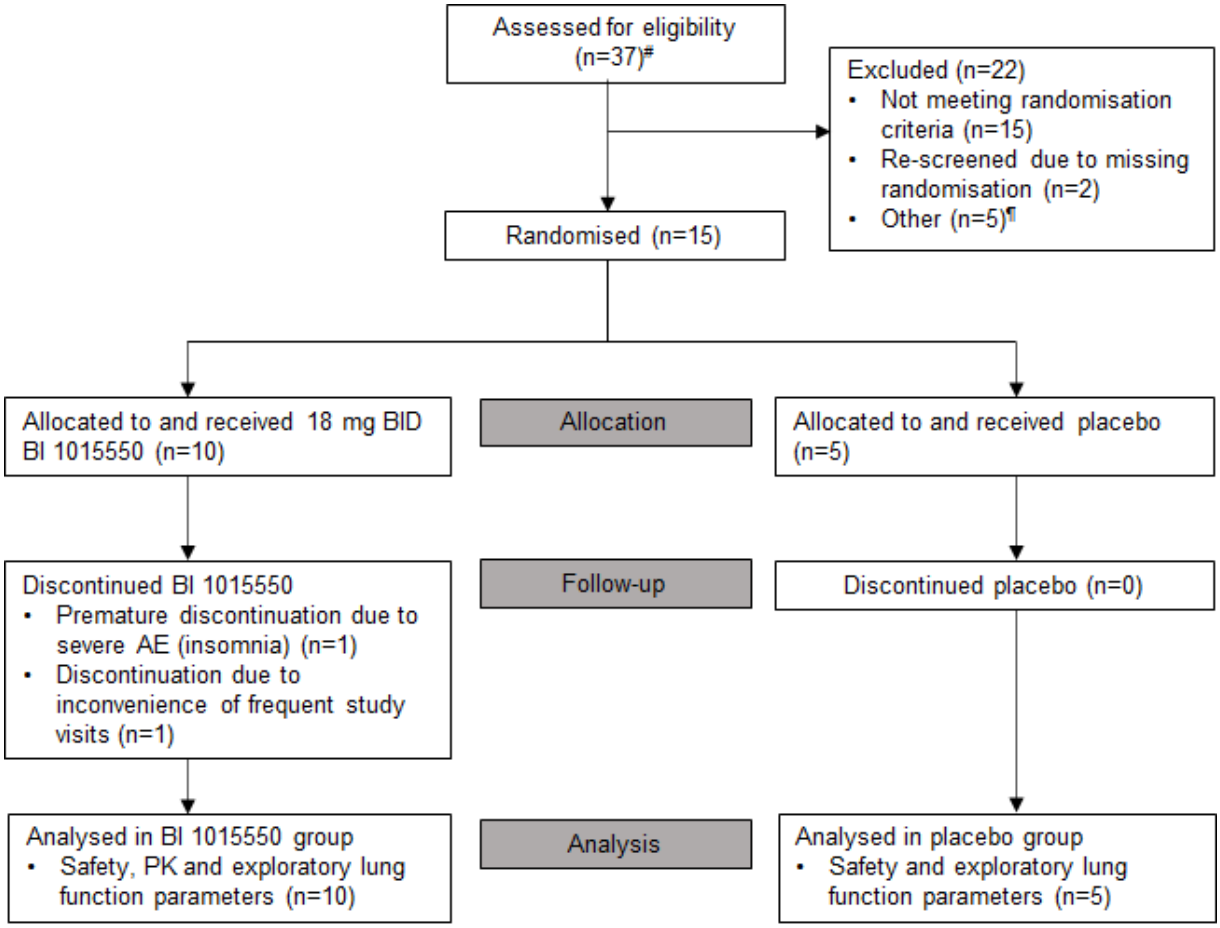
Figure 2. Phase Ic study in patients with IPF: patient flow

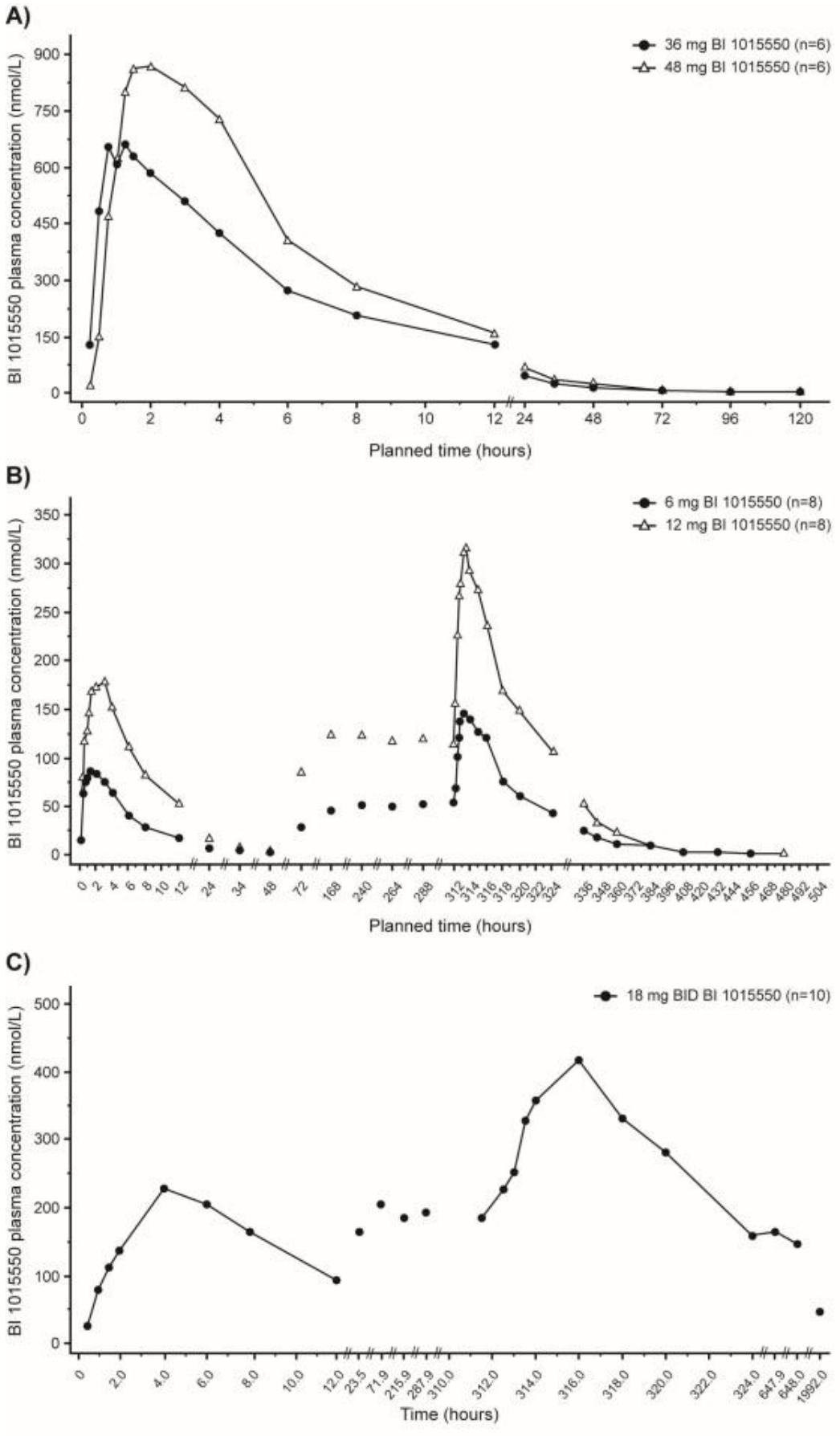
Of 10 patients treated with BI 1015550, 7 were treated up to a maximum duration of 12 weeks, and 3 up to a maximum of 4 weeks. Of 5 patients treated with placebo, 4 were treated up to a maximum duration of 12 weeks, and 1 up to a maximum of 4 weeks. [#]Four patients were screened twice; [¶]Other reasons for discontinuations (n=1 each) included: no longer willing to participate; administrative reason; randomisation timeline; study closed; unable to do calprotectin retest. AE, adverse event; BID, twice daily; IPF, idiopathic pulmonary fibrosis; PK, pharmacokinetic.

Figure 3. Geometric mean plasma concentration-time profiles of BI 1015550

Phase I study in healthy males after single oral administration of BI 1015550 36 mg or 48 mg in fasted condition (A) and single and multiple oral administrations of 6 mg or 12 mg BID BI 1015550 in fed condition (B). Phase Ic study in patients with IPF after single and multiple oral administration of 18 mg BID BI 1015550 (C).


Assessed for eligibility (n=42)
Partially randomised (n=42)
SRD 1A (n=9)
SRD 1B (n=9)
MRD 2A (n=12)
MRD 2B (n=12)
Allocated to and received 36 mg BI 1015550 (n=6)
Allocated to and received placebo (n=3)
Allocated to and received 48 mg BI 1015550 (n=6)
Allocated to and received placebo (n=3)
Allocated to and received 6 mg BID BI 1015550 (n=8)
Allocated to and received placebo (n=4)
Allocated to and received 12 mg BID BI 1015550 (n=8)
Allocated to and received placebo (n=4)
Discontinued 36 mg BI 1015550 (n=0)
Discontinued placebo (n=0)
Discontinued 48 mg BI 1015550# (n=0)
Discontinued placebo (n=0)
Discontinued 6 mg BID BI 101550 (n=0)
Discontinued placebo (n=0)
Discontinued 12 mg BID BI 1015550 (n=0)
Discontinued placebo (n=0)
Analysed in 36 mg BI 1015550 group (n=6)
Analysed in placebo group (n=3)
Analysed in 48 mg BI 1015550 group (n=6)
Analysed in placebo group (n=3)
Analysed in 6 mg BID BI 1015550 group (n=8)
Analysed in placebo group (n=4)
Analysed in 12 mg BID BI 1015550 (n=8)
Analysed in placebo group (n=4)


Assessed for eligibility (n=37)#
Excluded (n=22)
• Not meeting randomisation criteria (n=15)
• Re-screened due to missing randomisation (n=2)
• Other (n=5)¶
Randomised (n=15)
Allocated to and received 18 mg BID BI 1015550 (n=10)
Allocation
Allocated to and received placebo (n=5)
Discontinued BI 1015550
• Premature discontinuation due to severe AE (insomnia) (n=1)
• Discontinuation due to inconvenience of frequent study visits (n=1)
Follow-up
Discontinued placebo (n=0)
Analysed in BI 1015550 group
• Safety, PK and exploratory lung function parameters (n=10)
Analysis
Analysed in placebo group
• Safety and exploratory lung function parameters (n=5)


A)
36 mg BI 1015550 (n=6)
48 mg BI 1015550 (n=6)
BI 1015550 plasma concentration (nmol/L)
Planned time (hours)
B)
6 mg BI 1015550 (n=8)
12 mg BI 1015550 (n=8)
BI 1015550 plasma concentration (nmol/L)
Planned time (hours)
C)
18 mg BID BI 1015550 (n=10)
BI 1015550 plasma concentration (nmol/L)
Time (hours)

Supplementary Material

Phase I studies of BI 1015550, a preferential PDE4B inhibitor, in healthy males and patients with idiopathic pulmonary fibrosis

Toby M. Maher, Christina Schlecker, Doreen Luedtke, Sebastian Bossert, Donald F. Zoz, Armin Schultz

Supplementary Methods: Phase I study in healthy males

Inclusion criteria

1. Healthy male subjects according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory tests.
2. Age of 18 to 45 years (inclusive).
3. Body mass index of 18.5 to 29.9 kg/m^2 (inclusive).

Main exclusion criteria

1. Any finding in the medical examination (including vital signs or ECG) that deviated from normal and was judged as clinically relevant by the investigator.
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 55 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm.
3. Any laboratory value outside the reference range that the investigator considered to be of clinical relevance.
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator.
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders.

6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the study medication (except appendectomy).
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders, including but not limited to mood disorders and any history of suicidality.
8. History of relevant orthostatic hypotension, fainting spells or blackouts.
9. Chronic or relevant acute infections.
10. History of relevant allergy or hypersensitivity (including allergy to the study medication or its excipients).
11. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
12. Any suicidal ideation (i.e. type 1 to 5) on the Columbia Suicide Severity Rating Scale (C-SSRS) in the 12 months preceding screening (i.e. passive/active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent; only in the multiple-rising-dose [MRD] part).

Randomisation, blinding and allocation

Subjects were partially randomised within each dose group. The first block of each dose group was treated in a fixed sequence (BI 1015550 – placebo – BI 1015550), while the other block was randomised in a 2:1 ratio reflecting the ratio of subjects receiving BI 1015550 to placebo.

Randomisation was arranged by the sponsor Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany. The randomisation list was generated using a validated system, which involved a pseudo-random number generator and a supplied seed number so that the resulting allocation was both reproducible and non-predictable. Block size was 3.

In the single-rising-dose (SRD) part (1A and 1B), the treatments administered (BI 1015550 or placebo) were single-blind (blinded to subjects only); however, the current dose level was known to subjects. Subjects received a single dose of treatment. In the MRD part (2A and 2B), the treatments administered were double-blind to subjects, investigators and research staff at the study site; however, the current dose level was known to subjects and investigators.

Subjects were recruited to dose groups according to their temporal availability. As soon as enough subjects had been allocated to one of the two dose cohorts (two cohorts per dose group), subjects were allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts or groups was not influenced by study personnel, but only by the subjects' temporal availability.

Secondary endpoints

Pharmacokinetic parameters were analysed as secondary endpoints for BI 1015550: for the SRD part, these were area under the concentration−time curve (AUC) of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) and maximum measured concentration of the analyte in plasma (C_{max}); for the MRD part, AUC of the analyte in plasma over a uniform dosing interval τ after the first dose ($AUC_{\tau,1}$) and C_{max} were evaluated after the first dose. AUC of the analyte in plasma over the dosing interval τ at steady state ($AUC_{\tau,ss}$) and C_{max} at steady state over a uniform dosing interval τ ($C_{max,ss}$) were evaluated after the last dose. The following accumulation ratios were analysed: analyte in plasma after multiple dose administration over a uniform dosing interval τ, expressed as ratio of AUC at steady state and after single dose ($R_{A,AUC}$) and analyte in plasma after multiple dose administrations over a uniform dosing interval τ, expressed as ratio of C_{max} at steady state and after single dose ($R_{A,Cmax}$). Further pharmacokinetic parameters that were analysed were renal clearance of the analyte in plasma over the time interval 0 to 120 hours after first drug administration ($CL_{R,0-120}$) and fraction of administered drug excreted unchanged in urine over the time interval from 0 to 120 hours after first drug administration (fe_{0-120}). BI 1015550

concentrations in plasma and urine were determined using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS).

Secondary safety endpoints were treatment-emergent adverse events (TEAEs) including clinically relevant findings from the physical examination, 12-lead ECG, continuous ECG monitoring (SRD part only), vital signs (blood pressure, pulse rate, respiratory rate, aural body temperature), body weight (MRD part only) suicidality assessment (using the C-SSRS; MRD part only), and safety tests for the following functional laboratory groups: haematology, differentials, coagulation, enzymes, hormones, substrates, and electrolytes, as well as tests for faecal occult blood, faecal calprotectin and urinalysis for haematuria..

Determination of sample size

A total of 42 subjects were planned to be included in this study. The planned sample sizes were not based on a power calculation.

Supplementary methods: Phase Ic study in patients with idiopathic pulmonary fibrosis (IPF)

Inclusion criteria

1. Male or female patients aged ≥40 years at Visit 1.
2. A clinical diagnosis of IPF based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2011 Guidelines (P11-07084) within the previous 5 years as confirmed by the investigator based on a chest high-resolution computed tomography scan taken within 12 months of Visit 1, with a pattern of usual interstitial pneumonia confirmed by central review prior to Visit 2.
3. Forced vital capacity (FVC) ≥50% of predicted normal at Visit 1.
4. Diffusing capacity of the lung for carbon monoxide (corrected for haemoglobin [Visit 1]): >30% of predicted normal at Visit 1.

Main exclusion criteria

1. Patients with a significant disease or condition other than IPF, which in the opinion of the investigator may have put the patient at risk due to participation, may have interfered with study procedures, or may have caused concern regarding the patient's ability to participate in the study.
2. Any laboratory value outside the reference range that the investigator considered to be of clinical relevance.
3. Surgery of the gastrointestinal tract that could have interfered with the pharmacokinetics of the study medication (except appendectomy).
4. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke) and other relevant neurological or psychiatric disorders (including but not limited to mood disorders).
5. Evidence of active infection (chronic or acute) based on clinical examination or laboratory findings.
6. History of allergy or hypersensitivity to the study medication or its excipients.
7. Relevant airway obstruction (i.e. prebronchodilator forced expiratory volume in 1 second/ FVC <0.7) at Visit 1.
8. Patients who had previously been treated with nintedanib or pirfenidone within 30 days of Visit 1.
9. Positive faecal occult blood (no retest allowed).
10. Positive testing for haematuria if confirmed by microscopic urine analysis (retest allowed).
11. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
12. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought without method, intent or plan; active suicidal thought with method,

but without intent or plan; active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).

Randomisation, blinding and allocation

Randomisation was performed by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany. Randomisation was performed using an Interactive Response Technology, which was provided by PAREXEL International GmbH. The randomisation code was generated using a validated system, which involved a pseudo-random number generator and a supplied seed number so that the resulting allocation was both reproducible and non-predictable and verified by a trial-independent statistician.

This study was double-blind with regard to the patients, investigators and research staff at the study sites in order to eliminate observer or performance bias. According to the MRD study design, the dose level was known to patients and investigators.

Secondary endpoints

Pharmacokinetic parameters of BI 1015550 were evaluated as secondary endpoints after the first dose on Day 1 ($AUC_{\tau,1}$ and C_{max}) and after the morning dose on Day 14 ($AUC_{\tau,ss}$ and $C_{max,ss}$). BI 1015550 concentrations in plasma were determined using HPLC-MS.

Secondary safety endpoints were TEAEs including clinically relevant findings from the physical examination, 12-lead ECG, vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature, suicidality monitoring (using the C-SSRS) and safety laboratory tests for the following functional groups: haematology, differentials, coagulation, enzymes, hormones, substrates, plasma proteins, inflammatory parameters, and electrolytes, as well as tests for faecal occult blood, faecal calprotectin and urinalysis for haematuria.

Determination of sample size

It was planned to include 18 patients to be allocated to two dose groups in this study, but only one dose group was tested (see Modifications to the study design).

Modifications to the study design

Two sequential BI 1015550 dose groups were planned that were within the estimated therapeutic range and were based on the safety profile of this class of compound (18 mg and 24 mg; twice daily [BID]). However, only the 18 mg BID dose group was evaluated because one of the predefined stopping criteria for dose escalation was met (exposure predictions area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h at steady state [$AUC_{0-24,ss}$] for the 24 mg BID dose group exceeded the exposure threshold).

Originally, this study was to consist of a second study part, where BI 1015550 was planned to be evaluated on top of antifibrotic standard of care. However, due to recruitment challenges, and as this was the first investigation of the compound in MRD of 18 mg, as well as the first study in patients, the second study part was removed. This enabled a greater focus on safety in a more homogeneous group of patients with IPF not treated with background antifibrotics. Potential additive effects on the safety and/or efficacy of BI 1015550 in combination with background antifibrotic standard of care are being investigated in a Phase II study of BI 1015550, which has recently completed (NCT04419506).

Due to challenges in recruitment, duration of treatment was reduced from 12 weeks to 4 weeks. Patients who entered the study before approval of this amendment could be treated up to a maximum treatment duration of 12 weeks. These changes were implemented to help with recruitment and to keep the focus on the main objective of the trial, which was safety.

Additional patients were included based on the experience gained during the study (e.g. preliminary pharmacokinetic data). As the observed pharmacokinetic data of the first cohort showed higher variability in patients with IPF than in healthy volunteers, it was considered appropriate to extend the number of patients in the 18 mg BID group. Due to a protocol amendment, additional patients (four on active treatment and two on placebo) could be included in the 18 mg BID dose group.

Supplementary Table 1. Phase Ic study in patients with IPF: list of investigators for each study site

Principal Investigator	Site
I. Titlestad	Odense Universitetshospital Lungemedicinsk Afdeling J, Forskningsenheden Odense Denmark
M. Myllärniemi	HYKS Keuhkosairauksien tutkimusyksikkö Biomedicum Helsinki 2 Helsinki Finland
M. Kilpeläinen	TYKS, Keuhkosairauksien klinikka, T-sairaala Turku Finland
M. Kreuter	Universitätsklinikum Heidelberg Zentrum für interstitielle & seltene Lungenerkrankungen Thoraxklinik Heidelberg Germany
A. Prasse	Fraunhofer Institut für Toxikologie und Experimentelle Medizin (ITEM) Hannover Germany
L. Richeldi	Policlinico Gemelli Unità Complessa Pneumologia Unità Complessa Pneumologia

	Rome Italy
M. Wijsenbeek	Erasmus Medisch Centrum Rotterdam Netherlands
M. Veltkamp	St. Antonius Ziekenhuis, Locatie Nieuwegein R&D Lung Diseases Nieuwegein Netherlands
M. Molina-Molina	Hospital Universitari de Bellvitge Servicio de Neumologia L'Hospitalet de Llobregat Barcelona Spain
P. Molyneaux	Royal Brompton Hospital Dept of Respiratory Medicine Brompton & Harefield Hospital NHS Trust London United Kingdom
S. Fletcher	Southampton General Hospital Southampton Centre for Biomedical Research, C Level West Wing, University Hospital Southampton NHS Foundation Trust Southampton United Kingdom

IPF, idiopathic pulmonary fibrosis.

Supplementary Table 2. Phase I study in healthy males: baseline demographics

Demographic	SRD			MRD			Total
	Placebo	BI 1015550 36 mg	BI 1015550 48 mg	Placebo	BI 1015550 6 mg BID	BI 1015550 12 mg BID	
Number of subjects n (%)	6 (100.0)	6 (100.0)	6 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	42 (100.0)
Male n (%)	6 (100.0)	6 (100.0)	6 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	42 (100.0)
Age in years, mean (SD)	34.3 (7.9)	32.2 (6.6)	38.2 (7.9)	33.8 (6.6)	35.8 (8.7)	33.5 (5.3)	34.6 (7.0)
Height in cm, mean (SD)	174.2 (4.9)	180.7 (7.9)	175.8 (5.4)	174.8 (7.9)	176.9 (6.3)	177.4 (4.2)	176.6 (6.2)
Weight in kg, mean (SD)	76.5 (11.1)	79.3 (6.9)	79.3 (9.4)	70.7 (9.2)	79.2 (9.5)	83.5 (8.4)	78.0 (9.5)
BMI in kg/m^2, mean (SD)	25.2 (3.8)	24.3 (2.0)	25.6 (2.5)	23.1 (2.4)	25.4 (3.2)	26.5 (1.6)	25.0 (2.7)
Race, n (%)[#]							
White	6 (100.0)	5 (83.3)	6 (100.0)	6 (75.0)	8 (100.0)	8 (100.0)	39 (92.9)
Black or African American	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	2 (4.8)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.4)
Smoking history n (%)							
Never smoked	2 (33.3)	2 (33.3)	4 (66.7)	5 (62.5)	2 (25.0)	3 (37.5)	18 (42.9)
Former smoker	3 (50.0)	2 (33.3)	1 (16.7)	1 (12.5)	3 (37.5)	2 (25.0)	12 (28.6)
Currently smokes	1 (16.7)	2 (33.3)	1 (16.7)	2 (25.0)	3 (37.5)	3 (37.5)	12 (28.6)

Alcohol history n (%)							
Non-drinker	1 (16.7)	0 (0.0)	1 (16.7)	2 (25.0)	2 (25.0)	2 (25.0)	8 (19.0)
Drinks – no interference	5 (83.3)	6 (100.0)	5 (83.3)	6 (75.0)	6 (75.0)	6 (75.0)	34 (81.0)
Drinks – possible interference	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[#]None of the subjects were Hispanic/Latino. BID, twice daily; BMI, body mass index; MRD, multiple-rising-dose; SD, standard deviation; SRD, single-rising-dose.

Supplementary Table 3. Phase I study in healthy males: all AEs

System organ class, preferred term	SRD				MRD			
	Placebo n (%)	**BI 1015550** 36 mg n (%)	**BI 1015550** 48 mg n (%)	**BI 1015550** Total n (%)	**Placebo** n (%)	**BI 1015550** 6 mg BID n (%)	**BI 1015550** 12 mg BID n (%)	**BI 1015550** Total n (%)
Number of subjects	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	16 (100.0)
Total with AEs	1 (16.7)	4 (66.7)	4 (66.7)	8 (66.7)	3 (37.5)	2 (25.0)	5 (62.5)	7 (43.8)
Nervous system disorders	1 (16.7)	2 (33.3)	3 (50.0)	5 (41.7)	1 (12.5)	2 (25.0)	3 (37.5)	5 (31.3)
Headache	1 (16.7)	1 (16.7)	3 (50.0)	4 (33.3)	1 (12.5)	2 (25.0)	3 (37.5)	5 (31.3)
Dizziness	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (16.7)	2 (33.3)	1 (16.7)	3 (25.0)	1 (12.5)	2 (25.0)	1 (12.5)	3 (18.8)
Abdominal distension	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Upper abdominal pain	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	1 (12.5)	1 (12.5)	0 (0.0)	1 (6.3)
Nausea	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.3)
Oral hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)

Investigations	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	1 (12.5)	0 (0.0)	2 (25.0)	2 (12.5)
Blood creatine phosphokinase increased	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood triglycerides increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)
Occult blood positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	1 (6.3)
Infections and infestations	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.3)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.3
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament sprain	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Micturition urgency	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)
Ear pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)

AE, adverse event; BID, twice daily; MRD, multiple-rising-dose; SRD, single-rising-dose.

Supplementary Table 4. Phase I study in healthy males: salient laboratory parameters

Salient laboratory parameters	SRD			MRD		
	Placebo	**BI 1015550 36 mg**	**BI 1015550 48 mg**	**Placebo**	**BI 1015550 6 mg BID**	**BI 1015550 12 mg BID**
Number of subjects, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)
Haemoglobin in g/L, mean (SD)						
Baseline	145.3 (24.8)	139.8 (11.9)	134.6 (12.1)	135.4 (22.1)	129.1 (10.0)	135.2 (9.0)
Last value on treatment	135.4 (30.0)	129.4 (10.3)	134.4 (10.4)	132.8 (21.9)	125.0 (6.2)	129.7 (9.9)
Erythrocyte sedimentation rate in mm/h, mean (SD)						
Baseline	7.9 (3.7)	5.8 (2.0)	6.7 (4.1)	8.1 (6.4)	12.2 (8.9)	6.9 (3.7)
Last value on treatment	8.3 (3.8)	10.0 (7.7)	8.3 (8.2)	10.6 (10.8)	13.8 (9.8)	10.3 (14.0)
Fibrinogen in g/L, mean (SD)						
Baseline	2.4 (0.3)	2.6 (0.8)	1.9 (0.8)	2.0 (0.5)	2.2 (0.6)	1.8 (0.5)
Last value on treatment	2.4 (0.7)	2.4 (0.9)	1.9 (0.8)	2.0 (0.6)	2.4 (0.5)	2.1 (0.9)

Aspartate aminotransaminase in U/L, mean (SD)						
Baseline	21.7 (5.1)	19.0 (3.5)	20.9 (4.5)	22.2 (5.1)	21.9 (3.1)	23.4 (7.0)
Last value on treatment	21.3 (2.3)	23.6 (14.4)	21.6 (4.0)	20.3 (3.0)	19.6 (3.5)	22.6 (6.2)
Alanine aminotransaminase in U/L, mean (SD)						
Baseline	24.3 (17.0)	15.6 (3.6)	18.1 (5.3)	15.5 (4.7)	14.9 (7.1)	27.7 (20.0)
Last value on treatment	21.1 (9.6)	16.1 (2.5)	19.3 (5.3)	18.9 (8.2)	14.7 (7.1)	21.9 (11.9)
Creatinine kinase in U/L, mean (SD)						
Baseline	419.7 (156.4)	342.7 (184.6)	263.4 (126.9)	393.6 (373.7)	368.8 (260.9)	273.4 (80.1)
Last value on treatment	368.2 (124.4)	1889.3# (3865.5)	229.4 (121.2)	279.4 (189.0)	309.0 (148.1)	745.6^ (1137.6)
Total bilirubin in µmol/L, mean (SD)						
Baseline	8.8 (6.5)	11.8 (6.2)	8.6 (2.7)	14.1 (11.3)	11.6 (5.5)	7.0 (4.1)
Last value on treatment	7.8 (3.6)	8.1 (3.3)	7.5 (3.1)	11.0 (5.0)	7.9 (3.8)	8.1 (2.9)
High-sensitivity C-reactive protein in mg/L, mean (SD)						
Baseline	3.8 (3.2)	1.3 (0.5)	2.5 (3.3)	3.4 (4.5)	4.6 (4.3)	1.4 (0.8)
Last value on treatment	3.3 (3.0)	1.6 (1.0)	1.9 (1.6)	3.5 (4.0)	9.8 (11.3)	2.6 (1.5)
Triglycerides in mmol/L, mean (SD)						

Baseline	1.1 (0.9)	1.7 (1.1)	1.7 (0.8)	1.2 (0.9)	0.9 (0.5)	2.3 (1.4)
Last value on treatment	1.1 (0.8)	1.7 (1.1)	1.8 (0.4)	1.5 (0.9)	0.9 (0.4)	2.3 (3.2)
Urine pH, mean (SD)						
Baseline	5.0 (0.0)	5.5 (0.8)	5.3 (0.5)	5.1 (0.4)	5.1 (0.4)	5.0 (0.0)
Last value on treatment	5.0 (0.0)	5.4 (0.6)	5.3 (0.5)	5.5 (0.5)	5.4 (0.5)	5.5 (0.5)

[#]Increased blood creatine phosphokinase was reported as an adverse event for one participant in the 36mg SRD group. This was attributed to physical exertion and was not considered drug related by the investigators. ^After the treatment period, increased creatine kinase was reported for one participant in the 12mg BID MRD group. This was attributed to physical stress at work and was not reported as an adverse event.

BID, twice daily; MRD, multiple-rising-dose; SD, standard deviation; SRD, single-rising-dose.

Supplementary Table 5. Phase Ic study in patients with IPF: baseline demographics

Demographic	Placebo	BI 1015550 18 mg BID	Total
Number of patients (%)	5 (100.0)	10 (100.0)	15 (100.0)
Male, n (%)	4 (80.0)	9 (90.0)	13 (86.7)
Age in years, mean (SD)	70.2 (3.3)	69.5 (10.1)	69.7 (8.3)
Race, white n (%)	5 (100.0)	10 (100.0)	15 (100.0)
Weight in kg, mean (SD)	81.1 (17.7)	83.1 (7.0)	82.5 (11.1)
Smoking history n (%)			
Never smoked	4 (80.0)	5 (50.0)	9 (60.0)
Former smoker	1 (20.0)	5 (50.0)	6 (40.0)
Alcohol history n (%)			
Never	1 (20.0)	1 (10.0)	2 (13.3)
Former	0 (0.0)	1 (10.0)	1 (6.7)
Current	4 (80.0)	8 (80.0)	12 (80.0)
Time since first IPF diagnosis, median	886.0	90.5	412.0
FVC, mean (SD)			
mL	3322.2 (1024.6)	3699.9 (1179.1)	3574.0 (1108.0)
% predicted	91.1 (17.1)	92.0 (15.3)	91.7 (15.3)
FEV_1, mean (SD)			
mL	2639.6 (763.8)	2957.9 (747.2)	2851.8 (741.4)
% predicted	94.5 (12.7)	97.4 (10.7)	96.4 (11.1)
DL_{CO} Hb corrected	62.4 (18.8)	61.6 (30.2)	61.9 (26.2)

BID, twice daily; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; Hb, haemoglobin; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

Supplementary Table 6. Phase Ic in patients with IPF: all AEs

System organ class/preferred term	Placebo n (%)	BI 1015550 18 mg BID n (%)	Total on treatment n (%)
Number of subjects	5 (100.0)	10 (100.0)	15 (100.0)
Total with AEs	5 (100.0)	10 (100.0)	15 (100.0)
Nervous system disorders	1 (20.0)	2 (20.0)	3 (20.0)
Headache	1 (20.0)	1 (10.0)	2 (13.3)
Somnolence	0 (0.0)	1 (10.0)	1 (6.7)
Gastrointestinal disorders	2 (40.0)	8 (80.0)	10 (66.7)
Diarrhoea	2 (40.0)	4 (40.0)	6 (40.0)
Flatulence	1 (20.0)	3 (30.0)	4 (26.7)
Anal fistula	0 (0.0)	1 (10.0)	1 (6.7)
Anal incontinence	0 (0.0)	1 (10.0)	1 (6.7)
Constipation	0 (0.0)	1 (10.0)	1 (6.7)
Faeces soft	0 (0.0)	1 (10.0)	1 (6.7)
Frequent bowel movements	0 (0.0)	1 (10.0)	1 (6.7)
Gastrointestinal sounds abnormal	0 (0.0)	1 (10.0)	1 (6.7)
Nausea	0 (0.0)	1 (10.0)	1 (6.7)
Proctalgia	0 (0.0)	1 (10.0)	1 (6.7)
Investigations	1 (20.0)	3 (30.0)	4 (26.7)
Occult blood positive	1 (20.0)	3 (30.0)	4 (26.7)
General physical condition worsened	0 (0.0)	1 (10.0)	1 (6.7)
Infections and infestations	2 (40.0)	5 (50.0)	7 (46.7)
Nasopharyngitis	0 (0.0)	4 (40.0)	4 (26.7)
Pharyngitis	1 (20.0)	0 (0.0)	1 (6.7)
Respiratory tract infection	1 (20.0)	0 (0.0)	1 (6.7)
Bronchitis	0 (0.0)	1 (10.0)	1 (6.7)

Oral herpes	0 (0.0)	1 (10.0)	1 (6.7)
Injury, poisoning and procedural complications	0 (0.0)	1 (10.0)	1 (6.7)
Scar	0 (0.0)	1 (10.0)	1 (6.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	6 (60.0)	6 (40.0)
Muscle spasms	0 (0.0)	2 (20.0)	2 (13.3)
Muscle tightness	0 (0.0)	2 (20.0)	2 (13.3)
Pain in extremity	0 (0.0)	2 (20.0)	2 (13.3)
Spinal pain	0 (0.0)	1 (10.0)	1 (6.7)
Temporomandibular joint syndrome	0 (0.0)	1 (10.0)	1 (6.7)
Trigger finger	0 (0.0)	1 (10.0)	1 (6.7)
General disorders and administration site conditions	1 (20.0)	3 (30.0)	4 (26.7)
Fatigue	1 (20.0)	2 (20.0)	3 (20.0)
General physical health deterioration	0 (0.0)	1 (10.0)	1 (6.7)
Eye disorders	1 (20.0)	1 (10.0)	2 (13.3)
Vision blurred	1 (20.0)	0 (0.0)	1 (6.7)
Conjunctival hyperaemia	0 (0.0)	1 (10.0)	1 (6.7)
Psychiatric disorders	0 (0.0)	2 (20.0)	2 (13.3)
Insomnia	0 (0.0)	2 (20.0)	2 (13.3)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (10.0)	2 (13.3)
Dyspnoea exertional	1 (20.0)	0 (0.0)	1 (6.7)
Dyspnoea	0 (0.0)	1 (10.0)	1 (6.7)
Skin and subcutaneous tissue disorders	1 (20.0)	2 (20.0)	3 (20.0)

Skin odour abnormal	1 (20.0)	0 (0.0)	1 (6.7)
Pruritus	0 (0.0)	1 (10.0)	1 (6.7)
Rash	0 (0.0)	1 (10.0)	1 (6.7)
Cardiac disorders	0 (0.0)	1 (10.0)	1 (6.7)
Bradycardia	0 (0.0)	1 (10.0)	1 (6.7)

AE, adverse event; BID, twice daily; IPF, idiopathic pulmonary fibrosis.

Supplementary Table 7. Phase Ic in patients with IP: salient laboratory parameters

	Placebo	**BI 1015550 18 mg BID**
Number of subjects, n (%)	5 (100.0)	10 (100.0)
Haemoglobin in g/L, mean (SD)		
Baseline	153.7 (13.9)	140.6 (10.7)
Last value on treatment	143.1 (16.9)	132.4 (13.8)
Erythrocyte sedimentation rate in mm/h, mean (SD)		
Baseline	14.7[#] (12.1)	20.9 (12.9)
Last value on treatment	16.3 (9.8)	29.1 (21.5)
Fibrinogen in g/L, mean (SD)		
Baseline	3.6 (0.5)	4.0 (0.8)
Last value on treatment	3.6 (0.5)	4.2 (0.8)
Aspartate aminotransferase in U/L, mean (SD)		
Baseline	21.3 (13.0)	18.3 (7.2)
Last value on treatment	20.4 (11.8)	14.4 (6.3)
Alanine aminotransferase in U/L, mean (SD)		
Baseline	24.3 (14.7)	14.6 (5.2)
Last value on treatment	22.9 (16.6)	12.7 (3.0)
Creatinine in U/L, mean (SD)		
Baseline	79.9 (8.3)	86.8 (14.4)
Last value on treatment	81.5 (14.1)	86.4 (25.1)

Bilirubin in µmol/L, mean (SD)		
Baseline	7.5 (1.4)	9.5 (2.6)
Last value on treatment	7.7 (2.8)	8.0 (2.1)
High-sensitivity C-reactive protein in mg/L, mean (SD)		
Baseline	1.2 (0.8)	2.8 (2.5)
Last value on treatment	2.0 (1.3)	6.0 (9.9)
Triglycerides in mmol/L, mean (SD)		
Baseline	1.7 (1.1)	0.7 (0.3)
Last value on treatment	0.9 (0.24)	0.5 (0.1)
Urine pH, mean (SD)		
Baseline	5.7 (0.8)	5.5 (0.2)
Last value on treatment	5.7 (0.6)	5.6 (0.6)

[#]values available for n=4 patients in the placebo group. BID, twice daily; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.