



Clinical Trial Protocol

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BI Trial No.: 1305-0020

BI Investigational Product: BI 1015550

Title: Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects

Lay Title: This study in healthy men tests how food influences the amount of BI 1015550 in the blood.

Clinical Phase: I

Trial Clinical Monitor:

Phone:

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Principal Investigator:

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Status: Final Protocol

Version and Date: Version: 1.0 Date: 11 July 2017

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		Tabulated Trial Protocol		
Name of finished product: Not applicable				
Name of active ingredient: BI 1015550				
Protocol date: 11 July 2017	Trial number: 1305-0020		Revision date: Not applicable	
Title of trial:	Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects			
Principal Investigator:				
Trial site:				
Clinical phase:	I			
Objective:	To investigate the relative bioavailability of BI 1015550 as tablet formulation following oral administration under fed and fasted conditions			
Methodology:	Open-label, randomized, single dose, two-period, two-sequence crossover design			
No. of subjects: total entered: each treatment:	12 12			
Diagnosis:	Not applicable			
Main criteria for inclusion:	Healthy male subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m ²			
Test product:	BI 1015550 as tablet formulation			
dose:				
mode of admin.:	Oral with 240 mL of water following a high fat breakfast (treatment test (T)) and after an overnight fast of at least 10 h (treatment reference (R))			
Duration of treatment:	2 single doses (treatment R = fasted, treatment T = fed) separated by a washout phase of at least 7 days			
Criteria for pharmacokinetics:	Primary endpoints:	AUC _{0-tz} and C _{max}		
	Secondary endpoints:	AUC _{0-∞}		

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Name of company:		Tabulated Trial Protocol			
Boehringer Ingelheim					
Name of finished product:					
Not applicable					
Name of active ingredient:					
BI 1015550					
Protocol date: 11 July 2017	Trial number: 1305-0020		Revision date: Not applicable		
Criteria for safety:	Treatment emergent adverse events (TEAEs) including clinically relevant findings from the physical examination, safety laboratory tests including testing for fecal occult blood and fecal calprotectin, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])				
Statistical methods:	Descriptive statistics will be calculated for all endpoints. Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA.				

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FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Fecal occult blood and fecal calprotectin testing	PK blood	12-lead ECG	Vital signs	Questioning for AEs and concomitant therapy ⁹
SCR	1	-21 to -1			Screening ¹	x	x		x	x	x
1/2 (two identical periods with a washout of at least 7 days)	2/3	-5 to -1	-120:00	08:00	Ambulatory visit (visit 2 only)	x ⁸	x ⁸				x ⁸
		-1	-12:00	20:00	Admission to trial site ²	x ^{2,6}					x ²
		1	-03:00	05:00	Allocation to subject number ³ (visit 2 only)			x ³	x ³	x ³	x ³
			-00:30	07:30	High fat, high calorie breakfast (only in treatment T)						
			0:00	08:00	Drug administration						
			0:15	08:15				x			
			0:30	08:30				x			
			0:45	08:45				x			
			1:00	09:00				x			
			1:15	09:15				x			
			1:30	09:30				x			
			2:00	10:00	240 mL fluid intake ⁷			x			
			3:00	11:00				x			
			4:00	12:00	240 mL fluid intake, lunch ⁷			x	x	x	x
			6:00	14:00				x			
			8:00	16:00	Snack (voluntary) ⁷			x			
			10:00	18:00					x	x	
			11:00	19:00	Dinner						
			12:00	20:00				x			x
		2	24:00	08:00	Discharge ⁵	x		x	x	x	x
			34:00	18:00	Ambulatory visit			x			x
		3	48:00	08:00	Ambulatory visit			x			x
		4	72:00	08:00	Ambulatory visit			x			x
		5	96:00	08:00	Ambulatory visit			x			x
		6	120:00	08:00	Ambulatory visit	x		x			x
EOT	4	8 to 15			End of trial (EOT) examination ⁴	x	x		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), fecal occult blood and fecal calprotectin testing, demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; subjects should be admitted no later than 10 hours before scheduled drug administration.
3. The time is approximate; the respective procedure is to be performed and completed within 3 h prior to drug administration and prior to predose meal intake.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies

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5. Discharge by the investigator or his designee after confirmation of fitness of the subject
6. Only urine drug screening and alcohol breath test.
7. If several actions are indicated at the same time point, the intake of meals/fluid will be the last action.
8. Safety laboratory, fecal occult blood test and fecal calprotectin testing to be taken and to be medically evaluated within 5 days prior to first administration of study drug; these procedures can be omitted, if the screening examination is performed on Days -5 to -1.
9. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the [Flow Chart](#) above.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AUC _{0-∞}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC _{t₁-t₂}	Area under the concentration-time curve of the analyte in plasma over the time interval t ₁ to t ₂
AUC _{0-t_z}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BALF	Bronchoalveolar lavage fluid
BI	Boehringer Ingelheim
b.i.d.	<i>Bis in die</i> , twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
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
CML	Clinical Monitor Local
CNS	Central Nervous System
CRA	Clinical Research Associates
CRF	Case report form
CRO	Contract research organization
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
δ	Bioequivalence margin
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial

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ES	Entered set
F	Absolute bioavailability factor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
HPC	Human Pharmacology Centre
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
IEC	Independent Ethics Committee
IPF	Pulmonary fibrosis
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LI	Linearity index
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mode of action
MRT _{po}	Mean residence time of the analyte in the body after oral administration
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference treatment
RDC	Remote Data Capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment

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TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TEAEs	Treatment emergent adverse events
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{\max}	Time from dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

BI 101550 is a potent and selective inhibitor of the Phosphodiesterase 4 (PDE4) enzyme and has been shown to have both anti-inflammatory and anti-fibrotic activities.

This trial will investigate the effect of food on pharmacokinetics of BI 101550.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the effect of food on the pharmacokinetics of the oral tablet formulation of BI 1015550 by investigating the relative bioavailability of TF1 under fed and fasted conditions.

The assessment of safety and tolerability will be an additional objective of this part.

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 1015550

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

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catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

ECG electrodes may cause local and typically transient skin reactions.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be performed as a randomized, open-label, single dose, two-period, two-sequence crossover trial in healthy male subjects in order to compare the test treatment (treatment T = fed) to the reference treatment (treatment R = fasted). The subjects will be randomly allocated to the two treatment sequences (T-R or R-T).

A total of 12 healthy male subjects are planned to participate in this trial.

The treatments will be two single oral doses BI 1015550 separated by a washout period of at least 7 days between the treatments:

Treatment T: tablets of BI 1015550 as Trial Formulation 1 (TF1), **fed**

Treatment R: tablets of BI 1015550 as Trial Formulation 1 (TF1), **fasted**

For details refer to Section [4.1](#).

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 (TCM), 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.

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

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

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

Data management and statistical evaluation will be done by BI or by a suitable contract research organization (CRO) under the responsibility of BI and according to BI SOPs.

Tasks and functions assigned in order to organize, 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 relative bioavailability trials, the crossover design is preferred due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes intersubject variability from the comparison between treatments [cf. [R94 1529](#)].

Blinding is not possible because the treatments are distinguishable.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte provided by a bioanalytical laboratory which is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 12 healthy male subjects will enter the study. Subjects will be recruited from the volunteers' pool of the trial site.

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 55 years (incl.)

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3. BMI of 18.5 to 29.9 kg/m² (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 45 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)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders including but not limited to mood disorders and any signs of suicidality (ideation as well as behavior) in the past
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 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

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

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

24. Positive or missing fecal occult blood test
25. Positive testing for hematuria if confirmed by microscopic urine analysis

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, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥ 3 -fold ULN combined with an elevation of total bilirubin ≥ 2 -fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

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

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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 residual effect period (REP) (see Section [5.2.2.2](#)), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP 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.

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product

The characteristics of the test product are given below:

Substance: BI 1015550

Pharmaceutical formulation: Tablet formulation 1 (TF1)

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength:

Posology: 4-0-0

Route of administration: p.o.

Duration of use: Single dose in treatments T (fed) and R (fasted)

4.1.2 Method of assigning subjects to treatment groups

The randomization list of study subject numbers and assigned treatment sequences 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 in the morning of Day 1 (Visit 2). For this purpose, the subjects will be allocated to a study subject number by drawing lots. By the use of the randomization list subjects are then assigned to a treatment sequence.

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

The randomization procedure is described in Section [7.5](#).

4.1.5 Blinding and procedures for unblinding

No blinding was performed because the treatments are distinguishable from each another.

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

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Emergency envelopes will not be provided, since all subjects receive the same dose of the same formulation in this open label design.

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

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. 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
- 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

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- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol

Only authorized 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 authorization 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 authorize symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardized 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 milk served with breakfast in treatment T (see Table [4.1.4: 2](#)), the water administered with the drug, and an

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additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

For each study period, alcoholic beverages are not permitted starting 5 days before the first administration of trial medication until the last PK sample is collected; grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (*Hypericum perforatum*) are not allowed from 7 days before the first administration until collection of the last PK.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 hours before until 24 h after each administration of trial medication.

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

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study center 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

Safety and tolerability of the investigational drug will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event

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

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

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- requires inpatient hospitalization or
- requires prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,
or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize 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 hospitalization 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 duration between 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 given above.

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

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class.

AESIs need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
 - o 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
 - o aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

These lab findings constitute a hepatic injury alert and the patients 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

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(ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analyzed, 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.

With the exception of DILI, no AESIs have been defined for this trial.

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 etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

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- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AEs collection

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

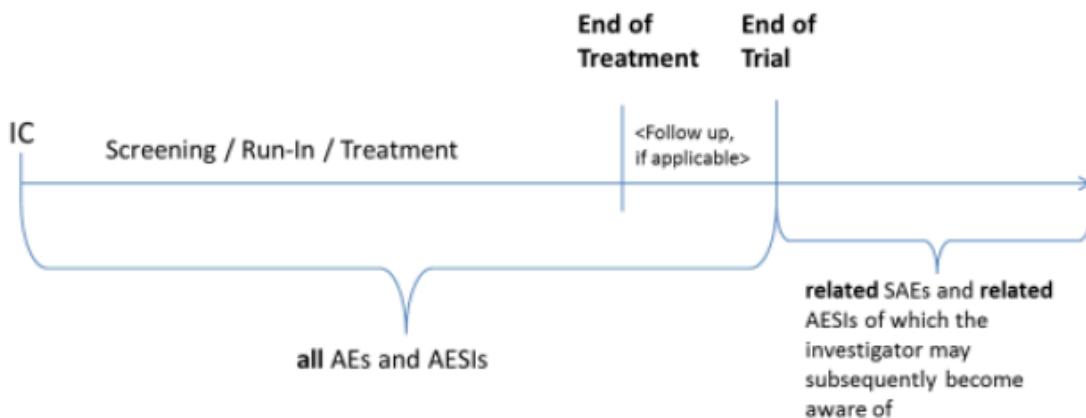
Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will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

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

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

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

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The Residual Effect Period (REP) for BI 101550, when measurable drug levels or PD effects are still likely to be present, is defined as _____ after the last administration of BI 101550. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section [7.3.3](#). Events which occurred after the REP will be considered as follow-up events.

AE reporting to sponsor and timelines

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication.

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

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

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

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

Pregnancy

If applicable:

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

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. 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 B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

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

The parameters that will be determined are listed in Tables [5.2.3: 1](#) and [5.2.3: 2](#). Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count will only be performed if there is an abnormality in the automatic blood cell count. In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein, microscopic examination of the urine sediment will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Fecal occult blood testing will be performed using an immunochemical test kit for hemoglobin. Fecal occult blood and calprotectin testing will be performed by the clinical laboratory at the time points indicated in the Flow Chart.

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Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	SCR	A¹	B²	EOT
Hematology	Hematocrit	X	X	X	X
	Hemoglobin	X	X	X	X
	Red blood cell count (RBC)	X	X	X	X
	Reticulocyte count	X	--	--	X
	White blood cell count (WBC)	X	X	X	X
	Platelet count	X	X	X	X
	Erythrocyte sedimentation rate (ESR)	X	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	X	X	X	X
Manual differential WBC (if automatic count is not feasible or differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes				
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X	X
	Prothrombin time (Quick's test and INR)	X	X	X	X
	Fibrinogen	X	X	X	X
Enzymes	Aspartate transaminase (AST/GOT)	X	X	X	X
	Alanine transaminase (ALT/GPT)	X	X	X	X
	Alkaline phosphatase (AP)	X	X	X	X
	Gamma-glutamyl transferase (GGT)	X	X	X	X
	Glutamate dehydrogenase (GLDH)	X	--	--	X
	Creatine kinase (CK); CK-MB only if CK is elevated	X	X	X	X
	Lactate dehydrogenase (LDH)	X	X	X	X
	Lipase	X	--	--	X
	Amylase	X	--	--	X
Hormones	Thyroid stimulating hormone (TSH)	X	--	--	--
Substrates	Plasma glucose	X	--	--	X
	Creatinine	X	X	X	X
	Total bilirubin	X	X	X	X
	Direct bilirubin	X	X	X	X
	Total protein	X	X	X	X
	high sensitivity C-Reactive Protein (hsCRP)	X	X	X	X
	Uric acid	X	--	--	X
	Total cholesterol	X	--	--	X
	Triglycerides	X	--	--	X
	Albumin	X	X	X	X
Electrolytes	Sodium	X	X	X	X
	Potassium	X	X	X	X
	Calcium	X	--	--	X
	Chloride	X	--	--	X
	Inorganic phosphate	X	X	X	X

¹ A: Days -5 to -1 (Visit 2)

² B: Days 2 and 6 (Visit 2/3)

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Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	Test name	SCR	A¹	B²	EOT
Urinalysis (Stix)	Urine nitrite	x	x	x	x
	Urine protein	x	x	x	x
	Urine glucose	x	x	x	x
	Urine ketone	x	x	x	x
	Urobilinogen	x	x	x	x
	Urine bilirubin	x	x	x	x
	Urine erythrocytes	x	x	x	x
	Urine leukocytes	x	x	x	x
	Urine pH	x	x	x	x
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

¹ A: Days -5 to -1 (Visit 2)

² B: Days 2 and 6 (Visit 2/3)

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table [5.2.3: 1](#) and [5.2.3: 2](#) will be performed at with the exception of the drug screening. This test will be performed at the trial site using e.g. AccuSign® DOA 10 test.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the [Flow Chart](#).

All ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

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

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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

5.2.5 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,

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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.

5.3 OTHER

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 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.

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.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for BI 1015550:

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

5.5.1.2 Secondary endpoint

The following secondary endpoint will be evaluated for BI 1015550:

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of analyte plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3 -EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the [Flow Chart](#). Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at about 4° to 8 °C. Two plasma aliquots will be obtained and stored in

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polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma. Plasma aliquots will be frozen within 2 hours after blood withdrawal (interim storage of blood/plasma at room temperature). For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration and prior to predose meal intake.

The acceptable deviation from the scheduled time for post-dose vital signs, ECG and laboratory tests will be \pm 30 min.

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

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, and fecal occult blood testing and fecal calprotectin testing), 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 periods

Each subject is expected to participate in two treatment periods (Days -1 to Day 6 in each period). The treatment periods will be separated by at least 7 days between drug administrations. In addition, an ambulatory visit (visit 2) will be necessary within 5 days prior to the first study drug administration for safety laboratory, fecal occult blood and fecal calprotectin testing.

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

For details on time points and procedures for collection of plasma samples for PK analysis, refer to [Flow Chart](#) and Section [5.5.2](#).

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

6.2.3 End of trial period

For AE assessment, laboratory tests including testing for fecal occult blood and fecal calprotectin testing, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections [5.2.2](#) to [5.2.5](#).

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

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 characterized, 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.

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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 relative bioavailability of BI 1015550 as tablet formulation in the fed state (Test, T) compared to 24 mg BI 1015550 as tablet formulation in the fasted state (Reference, R) following oral administration. The trial is designed to allow intrasubject comparisons and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments. The secondary objective(s) will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section [5.5.1](#)).

Safety and tolerability will be determined on the basis of the parameters specified in Section [5.2.1](#).

7.1.3 Model

The statistical model used for the assessments of relative bioavailability is described in Section [7.3.2](#)

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1015550 under fed and fasted conditions will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

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

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protocol violations (IPVs) will be identified no later than in the Report Planning Meeting and provided in the TSAP.

The statistical analysis will be based on the following analysis sets.

- Entered set (ES): This subject set includes all entered and randomized subjects, whether treated or not.
- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received.
- Pharmacokinetic set (PKS): The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one primary or secondary PK parameter that was not excluded according to the description below.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic 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 PK 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
- Use of restricted comedication

7.3.1 Primary analyses

The primary and 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](#)).

Point estimates of bioavailability, the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see [5.5.1.1](#), [5.5.1.2](#)), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and

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‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$$Y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

Y_{ijkm} = logarithm of response (endpoint, see Section [7.1.3](#)) measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the ith sequence effect, i = 1, 2,

s_{im} = the effect associated with the mth subject in the ith sequence, m=1,..., 6, i=1,2,

π_j = the jth period effect, j = 1, 2,

τ_k = the kth treatment effect, k = 1, 2,

e_{ijkm} = the random error associated with the mth subject in sequence i who received treatment k in period j.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.3.2 Secondary analyses

The secondary parameters (refer to Section [5.5.1](#)) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ ([001-MCS-36-472](#)) and will statistically be assessed using the same methods as described for the primary endpoints.

7.3.3 Safety analyses

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

The analyses will be done by ‘treatment at onset’.

Treatments will be compared 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 analyze continuous (quantitative) data.

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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 first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see [5.2.2.2](#)) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section [5.5.1](#) for BI 1015550 will be calculated using validated software programs (preferably Phoenix WinNonlin[®]) according to the relevant SOP of the Sponsor ([001-MCS-36-472](#)).

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

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).

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor ([001-MCS-36-472](#)).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ, or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

Subjects will be randomized to one of the two treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomization as well as packaging and labelling of trial medication. The randomization 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 randomization list will contain additional blocks to allow for subject replacement (refer to [3.3.5](#)).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 12 subjects in this trial because this sample size is considered sufficient to achieve the aims of this exploratory trial.

With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

Table 7.6: 1

Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2x2 crossover trial (N=12).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%][*]	Lower CL [%]	Upper CL [%]
10	1.105	80	72.40	88.40
10	1.105	100	90.50	110.50
10	1.105	125	113.12	138.13
10	1.105	150	135.74	165.75
10	1.105	200	180.99	221.00
15	1.161	80	68.90	92.89
15	1.161	100	86.13	116.11
15	1.161	125	107.66	145.13
15	1.161	150	129.19	174.16
15	1.161	200	172.26	232.21
20	1.219	80	65.61	97.54
20	1.219	100	82.01	121.93
20	1.219	125	102.52	152.41
20	1.219	150	123.02	182.89
20	1.219	200	164.03	243.86

^{*}Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

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The calculation was performed as described by Julius [R11-5230] using R Version 3.3.2.

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 Harmonized 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 finalization 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 authorized 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](#).

ClinBaseTM

In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBaseTM system is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBaseTM serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

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 into ClinBaseTM (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 ClinBaseTM 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.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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.

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

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

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/135/95)
- The BI-internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

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

R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2002:1-9.

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R94-1529 Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker Inc 1992

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group 2010

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9.2 UNPUBLISHED REFERENCES

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Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy male volunteers (a partially randomised, single-blinded, placebo-controlled Phase I study). 1305.1. 21 Jun 2013

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Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 1015550 powder for oral solution in healthy male volunteers q.d. or b.i.d. for 14 days (a randomised, double-blind, placebo-controlled within dose groups Phase I trial). 1305.2. 15 Apr 2014

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Safety, tolerability, and pharmacokinetics

of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in
healthy male subjects. 1305.11. 18 May 2017

001-MCS-36-472 Standards and processes for analyses performed within Clinical
Pharmacokinetics/Pharmacodynamics. Current version

10. APPENDICES

Not applicable.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
<hr/>		
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input type="checkbox"/>
<hr/>		
Section to be changed		
Description of change		
Rationale for change		



APPROVAL / SIGNATURE PAGE

Document Number: c17549115

Technical Version Number: 1.0

Document Name: clinical-trial-protocol

Title: Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		12 Jul 2017 09:44 CEST
Approval-Therapeutic Area		12 Jul 2017 10:12 CEST
Approval-Trial Clinical Monitor		12 Jul 2017 12:06 CEST
Approval-Team Member Medicine		12 Jul 2017 14:06 CEST
Verification-Paper Signature Completion		13 Jul 2017 10:53 CEST
Approval-Project Statistician		17 Jul 2017 17:13 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed