Boehringer Ingelheim

Clinical Trial Protocol

	Document Number: **c40079634-02**
EudraCT No.	2022-003080-18
BI Trial No.	1305-0025
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 renal impairment (severe and moderate) as compared with individually matched male and female participants with normal renal 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 kidney problems
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Tel: [redacted] Fax: [redacted]
Current Version, Date	Version 2.0, 10 Jan 2023
Original Protocol Date	25 Nov 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	25 Nov 2022
Revision date	10 Jan 2023
BI trial number	1305-0025
Title of trial	Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of renal impairment (severe and moderate) as compared with individually matched male and female participants with normal renal 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 renal impairment compared to individually matched participants with normal renal function will be assessed.
Trial objective(s)	To investigate the effect of severe and moderate renal impairment on the pharmacokinetics of BI 1015550
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1015550 Secondary endpoints: $AUC_{0-\infty}$ of BI 1015550
Trial design	Open-label, non-randomised, single dose, parallel, individual-matched design
Number of participants **total entered**	32* * additional participants may be included to ensure that the study objectives are reached
on treatment	• *Group 1:* 8 participants with severe renal impairment • *Group 2:* 8 participants with normal renal function matching Group 1 ** • *Group 3:* 8 participants with moderate renal impairment • *Group 4:* 8 participants with normal renal function matching Group 3** ** Each participant with normal renal function may be matched to multiple participants with renal impairment across groups (i.e., Group 1 and Group 3) and can be matched to only 1 participant within a renal impairment group. Thus, a participant with normal renal function may be in Group 2 as well as in Group 4 and the total sample size may be 24 to 32 participants.

Diagnosis	Participants with renal impairment (severe and moderate) and participants with normal renal function (matched controls to the participants with renal impairment)
Main inclusion criteria	Male/female participants (at least 25% of each gender), age of 18-79 years (inclusive), body mass index (BMI) of 18.5 to 35.0 kg/m^2 (inclusive) with renal impairment (severe, moderate) based on assessment of eGFR and not requiring dialysis: • Moderate renal impairment: 30-59 mL/min/1.73m² • Severe renal impairment: 15-29 mL/min/1.73m² Participants with normal (≥90 mL/min/1.73m^2) renal function age of 18-79 years (inclusive), BMI of 18.5 to 35 kg/m^2 (inclusive) – individually matched by age (± 10 years), gender, weight (± 15%) and race to the participants with renal impairment.
Test product **dose** **mode of administration**	BI 1015550 tablet, iCF 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 renal 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 renal 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 renal 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 [8]	PK blood [9]	PK urine [10]	Suicidality assessment [14]	12-lead ECG [11]	Vital signs (BP, PR) [12]	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[13]	B[5]					x[13,15]	x
	1	-2:00	06:00			x[2]	x[2,7]	x[2]	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)		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			x	┼		x	x	x
		36:00	20:00			x	┼				x
	3	48:00	08:00			x	┼ |				x
	4	72:00	08:00	Breakfast (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 eGFR, drug screening, alcohol breath test, serology, and SARS-CoV-2 PCR test, serum pregnancy test in WOCBP, and HbA1c determination in participants with diabetes), 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. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96 and 96-120 h.
8. Letters A, B and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
9. For details of PK blood sampling, refer to Section 5.3.2.1.
10. For details of PK urine sampling, refer to Section 5.3.2.2.
11. For details of 12-lead ECG, refer to Section 5.2.4.
12. For details of vital signs evaluation, refer to Section 5.2.2.
13. Including assessment of body temperature (if needed due to the current status of the pandemic).
14. For details of suicidality assessment, refer to Section 5.2.5.1.
15. Including measurement of body weight at this time point.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

[redacted]	[redacted]
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ANOVA	Analysis of variance
$AUC_{0-24,ss}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to time point 24 h in steady state
$AUC_{0-\infty}$	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
[redacted]	[redacted]
AV	Atrioventricular
BI	Boehringer Ingelheim
Bid	*Bis in die* (twice daily)
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	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
[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	Clinical Trial
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-foetal development
eGFR	Estimated glomerular filtration rate
EoS	End of Study (synonym for End of Trial)
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEED	Fertility and early embryonic development
[redacted]	[redacted]
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
gMean	Geometric mean
GMP	Good Manufacturing Practice
HbA1c	Glycated haemoglobin
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
iCF	Intended commercial formulation
IEC	Independent Ethics Committee

ILD	Interstitial lung disease
IPD	Important protocol deviation
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
IUS	Intrauterine hormone-releasing system
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOAEL	Lowest Observed Adverse Effect Level
MACE	Major Adverse Cardiovascular Events
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	[redacted]
NOAEL	No Adverse Effect Level
NOEL	No observable effect level
PCR	Polymerase chain reaction
PDE4	Phosphodiesterase 4
PDEi	Phosphodiesterase inhibitor
PE	Polyethylene
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SOP	Standard operating procedure
SRD	Single-rising dose
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TMF	Trial master file

TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
UGT	Uridine 5'-diphospho-glucuronosyl transferase
UID	Use of intrauterine device
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
[redacted]	[redacted]
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

BI 1015550, an oral preferential inhibitor of the PDE4B isoenzyme which hydrolyses and inactivates cAMP), 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 s, there is a group of patients with different underlying 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 [P17-10582, P18-04729, P19-01738, R19-0854, 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 Idiopathic Pulmonary Fibrosis [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 isoform with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, as well as available pre-clinical 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].

1.2.1.1 Non-clinical pharmacokinetics

Potential DDIs may occur for concomitantly administered medications that are substantially metabolised by CYP3A4, CYP2C8, or CYP2C9 due to induction of CYP3A4, CYP2C8, and CYP2C9 by BI 1015550 at the current therapeutic dose of 18 mg twice daily (bid) [redacted]. In addition, as CYP3A is predicted to contribute to ~70% of the hepatic metabolism of BI 1015550, concomitant therapies that are inhibitors or inducers of CYP3A may cause clinically significant changes in BI 1015550 exposure.

BI 1015550 is a P-gp substrate. As such, BI 1015550 exposure could be affected by co-administered drugs that modulate P-gp activity. One major metabolite, [redacted], has been identified in human plasma.

1.2.1.2 Non-clinical safety pharmacology and toxicology

Safety pharmacology

BI 1015550 administration did not result in any adverse effects on CNS, respiratory, liver, renal, and GI functions. Cardiovascular telemetry studies in the minipig and electrocardiographs recorded during the 2-week minipig toxicity study at doses of 3, 10, and 30 mg/kg indicated non-biologically significant changes in PR interval and HR, respectively. Because these changes were not of a significant magnitude, they were not considered adverse, but may indicate a threshold effect for cardiovascular changes above 30 mg/kg.

Single and repeat-dose toxicity

No single-dose toxicity studies have been conducted with BI 1015550. BI 1015550 has been assessed in repeat dose toxicity studies in the rat, minipig, and monkeys of up to 26, 39, and 13 weeks, respectively. Vasculopathy and mortality secondary to vasculopathy are the primary findings defining the NOAEL and LOAEL.

BI 1015550 treatment-related adverse findings in rats included vasculopathy in the stomach, duodenum, jejunum, ileum, colon, Peyer's patches, mesentery, pancreas, and vagina and hypertrophic osteopathy. The rat exhibited a [redacted] in the 26-week study.

In minipigs, perivascular/vascular degeneration/necrosis was observed at high dose levels in multiples tissues such as the mesenteric connective tissue or parenchyma of liver, gallbladder, kidney, urinary bladder, ovary, vagina, cervix, stomach, lungs, spleen, heart, coronary artery, peri-aortic, sciatic nerve, and connective tissues around the tarsus. A [redacted] was determined in the 39-week minipig study, in contrast to a previous 13-week study with a [redacted].

Exposures at the NOAEL in rats and the LOAEL in minipigs were equivalent to human exposure at 18 mg bid.

In monkeys at high exposure levels, focal myocardial degeneration or necrosis was observed in the interventricular septum near the apex of the heart, but accompanying vascular changes were not apparent. In the 13-week study in monkeys, [redacted] was determined. [redacted]

Toxicities observed in the rat and minipig studies do not preclude administering BI 1015550 to humans. The exposure margin in monkeys, considered the most relevant species to humans, suggests that primates are less sensitive to PDE4i-induced adverse vascular effects.

Genotoxicity

No evidence of mutagenicity was observed in the Ames test and BI 1015550 showed no potential for aneugenic or clastogenic activity in the *in vitro* chromosomal aberration assay or in the *in vivo* micronucleus assay. Therefore, genetic toxicology results have demonstrated that BI 1015550 is not genotoxic. Major human metabolite [redacted] showed no evidence of genotoxicity as well.

Reproductive and developmental toxicity

A FEED study in rats [n00290709] and dose range-finding plus definitive EFD studies in rats and rabbits have been conducted with BI 1015550.

In a FEED study in rats, decreased mating, fertility, and pregnancy indices were observed in males and females at [redacted]. As this dose level caused moribundity/mortality in both sexes due to PDEi-related toxicity, it remains undefined whether toxicity or an effect on male and/or female fertility is the cause. [redacted] No effect on the oestrous cycle was seen in female rats.

In EFD studies in rats or rabbits, no dysmorphogenesis (teratogenicity or skeletal variations) effects or foetotoxicity were observed up to the highest dose levels tested of [redacted] and included an increased number of early resorptions and increased post implantation loss, resulting in a reduced number of live foetuses. No embryo-foetal lethality was observed in rabbits. Therefore, the NOEL for EFD was 3 and 15 mg/kg/day in rats and rabbits. [redacted]

Photosafety

BI 1015550 was negative in an *in vitro* 3T3 NRU phototoxicity assay, suggesting its phototoxic potential is low. No adverse findings were observed in the eyes or skin of the rat or minipig toxicity studies, further suggesting a low likelihood for phototoxicity.

1.2.1.3 Clinical pharmacokinetics

Absorption

After oral administration, BI 1015550 is rapidly absorbed with peak plasma concentrations occurring between [redacted]. After reaching peak concentration, BI 1015550 exhibited bi-exponential disposition kinetics. BI 1015550 plasma exposure had a dose proportional increase following both single- and multiple-dose administration. [redacted]

Administration of BI 1015550 together with standard high-fat and high caloric meal (study 1305-0020) resulted in a delay in absorption as indicated by a shift in [redacted]. Otherwise the PK of BI 1015550 was not clinically significantly changed when taken with food compared to the fasted state (C_{max} decreased slightly by 20%, no change in AUC) [c20307414].

Distribution

Protein binding of BI 1015550 was moderate with 76.7% binding and no evidence of saturation was detected over the concentration range tested (100 – 3,000 nM) [n00201897].

BI 1015550 was preferentially distributed in plasma with a blood cells to plasma ratio of 0.4 [n00201905]. The apparent volume of distribution appeared to be moderate (gMean 111 L in trial 1305-0012 [c25085412]).

Metabolism

BI 1015550 is mainly metabolised by CYP3A with minor contributions from UGTs. In human plasma from healthy volunteers administered with [redacted] [n00261666]. Parent drug BI 1015550 was the most abundant drug-related component in the plasma, accounting for 72% of total $AUC_{0\text{-}24,ss}$. [redacted]

Elimination

The gMean $t_{1/2}$ was around 25 h following single and multiple doses. CL/F at steady state were comparable to the corresponding single-dose parameters. Based on the multiple-dose study with 6 mg and 12 mg bid dosing, approximately 19% of the administered BI 1015550 dose was excreted in urine as unchanged drug at steady state (study 1305-0011 [c22991937]). In the human ADME mass balance study 1305-0016 [c36151567], the total recovery of [^{14}C]BI 1015550-related material was on average 95.0% of the administered dose with 58.0% excreted in faeces and 36.4% excreted in urine where 11.9% was excreted unchanged as parent compound [c36151567].

Drug-drug interaction potential of BI 1015550

Based on the *in vitro* evaluation, BI 1015550 is mainly metabolised by CYP3A with minor contributions from UGTs. Additionally, BI 1015550 is a substrate of P-gp. To further investigate the DDI victim potential of BI 1015550 with regards to CYP3A4 and P-gp, the effect of the strong CYP3A4 and P-gp inhibitor itraconazole on the PK of BI 1015550 was investigated in healthy volunteers (n=16) with 6 mg single dose of BI 1015550 (study 1305-0015 [c24902949]). Itraconazole increased the exposure of BI 1015550 slightly with a [redacted]. Itraconazole reduced the exposure of the metabolite [redacted] to levels below the limit of quantification. Based on *in vitro* evaluation, BI 1015550 has the potential to induce CYP3A4. [redacted]

Based on the current knowledge of BI 1015550's non-clinical evaluation and nintedanib and pirfenidone's labelled ADME characteristics, neither a relevant DDI between BI 1015550 and nintedanib, nor between BI 1015550 and pirfenidone is expected. Results from the Phase II trial 1305-0013 [c37065416] in patients with IPF showed that pre- and post-dose concentration levels of BI 1015550 were similar between patients treated with nintedanib and those not treated with any antifibrotic, suggesting nintedanib did not impact the exposure of BI 1015550. However, a 35%-50% lower exposure was observed in IPF patients on background treatment with pirfenidone [c37065416].

Pharmacokinetics in IPF patients as compared to healthy participants

PK of BI 1015550 was investigated in IPF patients given multiple oral doses of 18 mg bid in study 1305-0012 [c25085412] and study 1305-0013 [c37065416]. Summarised gMean PK parameters obtained after multiple-dose administration (at steady state) are shown in Table 1.2.1.3: 1. The exposure in general did not differ between healthy volunteers and IPF patients with similar accumulation ratio and metabolite [redacted] exposure. [redacted]

Table 1.2.1.3: 1 PK parameters of BI 1015550 after multiple oral doses of 6 mg, 12 mg and 18 mg BI 1015550 twice daily

[redacted]

$_{norm}$ = normalised to dose; $_{ss,norm}$ = normalised to dose at steady state;
[1] Data for t_{max} are presented as median with minimum, maximum; --- not available

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 participants 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 participants, seven clinical studies in healthy participants 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 participants treated with BI 1015550 was observed in study 1305-0011 [c22991937] in healthy volunteers.

In the MRD trial (1305-0002), one participant after multiple doses of 6 mg bid experienced postprandial pain, constipation, lower abdominal pain, lower left quadrant abdominal pain, and increased CRP in blood. These events were classified as drug-related. They were of mild

intensity, with the exception of CRP increase which was of moderate intensity and led to discontinuation of the participant [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 and all AEs leading to discontinuation were reported in the BI 1015550 group. The frequency of SAEs in patients was numerically higher in placebo-treated patients, which was driven by placebo-treated patients without antifibrotic background treatment. Two patients with IPF treated with BI 1015550 had fatal AEs: one case of COVID-19 pneumonia and one case of suspected condition aggravated/suspected vasculitis; in both cases, risk factors were present. 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, 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.

Clinical efficacy

In the proof-of-clinical principle Phase II trial, a relevant treatment effect in favour of BI 1015550 18 mg bid was observed on the primary efficacy endpoint, the change from baseline in FVC at 12 weeks. Treatment with BI 1015550 prevented a decline in FVC in patients with IPF, irrespective of background antifibrotic treatment, in contrast to the placebo groups in which a marked decline in FVC was observed. Thus, treatment with BI 1015550 at 18 mg twice daily preserved lung function in patients with IPF over 12 weeks.

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

1.2.2 Residual Effect Period

[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

The rationale of this trial is to determine if decreased renal function alters the PK of BI 1015550 to such an extent that specific treatment recommendations need to be given in patients.

BI 1015550 is being developed for the treatment of IPF and other forms of progressive pulmonary fibrosis and is likely to be used in patients with impaired renal function. Based on the clinical PK data (see Section 1.2.1), BI 1015550 is mainly metabolised by CYP3A with minor contributions from UGTs and is mainly eliminated via faeces (58.0%) and urine (36.4%). Protein binding of BI 1015550 is moderate with 76.7% binding. [redacted]

In the proof of clinical principle study (1305-0013 [c37065416]), participants with eGFR ≤ 45 ml/min/1.73m^2 were excluded. About 76% of the IPF patients receiving BI 1015550 treatment in this study had CKD (eGFR value less than 90 ml/min/1.73m^2) with a majority of them having mild renal impairment (65 participants) and 9 participants having moderate renal impairment. The gMean steady state trough levels at week 12 were 20% and 28% higher in the groups with mild and moderate renal impairment, respectively, compared to patients with normal renal function. The gMean 3 h post-dose concentrations were 22% and 48% higher in mild and moderate renal impaired patients, respectively, at week 12. However, the overall exposure of BI 1015550 largely overlapped among patients with mild or moderate renal impairment compared with patients with normal renal function.

Impact of mild and moderate renal impairment on the PK of BI 1015550 will be further evaluated in Phase 3 trials. Since participants with mild renal impairment may already constitute a big portion of the Phase 3 patients and participants with severe renal impairment are excluded in Phase 3, the impact of moderate and severe renal impairment on the PK of BI 1015550 will be investigated in this dedicated renal impairment study.

This exploratory trial is designed to investigate the effect of moderate and severe renal impairment on the PK, safety and tolerability of BI 1015550 and its metabolite. The data obtained in this trial will provide a basis for the treatment of patients suffering from IPF with renal impairment.

The design of this trial follows the FDA draft guideline for Industry "Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function –Study Design, Data Analysis, and Impact on Dosing" [R22-3784] and the EMA "Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function" [R22-3783].

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for participants of this trial. 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		
Pharmacokinetic interaction with strong CYP3A4 inhibitors	• CYP450 3A4 is predicted to contribute to ~70% of hepatic metabolism of BI 1015550 • In a DDI trial, the strong CYP3A4 inhibitor (itraconazole) [redacted]	• Potent CYP3A inhibitors are restricted medication.
Vasculitis	• Vasculopathy is an established preclinical toxicity of PDE 4 inhibitors • Vasculitis has been shown in rats and minipigs following oral administration of BI 1015550 but not in monkeys • Vasculitis is listed as an important potential risk for the marketed PDE4 inhibitor apremilast • In marketed PDE4 inhibitors, vasculitis hast not been identified as an adverse drug reaction in humans.	• Active vasculitis (unstable or uncontrolled) is an exclusion criterion for participants. • Close monitoring for AEs of vasculitis.
Reproductive toxicity: foetal loss, decreased fertility	• No teratogenicity was seen in preclinical studies and exposure with BI 1015550 via semen is expected to be very low • In rats, male and female fertility was potentially reduced. Long-term toxicity studies with BI 1015550 in	• WOCBP need to use a highly effective method of contraception. Of note: oral hormonal contraceptives are not considered a highly effective

	rat and monkey showed no microscopic evidence of changes in female reproductive organs or male spermatogenesis • For another PDE4 inhibitor with comparable preclinical findings (class-effect), clinical data showed no effect on male fertility and sperm in humans. • Foetal loss was increased in female rats treated with BI 1015550 • Efficacy of oral hormonal contraceptives can be impacted by potential BI 1015550 CYP3A induction	method due to potential drug interactions. • Thorough counselling of women of childbearing potential about appropriate contraceptive measures. • Repeated pregnancy testing.
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 kg/m^2 is routine inclusion criterion in Phase I • With 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 Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 3 months or at Visit 1 are exclusion criteria. • Prospective monitoring for suicidal ideation and behaviour using the C-SSRS

		• Participant's withdrawal criteria in case of new-onset suicidal behaviour or any suicidal ideation of type 4 or 5 in the C-SSRS.
Severe infections including, serious, opportunistic and mycobacterium tuberculosis infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of severe and serious infections. • Serious infections were balanced between placebo and BI 1015550 in Phase II trial. • [redacted] was more frequently reported under treatment with BI 1015550 in Phase Ic/II but not in Phase I trials and the numbers were very small.	• Screening procedures for infections are defined for this trial. Participants with any relevant chronic or acute infections are excluded from the trial • Treatment of infections should be initiated promptly according to standards of care
Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast. • In preclinical studies with BI 1015550 no adverse cardiovascular findings detected (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 the whole period of 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.	• Participants 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
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).
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	• General risk by venipuncture 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. [redacted] This concentration is approximately 3,500-fold below the most conservative maximum plasma level of 2,300 nM at the NOAEL in rats in a fertility and early embryonic development study [n00290709], and in EFD studies in rats and rabbits. This 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 of 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. Even though an increased risk of SARS-CoV-2 infection - or of a more severe COVID-19 disease in case of such an infection appears unlikely, 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 active infection.

In case of severe COVID-19 infection during the conduct of the trial, treatment with BI 1015550 will not be started which is also applicable for any other active infection. 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 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.

In the current trial, adequate safety monitoring including vital signs, ECG, C-SSRS, safety laboratory, and AE monitoring with a special focus on vasculitis assessment has been implemented.

Taking into account these safety measures, potential risks to participants with normal renal function and those with impaired renal function are considered to be low and outweighed by the benefit of a successful clinical development of BI 1015550 in the context of the unmet medical need.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the effect of severe and moderate renal impairment on the PK of BI 1015550 following oral administration.

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 BI 1015550 in plasma over the time interval from 0 to the last quantifiable data point)

- C_{max} (maximum measured concentration of BI 1015550 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 BI 1015550 in plasma over the time interval from 0 extrapolated to infinity)

[redacted]

2.2.2.3 Safety and tolerability

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

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- Assessment of suicidal ideation and behaviour (C-SSRS)
- 12-lead ECG
- Vital signs (BP, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, parallel matched-group design trial in participants with renal impairment (severe and moderate) and participants with normal renal function (matched controls to the participants with renal impairment). The treatment will be one 18 mg BI 1015550 tablet administered to participants in the fasting state. For details, refer to Section 4.1.

- Group 1: 8 participants with severe renal impairment and not requiring dialysis
- Group 2: 8* participants with normal renal function matching Group 1
- Group 3: 8 participants with moderate renal impairment
- Group 4: 8* participants with normal renal function matching Group 3

*Each participant with normal renal function may be matched to multiple participants with renal impairment across groups (i.e., Group 1 and Group 3) and can be matched to only 1 participant within a renal impairment group. Thus, a participant with normal renal function may be in Group 2 as well as in Group 4.

Matching criteria of the participants with normal renal function to the participants with renal impairment:

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

Each group will contain at least 25% participants (i.e., 2) of each gender.

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.

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)

From preclinical and clinical data (see Section 1.2.1), no clinically relevant increase in exposure to BI 1015550 in patients with impaired renal function is expected.

The group size of 8 participants is considered sufficient for the exploratory evaluation of PK. The assignment of individually matched control participants with normal renal function is a useful method to control for other factors which may influence the PK of BI 1015550 in a renal impaired population.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma and urine concentrations of the analyte. Furthermore, all participants will receive the same dose, and participants will be stratified to the groups according to their renal function.

The PK of BI 1015550 are dose-linear and time-independent, therefore, a single dose study is considered adequate to meet the objectives of the trial.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 male and female participants with severe or moderate renal impairment (at least 25% of each gender per group) and up to 16 individually matched male and female control participants with normal renal function will enter the trial.

The control participants with normal renal function will be recruited from the volunteers' pool of the trial site. Participants with renal impairment will be recruited in cooperation with nephrological centres.

Participants will be assigned to one of the renal function groups (moderate renal impairment, severe renal impairment, normal renal function) based on their eGFR according to CKD-EPI (see Appendix 10.3). The assessment of renal function and assignment to the renal function groups will be conducted by the investigators at the screening examination. In addition, participants with normal renal function will be assigned to a group according to their match to a participant with renal impairment (Table 3.3: 1).

Table 3.3: 1 Overview of group stratification

Group	Renal function	eGFR (mL/min/1.73 m^2)	Number of participants
1	Severe impairment	15 – 29	8
2	Normal renal function	≥90	8*
3	Moderate impairment	30 – 59	8
4	Normal renal function	≥90	8*

* Each participant with normal renal function may be matched to multiple participants with renal impairment across groups (i.e., Group 1 and Group 3) and can be matched to only 1 participant within a renal impairment group. Thus, a participant with normal renal function may be in Group 2 as well as in Group 4.

Participants with normal renal function will be matched individually to a participant with impaired renal function by age (± 10 years), weight (± 15%), race, and gender. One participant with normal renal function may be matched to multiple participants with renal impairment across different groups and can be matched to only 1 participant with renal impairment within a group.

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 impaired renal function and matched control participants with normal renal 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

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

3.3.2.1 Inclusion criteria applying to all participants

1. Male or female participants
2. Age of 18-79 years (inclusive)
3. BMI of 18.5 to 35.0 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Male participants are not required to use contraception
6. WOCBP 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 (IUD) or intrauterine hormone-releasing system (IUS)
   - 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 renal function

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

7. Renal impairment based on assessment of eGFR at screening (moderate renal impairment: 30-59 mL/min/1.73m^2, severe renal impairment: 15-29 mL/min/1.73m^2); participants do not require dialysis and are not anticipated to require haemodialysis or

renal transplantation, and are anticipated to have renal function appropriate to moderate or severe renal impairment for the duration of the study

8. Chronic renal impairment > 12 months (documented renal impairment indicated by reduced eGFR for more than 12 months until screening)
9. Absence of clinically significant abnormalities, as based on a complete medical history including a full physical examination, clinical laboratory tests, vital signs (BP, PR) and 12-lead ECG at both screening and check-in visits, with the exception of findings that in the opinion of the investigator are consistent with participant's renal impairment.
10. 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.

3.3.2.3 Inclusion criteria applying only to participants with normal renal function

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

11. Individually matched to participants with renal impairment according to sex, age, and weight and race
12. eGFR > 90 mL/min/1.73m^2
13. Absence of clinically significant abnormalities identified by a detailed medical history, full physical examination, vital signs and 12-lead ECG at both screening and check-in visits
14. 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

Participants 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 GI tract that could interfere with the pharmacokinetics 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 their 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 (multiple dose trials) / 30 days (single dose trials) 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. Smoker (more than 15 cigarettes or 5 cigars or 5 pipes per day)
11. Inability to refrain from smoking on specified trial days
12. Alcohol abuse (consumption of more than 10 g per day for females and 20 g per day for males)
13. Drug abuse or positive drug screening
14. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
15. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
16. Inability to comply with the dietary regimen of the trial site
17. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
18. Participant is assessed as unsuitable for inclusion by the investigator, for instance, because the participant is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
19. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
20. For female participants: Lactation, pregnancy, or plans to become pregnant during the trial or within 7 days after trial completion, or positive pregnancy test
21. Active vasculitis, unstable or uncontrolled within 8 weeks prior to Visit 1 or during the screening period.
22. History of vasculitis
23. Relevant immunodeficiency
24. Patients with active tuberculosis at Visit 1 or medical history of incompletely treated tuberculosis

25. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
26. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 and/or Day 1 predose (i.e. active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan)
27. 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

3.3.3.2 Exclusion criteria applying only to participants with renal impairment

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

28. A marked prolongation of QT/QTc interval (such as QTc 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
29. Acute renal failure or active nephritis
30. Nephrotic syndrome
31. Impaired hepatic function, including relevant increases in liver enzymes indicating liver disease
32. Relevant diseases for which it can be assumed that the absorption of the study drugs will not be normal (i.e., relevant malabsorption, chronic diarrhoea)
33. Participant under dialysis or planned to start dialysis during participation in the study
34. History of myocardial infarction, cerebrovascular accident or severe arrhythmia within the 6 months prior to the screening visit
35. History of vascular surgery or intervention (e.g., coronary artery bypass, percutaneous transluminal angioplasty etc.) less than 6 months prior to dosing
36. Congestive heart failure of New York Heart Association grade III or IV, severe arrhythmia requiring antiarrhythmic treatment
37. History of clinically significant aortic or pulmonary valve stenosis, or renal artery stenosis
38. Any other disease or condition which could influence the physiological metabolic turnover (e.g., endocrine diseases, severe infections)
39. Significant uncorrected rhythm or conduction disturbances such as a second-or third degree AV block without a cardiac pacemaker, marked QTc prolongation (such as QTc intervals that are repeatedly greater than 480 ms in males or repeatedly greater than 500 ms in females at screening), or episodes of sustained ventricular tachycardia
40. Resting supine systolic BP below 99 or above 179mmHg and resting supine diastolic BP below 50 or above 100 mmHg at screening visit

41. Resting supine HR equal to or below 50 bpm or above 90 bpm, at screening visit
42. Haemoglobin <9 g/dL
43. Serum albumin <30 g/L
44. Platelet count <100 x 10^9/L
45. Other clinically relevant deviations in clinical chemistry (especially liver enzymes) or haematology
46. Participants with diabetes mellitus with a fasting blood glucose >220 mg/dL or glycated haemoglobin (HbA1c) >10%

3.3.3.3 Exclusion criteria applying only to matched participants with normal renal function

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

47. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
48. 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
49. Repeated measurement of systolic BP outside the range of 90 to 140 mmHg (for participants older than 60 years: 90 to 150 mmHg), diastolic BP outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
50. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
51. 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 participants 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 first administration of trial medication, the data of this participant will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2, the discontinued 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:

1. 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
2. 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.
3. The participant needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The participant can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, AEs, or diseases)
5. 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
6. The participant exhibits suicidality, in the clinical judgment 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)
7. 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 judgment.

If it is known that a participant becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the participant 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 treatment discontinuation.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, 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 intensity, or if more than two participants have drug-related severe non-serious adverse events, 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 participants

In case more than 2 participants in any group do not complete the trial (including participants non-evaluable for PK), additional participants may be enrolled and 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 treatment or assessments because of a drug-related AEs 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. In case of enrolment of additional participants, the trial site should ensure the requirements for distribution of gender (‘at least 25% of each gender within each group’) are still met within the comprising group of further on treated and additionally enrolled participants.

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)
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 selected for this trial is one of the standard clinical doses (see Section 1.2).

4.1.3 Method of assigning participants to treatment groups

There is only one treatment investigated in this trial.

Participants with renal impairment and matching control participants will be assigned to treatment groups according to their renal function (Section 3.1).

Groups 3 and 4 will only be conducted if the effect of severe renal impairment on the PK of BI 1015550 is obvious, as described in Section 3.1.

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

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 group 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 participant

This is a non-randomised, open-label, individual-matched parallel design trial. All participants will receive the same active treatment. The treatments to be evaluated are 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) as single dose	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.

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 investigational medicinal products 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 CRA (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

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

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 protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each 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 adverse events 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 except for hormonal contraceptives or ovary hormone replacement. Medications considered as exclusion criteria are also restricted during the trial.

In participants with renal impairment, contraceptives as well as concomitant medication for the treatment of the renal disorder or other concomitant diseases are allowed.

Strong CYP3A inhibitors are restricted medications in all trial participants due to potential DDI (see Appendix 10.2).

Short-term use of ibuprofen and acetylsalicylic acid is acceptable for symptomatic treatment of AEs, if necessary.

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) not allowed from 24 h before administration of trial medication until the end of in-house confinement at the trial site.

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 first administration of trial medication until the end of trial 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 and/or urinary excretion 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, a physical examination, concomitant therapies, and C-SSRS scale.

At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of body weight, recording of AEs, concomitant therapies, and C-SSRS scale.

5.2.2 Vital signs

Systolic and diastolic BP as well as PR or HR (HR is considered to be equal to PR) will be measured by a BP monitor (Dinamap Pro care DPC220x, [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 BP 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 white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	HbA1c (only in participants with diabetes)	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
	Prothrombin time	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	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	--	--
	Oestradiol (if applicable)	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	eGFR/ 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
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
	Calcium	X	X	X
	Phosphate (as Phosphorus, Inorganic)	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, or nitrite 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 Day -1 and 4 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (EoS examination)
* eGFR/CKD-EPI only on Day -1

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to the treatment period, and as part of the end of trial 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 A antibodies (qualitative) 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 in WOCBP (serum at screening and Day -1 and in 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 hours) 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, ACE Instruments) will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening and urine pregnancy tests. The urinalysis (Stix) will be performed with the Combur Test. These tests will be performed at the trial site using Drug-Screen Multi 10TC Urine (distributed by [redacted]) 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 AEs (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 parameters

5.2.5.1 Suicidality assessment

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

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal 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 adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant 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.

SAE reporting in case of suicidal risk assessed by the C-SSRS

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 protocol, and if it is considered an AE then it must be reported accordingly.

Adverse event report for diarrhoea events

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

- Diarrhoea is defined as at least 3 loose or 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

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe

- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.
The following are considered as AESIs:

- Potential severe DILI

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

  - 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 participants 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 trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels. The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning.

- 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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Participants will be required to report spontaneously any AEs. In addition, each participant will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, participants 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 (the 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 participants discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the participants' 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 end of trial:
    - The investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual participant's end of trial, must be followed up until they have resolved, have been sufficiently characterised (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 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for 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 and urine samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of PK 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 an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 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 barcode, BI trial number, participant 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.

5.3.2.2 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (ref. Flow Chart) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 3-L polyethylene (PE) containers and stored in the cooler. Participants are told to empty their bladders at the end of each sampling interval.

Due to the known adsorption (its metabolites) to the container wall and instability of the metabolites, 115.2 g citric acid and 30 mL of 20% Tween 20 solution will be added to the 3-L container prior to the start of urine sampling. The weight of the empty container including citric acid will be determined, 30 mL of 20% Tween 20 will be added, and the weight of the container at the end of each sampling interval will be determined. (however, no correction for the specific gravity of urine is done, i.e. 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurements. If more than one collection container is used in a sampling interval, the contents of all containers have to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a Single PE/PP or glass container, and stirring the mixed fractions for about I min (manually or using a stir bar or other stirring device made of PE, PP, Teflon or glass).

Generally, the collection container should be shaken upon addition of every urine fraction to ensure proper distribution of Tween and urine.

At a minimum, the sample tube labels should list barcode, BI trial number, subject number, visit, and planned collection time. Further information, such as matrix and analyte may also be provided.

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -20°C +/- 5°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After analysis, the urine samples may be used for further methodological investigations (e.g. for stability testing, 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) 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 has been archived.

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 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 participant and possible influence on physiological parameters.

For planned blood sampling times and urine collection intervals, 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 and urine samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining participant's written informed consent until the end of trial examination.

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

6.2.3 Follow-up period and trial completion

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

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

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

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a participant'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 renal 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 renal impairment group vs. the respective control group. Additionally, their 2-sided 90% 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 at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all participants in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in Section 7.2.1.2). Thus, a participant will be included in the PKS, even if he/she contributes only one PK parameter 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 and [redacted] will be calculated according to the relevant BI internal procedures.

Plasma and urine 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 dose of trial medication taken
- Use of restricted medications

Plasma and urine concentrations and/or parameters of a participant 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/urine 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 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 effects accounting for the following sources of variation: ‘degree of renal impairment” as a fixed effect as well as ‘matched pair’ as random effect.

The model is described by the following equation:

$y_{ik} = \mu + s_i + \tau_k + e_{ik}$, where

y_{ik} = logarithm of response measured for the degree of renal impairment k and matched pair i,

μ = the overall mean,

s_i = the effect associated with the i^{th} matched pair, m = 1, 2, …, 8

τ_k = the effect associated with the k^{th} degree of renal impairment, k = 1 for normal renal function (control) and k=2, 3 for moderate, severe renal impaired respectively,

e_{ik} = the random error associated with the degree of renal impairment k for matched pair i

where $s_i \sim N(0, \sigma_B^2)$ i.i.d., $e_{ik} \sim N(0, \sigma_W^2)$ i.i.d. and s_i, e_{ik} are independent random variables (note that the indices ‘B’ and ‘W’ correspond to ‘between’ and ’within’ matched pair variability, respectively).

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

For the evaluation of each primary endpoint, the difference between the expected mean for

log response of renal impaired group k (k=2, 3) – log response of normal control group

(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.

Further exploratory analyses

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

7.2.3 Secondary endpoint analyses

The secondary endpoints (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.

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 the 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 summarised 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.

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 severe renal impairment, 8 participants with moderate renal impairment and up to 16 matched control participants with normal renal function will be treated. Note, one participant with normal renal function may match a participant in only one or in both groups with renal 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 sufficient to detect major differences between the different groups of participants with renal impairment and the respective control group containing participants with normal renal function.

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 participant's treating physician.

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

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

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

8.1 TRIAL APPROVAL, PARTICIPANT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a participant's participation in the trial, written informed consent must be obtained from each participant 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 participant-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional participant information must be given to each participant.

The participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the participant's own free will with the informed consent form after confirming that the participant understands the contents. The investigator or his / her 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 participant 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 participants 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 participant 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 participant file.

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

- Participant identification: gender, year of birth (in accordance with local laws and regulations)
- Participant participation in the trial (substance, trial number, participant number, date participant was informed)
- Dates of participant'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 participant's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a participant 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 participant or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the participant 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 CRA, 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 PARTICIPANT PRIVACY

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

Individual participant 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 participant's personal physician or to other appropriate medical personnel responsible for the participant'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 participant in the whole trial signs informed consent.

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

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

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

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

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 participants 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 participant (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]. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

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 Managers (CT Managers), 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 [redacted] concentrations in plasma and urine 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.

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

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] *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.	**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?*** If yes, describe:	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 ☐
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 ☐
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 ☐
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 ☐
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 available 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

10.3 CKD-EPI FORMULA

eGFR (mL/min/1.73m^2) = 141 x min(SCr/κ, 1)$^{\alpha}$ x max(SCr /κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black]

- SCr (standardized serum creatinine) = mg/dL
- κ = 0.7 (females) or 0.9 (males)
- α = -0.329 (females) or -0.411 (males)
- min = indicates the minimum of SCr/κ or 1
- max = indicates the maximum of SCr/κ or 1
- age = years

See references [R12-1392, R13-4387].

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		10 Jan 2023
EudraCT number **EU number**		2022-003080-18
BI Trial number		1305-0025
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 renal impairment (severe and moderate) as compared with individually matched male and female participants with normal renal 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 2. Section 3.3.2.1 Inclusion Citeria No. 2
Description of change		1. Inclusion Criteria no. 2 Age changed to 18-79 years inclusive in Synopis and section 3.3.2.1
Rationale for change		1. BfArM Request

APPROVAL / SIGNATURE PAGE

Document Number: c40079634 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of renal impairment (severe and moderate) as compared with individually matched male and female participants with normal renal function (an open-label, non-randomised, single dose, parallel, individual-matched design trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	11 Jan 2023 13:46 CET
Author-Clinical Trial Leader		11 Jan 2023 13:49 CET
Author-Trial Statistician		12 Jan 2023 08:14 CET
Verification-Paper Signature Completion		12 Jan 2023 08:54 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed