Clinical Trial Protocol

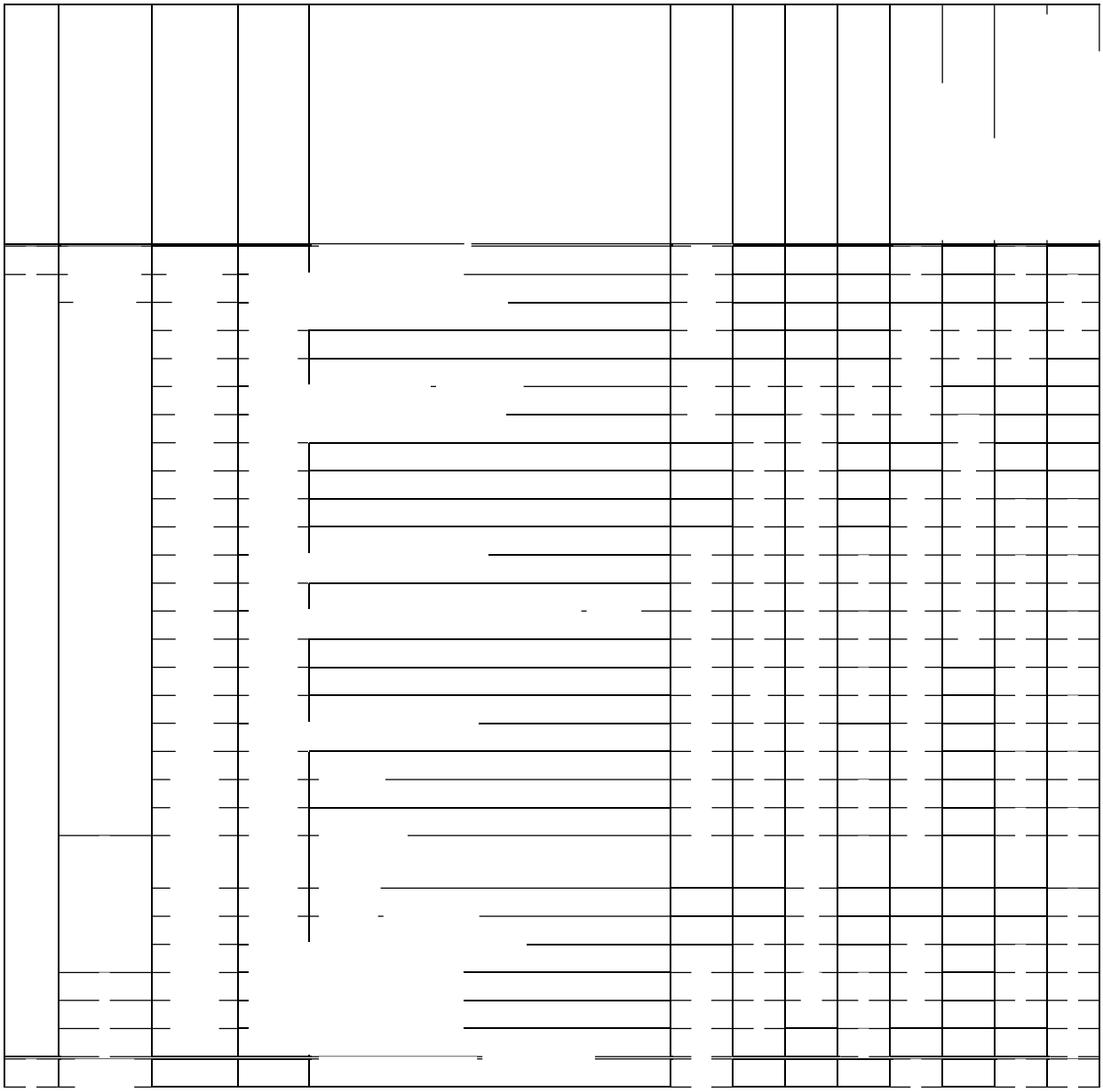
	Document Number: c21116620-03
EudraCT No.:	2017-004899-62
BI Trial No.:	1405-0001
BI Investigational Product:	BI 1323495
Title:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 1323495 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design)
Lay Title:	This study in healthy men tests how different doses of BI 1323495 are taken up in the body and how well they are tolerated.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 28 August 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1323495			
Protocol date: 24 April 2018	**Trial number:** 1405-0001		**Revision date:** 28 August 2018

Title of trial:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 1323495 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics following single rising oral doses of BI 1323495
Methodology:	Single-blind, partially randomised within dose groups, placebo-controlled, parallel-group
No. of subjects:	
total entered:	64*
each treatment:	8 per dose group (6 on active drug and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 64, but will not exceed 80 subjects.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test products:	BI 1323495 film-coated tablets (dose strengths mg)
dose:	mg as single dose
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator products:	Matching placebo tablets
dose:	Not applicable
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment:	one single dose

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1323495			
Protocol date: 24 April 2018	**Trial number:** 1405-0001		**Revision date:** 28 August 2018
Criteria for pharmacokinetics:	Secondary endpoints: AUC and C		
Criteria for pharmacodynamics:			
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 1323495 is the number [N (%)] of subjects with drug-related adverse events. Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]).		
Statistical methods:	Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 1323495 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed.		



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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration
β	Slope parameter associated with the power model used to evaluate dose proportionality
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
gMean	Geometric mean
HPC	Human Pharmacology Centre

HR	Heart rate
IB	Investigator's brochure
IC_{50}	Half-maximal inhibitory concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MRSD	Maximum recommended starting dose
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
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
ss	(at) steady state
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

In this study, BI 1323495 will be given to humans for the first time. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising doses of BI 1323495 will be investigated.

1.2 DRUG PROFILE

For details on nonclinical pharmacology refer to the current version of the Investigator's Brochure (IB, c21238478-01).

1.2.2 Toxicology

Details on toxicology results are provided in the current version of the IB (c21238478-01).

1.2.5 Clinical experience in humans

To date, no experience with BI 1323495 is available in human.

1.2.6 Drug product

Further details are given in the Investigator's Brochure (c21238478-01).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As a transition from preclinical investigations to clinical development in this first-in-man trial, safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 1323495 will be assessed in healthy male volunteers using single rising oral doses in order to provide the basis for a potential ongoing clinical development of BI 1323495

Healthy male subjects aged 18 - 45 years will be recruited for this study. They provide a relatively stable physiological, biochemical, and hormonal basis (steady state) for studying drug effects, they show no disease-related variation, and they are not taking concomitant medication.
Within each dose group, all actively treated individuals will receive the same BI 1323495 dose. The next higher dose will only be administered (to the next group) if the treatment in the preceding dose groups was safe and showed acceptable tolerability.

It is intended to investigate the following dose levels of BI 1323495 in this trial:
mg.
The background for this dose selection is described in the following paragraphs.

2.1.1 Starting dose

It is best practice to use different methods for dose selection and to take a starting dose at the lower end of the dose range if different methods give different estimates (err on the side of caution).

Applying the respective calculation as given in the US FDA Guidance for Industry 'Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers' (R06-1037), and assuming a no adverse effect level (NOAEL) of a maximum recommended starting dose (MRSD) as high as could be selected based on the 4 week toxicology data A detailed description of the derivation of the MRSD can be found in the IB (c21238478-01).

The therapeutic human dose of BI 1323495 is predicted to be (see Section 1.2.4). The starting dose should be sub-therapeutic; therefore it should be lower than the expected therapeutic dose. Application of a factor of 10 to the predicted therapeutic human dose results in a maximum recommended safe starting dose of approximately in humans.
A single dose of is predicted to achieve exposures of
which is well below expected therapeutic exposures of
providing even sufficient margin to therapeutic exposures should the bioavailability be higher than the predicted (see Section 1.2.4).

Finally, another commonly used NOAEL-based approach, following ICH guidance M3 (R2), is to use a fraction of the NOAEL, e.g. 1/50 or 1/100 (R09-1400). Based on the NOAEL of body weight and assuming a body weight of 50 kg the starting dose would be in the range of

Taken together, different approaches give a starting dose in the range of

is finally considered as an appropriate and safe starting dose based on:

- Published experience from clinical trials with administration of and achieving higher levels of target engagement over longer periods of time not revealing any mode of action-related adverse effects (Section 1.2.5);
- the toxicological profile of BI 1323495 in relevant animal models (Section 1.2.2);
- the effect being reversible;
- only single doses being applied;
- lower peak exposures being expected in

Therefore at expected exposures achieved with this dose, is not expected to trigger any relevant or unacceptable biological activity (Section 1.2.5).

2.1.2 Maximum dose and dose escalation

As stated above, a minimum daily dose of about may be required to achieve therapeutic systemic exposure of BI 1323495. Nevertheless, it is planned to explore higher doses / exposures in this trial for several reasons. Subsequent clinical trials in patients might show that required therapeutic doses and exposures are significantly higher than predicted. Also, higher doses / exposures might be required for more severe disease states, for induction vs. maintenance treatment, and for other indications. So while higher doses and exposures might still be well tolerated they provide a larger magnitude of therapeutic effects. Further, testing of doses higher than is also reasonable to compensate for any bioavailability and half-life being lower/shorter than expected. If, for example, bioavailability was significantly less than the predicted (see Section 1.2.4), the therapeutic dose could eventually turn out to be several fold higher than currently predicted. And even if the therapeutic dose turns out to be as low as higher than therapeutic doses / exposures are typically explored in the well-controlled clinical environment of first-in-man trials to provide a safety margin for following trials, e.g. drug-drug-interaction trials, trials with patients with impaired excretion function, etc., where substantial increases in exposure may be seen.

The maximum human exposure to BI 1323495 in this trial will be limited to nM for C_{max} and nM*h for AUC_{0-24}.

This provides a safety margin with a factor of at least 24 (C_{max}) and 21 (AUC) to the exposures achieved after 4-week administration of /kg in the most sensitive species,

These findings are not expected after a single administration of BI 1323495 at doses achieving exposure levels well below exposures
With respect to the NOAEL in the 4-week toxicity study
the maximum human exposure defined above provides safety factors of 16 and 10, respectively. The given safety margins refer to the lower exposures
With respect to the NOAEL in in the 4-week toxicity study
this maximum human exposure provides safety margins of approximately 28 and 34, respectively.
On the other hand, the defined acceptable maximum exposure for this trial provides a margin of factor (C_{max}) and (AUC) above the expected therapeutic exposure
to explore the therapeutic potential of the compound.

For the present trial, a maximum dose of has been selected, but this dose will only be administered if, based on interim PK measurements (see Section 7.3.4), individual C_{max} or AUC_{0-24} values at a lower dose or predicted geometric mean values of C_{max} or mean AUC_{0-24} do not exceed exposure limits defined above. Otherwise dose escalation will be stopped at lower doses. Based on the preclinical safety profile of BI 1323495, these exposure limits are anticipated to be safe and well tolerated.
The escalation schedule has been chosen in a way that a shallow escalation will be applied for the higher dose levels with a factor not greater than 1.5. This dose escalation is considered to be adequate and safe, particularly when the selected exposure safety margins are taken into consideration.

2.1.3 Conclusion

The safe starting dose in this study is determined to be This dose is not expected to trigger any relevant or unacceptable biological activities.

An exposure threshold is defined

The following dose escalation scheme is planned:
as single oral dose. Dose escalation will be guided by interim PK measurements (see Section 7.3.4) and projected exposure levels.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 1323495 in healthy male subjects following oral administration of single rising doses.

Secondary objectives are the exploration of the pharmacokinetics (PK) including dose proportionality and pharmacodynamics (PD) of BI 1323495 after single dosing and the assessment of the PK/PD relationship.

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 a new orally available drug, which might improve the therapy in patients with
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.

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

2.3.2 Drug-related risks

Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models and/or (4) findings in non-clinical safety studies.

2.3.2.5 Drug-induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.2.1, adverse events of special interest.

2.3.3 Safety measures

- Dose selection was based on a sound preclinical package including 4 week toxicological studies (see Section 1.2.3) and non-clinical pharmacology data (Section 1.2.1).

  Careful selection of starting dose as described in Section 2.1.

  Dose escalation will be shallow with an increase of not more than 1.5 fold at the higher dose groups.

- Measurement of BI 1323495 plasma concentrations and preliminary determination of PK parameters (C_{max}, $AUC_{0-24,}$ see Section 7.3.4). For precautionary reasons, drug plasma concentrations in this healthy volunteer trial should not exceed a C_{max} of or an AUC_{0-24} of and will be considered as a preliminary threshold (see Section 2.1). Further dose progression would only be allowed after a safety interim analysis and filing and approval of a substantial CTP amendment.
- For safety reasons, each dose group of 8 subjects (6 on active, 2 on placebo) will be divided into three cohorts. In the 1st cohort only 2 subjects will be treated: one subject will receive active treatment, the other subject will receive placebo. If BI 1323495 treatment is safe and well tolerated in this first cohort, the following 2 subjects on active will be treated in the 2nd cohort with drug administration occurring not earlier than 24 hours after the first subject of the dose level received active treatment. The remaining 4 subjects (either active or placebo) are the third cohort and will be treated no sooner than 48 hours following the 1st cohort. Within each cohort, a time interval of at least 10 min will be maintained between administrations of study drug.

  This design ensures that between first and second active dose of each dose level there is a time interval of at least 24 hours, which is expected to be sufficient to detect relevant first acute effects of BI 1323495.
- Only if the respective dose of BI 1323495 was safe and showed acceptable tolerability and if no stopping criterion was met (see Section 3.3.4.2), the next higher dose will be given at least 6 days later (referring to the 1st subject of each dose group).
  A documented Safety Review must take place prior to each dose escalation (see Section 3.1).
- An extensive safety laboratory will be performed (see Section 5.2.3).
- A thorough ECG monitoring including continuous ECG measurement over 4 hours post-dose and repeated 12-lead ECGs during the observation period following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.2 for details).
- The subjects will stay at the trial site (BI Human Pharmacology Centre) for at least 34 hours after study drug administration. Based on an anticipated half-life of BI 1323495 of approximately this is expected to cover the period of highest risk / peak effect.
- During in-house confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.

In summary, although not tested in humans to date, BI 1323495 has the potential to become an oral treatment for patients with . Based upon preclinical data for BI 1323495 and clinical information from competitor compounds as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this first-in-man clinical trial with BI 1323495. Considering the medical need of the development of an effective treatment for patients with the Sponsor considers

that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups.

A total of 64 healthy male subjects is planned to participate in the trial, according to 8 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g., preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 64, but will not exceed 80 subjects entered. Such changes may be implemented via non-substantial CTP Amendments provided additional doses are used for the further evaluation of pharmacokinetics or pharmacodynamics in the absence of new safety signals. The addition of dose groups to further evaluate safety findings may be implemented only after notification of a substantial amendment.

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. Each dose group will consist of 3 cohorts which will be treated subsequently for safety reasons.

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	4	5	6	7	8
Dose								
Number of subjects	8	8	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2	2	2
Subjects receiving active drug	6	6	6	6	6	6	6	6

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 6 days between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next dose group will be based upon the safety, tolerability, and pharmacokinetic data of the preceding dose groups. 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).

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested any time for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety

concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy).

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e., no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2).

The minimum data set for review consists of the following data:

- AEs in the current* and preceding dose groups including clinically relevant findings from ancillary safety testing listed below up to at least 48 h post-dosing.
  Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock.

- Vital signs in the current* and preceding dose groups up to at least 48 h post-dosing
- Clinical laboratory tests in the current* and preceding dose groups up to at least 24 hours post-dose
- Preliminary PK data for selected time points as per Section 7.3.4
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

*"Current dose group" means: all subjects of that dose group with at least 4 subjects being on active treatment.

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. 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 at the , under the supervision of the Principal Investigator.

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

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 or a contract research organisation appointed by BI and 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 1323495.

With the rising dose design, single-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 and tolerability. 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 64 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 64 if additional intermediate doses will be tested (see Section 3.1). 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 18 to 45 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
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
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
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
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
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 specified trial days
15. Alcohol abuse (consumption of more than 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 with female partner of childbearing potential who are unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after last administration of trial medication
24. Current or history of relevant kidney, urinary tract diseases or abnormalities (e.g. nephrolithiasis, hydronephrosis, acute or chronic nephritis, renal injury, renal failure)
25. Estimated glomerular filtration rate according to CKD-EPI formula < 90 mL/min at screening (R12-1392)
26. Within 10 days prior to administration of trial medication, use of any drug that could reasonably inhibit platelet aggregation or coagulation (e.g., acetylsalicylic acid)

27. Liver enzyme (ALT, AST, GGT) values above upper limit of normal at the screening examination

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. 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.

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 first 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. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity.

No further subjects will be dosed without thorough re-evaluation of the benefit-risk ratio, if severe non-serious adverse events considered as drug-related by the investigator are reported in 2 subjects of the same dose group or if at least one drug-related serious adverse event is reported.

2. The expected enrolment goals overall are not met
3. Violation of GCP, or the CTP 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. absolute QT or QTc greater than 500 which has been confirmed by a repeat ECG recording or 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 C_{max} or AUC_{0-24} of at least 1 subject of one dose group increases above the following exposure thresholds or if the estimated systemic exposure (group gMean values) of the next dose level is expected to exceed a C_{max} of nM or an AUC_{0-24} of nM*h. In this case, one or two dose levels lower than the planned next dose level may be given, as long as the expected systemic exposure (group gMean values) of each dose is not expected to exceed the aforementioned thresholds.

3.3.5 Replacement of subjects

In case some subjects do not complete the trial or there is not a sufficient number of subjects on active within one dose group (see Section 3.1), 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 products have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational and comparator products

The characteristics of the test products are given below:

Tablet

Substance:	BI 1323495
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	1-0-0 (DG 1), 3-0-0 (DG 2), 6-0-0 (DG 3)
Route of administration:	p.o.
Duration of use:	Single dose

Tablet

Substance:	BI 1323495
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	2-0-0 (DG 4), 4-0-0 (DG 5), 6-0-0 (DG 6)
Route of administration:	p.o.
Duration of use:	Single dose

Tablet

Substance:	BI 1323495
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	3-0-0 (DG 7), 4-0-0 (DG 8)
Route of administration:	p.o.
Duration of use:	Single dose

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

Placebo to Tablet

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

Placebo to Tablet

Substance:	Placebo matching in size and weight to mg tablet
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	2-0-0 (DG 4), 4-0-0 (DG 5), 6-0-0 (DG 6)
Route of administration:	p.o.
Duration of use:	Single dose

Placebo to Tablet

Substance:	Placebo matching in size and weight to mg tablet
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	3-0-0 (DG 7), 4-0-0 (DG 8)
Route of administration:	p.o.
Duration of use:	Single dose

In addition to the above listed test and reference products, BI 1323495 film-coated tablets and matching placebo tablets will be provided if need be to test doses that cannot be covered by tablets.

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose cohorts according to their temporal availability. As soon as enough subjects have been allocated to a dose cohort, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts 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 randomisation list with study subject numbers and allocated treatments 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

The doses selected for this trial cover the sub-therapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2 and 2.1).

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 1323495 and placebo treatments, oral administration

Dose	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total dose
1	BI 1323495	Film-coated tablet		1 tablet as single dose	
2	BI 1323495	Film-coated tablet		3 tablets as single dose	
3	BI 1323495	Film-coated tablet		6 tablets as single dose	
4	BI 1323495	Film-coated tablet		2 tablets as single dose	
5	BI 1323495	Film-coated tablet		4 tablets as single dose	
6	BI 1323495	Film-coated tablet		6 tablets as single dose	
7	BI 1323495	Film-coated tablet		3 tablets as single dose	
8	BI 1323495	Film-coated tablet		4 tablets as single dose	
1-8	Placebo*	Film-coated tablet	--	identical to respective active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The trial medication will be administered to the subjects, while in a standing or 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 24 h following drug administration. During the first 4 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. 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 treatments administered (active or placebo) will be single-blind (that is, subjects will not know whether they receive active treatment or placebo). However, the current dose level will be known to the subjects.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site. The trial bioanalyst and pharmacokineticist may receive the randomisation codes prior to official unblinding to perform the interim / preliminary PK analysis. He or she will treat the codes confidentially.
In addition, the drug metabolism scientist may receive the randomization codes prior to official unblinding to perform metabolites in safety testing analysis (MIST). He or she will confirm in writing that the codes will be treated confidentially.

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.
If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unblinded. This part of the staff will be strictly separated from the blinded staff members who are involved with ECG interval measurements and assessments of ECGs.

The database of this trial will be handled open-label, because no bias with regard to data cleaning or safety measures is expected. This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blinded, the treatment information will be known to the investigator. Therefore, no emergency envelopes will be provided.

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. The required information according to the German Drug Law as well

as Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes within the clinical trial supply 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

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. 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 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
- 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 will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

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

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator 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 disposal, the investigator 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.

should be avoided during the entire study. If necessary, short term use of ibuprofen or paracetamol is acceptable.

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 beverages 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 lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24h post-dose, total fluid intake is restricted to 2.75 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 administration of trial medication until after the last PK sample is collected.

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

Methylxanthine-containing beverages or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during the in-house confinement at the trial site.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the 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 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 1323495 is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

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

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.

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the CRF only.

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

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 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 eDC system, an electronic data capture system which allows the entry of trial data at the trial site. 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:

- o an elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
- o aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks

of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- 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 trial 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 carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's end of trial:
  - 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 new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs that 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 relevant to these events, a follow-up SAE form has to be provided.. For follow-up information, the same rules and timelines apply as for the initial information.

Information required

All (S)AEs, including those persisting after the 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 a 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 a male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point. This requires 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 well as non-trial specific information and consent for the pregnant partner.

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 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 Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Haematology	Haematocrit	x	x	x	x
	Haemoglobin	x	x	x	x
	Red Blood Cell Count/Erythrocytes [RBC]	x	x	x	x
	Reticulocytes, absol.	x	-	-	-
	Reticulocytes/Erythrocyte	x	-	-	-
	White Blood Cells/Leucocytes [WBC]	x	x	x	x
	Platelet Count/Thrombocytes (quant)	x	x	x	x
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	x	x	x	x
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	x	x	x	x
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.	x	x	x	x
Coagulation	Activated Partial Thromboplastin Time	x	x	x	-
	Prothrombin time – INR (International Normalization Ratio)	x	x	x	-
	Fibrinogen	x	x	-	-
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	x	x	x	-
	ALT [Alanine transaminase] /GPT, SGPT	x	x	x	-
	Alkaline Phosphatase [AP]	x	x	x	-
	Gamma-Glutamyl Transferase [GGT]	x	x	x	-
	Glutamate Dehydrogenase [GLDH]	x	x	x	-
	Creatine Kinase [CK]	x	x	-	-
	Creatine Kinase Isoenzyme MB [CK-MB], if CK is elevated	x	x	-	-
	Lactic Dehydrogenase [LDH]	x	x	x	-
	Lipase	x	x	-	-
Hormones	Thyroid Stimulating Hormone [TSH]	x	-	-	-
Substrates	Glucose Plasma (fluorid citrate)	x	x	-	-
	Creatinine	x	x	x	-
	GFR/ CKD-EPI	x	x	x	-
	Bilirubin, Total	x	x	x	-
	Bilirubin, Direct	x	x	x	-
	Protein, Total	x	x	-	-
	Albumin	x	x	x	-
	C-Reactive Protein (Quant)	x	x	x	-
	Uric Acid	x	x	-	-
	Urea	x	x	x	-
	Cholesterol, total	x	x	-	-
	Triglyceride	x	x	-	-
Electrolytes	Sodium	x	x	x	-
	Potassium	x	x	x	-
	Chloride	x	x	x	-
	Calcium	x	x	x	-

[1] A, B, C, and D are different sets of laboratory values. The Flow Chart defines at what time point which set is to be investigated

Table 5.2.3: 1 Routine laboratory tests (cont)

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Urinalysis (Stix)	Urine Nitrite (qual)	x	x	x[2]	-
	Urine Protein (qual)	x	x	x[2]	-
	Urine Glucose (qual)	x	x	x[2]	-
	Urine Ketone (qual)	x	x	x[2]	-
	Urobilinogen (qual)	x	x	x[2]	-
	Urine Bilirubin (qual)	x	x	x[2]	-
	Urine RBC/Erythrocytes (qual)	x	x	x[2]	-
	Urine WBC/Leucocytes (qual)	x	x	x[2]	-
	Urine pH	x	x	x[2]	-
Urine sediment (microscopic examination)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	x	x	x[2]	-
Spot urine	Urine Albumin (quant)	x	x	x[2]	-
	Urine Alpha-1 Microglobulin (quant)	x	x	x[2]	-
	Urine Creatinine	x	x	x[2]	-
	Urine Immunoglobulin G (quant)	x	x	x[2]	-

[1] A, B, C, and D are different sets of laboratory values. The Flow Chart defines at what time point which set is to be investigated

[2] Urinalysis will not be done at time point 4h (Day 1/Visit 2)

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. Infectious serology tests will be performed during screening only. Drug screening will be performed at screening and prior to drug administration on Day 1.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to treatment, 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 with the exception of the drug screening tests. These tests will be performed at the trial site using M-10/14-PDT test (or comparable test kit).

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

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 (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) 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 inhouse confinement.

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 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording should precede all other study procedures scheduled for the same time 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 repetition within triplicate ECGs the time window of 180 sec applies as well. 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

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab for evaluation.

All ECG recordings including repeat ECGs will be sent to the central ECG lab which will select the ECGs with the best quality at each time point.

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).

Abnormal findings, irrespective of whether they originate from central or local evaluation, 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 using the CARESCAPE Monitor B450 (GE Healthcare, Freiburg, Germany) 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) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

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), 12-lead ECG (including rhythm strip of at least 15 minutes), laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.4 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, 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. The biomarkers and measurements outlined in Section 5.6 are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded. Exact time points of plasma sampling will be derived from the study management system ClinBase™ and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g., preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 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

For quantification of BI 1323495 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

After completion of the trial, the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The 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

BI 1323495 concentrations in plasma will be determined by validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assays. All details of the analytical methods will be available prior to the start of sample analysis. The analyses will be performed at

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

The relationship of BI 1323495 plasma concentrations and biomarker results will be investigated in an exploratory manner Other correlations will be explored as applicable.

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 and biomarkers).

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 4 h after trial drug administration and ± 30 min thereafter. Starting from 48 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests (including PK) of ±120 min is acceptable.

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

For planned individual plasma concentration sampling times
refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will 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), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

Pharmacogenomic genotyping will be performed in those volunteers whose genotypes are not known (for details see Section 5.3).

6.2.2 Treatment period

Each subject will receive one dose of the respective trial medication (BI 1323495 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.

Study participants will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 34 h following 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. From Day 3 onwards, the study will be performed in an ambulatory fashion.

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

For details on time points and procedures for collection of blood samples for PD analysis, refer to Flow Chart and Section 5.6.2.

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 withdraw before the end of the planned treatment period should undergo the end of trial visit.

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

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 1323495 by using descriptive statistics for all endpoints comparing active dose groups to placebo.

The secondary objective is the exploration of the pharmacokinetics (PK) and pharmacodynamics (PD) of BI 1323495.

7.1.2 Endpoints

Safety and tolerability will be determined on the basis of the primary endpoint and the additional criteria specified in Section 5.2.1. PK and PD endpoints are specified in Sections 5.5.1 and 5.6.1, respectively.

7.1.3 Model

Endpoints will be analysed by descriptive statistics. Inferential statistics is not planned (as explained in Section 7.2).

Secondary endpoints, as defined in Section 5.5.1.1, will be subjected to analysis of dose proportionality by use of the power model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of the different dose groups of BI 1323495 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 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.

α β

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

To support the analyses of dose proportionality, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of plasma concentrations and the (geometric) mean plasma concentration time profiles.

7.3.3 Safety analyses

Safety will be assessed for the endpoints and parameters of interest 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. For additional analyses sets used in the ECG evaluation see TSAP for further details. 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 ‘treatment at onset’.

The REP for BI 1323495, the time interval when measurable drug levels or PD effects are still likely to be present after administration, is not known for this first-in-human trial. Therefore, all AEs with an onset between start of treatment and the end of trial examination (last per protocol contact) will be considered on 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).

Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to 'screening' and those between trial medication intake until the end of trial visit will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing 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.

7.3.4 Preliminary PK analyses

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 1323495) provided as individual values and geometric means will be performed for

- DG 1 before proceeding to DG 3
- DG 1-2 before proceeding to DG 4
- DG 1-4 before proceeding to DG 5
- DG 1-5 before proceeding to DG 6
- DG 1-6 before proceeding to DG 7
- DG 1-7 before proceeding to DG 8

Note: Data from the first cohorts of the above mentioned dose levels will be sufficient as long as the data from at least 2 subjects on active were available.

In contrast to the final PK/PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification. The preliminary results will be distributed to the Investigator and the trial team.

Depending on the results of available preliminary PK/PD analyses, the tolerability and safety of the compound, and changes of dosing schedule (e.g. additional intermediate doses) additional PK/PD preliminary analysis may be performed based on the request of the Trial Clinical Monitor, 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.

The pharmacokinetic parameters AUC_{0-24} and C_{max} for BI 1323495 will be calculated according to the BI SOP

The non-compartmental analysis will be performed using the validated software program A quality check of the interim data will be performed.

Available information on dose linearity from preceding dose groups will be considered when estimating C_{max} and AUC values to be expected for the next higher dose to be administered.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for BI 1323495 will be calculated according to the BI SOP

Subjects who are not included in the PKS (refer to Section 7.3.1) 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.

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

7.3.6 Biomarker analysis

The biomarker parameters listed in Section 5.6 will be evaluated according to the BI SOP

Graphical representations versus time and descriptive statistics will be provided for above mentioned biomarkers as well as for raw data thereof. If applicable, a statistical model will be applied to the biomarker data. Biomarker assessments might be used to establish a PK/PD relationship. Further details will be provided in the TSAP.

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

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), or BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor

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 will be set to zero. All other BLQ 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

Each dose group will be divided into three cohorts. The subjects of the first and second cohorts will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. In the third cohort of each dose level the subjects will be assigned to active or placebo treatment using a 3:1 allocation ratio.

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 64 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).

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 64, but will not exceed 80 subjects entered.

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.

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.

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 must be given to each subject and 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/her 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 or her 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. 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.

Data directly entered (that is, without prior written or electronic record) are considered to be source data. The place where data is entered first will be defined in a trial specific Source Data Agreement. The data in are available for inspection at any time.

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 and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

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, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		4 July 2018
EudraCT number		2017-004899-62
BI Trial number		1405-0001
BI Investigational Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 1323495 in healthy male subjects (single-blind, partially 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	1) 2) 3) 4) 5) 6) 7) 8) 9) 10) 11) 12) 13)	Synopsis Flow Chart 2.1 Rationale for performing the trial 2.1.2 Maximum dose and dose escalation 2.3.3 Safety measures 3.1 Overall trial design and plan 3.3.3 Exclusion criteria 3.3.4.2 Discontinuation of the trial by the sponsor 5.2.3 Assessment of safety laboratory parameters 5.6.1 Biochemical and cellular biomarkers 6.2.2 Treatment period 7.3.4 Preliminary PK analyses 7.3.6 Determination of sample size

Number of global amendment		1
Description of change	1)+ 6)+ 13)	Clarification under which circumstances additional subjects / dose groups may be entered
	2)	
	3)	"X" deleted in heading
	4)	Individual exposure limits defined
	5)	Individual exposure limits defined; inhouse observation period extended
	7)	Amended eGFR value (exclusion criterion 25) and limits for liver enzyme values (new ex-criterion 27)
	8)	Stopping criteria with respect to adverse events and exposure limits revised
	9)	Added parameter Set D in Table 5.2.3: 1 and specified that fasting is not required for timepoints when Set D is to be taken
	10)	
	11)	Text adapted to extended inhouse oberservation period
	12)	Specified methods and software used for preliminary PK analyses
Rationale for change	1)	Request by Competent Authority/risk mitigation
	2)	Flow chart amended according to changes introduced
	3)	Typo corrected
	4)	Request by Competent Authority/risk mitigation
	5)	Request by Competent Authority/risk mitigation
	6)	Request by Competent Authority/risk mitigation
	7)	Request by Competent Authority/risk mitigation
	8)	Request by Competent Authority/risk mitigation
	9)+ 10)	
	11)	Amended according to changes introduced
	12)	Request by Competent Authority
	13)	Request by Competent Authority/risk mitigation

Number of global amendment		2
Date of CTP revision		28 August 2018
EudraCT number		2017-004899-62
BI Trial number		1405-0001
BI Investigational Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 1323495 in healthy male subjects (single-blind, partially 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		Flow Chart
Description of change		New time points for PK blood sampling introduced:

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 1323495 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		29 Aug 2018 10:10 CEST
Approval-Team Member Medicine		29 Aug 2018 10:42 CEST
Approval-Therapeutic Area		29 Aug 2018 11:01 CEST
Author-Trial Clinical Pharmacokineticist		29 Aug 2018 12:10 CEST
Verification-Paper Signature Completion		29 Aug 2018 14:17 CEST
Author-Trial Statistician		03 Sep 2018 09:27 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed