Boehringer Ingelheim

Clinical Trial Protocol

Document Number:	**c39880555-03**
EudraCT No.	2022-002811-45
BI Trial No.	1305-0027
BI Investigational Medicinal Product	BI 1015550
Title	Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Lay Title	A study to test how BI 1015550 is taken up in the blood of people with and without liver problems
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: + [redacted] Fax: [redacted]
Current Version, Date	Version 3.0, 30 Mar 2023
Original Protocol Date	28 Oct 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	28 Oct 2022
Revision date	30 Mar 2023
BI trial number	1305-0027
Title of trial	Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	In this trial, pharmacokinetics, safety and tolerability of BI 1015550 single oral dose in participants with different degrees of hepatic impairment compared to individually matched participants with normal hepatic function will be assessed.
Trial objectives	To investigate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on the pharmacokinetics, safety and tolerability of BI 1015550
Trial endpoints	Primary endpoints: $AUC_{0\text{-}tz}$ and C_{max} of BI 1015550 Secondary endpoints: $AUC_{0\text{-}\infty}$ of BI 1015550
Trial design	Open-label, non-randomised, parallel, individual matched design
Number of participants **total entered** **on treatment**	32* • *Group 1:* 8 participants with mild hepatic impairment (Child-Pugh A) • *Group 2:* 8 participants with moderate hepatic impairment (Child-Pugh B) • *Group 3:* 8* participants with normal hepatic function individually matched to participants of Group 1 ** • *Group 4:* 8* participants with normal hepatic function individually matched to participants of Group 2** ** Matching criteria: age (± 10 years), gender and weight (± 15%) * One participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment. Thus, the total sample size may be 24 to 32 participants. Additional participants may be included to ensure that the study objectives are reached.

Diagnosis	Participants with hepatic impairment (Child-Pugh A or B) and participants with normal hepatic function (matched controls to the participants with hepatic impairment)
Main inclusion criteria	Male/female participants (at least 25% of each gender), age 18 - 79 years (inclusive), body mass index (BMI) of 18.5 to 35 kg/m^2 (inclusive) with hepatic impairment of Child-Pugh A (mild) and B (moderate) classification. Male/female participants (at least 25% of each gender) with normal hepatic function individually matched to participants with hepatic impairment with respect to age, gender, and weight 18-79 years (inclusive), BMI of 18.5 to 35 kg/m^2 (inclusive)
Test product **dose** **mode of administration**	BI 1015550 film-coated tablet 18 mg Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	Single dose
Statistical methods	To assess the effect of hepatic impairment on the primary and secondary pharmacokinetic endpoints of BI 1015550, the relative bioavailability will be estimated by the ratios of the geometric means of the respective pairwise comparison of interest, i.e., for each hepatic impairment group vs. the respective control group. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified for any comparison of interest. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect ‘degree of hepatic impairment’ and the random effect ‘matched pair’. 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 [7]	PK $_{blood}$ [8]	Suicidality assessment [12]	12-lead ECG [9]	Vital signs (BP, PR) [10]	Questioning for AEs and concomitant therapy [6]
1	-21 to -2			Screening (SCR) [1]	A		x	x	x	
2	-1	-24:00	08:00	Admission to trial site	B [5]				x[11]	x
	1	-2:00	06:00			x[2]	x	x[2]	x[2]	x[2]
		0:00	08:00	Drug administration						
		0:30	08:30			x				
		0:45	08:45			x				
		1:00	09:00			x		x	x	x
		1:15	09:15			x				
		1:30	09:30			x				
		1:45	09:45			x				
		2:00	10:00	240 mL fluid intake (snack for participants with diabetes) [3]		x		x	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	x
		6:00	14:00			x				
		8:00	16:00	Snack (voluntary) [3]		x		x	x	x
		10:00	18:00			x				
		11:00	19:00	Dinner [3]						
		12:00	20:00			x				
		14:00	22:00			x				x
	2	24:00	08:00		B	x		x	x	x
		36:00	20:00			x				x
	3	48:00	08:00			x				x
	4	72:00	08:00	Breakfast [3] (voluntary), discharge from trial site	B	x	x	x	x	x
	5	96:00	08:00	Ambulatory visit		x				x
	6	120:00	08:00	Ambulatory visit		x				x
	7	144:00	08:00	Ambulatory visit		x	x			x
3	8 to 14			End of study (EoS) examination [4]	C		x	x	x	x

1. Participant must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination (including assessment of suicidal ideation and behaviour using the C-SSRS questionnaire), check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath test, serology, and SARS-CoV-2 PCR test, serum pregnancy test in WOCBP), 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 2 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 (including assessment of suicidal ideation and behaviour using the C-SSRS questionnaire), body weight, vital signs, ECG, safety laboratory (including urine pregnancy test in WOCBP), recording of AEs and concomitant therapies.
5. In addition: urine drug screening, alcohol breath test, SARS-CoV-2 antigen test, as well as serum pregnancy test in WOCBP

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. Letters A, B and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. For details of PK blood sampling, refer to Section 5.3.2.
9. For details of 12-lead ECG, refer to Section 5.2.4.
10. For details of vital signs evaluation, refer to Section 5.2.2.
11. Only assessment of body temperature (if needed due to the current status of the pandemic).
12. For details of suicidality assessment, refer to Section 5.2.5.1.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

[redacted]	[redacted]
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
COVID-19	SARS-CoV-2 induced disease
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form

eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-foetal development
EoS	End of Study (synonym for End of Trial)
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEED	Fertility and early embryonic development
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GLDH	Glutamate dehydrogenase
gMean	Geometric mean
HIV	Human immunodeficiency virus
[redacted]	[redacted]
HR	Heart rate
IB	Investigator's brochure
iCF	Intended commercial formulation
IEC	Independent Ethics Committee
IME	Important medical event
IPD	Important protocol deviation
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LOAEL	Lowest observed adverse effect Level
MACE	Major Adverse Cardiovascular Events
MDA	Methylenedioxyamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	[redacted]
NCT	Number Connection Test
NOAEL	No adverse effect level
NOEL	No observable effect level

norm	Normalised to dose
NOTEL	No toxic effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PE	Polyethylene
P-gp	Permeability glycoprotein
PIB	Powder in the bottle
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
PTF	Peak-trough fluctuation
PTS	Peak-trough swing
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)
$RAUC_{0\text{-}tz,M/P}$	ratio of $AUC_{0\text{-}tz}$ of metabolite to $AUC_{0\text{-}tz}$ of parent compound
RBC	Red blood cells
$RC_{max,M/P}$	ratio of C_{max} of metabolite to C_{max} of parent compound
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
$t_{\lambda z,start(end)}$	Lower (upper) limit on time for values to be included in the calculation of λ_z
[redacted]	[redacted]
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
[redacted]	[redacted]
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal

[redacted]	[redacted]
WBC	White blood cells
WOCBP	Women of childbearing potential

1. INTRODUCTION

BI 1015550, [redacted], is being developed by BI for the treatment of IPF and other forms of progressive pulmonary fibrosis.

1.1 MEDICAL BACKGROUND

IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP [P22-03204]. Apart from IPF, there is a group of patients with different underlying clinical ILD diagnoses who develop a phenotype similar to patients with IPF during the course of their disease which is characterised by increasing extent of pulmonary fibrosis on imaging, declining lung function, worsening respiratory symptoms and quality of life despite disease management considered appropriate in clinical practice, and, ultimately, early mortality [P17-10582, P18-04729, P19-01738, P20-01299, P22-03204, R19-0854].

Nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and both treatments are recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of IPF [P15-07539]. Nintedanib is also registered for the treatment of adults with other chronic fibrosing ILDs with a progressive phenotype and systemic sclerosis-associated ILD. However, despite existing treatment, there remains a high unmet need for new treatments for IPF and other fibrosing ILDs that have greater efficacy and fewer side effects than existing therapies [P18-06345].

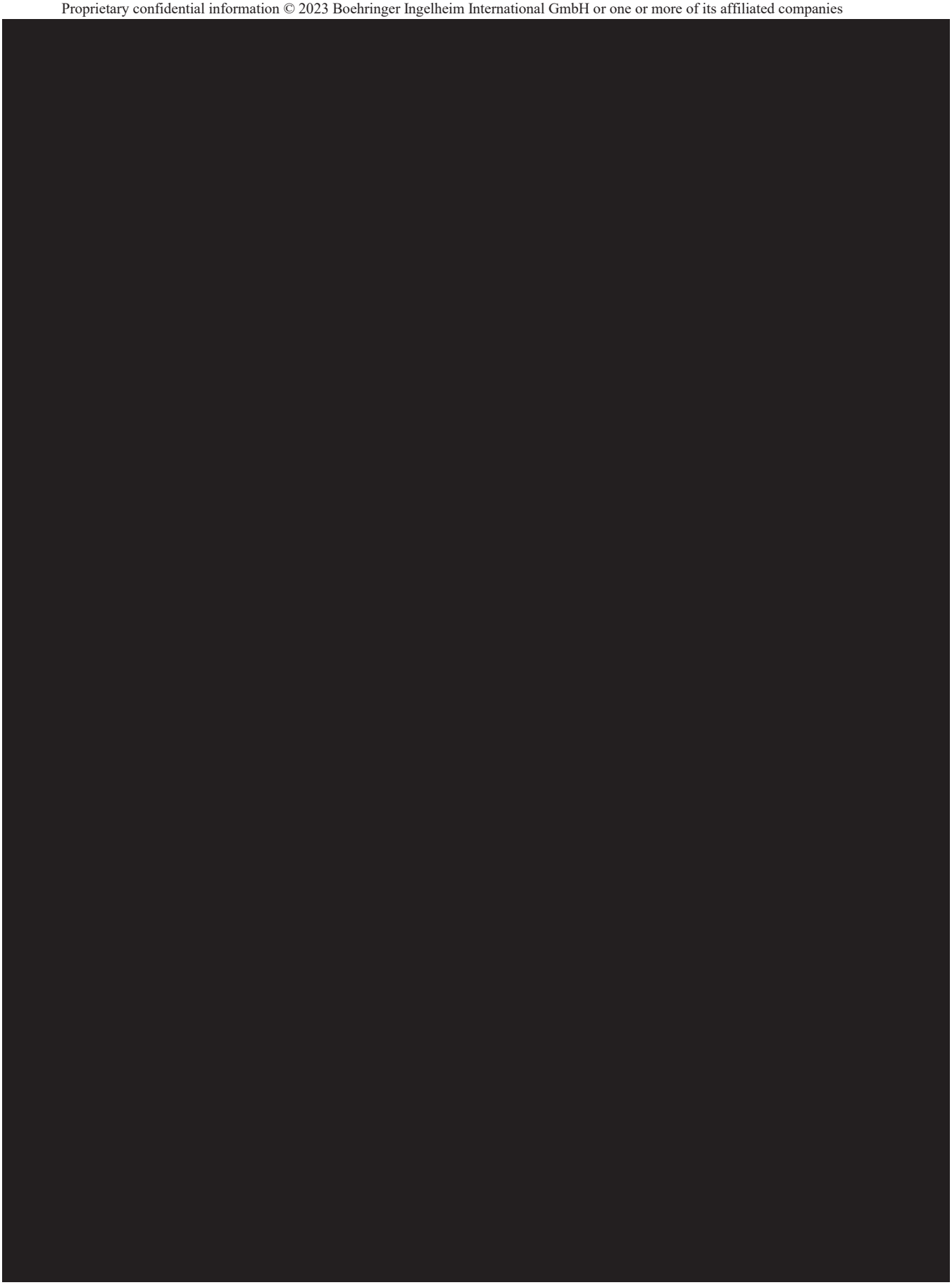
BI 1015550 is an oral preferential inhibitor of the PDE4B with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, as well as available preclinical and clinical data, BI 1015550 is hypothesised to have complementary activity to current therapies in IPF and other forms of progressive pulmonary fibrosis.

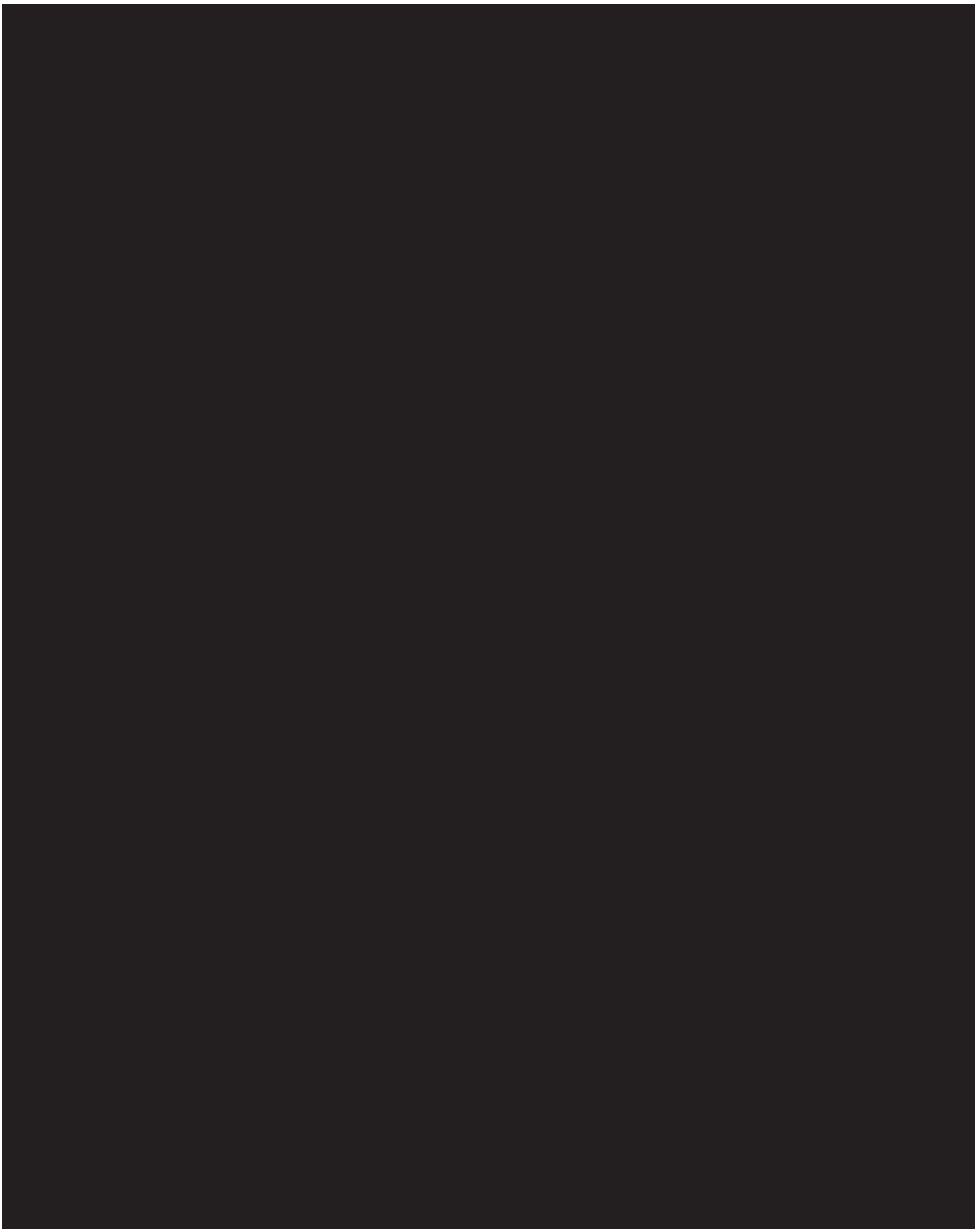
1.2 DRUG PROFILE

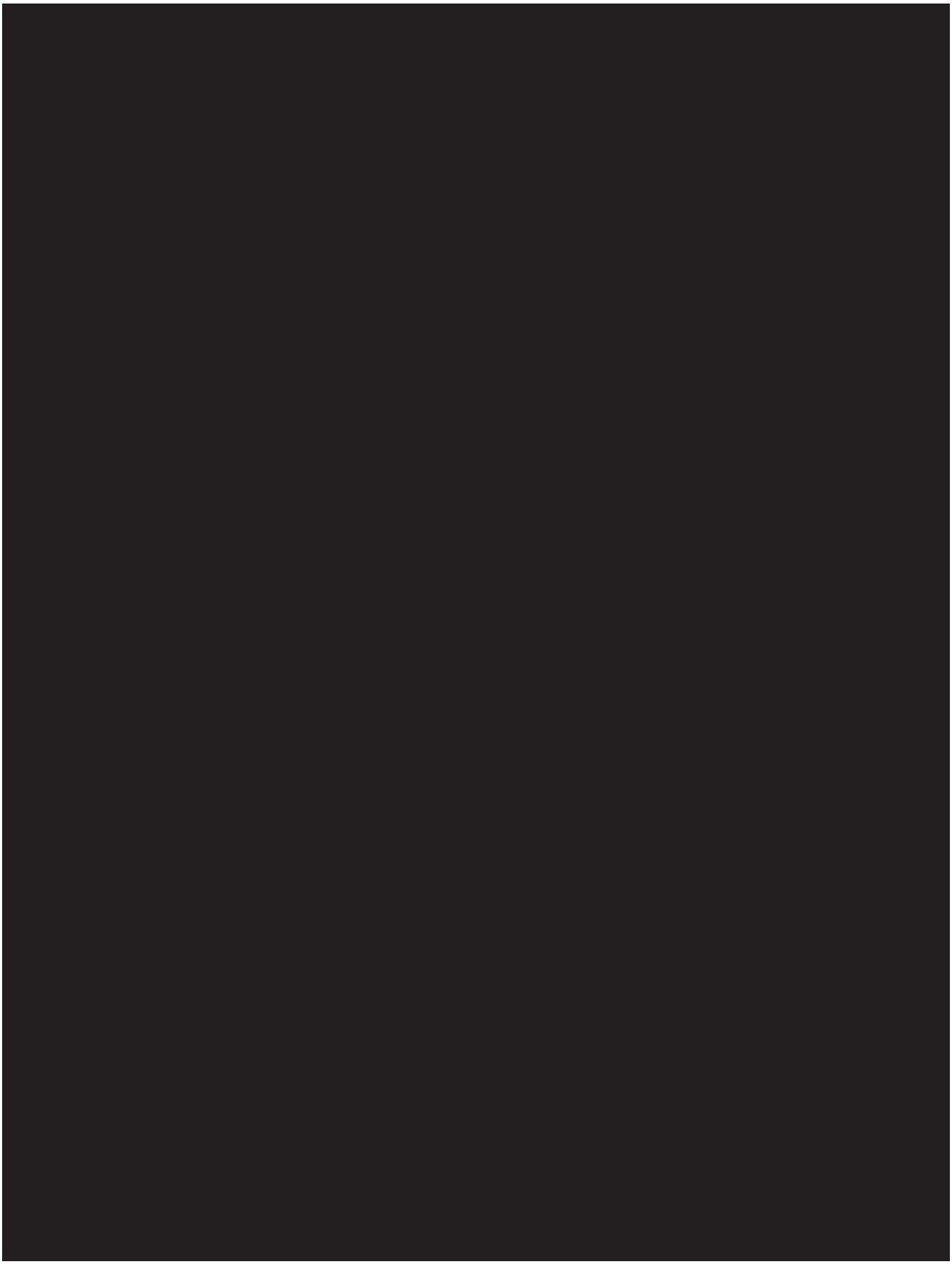
1.2.1 BI 1015550

For a more detailed description of BI 1015550 profile, please refer to the current IB [c02094779].

[redacted]







[redacted]

1.2.1.4 Clinical safety and efficacy

BI 1015550 has been investigated in a total of 9 clinical studies: 8 Phase I trials (seven trials in healthy subjects and one in patients with IPF), and a proof-of-clinical principle Phase II trial in patients with IPF. Overall, 146 healthy volunteers and 107 patients with IPF have been exposed to BI 1015550.

BI 1015550 was well tolerated following single dose administration up to 48 mg in healthy volunteers and following multiple administrations up to 18 mg bid over a treatment period of up to 12 weeks in patients.

Clinical safety

In healthy subjects, seven clinical studies have been completed with BI 1015550. Overall, BI 1015550, up to a 48 mg single-dose and 12 mg bid multiple-dose appeared to show

acceptable safety and tolerability. Headache, abdominal pain, nausea and diarrhoea, all of mild to moderate intensity, were the most commonly reported events. A trend toward weight loss in subjects treated with BI 1015550 was observed in study 1305-0011 [c22991937] in healthy volunteers.

In the MRD trial (1305-0002), one subject after multiple doses of 6 mg bid experienced postprandial pain, constipation, lower abdominal pain, lower left quadrant abdominal pain, and [redacted] in blood. These events were classified as drug-related. They were of mild intensity, with the [redacted] which was of moderate intensity and led to discontinuation of the subject [c02191718].

No severe, serious, fatal AEs, nor SUSARS have been reported in the healthy volunteer studies. No dose-dependency was observed.

In patients with IPF, two clinical studies have been completed with BI 1015550: a Phase Ic MRD study in patients without background antifibrotic treatment (1305-0012 [c25085412]) and a proof-of-clinical principle Phase II study in patients stratified by background antifibrotic treatment (1305-0013 [c37065416]).

Overall, in Phase Ic and II trials in patients with IPF, BI 1015550 at a dose of 18 mg bid for up to 12 weeks showed acceptable safety and tolerability, both in patients without or with background antifibrotic treatment (nintedanib or pirfenidone). The most common AEs were GI events (more specifically diarrhoea), which were reported with a higher frequency under BI 1015550 treatment (vs. placebo) and in patients with background antifibrotic treatment.

In the Phase II trial which investigated treatment with BI 1015550 18 mg bid for 12 weeks in patients with IPF, diarrhoea was the most common AE leading to discontinuation of treatment. AEs leading to discontinuation of trial treatment were only observed in the BI 1015550 treatment group. Apart from the mentioned 3 patients with diarrhoea and 2 patients with Covid-19, all events occurred in single patients without any pattern or cluster. The frequency of SAEs in patients was numerically higher in placebo-treated patients, which was driven by placebo-treated patients without antifibrotic background treatment. There were two events with fatal outcome in the BI 1015550 treatment group, one patient with Covid-19 pneumonia and one patient with suspected IPF exacerbation and suspected vasculitis (the diagnosis of vasculitis could not be confirmed by the sponsor nor the independent external data monitoring committee). Risk factors were present in both fatal events. One AESI was reported (the fatal AE of suspected vasculitis), and evaluation by an external, independent Data Monitoring Committee could neither confirm the diagnosis of vasculitis, nor a causal relationship with BI 1015550. There were no AESIs of hepatic injury. No relevant patterns, clusters or imbalances were observed for any of the other safety topics of interest, including depression, suicidal ideation and behaviour, anxiety, malignancies, insomnia, major adverse cardiac events, or tachyarrhythmia. No clinically relevant changes in vital signs (including body weight) or ECG parameters (including QTc) were observed. No changes in the C-SSRS and no AEs of suicidal ideation or behaviour were reported during trial treatment.

[redacted]

1.2.2 Residual Effect Period

The REP of BI 101550 [redacted]. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

[redacted]

This exploratory trial is designed to investigate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on the pharmacokinetics, safety and tolerability of BI 1015550. The data obtained in this trial will provide a basis for the treatment of patients suffering from IPF and other forms of progressive pulmonary fibrosis with hepatic impairment, as well as a potential dose adaptation for this category of patients. The design of this trial follows the FDA guideline for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" [R05-0337] and the EMA "Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function" [R05-0340].

For ethical and safety reasons, also the low prevalence of severe hepatic impaired patients in target population, patients with severely impaired hepatic function (Child-Pugh C) will not be enrolled in this trial.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for participants with impaired hepatic function and participants with normal hepatic function. Their participation, however, is of major importance for the development of BI 1015550.

1.4.2 Risks

Participants 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.

To date, no side effects have been identified for BI 1015550. Potential side effects of BI 1015550 will be under continuous evaluation during clinical development. Vasculitis and foetal loss are considered as important potential risk based only on non-clinical findings. 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. For AEs 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	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1015550		
[redacted]		

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Weight decrease in underweight patients (BMI < 18.5 kg/m^2)	• For the marketed PDE4i apremilast and roflumilast weight loss in underweight participants is an identified important risk [redacted]	• Inclusion of participants with BMI > 18.5 only is routine inclusion criterion in Phase I (With a single dose administration the risk is considered to be very 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 18 mg BI 1015550 bid 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 a single administration of BI 1015550 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 participants with no relevant medical history including psychiatric disorders will be enrolled • Any suicidal behaviour in the past 2 years and any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 are exclusion criteria. • Prospective monitoring for suicidal ideation behaviour using the C-SSRS • Patient's withdrawal criteria in case of new-onset suicidal behaviour or any suicidal ideation of type 4 or 5 in the C-SSRS.

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

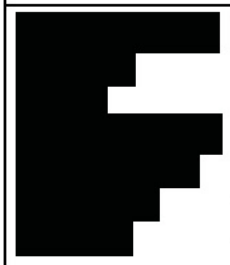
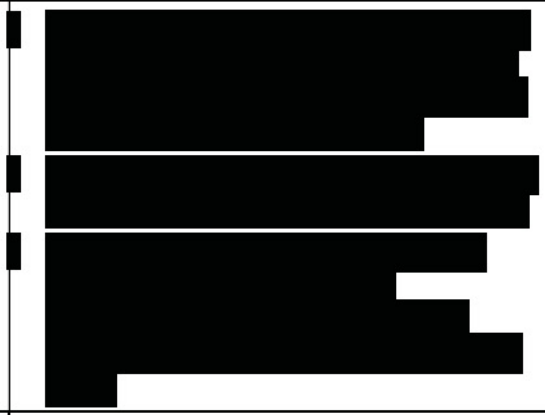
Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
		
Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast. • In preclinical studies with BI 1015550 no adverse cardiovascular findings detected (focal myocardial degeneration or necrosis in monkeys were with no apparent vascular changes). • 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 • Participants will stay under close medical surveillance during 72 h after treatment with BI 1015550
Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus, theoretically decrease immune defence against malignancies.	• Volunteers with a recent history of malignancy within 5 years will be excluded from participation in this trial.
Gastrointestinal disorders (e.g., diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhoea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • In Phase II study of BI 1015550, diarrhoea was the most frequently reported AE.	• Increased awareness of symptoms • Careful monitoring of hydration in participants with diarrhoea recommended • Symptomatic treatment if required.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure participants´ safety Increased awareness and expedited reporting (AESI).
<u>Trial procedures</u>		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venepuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

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

Considerations on male contraception requirements:

The exposure through seminal fluid to sexual partners of males receiving BI 1015550 is expected to be minimal. At a plasma BI 1015550 [redacted] following an 18 mg bid dose, the worst-case seminal fluid level is anticipated [redacted] his large safety margin, the absence of dysmorphogenesis in two species, and lack of genotoxicity suggest that barrier methods of contraception should not be required for a male administered a single dose of BI 1015550 [c39775503], where C_{max} is lower and the safety margin is even higher.

Considerations on female contraception requirements, pregnancy, and lactation:

Women who are pregnant or planning to become pregnant and women who are breast-feeding are not allowed to participate in studies with BI 1015550. Based on results of the

reproductive toxicity studies, women of childbearing potential are allowed to participate provided they use a highly effective method of contraception.

Of note, oral hormonal contraceptives are not considered as highly effective due to the potential CYP3A induction by BI 1015550, but possible reduced efficacy would not put the participants at risk since additional contraceptive measures are mandatory (see Section 3.3.2).

Considerations on COVID-19:

Generally, in the participants if this trial, the risk of severe COVID-19 infection is not higher, and study participation would not increase the risk of becoming infected with SARS-CoV-2 beyond the potential risk associated with any need for the study participant to leave their home for study related activities. The appropriate risk minimisation measures will be taken in accordance with the public health precautions if needed due to the current status of the pandemic.

Based on the pharmacological mechanism and existing non-clinical and clinical data, there is no indication that treatment with BI 1015550 may increase the risk of infection in general including SARS-CoV-2 infection. As for any active infection, participants with active or recent (i.e., within the 4 weeks prior to screening) SARS CoV-2 infection should not be included in the trial which is also applicable for any other relevant acute infection (exclusion criterion No. 8).

In case of severe COVID-19 infection during the conduct of the trial, treatment with BI 1015550 will not be given which is also applicable for any other relevant acute infection (criterion of withdrawal from trial treatment No. 6). The appropriate diagnostic and treatment measures will be taken in accordance with the public health precautions.

Of note, depending on the current status of the COVID-19 pandemic, all participants with confirmed SARS CoV-2 infection will be handled in accordance with local guidance and SOPs meaning that any confirmed SARS CoV-2 infection during the conduct of the trial will lead to withdrawal of the participant from further trial procedures to avoid undue risks to other participants at the trial site and the site personnel. The appropriate diagnostic and treatment measures will be taken in accordance with the public health precautions. If feasible, the EoS examination to be performed as early as possible after the SARS CoV-2 infection is resolved.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 1015550 is well understood. BI 1015550 is [redacted]

[redacted]

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this study is to investigate the effect of mild (Child-Pugh A, score 5-6) and moderate (Child-Pugh B, score 7-9) hepatic impairment on the PK of BI 1015550.

2.1.2 Primary endpoints

The following PK parameters will be determined for BI 1015550:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following PK parameter will be determined for BI 1015550:

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

[redacted]

2.2.2.2 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
- Assessment of suicidal ideation and behaviour (C-SSRS)
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, single-dose, open-label, parallel, individual matched design in order to investigate PK of BI 1015550, as well as safety and tolerability of BI 1015550 in male and female participants with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment compared to individually matched control participants. The treatment will be one 18 mg tablet administered to trial participants in the fasting state. For details, refer to Section 4.1.

- Group 1: 8 participants with mild hepatic impairment (Child-Pugh A)
- Group 2: 8 participants with moderate hepatic impairment (Child-Pugh B)
- Group 3: 8 participants with normal hepatic function individually matched to participants of Group 1
- Group 4: up to 8 participants with normal hepatic function individually matched to participants of Group 2

One participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment.

The matching criteria of the participants with normal hepatic function to the participants with hepatic impairment:

- Age (± 10 years)
- Gender
- Weight (± 15%)

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.

Recruitment will start with Group 1. After 4 participants in Group 1 have been treated, relevant safety data (i.e., AEs, medically relevant abnormalities in vital signs, ECG, and safety laboratory up to Day 4) will be reviewed by the Principal Investigator (or an authorised deputy) and the Clinical Trial Leader (or an authorised deputy). If these data do not raise safety concerns, treatment of participants of Group 2 may be started. Participants of Group 3 and 4 may be recruited in parallel to Groups 1 and 2. See also Section 4.1.3 for dosing in subcohorts.

Definition of trial start and end are given in Section 8.6.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The defined single-dose individual-matched comparison is deemed appropriate to meet the objectives of the study. There was no indication of a deviation from dose proportionality of either C_{max} or AUC, both after single administration as well as at steady state following twice daily dosing. For the purpose of evaluating hepatic impairment on the exposure of BI 1015550, the single dose design is sufficient since the multiple dose PK of BI 1015550

can be predicted by the single dose PK and the major metabolite is inactive. The single dose of 18 mg of BI 1015550 selected in this trial is the currently expected therapeutic dose in a twice daily (bid) regimen and has been considered safe for the trial populations and sufficient for the planned PK evaluations.

The resulting group sizes (see Section 7.5) are considered to be sufficient for the exploratory evaluation of PK. The assignment of matched control participants with normal hepatic function is a useful method to control for other factors which may influence the PK of BI 1015550 in a hepatic impaired population. The open-label treatment is not expected to bias results, since the main study endpoints are derived from measurement of plasma concentrations of the analyte.

The study design is in accordance with the guidance on PK in patients with impaired hepatic function [R05-0337]; this requires applying a single dose administration regimen to patients fulfilling the Child-Pugh A or B criteria and was deemed appropriate for the present trial.

As discussed in Section 1.3, participants with severely impaired hepatic function (Child-Pugh C) will not be enrolled in this trial for ethical and safety reasons.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 8 male or female participants with mild hepatic impairment (Child-Pugh A, Group 1) and 8 male or female participants with moderate hepatic impairment (Child-Pugh B, Group 2) and up to 16 individually matched participants with normal hepatic function (Group 3, 4) will enter the trial. Each group will consist of at least 25% of each sex.

Participants will be recruited from the volunteers' pool of the trial site. In addition, participants with hepatic impairment will be recruited in cooperation with different hepatology centres who primarily diagnose the underlying medical condition leading to chronic hepatic impairment.

Participants with hepatic impairment will be assigned to one of the hepatic impairment groups (mild or moderate), according to Child-Pugh score (see Table 3.3: 1 and 3.3: 2). The hepatic function assessment and assignment to the hepatic impairment groups will be conducted by the investigators at the screening examination.

Table 3.3: 1 Child-Pugh scoring

Measure	**1 Point**	**2 Points**	**3 Points**
Total Bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34 - 50 (2 - 3)	> 50 (> 3)
Serum albumin, g/dL	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time, prolongation (s) / or INR	< 4.0 < 1.7	4.0 - 6.0 1.7 - 2.3	> 6.0 > 2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

Table 3.3: 2 Child-Pugh scoring interpretation

Total Points	**Hepatic Impairment Class**
5–6	Child-Pugh A (mild hepatic impairment)
7–9	Child-Pugh B (moderate hepatic impairment)
10–15	Child-Pugh C (severe hepatic impairment)

Encephalopathy Grading System:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Number Connection Test (NCT):

The exclusion of a possible hepatic encephalopathy will be performed using the Number Connection Test (NCT). This test measures cognitive motor abilities. In the NCT, subjects have to connect numbers printed on paper consecutively from 1 to 25, as quickly as possible.

Errors are not enumerated, but subjects are instructed to return to the preceding correct number and then carry on. The test score is the time the subject needs to perform the test, including the time needed to correct the errors. A low score indicates a good performance. If the time needed exceeds 80 seconds, subjects will be excluded from the study. In addition, an experienced physician may assess hepatic encephalopathy by performing a standard neurological examination, which includes handwriting and common amnestic testing.

Participants with normal hepatic function will be matched individually by gender, age (within ±10 years) and weight (within ±15%) to the participants with hepatic impairment. One participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment.

Please refer to Section 4.1.3 regarding the method of assigning participants to hepatic function groups.

A log of all participants 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 participants with mild or moderate hepatic impairment and matched control participants with normal hepatic function.

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

3.3.2.1 Inclusion criteria applicable to all participants

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

1. Male or female participants
2. Age 18-79 years (inclusive)
3. BMI of 18.5 to 35 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. Male participants are not required to use contraception
6. Women of childbearing potential are allowed to participate provided they use a highly effective contraception from at least 30 days before the administration of trial medication until 7 days after trial completion.
   Of note, oral hormonal contraceptives are not considered as highly effective in this study due to the potential CYP3A induction by BI 1015550. Therefore, the following

methods of contraception are considered adequate for female participants of childbearing potential:

- Use of combined (oestrogen and progestogen containing) hormonal contraception that prevents ovulation (oral, intravaginal or transdermal), *plus condom*
- Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants*), plus condom*
- Use of intrauterine device or intrauterine hormone-releasing system
- Sexually abstinent
- A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant.

Female participants are not considered to be of childbearing potential if they are either surgically sterilised (including hysterectomy) or postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and oestradiol below 30 ng/L is confirmatory).

3.3.2.2 Inclusion criteria applying only to participants with impaired hepatic function

In addition to the inclusion criteria given in Section 3.3.2.1, participants with impaired hepatic function must fulfil the following criteria:

7. Hepatic impairment classified as Child-Pugh A (score 5-6 points) or Child-Pugh B (score 7-9 points)

8. Absence of clinically significant abnormalities, as based on a complete medical history including a full physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests at both screening and admission to trial site, with the exception of findings that in the opinion of the investigator are consistent with the participant's hepatic impairment.

9. Medication and/or treatment regimens must have been stable (i.e., no dose adjustments) for at least 4 weeks prior to the screening period and should be kept stable until study completion.
   Fluctuating treatment regimens may be considered for inclusion on a case-by-case basis if the underlying disease is under control in the opinion of the investigator and must be agreed to by both the investigator and the sponsor's medical monitor.

3.3.2.3 Inclusion criteria applying only to participants with normal hepatic function

In addition to the inclusion criteria given in Section 3.3.2.1, participants with normal hepatic function must fulfil the following criteria:

10. Individually matched to participants with hepatic impairment according to sex, age, and weight

11. Absence of clinically significant abnormalities identified by a detailed medical history, full physical examination, vital signs and 12-lead ECG at both screening and admission to trial site

12. Absence of clinically significant abnormalities identified by a laboratory test at screening visit

3.3.3 Exclusion criteria

3.3.3.1 Exclusion criteria applying to all participants

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

1. Any evidence of a concomitant disease assessed as clinically relevant by the investigator

2. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the PK of the trial medication (except appendectomy or simple hernia repair)

3. Diseases of the CNS (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)

4. History of relevant orthostatic hypotension, fainting spells, or blackouts

5. Relevant chronic or acute infections

6. 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 or squamous cell carcinoma in situ of the skin or in situ carcinoma of uterine cervix

7. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

8. Use of drugs within 30 days (or 5 of its half-lives, whichever is longer) of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)

9. Intake of an investigational drug in another clinical trial within 60 days (for multiple dose studies) / within 30 days (for single dose studies) or 5 half-lives (whichever is longer) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered

10. Intake of strong CYP3A inhibitors, e.g., amprenavir, indinavir, nelfinavir, ritonavir, itraconazole or ketoconazole within 30 days or 5 half-life times (whichever is longer) to administration of trial medication.

11. Smoker (more than 15 cigarettes or 5 cigars or 5 pipes per day)

12. Inability to refrain from smoking on specified trial days

13. Alcohol abuse (consumption of more than 10 g per day for females and 20 g per day for males)

14. Drug abuse or positive drug screening

15. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

16. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial

17. Inability to comply with the dietary regimen of the trial site

18. A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)

19. 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

20. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection

21. For female participants: Lactation, pregnancy or positive pregnancy test, or plans to become pregnant during the trial or within 7 days after trial completion

22. Active vasculitis, unstable or uncontrolled within 8 weeks prior to Visit 1 or during the screening period.

23. History of vasculitis

24. Relevant immunodeficiency

25. Patients with active TB at Visit 1 or medical history of incompletely treated TB.

26. Any suicidal behaviour in the past 2 years (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).

27. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 and/or Visit 2 predose (i.e., active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).

28. Cardiovascular diseases, any of the following:

    a. Severe hypertension within 3 months of Visit 1
    b. Myocardial infarction, stroke or transient ischaemic attack within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1

29. Chronic kidney disease with eGFR less than 60 ml/min/1.73m^2 at Visit 1 (CKD-EPI formula or Japanese version of CKD-EPI for Japanese patients)

3.3.3.2 Exclusion criteria applying only to participants with hepatic impairment

In addition to the exclusion criteria listed in Section 3.3.3.1, participants with hepatic impairment fulfilling any of the following criteria will not be included into the trial:

30. A marked prolongation of QT/QTc interval (such as QTcF intervals that are repeatedly greater than 480 ms in males or repeatedly greater than 500 ms in females) or any other relevant ECG finding at screening

31. Repeated measurement of systolic blood pressure outside the range of 90 to 170 mmHg, diastolic blood pressure outside the range of 50 to 100 mmHg, or pulse rate outside the range of 50 to 90 bpm

32. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, except for laboratory values outside the reference range due to underlying disease

33. Thrombocytes < 40.000 10E9/L

34. Gastrointestinal bleeding within 3 months of Visit 1

35. Encephalopathy > grade II or the time needed for the Number Connection Test exceeds 80 seconds

36. Oesophageal varices > stage 2

37. Severe ascites

3.3.3.3 Exclusion criteria applying only to participants with normal hepatic function

In addition to the exclusion criteria listed in Section 3.3.3.1, participants with normal hepatic function fulfilling any of the following criteria will not be included into the trial:

38. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator

39. 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

40. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg (for participants older than 60 years: 90 to 150 mmHg), diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm

41. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

42. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Participants 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 participant is removed from or withdraws from the trial prior to the administration of trial medication, the data of this participant will not be entered in the CRF and will not be reported in the CTR.

If a participant is removed from or withdraws from the trial after the 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 EoS examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2), the discontinued participant 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 participant.

3.3.4.1 Withdrawal from trial treatment

An individual participant will be withdrawn from trial treatment if:

- The participant wants to withdraw from trial treatment. The participant will be asked to explain the reasons but has the right to refuse to answer
- The participant 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 participant cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.

- The participant needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The participant can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, AEs, or diseases)
- Participants with normal hepatic function: The participant 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
  Participants with impaired hepatic function: Elevation of AST and/or ALT of at least 3-fold together with an increase in total bilirubin of at least 2-fold compared to screening values
- The patient exhibits suicidality, in the clinical judgement of the investigator or according to the following criteria:
  - any suicidal behaviour (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
  - any suicidal ideation of type 4 or 5 in the C-SSRS (i.e., active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
- If any of the following AEs is reported, the treatment has to be discontinued:
  - Severe or serious infections, opportunistic or mycobacterium tuberculosis infections
  - Malignancies
  - Vasculitis

Of note, depending on the current status of the COVID-19 pandemic, all participants with confirmed SARS CoV-2 infection will be handled in accordance with local guidance and SOPs meaning that any confirmed SARS CoV-2 infection during the conduct of the trial will lead to discontinuation of the participant (refer to Section 1.4.2).

In addition to these criteria, the investigator may discontinue participants at any time based on his or her clinical judgement.

If it is known that a participant becomes pregnant during the trial, she is to be removed from the trial. The participant is to be followed until she has given birth or until the end of the pregnancy. The participant's data are to be collected until the end of the trial (last visit of last participant) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.

If new efficacy or safety information becomes available, BI will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all participants or take any other appropriate action to guarantee the safety of the trial participants.

3.3.4.2 Withdrawal of consent to trial participation

Participants may withdraw their consent to trial participation at any time without the need to justify the decision. If a participant wants to withdraw consent, the investigator should be involved in the discussion with the participant and explain the options for continued follow-up after trial discontinuation

3.3.4.3 Discontinuation of the trial by the sponsor

BI 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, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the participants show drug-related and clinically relevant AEs of moderate or severe intensity, or if more than two participants have drug-related severe non-serious AEs, or if at least one drug-related SAE is reported

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

In case more than 2 participants do not complete the trial in any trial group (including participants non-evaluable for PK), additional participants may be treated in this respective trial group, i.e., ‘replaced‘, if considered necessary to reach the objective of the trial. Participants who withdraw or are withdrawn from 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 participants will be replaced. The total number of replacements may not exceed 1/3 of the total number of evaluable participants anticipated to complete the trial. A ‘replacement’ participant will be assigned a unique trial participant number, and will be assigned to the same treatment as the participant he or she replaces. The ‘replacement’ participant does not have to have the same gender he/she replaces, but the distribution of at least 25% of each gender per group has to be adhered to.

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 (iCF formulation)

Source: BI Pharma GmbH & Co. KG, Germany

Unit strength: 18 mg

Posology: 1-0-0

Mode of administration: Oral

4.1.2 Selection of doses in the trial

The dose of 18 mg of BI 1015550 selected for this trial is the expected therapeutic dose that is used in clinical drug development (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment investigated in this trial. The participants with hepatic impairment and the matching participants with normal hepatic function will be assigned to treatment groups according to the Child-Pugh classification and as control groups as outlined in Table 4.1.3: 1.

Table 4.1.3: 1 Trial treatment groups

Treatment Groups	Child-Pugh classification	Child-Pugh score (points)	Number of participants
Group 1 (mild hepatic impairment)	A	5-6	8
Group 2 (moderate hepatic impairment)	B	7-9	8
Group 3 (matching participants with normal hepatic function individually matched to participants of Group 1)	-	-	8
Group 4 (matching participants with normal hepatic function individually matched to participants of Group 2)	-	-	8*

* if a participant of Group 3 is matching by age (± 10 years), gender, and weight (± 15%) to participant of Group 2, this participant will also be considered in Group 4 (i.e., one participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment). Hence, the sample size of participants to be treated for the composition of Groups 3 and 4 may be below 16.

Once a participant number has been assigned, it cannot be reassigned to any other participant.

Dosing will start with 4 participants of Group 1. Participants in this subcohort may be treated on the same calendar day. After review of safety data (see Section 3.1) and decision to continue, all participants may be treated in one cohort, i.e., all participants may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the groups may be split into several cohorts as required. For discussion of trial-associated risks and safety measures, see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This is a non-randomised, open-label, individual-matched parallel design trial. All participants will receive the same active treatment. The treatment to be evaluated is summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1015550	Film-coated tablet	18 mg	1 tablet (18 mg) single dose for 1 day	18 mg

Administration of trial medication will be performed after participants 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 participants who are in a sitting/standing 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.

Participants will be kept under close medical surveillance until 72 h after drug administration. During the first 4 h after drug administration, participants are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture), except for examinations and assessments.

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. There will be only one treatment, so the treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The IMPs will be provided by BI. They will be packaged and labelled in accordance with the principles of 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 participant information form. The EudraCT number is indicated on the title page of this protocol as well as on the participant information and informed consent forms.

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 CTP by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- 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 CTP

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

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 participant, 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 participants. The investigator or designee will maintain records that document adequately that the participants were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal 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.

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 AE require treatment, the investigator can authorise symptomatic therapy. In those cases, participants 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 for participants with normal hepatic function, except for hormonal contraceptives or ovary hormone replacement. In participants with hepatic impairment, contraceptives as well as concomitant medication for treatment of the hepatic or other concomitant diseases are allowed.

Strong CYP3A inhibitors are restricted medication in all trial participants due to potential drug-drug interactions (see Appendix 10.2). See also Section 3.3.3 for excluded medication.

If necessary, short-term use of ibuprofen or acetylsalicylic acid is acceptable for symptomatic treatment of AEs.

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the participants 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. Only participants with diabetes will receive a snack at 2 h post dose, if necessary.

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 at 2 h and 4 h post-dose (mandatory for all participants). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements are not permitted from 7 days before the administration of trial medication until after the last PK sample is collected.

Products containing St. John's wort (*Hypericum perforatum*) are not permitted from 30 days before the administration of trial medication until after the last PK sample is collected.

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 administration of trial medication.

Smoking is not allowed from 10 h before until 8 h after administration of trial medication.

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

4.2.2.3 Contraception requirements

If WOCBP are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

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.

Participants 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.

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 EoS examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of body weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures as well as pulse rate or HR (HR is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted]) at the times indicated in the Flow Chart, after participants have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

Body temperature will be monitored as part of vital signs assessment if still needed due to the current status of the pandemic. Body temperature will not be entered into the eCRF.

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 participants 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 WBC 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	X	X
	Prothrombin time – Quick	X	X	X
	Prothrombin time – INR (International Normalisation Ratio)	X	X	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
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
	FSH (if applicable)	X	--	--
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
	Albumin	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
	Calcium	X	X	X
	Magnesium	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 on Days -1, 2 and 4 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (EoS examination)

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 WOCBP will be performed at screening, prior to treatment, and as part of the EoS examination. Drug screening will be performed at screening and prior to treatment.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) Hepatitis B DNA PCR (quantitative)[2]
Pregnancy test (serum at screening and Day -1) and urine at EoS)	Beta human chorionic gonadotropin (beta-HCG)
COVID-19 (nasopharyngeal swab)[1]	SARS CoV-2 PCR test (screening) and antigen test on Day -1

[1] if needed due to the current status of the pandemic, evaluation will be performed at screening and shortly (within 72 h) before admission to trial site as per Flow Chart.

[2] to be conducted if Hepatitis B core antibody is positive and Hepatitis B surface antigen is negative.

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. ACE AF-33, [redacted]) will be performed prior the 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 at [redacted], with the exception of urine drug screening, dipstick urinalysis (Combur Test), and urine pregnancy tests. These tests will be performed at the trial site using Drug-Screen Multi 10TC Urine (distributed by nal von minden) and meditrol hCG, urine test stripe (distributed by [redacted] respectively, or comparable test systems.

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

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 (CardioSoft EKG System, [redacted] at the times provided in the Flow Chart.
To achieve a stable HR at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all participants are at complete rest.
All ECGs will be recorded for a 10 sec duration after participants 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 ECGs will be stored electronically on the Muse CV Cardiology System [redacted]. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.
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 participant 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 assessments

5.2.5.1 Suicidal risk (C-SSRS)

Prospective monitoring will be conducted throughout this trial using C-SSRS.

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

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the ‘screening/baseline’ version) with the aim to exclude participant’s suicidal ideation type 4 to 5 within the preceding 3 months or at Visit 1 or any suicidal behaviour in the past 2 years. The lifetime history of suicidal ideation and behaviour will also be recorded.

After Visit 1, the assessment ‘since last visit’ will be performed at each clinic visit (‘since last visit’ version).

Appendix 10.1 provides details how the C-SSRS will be assessed.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.2.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An 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.

<u>SAE reporting in case of suicidal risk assessed by the C-SSRS</u>

All C-SSRS reports of suicidal ideation type 4 and 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator.
For 'self-injurious behaviour, no suicidal intent' (type 11) standard AE/SAE reporting rules are to be applied.
For each negative report (Suicidal ideation type 1, 2, or 3) after the start of the trial, the investigator is to decide based on clinical judgement whether it represents an AE as defined in the CTP, and if it is considered an AE then it must be reported accordingly.

<u>Adverse event report for diarrhoea events</u>

In case of events of diarrhoea the following definitions should be followed:

- Diarrhoea is defined ≥3 loose/liquid stools per day (WHO definition)
- Diarrhoea episode = 2 diarrhoea episodes are separated by at least 7 days without any diarrhoea

5.2.6.1.2 Serious adverse event

An 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

In accordance with the EMA initiative on Important Medical Events, BI 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 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 DILI that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - 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
  - 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. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

- Vasculitis events

In this CTP, 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.

The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning.

In case of (suspected) events of vasculitis, further work-up and management as outlined in Section 4.2.1 has to be followed, including biopsy, appropriate imaging/angiography, laboratory measures (e.g. ESR, additional lab sample for immunological and further inflammation markers).

- Serious infections, opportunistic or mycobacterium tuberculosis infections.

  These include Pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy (PVAN), Cytomegalovirus (CMV), post-transplant lymphoproliferative disorder (Epstein–Barr virus [EBV]), 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), HCV progression [R17-2617]

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

Infections classified as 'severe' are considered as AESIs, see Section 5.2.6.1.4.

5.2.6.1.6 Causal relationship of AEs

Medical judgement 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
- 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)

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, 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

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 participant's end of trial (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 participant's EoS:
    - 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 h 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 participant's EoS, 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 participant 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 h) 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 PK, 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 and [redacted] concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into a 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 x g to 4000 x g and 4 to 8 °C within 1 h after blood draw. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The remaining plasma will be transferred into a second polypropylene tube. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 2 h, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. 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]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between PK and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor participants' safety and to determine PK parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, suicidal risk, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The PK parameters and measurements outlined in Section 5.3 are generally used for the 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.

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

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min during the inhouse period, and ± 2 h for ambulatory visits.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the procedures 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 PK parameters.

To allow for a streamlined operational conduct of trials at trial site, the following flexibility as regards time-windows for PK sampling times will be allowed:

- Predose: within 2 h prior to drug administration
- Postdose:
  - From dosing until 2 h: ± 2 min;
  - >2 h until 4 h: ± 5 min;
  - >4 h until 72 h: ± 15 min;
  - >72:00: ± 60 min

If a participant 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 participants 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 5.2.5.

6.2.2 Treatment period

On Day -1 of the treatment period, trial participants will be admitted to the trial site. They will be kept under close medical surveillance for at least 72 h following drug administration on Day 1. The participants will then be allowed to leave the trial site on Day 4 after formal assessment and confirmation of their fitness. On all other trial days, participants will come to the trial site for ambulatory visits.

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 CTP and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining participant's written informed consent until the EoS 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.

Participants who discontinue prematurely 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

To assess the effect of hepatic impairment on the PK of BI 1015550, the relative bioavailability will be estimated by the ratios of the geometric means of the respective pairwise comparison of interest for the primary and secondary endpoints, i.e., for each hepatic impairment group vs. the respective control group. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

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 participants who were treated with one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all participants in the treated set (TS) who provide at least one primary or secondary PK endpoint and who were 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 participant will be included in the PKS, even if he/she contributes only one of the main PK parameter value to the statistical assessment. Descriptive and model-based 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 PK parameters listed in Section 2.1 and 2.2.2 for drug BI 1015550 [redacted] will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a participant will be included in the statistical 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 participant’s data will be documented in the CTR.

Important protocol deviations may be

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

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

- The participant 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 participants experiencing emesis),
- A predose concentration is >5% C_{max} value of that participant
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a participant 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 PK parameters. Concentrations used in the PK calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include the effect ‘degree of hepatic impairment’ as a fixed effect and ‘matched pair’ as random effect. The model is described by the following equation:

$y_{km} = \mu + \tau_k + s_m + e_{km}$, where

y_{km} = logarithm of response measured on participant m with degree of impairment k,
μ = the overall mean,
τ_k = the effect of the k^{th} degree of impairment, k = 1 for no impairment (control) and k = 2, 3 for Child-Pugh class A and B, respectively,
s_m = the effect of the m^{th} matched pair, m=1, …, 8,
e_{km} = the random error associated with the k^{th} degree of hepatic impairment for matched pair m
where e_{km} is assumed to be independent and identically normally distributed.

The model described above will be fitted separately for the two hepatic impaired groups, i.e., one model for the participants with moderate hepatic impairment and their matched controls, and one model for the participants with mild hepatic impairment and their matched controls.

For evaluation of each primary endpoint, the difference between the expected means for $\log(\tau_k)$-$\log(\tau_l)$, for $k>1$, will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% CIs will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

In addition to the model-based approach, all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

[redacted]

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated participants (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

Hepatic function groups 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 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 intake of trial medication and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to EoS examination 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 of the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.2 and will be summarized as such. Results of the C-SSRS will be provided as listing.

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

In general, unless otherwise specified in the TSAP, the last non-missing measurement prior to study treatment will be used as baseline for safety variables.

Laboratory data will be compared to their reference ranges. Values outside the reference range 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 formal interim analysis is planned for this trial.

A preliminary, exploratory analyses of all available or specific data (e.g. safety, PK) may be performed prior to final database lock to inform other activities during the development of BI 1015550. In case of preliminary assessment of PK data, the PK parameters will be calculated according to the relevant BI internal procedure. In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The possible preliminary PK analysis will provide individual and gMean concentration profiles and summary statistics of PK parameters per group. No inferential statistical preliminary 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

The trial will not be randomised, thus this section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a maximum of 32 participants in the trial: 8 participants with mild hepatic impairment (Child-Pugh A), 8 participants with moderate hepatic impairment (Child-Pugh B) and up to 16 matched control participants with normal hepatic function will be treated. Note, one participant with normal hepatic function may match a participant in only one or in both groups with hepatic impaired participants. The matching criteria are described in Section 3.1.

The planned sample size is not based on a power calculation but is considered as sufficient to detect major differences between the different groups of participants with hepatic impairment and the respective control group with participants with normal hepatic function. Furthermore, a sample size of 8 participants in each hepatic impairment and control group is considered sufficient for hepatic impairment trials [R05-0337].

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), the EU directive 2001/20/EC 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 BI 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.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

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 IRB / IEC and 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 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 participant.

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 participant 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 participant 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 participant, documented in their medical records, would be acceptable.

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

If the participant 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(s) must retain the source and essential documents (including ISF) according to contract or 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.

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.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted] under the supervision of the Principal Investigator.

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 (CT Leader), 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 (CT Managers), 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 ([redacted]

Analyses of BI 1015550 and BI 764333 concentrations in plasma will be performed at [redacted]

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 appointed by BI, 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

P15-07539 Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015; 192(2): e3-e19.

P17-10582 Flaherty KR, Brown KK, Wells AU, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res 2017; 4: e000212.

P18-04729 Wells AU, Brown KK, Flaherty KR, et al. IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J 2018; 51:1800692.

P18-06345 Sisson TH, Christensen PJ, Muraki Y, et al. Phosphodiesterase 4 inhibition reduces lung fibrosis following targeted type II alveolar epithelial cell injury. Physiol Rep 2018; 6(12): e13753.

P19-01738 Cottin V, Wollin L, Fischer A, et al. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev 2019; 28:180100.

P20-01299 Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. Respir Res 2020; 21(1):32.

P22-03204 Raghu G, Remy-Jardin M, Richeldi L, et al. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Asociacion Latinoamericana de Torax. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205(9):e18-e47

R05-0337 United States Food and Drug Administration (FDA). Guidance for Industry “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling”. May 2003.

R05-0340 European Medicines Agency (EMA): Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. CPMP/EWP/2339/02. 17 Feb 2005

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

R19-0854 Kolb M, Vasakova M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res 2019; 20(1):57.

9.2 UNPUBLISHED REFERENCES

c02094779 [redacted] Investigator's Brochure BI 1015550 for 1305.P3, 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). 1305.0002.

c20307414 Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects. 1305-0020.

c22991937 Safety, tolerability and pharmacokinetics of single and multiple rising oral doses of BI 1015550 in healthy subjects. 1305-0011.

c24902949 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.

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.

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.

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.

c39775503 [redacted] Assessment of requirement for male contraception. Memo. 09 June 2022

n00201897 In vitro determination of BI 1015550 protein binding in human and animal plasma and in human serum albumin and α1-acid glycoprotein solutions. (DM-11-1046).

n00201905 In vitro blood cell partitioning of 14C-BI 1015550 in rat, Göttingen minipig, and human blood. (DM-11-1045).

n00261666 BI 1015550: Metabolite profiling in plasma after multiple oral administration to healthy volunteers and metabolite exposure determination in human and the relevant toxicity species.

n00290709 A fertility and early embryonic development to implantation study of BI 1015550 by oral gavage in male and female rats. CRL study no. 9001829, BI no. 21R070.

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

For reprints of the C-SSRS contact [redacted] *tate Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION *The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.* Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

For reprints of the C-SSRS contact [redacted] *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

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

Most Severe

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

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

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

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

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

Version 1/14/09

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

10.2 LISTING RESTRICTED CONCOMITANT MEDICATION

10.2.1 Strong CYP3A4 inhibitors

- boceprevir
- ceritinib
- clarithromycin
- cobicistat
- conivaptan
- diltiazem
- idelalisib
- indinavir
- itraconazole
- ketoconazole oral administration
- LCL161
- mifepristone
- mibefradil
- nefazodone
- nelfinafir
- posaconazole
- ribociclib
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- troleandomycin
- VIEKIRA PAK2
- voriconazole

10.2.2 Combinations of CYP 3A4 inhibitors

- danoprevir/ritonavir
- elvitegravir/ritonavir
- indinavir/ritonavir
- lopinavir/ritonavir
- paritaprevir/ritonavir/ombitasvir/dasbuvir
- saquinavir/ritonavir
- tipranavir/ritonavir

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		14 Dec 2022
EudraCT number **EU number**		2022-002811-45
BI Trial number		1305-0027
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1. Synopsis and Section 3.3.2 Inclusion Criteria 2. Section 3.3.3 Exclusion Criteria 3. Section 10.1 Columbia Suicide Severity Rating Scale
Description of change		1. Inclusion Criteria no. 2 Age changed to 18-79 years inclusive 2. Exclusion Criteria no. 21: For female participants: Lactation, pregnancy or positive pregnancy test, or plans to become pregnant during the trial or within 7 instead of 30 days after trial completion 3. Change of screenshot for C-SSRS Baseline/Screening Version
Rationale for change		1. BfArM Request 2. Inconsistency between Inclusion Criteria no. 2 and Exclusion Criteria no. 21 3. Incorrect screenshot for Baseline/Screening Version used

11.2 GLOBAL AMENDMENT 2

Date of amendment		30 Mar 2023
EudraCT number **EU number**		2022-002811-45
BI Trial number		1305-0027
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1. Abbreviations 2. Section 3.3 Assessment of Encephalopathy and description of the Number Connection Test (NCT) added 3. Section 3.3.3.2 Exclusion criterion 35 (Encephalopathy) updated with NCT performance 4. Section 8.7. Administrative Structure of the trial
Description of change		1. NCT added 2. Assessment of Encephalopathy added 3. Exclusion criterion 35 (Encephalopathy) updated with NCT performance 4. Name [redacted] added to [redacted]
Rationale for change		1. Definition of Abbreviation was missing 2. Description of procedure was missing 3. Description of procedure was missing 4. Name added to Lab Address [redacted]

APPROVAL / SIGNATURE PAGE

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Title: Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	30 Mar 2023 15:16 CEST
Author-Clinical Trial Leader		30 Mar 2023 16:13 CEST
Approval-Clinical Program [redacted]		30 Mar 2023 18:13 CEST
Verification-Paper Signature Completion		03 Apr 2023 09:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed