Clinical Trial Protocol

	Document Number: c19450453-02
BI Trial No.:	1305-0017
BI Investigational Product:	BI 1015550
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled, parallel group design)
Lay Title:	This study is done in healthy Japanese volunteers. It looks at how different doses of BI 1015550 are taken up in the body and how well they are tolerated.
Clinical Phase:	I
Trial Clinical Monitor:	Tel: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment1))
Version and Date:	Version: 2.0 Date: 1 May 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1015550			
Protocol date: 22 Mar 2018	**Trial number:** 1305-0017		**Revision date:** 1 May 2018

Title of trial:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled, parallel group design)
Principal Investigator:	
Trial site(s):	
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics following single rising doses of BI 1015550
Methodology:	Double-blind randomised within dose groups, placebo-controlled, parallel-group design
No. of subjects:	
total entered:	24 Japanese
each treatment:	8 per dose group (6 on active drug and 2 on placebo)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy Japanese male subjects Age ≥20 and ≤45 years BMI range: ≥18.5 and ≤25.0 kg/m^2
Test product:	BI 1015550 as tablet formulation (TF 1 containing 6 mg BI 1015550)
dose:	Single dose of 12 mg, 24 mg and 36 mg
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator product:	Matching placebo as tablet formulation
dose:	Not applicable
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment:	Single dose
Criteria for pharmacokinetics:	The following pharmacokinetic parameters of BI 1015550 will be calculated. Secondary endpoints: $AUC_{0-\infty}$ and C_{max}

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1015550			
Protocol date: 22 Mar 2018	**Trial number:** 1305-0017		**Revision date:** 1 May 2018
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 1015550 is the number [N (%)] of subjects with drug-related adverse events. Further criteria of interest: Treatment emergent AEs (TEAEs) including clinically relevant findings from the physical examination, safety laboratory tests (including testing for fecal occult blood and fecal calprotectin, urinalysis for hematuria), 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR], body temperature).		
Statistical methods:	Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory/Urinalysis		Vital signs [8,12]	12-lead ECG[12]	Continuous ECG monitoring	PK blood				Questioning for AEs and concomitant therapy[7]
1	-28 to -1			Screening examination[1]	x		x	x[3]						
2	-3 to -1	-72:00	9:00	Ambulatory visit	x[11]									x
	-1	-12:00	21:00	Admission	x[11]									x
	1	-3:00	6 :00	Randomization	x[14, 17]		x[14]	x[3,14, 18]		x[14]				x
		0:00	9:00	Drug administration					⊤					x
		0:15	9:15						|	x				x
		0:30	9:30				x	x[3]	|	x				x
		0:45	9:45						|	x				x
		1:00	10:00				x	x[3]	|	x				x
		1:15	10:15						|	x				x
		1:30	10:30				x	x[3]	|	x				x
		2:00	11:00	240 mL fluid intake[10]			x	x[3]	|	x				x
		3:00	12:00						|	x				x
		4:00	13:00	Lunch[10]	x		x	x[3]	⊥	x				x
		6:00	15:00							x				x
		8:00	17:00	Snack (voluntary)[10]			x	x[3]		x				x
		10:00	19:00				x	x[3]						x
		11:00	20:00	Dinner										x
		12:00	21:00							x				x
	2	24:00	9:00	Breakfast[10]	x[19]		x	x[3]		x				x
		28:00	13:00	Lunch										
		34:00	19:00							x				x
		35:00	20:00	Dinner										
	3	48:00	9:00	Breaskfast[10]			x	x[3]		x				x
		52:00	13:00	Lunch										
		59:00	20:00	Dinner										
	4	72:00	9:00	Discharge[5]	x[19]		x	x[3]		x				x
	5	96:00	9:00	Ambulatory visit[20]			x	x		x				x
	6	120:00	9:00	Ambulatory visit[20]	x[19]		x	x		x				x
3	8 to 9			End of trial (EOT) examination[4]	x		x	x						x

1. Screening (28 to 1 days before drug administration) including subject information, informed consent, check of inclusion/exclusion criteria, physical examination, laboratory including fecal occult blood and fecal calprotectin testing, vital signs, ECG, demographics including body weight and height, drug and virus screening, alcohol breath test, medical history and concomitant therapy (cf. Section 6.2.1).

3. Three 12-lead ECGs (triplicate ECG) will be recorded.
4. End-of-trial examination to be performed within 2-3 days after last PK sampling; including physical examination, vital signs, ECG, laboratory, concomitant therapy, AE review.
5. Discharge by the investigator or designee after confirmation of fitness of the subject

7. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
8. Blood pressure (BP), pulse rate (PR), body temperature, and respiratory rate (RR).

10. If several actions are indicated at the same time point, the intake of meals/fluid will be the last action.
11. Drug screen and alcohol breath test will be performed on admission. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
12. Blood pressure (BP), pulse rate (PR), respiratory rate and ECG after 10 minutes lying in supine position

14. The time is approximate; the respective procedure is to be performed and completed within 3 h prior to drug administration.

17. Only urinalysis
18. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
19. Urinalysis on Days 2, 4, and 6 to be performed within ±3 hours from planned time
20. Procedures on Days 5 and 6 to be performed within ±3 hours from planned time

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
b.i.d.	*Bis in die*, twice daily
BLQ	Below the limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P
DDI	Drug drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case report form
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
F	Absolute bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice

gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in safety testing
MRD	Multiple-rising dose
MTD	Maximum tolerated dose
nM	Nanomolar
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)

REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SD	Standard Deviation
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE(s)	Treatment emergent adverse event(s)
TMF	Trial master file
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WBC	White Blood Cells

1. INTRODUCTION

1.2 DRUG PROFILE

1.2.5.1.4 Clinical experience with other PDE4 inhibitors

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

Cilomilast
Cilomilast was the first selective PDE4 inhibitor developed for the maintenance of lung function (FEV_1) in patients with COPD but failed to demonstrate efficacy to support approval of the drug. Cilomilast nonclinical findings include mesenteric arteritis in rats. In the clinical program the frequency of gastrointestinal AEs was high. Fecal occult blood testing was benign with unremarkable colonoscopy findings in the few patients with blood in the stool. Lack of approval was based on inadequate evidence of efficacy rather than any safety concern [P06-08316].

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

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

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The objective of this trial 1305-0017 is to investigate safety, tolerability and pharmacokinetics of BI 1015550 and thereby provide essential information for a clinical development of BI 1015550 as a treatment for IPF.

In this study, safety, tolerability and pharmacokinetics of BI 1015550 will be assessed in healthy male volunteers to define a safe and tolerable dose for use in Japanese subjects.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 1015550 in healthy male subjects following oral administration of single rising doses of 12 mg, 24 mg, and 36 mg.

Secondary objectives are the exploration of the pharmacokinetics (PK)
after single dosing.

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 1015550 as a treatment for IPF. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

2.3.1 Procedure-related risks

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

ECG electrodes may cause local and typically transient skin reactions.

The total volume of blood withdrawn during the entire study per subject will not exceed the volume of a normal blood donation (400 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

2.3.2 Drug-related risks and safety measures

BI 1015550 is considered a low risk compound for the purpose of this trial:

In this trial a single dose of 12 mg, 24 mg and 36 mg BI 1015550 will be administered that has been investigated and well tolerated in humans before.

2.3.3 Safety measures

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

- Careful dose selection as described in Section 2.1.
- Dose escalation is only permitted if there are no safety concerns and if none of the pre-specified stopping criteria are met. The minimum time interval between last dosing in a given dose group and the first dosing in the next higher dose group is 7 days. For details see Section 3.1 and Section 3.3.4.2.
- Safety laboratory examinations including surrogate markers of inflammation/vasculitis will be performed as described above
- A thorough ECG and heart rate monitoring including continuous ECG measurement over 4 hours post dose to cover the anticipated period of highest drug exposure and additional repeated single and triple 12-lead ECGs
- During in-house confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Subjects have to use adequate contraception as detailed in Section 3.3.3.

2.3.4 Overall assessment

BI 1015550 is a PDE4 inhibitor that has been safely administered to humans before.

The currently available toxicology data suggest that BI 1015550 can be safely administered to men and women of non-childbearing potential for up to13 weeks. Considering the good tolerability of BI 1015550 in two previous clinical trials, the well characterized target structure and its mode of action and taking into account the safety measures described above, participation in this trial does not represent an undue risk to healthy subjects.

Vasculopathy is the main concerns related to PDE4 inhibitors. Although vasculitis has not been observed in humans with the marketed PDE4 inhibitors close monitoring of surrogate markers of intestinal inflammation will be performed. Further the investigator will pay special attention of any signs of mood changes.

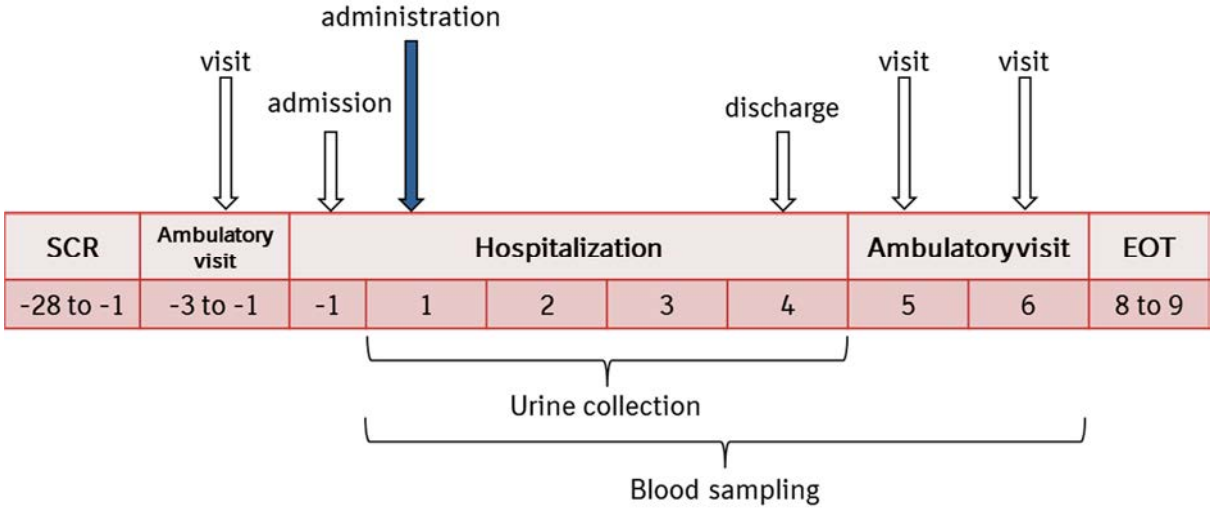
IPF is a devastating disease with significant associated morbidity and mortality and limited treatment options. BI 1015550 as a selective PDE4 B inhibitor has the potential to offer improved efficacy and/or tolerability as add-on to registered anti-fibrotics or as a mono therapy in IPF. Considering the medical need for a better treatment of IPF the sponsor feels that the benefit of this trial outweighs the potential risks and justifies exposure of healthy volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups. (Figure 3.1:1)

Figure 3.1:1 Study Design Overview



Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group.

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups

Dose Group	1	2	3
Dose (mg)	12	24	36
Number of subjects	8	8	8
Subjects receiving placebo	2	2	2
Subjects receiving active drug	6	6	6

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 7 days between the last drug administration in the previous dose group and the first drug administration of the subsequent dose group. The next dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2). The decision to proceed to the 36 mg dose group will be based upon the safety, tolerability, pharmacokinetic of the preceding dose groups.

The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

3.1.1 Administrative structure of the trial

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

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required 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 monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

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

The trial will be conducted in under the supervision of the Principal Investigator.

Safety laboratory tests will be performed by the local laboratory of the trial site or/and at a CRO designated by the sponsor.

The analyses of BI 1015550 will be performed at a suitable contract research organization (CRO) under the responsibility of the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ( ) for evaluation.

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 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.

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

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

With the rising dose design, double-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacodynamic effects. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 healthy male subjects will enter the study. Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 20 to 45 years (incl.) at screening.
3. BMI of 18.5 to 25.0 kg/m^2 (incl.) at screening.

4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm at screening
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance at screening
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and 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 mood disorders and any history of suicidality
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections including viral hepatitis, human immunodeficiency virus (HIV) and/or syphilis. (Subject with positive Hepatitis B core antibody will not allowed to participate in this trial)
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on trial days
15. Alcohol abuse (consumption of more 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site

20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Male subjects who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until three months after the study completion. Acceptable methods of contraception comprises barrier contraception and a medically accepted contraceptive method for the female partner (intra-uterine device or hormonal contraceptive since at least two months)

In addition, the following trial-specific exclusion criteria apply:

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the ‘DILI checklist’ provided in the ISF.

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
6. Dose escalation will be stopped, if the predicted gMean C_{max} or AUC of 36 mg dose group is above the experienced gMean exposure of the 48 mg single dose in 1305.11 Prediction will be done after 24 mg dose group based on preliminary pharmacokinetics results of preceding dose groups as specified in Section 7.3.4.

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

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Tablet formulation 1 (TF1)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mg
Posology:	Dose group 1: 2-0-0
	Dose group 2: 4-0-0
	Dose group 3: 6-0-0
Route of administration:	p.o.
Duration of use:	Single dose

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

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

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of 3 dose groups, the following subjects will be allocated to one of the other dose group. Therefore, the allocation of subjects to dose group is not influenced by trial personnel, but only by the subjects'

temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

Three dose groups are to be investigated in this trial.

This trial is designed to evaluate the safety, tolerability, and pharmacokinetics of BI 1015550 in Japanese healthy young male volunteers. A safe and tolerable dose achieved in previous trials is used as a reference for the dose selection in this trial.

Furthermore, there will be preliminary PK analysis of dose groups 1 and 2 to decide whether dose group 3 is warranted.

For safety margins and further details on dose selection see Section 2.1.1.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the respective dose level.

Table 4.1.4: 1 BI 1015550 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total dose
1	BI 1015550	Tablet	6 mg	2 tablets as single dose	12 mg
2	BI 1015550	Tablet	6 mg	4 tablets as single dose	24 mg
3	BI 1015550	Tablet	6 mg	6 tablets as single dose	36 mg
1-3	Placebo*	Tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

Subjects will be kept under close medical surveillance until at least 72 h following drug administration. During the first 4 hours after drug administration subjects will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG) or medical reasons (e.g., adverse events).

For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to database lock.

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist, as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician.

In addition, the trial bioanalyst will receive the randomization codes prior to official unblinding to perform the preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

4.1.5.2 Procedures for emergency unblinding

For blinded trials, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation 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.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. Containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Subject or medication number
- Batch number

Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial 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 as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication must be returned to sponsor. Receipt, usage and

return must be documented on the respective forms. Account must be given for any discrepancies.

The investigator or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor 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 products and trial subjects. The investigator or pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of return to the sponsor, the investigator or pharmacist must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of 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 medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until 4 hours post-dose liquid intake is restricted to the fluid administered with the drug and an additional 240 mL of water served at 2 h (mandatory for all subjects). From 4 hours post-dose until 24 hours post-dose water intake is restricted to 3000 mL. During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

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

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

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

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

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 1015550 is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

- TEAEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests, including fecal occult blood and fecal calprotectin testing and urinalysis
- 12-lead ECG
- Abnormal findings in the Continuous ECG monitoring if rated as AE
- Vital signs (blood pressure, pulse rate, respiratory rate and body temperature)

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence 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 or not considered related to the medicinal product.

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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,

  or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical 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.

The following events will be handled as 'deemed serious for any other reason'. AEs which possibly lead to disability will be reported as SAEs.

AEs considered 'Always Serious'

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

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

The latest list of 'Always Serious AEs' can be found in the RDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.2.2.

The following are considered as AESIs:

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

- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the 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 these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) 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

Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE collection

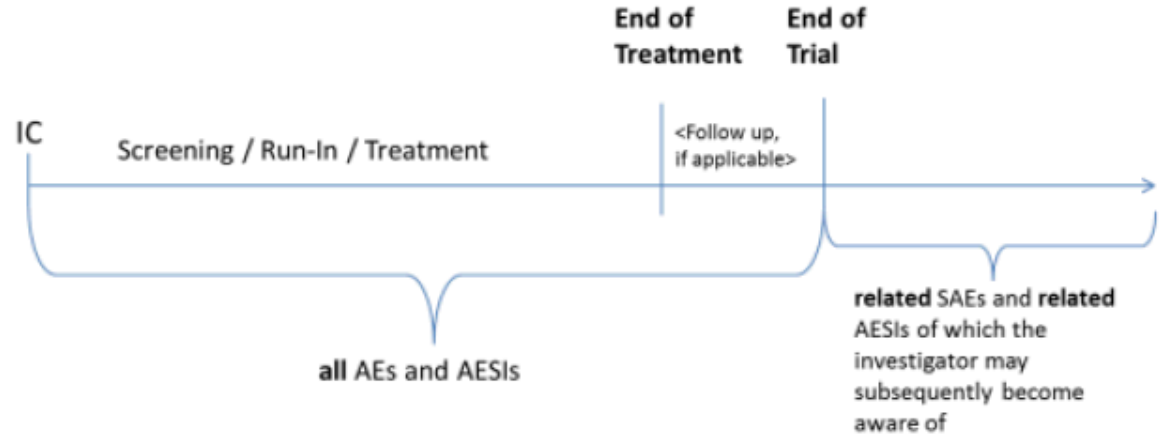
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. 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 careful 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, and intensity of the event as well as 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:
    - 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 or trial database 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 AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.



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

AE reporting to sponsor and timelines

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

With receipt of any 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication. The following should also be recorded as an (S)AE in the CRF and on the 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 CRF only.

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

Pregnancy
Once the male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and 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 Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

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

The parameters that will be determined are listed in Table 5.2.3:1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count will only be performed if there is an abnormality in the automatic blood cell count, i.e. if automatic count is not feasible or differential WBC is abnormal (i.e. pathological or atypical cells) and clinically relevant in the opinion of the investigator.

In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein and clinically relevant in the opinion of the investigator, microscopic examination of the urine sediment will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	EOT
Hematology	Hematocrit	x	x	x	x	x
	Hemoglobin	x	x	x	x	x
	Red blood cell count (RBC)	x	x	x	x	x
	Reticulocyte count	x	x	x	x	x
	White blood cell count (WBC)	x	x	x	x	x
	Platelet count	x	x	x	x	x
	Erythrocyte sedimentation rate (ESR)	x	x	x	x	x
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x	x	x
Manual differential WBC (if automatic count is not feasible or differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes					
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x	x
	Prothrombin time (Quick's test and INR)	x	x	x	x	x
	Fibrinogen	x	x	x	x	x
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x	x	x
	Alkaline phosphatase (AP)	x	x	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x	x	x
	Creatine kinase (CK); CK-MB only if CK is elevated	x	x	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x	x	x
	Lipase	x	x	x	x	x
	Amylase	x	x	x	x	x
Hormones	Thyroid stimulating hormone (TSH)	x	--	--	--	x
	fT3, fT4	x	--	--	--	x
Substrates	Plasma glucose	x	--	--	x	x
	Creatinine	x	x	x	x	x
	Total bilirubin	x	x	x	x	x
	Direct bilirubin	x	x	x	x	x
	Total protein	x	x	x	x	x
	high sensitivity C-Reactive Protein (hsCRP)	x	x	x	x	x
	Uric acid	x	x	x	x	x
	Total cholesterol	x	x	x	x	x
	Triglycerides	x	x	x	x	x
	Albumin	x	x	x	x	x
Electrolytes	Sodium	x	x	x	x	x
	Potassium	x	x	x	x	x
	Calcium	x	x	x	x	x
	Chloride	x	x	x	x	x
	Inorganic phosphate	x	x	x	x	x
Urinalysis (Stix)[4]	Urine nitrite	x	x	-	x	x
	Urine protein	x	x	-	x	x
	Urine glucose	x	x	-	x	x
	Urine ketone	x	x	-	x	x
	Urobilinogen	x	x	-	x	x

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	EOT
	Urine bilirubin	x	x	-	x	x
	Urine erythrocytes	x	x	-	x	x
	Urine leukocytes	x	x	-	x	x
	Urine pH	x	x	-	x	x
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine and clinically relevant in the opinion of the investigator)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)					

[1] A: Days -3 to -1
[2] B: post-dose on Day 1
[3] C: Days 2, 4, 6
[4] Urinalysis will be done at pre-dose on Day 1

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

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

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (MAC 800 ECG machines, GE Healthcare) at the time points given in the Flow Chart.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

All ECGs will be recorded for 10 seconds duration after subjects have rested for at least 10 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

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

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For time points with triple ECGs, all three single ECGs will be repeated. The repeat ECGs are assigned to the respective scheduled time point.

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

Storing

All ECGs will be stored electronically on the Muse Cardiology Information System (GE Medical Systems, Freiburg, Germany).

Data transfer

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

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

Evaluation

a) Central ECG lab

A post-study centralized evaluation of all 12-lead ECGs recorded after Days 1 up to 72 h after drug administration will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECG at a single assessment time will be evaluated. The remaining second and third replicate ECG will be stored for additional analyses if required, e.g. by authorities at a later time point. HR and QTc (QT interval corrected for HR, e.g. QTcF and QTcB) will be determined in house (see TSAP for details).

Abnormalities detected during centralized ECG evaluation will not necessarily qualify as AE. All interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For blinding arrangements see Section 4.1.5.1. No more than two different blinded readers will evaluate all ECGs of the study. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs. After the quality control the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration. This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will not be transferred to the clinical trial database. Abnormal findings during continuous ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 10 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

Further, respiratory rate [RR] and body temperature will be monitored. Body temperature will be determined at the time points indicated in the Flow Chart using electronic thermometers (Name of device at site). Respiratory rate will be counted by trained study personal by observing the chest movements over a period of one minute after the subject has rested in the supine position for 10 minutes. Recording of the values will be done at the time points indicated in the Flow Chart.

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body temperature and respiratory rate), 12-lead ECG, laboratory tests including fecal occult blood and fecal calprotectin testings and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests and a physical examination.

5.4 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 and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values including surrogate markers for gastrointestinal vasculitis, 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 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters for BI 1015550 will be determined if feasible:

5.5.1.1 Primary endpoints

- Not applicable

5.5.1.2 Secondary endpoints

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis of BI 1015550

For quantification of analyte plasma concentrations,3 mL of blood will be taken from an antecubital or forearm vein into an EDTA (ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Centrifugation will be started within 45 min after blood withdrawal (with interim storage of blood samples in ice water or on ice). Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma. Plasma aliquots will be frozen within 2 hours after blood withdrawal (interim storage of plasma at room temperature or in ice/water or on ice). For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the

bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information such as “PK”, matrix and aliquot number (e.g. 1 or 2/back-up) may also be provided.

After bioanalysis of BI 1015550, left-over plasma samples may be used for further methodological investigations**,** e.g. for stability testing and/or, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of drug plasma concentration

Concentrations of BI 1015550 in plasma from subjects will be determined by a validated LC-MS/MS assay (liquid chromatography, tandem mass spectrometry). The bioanalyst will be unblinded during sample analysis. The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization (CRO).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK

The acceptable deviation on profile days from the scheduled time for vital signs and ECG will be -15 min and for laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter.

will be done as indicated and described in the Flow Chart.

The tolerance for drug administration will be ± 1 min on Days 1.

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

For planned individual plasma concentration sampling times and
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.

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.

Relevant time violations will be identified and their handling discussed no later than at the (Blinded) Report Planning Meeting (cf. Section 7.4).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Each subject will receive one dose of the respective trial medication (BI 1015550 or placebo) at Visit 2. Trial medication will be taken orally by each subject under direct supervision of the investigator or designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 72 h following the drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.

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

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

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1015550 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) of BI 1015550. Endpoints as specified in Sections 5.5.1 and 5.6.1 will be analysed by descriptive statistics. Secondary endpoints as defined in Section 5.5.1.2 will be subjected to analysis of dose proportionality by use of the power model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 3 different dose groups of BI 1015550 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

7.3 PLANNED ANALYSES

All individual data will be listed.

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

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ (001-MCS-36-472). Analyses will be performed for parent drug. 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 violation 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.

Relevant protocol violations may be

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

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

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

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

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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

The analyses will be done by ‘randomised treatment’.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs(TEAEs)).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake and end of REP (see Section 5.2.2.2) will be assigned to the treatment period. Events after the residual effect period but prior to end of trial examination will be summarized as ‘post-treatment’, those after the end of trial examination will be assigned to ‘post-study’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the ECG variables QT, HR, QTcF, QTcB, PR, QRS, RR, and further derived ECG parameters. The derivation of the quantitative and qualitative ECG parameters and their analyses will be described in the TSAP.

7.3.4 Preliminary pharmacokinetic analyses

A preliminary analysis of PK parameters of dose groups 1 and 2 ($AUC_{0-\infty}$ and C_{max} of BI 1015550), provided as individual values and geometric means of all subjects, will be performed before proceeding to dose level 3.

Data from the above mentioned dose levels will be sufficient as long as PK data up to 48h after drug administration from at least 4 subjects on active treatment are available.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times. Therefore, minor deviations of preliminary and final results may occur. The preliminary analysis will provide summary statistics of individual PK parameters without subject identification. The preliminary results will be distributed to the investigator and the trial team.

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

No inferential statistical interim analysis is planned. However, after each dose group the investigator (or deputy) is allowed to postpone further dose progression until a preliminary analysis of the data already obtained has been performed.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1015550 will be calculated using validated software (preferably Phoenix WinNonlin®) according to the BI

SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment. Descriptive evaluations of PK parameters are based on 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).

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak

detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

7.5 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 24 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

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

Insurance Coverage: The terms and conditions of the insurance coverage are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

The subject must be informed that his medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, or by regulatory authorities. The quality assurance

auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:
The trial site must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

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

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

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

8.6 COMPLETION OF TRIAL

When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

The investigator or sub-investigator should record all CTP violations. The investigator should provide and submit the sponsor and the head of the trial site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial subjects and for other medically inevitable reasons.

8.8 COMPENSATION AVAILABLE TO THE SUBJECT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		1 May 2018
EudraCT number		
BI Trial number		1305-0017
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled, parallel group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title page
Description of change		Information of Trial Clinical Monitor (TCM) Changed the information from ‘ Phone: + Fax: + to ‘ . Tel: Fax: ’
Rationale for change		Affiliation of TCM is changed

Number of global amendment		1
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Exclusion Criteria #9 Added the sentence in 'including viral hepatitis, human immunodeficiency virus (HIV) and/or syphilis (Subject with positive Hepatiits B core antibody will not be allowed to participate in this trial.)'
Rationale for change		To address PMDA requirement
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Exclusion Criteria #23 Changed the contraception periods from two months to three months
Rationale for change		To address PMDA requirement

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		02 May 2018 13:14 CEST
Approval-Therapeutic Area		02 May 2018 13:15 CEST
Author-Trial Statistician		07 May 2018 01:08 CEST
Author-Trial Clinical Pharmacokineticist		08 May 2018 01:52 CEST
Approval-Team Member Medicine		09 May 2018 13:30 CEST
Verification-Paper Signature Completion		09 May 2018 13:34 CEST

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