Clinical Trial Protocol

	Document Number: **c39429830-02**
BI Trial No.	1305-0024
BI Investigational Medicinal Product	BI 1015550
Title	Pharmacokinetics, safety and tolerability of doses of BI 1015550 in healthy Chinese male and female subjects (open-label, parallel group design)
Lay Title	A study in healthy Chinese people to test how different doses of BI 1015550 are taken up in the body
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted]
[redacted] **Investigator**	[redacted]
Current Version, Date	Version 2.0, 16 Mar 2023
Original Protocol Date	29 Jun 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	29 Jun 2022
Revision date	16 Mar 2023
BI trial number	1305-0024
Title of trial	Pharmacokinetics, safety and tolerability of doses of BI 1015550 in healthy Chinese male and female subjects (open-label, parallel group design)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This trial is conducted to investigate the PK and safety of BI 1015550 in Chinese healthy subjects.
Trial objectives	To investigate the pharmacokinetics, safety and tolerability following single dose of BI 1015550
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 1015550 Secondary endpoint regarding Safety: Occurrence of any treatment-emergent adverse event. This is expressed as the percentage of subjects treated with investigational drug who experience such an event.
Trial design	Open-label without placebo, single-dose, parallel-group design
Number of subjects **total entered** **on each treatment**	 Up to 32 subjects including up to 8 subjects for replacement of early discontinuation 12 per dose group
Diagnosis	Not applicable
Main inclusion criteria	Healthy Chinese subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 28.0 kg/m^2 (inclusive)

Test product **dose** **mode of administration**	BI 1015550 Single doses of 9 mg and 18 mg Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator product **dose** **mode of admin.**	Not applicable Not applicable Not applicable
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood	12-lead ECG[9]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-28 to -1			Screening (SCR)[1]	x[A,1]		x	x	
2	-1	-12:00	20:00	Admission to trial site[2]	x[5,2]				x[2]
	1	-1:00	07:00	Allocation to treatment[8] (visit 2 only)	x[7, B]	x[10]	x[10]	x[10]	x[10]
		0:00	08:00	Drug administration					
		0:30	08:30			x			
		0:45	08:45			x			
		1:00	09:00			x			
		1:15	09:15			x			
		1:30	09:30			x			
		1:45	09:45			x			
		2:00	10:00	240 mL fluid intake		x		x	
		2:30	10:30			x			
		3:00	11:00			x			
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x
		6:00	14:00			x			
		8:00	16:00			x			
		11:00	19:00	Dinner					
		12:00	20:00			x			x
	2	24:00	08:00	Breakfast[3] (voluntary), discharge from trial site	x[B]	x	x	x	x
	3	48:00	08:00	Ambulatory visit		x			x
	4	72:00	08:00	Ambulatory visit		x			x
	5	96:00	08:00	Ambulatory visit		x			x
	6	120:00	08:00	Ambulatory visit	x[B]	x			x
	7	144:00	08:00	Ambulatory visit		x			x
3	8 to 14			End of study (EoS) examination[4]	x[C]		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 12 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory (including pregnancy test in women), recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this safety laboratory assessment can be omitted if the screening examination is performed on Days -3, -2 or -1. Letters A, B, and C define different sets of safety laboratory examinations (see Section 5.2.3)
8. The time is an approximate. The procedure is to be completed no later than 10 hours prior to drug administration.

9. The ECG recording must be performed in triplicate ECGs at this time. The 3 triplicate ECGs are recorded within approximately 1 h. The recordings should be separated by about 5 min intervals.
10. Trial measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ATS	American Thoracic Society
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CL	Total clearance of the analyte in plasma after intravascular administration
[redacted]	[redacted]
Cmax	Maximum measured concentration of the analyte in plasma
[redacted]	[redacted]
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FU	Follow-up
GCP	Good Clinical Practice
GI	Gastro-intestinal

gMean	Geometric mean
[redacted]	[redacted]
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
JRS	Japanese Respiratory Society
[redacted]	[redacted]
LATS	Latin America Thoracic Society
[redacted]	[redacted]
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
PE	Polyethylene
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
t1/2	Terminal half-life of the analyte in plasma
tmax	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
tz	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

1. INTRODUCTION

BI 1015550, a selective inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP), is being developed by Boehringer Ingelheim (BI) for the treatment of idiopathic pulmonary fibrosis (IPF). This clinical trial is to investigate safety, tolerability and pharmacokinetics of single oral doses of BI 1015550

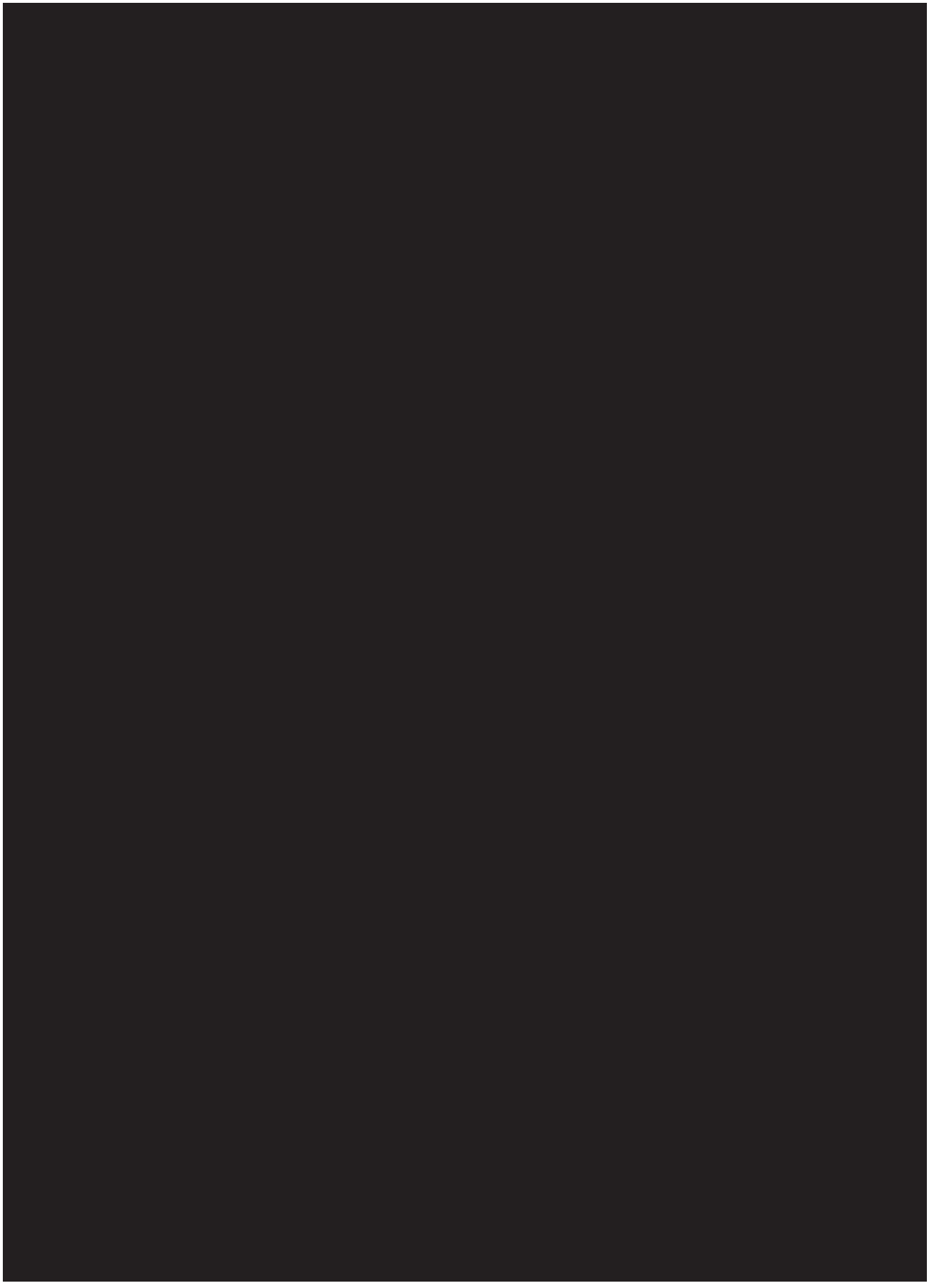
1.1 MEDICAL BACKGROUND

IPF and other progressive fibrosing ILDs (PF-ILDs) share common pathophysiologic characteristics; alveolar epithelial cell injury and subsequent dysregulated repair, characterized by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function [P11-07084]. In IPF, fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis [P12-03241]. Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in pulmonary fibrosis.

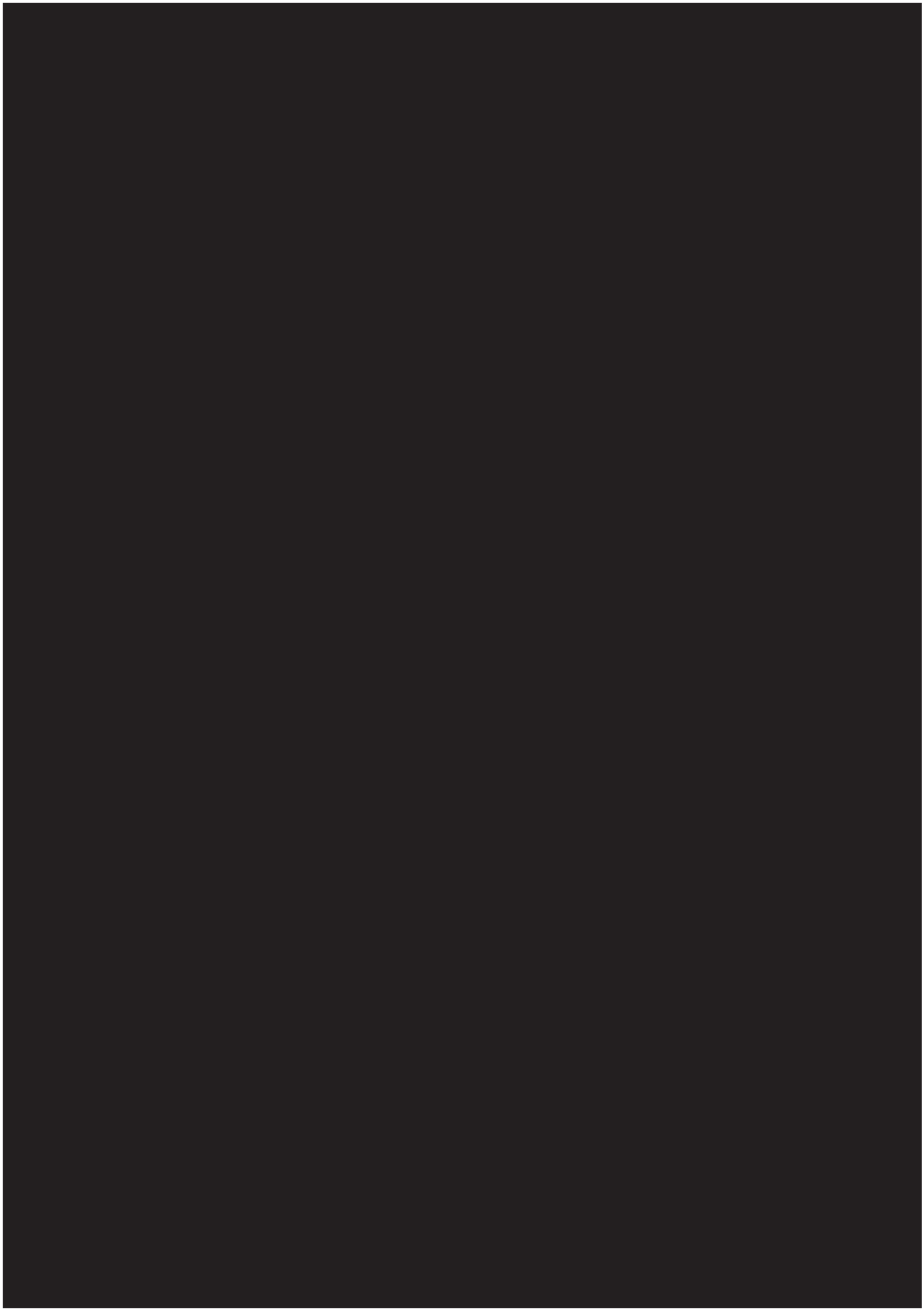
As of date, nintedanib and pirfenidone are the only drugs registered for the treatment of IPF in several countries including China and recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [R18-2794]. Nintedanib is also approved in the U.S., the European Union, China and many other countries for the treatment of other fibrosing ILDs with progressive phenotype.

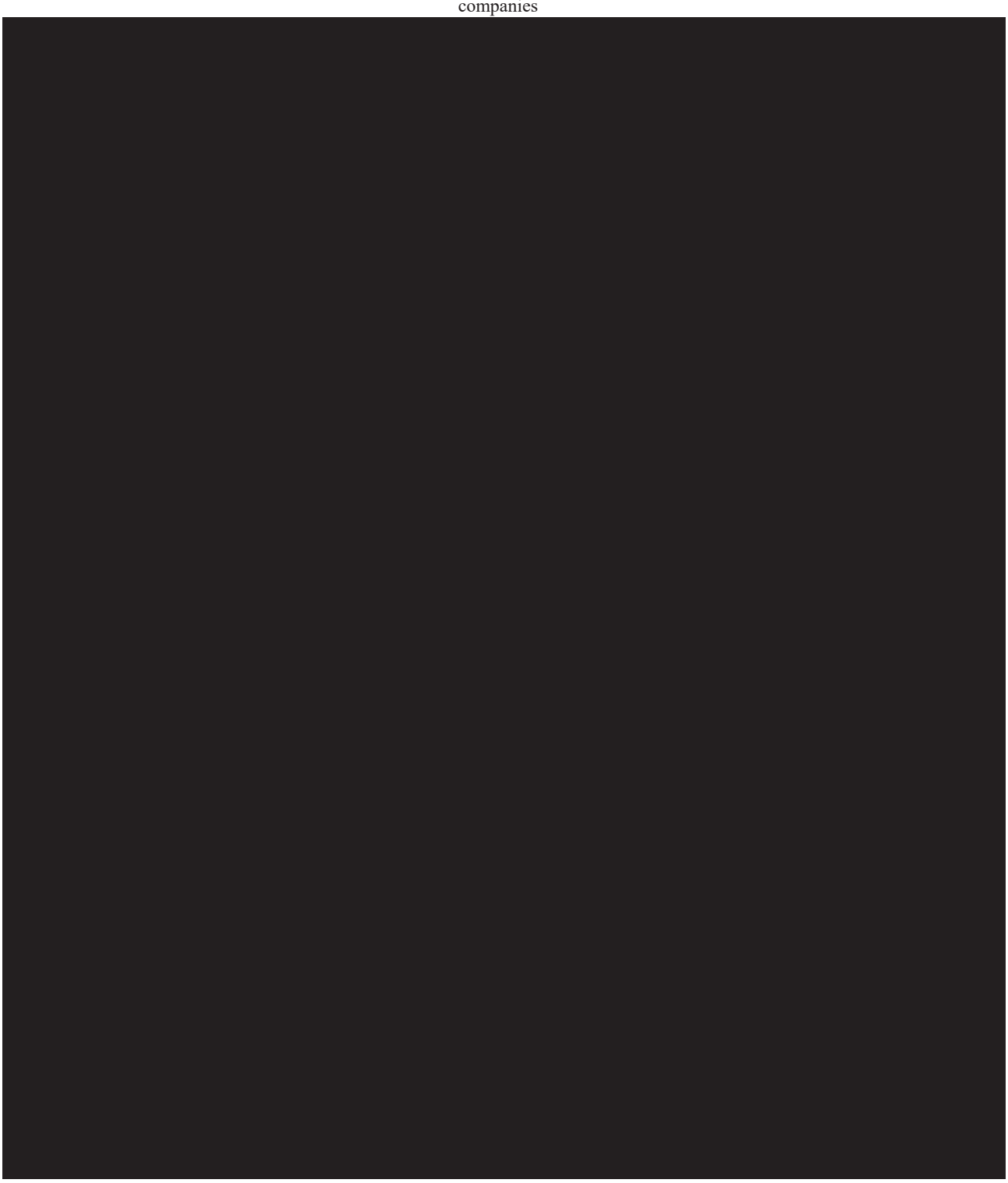
BI 1015550 is a selective inhibitor of the PDE4 B with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, BI 1015550 is hypothesized to have complementary activity to current therapies in IPF, as well as improved tolerability compared to other marketed PDE-4 inhibitors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

For further information please refer to the Investigator's Brochure (IB) [c02094779].



[redacted]





1.3 RATIONALE FOR PERFORMING THE TRIAL

The rationale of this trial is to assess the PK, safety and tolerability of BI 1015550 in healthy Chinese male and female subjects following single oral administration. The chosen population of healthy male and female subjects receiving single oral doses is considered adequate to provide the basis for the clinical development program of BI 1015550 in China.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1015550.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

There are no identified risks for BI 1015550, based on the toxicology program or any clinical trials conducted for this product to date. Vasculitis and foetal loss are considered as important potential risk based only on nonclinical findings (see section 1.2.1).

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs and from preclinical and clinical data of compounds with a comparable mode of action (see section 1.2.3). For adverse events reported during clinical trials with BI 1015550 please refer to section 1.2.1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product BI 1015550		
[redacted]	[redacted]	[redacted]
Vasculitis	• Vasculopathy is an established preclinical toxicity of PDE4 inhibitors. • Vasculitis has been shown in both the rats and minipigs following oral administration of BI 1015550 but not in a 13-week study in monkeys. • Vasculitis is listed as an important potential risk in the risk management plan (RMP) for the marketed PDE4-inhibitor apremilast. • In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans	• Close clinical monitoring for AEs of vasculitis

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Fetal loss, decreased fertility	• No teratogenicity was seen in 2 species in preclinical studies and exposure with BI 1015550 via the semen is expected to be very low. • In rats, male and female fertility was potentially reduced. Long term toxicity studies with BI 1015550 in rat and monkey showed no microscopic evidence of changes in male or female reproductive organs or on male spermatogenesis. For another PDE4 inhibitor with comparable preclinical findings, clinical data showed no effect on male fertility and sperm in humans. • Fetal loss was increased in female rats treated with BI 1015550 • Efficacy of oral hormonal contraceptives can be impacted by potential BI 1015550 [redacted]	• Only WOCBP that use a highly efficient way of birth control are allowed to participate. Oral hormonal contraceptives are not allowed. • Repeated pregnancy testing including prior first dosing in WOCBP Discontinuation of treatment in case of pregnancy
Weight decrease in underweight subjects (BMI < 18.5 kg/m2)	• For the marketed PDE4-inhibitors apremilast and roflumilast weight loss in underweight subjects is an identified important risk. • Presumably caused by increased energy expenditure and causing predominately loss of body fat	• Inclusion of subjects with BMI> 18.5 only is routine inclusion criterion in Phase I • The risk after single dose administration is considered low
Psychiatric disorders: • Depression and anxiety • Suicidality	• For the marketed PDE4i depression is listed as side effect and they are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also reported cases of completed suicide. • In IPF patients treated with 18mg BI 1015550 bid for up to 12 weeks, no on-treatment events of suicidal ideation or behaviour and no events of depression or anxiety were reported.	• The risk after single dose administration in Phase I (done on site) is considered low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression and anxiety as well as for signs and symptoms of suicidal ideation and behaviour • Only healthy subjects with no relevant medical history including psychiatric disorders will be enrolled.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Severe Infections including serious, opportunistic and mycobacterium tuberculosis infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of infections, including Covid-19. • Serious infections were balanced between placebo and BI 1015550 in Phase II trial. • Nasopharyngitis was more frequently reported under treatment with BI 1015550 in Phase Ic/II but not in Phase I trials and the numbers were very small.	Screening procedures for infections are defined for this trial. Subjects with any relevant chronic or acute infections including human immunodeficiency virus (HIV), or viral hepatitis are excluded from the trial. • Treatment of infections should be initiated promptly according to standards of care.

Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast.
	• In preclinical studies with BI 1015550 no adverse cardiovascular findings detected.
	• In clinical trials with BI 1015550 no relevant findings were observed.
		• These risks will be addressed by careful safety monitoring and safety measures such as
		  • close clinical monitoring for AEs;
		  • regular monitoring of vital signs and ECG assessments.

Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defense against malignancies.	• Subjects with a recent history of malignancy within 5 years will be excluded from participation in this trial. • Diagnostics and treatment have to be initiated according to local standard of care.
Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • Diarrhoea was the most frequently reported adverse event in Phase II with the majority of events being of mild intensity.	• Increased awareness of symptoms. • Careful monitoring of hydration in subjects with diarrhoea recommended. • Symptomatic treatment if required
General safety topics		
Drug-induced liver injury (DILI)	• Rare but severe event, standard topic of interest for products in development thus under constant surveillance by sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety. Increased awareness and expedited reporting (AESI).

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Trial procedures		
Blood Sampling	• As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain.	• These risks will be addressed by careful safety monitoring and risk mitigation measures such as • close clinical monitoring for AEs; • selection of experienced sites and site staff

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 1015550 is well understood. Based on its mode of action, BI1015550 is hypothesized to have complementary activity to current therapies in IPF.

In the context of the unmet medical need and anticipated benefit of BI 1015550, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate PK, safety and tolerability of BI 1015550 in Chinese healthy male and female subjects following oral administration of single doses.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1015550:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoints

- The occurrence of any treatment-emergent adverse events, assessed as the percentage of subjects treated with investigational drug who experience such an event.

[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 1015550 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure [BP], pulse rate [PR])

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as open-label, single dose parallel dose groups.

It is planned to include a total of 24 healthy Chinese male and female subjects in the trial. The subjects will be assigned to 2 groups, each consisting of 12 subjects with at least 3 female subjects within each dose group. In case of subjects not completed the trial, up to 8 replacement will be recruited for whole study, see section 3.3.5. The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups receiving BI 1015550

Dose group	**1**	**2**
Dose	9 mg	18 mg
No. of subjects entered	12	12
No. of subjects receiving active	12	12

The groups will be dosed sequentially in ascending order of doses. At any time during the ongoing study, further dosing will be stopped in case of safety and tolerability concerns based on the pre-specified trial-specific stopping criteria (refer to Section 3.3.4.3).

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

The study will be conducted according to a single-dose, open-label parallel-group design.

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte.

The placebo group is not needed since primary objective is to evaluate PK parameters but not to evaluate safety

The dose to be tested in this trial is identical to those in the pivotal Phase III trials.

3.3 SELECTION OF TRIAL POPULATION

It is planned that at least 24 healthy male and female subjects (at least 3 female subjects in each dose group) will enter the trial. Subjects will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

Chinese subjects will only be included in the trial if they meet the following criteria:

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 28.0 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Women of childbearing potential (WOCBP) must be ready and able to use highly effective methods of birth control. Of note, oral hormonal contraceptives are not considered a highly effective method due to potential drug-drug interactions. A list of contraception methods meeting these criteria and instructions on the duration of their use is provided in the patient information; please refer to section 4.2.2.3.

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders (including but not limited to major depressive disorder or any history of suicidal ideation or behaviour)
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days or five $t_{1/2}$ of investigational drug (whichever is longer), prior to the planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked 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
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
25. For female subjects: Positive pregnancy test
26. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 30 days after trial completion
27. Use of any Chinese traditional medicines and drugs (including prescription drug or over the counter) within 30 days of planned administration of trial medication.

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole (‘withdrawal of consent’) with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

28. In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.
29. Based on the inclusion criteria (i.e. women of non-childbearing potential) it is highly unlikely that a female trial participant becomes pregnant.
    However, if it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.
30. If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be

involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)

3.3.5 Replacement of subjects

If some subjects do not complete the trial (including subjects non-evaluable for PK), they may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide if and how many subjects will be replaced. The total number of replacements may not exceed 4 subjects per dose group. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	9mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	18 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose

Excipients include hydroxypropylcellulose, lactose, microcrystalline cellulose type 101, croscarmellose sodium, magnesium stearate, ready to use film-coating dry mixture (Opadry ® pink).

4.1.2 Selection of doses in the trial

The dose selected for this trial is the standard clinical dose (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects who are willing to participate will be recruited to dose groups according to their temporal availability.

As soon as enough subjects have been allocated to one of the 2 dose groups, the following subject will be allocated to the other dose group. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the trial includes healthy subjects of only Chinese ethnicity, relevant imbalances between the dose groups are not expected.

It is an open-label trial without randomisation.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total dose
1	BI 1015550	Tablet	9 mg	1 film-coated tablet, single dose	9 mg
2	BI 1015550	Tablet	18 mg	1 film-coated tablets, single dose	18 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in an upright position. For drug administration, the so called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) or to sleep.

4.1.5 Blinding and procedures for unblinding

The trial will be conducted in an open-label fashion.

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias is low and does not outweigh practical considerations. Emergency envelopes will not be provided, since the treatments of all subjects are known in this open-label trial.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by [redacted] They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form.

Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If 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 Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor

when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

The use of known PDE-inhibitors such as: theophyllin, theobromin, sildenafil, tadalafil, vardenafil and roflumilast must be avoided during the whole course of the study. [redacted]

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose on Day 1 (mandatory for all subjects).

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of each trial period is collected.

Poppy-seeds containing foods should not be consumed within 3 days before each admission to trial site, in order to avoid false-positive results in the drug screen.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before until 24 h after each administration of trial medication.

Smoking is not allowed during in-house confinement.

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

4.2.2.3 Contraception requirements

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial. Of note, oral hormonal contraceptives are not considered a highly effective method due to potential drug-drug interactions (see Section 3.3.2 for the definition of adequate measures, a list of contraception methods meeting these criteria is provided in the subject information).

4.3 TREATMENT COMPLIANCE

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

Subjects 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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported),, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a sitting position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

The parameters to be assessed are listed in Tables 5.2.3: 1 and 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.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	--
	Prothrombin time	X	--	--
	Prothrombin time – INR (International Normalization Ratio)	X	--	--
	Fibrinogen	X	--	--
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
Blood Pregnancy #		X		
Urine Pregnancy #			X	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)
ß-HCG will be performed at Visit 1, Visit 2 (Day -1) and EoS only. Blood Pregnancy test should be done at Visit 1, urine pregnancy test will be done at Visit 2 (Day -1) and EoS.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Although only women of non-childbearing potential are included in this trial, these tests are performed as precautionary measure. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Tetrahydrocannabinol acid)
	Cocaine
	Methamphetamines
	MDMA
	Morphine
	Ketamine
Infectious serology (blood) (At screening only)	Hepatitis B surface antigen (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (blood/urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory of the trial site or/and at a clinical research organization designated by the sponsor.

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an 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.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is 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 prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment 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

5.2.6.1.3 AEs considered ‘Always Serious’

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of

'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections AE Collection' and '**AE reporting to sponsor and timelines'**.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (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 Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

- Potential severe DILI

  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

  - o An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. 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 that these parameters are analysed, if necessary in an unscheduled blood test that needs to be sent to central laboratory. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

- Severe or serious infections, opportunistic or mycobacterium tuberculosis infections

  The opportunistic infections include pneumocystis jirovecii, Human Polyoma-1 virus disease including polyomavirus-associated nephropathy, Cytomegalie Virus, post-transplant lymphoproliferative disorder (Epstein-Barr-Virus), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/ pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only),

paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), Hepatitis C progression [R17-2617].

- Vasculitis events

  In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels.

5.2.6.1.5 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) that 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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, 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 reduced)

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
- There is an 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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
  - All AEs (serious and non-serious) and all AESIs
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the 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 to the sponsor's unique entry point within

24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject 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 written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for 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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and Part 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 Studies 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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1015550 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant 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.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at about 4 to 8 °C.

Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 120 min. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. 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 trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic 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 pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Chart.

Trial measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, laboratory tests, and AEs/concomitant therapies questioning will be:

± 30 min up to 48 h after drug administration (planned time)

± 120 min after 48 h to the end of study

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood 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 the determination of pharmacokinetic parameters.

If a subject 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 Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

6.2.2 Treatment periods

Each subject will receive one dose of trial medication at Visit 2.

On the evening of Day -1, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed

continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this trial.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment. Descriptive analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1015550 will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the 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.

Important protocol deviations 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

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic 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).

7.2.2 Primary endpoint analyses

The primary endpoints (refer to Section 2.1.2) will be calculated according to BI standards. The analysis will be based on the PKS and will be descriptive in nature.

7.2.3 Secondary endpoint analyses

The analysis of secondary safety endpoint will be based on the TS and will be descriptive in nature (refer to Section 7.2.5)

[redacted]

7.2.5 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.3 and 2.2.2.1 based on the treated set (TS). Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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 time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and

post-study intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include 12 subjects per dose group, and a total of up to 32 subjects including up to 8 replaced subjects in this trial. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group is commonly used in studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and PK.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, 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 subject's participation in the trial, written informed consent must be obtained from each subject (or the subject'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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment

of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC 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.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history

- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:

The trial site must retain the source and essential documents (including ISF) according to the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial Leader (CTL), responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Mangers (CTM), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site.

Analyses of BI 1015550 concentrations in plasma will be performed at a CRO – [redacted] or an appropriate CRO with validated bioanalytical method. On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by BI or a contract research organisation according to BI SOPs.

Tasks and functions assigned in order to organise, 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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 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.

P12-03241 King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet 2011. 378: 1949-1961

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).http://www.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.

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

R17-0915 Roflumilast 500 mcg tablets (Forest Research Institute): pharmacology/toxicology NDA/BLA review and evaluation, application number: 022522Orig1s000. Source: http://www.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.

R17-0919 Otezla (apremilast) (Celgene): pharmacology/toxicology NDA/BLA review and evaluation, application number: 205437Orig1s000. Source: http://www.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). Source: https://ec.europa.eu/health/documents/community-register/2015/20150115130395/anx _130395_en.pdf (access date: 19 April 2017); 2015.

R17-2617 Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis; 2015, 74; 2107-2116.

R18-2794 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al, American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018; 198(5); e44-e68.

9.2 UNPUBLISHED REFERENCES

c02094779 BI 1015550 - Investigator's Brochure, current version

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

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

c24902949 [redacted]. Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects. 1305-0015. Clinical Trial Report, 15 March 2019

c25085412 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. 1305-0012. Clinical Trial Report, 13 Jan 2020

c36151567 A Phase I, open-label, non-randomized, single-dose, single-arm, single period study to investigate the metabolism and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects. 1305-0016. Clinical Trial Report, 28 Feb 2022

c37065416 A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally. 1305-0013. Clinical Trial Report

U10-3777 BI 137882 – Investigator's Brochure, 11 February 2011

U11-2788 [redacted] Safety, tolerability and pharmacokinetics of single rising doses of BI 137882 in healthy male volunteers (A randomised, single-blind, placebo–controlled Phase I study. Clinical Trial Report, 28 December 2011

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 Mar 2023
EudraCT number **EU number**		Not applicable
BI Trial number		1305-0024
BI Investigational Medicinal Product		BI 1015550
Title of protocol		Pharmacokinetics, safety and tolerability of doses of BI 1015550 in healthy Chinese male and female subjects (open-label, parallel group design)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title Page: Clinical Trial Lead
Description of change		• The name of Clinical Trial Lead "[redacted]" was changed into "[redacted]" • The address of Clinical Trial Lead was changed into [redacted] • The phone number of Clinical Trial Lead was changed into [redacted]
Rationale for change		CTL handover
Section to be changed		Clinical Trial Protocol Synopsis Table: Trial Endpoints and Main inclusion criteria
Description of change		• Trial Endpoints: AUC0-∞ and Cmax was replaced by **$AUC_{0-\infty}$** and **C_{max}**. • Main inclusion criteria: 28 kg/m2 was replaced by **28.0 kg/m²**.
Rationale for change		Typo correction
Section to be changed		Flow Chart: Footnote 2, 7 and 8
Description of change		• Updated Footnote 2, 7 and 8 on the Flow Chart for chronological collection
Rationale for change		Correction and clarification
Section to be changed		Flow Chart: Footnote 10
Description of change		• Updated safety and vital status collection time points on the flow chart • Footnote 10 was added as following: **Trial measurements and assessments scheduled to**

		occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.
Rationale for change		Time collecting points clarified.
Section to be changed		Table 1.4.2: 1 Overview of trial-related risks for this trial
Description of change		Updated the text as following (See text in bold): • ~~An exception~~ **This is also applicable for** Paxlovid in the treatment of Covid-19: if treatment with Paxlovid is needed trial medication needs to be paused
Rationale for change		Clarification. Paxlovid is a type of CYP3A inhibitors and should be avoided in this trial.
Section to be changed		4.1.8 Drug accountability
Description of change		Updated the text as following (See text in bold): • At the time of ~~disposal~~ **return** of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession. • ~~All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies~~.
Rationale for change		Clarification. The remaining trial medication can't be disposed at local site in this trial, so the remaining trial medication will be returned to Sponsor and the description about remaining medication disposal at local site was no longer required. This revision has been clarified in the Protocol Administrative Letter (date: on 8 Nov 2022) and approved by site Ethic Committee on 10 Dec 2022 .
Section to be changed		5.2.2 Vital signs
Description of change		Updated the text as following (See text in bold): • …after subjects have rested for at least 5 min in a ~~supine~~ **sitting** position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.
Rationale for change		Adapted to match the wording in section 4.1.4: …during the first 4h after drug

		administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) or to sleep. This revision has been clarified in the Protocol Administrative Letter (date: on 1 Feb 2023) and approved by site Ethic Committee on 6 Feb 2023.
Section to be changed		Table 5.2.3: 1 Routine laboratory tests: Footnote
Description of change		Updated the text as following (See text in bold): # ß-HCG will be performed at Visit 1, Visit 2 (Day ~~1~~ **-1**) and EoS only. Blood Pregnancy test should be done at Visit 1, urine pregnancy test will be done at Visit 2 (Day ~~1~~ **-1**) and EoS.
Rationale for change		Adapted to match description in the Flow Chart
Section to be changed		6.2.2 Treatment periods
Description of change		Updated the text as following (See text in bold): • On the evening of Day -1, trial participants will be admitted to the trial site and kept under close medical surveillance for at least ~~48~~**24**h following drug administration
Rationale for change		Updated to keep consistency with Flow Chart. This revision has been clarified in the Protocol Administrative Letter (date: on 1 Feb 2023) and approved by site Ethic Committee on 6 Feb 2023.