Clinical Trial Protocol

	Document Number: c17703547-05
EudraCT No.:	2017-002736-16
BI Trial No.:	1305-0012
BI Investigational Product:	BI 1015550
Title:	Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy.
Lay title:	This study tests different doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF). The study tests how BI 1015550 is taken up by the body and how well it is tolerated.
Clinical Phase:	Ic
Clinical Trial Leader:	Phone:
Co-ordinating Investigator:	Phone:
Status:	Final Protocol (Revised protocol (based on Global Amendment 4))
Version and Date:	Version: 5.0 Date: 27 Mar 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Tabulated Trial Protocol**	
Boehringer Ingelheim			
Name of finished product:			
Not applicable			
Name of active ingredient:			
BI 1015550			
Protocol date:	**Trial number:**		**Revision date:**
02 Nov 2017	1305-0012		27 Mar 2019
Title of trial:	Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy.		
Co-ordinating Investigator:	Phone:		
Trial site(s):	Multi-Centre study		
Clinical phase:	Ic		
Objectives:	Multiple Rising Dose (MRD) The primary objective is to investigate safety and tolerability of BI 1015550 in patients with IPF. The secondary objectives are to investigate the effect of BI 1015550 on he pharmacokinetics (PK) of BI 1015550.		
Methodology:	Double-blind, randomised within dose groups, placebo-controlled, parallel-group design		
No. of patients: **total entered:**	N= 24		
each treatment:	DG 1A*: 9 (6 on active drug and 3 on placebo) plus additional 6 (4 on active drug and 2 on placebo) DG 1B*: 9 (6 on active drug and 3 on placebo) * Additional patients may be entered to allow for testing of additional doses within the planned dose range on the basis of experience gained during the trial conduct (e.g. preliminary PK data), i.e. the actual number of patients entered may exceed 18		
Diagnosis:	Idiopathic Pulmonary Fibrosis		
Main criteria for inclusion:	Patients with IPF ages ≥40 years, who have not been treated with nintedanib or pirfenidone within 30 days of visit 1 and not planning to be initiated on nintedanib or pirfenidone for the duration of the study.		
Test product:	BI 1015550 as tablet formulation (TF 1 containing 6mg of BI 1015550)		
dose:	Starting dose of 18mg b.i.d		

Name of company:		**Tabulated Trial Protocol**	
Boehringer Ingelheim			
Name of finished product:			
Not applicable			
Name of active ingredient:			
BI 1015550			
Protocol date:	**Trial number:**		**Revision date:**
02 Nov 2017	1305-0012		27 Mar 2019
mode of admin.:	Oral		
Reference Product	Matching placebo as tablet formulation		
dose:	Not applicable		
mode of admin.:	Oral		
Duration of treatment:	4 weeks		
Criteria for pharmacokinetics:	Secondary endpoint: **BI 1015550** Day 1: $AUC_{\tau,1}$ and C_{max} Day 14: $AUC_{\tau,ss}$ and $C_{max,ss}$		
Criteria for safety:	<u>Primary endpoint</u> To assess safety and tolerability of BI 1015550 by the number (%) of patients with drug-related adverse events (AEs) on-treatment. Further criteria of interest: Treatment emergent AEs (TEAEs) (including clinically relevant findings from the physical examination), safety laboratory tests (including testing for fecal occult blood and fecal calprotectin, urinalysis for hematuria), 12-lead electrocardiogram (ECG), vital signs (blood pressure (BP), pulse rate (PR), respiratory rate (RR), oral body temperature and body weight), and suicidality monitoring.		
Statistical methods:	Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Flow chart 1A: Overview

Trial Period	**Screening**	**Treatment**										**End of Trial**
Visit	**1**	**2**	**3**[1]		**4**	**5**	**6**	**7**	**8**[1]	**9/ EOT**[17]	☎	**End of Trial**
Day	-28 to -2	-1	1	2	4 ± 1	7 ± 1	10 ± 1	13	14	28 ± 4		+7 +3
Visit type	**O**	**O**	**I**		**O**	**O**	**O**	**O**	**V**	**O**	**C**[2]	**O**
Informed consent	X											
Demographics[3]	X											
Body Weight	X	X							X	X		
Medical History	X	X										
Physical Examination	X	X							X	X		X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X		X
Safety Laboratory test[5]	X	X[6]		X	X	X	X	X		X		X
Fecal Occult blood/ Fecal Calprotectin	X	X		X		X			X	X		X
Drug Screen/ Alcohol breath test		X										
ECG	X	X	X	X	X	X	X		X	X		X

Suicide Questionnaire[8]	X	X							X	X		X
HRCT[9]	X											
Review of in/exclusion criteria	X	X										
Randomisation			X									
BI 1015550 dispensed			X	X	X	X	X	X	X			
BI 1015550 administration in clinic			X[10]	X[10]	X[11]	X[11]	X[11]	X[11]	X[10]			
BI 1015550 returned					X	X	X	X		X		
Compliance Check					X	X	X	X		X		
Dispense diary			X		X	X	X	X				
Review diary					X	X	X	X		X		
PK Plasma: BI 1015550			X[12]	X[13]	X[13]		X[13]	X[13]	X[12]	X[13]		

Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

O= Outpatient visits; **I**= Inpatient visit with monitored overnight stay; **V**= Overnight stay either inpatient or nearby facility; **C** telephone call follow-up

Footnotes Flow chart 1A

1. Please refer to flow chart 1B and flow chart 1C for specifics pertaining to these visits.
2. Daily phone calls between study visits to assess and collect AE and confirm compliance until Day 14, with weekly phone calls between study visits thereafter until end of treatment (EOT).
3. Demographics (including determination of height, smoking status and alcohol history)
4. Vital signs include BP, PR, RR, body temperature.
5. Safety laboratory tests to be taken pre morning dose.
6. Safety laboratory tests to be taken and to be medically evaluated within 3 days prior to first administration of study drug at visit 3; this safety laboratory can be omitted, if the screening examination is performed on Days -3 or -2
7. DLCO is required at screening to confirm eligibility. For scheduling reasons, DLCO may be performed during or shortly following visit 1, providing results are available for review at visit 2.
8. Prospective suicidality monitoring, will be performed throughout this trial using the Columbia Suicidal Severity Rating scale (C-SSRS). Refer to section 5.2.5.3 and appendix 10.1 for additional details.
9. IPF diagnosis may be confirmed using a historical HRCT scan. If a historical scan taken within the past 12 months is not available, or an available scan fails to meet the required image acquisition specification, an HRCT may be performed after consent to determine eligibility. All HRCT scans will be sent to a central vendor for review and confirmation of IPF diagnosis, prior to randomization. HRCT should not be repeated for eligibility if previous scan was taken within the past 3 months.
10. All applicable doses to be administered in clinic
11. Morning dose to be administered in clinic
12. On day 1 and day 14, PK sample for BI 1015550 to be taken pre morning dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12h post dose; 12 h sample should be immediately prior to the evening dose.
13. PK sample for BI 1015550 to be taken pre morning dose in the morning on Days 2, 4, 10, and day 13. At day 28, PK sample to be taken ~12h post day 27 evening dose.

17. EOT visit is required for all patients, including patients who discontinue treatment early.

Flow chart 1B: Visit 3

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	BI 1015550 PK $_{blood}$	Fecal occult blood and fecal calprotectin testing	12-lead ECG	Vital signs	Questioning for AEs and concomitant therapy	Other trial procedures [6]
3	1	-2:00	6:00-8:00	Randomization		x[1]		x[1, 5]	x[1]	x[1]	x
		-0:30	07:30	Breakfast							
		0:00	**08:00**	First study drug administration						x	
		0:30	08:30			x					
		1:00	09:00			x[2]		x[5]	x	x	
		1:30	09:30			x					
		2:00	10:00	240 mL fluid intake [2]		x		x[5]	x	x	
		4:00	12:00	240 mL fluid intake, thereafter lunch[2]		x		x[5]	x	x	
		6:00	14:00			x[2]		x[5]	x	x	
		8:00	16:00	Snack (voluntary)[2]		x		x[5]	x	x	
		10:00	18:00	Dinner							
		12:00	20:00	Study drug administration		x[2, 3]		x[3,5]	x[3]	x	
	2	23:30	7:30	Breakfast[2]	x	x	x	x[5]	x	x	
		24:00	08:00	Study drug administration							
		28:00	12:00	240 mL fluid intake, thereafter lunch[2]				x	x	x	
		34:00	18:00	Dinner							
		36:00	20:00	Study drug administration							
		38:00	22:00	Discharge from trial site				x	x	x	

Flow chart 1C: Visit 8

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	BI 1015550 PK blood	Fecal occult blood and fecal calprotectin testing	12-lead ECG[5]	Vital signs	Questioning for AEs and concomitant therapy	Other trial procedures[6]
8	14	311:30	07:30	Breakfast[2]	x[3]	x[4]	X	x	X	x
		312:00	**08:00**	Study drug administration					X	
		312:30	08:30		x					
		313:00	09:00		x[2]		X	x	X	
		313:30	09:30		x					
		314:00	10:00	240 mL fluid intake[2]	x		X	x	X	
		316:00	12:00	240 mL fluid intake, thereafter lunch[2]	x		X	x	X	
		318:00	14:00		x		X	x	X	
		320:00	16:00	Snack (voluntary)[2]	x		X	x	X	
		322:00	18:00	Dinner						
		324:00	20:00	Study Drug administration	x[2,3]		x[3]	x[3]	X	

Footnotes (flow chart 1B and 1C)

1. The time is approximate; the respective procedure is to be performed and completed within 2 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
2. If several actions are indicated at the same time point, venipuncture should be the last of the measurements and the intake of meals will be the last action.
3. Samples will be taken just before administration of dose.
4. Fecal occult blood and fecal calprotectin testing for visit 8 may be taken within 3 days of day 14 (i.e day 12-14).
5. The ECG recording has to be performed as triple at these time points. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
6. Other trial procedures to be performed during the visit as outlined in flow chart 1A.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of Covariance
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
b.i.d.	twice daily
BLQ	Below limit of quantification
BP	Blood pressure
CA	Competent authority
CK	Creatine Kinase
C-SSRS	Columbia-suicide severity rating scale
CTR	Clinical trial report
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Local clinical monitor
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease

CRA	Clinical research associate
CRF	Case report form
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver impairment
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of treatment
FC	Fecal Calprotectin
GI	Gastro-intestinal
gMean	Geometric mean
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HRCT	High-resolution computed tomography
HR	Heart rate
ICH-GCP	ICH Harmonised Tripartite Guideline for Good Clinical Practice
IEC	Independent Ethics Committee
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site file
MedDRA	Medical Dictionary for Drug Regulatory Activities
MetID	A blank sample for metabolic analysis
MRD	Multiple-rising dose
NC	Not calculated
NIMP	Non-investigational medicinal product
nM	Nanomolar
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PDE4 B	Phosphodiesterase 4 B
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set/ parameter analysis set
PR	Pulse rate
PV	Pharmacovigilance
q.d.	once daily

QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
RR	Respiratory Rate
SAE	Serious adverse event
SOP	Standard operating procedure
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment emergent adverse events
t.i.d.	three times daily
TMF	Trial master file
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

1. INTRODUCTION

BI 1015550 is a selective inhibitor of the Phosphodiesterase 4 B (PDE4 B) with broad anti-inflammatory and anti-fibrotic activities. It is under development for the treatment of idiopathic pulmonary fibrosis (IPF).

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia [P11-07084]. IPF is the most common of the 7 idiopathic interstitial pneumonias. It is a rare and fatal disease, with a median survival time of 2 to 3 years following diagnosis [R12-5527], [P11-07084]. The natural history of IPF is variable and unpredictable [R11-2587]. Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, acute respiratory decline, and death.

Nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [P15-07539]. Despite the availability of these drugs, the medical need remains high in this devastating disease.

BI 1015550 is a selective inhibitor of the PDE4 B with broad anti-inflammatory and anti-fibrotic activities. Based on its mode of action, BI 1015550 is hypothesized to have complementary activity to current therapies in IPF, as well as improved tolerability compared to other marketed PDE-4 inhibitors due to lower affinity for PDE4 D.

For further information, please refer to the Investigator's Brochure [c02094779-03].

1.2 DRUG PROFILE

For details on nonclinical pharmacology, refer to section 5.1 in the IB [c02094779-03].

1.2.3 Toxicology

The toxicology data support administration of BI 1015550 to women of non-child bearing potential and to men for up to 13 weeks.

The toxicity profile for BI 1015550 has been assessed in safety pharmacology studies, genetic toxicology studies, and repeat dose toxicity studies in the rat and minipig of up to 13 weeks including:

- *Repeat dose toxicity studies in the rat*
  - 4 weeks (dose groups 0.2-6/12 mg/kg/day), and 13 weeks (dose groups 3-9 mg/kg/day) with 4 weeks recovery
- *Repeat dose toxicity studies in the minipig*
  - 2 weeks (3-30 mg/kg/day, 2 week recovery) and 13 weeks (3-20 mg/kg/day, 4 week recovery)

Overall, vasculopathy and mortality secondary to vasculopathy are the primary findings defining the no observed adverse effect level (NOAEL) in the rat and minipig and are consistent with findings from other known PDE4 inhibitors [R10-1559]. Vasculopathy in toxicology species is thought to be a consequence of vascular tone dysregulation and subsequent inflammatory response [R17-0158]. Areas affected by vasculopathy are dependent on the nonclinical species tested. The GI tract/mesentery has been shown to be affected in multiple species (rats, minipigs, monkey) after administration of PDE4 inhibitors, including marketed compounds apremilast and roflumilast [R17-0915], [R17-0916], [R17-0919]. Additional target organs/tissues of PDE4 inhibitors include heart, liver, lung, thymus, and pancreas, and PDE4 inhibitors effects have been noted in male and female reproductive tracts of nonclinical species such as the mouse, rat, hamster, dog and monkey. Vasculopathy is considered reversible, as demonstrated in a longitudinal study performed in mice with apremilast, which showed the recovery of PDE4 inhibitor-related vasculopathy following repeated administration over 90 days [R17-0919].

Moreover, despite the observed effects in nonclinical species, two PDE4 inhibitors are used clinically and vascular injury has not been documented in humans.

PDEi-related effects on the testes and uterus have been reported for previously marketed PDE inhibitors [R17-0915], [R17-0919].

Both marketed PDE4 inhibitors have demonstrated adverse effects in preclinical reproductive toxicity studies that include embryotoxicity or fetotoxicity and are labelled accordingly [R17-0915], [R17-0919]. Specific studies to evaluate the potential for BI 1015550 to affect male and female fertility and developmental toxicity have not yet been conducted. Therefore, adequate contraception as detailed in Section 3.3.3 is required.

For further information please refer to the IB [c02094779-03]

1.2.5 Clinical experience in humans

1.2.5.1 Clinical Safety

Four clinical trials have been completed with BI 1015550 in healthy male volunteers:

- a single rising dose First-in-Men trial (1305.1) [U13-1792-01]
- a multiple rising dose trial (1305.2) [c02191718-02]
- a single rising dose/multiple rising dose trial (1305.11)
- a food effect trial (1305.20) [c20307414-01]

1.2.5.1.1 Single-Rising Dose (SRD) Study (1305.1)

BI 1015550 (0.02 mg, 0.06 mg, 0.2 mg, 0.6 mg, 2 mg, 4 mg, 8 mg, 16 mg and 24 mg dose levels) has been tested in 70 healthy male subjects. Sixteen subjects received placebo and 54 received BI 1015550. There were no notable differences between the dose groups with respect to safety and tolerability.

A total of 41 treatment emergent adverse events (TEAEs) were reported by 27 (39%) subjects. Five of these subjects (31%) received placebo. Nine subjects (12.9%) reported TEAEs that were considered drug-related by the investigator. These include drug-related diarrhea (N=3), abdominal pain (N=3), headache (N=2), and nausea/vomiting/fatigue/oral herpes in 1 subject. There was no correlation of the administered drug-dose and the number of subjects reporting at least 1 TEAE. Four of the subjects (including one subjects on placebo) reported moderate TEAEs. All subjects were reported to have recovered from TEAEs by the end-of-study examination.

There were no suspected unexpected serious adverse reaction (SUSAR), nor any significant (based upon ICH E3), severe, serious or fatal AEs. No subject was discontinued due to AEs. In addition, no clinically relevant laboratory, vital signs and ECG changes were observed following administration of single doses of BI 1015550.

Further details can be found in IB [c02094779-03].

1.2.5.1.2 Multiple-Rising Dose (MRD) study (1305.2)

BI 1015550 (1 mg and 6 mg b.i.d. for two weeks) has been tested in 24 healthy male subjects. Six subjects received placebo and 18 received BI 1015550.

A total of 10 TEAEs were reported by 6 (25%) patients, 1 patient in the placebo group, 4 patients in the 1 mg group and 1 patient in the 6 mg group. The most frequent TEAEs, all of mild intensity, occurred within the CNS and GI organ classes. Reported TEAEs included headache, mild diarrhea, abdominal pain, aphtous stomatitis, mild constipation and abdominal pain. There were no GI TEAE reported in the placebo group.

Two patients were discontinued, one for personal reasons in the 1 mg b.i.d. group and one due to TEAEs in the 6 mg b.i.d. group. The latter discontinuation occurred on study Day 12 because of adverse events that were considered drug-related by the investigator. All TEAEs in this patient were of mild intensity, with the exception of C-reactive protein (CRP) increase which was of moderate intensity. Apart from the CRP increase of moderate intensity, described above, no clinically relevant laboratory findings or clinically relevant changes in vital signs or ECGs were observed following administration of repeated doses of BI 1015550.

There were no TEAEs of severe intensity, SUSARS, severe, serious or fatal AEs.

1.2.5.1.3 SRD and MRD study (1305-0011) (completed) [c22991937-01]

This partially randomized within dose groups, placebo-controlled trial investigated the safety, tolerability, and pharmacokinetics of single and multiple rising oral doses of BI 1015550 as tablet formulation and is an extension of the previous trials 1305.1 and 1305.2. The investigation of single (36 mg and 48 mg) and multiple (6 mg b.i.d. and 12 mg b.i.d) rising doses of BI 1015550 beyond the doses tested in the previous two trials is supported by new toxicological investigations of BI 1015550. In Part 1, BI 1015550 (36 mg and 48 mg single dose levels) was tested in 18 healthy male subjects in a partially randomised, placebo-controlled within dose groups design. Following completion of the SRD part, BI 1015550 (6 mg and 12 mg b.i.d. for two weeks) was tested in 24 healthy male subjects in a randomised, double-blind, placebo-controlled within dose groups study.

For further details, see 'Investigator's Brochure' [c02094779-03].

1.2.5.1.4 Food Effect (1305-0020) (completed)

This open-label, randomized two-sequence, two-period crossover trial investigated the relative bioavailability of BI 1015550 following oral administration of 24 mg BI 1015550 under fed and fasted conditions. Twelve (12) healthy male subjects were entered.

[c20307414-01].

1.2.5.1.5 Clinical experience with other PDE4 inhibitors

Selective PDE4 inhibitors have been approved for chronic obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbations (roflumilast), and for moderate to severe plaque psoriasis and active psoriatic arthritis (apremilast). Roflumilast has been tested in Phase III studies for asthma and apremilast in Phase III studies for active Behcet's disease. No PDE4 inhibitor has been tested in IPF, yet.

Cilomilast
Cilomilast was the first selective PDE4 inhibitor developed for the maintenance of lung function (forced expiratory volume in one second (FEV1)) in patients with COPD but failed to demonstrate efficacy to support approval of the drug. Cilomilast nonclinical findings

include mesenteric arteritis in rats. In the clinical program the frequency of GI AEs was high. Fecal occult blood testing was benign with unremarkable colonoscopy findings in the few patients with blood in the stool. Lack of approval was based on inadequate evidence of efficacy rather than any safety concern [P06-08316].

Roflumilast

This PDE4 inhibitor (Daxas® in EU, Daliresp® in US) got approved for treatment of COPD. More than 5,000 patients with COPD were included in the "COPD Safety Pool". The most frequently reported AEs associated with roflumilast treatment were GI events (diarrhea, weight loss, nausea, abdominal pain) and headache followed by insomnia, dizziness and decreased appetite. There was an increased incidence of neuropsychiatric adverse reactions such as insomnia, anxiety, nervousness and depression; in rare instances suicidal ideation behavior (including completed suicide). Atrial fibrillation as SAE was reported more often in patients treated with
roflumilast. Among the AEs leading to death, cardiac arrest was reported in a higher number of patients who received roflumilast [R10-1555]. Clinical manifestation of mesenteric vasculitis, an adverse effect that has been a concern with PDE4 inhibition in general, was not reported in these clinical studies.

Apremilast

One PDE4 inhibitor for treatment of active psoriatic arthritis (Otezla®) has been approved by the FDA for moderate to severe plaque psoriasis. Otezla® has been evaluated in 1493 patients with active psoriatic arthritis in three randomized placebo-controlled studies [R17-1427] Access date 29, March 2017.). The most common adverse reactions were diarrhea, headache and nausea, followed by vomiting, upper respiratory tract infection, nasopharyngitis and abdominal pain. The product information of Otezla® recommends the close monitoring of patient's body weight and its cautious use in patients with history of depression and/or suicidal thoughts or behavior [R14-1795].

1.2.5.2.2 Multiple-rising dose trial (1305.2 and 1305.11, part 2)

Pharmacokinetics of BI 1015550 was investigated in healthy male volunteers given multiple oral doses of 1 mg and 6 mg b.i.d. with solution formulation in a fasted condition (Study 1305.2) and 6 and 12 mg bid with tablet formulation in a fed condition (Study 1305.11).

1.2.5.2.3 Food effect trial (1305.20) [c20307414-01]

A two-way crossover, single dose, food effect study (24 mg, N=12) was performed.

1.2.5.2.4 Prediction of human therapeutic dose range

Observed target engagement data in the previous clinical trials [U13-1792-01] and [c02191718-02] supported by population pharmacokinetic-pharmacodynamic (PK-PD) modelling predicts a human therapeutic dose range of 12 mg - 24 mg BI 1015550 b.i.d. The

estimated exposure at these doses range from free maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ (free $C_{max,ss}$_ of 81.1 nM and free $AUC_{0-24,ss}$ of 1072 nM·h at the 12 mg bid dose to free $C_{max,ss}$ of 193 nM and free $AUC_{0-24,ss}$ of 1983 nM·h at 24 mg b.i.d., respectively). These exposures are below the target maximum exposure margin for humans of 277 nM (free $C_{max,ss}$) and 2284 nM·h (free $AUC_{0-24,ss}$) based on the 13-week rat study (section 4.1.3.1).

1.2.6 Drug product

BI 1015550 is a non-hygroscopic, white to off-white to light yellow powder. It is a poorly soluble compound with high permeability.

For further details, see 'Investigator's Brochure' [c02094779-03].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Based on the limitations of the current therapy of IPF there is a medical need to slow or halt the progression of this disease (see section 1.1). BI 1015550 is a selective PDE4 B inhibitor with a pleiotropic and broad mode of action (MoA) that has the potential to offer improved efficacy and/or tolerability as add-on to registered anti-fibrotics or as a mono therapy in IPF.

As the planned doses to be tested fall within the estimated therapeutic range and based on the safety profile of this class of compound, the safety, tolerability and PK of rising doses of BI 1015550 will be evaluated in IPF patients.

The current design will provide essential information for clinical development of BI 1015550 as a treatment for IPF with the aim of determining the optimal dose of BI 1015550 based on PK, safety and tolerability.

2.2 TRIAL OBJECTIVES

Description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in section 5.

The primary objective is to investigate safety and tolerability of BI 1015550 in patients with IPF. The secondary objectives are to

evaluate the pharmacokinetics (PK) of BI 1015550 in patients with IPF.

2.3 BENEFIT - RISK ASSESSMENT

Experiments have shown that BI 1015550 affects the fibrotic pathway and the effects may be complementary and synergistic to those of nintedanib. It is postulated that BI 1015550 may provide therapeutic benefit to patients with lung fibrosis, but this has not yet been shown clinically [c02094779-03]. Patient participation in the study is of major importance to investigate the safety, tolerability and PK profile of BI 1015550.

Based on study 1305.11 using indirect target engagement in healthy volunteers at single doses up to 48 mg q.d., therapeutic efficacy might be expected from 12 mg b.i.d but may not plateau at that dose. Given the morbidity associated with IPF, dose escalation within the therapeutic range in a patient population rather than healthy subjects is considered acceptable to also assess target engagement in the relevant population. Given the morbidity associated with IPF, dose escalation within the therapeutic range in a patient population rather than healthy subjects is considered acceptable. The expected exposure at the planned doses of 18 mg b.i.d and 24 mg b.i.d fall within range of the estimated therapeutic range and are below the pre-defined maximal acceptable human systemic exposure limit. As such, the benefit-risk of these doses in a patient population is considered positive. Accordingly, dose escalation within the current protocol starting with administration of 18 mg b.i.d will be assessed in IPF patients. Evaluation of the 12 mg b.i.d dose, which has been evaluated in healthy volunteers (1305.11), will only be performed in this study if the safety and tolerability of the 18 mg b.i.d dose is not supported.

Furthermore, given the potential overlap in tolerability profile between BI 1015550 and the currently approved standard of care for IPF, dose escalation will be performed on no background therapy in order to adequately evaluate the tolerability and safety profile of the compound. To mitigate potential risk associated with a placebo controlled study in this patient population, only patients not currently treated with anti-fibrotic or not planned to be treated within 4 weeks of Visit 3 will be targeted for participation. Initiation of treatment for management of acute deterioration will be allowed at any time during the study at the discretion of the treating physician.

The patients are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication (see section 2.3.1).

It is hypothesized that BI 1015550 will ultimately lead to improved efficacy and an acceptable tolerability profile, resulting in a positive benefit/risk profile.

2.3.1 Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

ECG electrodes may cause local and typically transient skin reactions.

The total volume of blood withdrawn during the entire study will not exceed 400 mL per patient over the duration of the trial. This is less than the volume of a normal blood donation (500 mL). No health-related risk to the patients is expected from this blood withdrawal.

2.3.2 Drug-related risks and safety measures

There are no listed adverse events or expected events defined for BI 1015550 based on the available data.

BI 1015550 is considered a low risk compound for the purpose of this trial based on the following observations:

- BI 1015550 has been used in humans before (although in lower doses) and was considered safe and well-tolerated
- BI 1015550 is not a first in class compound. Other PDE4-inhibitors have been previously evaluated by other companies and two are approved (see section 1.2.5.1.5)
- Both rat and minipig are considered relevant species for BI 1015550 with toxicology data showing the rat as the most sensitive species [c02094779-03].
- The nature of the target and the mechanism of action of BI 1015550 are well understood [c02094779-03].

Below is a summary of the known safety profile for the PDE4 class of compounds:

Vasculopathy: Vasculopathy is a typical side effect of PDE4 inhibitors in rats.

The predicted exposure for the doses to be tested in the current study falls below the maximum tolerable limit set based on the NOAEL.

As there are no validated biomarkers for vasculitis, routine monitoring of surrogate markers as performed in previous PDE-4 programs will be done as part of standard safety assessment including:

- Hematology panel (to detect changes by bleeding or inflammation)
- Inflammation markers (hsCRP, fibrinogen, erythrocyte sedimentation rate (ESR), fecal calprotectin)
- Immunochemical based fecal occult blood test as a sensitive method to detect occult blood in the stool
- Urinalysis (dipstick to detect hematuria followed by urine microscopy in case of positive results)

Of note, safety monitoring as described above was suggestive of an inflammatory process in the GI tract of one subject in trial 1305.2, where moderate elevation in CRP was observed. At the same time, the subject developed mild GI-AEs (section 1.2.5.1.2). The subject was therefore discontinued from study drug administration.
Safety monitoring continued showing normalization within days and the subject recovered.

Emesis and further GI adverse events:

Based on the two completed clinical trials [U13-1792-01] and [c02191718-02] BI 1015550 was generally well tolerated at the doses tested with only mild to moderate GI side effects.

Depression and Suicidality: Apremilast and roflumilast, two of the currently marketed PDE4 inhibitors, are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also reported cases of completed suicide. Accordingly, symptoms of depression and suicidality will be monitored using the Columbia-suicide severity ranking score (C-SSRS). If a patient exhibits serious suicidality in the clinical judgment of the investigator or according to the C-SSRS, assessment the patient will be discontinued (for details refer to section 3.3.4.1 and appendix 10.1).

Reproductive toxicity: PDEi-related effects on the testes have been shown nonclinically for the marketed compounds ampremilast and roflumilast (section 1.2.5.1.5).

Developmental and reproductive studies have not yet been conducted; therefore the effect of sub therapeutic concentrations of BI 1015550 or its metabolites with regards to embryofetal risk has not been explored. In order to address this risk, patients will be informed accordingly and be required to use adequate contraception as detailed in section 3.3.3.

2.3.3 Safety measures

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of alterations in selected liver laboratory parameters to ensure patients' safety. See also section 5.2.2.1, adverse events of special interest.

The following precautionary measures will be taken in this study in order to minimize the risk for patients:

- Careful dose selection as described in section 4.1.3. For each group, patients will be divided into two cohorts. The first cohort will consist of 3 patients (2 on active and 1 on placebo), the second of 6 patients (4 on active, 2 on placebo). Within each dose level, the two cohorts will be separated by at least 72 hours (between 1st patients of each cohort)
- A maximum acceptable human exposure has been defined based on toxicity findings (see section 4.1.3.1).
- Dose escalation will be guided by measurements of BI 1015550 (free C_{max} and free $AUC_{0-24,ss}$). Prior to each dose escalation, the estimated systemic exposure of the next higher dose group will be calculated using PK data from the preceding dose group to ensure that the estimated exposure does not exceed the pre-defined maximum acceptable human exposure limit.
- Decision for dose escalation will be made after blinded review of the data by the safety review committee (see section 3.1.1 and section 4.1.5.2), in a documented Safety Review meeting which will take place after all patients in the first dose group

(18mg b.i.d, group 1A) have completed 14 days of treatment. Dose escalation to 24 mg b.i.d. is only permitted if both safety/tolerabilty (from all 9 patients) and PK projections (from a minimum of 4 patients on active treatment) are acceptable and if none of the pre-specified stopping criteria are met (section 3.3.4). The minimum time interval between last patient completing dosing at day 14 in the first cohort of a given dose group and the first dosing in the next higher dose group is 7 days. For details see section 3.1 and section 3.3.4.

- Safety laboratory examinations including surrogate markers of inflammation/ vasculitis will be performed as described in section 2.3.2.
- Repeated single and triple 12-lead ECGs during inpatient PK visits will be performed.
- During inpatient visits, the patients will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Male Subjects have to use adequate contraception as detailed in section 3.3.3 and female subjects of childbearing potential are not eligible to participate.

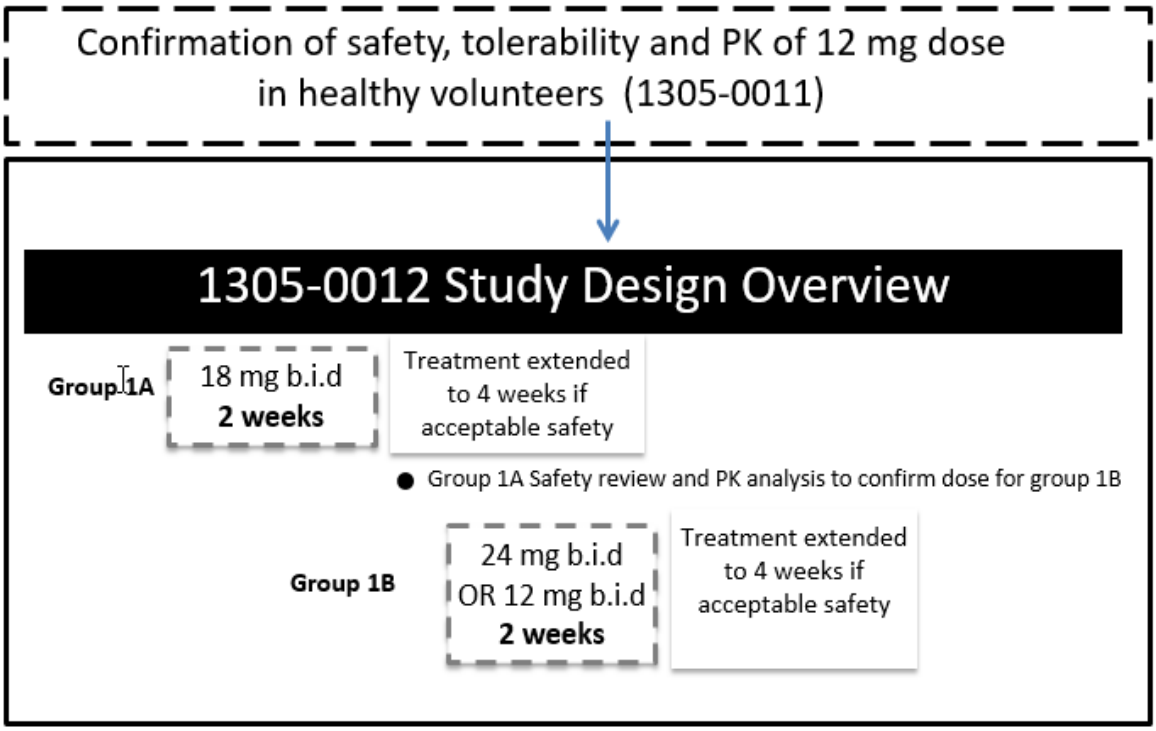
After completing the first 14 days of treatment, the appropriateness of the patients to remain and continue treatment will be done by PI or delegate based on continued assessment of benefit-risk profile for each patient.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will test multiple doses of BI 1015550. For a schematic overview, refer to figure 3.1:1.

Figure 3.1:1 1305-0012 Study Design Overview



This trial is double-blind, randomised, and placebo-controlled within parallel dose groups. A total of 18 male and female patients with IPF are planned to participate in 2 sequential groups consisting of 9 patients per group. However, additional patients may be entered to allow testing of additional doses within the planned dose range on the basis of results obtained from the 1305-0011 trial as well as experience gained during trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of patients entered may exceed 18, but will not exceed 30 patients entered. Such changes may be implemented via non-substantial clinical trial protocol (CTP) amendments**.

Within each dose group, 6 patients will receive the active drug and 3 will receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 2 cohorts which will be treated subsequently for safety reasons as outlined in section 2.3.3.

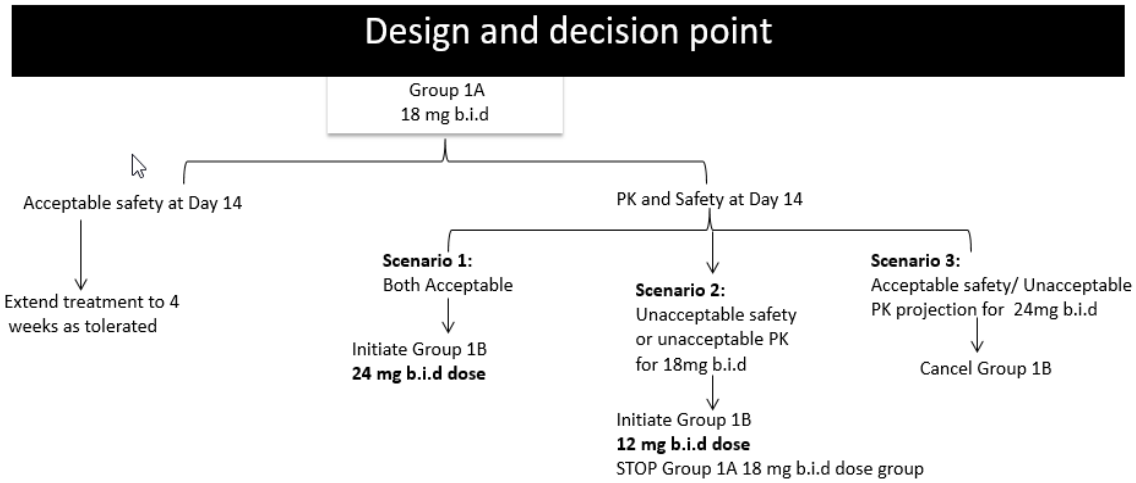
**An additional 6 patients (4 on active, 2 on placebo) will be entered in dose group 1A (18mg bid)

The first 36 hours of drug administration will be done in an inpatient setting to monitor for any acute reaction. Patients will then be treated outpatient with daily follow up by study

personnel by telephone, and interim clinic visits for monitoring during the first 14 days. Thereafter, patients will be contacted weekly by telephone, for monitoring with interim clinic visits until 4 weeks. This monitoring schedule was selected in order to optimize feasibility and based on known safety profile of this class of compound which are primarily limited to GI tolerability in clinical studies.

For a schematic overview of design and decision points, refer to figure 3.1:2.

Figure 3.1:2 Design and decision point



The dose groups to be evaluated are outlined in Table 3.1: 1. Patients will take medication twice daily, for the duration of the trial.

Table 3.1: 1 Dose groups

Dose Group	**1A**		**1B***	
Dose Level	0		-1	1
Daily Dose (mg)	36		24	48
Dose Regimen	18 mg b.i.d		12 mg b.i.d	24 mg b.i.d
Number of patients	9	6**	9	9
Patients receiving placebo	3	4	3	3
Patients receiving active drug	6	2	6	6

*The daily dose for group 1B may be reduced to 24 mg delivered as 12 mg b.i.d dosing regimen, if the safety, tolerability or PK profile of the 18 mg b.i.d dose is determined to be unacceptable.

** An additional 6 patients (4 on active, 2 on placebo) will be entered in dose group 1A (18mg bid). A documented safety review meeting will take place to review the full 18mg bid group data (9 + 6 patients), prior to dose escalation.

The dose groups (group 1A and group 1B) will be investigated consecutively, maintaining a time interval of at least 7 days between the last patient completing dosing at day 14 in the previous dose group and the first drug administration of the subsequent dose group.

A documented safety review meeting will take place prior to dose escalation. The decision to escalate the dose will be made by the sponsor after consultation with the safety review committee (see section 3.1.1) based on in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant) and PK data (from a minimum of 4 patients on active treatment). Safety Reviews may be conducted face-to-face or by video/telephone conference. The clinical trial leader is responsible for organization and minutes of the reviews. A summary will be filed in the ISF at each site and in trial master file (TMF).

- The dose will be escalated to 24 mg b.i.d if no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to section 3.3.4.2).

- In the event the 18 mg b.i.d dose is found to have acceptable safety but an unacceptable PK projection for 24 mg, the second dose group 1B will be cancelled.

- In the event the 18 mg b.i.d dose is determined to have unacceptable safety or tolerability, the dosing of group 1B will be reduced to 12 mg b.i.d and the patients continuing with extended treatment in the 18 mg b.i.d group 1A will be stopped. The 12 mg b.i.d dose will be used to confirm the safety and tolerability of the 12 mg b.i.d dose previously tested in healthy volunteers, in the target patient population, as well as to evaluate disease specific biomarkers over 12 weeks.

An unscheduled safety review meeting can be requested anytime for any reasonable cause by the coordinating investigator or the sponsor of the study, e.g. because of any unforeseen adverse events, etc.

The minimum data set for safety review consists of the following data:

- AEs in the current and preceding dose group (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead EGG in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK data for selected time as per section 7.3.4.
- Check of criteria for stopping patient treatment as per section 3.3.4.1

The sponsor is allowed to alter the scheduled dose levels (e.g. add an intermediate dose level) within the planned dose range on the basis of experience gained during the study. This may include PK data suggesting an exposure close to or just above predefined thresholds or initial safety signals with open causality (not dose limiting), providing the planned and approved

highest dose is not exceeded. In this case, the total number of patients in this trial might increase. The sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

An overview of all relevant activities is provided in the Flow Charts 1A, 1B, and 1C. For visit schedules and details of trial procedures at selected visits, refer to sections 6.1 and section 6.2, respectively.

The trial will terminate after all patients have completed the scheduled study visits or discontinue study treatment, whichever comes first.

3.1.1 Administrative structure of the trial

The trial will be conducted in approximately 20 sites in Europe.

A safety review committee will be responsible for blinded review of safety and PK data in order to guide decisions pertaining to dose used in subsequent treatment groups. The safety review committee will be composed of representatives from the sponsor, the coordinating investigator as well as an external expert not otherwise involved in the trial. The committee will retain the ability to unblind patients(s) as required (refer to section 4.1.5.2). This is not expected to cause bias with regards to data assessment or analyses. Following each data safety review meeting, a meeting will be held with trial investigators to review the blinded data and discuss the recommendation from the safety review committee.

A coordinating investigator is responsible to coordinate investigators at the different sites participating in this trial. The coordinating investigator (or appropriately qualified delegate) will participate in safety review meetings and will be involved in the discussions to escalate the dose.

BI has appointed a clinical trial leader, responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal standard operating procedure (SOP),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of local clinical monitors (CML) , clinical research associate (CRA), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany.

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Safety laboratory tests will be performed by a central laboratory appointed by BI.

The analyses of BI 1015550 in plasma will be performed at BI or a suitable contract research organization (CRO).

The digitally recorded 12-lead ECGs will be sent to a specialized contract research organization for evaluation.

Data management and statistical evaluation will be done by BI or by a suitable contract research organization (CRO) under the responsibility of BI and according to BI SOPs.

Tasks and functions assigned in order to organize, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

The trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

For multiple-rising dose trials, the design described in section 3.1 is viewed favourable under the provision not to expose the patients involved to undue risks since the main study objective is to investigate safety and tolerability of BI 1015550.

A double blind design is appropriate to reduce observer bias and evaluate safety and tolerability.

Given the morbidity associated with IPF, and potential differences regarding fibrotic status dose escalation within the therapeutic range in a patient population for 4 weeks rather than healthy subjects is considered acceptable. The expected exposure at the planned doses of 18 mg bid and 24 mg bid fall within range of the estimated therapeutic range and are below the pre-defined maximal acceptable human systemic exposure limit. As such, the benefit-risk of evaluating of these doses in a patient population is considered positive. Accordingly, within the current protocol dose escalation starting with administration of 18 mg b.i.d is planned in IPF patients to minimize exposure of patients to sub-therapeutic doses and build on the data already obtained in healthy volunteers at 12 mg for 2 weeks. Evaluation of the 12 mg b.i.d dose for 4 weeks is only planned in this trial if the safety and tolerability of the 18 mg b.i.d dose is not supported.

It is standard in Phase 1 trials to include a placebo group as control for the evaluation of safety and tolerability. Each dose group consists of 9 patients with 6 on active treatment, and 3 on placebo**. The placebo control group includes all patients of all dose groups treated with placebo. 6 patients per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

** An additional 6 patients (4 on active, 2 on placebo) will be entered in dose group 1A (18mg bid).

Non clinical toxicology data currently supports studies up to 12 weeks of durations. The treatment duration of 4 weeks is sufficient to capture safety and tolerability of a PDE4 inhibitor in support of longer term studies, evaluate PK and exploration of induction potential, .

Disease specific biomarkers and pulmonary function outcomes would require longer than 4 weeks. Recent disease specific biomarker data from the INMARK study (1199-0227) suggest that effects in disease specific biomarkers would require much larger sample size and with longer duration, even beyond 12 weeks to gain a robust evaluation of disease specific biomarkers. Four weeks data allows first generation of normative data on BI 1015550.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 male and female patients with a confirmed diagnosis of IPF will enter the study. The actual number of patients entered may exceed the total of 18 if additional intermediate doses will be tested (see section 3.1).

Only male patients and postmenopausal or surgically sterilised female patients will be included into the study because hitherto no data on reproductive toxicology are available.

A log of all patients enrolled into the study (i.e. having given informed consent) will be maintained in the investigator site file (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

Reasons for screen failures will be collected in the electronic Case Report Form (eCRF). The re-screening of screen failed patients may be permitted in certain cases after discussion with the trial team. A patient will not be permitted to re-screen more than one time and must meet inclusion/exclusion to be eligible for randomization. For patients re-screened, a new informed consent should be signed and the patient will be assigned a new unique patient number.

3.3.1 Main diagnosis for study entry

Patients diagnosed with IPF and who comply with eligibility requirements may qualify for participation in the trial.

3.3.2 Inclusion criteria

Patients will only be included into the trial, if they meet the following criteria:

1. Signed and dated written informed consent prior to admission to the study in accordance with ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and local legislation
2. Male or female patients aged ≥40 years at visit 1.
3. A clinical diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 guideline (P11-07084) within the previous 5 years as confirmed by the investigator based on chest high-resolution computed tomography (HRCT) scan taken within 12 months of visit 1 and confirmed by central review prior to visit 2.
4. Forced Vital Capacity (FVC) ≥50% of predicted normal at visit 1
5. Diffusion capacity of the lung for carbon monoxide (DLCO) (corrected for haemoglobin [Hb] [Visit 1]): > 30% of predicted normal at visit 1

3.3.3 Exclusion criteria

Patients will not be allowed to participate if any of the following general criteria apply:

1. Patients with a significant disease or condition other than IPF which in the opinion of the investigator, may put the patient at risk because of participation, interfere with study procedures, or cause concern regarding the patient's ability to participate in the study.
2. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance.
3. Surgery of the GI tract that could interfere with PK of the trial 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 exam or laboratory findings.
6. History of allergy or hypersensitivity to the trial medication or its excipients
7. Use of drugs within 30 days prior to administration of trial medication that are known to influence the results of the trial including time between start of the Q-wave and the end of the T-wave in an electrocardiogram (QT) / QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB) (QTc)
8. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
9. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
10. Participation in another trial where an investigational drug has been administered within 30 days or less than 5 half-lives (whichever is greater) of the respective drug prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug.
11. Inability to refrain from smoking on trial days
12. Alcohol abuse (consumption of more than 20 g per day)
13. Active drug abuse
14. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
15. Inability to comply with dietary regimen required for the trial

16. Patient is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
17. Male patients who do not agree to minimize the risk of female partners becoming pregnant from first dosing day until two months after the study completion. Acceptable methods of contraception comprises barrier contraception and a medically accepted contraceptive method for the female partner (intra-uterine device with spermicide, hormonal contraceptive used for at least two months prior), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), or surgically sterilized, including vasectomy.
18. Females who are not surgically sterilised or who are not postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of Follicle-stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L is confirmatory).
19. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC <0.7) at visit 1
20. Patients who have previously been treated with nintedanib or pirfenidone within 30 days of visit 1.
21. Positive fecal occult blood (no retest allowed),
22.
23. Positive testing for hematuria if confirmed by microscopic urine analysis (retest allowed)
24. Any lifetime history of suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
25. 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).

For study restrictions, refer to section 4.2.2.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be removed from the trial if:

1. The patient withdraws consent, without the need to justify the decision
2. The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The patient is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100

mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.

5. The patient shows an elevation of AST and/or ALT ≥3-fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the drug induced liver impairment (DILI) checklist provided in the case report form (CRF).
6. The subject exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:

   - any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
   - any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

In addition to these criteria, the physician may discontinue patients at any time based on his or her clinical judgment.

A patient can also be removed from the trial if eligibility criteria are being violated or if the patient fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a patient is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the clinical trial report (CTR). At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.

3.3.4.2 Stopping criteria for dose escalation

Dose escalation will not proceed if

1. More than 50% of the patients of one dose group on active drug show drug-related and clinically relevant adverse events of moderate or severe intensity during planned safety review.
2. At least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
3. The measured gMean free C_{max} or free AUC of one dose group increases above the following exposure thresholds or if the estimated gMean exposure of the next dose group is expected to exceed a free $C_{max,ss}$ of 277 nM or a free $AUC_{0-24,ss}$ of 2284 nM·h. Estimation will be done at specified time points based on preliminary PK results of preceding dose groups as specified in section 7.3.4.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events (SAE) invalidate the earlier positive benefit-risk-assessment.
2. The trial will be terminated if at least one drug-related SAE is reported that is considered to be unacceptable.
3. The expected enrolment goals overall or at a particular trial site are not met
4. Violation of ICH-GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
5. The sponsor decides to discontinue the further development of the investigational product.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the fourth reason).

3.3.5 Replacement of patients

In case some patients do not complete the trial, the clinical trial leader together with the trial pharmacokineticist and the trial statistician are to decide if and how many patients will be replaced. A replacement patient will be assigned a unique study patient number, and will be assigned to the same treatment as the patient he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Tablet Formulation (TF1)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mg
Posology:	Dose group 1A: 3-0-3
	Dose group 1B: 2-0-2 or 4-0-4
Route of administration:	p.o.
Duration of use:	28 days b.i.d. dosing

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo matching in size and weight to 6 mg tablet
Pharmaceutical formulation:	Tablet formulation
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	Dose group 1A: 3-0-3
	Dose group 1B: 2-0-2 or 4-0-4
Route of administration:	p.o.
Duration of use:	28 days b.i.d. dosing

4.1.2 Method of assigning patients to treatment groups

At the screening visit, patients will be informed about the planned visit dates. The patients willing to participate will be recruited to groups according to their temporal availability (group 1A vs group 1B).

At visit 3, eligible patients will be randomised to receive active drug or placebo. The randomisation will occur in a blinded fashion via Interactive Response Technology (IRT). The IRT system will assign the appropriate medication number based on the treatment allocated. The randomisation code will be controlled and documented. All instructions for use of the IRT system will be described in a user guide/ manual which will be available in the ISF.

The randomisation procedure is described in section 7.5.

4.1.3 Selection of doses in the trial

Trial 1305-0012 is an extension of the previous multiple rising dose trial (1305-0011) and proceeds with dose escalation. The doses selected for this trial cover a lower estimated therapeutic range and fall below the maximum acceptable systemic exposure.

The recommended maximum target dose is based on an exposure multiple against the pre-defined maximal acceptable human systemic exposure limit. This is calculated as a ratio of the maximal acceptable human exposure (see section 4.1.3.1) divided by predicted systemic exposure after single dosing based on the free fraction.

A starting dose of 18 mg b.i.d. of BI 1015550 has been selected, based on safety, tolerability and PK data, as well as indirect target engagement data from the completed study 1305.11 and multiple doses up to 12 mg bid in healthy volunteers. These data will be provided through an annually updated IB. If supported by the safety and PK data from the 18 mg b.i.d. dose group, a second dose group will be initiated at the maximum targeted dose of 24 mg b.i.d. Based on simulations incorporating pre-clinical data and data from previously conducted clinical trials, it is expected that following escalation from 18 mg b.i.d. to 24 mg b.i.d., exposure will increase in a dose proportional manner. As such, this is the highest dose where the expected systemic exposure is within the therapeutic range and below the pre-defined human maximum acceptable exposure limit (Table 4.1.3.1: 1).

A b.i.d dosing allows administration of the same daily dose with an increased safety margin with regards to Cmax. Further, a lower Cmax following b.i.d. dosing compared to q.d dosing is also assumed to lead to fewer tolerability issues.

4.1.3.1 Maximum acceptable systemic exposure, and exposure multiples of selected doses

The maximal acceptable human systemic exposure limit is derived from the primary toxicological findings of vasculopathy and mortality observed in the rat and minipig (see section 1.2.3).

Table 4.1.3.1:1 shows the predicted maximum human exposure (AUC) for the planned doses to be tested in the current protocol, all of which fall below the pre-defined human maximum acceptable exposure limit.

4.1.4 Drug assignment, dispensing and administration of doses for each patient

4.1.4.1 Drug Assignment

The treatments to be evaluated are outlined in Table 4.1.4.1: 1 below. The number of units for placebo corresponds to the number of units of the respective dose level.

Table 4.1.4.1: 1 BI 1015550 and placebo treatments, oral administration

Dose	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1A	BI 1015550	Tablet	6mg	3 tablets in the morning and evening	36 mg
1B	BI 1015550	Tablet	6mg	2 or 4 tablets in the morning and evening	24 or 48 mg
1A-1B	Placebo*	Tablet	--	Identical to active treatment	--

* Patients receiving placebo are equally distributed across dose groups

4.1.4.2 Dispensing of medication

Based on the treatment allocated at randomization, the IRT system will be used to dispense the appropriate medication kits at each visit.

Medication is packaged in bottles containing 20 tablets. To ensure patients receive adequate supply of study medication, kits (bottles) will be dispensed at clinic visits in quantities as outlined in table 4.1.4.2: 1.

Table 4.1.4.2: 1 Quantity of medication kits dispensed per visit

Visit	Day	Group 1A: 18mg b.i.d # bottles dispensed	Group 1B: 24mg b.i.d[1] # bottles dispensed	Group 1B: 12mg b.i.d[1] # bottles dispensed
3	1	1[2]	1[2]	1[2]
3	2	1	1	0
4	4	2	2	1
5	7	2	2	1
6	10	2	2	1
7	13	1[3]	1[3]	1[3]
8	14	5	7	3

1. Dose tested in group 1B will be based on safety and PK result from dose group 1A.

2. Patients will retain bottle dispensed at day 1, when discharged at day 2.

3. Patients will retain bottle dispensed at day 13, when discharged at day 14.

4.1.4.3 Administration of Doses

Study Medication- BI 1015550

The first administration of trial medication will be in the clinic, at visit 3 (day 1).

When in clinic, the trial medication will be administered to the patients, while in a standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication

During the first 2 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. Patients will be kept under close medical surveillance from the morning of Day 1 to the evening of Day 2 and all day on Day 14.

To ensure a dosing interval of 12 h, the administration of trial medication should take place at the same time every morning and evening.

While at home, the trial medication should be taken at approximately the same time each morning and evening, with one glass of water.

Patients will be given a medication diary to record daily intakes of medication taken at home since the last clinic visit.

For restrictions with regard to diet see section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial is designed double-blind with regard to the patients and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the patient's treatment (active or placebo). According to the trial design, the current dose level will be known to patients and investigators.

At the sponsor, access to the randomisation schedule is restricted to the Clinical Trial Support group, who generates the randomisation code and labels, and to the Pharmaceutics Department, where the packaging takes place. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded with respect to the treatment and also with regard to the recording date and time as well as the time points of the ECGs. The interval measurements for a given patient will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

If an interim safety analysis of ECG data is required, a part of the staff of the ECG laboratory may be unblinded. This part of the staff is strictly separated from those parts of the staff, which is involved with interval measurements and assessments of single ECGs (blinded).

Prior to unblinding of the trial database, the randomisation codes may be provided to bioanalytical staff/trial pharmacokineticist to perform preliminary PK analyses. The Trial Bioanalyst and trial pharmacokineticist will sign a confirmation that the codes will be treated confidentially and results will only be shared in a blinded fashion.

The trial will only be unblinded after locking of the database.

4.1.5.2 Procedures for (emergency) unblinding

The safety review committee (except the coordinating investigator) will retain the ability to unblind patients(s) via IRT as required to review the trial specific stopping criteria based on active treatment (see section 3.3.4.2). By this the members of the review committee (except the coordinating investigator) will be unblinded but the unblinding information will not be distributed to other personnel involved in the study. The reason for unblinding must be documented in the minutes along with the date and initials of the person who broke the code.

Emergency unblinding will be available to the investigator/ pharmacist/ investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page, along with the date and initials of the person who broke the code.

Due to the requirements to report SUSARs, it may be necessary for a representative from BI's Pharmacovigilance (PV) group to assess the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised PV representatives and not shared further.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by Boehringer Ingelheim..

The investigational product will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

The clinical trial supply will be packaged in bottles holding the trial medication (20 tablets per bottle), which are labelled with trial identification.

The sponsor and name, address and telephone number of the trial site are given in the patient information form. The EudraCT number is indicated on the title page of this protocol as well as on the patient information and informed consent forms. Examples of the labels will be available in the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the principle investigator
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol.

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial patients. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of return to the sponsor (and/or) appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. In case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

All concomitant or rescue treatment taken during the course of the trial must be recorded in the source document and on the CRF.

4.2.1.1 Management of acute IPF exacerbations

In case of acute IPF exacerbation or worsening in baseline condition, all treatment options considered adequate by the Investigator are allowed. Efforts should be made to keep the subject on study medication. Sponsor should be contacted prior to stopping study drug.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

Table 4.2.2.1:1 Restricted medication

Medication	Prior to Study	Screening Period	PK Evaluation Period (Day 1-14)	Extended treatment period (Day 15+)	Follow up period
Potent p-gp inhibitor or inducer	Not permitted[1]	Not permitted	Not permitted	Not permitted	Permitted
Potent and moderate CYP3A inhibitors or inducers	Not permitted[1]	Not permitted	Not permitted	Not permitted	Permitted
Nintedanib	Refer to exclusion 20	Not permitted	Not permitted	Not permitted[3]	Permitted
Pirfenidone	Refer to exclusion 20	Not permitted	Not permitted	Not permitted[3]	Permitted
Other anti-fibrotic therapies	Not permitted[1]	Not permitted	Not permitted	Not permitted	Permitted
PDE inhibitors[2]	Not permitted[1]	Not permitted	Not permitted	Not permitted	Permitted
Sensitive substrate of CYP3A	Permitted	Permitted	Use with caution	Use with caution	Permitted

Footnotes to restricted medication Table 4.2.2.1:1

1. Not permitted 30 days prior to randomization (visit 3)
2. Includes, for example: Sildenafil, tadalafil, vardenafil, roflumilast, apremilast.
3. Based on clinical status, standard of care treatment may be initiated prior to the end of 4 weeks, but should be avoided where possible as the safety has not been previously assessed and interference with trial related endpoints cannot be excluded. To allow for assessment of disease relevant markers at 4 weeks, use of SOC should be limited where possible.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the patients are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4 h after drug intake.

On PK profile days (i.e., Day 1 and Day 14) liquid intake is restricted from 1 hour before administration until lunch with exception of the fluid administered with the breakfast and the drug, and ~240 mL of water at 2 and 4 hours post-dose (mandatory for all patients). From lunch until 24 hours post-dose, water intake is restricted to 3000 mL. On PK profile days (i.e., Day 1 and Day 14), standardized meals will be served at 4, and 10 hours following drug administration. Snacks should be served at times as outlined in the flow chart.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7

days before the first administration of trial medication until after the last PK sample is collected.

Alcoholic beverages are not permitted starting 7 days before the first administration of trial medication until after the last PK sample is collected at day 14. After day 14 the use of alcohol should be limited but is not prohibited.

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h preceding the administration of trial medication and until the end of plasma PK sampling of the respective visit.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

During visits, compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

Patients are requested to bring all remaining trial medication, including empty bottles with them when attending visits.

Based on tablet counts (unused), treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance \%} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

If the number of doses taken is not between 80% and 120%, site staff will explain to the patient the importance of treatment compliance.

Patients who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see section 3.3.4.1).

5. VARIABLES AND THEIR ASSESSMENT

5.2 SAFETY

5.2.1 Endpoints of safety

The primary endpoint to assess safety and tolerability of BI 1015550 by the number (%) of patients with drug-related AEs on-treatment.

Further endpoints:

Further criteria of interest:

- TEAEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests (including testing for fecal occult blood and fecal calprotectin and urinanalysis for hematuria)
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature and body weight)
- Suicidality monitoring

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A SAE is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is immediately life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly/birth defect, or

- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in section 5.2.2.2, subsections 'AE collection' and '**AE reporting to sponsor and timelines**'.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

The latest list of 'Always Serious AEs' can be found in the electronic data capture (EDC) system. These events should always be reported as SAEs as described above.

Suicidal Risk assessed by the C-SSRS

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behavior will also be recorded.

After the screening/baseline visit the assessment 'since last visit' will be performed at each clinic visit ('since last visit' version).

The investigator is to review all positive and negative reports for plausibility and clinical relevance. Doubtful reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 and 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

For self-injurious behavior, no suicidal intent' standard AE/SAE reporting rules are to be applied.

For each negative report (Suicidal ideation type 1, 2 or 3) after the start of the trial, the investigator is to decide based on clinical judgement whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's PV Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST and/or ALT ≥3fold ULN combined with an elevation of total bilirubin ≥2fold ULN measured in the same blood sample, and/or
  - aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the DILI checklist provided in the eCRF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AES in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial:

-all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:

The investigator does not need to actively monitor the patient for AEs but should only reported related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

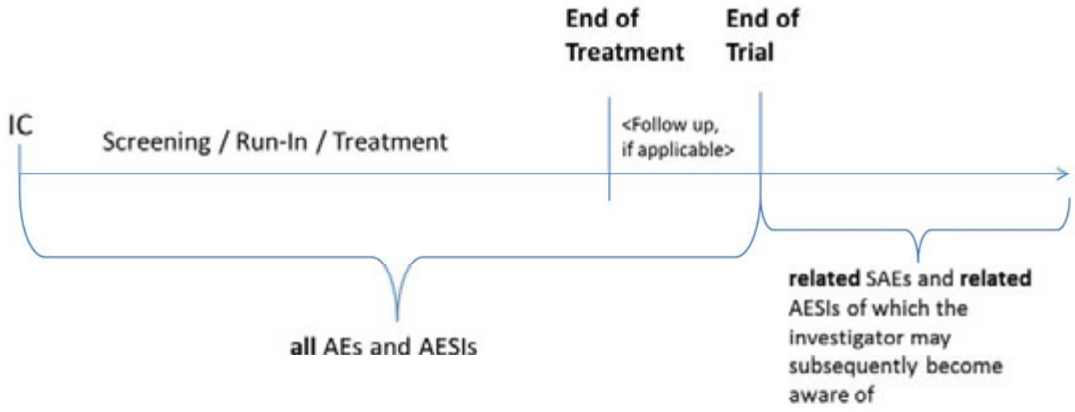


Figure 5.2.2.2:1 AE reporting requirements

The REP for BI 1015550, when measurable drug levels or PD effects are still likely to be present, is defined as 7 days after the last administration of BI 1015550. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3. Events which occurred after the REP but prior to the last per protocol contact will be considered as follow up events.

AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs and non-serious AEs which are relevant for the reported SAE or AESI on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timelines applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timelines apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages, and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" or no further information can be obtained.

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE Form is to be completed. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the patients have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designate for retests.

The parameters that will be determined are listed in Table 5.2.3: 1 and table 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively, i.e. if automatic count is not feasible or differential WBC is abnormal (i.e. pathological or atypical cells) and clinically relevant in the opinion of the investigator. In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein, microscopic examination of the urine sediment will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Fecal occult blood testing and fecal calprotectin testing will be performed by the central laboratory. Both tests will be performed at the time points indicated in the Flow Chart.
As patients may not be able to defecate at the trial site in the morning of the visit, after screening (visit 1) they may collect the specimen at home and bring the test specimen to the trial site after the screening visit, within the screening period. In addition, samples collected within 3 days prior to first dosing (ie day -3 to day -1) may be collected as visit 2 (day -1) sample and samples collected within 3 days prior to subsequent visits may be used, with the exception of the sample taken at day 2.

In case of GI AEs (e.g. diarrhea, constipation), additional testing for fecal occult blood and fecal calprotectin may be carried out at the discretion of the investigator. If a patient tests positive for occult blood in feces, further tests will be performed and the patient will be monitored closely.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count Erythrocyte sedimentation rate (ESR)
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase Amylase
Hormones[1]	Thyroid stimulating hormone (TSH) fT3, fT4
Substrates[1]	Plasma glucose Creatinine Total bilirubin Direct and indirect bilirubin Total protein High sensitivity C-Reactive Protein (hs CRP) Uric acid Total cholesterol Triglycerides Albumin
Electrolytes	Sodium Potassium Chloride Calcium Inorganic phosphate

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infectious serology will be tested at screening (visit 1) only. Drug screening is to be performed at visit 2 (day -1).

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at visit 2, and may be repeated at any time during the study at the discretion of an investigator or designate. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at a central lab as selected by Boehringer Ingelheim, with the exception of the drug screening, which will be performed at the trial site.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph which will be provided to the sites, at the time points given in the Flow Chart.

In order to achieve a stable heart rate (HR) at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for 10-sec duration after the patients have rested for at least 10 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all patients are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid compromising the ECG quality.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven or limb leads modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

ECGs will be recorded as single ECGs or as triple ECGs (three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database.

Data transfer

All ECGs will be transferred electronically to the central ECG lab for storage and evaluation.

In case of repeat ECGs due to quality reasons, all ECGs will be transferred to the central ECG lab who will select the correct one for analysis.
Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab

Central ECG lab evaluation will be performed for the first of three replicate ECGs per time point on Day 1, day 2 (planned time 23:30h only) and day 14. For baseline, where 3 triplicate ECGs are recorded, only the first single ECG per triplicate ECG (i.e. 3 single ECGs) will be evaluated.

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided.

For blinding arrangements see section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a

subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study. Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see section 3.3) of a patient and for the assessment of cardiac safety during the study, the QT and QTc values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralised evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the patient will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic BP as well as HR (considered to be equal to PR) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after patients have rested for at least 10 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Further, respiratory rate [RR] and oral body temperature will be monitored. Body temperature will be determined at the time points indicated in the Flow Chart using electronic thermometers. Respiratory rate will be counted by trained study personal by observing the chest movements over a period of one minute after the subject has rested in the supine position for 5 minutes. Recording of the values will be done at the time points indicated in the Flow Chart.

5.2.5.2 Medical examinations

At the screening visit, after informed consent is obtained, the medical examination will include documentation of patient information, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body temperature, respiratory rate), 12-lead ECG, laboratory tests including fecal occult blood and fecal calprotectin testing, suicidality assessment (C-SSRS) and, and a physical examination. At the end of treatment (EOT) examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination with determination of weight. Body weight should be measured with the patient wearing indoor clothing and no shoes. For each

individual patient, weight should be measured consistently in the morning or afternoon at all visits.

5.2.5.3 Suicidal risk assessed by the C-SSRS

For the marketed PDE4-inhibitors apremilast [R17-1427];[R17-1539];[R17-1540] and roflumilast [R17-1542] an increased risk of suicidality has been described. Therefore prospective suicidality monitoring, will be performed throughout this trial using the Columbia Suicidal Severity Rating scale (C-SSRS).

C-SSRS results will be reported in terms of AEs as described in Section 5.2.2.1.

For additional details refer to appendix 10.1.

5.3 OTHER

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor patients' safety and to determine PK and pharmacodynamics (PD) parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The PK parameters and measurements outlined in section 5.5

are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and PK sampling will be recorded in the CRFs.

The actual sampling times will be used for determination of PK parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per patient does not exceed 400 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following PK parameters will be determined, if feasible:

5.5.1.1 Secondary endpoints

BI 1015550

After the first dose (Day 1):

- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)

- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose (Day 14):

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of drug plasma concentrations of BI 1015550, BI 764333 , venous blood will be collected using a pre-labeled EDTA containing blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

A detailed description of sample collection and handling is provided in the Lab Manual in the ISF.

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of plasma concentrations

BI 1015550 and BI 764333 concentrations in plasma will be determined by a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay. The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization (CRO).

As described in section 4.1.5, the bioanalyst will be unblinded during sample analysis.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for visits are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK

The acceptable deviation on profile days (day 1, day 14) from the scheduled time is as follows: For the first 4h after trial drug administration: vital signs and ECG, -10min and for laboratory tests ± 30 min. After the first four hours after drug administration, vitals, ECG and laboratory tests ± 30 min.

Effort should be made to ensure that drug administration occurs at same time every day +/- 30 min. On day 1 and 14 extra care should be made to maintain consistency with accurate documentation of actual time of administration.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the patient and possible influence on physiological parameters.

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of PK parameter.

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Blinded Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

After having been informed about the trial, all patients will give their written informed consent in accordance with ICH-GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to sections 5.2.3 to section 5.2.5.

An historical HRCT can be used to determine eligibility, providing the scan was performed within the past 12 months prior to screening. If historical scan is not available, or an available scan fails to meet the required image acquisition specification, an HRCT may be performed after consent to determine eligibility. All HRCT scans will be sent to a central vendor for

review and confirmation of IPF diagnosis, prior to randomization. HRCT should not be repeated for eligibility if previous scan was taken within the past 3 months.

If required, the HRCT scan should be performed as close to screening date as possible, preferably once eligibility is confirmed based on other parameters, to avoid unnecessary scans for patients who are found ineligible based on other criteria. HRCT scans will be sent to a central reviewer for confirmation of IPF diagnosis. Confirmation of diagnosis must be available prior to visit 2.

Screening period may be extended for administrative reasons. Approval should be obtained from the sponsor who will also determine if any tests specified in the protocol must be repeated before the randomization visit.

6.2.2 Treatment period

During the treatment period, patients will take trial medication twice daily.

At least one visit (visit 3), will be conducted inpatient; during which time patients will be kept under close medical surveillance. The patients will be allowed to leave the trial site only after formal assessment and confirmation of their fitness by the investigator or designee.

On all other study days, the study will be performed in an ambulatory fashion.

In addition to clinic visits, daily phone calls are required between study visits to assess and collect AE information and confirm compliance until day 14, with weekly phone calls between study visits thereafter until end of treatment.

Inpatient Visit 3: Day 1 and 2

Visit 3 will span at minimum, a two day period, day 1 and 2.

All patients must be admitted (inpatient) at the morning of day 1, and kept under close medical surveillance for at least 2 hours following evening drug administration on day 2. The patients will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee.

Each patient will receive the first dose of BI 1015550 or placebo the morning of Day 1 and the second dose the evening of day 1. Patients will take BI 1015550 (or placebo) twice daily (b.i.d) from Day 1 onwards. Trial medication will be taken orally. At clinic visits, trial medication will be taken under direct supervision of the investigator or designee. Details on treatments and procedures of administration are described in section 4.1.4.

Patients will be given a diary to record intake of study medication taken at home since the last clinic visit, during the treatment period. At each visit, the diary will be collected and reviewed for compliance and a new diary will be dispensed.

Visit 8: Day 14

Study participants are required to be on site under medical surveillance for approximately 16 hours at day 14 to allow for required sampling and safety assessments as outlined in the Flow Chart. The patients are permitted to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. As an alternative, the patient may be admitted or relocated to a nearby facility overnight. No additional testing is required during this period.

General:

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and section 5.5.2.

The safety measurements performed during the treatment period are specified in section 5.2. of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

End of Treatment Visit:

The EOT visit is required for all patients. The EOT visit is conducted when patients have concluded treatment with BI 1015550.

For patients who complete the full treatment period, this will be after 4 weeks of treatment, at visit 9.

For patients who prematurely discontinue trial medication, for any reason prior to 4 weeks, the abbreviated EOT visit should be completed as indicated in the Flow Chart, as soon as possible after stopping treatment.

6.2.3 Follow-up period and end of trial

A follow up period of a minimum of 7 days (+3 days) will be required. All patients will complete an end of trial visit, including patients who discontinue treatment early. For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see sections 5.2.2 to 5.2.5.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

The end of the trial as a whole is defined by the ‘last regular visit completed by last patient’ or ‘end date of the last open AE’ or ‘date of the last follow-up test’ or ‘date of an AE has been decided as sufficiently followed-up’, whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

Trial objectives are given in Section 2.2.

The primary safety endpoint is defined in section 5.2.1. Inferential statistics are not planned (as explained in section 7.2).

PK endpoints as specified in section 5.5.1 will be analysed by descriptive statistics. Trough concentration values of BI 1015550 will be analysed regarding attainment of steady state as a pre-requisite for calculation of steady state parameters.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of different dose strengths of BI 1015550 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol deviations will be identified no later than in the Blinded Report Planning Meeting and provided in the TSAP.

7.3.1 Primary analyses

Analysis of safety and tolerability is described in section 7.3.3.

7.3.2 Secondary analyses

The secondary PK parameters (refer to section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (01-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Blinded Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications.

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- missing samples/concentration data at important phases of PK disposition curve.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above.

Attainment of steady state

Attainment of steady state will be explored by using the trough concentrations of BI 1015550 and BI 764333 between days 2 and 14 and the concentrations taken directly at the end of the dosing interval after the first drug administration and after the morning administration on Day 14 ($C_{\tau,1}$, $C_{\tau,27}$) for each dose level.

A nonlinear mixed effects model will be used to estimate the time to reach steady-state according to Hoffman et al. [R05-0788]. Accordingly, the observed trough plasma concentration C_{ij} for subject i after the j^{th} administration can be fitted by the following model:

$$C_{ij} = C_{ss} \cdot \exp(c_i) \cdot (1 - \exp(-(\gamma \cdot \exp(g_i) \cdot j))) \cdot \exp(e_{ij})$$

where

C_{ss} is the average steady-state trough concentration in the population,
c_i is the random deviation from C_{ss} with respect to subject i,
γ is the average first-order elimination rate in the population,

g_i is the random deviation from γ with respect to subject i,
e_{ij} is the i.i.d. normally distributed random within-subject error ($\sim N(0, \sigma_e^2)$).

The random effects c_i and g_i are multivariate normal distributed and independent of e_{ij}:

$$\begin{pmatrix} c_i \\ g_i \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_c^2 & \sigma_{gc} \\ \sigma_{gc} & \sigma_g^2 \end{pmatrix} \right).$$

The time-point of sufficient approximation to the steady-state asymptote concentration is then determined from the fitted function. In other words, the time t_f to reach $f = 85$, 90 and 95% of steady-state can be calculated as follows:

$$t_f = \log(1 - f) / (-\gamma),$$

where γ is again the average first-order elimination rate in the population.

Graphical displays

To support the analyses of attainment of steady state, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

7.3.3 Safety analyses

Safety will be assessed for the endpoints and parameters of interest listed in section 5.2.1. All treated patients (that is, all patients who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated patients, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by 'treatment at onset'.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.
Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the database lock.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake and end of REP will be assigned to the treatment period, and all AEs occurring between the end of REP and trial termination date will be assigned to ’follow-up’. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Additionally, differences from baseline will be evaluated.

For vital signs, the differences from baseline will be evaluated.

The ECG variables QT, PR, QRS, and RR are obtained from the centralised evaluation of 12-lead ECG recordings.
The ECG variables HR, QTcF, QTcB will be derived from QT and RR interval obtained from central ECG evaluation.

These variables will be the basis for the derivation of quantitative and categorical ECG endpoints. The endpoints and their analyses will be described in the TSAP.

7.3.4 Interim analyses

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 1015550), provided as individual values and gMean of the first cohort per dose level, will be performed before proceeding to the next dose.

(Note: Data from the first cohorts of the above mentioned dose levels will be sufficient as long as the data from at least 4 patients on active drug were available)

In contrast to the final PK calculations, the preliminary analysis may be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without patient identification. The preliminary results will be distributed to the Investigator and the trial team.

Depending on the results of available preliminary PK analyses, the tolerability and safety of the compound, and changes of dosing schedule (e.g. additional intermediate doses) additional PK preliminary analysis may be performed based on the request of the clinical trial leader, the investigator, or Trial Clinical Pharmacokineticist. No formal preliminary PK/PD report will be written.

No formal inferential statistical interim analysis is planned. However, after each dose group, summaries and listings may be created to support the safety reviews. The investigator (or deputy) is allowed to postpone further dose progression until a preliminary analysis of the data already obtained has been performed

7.3.5 Pharmacokinetic analyses

The PK parameters listed in section 5.5.1 for drug BI 1015550 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (01-MCS-36-472).

Patients who are not included in the PKS (refer to section 7.3.1.) will be reported with their individual plasma concentrations and individual PK parameters; however, they will not be included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessment.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (01-MCS-36-472).

Drug concentration data identified with no sample available (NOS), no valid result (NOR), not analysed (NOA), or below the lower limit of quantification (BLQ) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (01-MCS-36-472).

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Patients will be randomised within each dose/treatment group in a 2:1 ratio, which reflects the ratio of patients receiving active drug to placebo.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for patient replacement (refer to section 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 18 patients in this trial.

Additional patients may be entered to allow testing of additional intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of patients entered may exceed 18.

The planned sample size is not based on a power calculation. The size of 9 patients per dose group (6 on active treatment, and 3 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and PK.

An additional 6 patients (4 on active, 2 on placebo) will be entered in dose group 1A (18mg bid), therefore the total number of patients planned to be included in the trial is up to 24.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH-GCP and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH-GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a patient's participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his or her medical records may be examined by authorised monitors CML/CRA or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the clinical TMF.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA /on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is 'listed', i.e. is a known side effect of the drug. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 1015550 this is the current version of the Investigator's Brochure (c02094779-03). The current version of this reference document is to be provided in the ISF.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of SAEs, e.g. SUSARs to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be provided to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial

need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 26 (2), 319 - 338 (2005).

P06-08316 Giembycz MA. An update and appraisal of the cilomilast phase III clinical development programme for chronic obstructive pulmonary disease. Br J Clin Pharmacol 2006;62(2):138-152.

P11-07084 Raghu G, et al, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788-824.

P15-07539 Raghu G, et al, American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Latin American Thoracic Association (ALAT). An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015;192(2):e3-e19.

R05-0788 Hoffman D, Kringle R, Lockwood G, Turpault S, Yow E, Mathieu G. Nonlinear mixed effects modelling for estimation of steady state attainment. Pharm Stat 4, 15 - 24 (2005).

R06-2002 Macintyre N, Crapo RO, Viegi G, Johnson DC, Grinten CPM van der, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J . Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26:720-35.

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005)

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R10-1555 Daxas (roflumilast) in chronic obstructive pulmonary disease, NDA 22-522, FDA Advisory Committee briefing document presented to: Pulmonary-Allergy Drugs Advisory Committee (briefing book, April 7, 2010). website.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm207376.htm (access date: 23 November 2010); Jersey City: Forest Research Institute; 2010.

R10-1559 Giembycz MA. Life after PDE4: overcoming adverse events with dual-specificity phosphodiesterase inhibitors. Curr Opin Pharmacol 2005;5:238-244.

R11-2587 Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183:431-440.

R12-5527 Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev 2012; 21(126):355-361.

R14-1795 Otezla (apremilast) tablets, for oral use (Celgene) (U.S. prescribing information, revised: 3/2014).

R16-0366 E14 Implementation Working Group ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2015) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015)

R16-1924 Gisbert JP, Bermejo F, Perez-Calle JL, Taxonera C, Vera I, McNicholl AG, Algaba A, Lopez P, Lopez-Palacinos N, Calvo M, Gonzalez-Lama Y, Cameros JA, Velasco M, Mate J. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis. 15 (8), 1190-1198 (2009).

R17-0158 Korkmaz S, Maupoil V, Sobry C, et al. An increased regional blood flow precedes mesenteric inflammation in rats treated by a phosphodiesterase 4 inhibitor. Tox Sci 2009; 107(1):298-305.

R17-0915 Roflumilast 500 mcg tablets (Forest Research Institute): pharmacology/toxicology NDA/BLA review and evaluation, application number: 022522Orig1s000. website.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000PharmR.pdf (access date: 13 March 2017) ; Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research (2011)

R17-0916 Losco PE, Evans EE, Barat SA, et al. The toxicity of SCH 351591, a novel phosphodiesterase-4 inhibitor, in cynomolgus monkeys. Toxicol Pathol 2004; 32:295-308.

R17-0919 Otezla (apremilast) (Celgene): pharmacology/toxicology NDA/BLA review and evaluation, application number: 205437Orig1s000. website.accessdata.fda.gov/drugsatfda_docs/nda/2014/205437Orig1s000PharmR.pdf (access date: 13 March 2017) ; Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research (2014)

R17-1427 Otezla 10 mg, 20 mg, 30 mg film-coated tablets, Otezla 30 mg film-coated tablets (Celgene) (summary for product characteristics, manufacturer responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet (first published 16/02/2015). website.ec.europa.eu/health/documents/community-register/2015/20 150115130395/anx_130395_en.pdf (access date: 19 April 2017); 2015.

R17-1539 Otezla 30mg tablets (Celgene) (summary of product characteristics updated 05-Jan-2017). website.medicines.org.uk/emc/print-document?documentId=29792 (access date: 2 May 2017); 2017.

R17-1540 Otezla 10mg, 20mg, 30mg treatment initiation pack (Celgene) (summary of product characteristics updated 05-Jan-2017). website.medicines.org.uk/emc/print-document?documentId=29793 (access date: 2 May 2017); 2017.

R17-1542 Daxas 500 micrograms film-coated tablets (AstraZeneca) (summary of product characteristics updated 06-Dec-2016). website.medicines.org.uk/emc/print-document?documentId=23416 (access date: 2 May 2017); 2016.

R17-3686 Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017; 49: 1600016 [https://doi.org/10.1183/ 13993003.00016-2016].

9.2 UNPUBLISHED REFERENCES

01-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

001-MCG-312 Biomarker Assessments on Trial Level. Current version

U10-3777-01 Investigator Brochure BI 137882 BS. 11 Feb 2011

U13-1792-01 Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy male volunteers (a partially randomised, single-blinded, placebo-controlled Phase I study). 1305.1. 21 Jun 2013

c02094779-03 Investigator's Brochure BI 1015550 for Idiopathic Pulmonary Fibrosis. 22Feb2018

c02191718-02 Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 1015550 powder for oral solution in healthy male volunteers q.d. or b.i.d. for 14 days (a randomised, double-blind, placebo-controlled within dose groups Phase I trial). 1305.2. 15 Apr 2014

c20307414-01 Final Clinical Trial Report (1305-0020). Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects. 16 July 2018

c22991937-01 Final Clinical Trial Report (1305-0011). Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects. 15 November 2018

10. APPENDICES

10.1 COLUMBIA SUICIDAL SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behavior and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

At screening, C-SSRS (screening version) will be assessed with the aim to exclude patients with suicidal ideation type 2-5 within the preceding 12 months and patients with any lifetime history of suicidal behavior. Subsequently, the C-SSRS "since last visit" assessment will be performed at the time points given in the Flow Chart. For assessment, paper forms will be used and results will be transcribed into the CRF.

All positive reports during trial treatment are treatment-emergent adverse events (AEs).
The results of further medical, including psychiatric examinations should be documented as adverse events where appropriate.

The original Columbia Suicidal Severity Rating scales used in this trial are shown as follows:
Visit 1 –Screening version
Subsequent visits- Since last visit version.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to Be Dead — Yes ☐ No ☐
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

2. Non-Specific Active Suicidal Thoughts — Yes ☐ No ☐
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — Yes ☐ No ☐
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — Yes ☐ No ☐
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — Yes ☐ No ☐
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency — ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration — ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability — ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents — ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation — ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy; somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		21 Jun 2018
EudraCT number		2017-002736-16
BI Trial number		1305-0012
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic (Part 1) and safety and tolerability of BI 1015550 on top of Nintedanib and Pirfenidone (Part 2)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow chart 1A- MRD Overview Flow chart 1B- part 1: Visit 3 Flow chart 1C- part 1: Visit 8
Description of change		
Rationale for change		The risk of human disproportionate metabolite is turned out to be low based on the recently available metabolite identification data from Study 1305-0011. Therefore, samplings for

Number of global amendment		1.0
		metabolite identification were eliminated to reduce the burden of patients.
Section to be changed		Flow chart 2A: SOC Overview
Description of change		Phone visit: Compliance check removed from part 2 flow chart Concomitant therapy added to part 2 flow chart
Rationale for change		Phone visits updated for consistency between part1 and 2
Section to be changed		Flow chart 1A: MRD Overview Flow chart 2A: SOC Overview
Description of change		Footnote 13 regarding pre dose PK samples, updated for clarification that day 84 (part 1) and day 28 (part 2) pk samples are taken the morning of the visit, similar to other samples listed. These samples are not considered pre dose as there is no dosing at day 84 (part 1) or day 28 (part 2) and are therefore considered post (previous day) dose.
Rationale for change		Clarification
Section to be changed		Abbreviations
Description of change		Columbia-suicide severity ranking score corrected to Columbia-suicide severity rating scale
Rationale for change		Correction
Section to be changed		1.2.4
Description of change		Missing information about CYP3A induction and no clinically relevant PK-DDI potential of BI 1015550 with nintedanib and pirfenidone was added.
Rationale for change		Updated as applicable to DDI potential with SOC.
Section to be changed		1.2.5.1.3 1.2.5.2.2
Description of change		Preliminary results pertaining to clinical safety and clinical pharmacokinetics for trial 1305-0011 added to introduction section.
Rationale for change		Preliminary results have become available since finalization of protocol.
Section to be changed		1.2.5.1.4 1.2.5.2.3 (new section added)

Number of global amendment		1.0
Description of change		Preliminary results pertaining to clinical safety and clinical pharmacokinetics for trial 1305-0020 added to introduction section.
Rationale for change		Preliminary results have become available since finalization of protocol
Section to be changed		1.2.5.2.3 updated to section 1.2.5.2.4
Description of change		Statement "Exposure estimate will be updated to include PK data from ongoing trials (1305.11, 1305.20) as they become available" has been removed and the respective expected exposures in Section 1.2.5.2.4 were updated.
Rationale for change		PK information has been updated and therefore statement is no longer applicable.
Section to be changed		3.1.1
Description of change		Additional description added regarding meeting with investigators
Rationale for change		This will ensure key findings of safety review committee are outlined with investigators and investigators have intimate knowledge of the data.
Section to be changed		3.3
Description of change		Description of re-screening added.
Rationale for change		Re-screening may be permitted in specific circumstances. Clarification in protocol added to ensure sites are aware of requirements.
Section to be changed		3.3.3
Description of change		Exclusion 3, cholecystectomy removed.
Rationale for change		Cholecystectomy was eliminated from the exclusion criteria because food effect trial show negligible effect of food on AUC and the risk that cholecystectomy could interfere with PK of BI 1015550 is low considering the contribution of major drug transporters in BI 1015550 disposition is minimal based on in vitro data.
Section to be changed		3.3.3
Description of change		Exclusion 17 updated with respect to abstinence requirements.
Rationale for change		Clarification that only true abstinence is Permitted. Periodic abstinence (e.g calendar, ovulation), declaration of abstinence for the duration of exposure to IMP, and withdrawal are

Number of global amendment		1.0
		not acceptable methods of contraception
Section to be changed		3.3.3 and table 4.2.2.1:1
Description of change		Exclusion 20 updated- prior use of SOC is acceptable, but restricted if taken within 30 days prior to screening (V1).
Rationale for change		More in line with clinical practice. Patients are often tried on antifibrotic therapy for longer than 3 months before discontinuation due to the severity of the disease. Time window of 30 days is considered adequate to minimize any potential carried over effects of these treatments on the PK and safety of BI 1015550.
Section to be changed		4.1.3.1
Description of change		Table 4.1.3.1 was updated based on the most recent data.
Rationale for change		Expected exposure in the present trial in Table 4.1.3.1 was updated based on the most recent data (1305-0011 and 1305-0020).
Section to be changed		4.2.2.1
Description of change		Clarification to medication restrictions part 2 Table 4.2.2.1:2, footnote 7 added, additional text in note
Rationale for change		Clarifications of potential drug-drug interactions as applicable to pirfenidone SOC.
Section to be changed		5.2.3
Description of change		Clarification that stool sample collection 3 days prior to first dose is collected as v2 (day (-1) sample. No sample is required at randomization (day 1).
Rationale for change		Correction
Section to be changed		5.2.3 Table 5.2.3:1
Description of change		Glutamate dehydrogenase (GLDH) removed as a required parameter to be measured.
Rationale for change		Based on current liver safety profile collected, additional collection of this parameter was removed as it is not considered necessary for monitoring of potential liver injury.
Section to be changed		5.5.1.2, 5.5.2.1, 5.5.3.1 and 7.3.2

Number of global amendment		1.0
Description of change		Update to include name of metabolite.
Rationale for change		The name of metabolite to be measured was added based on the recent data.
Section to be changed		5.2.4.1
Description of change		Clarification on timing and evaluation of triple ECGs.
Rationale for change		Clarification
Section to be changed		9.2 References
Description of change		Updated reference c02094779-02 to c02094779-03. Added missing references R05-0788 and R09-4830.
Rationale for change		Reference (Investigator brochure) has been updated since final protocol.
Section to be changed		-2.2 -2.3.2 -2.3.3 -4.1.3 -5.2.5.1 -5.5.3.1 -6.2.2 -Appendix 10.1
Description of change		-BI1015555**0** typo corrected -typo- know corrected to know**n** - ‘one’ corrected to ‘on’ and duplicate word ‘patient’ removed -typo in half-life corrected (16-29 hours) was incorrectly listed as (2016 -29) -reference to ear removed as oral temperature is required -removed duplicate wording ‘or relocate to a nearby facility overnight’ -deleted typo ‘o’
Rationale for change		Correction of typos

Number of global amendment		2.0
Date of CTP revision		06 Dec 2018
EudraCT number		2017-002736-16
BI Trial number		1305-0012
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic (Part 1) and safety and tolerability of BI 1015550 on top of Nintedanib and Pirfenidone (Part 2)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis
Description of change		Main criteria for inclusion. Part 1 SOC requirements updated for consistency with changes to exclusion 20 made in global amendment 1.
Rationale for change		Correction
Section to be changed		Flow chart 1A and 2A
Description of change		Weight measurement updated for consistency between part1 and part 2. Baseline weight measurement added.
Rationale for change		Correction.
Section to be changed		Flow chart 1A
Description of change		

Number of global amendment		2.0
		evening dose.
Rationale for change		Clarification of meaning of "post dose" sample at part 1 EOT visit. As there is no dose taken on day 84 the last dose is taken the evening of day 83.
Section to be changed		Flow chart 2A
Description of change		Footnote 16 updated to clarify, at day 28 sample to be taken ~12h post day 27 evening dose.
Rationale for change		Clarification of meaning of "post dose" sample at part 2 EOT visit. As there is no dose taken on day 28, the last dose is taken the evening of day 27.
Section to be changed		3.3 Exclusion Criteria
Description of change		Exclusion 22 "positive testing for fecal calprotectin' has been removed.
Rationale for change		Calprotectin is a stable protein released by white blood cells during inflammation. Fecal Calprotectin (FC) constitutes an unspecific biomarker of gastrointestinal inflammation. A considerable variability among measurements in the same fecal sample or different samples from stools of consecutive days of the same patient is possible [R16-1924]. FC is established in general practice to only help clinicians differentiate between Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD) in the presence of suspicious symptoms, or in the ongoing monitoring of established IBD. It is not established for any other purpose. Experience in the first IPF cohort of this study shows unexpectedly high baseline values (average above 50 mcg/g) together with a very high intra-patient variability also without drug treatment (with changes of up to 10 fold), independent of any GI symptoms or changes in other laboratory parameters. FC is increased with increase age, concomitant diseases such as GERD, colonic polyps, diabetes, and concomitant medications such as NSAIDs and PPIs. The high frequency of such

Number of global amendment		2.0
		concomitant diseases and medications in IPF and in the elderly population highly contribute to FC fluctuations. As FC has not been systematically evaluated in IPF, an influence of the underlying disease cannot be excluded. Overall, given the high variability in the measure in this population within and between patients, also independent of study medication and multiple underlying reasons for increase, the utility of FC cut off values for inclusion in the current study is not appropriate. Consequently, FC will no longer be considered an exclusion criterion in this trial. FC will continue to be measured at the specified time points in the trial, to allow an exploratory analysis. Investigator judgment on the overall clinical picture will continue to apply during the study.
Section to be changed		5.2.5.3
Description of change		Information added to standardize weight measurements
Rationale for change		To ensure consistency and minimize variability in weight due to time of day or clothing.
Section to be changed		9.2 References
Description of change		Gisbert 2009 reference added [R16-1924]
Rationale for change		New reference.

Number of global amendment		3.0
Date of CTP revision		12 Feb 2019
EudraCT number		2017-002736-16
BI Trial number		1305-0012
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Cover page, Synopsis
Description of change		Title, lay title
Rationale for change		Updated to reflect removal of part 2 (on top of standard of care)
Section to be changed		Cover page, Section 3.1.1, 3.3.5,
Description of change		Trial clinical monitor updated to Clinical trial leader
Rationale for change		For consistency with updated Boehringer Ingelheim trial team titles.
Section to be changed		Synopsis, Flow chart (2a, b, c), Section 2, Section 3 (including figure 3.1:1 and 3.1:2), Section 4, Section 5, Section 6, Section 7
Description of change		All references to part 2 – BI 1015550 on top of SOC have been removed. Terminology stating Part 1 has removed as no longer required.
Rationale for change		Part 2 ‘BI 1015550 on top of standard of care’ is no longer planned to be conducted within this phase 1C trial. A short treatment duration of 4

Number of global amendment		3.0
		weeks is not adequate to support efficacy or biomarker endpoints given recent data from the INMARK trial (1199.227), and therefore removal of part 2 helps to focus the study from a logistic and practical point of view on safety and tolerability and pharmacodynamics of BI 1015550 in a treatment naïve population.
Section to be changed		Synopsis, Section 3.3, section 7.6
Description of change		Number of patients has been updated from 36 to 18
Rationale for change		Result of removal of part 2, only 18 treatment naïve patients will be recruited.
Section to be changed		Section 1.2.4, 2.3.2, 3.1.1, 4.1.4.3, 4.2.1, section 5, section 6.2.2
Description of change		References to nintedanib and pirfenidone or standard of care (SOC) (within the context of the removal of study part 2) have been removed.
Rationale for change		See rationale for removal of part 2, above.
Section to be changed		Synopsis: Duration of treatment
Description of change		Changed from 12 weeks to 4 weeks for treatment naïve patients.
Rationale for change		Consistency with change in treatment period. See rationale for change section 3.2 Discussion of trial design, including choice of control group
Section to be changed		Synopsis: Criteria for safety
Description of change		Primary endpoint changed from 12 weeks to on treatment AEs, for treatment naïve patients.
Rationale for change		To allow primary endpoint analysis for all patients whether at 4 weeks for new patients or 12 weeks for completed (treatment naïve) patients.
Section to be changed		Synopsis: Criteria for safety
Description of change		
Rationale for change		
Section to be changed		Flow chart 1A: overview
Description of change		Visits 10, 11, 12 removed Visit 9 updated to include EOT (end of treatment)

Number of global amendment		3.0
		procedures "Visit 13/End of Trial" renamed to "End of Trial"
Rationale for change		With change in treatment duration, visits after day 28 visit 9 are no longer required.
Section to be changed		Flow chart 1A: Footnote 13 and 15
Description of change		Requirements updated in consideration of new treatment duration.
Rationale for change		Requirement for sampling for PK updated to remove samples past day 28.
Section to be changed		1.2.5.1 Clinical Safety
Description of change		Information on completed and ongoing trials has been updated. New references have been added.
Rationale for change		Trial results have become available since initial protocol and have been updated accordingly. Information on additional trials in program (1305-0015 and 1305-0017) have been added.
Section to be changed		1.2.5.1.3 SRD and MRD Study
Description of change		Addition of weight data from study 1305.11
Rationale for change		For completion with final study report of 1305.11
Section to be changed		Tables 1.2.5.2.1:1 and 1.2.5.2.2:1
Description of change		Updated results
Rationale for change		Consistent with final study report for 1305.11
Section to be changed		1.2.5.2.1 Single rising dose trial
Description of change		Statement 'data from 1305-0011 are preliminary' has been removed Data updated based on final report.
Rationale for change		Data are no longer preliminary as trial is complete. Updated values based on final report.
Section to be changed		1.2.5.2.2 Multiple rising dose trial
Description of change		Final report pending removed and reference added.
Rationale for change		Final report is now available
Section to be changed		1.2.5.2.3 Food effect trial
Description of change		Reference added.
Rationale for change		Based on final report.
Section to be changed		2.3 Benefit risk assessment

Number of global amendment		3.0
Description of change		Rewording regarding target engagement in completed study 1305.11
Rationale for change		Consistency with final report
Section to be changed		2.3 Benefit risk assessment
Description of change		References to 1305-0011 are updated from preliminary and statement regarding TE biomarkers added.
Rationale for change		Information now based on final report.
Section to be changed		2.3 Benefit risk assessment
Description of change		Update of treatment period from 12 to 4 weeks.
Rationale for change		Consistency with change in treatment period. See rationale for change section3.2 Discussion of trial design, including choice of control group
Section to be changed		3.1 Overall trial design and plan & Figure 3.1:1 1305-0012 study design overview Figure 3.1:2 Design and decision point
Description of change		Updated references to treatment period from 12 to 4 weeks.
Rationale for change		Consistency with change in treatment period. See rationale for change section 3.2 Discussion of trial design, including choice of control group
Section to be changed		3.1.1 Administrative structure
Description of change		Updated number of trial sites to approximately 20
Rationale for change		Trial site participation has been expanded to include additional sites as needed to support recruitment.
Section to be changed		3.2 Discussion of trial design, including choice of control group
Description of change		Rationale included supporting reduction of treatment duration from twelve to four weeks.
Rationale for change		Non clinical toxicology data currently supports studies up to 12 weeks of durations. A treatment duration of 4 weeks however, is sufficient to capture safety and tolerability of a PDE4 inhibitor in support of longer term studies, evaluate PK and explore induction potential, in a patient population. Disease specific biomarkers and pulmonary function outcomes would require longer than 4

Number of global amendment		3.0
		weeks. Recent disease specific biomarker data from the INMARK study (1199-0227) suggest that effects on disease specific exploratory biomarkers would require much larger sample size and with longer duration, to gain a robust evaluation of disease specific biomarkers. Four weeks data allows first generation of normative data on BI 1015550.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion 6 removed
Rationale for change		No longer relevant with removal of study part 2 (SOC)
Section to be changed		4.1.1 Identity of BI investigational product and comparator product
Description of change		Duration of use updated from 84 days to 28 days for both BI 1015550 and Placebo matching.
Rationale for change		Consistency with change in treatment period. See rationale for change section 3.2 Discussion of trial design, including choice of control group
Section to be changed		4.1.3 Selection of doses in the trial
Description of change		Information regarding 1305-0011 trial was updated to final. Rewording of starting dose justification.
Rationale for change		Information now based on final report.
Section to be changed		4.1.4.2 Dispensing of medication
Description of change		Table 4.1.4.2:1 Quantity of medication kits dispensed per visit
Rationale for change		Updated based on revised treatment duration and visit schedule.
Section to be changed		4.1.4.3 Administration of dose
Description of change		Added “taken at home since last clinic visit”
Rationale for change		For clarification on when the diary should be filled in
Section to be changed		5.1.1 Endpoints of Efficacy
Description of change		12 week time point removed from all endpoints as per revised treatment duration. Rewording to “over time” rather than 4 and 12 weeks
Rationale for change		To allow PE analysis for all patients whether at 4

Number of global amendment		3.0
		weeks for new patients or 12 weeks for completed patients
Section to be changed		5.2.1 Endpoints of safety
Description of change		Primary endpoint (for treatment naïve patients) changed to "AEs on treatment" rather than 4 weeks or 12 weeks. To allow PE analysis for all patients whether at 4 weeks for new patients or 12 weeks for completed patients.
Rationale for change		Consistency with change in treatment period. See rationale for change section 3.2 Discussion of trial design, including choice of control group
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		6.2.1 Screening and run in period(s)
Description of change		Addition of "Screening period may be extended for administrative reasons. Approval should be obtained from the sponsor who will also determine if any tests specified in the protocol must be repeated before the randomization visit."
Rationale for change		To allow flexibility between screening and pre-randomisation visit especially when escalating to the next dose level, hence potential time gap for safety review of previous cohort
Section to be changed		6.2.2 Treatment period
Description of change		Addition of "will be given a diary to record intake of study medication taken at home since the last visit"
Rationale for change		To clarify the timing of the recording of the study medication intake since the last visit.
Section to be changed		6.2.2 Treatment period
Description of change		End of treatment visit: End of treatment visit timing changed from visit 12 (day 84)to visit 9 (day 28) for treatment naïve

Number of global amendment		3.0
		patients. Explanation of requirements for EOT visit for prematurely discontinued patients if patients discontinue, changed from 'prior to 12 weeks' to 'prior to 4 weeks'.
Rationale for change		Consistency with change in treatment period. See rationale for change section3.2 Discussion of trial design, including choice of control group
Section to be changed		9.0 References
Description of change		New references added
Rationale for change		New reference.

Number of global amendment		4.0
Date of CTP revision		27 MAR 2019
EudraCT number		2017-002736-16
BI Trial number		1305-0012
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Synopsis Section 3.1 Table 3.1:1 Section 3.2 Section 7.6
Description of change		Information regarding the addition of 6 patients (4 active, 2 placebo) to the 18mg bid dose group, has been added.
Rationale for change		Further to the safety review, for the purpose of escalation, of the completed 2 weeks treatment of the 9 patients in the 18 mg bid cohort, whilst safety and tolerability were considered acceptable, the prediction for the 24 mg bid cohort regarding the AUC gMean (2290 nM*h) exceeded the threshold (2284 nM*h) as set in the protocol on the basis of the 13 weeks rat toxicology data. The observed PK data of the 18 mg bid cohort showed a higher variability, including outliers, in IPF patients as compared to the HV data. It is therefore deemed appropriate to

Number of global amendment		4.0
		extend the current 18 mg bid cohort (4 on verum and 2 on placebo) to further characterize, understand and refine PK variability at 2 weeks in the target IPF population. Increasing the number of patients may confirm the magnitude of the PK variability. After 6 additional patients, the safety review committee will review all 18mg bid patient data, in order to determine if escalation can proceed to the 24 mg bid cohort. This will only occur if the safety and tolerability are maintained as acceptable and if PK projections for the next dose are within defined limits.
Section to be changed		Section 7.3.4
Description of change		Third paragraph, change in wording “In contrast to final PK calculations, the preliminary analysis will be based on planned sampling times rather than actual times” was changed to “In contrast to final PK calculations, the preliminary analysis may be based on planned sampling times rather than actual times”
Rationale for change		This modification is made to allow a decision to proceed with analysis using planned times or directly with actual times. As there may be a relevant discrepancy in actual sampling times and planned sampling times, actual times can be preferable in the PK analysis.

APPROVAL / SIGNATURE PAGE

Document Number: c17703547 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		27 Mar 2019 15:55 CET
Author-Trial Statistician		27 Mar 2019 15:58 CET
Author-Trial Clinical Pharmacokineticist		27 Mar 2019 16:02 CET
Approval-Team Member Medicine		27 Mar 2019 16:31 CET
Approval-Therapeutic Area		28 Mar 2019 10:16 CET
Verification-Paper Signature Completion		28 Mar 2019 14:11 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed