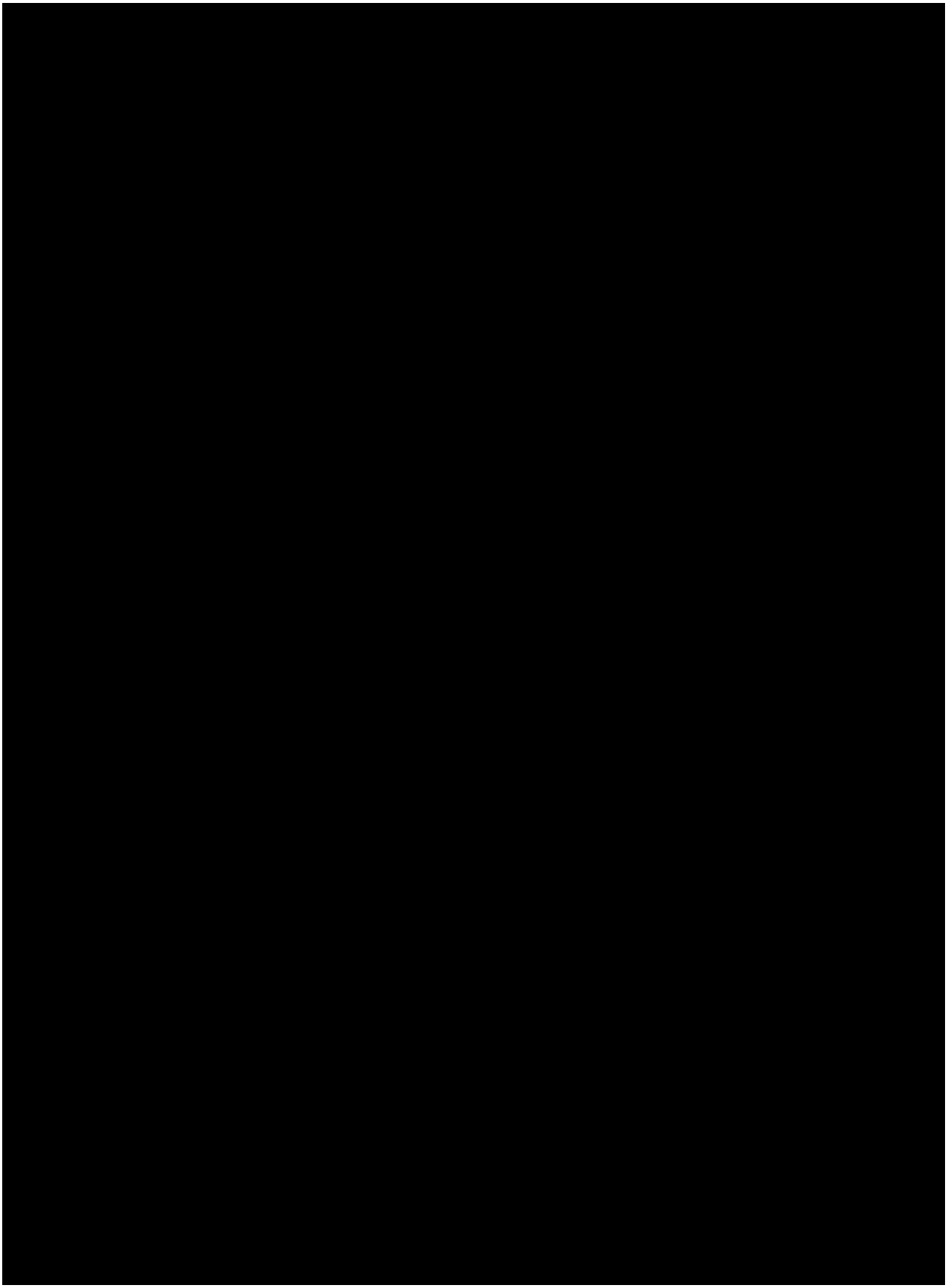
Clinical Trial Protocol

	Document Number: **c41839189-04**
IRAS ID No. **Universal Trial No.**	1008273 U1111-1295-4664
BI (QSC) Trial No.	1305-0026 (QSC301328)
BI Investigational Medicinal Product	BI 1015550
Title	Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects
Lay Title	A study in healthy people to test whether different doses of BI 1015550 have potential to induce heart rhythm abnormalities
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 3.0, 21 MAR 2024
Original Protocol Date	01 SEP 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	01 SEP 2023
Revision date	21 MAR 2024
BI trial number	1305-0026
Title of trial	Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This trial is intended to investigate the effects of BI 1015550 on cardiac safety parameters according to the guideline ICH E14 (CHMP/ICH/2/04 2005) 'The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs'
Trial objective	To evaluate the effects of a single therapeutic and a single supra-therapeutic dose of BI 1015550 on the QT/QTc interval and other ECG parameters
Trial endpoints	*Primary endpoints:* The maximum mean difference between each single dose of [redacted] of BI 1015550 and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration. *Secondary endpoint:* The maximum mean difference between moxifloxacin and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration. (The formal test for assay sensitivity will be based on the results for the pre-selected time points 2, 3 and 4 h post dosing.)
Trial design	Double-blind (moxifloxacin: open-label), randomized, placebo-controlled, crossover with five treatment periods: [redacted] BI 1015550, 400 mg moxifloxacin (positive control) and [redacted]
Number of subjects **total entered** **on each treatment**	 45 45 (at least 10 of each sex)
Diagnosis	Not applicable

Main inclusion criteria	Healthy male/female subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 32 kg/m^2 (inclusive)
Test Product	BI 1015550, [redacted]
[redacted]	[redacted]
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product	Placebo tablets, [redacted]
[redacted]	[redacted]
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Auxiliary medicinal product	Moxifloxacin (Avelox® [redacted] plc) film-coated tablets (400 mg)*
dose	400 mg in treatment period [**M**])
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h * Moxifloxacin is an auxiliary medicinal product (AxMP) in this trial
Duration of treatment	One day (single dose) for each treatment period
Statistical methods	For the analysis of QTcF changes from baseline (ΔQTcF) at each time point between 20 min to 24 hours post drug administration, a linear mixed-effects model for repeated measurements will be used. The comparison between each dose of BI 1015550 and placebo will be performed pairwise, i.e., data not relevant for the comparison of interest will be excluded. The model includes the covariates 'period baseline' and 'subject baseline' (defined as the arithmetic mean of the respective period baselines), the fixed categorical effects 'treatment', 'period', and 'time', the interaction terms 'period baseline-by-time', 'subject baseline-by-time', 'treatment-by-time', and 'period-by-time'. For comparisons between BI 1015550 and placebo, two-sided 90% confidence intervals (CI) for the mean differences per time point and corresponding point estimators will be computed. For assessment of assay sensitivity, the same model will be used to compare QTcF changes from baseline between moxifloxacin and placebo including all time points between 20 min to 24 hours post drug administration. The relationship between the placebo-corrected QTcF changes from baseline (ΔΔQTcF) and corresponding plasma concentrations of R-BI 1015550 will be examined based on a random coefficient model. The mean placebo-corrected QTcF change from baseline and its 90% CI at the geometric mean of C_{max} for each dose of BI 1015550 will be estimated. Descriptive statistics for safety endpoints and PK parameters will be calculated.



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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
[redacted]	
AxMP	Auxiliary medicinal product
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
CDISC	Clinical Data Interchange Standards Consortium
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	
CNS	Central nervous system
COVID-19	Corona virus disease 2019
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
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-fetal development
EoS	End of Study (synonym for End of Trial)
FEED	Fertility and early embryonic development
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
GI	Gastro-intestinal
GLP	Good Laboratory Practice
gMean	Geometric mean
hERG	Human Ether-a-go-go Related Gene
HEK	Human embryonic kidney (cells)
HR	Heart rate
HV	Healthy Volunteer
IB	Investigator's brochure
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
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOAEL	Lowest observed adverse effect Level
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measurements
MRD	Multiple-rising dose
MSEC	Millisecond
NOAEL	No adverse effect level
PD	Pharmacodynamic(s)
PDE4B	Phosphodiesterase 4B
PDEi	Phosphodiesterase inhibitor

P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PPF	Progressive Pulmonary Fibrosis
PR	Pulse rate
PXR	Pregnane X receptor
QRS duration	Combination of the Q, R, and S waves
[redacted]	
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
StaR	Statistical randomization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
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
TB	Tuberculosis
tQT	Thorough QT
TS	Treated set
TSAP	Trial statistical analysis plan
UGT	Uridine diphosphoglucuronosyl transferase
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
WBC	White blood cells
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. INTRODUCTION

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

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) [P11-07084]. While IPF is considered a prototypical form of progressive pulmonary fibrosis, there is a group of patients with different underlying clinical interstitial lung disease (ILD) diagnoses who develop a phenotype similar to patients with IPF during the course of their disease [P17-10582, P18-04729, P19-01738, R19-0854, P20-01299], which is characterised by increasing extent of pulmonary fibrosis on imaging, declining lung function, worsening respiratory symptoms and quality of life despite disease management considered appropriate in clinical practice, and, ultimately, early mortality [P17-10582, P18-04729, P19-01738, R19-0854, P20-01299].

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 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 Investigator's Brochure (IB) [c02094779].

1.2.1.1 Non-clinical pharmacokinetics

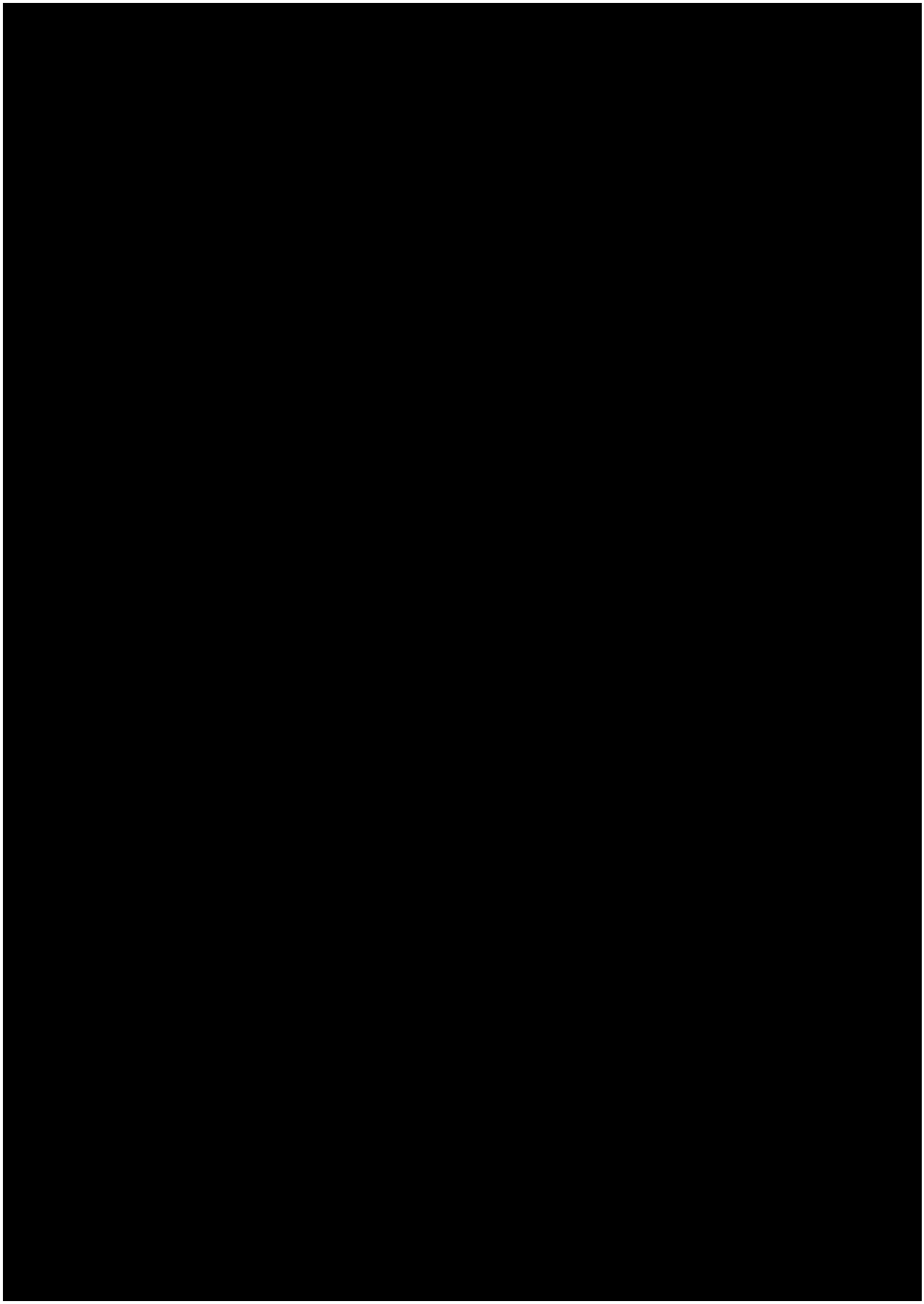
The disposition of BI 1015550 in non-clinical species is characterized [redacted]. The half-life of BI 1015550 is short in rats, moderate in mice, and long in monkeys and minipigs.

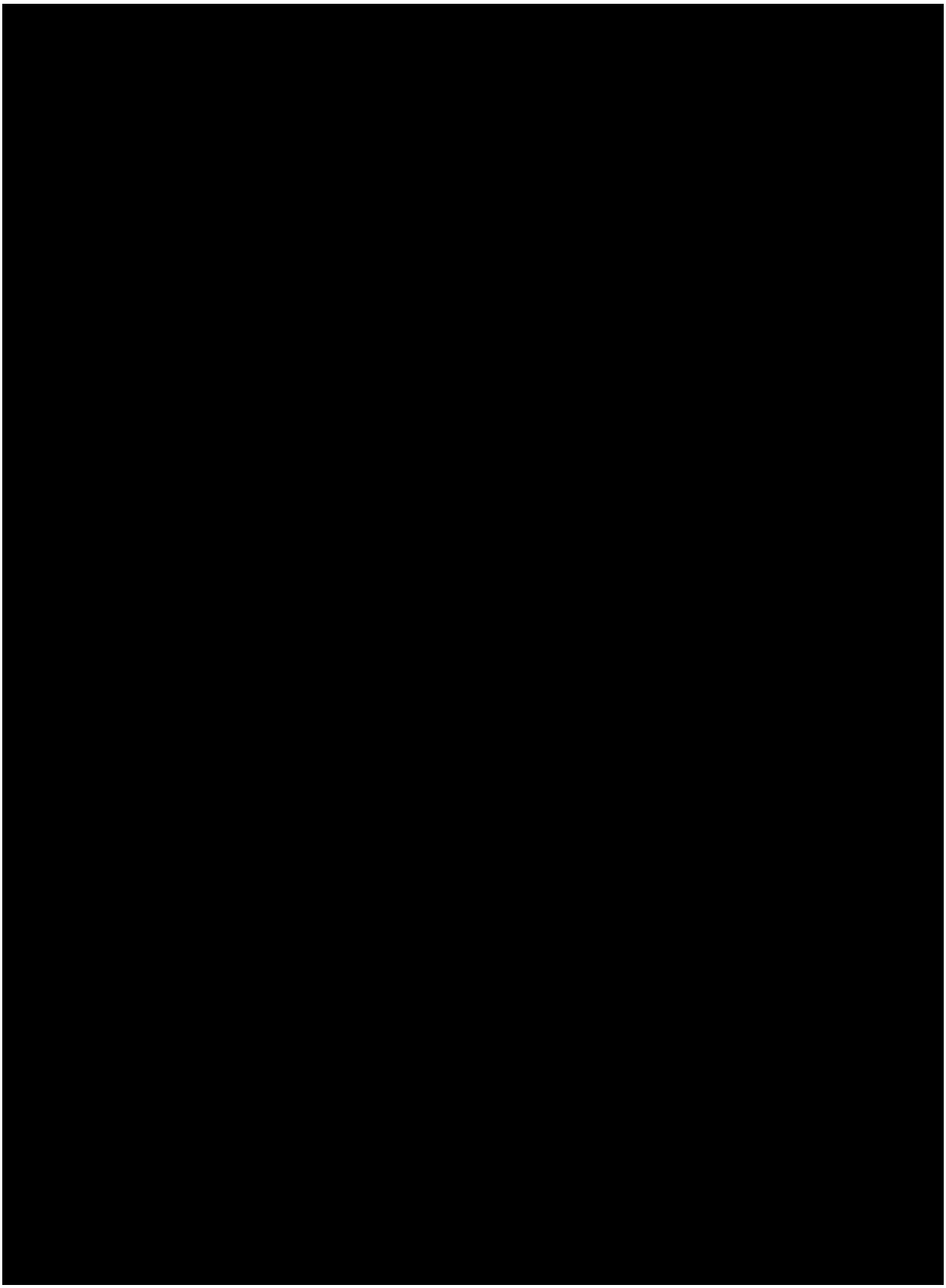
Potential DDIs may occur for concomitantly administered medications that are substantially metabolized by [redacted]

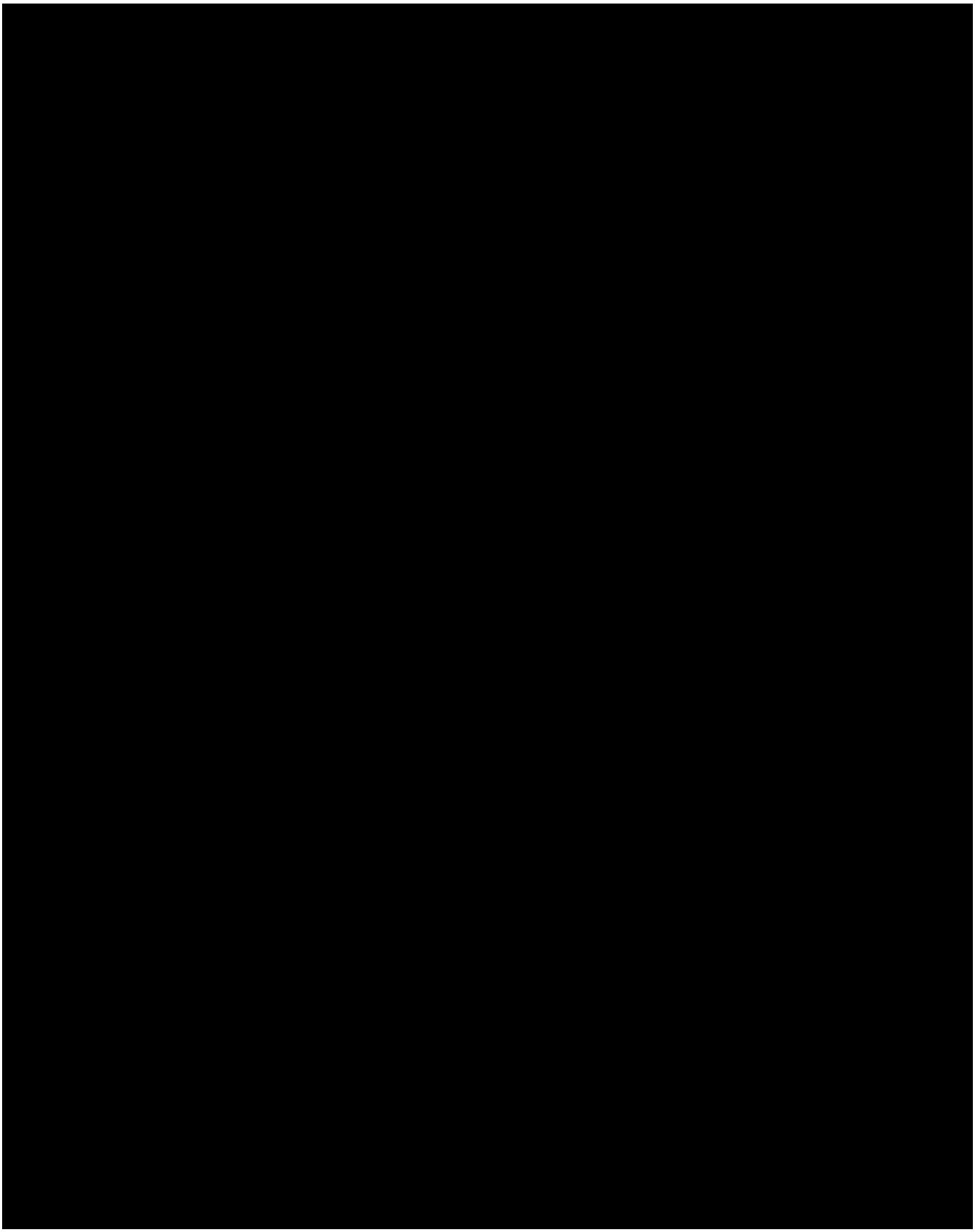
[redacted] by BI 1015550 at the [redacted] In addition, [redacted] of BI 1015550, concomitant therapies that are [redacted] may cause clinically significant changes in BI 1015550 exposure.

BI 1015550 [redacted]. As such, BI 1015550 exposure could be affected by co-administered drugs [redacted]. One [redacted], has been identified in human plasma.

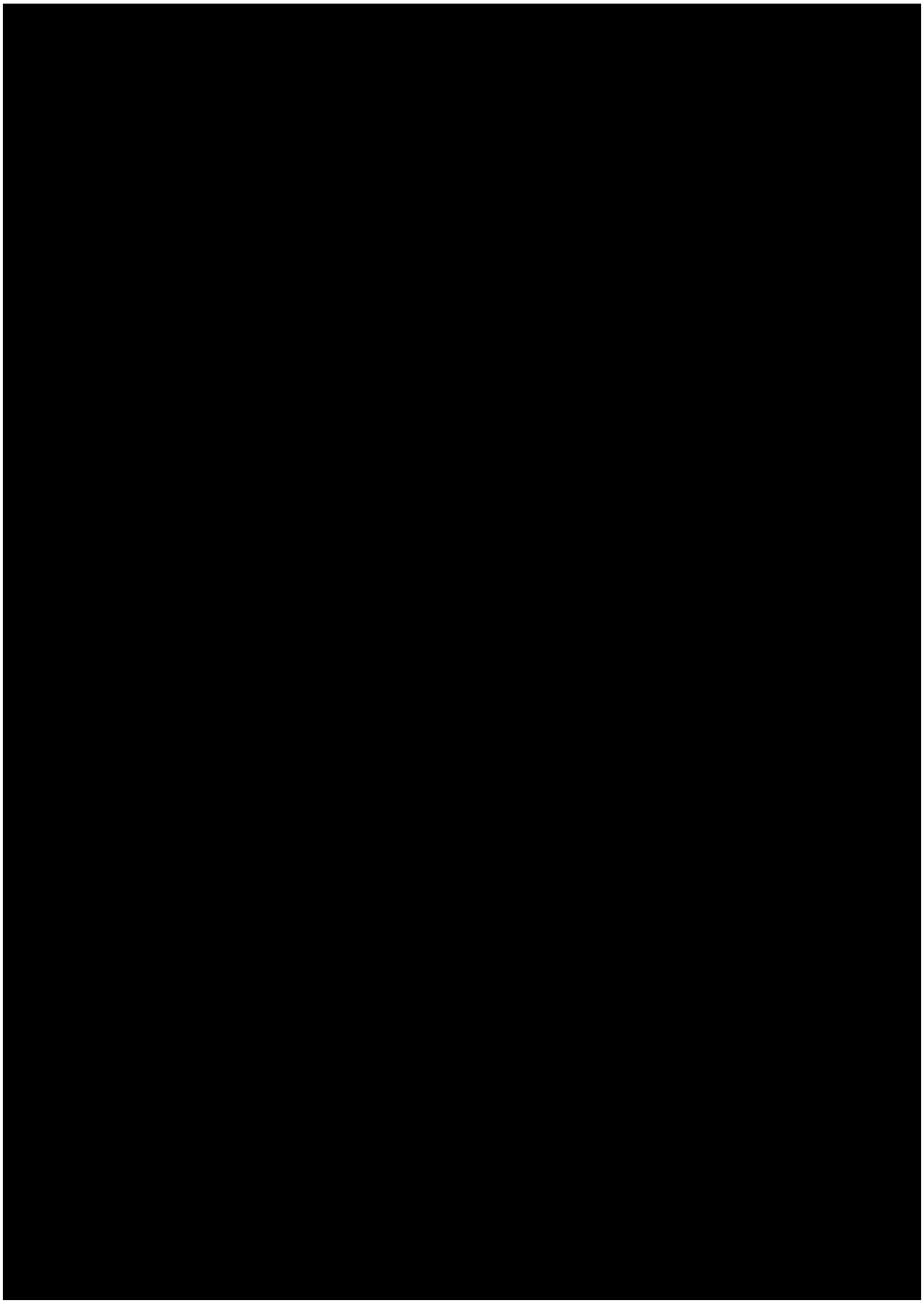
[redacted]







[redacted]



[redacted]

1.2.1.4 Clinical safety and efficacy

BI 1015550 has been investigated in a total of 11 clinical studies: 10 Phase I trials (nine trials in healthy subjects and one in patients with IPF), and 1 proof-of-clinical principle Phase II trial in patients with IPF. Overall, 185 healthy volunteers and 107 patients with IPF have been exposed to BI 1015550. Currently, 2 Phase III trials are ongoing in patients with IPF and PPF with a planned number of approximately 2.000 patients treated.

BI 1015550 was well tolerated in healthy volunteers following single dose administration [redacted] (136 volunteers) and multiple dose administration [redacted] (49 volunteers), and in patients following multiple administrations [redacted].

Clinical safety

In healthy subjects, nine clinical studies in healthy subjects have been completed with BI 1015550. Overall, BI 1015550, [redacted] 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. Overall, no clear dose-dependency in the frequency and intensity of these AEs was observed. A trend toward weight loss in subjects treated with BI 1015550 was observed in study 1305-0011 [c22991937] in healthy volunteers.

In the MRD trial (1305-0002), [redacted] 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 subject [c02191718].

In the bioavailability and food effect study (1305-0028 [c40013550]), one subject was reported with an AE of bradycardia [redacted] and did not continue to receive further treatment because of this AE.

No severe, serious, fatal AEs, nor SUSARS have been reported in the healthy volunteer studies. No cardiac safety signals were observed in healthy volunteer studies.

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 [redacted] 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 [redacted] in patients with IPF, diarrhoea was the most common AE leading to discontinuation of treatment. AEs leading to discontinuation of trial treatment were only observed in the BI 1015550 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 [redacted] was observed on the primary efficacy endpoint, the change from baseline in forced vital capacity (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 [redacted] preserved lung function in patients with IPF over 12 weeks.

1.2.2 Moxifloxacin

Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent. It is marketed worldwide for treatment of a number of infections including respiratory tract infections, cellulitis, anthrax, intra-abdominal infections, endocarditis, meningitis, and tuberculosis.

Moxifloxacin has been used in several QT trials in healthy volunteers as a positive control due to its modest QT-prolonging properties at a dose of 400 mg. Moxifloxacin was shown to induce a mean increase in the QTc interval of between 7.5-12.5 msec with a median t_{max}

of 2 h after a single oral dose of 400 mg [R10-0867]. Because the magnitude of the QT prolongation is small after 400 mg, there is minimal risk of moxifloxacin-induced Torsade de Pointes.

The pattern of side effects of moxifloxacin is well established, with the most common adverse effects being headache, dizziness, nausea, vomiting, diarrhea, gastrointestinal/abdominal pain and aspartate transaminase (AST)/alanine transaminase (ALT) increase [R22-1459]. Apart from nausea and diarrhea all adverse reactions were observed at frequencies below 3%.

Following oral administration, moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91%. Following a 400 mg oral dose, peak concentrations of 3.1 mg/l are reached within 0.5-4 h post administration. Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/fecal pathways as unchanged drug as well as in the form of a sulpho-compound and a glucuronide. Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 h.

For a more detailed description of the moxifloxacin profile including the list of adverse reactions, please refer to the SmPC [R23-2891]

1.2.3 [redacted]

[redacted]

The REP of moxifloxacin is 4 days.

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

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

(BI1015550) that will support the patient population in the treatment of IPF and other forms of progressive pulmonary fibrosis.

1.4.2 Risks

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

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 adverse events reported during clinical trials with BI 1015550 please refer to Section 1.2.1.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1015550		
[redacted]		
Vasculitis	• Vasculopathy is an established preclinical toxicity of PDE4 inhibitors • Vasculitis has been shown in rats and minipigs following oral administration of BI 1015550 but not in monkeys treated for up to 13 weeks • Vasculitis is listed as an important potential risk for the marketed PDE4- inhibitor apremilast • In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans.	• Close clinical monitoring for AEs of vasculitis • Treatment interruption in case of any suspected vasculitis adverse event.
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 • Presumably caused by increased energy expenditure and causing predominately loss of body fat.	• Inclusion of subjects with BMI > 18.5 only is routine inclusion criterion in Phase I • Subjects who reach a BMI <18.5 kg/m2, and subsequently experience unexplained and clinically significant weight loss (>10%) will be discontinued from trial treatment • Weight will be monitored throughout the study. With 2 single dose administrations of BI 1015550, the risk is considered to be very low.

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

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: **BI 1015550**		
Reproductive toxicity: foetal loss, decreased fertility	• No teratogenicity was seen in preclinical studies and exposure with BI 1015550 via the semen is expected to be very low • In rats, male and female fertility was potentially reduced. Long-term toxicity studies with BI 1015550 in rat and monkey showed no microscopic evidence of changes in 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	• Women of childbearing potential (WOCBP) need to use a highly effective method of contraception from the time of informed consent until 37 days after the last trial drug administration (i.e., REP of BI 1015550 of 7 days plus 30 days). WOCBP taking oral contraceptives (OCs) also have to ensure the use of one barrier method during sexual intercourse with their partner, e.g.,condom to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea • Thorough counselling about appropriate contraceptive measures • Repeated pregnancy testing • Discontinuation of trial treatment in case of pregnancy
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 • Subjects will stay in the Phase I unit under close medical surveillance until at least 24 h after the drug administration in each treatment period

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

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: **BI 1015550**		
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 wit [redacted] no on treatment events of suicidal ideation or behaviour and no events of depression or anxiety were reported. • Prospective assessment of suicidal ideation and behaviour and depression are not required in single-dose trials in healthy volunteers	• The risk after 2 single dose administrations in Phase I (done on site) is considered low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression and anxiety as well as for signs and symptoms of suicidal ideation and behaviour • Only healthy subjects with no relevant medical history including psychiatric disorders will be enrolled
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. • Nasopharyngitis was more frequently reported under treatment with BI 1015550 in Phase Ic/II but not in Phase I trials and the numbers were very small.	• Screening procedures for infections are defined for this trial. Subjects with any relevant chronic or acute infections are excluded from the trial • Treatment of infections should be initiated promptly according to standards of care • Treatment interruption in case of severe acute infection until the subject has recovered based on the investigator's medical judgement. • Close monitoring to detect potential infections promptly will minimise the risk of serious infection.

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

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: **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.	• Subjects with a recent history of malignancy within 5 years will be excluded from participation in this trial • In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue trial treatment • Diagnostics and treatment have to be initiated according to local standard of care. • The risk after 2 single dose administrations in Phase I is considered low
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 subjects 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 subjects´ safety • Increased awareness and expedited reporting (AESI).

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

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational medicinal product: **Moxifloxacin**		
Common (≥1/100 to <1/10) adverse drug reactions (ADR) - Superinfections due to resistant bacteria or fungi - Headache, dizziness - QT prolongation in patients with hypokalaemia - Nausea, vomiting, gastrointestinal and abdominal pains, diarrhea - Increase in transaminases Uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) ADRs (see the SmPC [R23-2891])	• For a more detailed description please refer to Section 1.2.2 and the SmPC for Moxifloxacin (Avelox®) 400 mg film-coated tablets [R23-2891].	• A thorough screening examination: specifically subjects with high liver enzymes, a marked baseline prolongation of QT/QTc interval, a history of additional risk factors for Torsade de Pointes will be excluded (see Section 3.3.3) • Only single doses of moxifloxacin will be given • The subjects will be closely monitored through assessment of adverse events, safety lab, ECG and vital signs in each treatment period • The subjects will maintain under close medical surveillance for at least 24 hours post dosing in each treatment period
Effects on ability to drive and use machines	• No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision) or acute and short lasting loss of consciousness (syncope).	• The subjects will maintain under close medical surveillance for at least 24 hours post dosing in each treatment period • The subjects should be advised to see how they react to moxifloxacin before driving or operating machinery

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

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational medicinal product: **Moxifloxacin**		
Effects on pregnancy and lactation	• The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity The potential risk for humans is unknown. • There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk.	• Moxifloxacin must not be used in pregnant or lactating women, they will be excluded (see Section 3.3.3) • Women of childbearing potential need to use a highly effective method of contraception. • Thorough counselling of women of childbearing potential about appropriate contraceptive measures • Repeated pregnancy testing • Discontinuation of trial treatment in case of pregnancy
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
Local skin irritation and discomfort	General risk from ECG stickers, acceptable in the framework of trial participation.	Medical expertise of the trial site

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

[redacted]

[redacted]

Considerations on COVID-19:

Generally, in healthy volunteers' population, 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/endemic.

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 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, subjects with active or recent (i.e. within the 4 weeks prior to screening) SARS CoV-2 infection should not be included in the trial which is also applicable for any other relevant acute infection (exclusion criterion No. 9).

In case of severe COVID-19 infection during the conduct of the trial, treatment with BI 1015550 has to be interrupted which is also applicable for any other relevant acute infection (criterion of withdrawal from trial treatment No. 9). 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/endemic, all subjects 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 subject from further trial treatment and/or trial procedures to avoid undue risks to other subjects 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.

COVID-19 testing may be performed based on current infection rates, status of the pandemic/endemic and availability of tests. If required, testing will comprise an antigen test performed on screening and within 72 h prior to admission to the clinical unit. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick-Off Meeting minutes or in a file note if the study is ongoing.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

1.4.3 Discussion

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

In summary, BI 1015550 has a favorable benefit-risk-assessment based on a thorough pre-clinical data package as well as knowledge gained from previous clinical trials using BI 1015550, which justifies further investigation in humans.

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 BI 1015550 on the QT/QTc interval as measured by the QTcF changes from baseline compared with placebo in healthy male and female volunteers following oral administration. The QT effect will be assessed [redacted] that provides exposures exceeding the high clinical exposure scenario accounting for potential exposure increase due to intrinsic and extrinsic factors (see Section 4.1.3).

The secondary objective is to show the assay sensitivity of the trial, by reproducing the typical effect of the positive control moxifloxacin on the QT/QTc interval.

The assessment of safety and tolerability of BI 1015550 particularly with regard to cardiac safety are additional objectives of this trial.

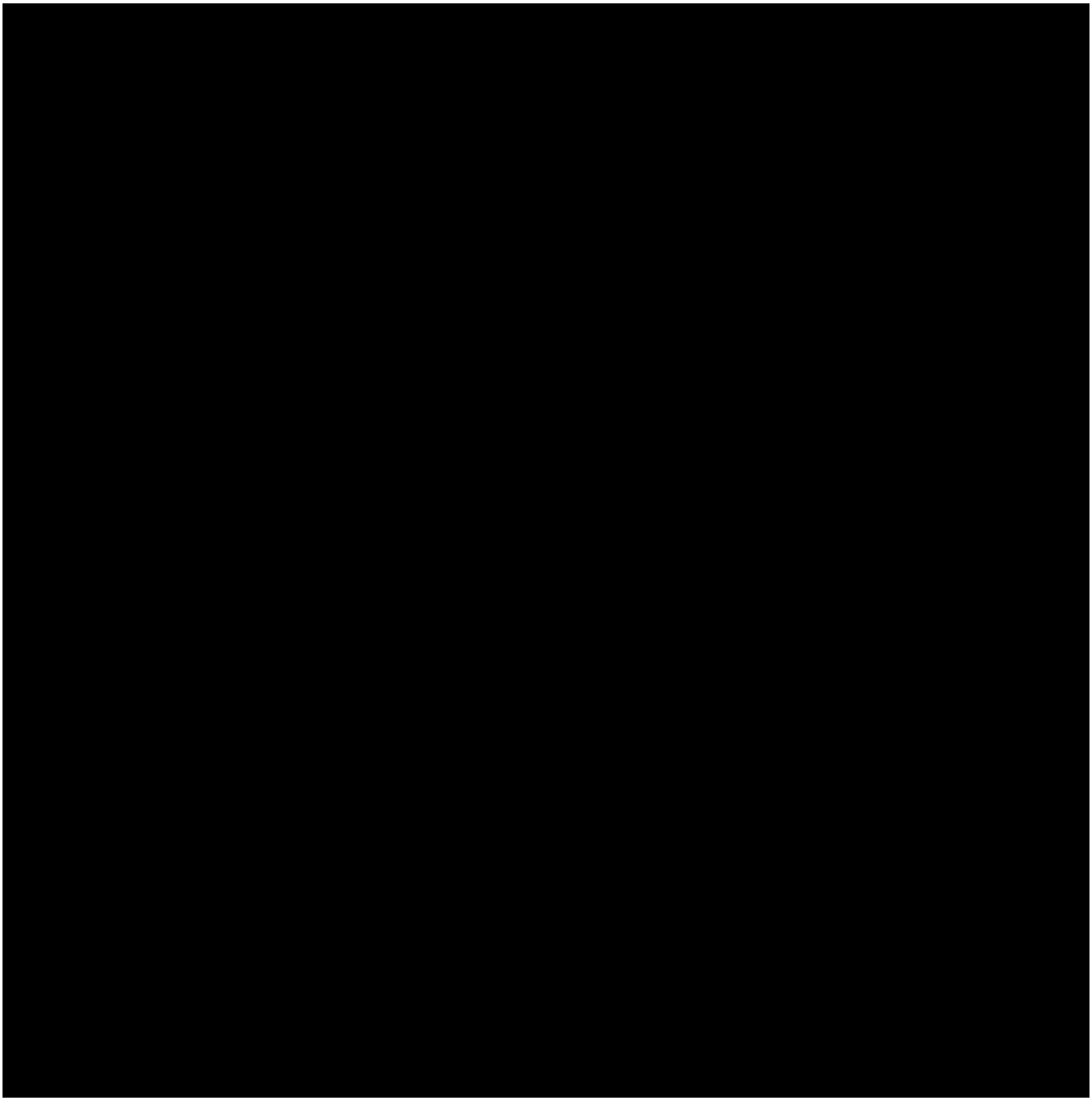
2.1.2 Primary endpoints

The maximum mean difference between [redacted] in QTcF changes from baseline between 20 min to 24 hours after drug administration.

2.1.3 Secondary endpoint

The maximum mean difference between moxifloxacin and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration. (The formal test for assay sensitivity will be based on the results for the pre-selected time points 2, 3, and 4 hours post dosing.)

[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 (only abnormal findings will be reported as AEs)
- 12-lead single safety ECGs or triplicate ECGs derived from Holter ECG recordings
- Vital signs (blood pressure (BP), pulse rate (PR)), body weight

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a randomized, placebo controlled, double-blind, five-period, four treatment crossover trial with two placebo periods and moxifloxacin (open-label) as positive control in healthy male and female subjects. The replicate design with respect to placebo allows for estimating the treatment contrasts of each active drug to placebo more precisely than with only one single placebo period, thus enabling a reduced sample size (see [R12-0517] and Section 7.5).

The treatments will be:

[redacted]

- Treatment 3 ([**M**] – moxifloxacin):
  400 mg moxifloxacin (1 tablet) in the fasting state, single dose

[redacted]

For details, refer to Section 4.1.

The subjects will be randomly allocated to one of the 15 treatment sequences (3 subjects per sequence) planned in this trial (see Section 7.2.1). There will be a [redacted] between the treatments.

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

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

According to the guideline ICH E14 (CHMP/ICH/2/04 2005) 'The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs' (2005) [R07-4722] and the respective 'Questions and Answers Document' (2017) [R17-2903] concerning the evaluation of QT/QTc-interval prolongation, a randomized trial with concurrent placebo control and a positive control will be conducted in order to investigate the effect of a drug (BI 1015550) on QT/QTc-interval in healthy volunteers.

As positive control, the subjects will receive a single dose of moxifloxacin 400 mg, which is known to induce moderate QT/QTc-prolongation (see Section 1.2.2) and will therefore verify the ability of the trial to detect relevant changes in the QT/QTc-interval. Moxifloxacin is an auxiliary medicinal product (AxMP) in this trial and marketed in the UK/EU. It is to be used

in the clinical trial within the terms of the marketing authorization, other than being administered to healthy volunteers.

For thorough QT trials, the crossover design is preferred due to its efficiency: since each subject serves as his/her own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes inter-subject variability from the comparison between treatments [R94-1529]. Moreover, with proper randomization of subjects to the different sequences of treatment administrations, it provides the best unbiased estimates for the differences between treatments. Additionally, the total number of subjects needed to participate in this trial is minimized compared to a parallel group design trial. Since all assessments in tQT trials are based on the comparisons between active treatment and placebo, these treatment contrasts should be estimated with the highest statistical efficiency. To account for this, the selected crossover design for this trial will include a second placebo period instead of only one. The sample size for the resulting 4-treatment 5-period crossover design can be determined as 3/4 of the sample size of the corresponding 4-period crossover design (see also Section 7.5).

Blinding with regard to the study drug substances to be investigated versus their matching placebos is essential in such a trial. ECG profiles will be performed for BI 1015550 and placebo in a double-blind fashion. The positive control (moxifloxacin) will be administered open-label. This is not expected to bias results, since moxifloxacin is known to robustly induce a mean increase in the QTc interval of between 7.5 - 12.5 msec with a median t_{max} of 2 hours after a single oral dose of 400 mg [R10-0867]. The technicians and cardiologists at the ECG laboratory performing the ECG interval measurements and assessments will remain blinded in this trial with regard to all treatments, including moxifloxacin and placebo (see Section 4.1.5).

BI 764333, major human metabolite of BI 1015550, have been evaluated in nonclinical studies, and pharmacological contribution of this metabolite is considered to be low. Also, BI 764333 was evaluated in a cardiovascular safety pharmacology study in minipigs under GLP [redacted] with no effects observed. Thus, [redacted] is not considered for analyses of the current clinical trial.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 45 healthy male and female subjects (at least 10 of each sex) will enter the trial. They will be recruited from the volunteers' pool of the trial site.

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

[redacted]must have a full medical history from each subject's general practitioner (GP) within the last 24 months, prior to enrolment in the study. Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 90 days of the dosing date.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests without any clinically significant abnormalities
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 32 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. Either male subjects, or female subjects meet the following criteria requiring highly effective contraception from at least 30 days before the first administration of trial medication until 37 days after the last administration of the study drug:
   - Male participants must use condom plus their partner, if identified as a WOCBP, must use an oral contraceptive or highly effective contraception as defined below
   - Female participants must be using highly effective contraception and in addition their male partner must use a condom if they are using an oral contraceptive (as per Table 1.4.2: 1)

Highly effective methods of contraception include:

- Use of combined (estrogen and progestogen containing) hormonal contraception that prevents ovulation (intravaginal or transdermal)
- Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants)
- Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Sexually abstinent is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
- Vasectomy in males, or a vasectomised sexual partner of females 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
- Bilateral tubal occlusion

Women of non-childbearing potential (WONCBP) include:

- Permanently surgically sterilised (including hysterectomy, bilateral oophorectomy and bilateral salpingectomy)
- 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 is confirmatory)

WONCBP are not required to use any methods of contraception.

Female subjects should not participate in egg donation and male subjects should not participate in sperm donation from the first study drug administration, for the duration of the study and for at least 37 days after the last study drug administration.

3.3.3 Exclusion criteria

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

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

12. Use of drugs within 30 days (or 5 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)
13. Intake of an investigational drug in another clinical trial within 90 days of planned administration of investigational drug in the current trial or less than 5 elimination half-lives (whichever is longer), or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker including electronic cigarettes and shisha, as well as user of nicotine replacing products (e.g. nicotine chewing gum and patches)
15. A confirmed breath carbon monoxide test of greater than 10 ppm at screening or admission at Period 1
16. Alcohol abuse (consumption of more than 14 units per week for females and 21 units per week for males [1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type]) or a positive alcohol breath test at screening or admission at Period 1
17. Drug abuse within the past 2 years or positive drug screening
18. Donation of blood or plasma or loss of greater than 400 mL of blood within the previous 3 months or intended blood or plasma donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTcF intervals that are repeatedly greater than 450 msec) or any other relevant ECG finding (such as QRS greater than 120 msec, PR interval less than 120 msec or greater than 210 msec) at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Presence of electrolyte disturbances, particularly in uncorrected hypokalaemia (i.e. potassium below the LLN)
24. Previous history of symptomatic arrhythmias
25. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
26. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 37 days after trial completion
27. For female subjects: Positive pregnancy test
28. Subjects with any condition that would preclude administration of moxifloxacin (i.e., contraindicated as per SmPC), such as but not limited to history of tendon disease/damage as a result of quinolone therapy, clinically relevant bradycardia,

clinically relevant heart failure with reduced left ventricular ejection fraction or a history of serious adverse reactions in the past when using quinolone or fluoroquinolone containing products

29. Concomitant intake [redacted]
30. History or signs of vasculitis
31. Relevant immunodeficiency
32. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of screening
33. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results at screening
34. Subjects with [redacted] at screening
35. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
36. Subjects who are, or are immediate family members of, a study site or sponsor employee

The following exclusion criteria will be re-assessed on admission for Period 1: 1, 2, 3, 8, 9, 12, 15, 16, 18, 19, 20, 21, 23, 27, 28 and 29.

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.3, the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases), in particular, if an AE of severe intensity or a serious adverse event (SAE) occurs
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN or 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 subject has relevant individual QT prolongations, i.e. a QTcF increase of greater than 60 ms from baseline and/or with absolute QT or QTcF greater than 500 ms, as confirmed by a repeat ECG recording
7. Subjects that experience an unexplained and clinically significant (>10%) weight loss during trial treatment
8. 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/endemic, all subjects 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 subject (refer to Section 1.4.2).

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

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.5.2.3.

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

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at the trial site
2. The sponsor decides to discontinue the further development of the investigational product
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1). More specifically, the trial will be halted, and the risk to other subjects evaluated if:

   - a serious adverse reaction (i.e. a SAE considered at least possibly related to the IMP administration) occurs in one subject;

   or

   - severe non-serious adverse reactions (i.e. severe non-serious AE considered as, at least possibly related to the IMP administration) occur in two subjects, independent of within or not within the same system organ class.

   Relatedness will be determined by the investigator.
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity

If the trial is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The trial may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

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

3.3.5 Replacement of subjects

In case some subjects do not complete the trial (including subjects non-evaluable for PK, see section 7.2.1.4), additional subjects may be enrolled and treated, i.e. “replaced” if considered

necessary to reach the objective of the trial (see Section 7.5). The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A maximum of 7 subjects will be replaced. Thus, the total number of subjects entered and dosed in this trial will not exceed 52. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment sequence as the subject he or she replaces.

In case of replacement of subjects, the trial site should ensure that the requirements for distribution of sex (‘at least 10 of each sex) are still met within the overall group of further on treated and additionally entered subjects.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the **test product** are given below:

[redacted]

The characteristics of the **reference product** are given below:

Substance: Placebo

[redacted]

4.1.2 Identity of the Auxiliary Medicinal Products

Name: Avelox®

Substance: Moxifloxacin

Pharmaceutical formulation: Film-coated tablet

Source: [redacted]

Unit strength: 400 mg

Posology:	Treatment 3 [**M**]: 1 x 400 mg tablet
Mode of administration:	Oral
Duration of use:	Single dose in Treatment 3 [**M**]

4.1.3 Selection of doses in the trial and dose modifications

Currently, [redacted] doses are being evaluated in the Phase III trials. The dose of [redacted]) was selected in order to achieve the anticipated clinical therapeutic exposure at steady state following oral administration of [redacted] (the highest therapeutic dose being evaluated in the Phase III trials). Following [redacted] (1305.2, 1305-0011, 1305-0012, see Section 1.2.1.3). Therefore [redacted].

The dose of [redacted] was selected in order to measure the effect of a tolerable supra-therapeutic dose of BI 1015550 on cardiac safety (see Section 1.2.1.4). The selected supra-therapeutic dose of [redacted] is based on the highest dose of BI 1015550 being tested in clinical trials to date, the therapeutic doses being evaluated in the phase 3 trials ([redacted]) and the potential increase in BI 1015550 concentration due to intrinsic and extrinsic factors. This dose of [redacted] is estimated to provide [redacted] compared with the clinical steady state exposure at [redacted] of BI 1015550), while the worst case intrinsic/extrinsic factors, namely DDI interaction with a [redacted] (see Section 1.2.1.4).

The dose of 400 mg of moxifloxacin (single oral dose) was selected as it demonstrated to induce a mean increase in the QTc interval of between 7.5-12.5 msec (median t_{max} of 2 h) and was already used in several QT trials in healthy volunteers as a positive control due to its modest QT-prolonging properties [R10-0867]. Because the magnitude of the QT prolongation is small after a single dose of 400 mg, the risk of moxifloxacin-induced Torsade de Pointes is considered minimal.

4.1.4 Method of assigning subjects to treatment groups

According to the planned sample size, at least 5 cohorts are planned. Prior to the start of the trial, subjects willing to participate will be recruited to cohorts according to their temporal availability. In the morning of Day 1 (Visit 2), each subject will be allocated to 1 of the 15 treatment sequences prior to the first administration of trial medication. For this purpose, numbers of the randomization scheme will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomization scheme.

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

All subjects in one cohort may be treated on the same calendar day as close as 3 min apart (minimum). Actual dosing stagger will be dependent on logistics as required by the site. For discussion of trial-associated risks and safety measures, see Section 1.4.

The randomization procedure is described in Section 7.4.

4.1.5 Drug assignment and administration of doses for each subject

This is a 5-way crossover trial. All subjects will receive the 4 treatments (including 2 placebo periods in the placebo treatment) in randomised order. The treatments to be evaluated are summarised in Table 4.1.5: 1 below.

Table 4.1.5: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
[redacted]					
Treatment 3 [M]	Moxifloxacin	Tablet	400 mg	1 x 400 mg tablet, single dose	400 mg
[redacted]					N/A

In Treatment 1 [redacted] of BI 1015550 will be administered as [redacted]. In addition, placebo tablets ([redacted] will be administered concomitantly to BI 1015550 in order to mask the treatment to other trial treatments and maintain double-blind conditions in the trial.

In Treatment 3 [**M**], administration of moxifloxacin will be handled open label.

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. In each treatment period, subjects will be provided with a light snack and then fast from all food and drink (except water) for a minimum of 10 h on the day prior to dosing until approximately 6 h post-dose at which time lunch will be provided. A voluntary snack will be suggested at 8 h post-dose. An evening meal will be provided at approximately 12 h post-dose. On subsequent days, meals will be provided at appropriate times.

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting or standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. dispensing), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until at least 24 h after drug administration (exact requirements for medical supervision to be outlined in the study

specific Risk Management Plan authored by the study PI). During the first 2 h after drug administration, subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture) except for medical examinations, single ECG recordings, and triplicate ECG extraction time points and preceding resting time. For restrictions with regard to diet see Section 4.2.2.2.

The treatments will be separated by a wash-out phase [redacted].

4.1.6 Blinding and procedures for unblinding

4.1.6.1 Blinding

The table below summarizes the masking/ blinding level of individual functions, roles and responsibilities involved in the trial. In addition, further details on blinding, roles and responsibilities in relation to blinding and how the blind will be maintained will be detailed within the study specific site Blinding Plan.

Table 4.1.6.1: 1 Blinding level of individual functions

Role/function	**Timing of unblinding/ receiving access to the treatment information (including rationale)**
Subject/Participant	This trial is blinded to the subject/ participant. The subject/ participant's treatment information will be provided to the site after the trial has been completed.
Investigator/Site Staff	The subject/ participant's treatment information will be provided to the site after the trial has been completed except for the moxifloxacin treatment which will be known to the trial site. This will be implemented as follows: Prior to trial initiation, a member of StaR (Statistical randomization) will generate a list indicating the moxifloxacin treatment period for each subject in the form of e.g. X-X-M-X-X or M-X-X-X-X based on the randomization scheme. This list will be provided to the clinical site to enable trial set up.
Sponsor trial team and database	Once the data has been declared ready for unblinding.
Bioanalytical Staff	As requested for analysis of bioanalytical samples. Prior to unblinding of the treatment information, the randomization codes will be provided to bioanalytical staff to allow them to exclude from the bioanalytical analyses PK samples taken from placebo-treated subjects. Bioanalytical staff will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.
Pharmacokineticist/ Pharmacometrician	Once the data has been declared ready for unblinding.

Table 4.1.6.1: 1 Blinding level of individual functions (cont)

Role/function (cont)	Timing of unblinding / receiving access to the treatment information (including rationale)
ECG laboratory	Within the central ECG laboratory, the staff involved with interval measurements will be blinded with respect to subject, treatment, recording date and time as well as planned time points of ECGs. The staff involved with the morphological analyses will be blinded with respect to treatment. For the quality control of the measurements, certain members of the ECG evaluation team will review the entire portfolio of ECG measurements for each subject blinded to recording date and time as well as the planned time point.

During the time a role/ function is blinded according to the table above, the randomisation schemes and medication kit lists (i.e., the treatment information) are kept restricted by the global Randomization Team within StaR per Sponsor SOP.

The evaluation of the effect of BI 1015550 on the QT/QTc interval and other ECG parameters as compared to placebo (Treatments 1, 2, and 4) will be handled in a double-blind fashion.

The evaluation of the effect of moxifloxacin (Treatment 3) on the QT/QTc interval and other ECG parameters will be handled in an open fashion throughout the trial.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6.2 Procedures for emergency unblinding

For this blinded trial, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomization scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

4.1.7 Packaging, labelling, and re-supply

Investigational Medicinal Products - BI 1015550 and placebo:

The investigational medicinal products BI 1015550 and placebo will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

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

indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

Auxiliary medicinal product - Moxifloxacin:

The auxiliary medicinal product moxifloxacin (Avelox® [redacted] plc) will be sourced from a local pharmacy (or suitable approved supplier). A simple study specific product label will be applied by [redacted] Moxifloxacin is marketed in the UK/EU and is to be used in the clinical trial within the terms of the marketing authorisation, other than being administered to healthy volunteers.

4.1.8 Storage conditions

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

4.1.9 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 'Delegation Log' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of 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, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

Vasculitis

In case of events suspicious for vasculitis, trial treatment will be discontinued. A thorough work-up has to be initiated including at least but not limited to

- appropriate imaging, including angiography
- biopsy if possible
- appropriate laboratory screening, including measurements of vasculitis markers at the local lab, see Section 5.2.3. In addition, an analysis of the previously collected and stored samples will need to be requested and considered.
- thorough documentation of all reported symptoms

Referral to a vasculitis expert is recommended. If required, vasculitis treatment should be initiated according to standard of care.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed.

No prescribed, over-the-counter medication or herbal remedies will be permitted from 14 days before study drug administration until the EoT examination except short-term use of ibuprofen or paracetamol for treatment of headache, if necessary, hormone replacing therapy and hormonal contraception and those deemed necessary by the investigator to treat AEs.

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

4.2.2.2 Restrictions on diet and lifestyle

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 6 h after drug intake.

On Day 1 of each treatment period, 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 subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

[redacted]

Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to admission until the end of in-house confinement in each treatment period.

[redacted].

Alcoholic beverages are not allowed from 48 h before administration of trial medication until the end of in-house confinement in each treatment period.

Must not donate blood or plasma (outside of this study) from screening until for at least 90 days following last dose of study medication.

There is no evidence [redacted]

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

4.2.2.3 Contraception requirements

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

Female subjects should not participate in egg donation and male subjects should not participate in sperm donation from dosing, for the duration of the study and for at least 37 days after last IMP administration.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g. [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible. Further, body temperature will be monitored as part of vital signs assessment if still needed due to the current status of the pandemic/endemic.

5.2.3 Safety laboratory parameters

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

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

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

quant = quantitative;
qual = qualitative;
A: Parameters to be determined at Visit 1 (screening examination)
B: Parameters to be determined: in Period 1 (Visit 2) from Day -3 to -1, in Periods 2-5 (Visits 3-6) on Day 1 prior to drug intake. In Period 1, safety laboratory test can be omitted if the screening examination is performed on Days -3 or -2.

C: Parameters to be determined at Visit 7 (end of trial examination)

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group (cont)	BI test name [comment/abbreviation]	A	B	C
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 HGB (qual)	X	X	X
	Urine leukocyte esterase (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

quant = quantitative;
qual = qualitative;
A: Parameters to be determined at Visit 1 (screening examination)
B: Parameters to be determined: in Period 1 (Visit 2) from Day -3 to -1, in Periods 2-5 (Visits 3-6) on Day 1 prior to drug intake. In Period 1, safety laboratory test can be omitted if the screening examination is performed on Days -3 or -2.
C: Parameters to be determined at Visit 7 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. 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 admission at each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to admission at each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) Hepatitis B DNA PCR (quantitative)[1] QuantiFERON®-TB Gold Test (IGRA)[2]
Pregnancy test (urine)[3]	Beta human chorionic gonadotropin (beta-HCG)
[redacted]	[redacted]
COVID-19 (nasopharyngeal swab)[4]	SARS CoV-2 PCR test or antigen test at screening and prior to admission in each treatment period

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

[2] if the first QuantiFERON®-TB Gold Test result is undetermined, a retest should be performed. If the retest is undetermined as well, a tuberculin skin test (PPD or Mantoux) should be performed.

[3] pregnancy tests in serum only at screening and EOT and in urine at each other time point as per Flow Chart

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

To encourage compliance with alcoholic and smoking restrictions, a breath alcohol test (e.g. [redacted] or equivalent) and carbon monoxide breath test will be performed at screening and prior to admission at 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 pregnancy tests. These tests will be performed at the trial site using Alere Drug Screen Test Cup and SureScreen Diagnostics HCG Pregnancy Rapid Test, respectively, or comparable test systems. Urinalysis assessments also will be performed at the trial site using, e.g., [redacted] Urine Test Strips. If urine microscopy is required, a sample will be shipped to "[redacted] for analysis.

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

The safety laboratory tests' results will not be entered in the CRF. It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.5).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.5.1.4).

5.2.4 Electrocardiogram

5.2.4.1 12-lead continuous (Holter) ECG recording

To determine potential effects of BI 1015550 on cardiac safety parameters, 12-lead continuous 24-hour Holter ECG recordings will be used to extract 10-second triplicate ECGs for analysis (see Section 5.2.4.2).

The continuous ECGs will be recorded using digital Holter devices (e.g. [redacted]) provided by the central ECG laboratory. Specific site training and procedures for ECG Holter recording and data transfer will be provided by the core lab to the Clinical Unit. Separate operational documents will be generated to detail the procedures and processes used for the Holter ECG data recording.

Recordings will be started within 2 h prior to drug administration and will last at least until 24 h post drug administration in each treatment period. A lead system with modified Einthoven/Goldberger leads (the so-called Mason/Likar lead system) and precordial leads according to Wilson will be applied. Electrode placement will be performed by trained personnel according to established anatomical landmarks to ensure individual placement of electrodes will be identical throughout all 5 treatment periods.

Recordings will be started at the time points specified in the Flow Chart and will be stopped after the last time point in the respective period. The exact starting and end times of the Holter recordings as well as the medication intake will be documented and also provided to the core lab.

Before and at the planned time points at which resting ECGs are to be extracted from 24-hour Holter ECG recordings, the subjects should be kept in a relaxed and quiet environment. Thus, at least 10 minutes prior to the triplicate ECG extraction time points (see Flow Chart), subjects will take a supine position to ensure a stable heart rate at rest and high ECG quality during the recordings. These resting periods and ECG recordings will always precede all other trial procedures planned for the same time point to avoid compromising ECG quality.

To guide the extraction of the ECGs by the core lab, the trial staff will record the start and end times of rest periods and provide this to the core lab as well.

The Holter ECG recordings will be transmitted to a central ECG laboratory using a provided secure transfer program. The data will be checked by the core laboratory for any demographic and timing inconsistencies prior to the evaluation of the ECGs. In case of issues, queries will be sent to the site.

5.2.4.2 Central 12-lead triplicate ECG extraction and evaluation

At the central ECG laboratory, triplicate 10-second ECGs will be extracted in a defined time window during the resting periods. The evaluation of the extracted ECGs comprises the determination of cardiac axis (measured automatically) as well as the intervals RR, PR, QRS, and QT, measured semi-automatically. All semi-automatic interval measurements in an

individual subject will be performed on the same lead. The intervals will be measured from 4 cardiac cycles (beats) in Lead II. If Lead II shows a flat T wave or is not measurable for any reason, Lead V5 will be used, or if that lead is not measurable, then Lead I will be used. The lead actually used will be reported in the CTR. Heart rate and the QT interval corrected for HR (QTc, e.g. QTcF) will be determined by BI (see TSAP for details).

Morphological analyses of the extracted triplicate ECGs will be performed by a board certified cardiologist or equivalent for one randomly selected ECG per extraction time point. The cardiologists' assessments will include an overall assessment (classifications are: 'normal', 'abnormal, clinically relevant', 'abnormal, clinically not relevant', 'not evaluable') as well as qualitative ECG findings with respect to e.g., rhythm, conduction and morphological abnormalities, presence of myocardial infarction, ST segment deviations, T wave morphology and presence of U-wave. Basis of the terminology used for the evaluation is the most current published version of CDISC controlled terms at the time of the final ECG transfer. Abnormalities detected during central ECG evaluation will be entered as AEs if assessed as clinically relevant based on the investigator's judgement (the investigator takes the final decision on AE documentation after having reviewed the cardiologist assessment provided by the core laboratory).

For blinding arrangements see Section 4.1.5. Within the ECG laboratory, the staff involved with ECG interval measurements will be blinded with regard to subject, treatment, date and time as well as time points of the ECG measurements. The staff involved with the morphological analyses will be blinded with respect to treatment. No more than two blinded readers will evaluate all ECGs of the trial. The interval measurements for a given subject will be performed in random and blinded sequence by a single reader. For quality assurance and control of the measurements, all ECGs of an individual subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the trial.

Evaluation of extracted triplicate ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R17-2903] as well as the FDA requirements for annotated digital ECGs [R09-4830].

Where any scheduled rest times are missed or where there is less than a 10 min rest period a protocol deviation will be recorded and the Holter provider informed. Where there is an interruption(s) to the rest period, a comment will be recorded in the source (e.g. subject movement or loss of leads) and where possible, the time of interruption will be captured. The Holter provider will be informed of any interruptions during the rest period. Loss of leads or interruption of the recording outside of the scheduled rest times will not be considered a protocol deviation but should be recorded in the source.

5.2.4.3 Safety 12-lead single standard ECG

For immediate cardiac safety assessment, a single standard 12-lead ECG will be recorded at the times provided the Flow Chart.

These 12-lead single ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph (e.g., [redacted] or equivalent) provided by the site. Electrode placement for the chest leads will be performed according to the method of Wilson adjacent to the Holter ECG electrodes either using so- called "dual snap" or separate electrodes. The limb leads will be placed according to Goldberger and Einthoven.

All ECGs will be stored at the trial site. For each time point, a printout should be obtained and filed at the investigational site.

All locally printed ECGs will be evaluated by the investigator or a designee. These ECGs will not be sent to the central ECG laboratory. Abnormal findings will be reported as AEs (during the trial) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of adverse events

5.2.5.1.1 Adverse event

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

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

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator
- If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Adverse event report for diarrhea events:

- In case of events of diarrhoea the following definitions should be followed:
- Diarrhoea is defined ≥3 loose/liquid stools per day (WHO definition)
- If <3 stools please report as “frequent bowel movements”

5.2.5.1.2 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

5.2.5.1.3 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 5.2.5.2.

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 5.2.5.2, subsections ‘AE Collection’ and ‘**AE reporting to sponsor and timelines’**.

5.2.5.1.4 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 5.2.5.2.2.

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

- Vasculitis events

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

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

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

- Serious infections, opportunistic or mycobacterium tuberculosis infections.

  These include Pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy (PVAN), Cytomegalovirus (CMV), post-transplant lymphoproliferative disorder (Epstein–Barr virus [EBV]), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), Scedosporium/Pseudallescheria boydii, fusarium), legionellosis, Listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, Penicillium marneffei, Sporothrix

schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), Trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617]

5.2.5.1.5 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

5.2.5.1.6 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. An AE for which a causal relationship to the trial treatment is at least reasonably possible (i.e. the relationship cannot be ruled out) is to be classified as drug-related.

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

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.5.2.2), but not on the CRF.

5.2.5.2.2 AE reporting to the sponsor and timelines

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

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

5.2.5.2.3 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

In Treatment 3 [**M**], no assessment of moxifloxacin pharmacokinetics will be done, thus, there will be no PK blood sampling after open-label moxifloxacin administration.

5.3.2 Methods of sample collection

[redacted]. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. The first 0.5 mL withdrawn by an indwelling cannula will be discarded.

[redacted]

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time and aliquot (‘A1’ or ‘A2’).

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.

There will no blood samples taken in the open-label Moxifloxacin treatment arm.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

The relationship between the placebo-corrected QTcF changes from baseline (ΔΔQTcF) and corresponding plasma concentrations of [redacted] will be evaluated (see Section 7.2.4.3).

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 subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented.

Time windows are permitted as follows:

- 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
- The acceptable deviation from the scheduled time for vital signs and single safety 12-lead ECGs will be ±30 min on Day 1 and 2 of each treatment period except for procedures which are to be completed within 2 h prior to drug administration as outlined in the Flow Chart
- The timing of ECG extractions from 24-hour Holter recordings (see Flow Chart) is of particular importance in this clinical trial. Thus, triplicate ECG extraction from Holter ECG recordings will always precede PK sampling and measurements of vital signs if scheduled for the same time point. The acceptable time windows for ECG extractions in Holter ECG recordings (see Section 5.2.4) are ±5 min up to 2 h after dosing and ±10 min from more than 2 h to 24 h after dosing
- For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter. The acceptable deviations from the nominal blood sampling times are as follows:

  - The pre-dose samples will be taken ≤2 h before dosing
  - 0 to 1 h post-dose samples will be taken within ± 2 min of the planned post-dose sampling time
  - 1.5 to 12 h post-dose samples will be taken within ± 10 min of the planned post-dose sampling time
  - 24 h post-dose samples will be taken within ± 30 min of the planned post-dose sampling time

- Regarding the intended exposure-response analysis, ECG extractions and actual times of PK sampling at a planned time point need to be time-matched and should be as close as technically feasible
- If scheduled in the Flow Chart at the same time as a meal, blood sampling or vital signs assessment, the end of the ECGs extraction from Holter ECG recordings have to be performed first with the exception of single safety ECGs which should be printed before the actual ECG extractions. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due

to its inconvenience to the subject and possible influence on physiological parameters, including ECG time intervals

- For a particular subject, the clock time of dosing should be similar in all 5 treatment periods (±90 min). In case the time switch from normal time to daylight saving time (or vice versa) occurs throughout the trial conduct, the actual clock times will be followed (and not the clock times of first dosing).

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening, and pregnancy test in females), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

Screening safety procedures such as safety bloods, ECGs, vital signs, smoking (carbon monoxide) breath tests, alcohol breath tests and urinalysis can be repeated as clinically indicated under the discretion of the investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the trial.

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e. subject has not been randomized); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

6.2.2 Treatment periods

Each subject is expected to participate in 5 treatment periods (Days -1, 1, and 2 in each period). At least 7 days will separate drug administrations between treatment periods.

On Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration in all treatment periods. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2. After administration of moxifloxacin, no blood samples for pharmacokinetic analysis will be taken.

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

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

Admission/pre-dose safety procedures such as safety bloods, ECGs, vital signs, urinalysis and drugs abuse tests can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the clinical trial.

Reserve subjects for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days. If dosing is subjects who have completed admission procedures do not need admission procedures to be repeated if dosing is within 2 days and the subjects have remained resident in the clinical unit.

6.2.3 Follow-up period and trial completion

For AEs and concomitant therapies assessment, laboratory tests (including pregnancy test in females), recording of ECG and vital signs, as well as physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial (EoS) visit.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The primary objective of this clinical trial will be assessed by testing the null hypothesis for each single dose of [redacted] of BI 1015550 that the maximum mean difference between BI 1015550 and placebo in QTcF changes from baseline between 20 min to 24 hours is greater than or equal to 10 msec, against the alternative hypothesis that the maximum mean difference is below the threshold of 10 msec.

The conclusion that this tQT trial is negative as per ICH E14 will be based on the rejection of this null hypothesis for each of the two doses of BI 1015550. The one-sided tests will be performed at the 5% level, which is equivalent to the estimation of two-sided 90% confidence intervals because of the symmetry of the normal distribution. The trial will then be deemed as negative if the upper limit of the two-sided 90% confidence bound for the maximum mean difference between BI 1015550 and placebo in QTcF changes from baseline is less than 10 msec, for both doses of BI 1015550.

For the assessment of assay sensitivity of the trial, the null hypothesis that the mean difference in the QTcF changes from baseline between moxifloxacin and placebo is less than or equal to 5 msec for all of the time points 2, 3, and 4 hours after dosing will be tested at the 5 % level, against the alternative hypothesis that the mean difference is above the threshold of 5 msec for at least one of the three time points. The Hochberg correction will be used for adjusting for multiplicity (see Section 7.2.3).

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Trial design

The trial will be performed as a randomized, double-blind, 5-period crossover of single dose treatments including BI 1015550 [redacted], as well as open-label moxifloxacin. The placebo will be given twice in two separate periods. This choice of BI 1015550 doses allow subjects to reach BI 1015550 exposure levels at and above the anticipated daily exposure of BI 1015550 in the target population. The replicate design with respect to placebo allows for estimating the treatment contrasts of each active drug to placebo more precisely than with only a single placebo period, thus enabling a reduced sample size (see [R12-0517] and Section 7.5).

There will be 15 treatment sequences based on a Prescott triple Latin square design for 5 treatments and 5 periods, which is a balanced, efficient design [R14-5088]. Fifteen sequences will be formed according to the following scheme:

Table 7.2.1.1: 1 Prescott triple Latin square crossover design for 5 treatments and 5 periods

Sequence	Treatment Period 1	2	3	4	5
1	A	B	D	E	C
2	B	C	E	A	D
3	C	D	A	B	E
4	D	E	B	C	A
5	E	A	C	D	B
6	A	C	E	D	B
7	B	D	A	E	C
8	C	E	B	A	D
9	D	A	C	B	E
10	E	B	D	C	A
11	A	E	D	B	C
12	B	A	E	C	D
13	C	B	A	D	E
14	D	C	B	E	A
15	E	D	C	A	B

The allocation of the codes (A, B, C, D, E) to the 4 treatments [redacted] (see Section 3.1) will be done prior to the randomization in a way that the knowledge of the open-label treatment **M** does not unblind the other 3 treatments.

7.2.1.2 Derivation of ECG variables

[redacted]

In the second step, for obtaining one ECG variable value per subject per time point, the calculated values of the three 10-second ECGs (triplicate ECGs extracted from the Holter recordings) will be averaged.

Since it is not expected that the mean of the placebo-corrected HR change from baseline will be larger than 10 beats/min (bpm) for both doses of BI 1015550, QTcF will be selected as the heart rate correction method for the present trial.

Throughout the trial protocol, the term 'baseline' (if not specified further) refers to the 3 pre-dose triplicate ECG measurements at Visits 2-6 (i.e., a separate baseline for each period will be derived from the 9 ECG recordings that comprise 4 cardiac cycles each).

7.2.1.3 Analysis sets

Statistical analyses will be based on the following analysis sets:

- *Treated set (TS):* The treated set includes all subjects who were treated with at least one dose of trial drug.
- *ECG set (ECGS):* This subject set includes all subjects in the TS who have at least one on-treatment value for at least one ECG endpoint, which is not excluded due to ECG relevant iPDs. Such iPDs may be e.g., the use of pro-arrhythmic medications. Exclusion of single ECG values due to relevant iPDs is to be decided no later than in the Report Planning Meeting before data base lock and will be documented in the CTR
- *Pharmacokinetic parameter analysis set (PKS):* This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as a further endpoint and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.
- *ECG pharmacokinetic concentration set (ECGPCS):* This subject set includes all subjects from the ECGS who provide at least one pair of a valid [redacted] plasma concentration and a corresponding (i.e., time-matched) ECG endpoint to be used in the exposure-response analysis. The decision whether the time differences at each PTM between the respective ECG recording and PK blood sampling are acceptable (and thus whether the pairs of values will be used) is to be made no later than at the Report Planning Meeting before data base lock. For subjects treated with BI 1015550, the decision about concentration value validity needs to be made within the Clinical Pharmacology Group

The ECGS will be used for all analyses of the centrally assessed ECG data, except for the exposure-response analyses, which will be performed on the ECGPCS. The TS will be used for all other safety summaries and all safety listings. Descriptive analyses 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.

7.2.1.4 Pharmacokinetics

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

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

Important protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis). A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.2.2 Primary endpoint analyses

Primary analyses

For the analysis of the QTcF changes from baseline at each time point between 20 min to 24 hours after dosing, a linear mixed-effects model for repeated measurements (MMRM) will be used.

The comparison between each dose of BI 1015550 and placebo will be performed pairwise, i.e., data not relevant for the comparison of interest will be excluded. Data from both placebo periods per subject will be included simultaneously in the analysis, using the same treatment

code 'placebo' but differentiated by the respective period numbers. This means that the model defined below can directly be used for estimating the treatment contrast between the active drug under consideration and placebo, using the observations from both placebo periods. In the following, the 'subject baseline' is defined as the arithmetic mean of the period baselines per subject (only from the periods involved in the comparison, i.e., the period baseline of the active treatment period and those of the 2 placebo periods).

The MMRM is based on Schall and Ring [R10-5353] and includes the fixed categorical effects of 'treatment', 'period' and 'time', the 'treatment-by-time' interaction and 'period-by-time' interactions, as well as the continuous fixed covariates 'period baseline' and 'subject baseline', and the 'period baseline-by-time' interaction and 'subject baseline-by-time' interaction. Subject is included as a random effect on the intercept. For the repeated effect 'time', an unstructured covariance pattern is chosen, using the blocking factor 'subject-by-period'. Note that the 'subject baseline' is included in the model to avoid cross-level bias affecting treatment comparisons; see Kenward and Roger [R10-4391].

More precisely, the model is given by

$$Y_{ikm(j)} = \mu + \gamma B_{im} + \gamma' \bar{B}_i + \pi_m + \tau_j + \zeta_k + \gamma_k B_{im} + \gamma'_k \bar{B}_i + (\pi\zeta)_{mk} + (\tau\zeta)_{jk} + s_i + e_{ikm},$$

$$s_i \sim N(0, \sigma_s^2),\ (e_{i1m}, \ldots, e_{iKm}) \sim N_K\ (\mathbf{0}, \Psi),$$

where $i=1,\ldots,I$ indicates the subject, $k=1,\ldots,K$ the time point within period, $m=1,\ldots,M$ the period and $j=1,2$ the treatment,

$Y_{ikm(j)}$	the QTcF change from period baseline for subject i receiving treatment j in period m at repeated measures time point k,
μ	the overall intercept,
B_{im}	the baseline value for subject i in period m (period baseline),
γ	the associated covariate effect of period baseline,
$\bar{B}_i$	the subject baseline value (mean of 3 period baselines) for subject i,
γ'	the associated covariate effect of subject baseline,
π_m	the effect of period m,
τ_j	the effect of treatment j,
ζ_k	the effect of time k,
γ_k	the interaction effect of period baseline and time,
γ'_k	the interaction effect of subject baseline and time,
$(\pi\zeta)_{mk}$	the interaction effect of period and time,
$(\tau\zeta)_{jk}$	the interaction effect of treatment and time,

s_i the random effect of subject *i* on intercept, assumed mutually independent across subject,

e_{ikm} the random error associated with subject *i* for time *k* and period *m,* assumed independent across period and subject (indices *m, i*), and

Ψ an unstructured *K-by-K* covariance matrix.

The random subject effects s_i and the random errors e_{ikm} are assumed to be independent of one another.

The primary analyses use the MMRM described above for the QTcF data from BI 1015550 and placebo treatments, based on the ECG set.

For the pairwise comparisons between each dose of BI 1015550 and placebo, mean treatment differences in the QTcF changes from baseline at each time point will be estimated by the differences in the corresponding least-squares means. Two-sided 90% confidence intervals based on the t-distribution will also be computed for each time point.

Further exploratory analyses

For assessing the robustness of the MMRM defined above, a reduced model without the 'period-by-time' and the 'subject baseline-by-time' interactions will be fitted.

Subgroup analyses with respect to sex will be performed as supportive, non-confirmatory analyses.

In addition to the model based approach the QTcF changes from baseline will be analyzed descriptively.

Further analyses will be described in the TSAP, if applicable.

7.2.3 Secondary endpoint analyses

Assessment of assay sensitivity

The effect of moxifloxacin on the QTcF changes from baseline in comparison with placebo will be assessed using the same MMRM as applied in the primary analysis.

For this analysis, only the data from the moxifloxacin and placebo periods will be used.

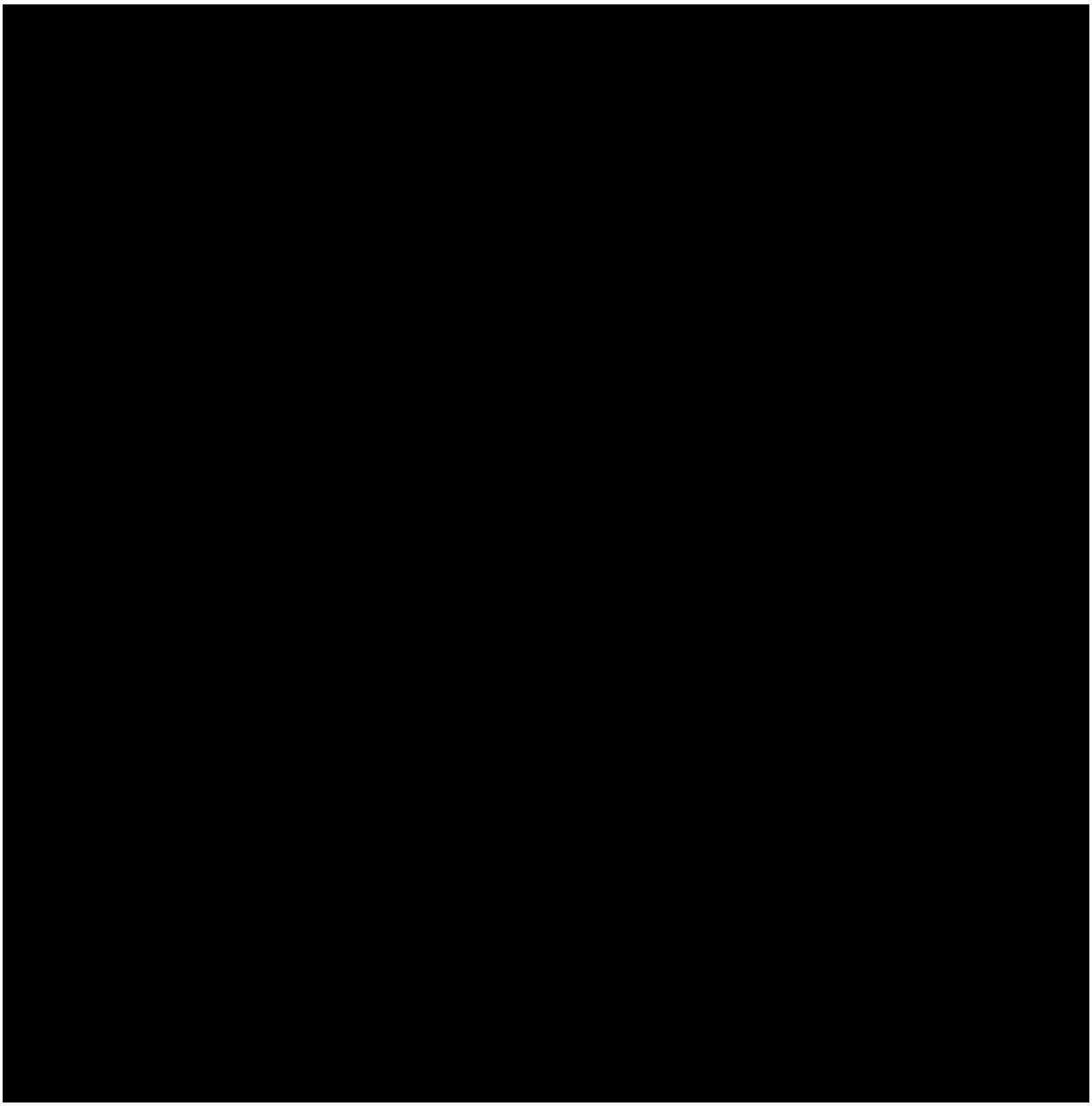
For describing the time course of the effect of moxifloxacin on QTcF, 90% confidence intervals for the mean differences of the QTcF changes from baseline between moxifloxacin and placebo will be provided.

For the formal test of assay sensitivity at level α=5%, the method by Hochberg [R97-1003] will be applied. To this end, the three single hypotheses that the mean difference in the QTcF change from baseline between moxifloxacin and placebo is less than or equal to 5 msec at a given time point (out of the three time points 2, 3, and 4 hours after drug administration) will be tested based on the results of the MMRM (fitted to the data for all time points). If the largest of the three p-values is less than 5% (=α), then all single hypotheses can be rejected. If

the second largest p-value is less than 2.5% (=α/2), then the corresponding null hypothesis and the one regarding the test with the lowest p-value can be rejected. If the lowest p-value is less than 1.667% (=α/3), then only the null hypothesis corresponding to this p-value can be rejected. Note that it is sufficient to reject only one of the three single null hypotheses in order to reject the overall null hypothesis stated in Section 7.1 (i.e., the intersection of the three single hypotheses), and hence to show assay sensitivity.

Further exploratory analyses

For assessing the robustness of the MMRM defined above, a reduced model without the 'period-by-time' and the 'subject baseline-by-time' interactions will be fitted.



7.2.5 Safety analyses

Safety will be analyzed based on the assessments described in Section 2.2.2.3. 2.2.2.3. All treated subjects (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.

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period, i.e., all adverse events with an onset between start of treatment and end of the REP, [redacted] days after the last dose of trial medication (in treatment periods with BI drug or placebo) or a period of 4 days after the last dose of trial medication (in moxifloxacin treatment period), will be assigned to the on-treatment period for evaluation. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. 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 unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.5.1), and other significant AEs (according to ICH E3) will be listed separately.

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

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

Relevant ECG findings or findings in safety laboratory data will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

Subjects will be randomized to the 15 treatment sequences in a balanced ratio. The block size will be documented in the CTR.

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

The randomization scheme will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

Access to the codes will be controlled and documented according to the standard procedures in place at BI.

7.5 DETERMINATION OF SAMPLE SIZE

The following sample size considerations are performed for the MMRM based analysis of the primary endpoint.

Thorough QT trials conducted at BI under similar conditions to the present trial, e.g. single-center, crossover, including male and female subjects, with agents not showing QTc prolongation, revealed within-subject standard deviations for the mean difference between BI drug and placebo in QTc change from baseline of about 8.5 to 11.5 msec (reference trials 1289-0038 [c30409140-01], 1245.16 [U11-1908-01], 1220.16 [U09-1853-01], 1218.32 [U09-1067-01], 1222.8 [U08-1543-02].

Based on results of trial 1305-0011, the maximum effect of BI 1015550 on the QTc interval is expected within the first 4-6 hours after drug administration. This closely related to the PK results from previous trials in healthy volunteers, where the t_{max} is expected within the first 4 hours after a single administration of BI 1015550 (Section 1.2.1.3).

In case of a QT prolonging drug effect of BI 1015550, the highest effect would be expected for the higher dose. Since the effects of the two doses on QTc are considered to be highly correlated (especially since all comparisons are done with the same comparator), the sample size determination will be based on the assumptions for the higher dose. Hence, in the following, we focus only on one single testing problem (i.e., for only one dose).

Further, since the above worst case scenarios (maximum effect over time, maximum standard deviation of the difference over time) will be used, the following power calculations are performed only for the univariate testing problem of non-inferiority at a single time point.

Since all assessments in tQT trials are based on the comparisons between active treatment and placebo, these treatment contrasts should be estimated with the highest statistical efficiency. To account for this, the selected crossover design for this trial will include a second placebo period instead of only one, following the arguments in [R12-0517]. The sample size for the resulting 4-treatment 5-period crossover design can be determined as 3/4

of the sample size for the corresponding 4-period crossover design (i.e., with the number of treatments and periods being equal); see formula (2) in [R12-0517].

Thus, in a first step the sample sizes for a crossover tQT trial with equal number of treatments and periods will be determined, which then lead to the sample size for the selected 5-period design through multiplication by 0.75 in a second step.

Using a one-sided confidence level of $\alpha = 0.05$ and a power of 90%, Table 7.5: 1 displays the required sample sizes for showing that the mean difference between BI 1015550 and placebo in the QTcF change from baseline is smaller than 10 msec under various assumptions for the within-subject variability and expected differences between the means.

Table 7.5: 1 Sample sizes assuming a power of 90% for concluding that the mean difference between BI 1015550 and placebo is less than 10 msec

LEL for difference	-999	-999	-999	-999	-999	-999
UEL for difference	10	10	10	10	10	10
Expected difference	4	4	4	5	5	5
Standard deviation of differences	10	11	12	10	11	12
Total N	26	32	36	36	44	52

LEL: Lower equivalence limit, UEL: Upper equivalence limit (one-sided $\alpha = 0.05$)
The calculations were performed using the MTE1co routine from commercial software nQuery Advisor® 7.0[R15-1331].

Therefore, in a standard crossover design with equal number of treatments and periods, a total sample size of 52 subjects will provide a power of 90% to conclude that the mean difference between BI 1015550 and placebo in QTcF change from baseline is smaller than 10 msec, if the true difference is even up to 5 msec and the standard deviation of the differences is at most 12 msec. Accounting for up to 8 potential drop outs, a total of 60 subjects would be required.

As the sample size for the 5-period crossover with 2 placebo periods can be determined as 3/4 of the sample size of the corresponding 4-period crossover, the required sample size for this trial is 45 subjects. A power of roughly 90% will be achieved under the assumptions specified above, even if up to 6 subjects are to discontinue the trial prematurely.

Regarding the assessment of assay sensitivity, the maximum mean difference in the QTcF change from baseline between moxifloxacin and placebo can be expected to be around 12 msec, with a standard deviation of up to 10 msec, based on previous BI tQT trials. If just one single test (for one time point out of the three; see Section 7.2.3) was performed at level $\alpha/3=1.667\%$, and taking into account the design with 2 placebo periods, the power to reject the corresponding null hypothesis given a sample size of 45 would be 99.7%. If the true value of the maximum placebo-corrected change from baseline would be only 11 msec, still the power for the single test would be 98.2 %. The power to reject the overall null hypothesis stated in Section 7.1 using the Bonferroni method would be larger than the above values in each scenario, since in that case all three single tests would be performed at level $\alpha/3$, and

only one would have to be significant. The power of the Hochberg method described in Section 7.2.3 is again larger than that of the Bonferroni method [R97-1003].

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 Medicines for Human Use (Clinical Trials) Regulations SI 2004, No 1031, as amended 2006 (SI No. 1928 and No. 2984), 2008 (SI No 941) and 2019 (SI No. 744), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding.

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

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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

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

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

- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the contract research organisation [redacted] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. 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 Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany, or will be obtained by the clinical trial site from public pharmacy (Moxifloxacin (Avelox® [redacted] plc)).

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]

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

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

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

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

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n00201162

n00201163

n00201440

n00261809

U08-1543-02

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 SEP 2023
IRAS ID No.		1008273
BI Trial number		1305-0026
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1) 3.3.4.1 2) 3.3.4.3
Description of change		1) Withdrawal from trial treatment Criterion 5 is updated 2) Discontinuation of the trial by the sponsor Criterion 4 is updated
Rationale for change		The CTP is amended in response to the RA/EC comments

11.2 GLOBAL AMENDMENT 2

Date of amendment		21 MAR 2024
IRAS ID No.		1008273
BI Trial number		1305-0026
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		See below
Description of change		Title Page: Clinical Trial Leader changed Synopsis: The pharmacokinetic analyte was corrected to R-BI 1015550. Flow Chart: The time point of 30 min post dose (Holter ECG extraction, PK, AE) was changed to 20 min post dose for reasons of consistency with the primary ECG-endpoint. The pharmacokinetic analyte was corrected to R- BI 1015550. Section 1.2.1.3: Description of the chiral nature of BI 1015550. [redacted] Section 3.3.2:Inclusion Criterion 5 was updated: estradiol below 30 ng/L was removed as confirmatory in questionable cases of postmenopausal status definition, since FSH above 40 U/L alone is confirmatory.

		Section 5.2.3:Table 5.2.3: 2 is updated: G6PD blood test added to Exclusionary tests as per Exclusion Criterion 34. [redacted]
Rationale for change		Change in Clinical Trial Leader. Correction of inconsistencies, typos and obvious mistakes.

APPROVAL / SIGNATURE PAGE

Document Number: c41839189 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-03

Title: Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	21 Mar 2024 14:37 CET
Approval-Clinical Program [redacted]		21 Mar 2024 16:01 CET
Verification-Paper Signature Completion		22 Mar 2024 09:40 CET
Author-Trial Statistician		22 Mar 2024 09:58 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed