Clinical Trial Protocol

	Document Number: c15772185-03
EudraCT No.:	2017-002003-10
BI Trial No.:	1305-0011
BI Investigational Product:	BI 1015550
Title:	Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects
Lay Title:	This study tests how healthy men tolerate different doses of BI 1015550. The study also tests how BI 1015550 is taken up by the body.
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 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: 18 May 2017	**Trial number:** 1305-0011		**Revision date:** 28 August 2017

Title of trial:	Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects
Principal Investigator:	
Trial site:	Phone: Fax:
Clinical phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics following single and multiple rising doses of BI 1015550
Methodology:	Part 1: Single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design Part 2: Double-blind, partially randomized within dose groups, placebo-controlled, parallel-group design
No. of subjects:	
total entered:	N= 42
each treatment:	Part 1: 18 (9 per dose group: 6 on active drug and 3 on placebo) Part 2: 24* (12 per dose group: 8 on active drug and 4 on placebo) *Subjects in Part 2 are only to be dosed after completion of dosing in Part 1.

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Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 1015550 as tablet formulation (TF 1 containing 6 mg BI 1015550)
dose:	Part 1: 36 mg, 48 mg Part 2: 6 mg b.i.d., 12 mg b.i.d.
mode of admin.:	Part 1: Oral with 240 mL of water after an overnight fast of at least 10 h Part 2: Oral with 240 mL of water after a moderate fat meal
Reference products:	Matching placebo as tablet formulation
dose:	Not applicable
mode of admin.:	Part 1: Oral with 240 mL of water after an overnight fast of at least 10 h Part 2: Oral with 240 mL of water after a moderate fat meal
Duration of treatment:	Part 1: Single dose Part 2: Subjects will be treated for 14 days and will receive a single morning dose on Day 1, followed by a 11 day treatment (i.e., 6 mg b.i.d., 12 mg b.i.d. or matching placebo on Days 3 to 13), and a single morning dose on Day 14.

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Criteria for pharmacokinetics:

Part 1:

Secondary endpoints:

$AUC_{0-\infty}$ and C_{max}

Part 2:

Secondary endpoints:

After the first dose: $AUC_{\tau,1}$ and C_{max}

After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$

Accumulation ratios: $R_{A,AUC}$, $R_{A,Cmax}$,

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Criteria for safety:

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

Further criteria of interest:

Treatment emergent AEs (TEAEs) including clinically relevant findings from the physical examination, safety laboratory tests , 12-lead electrocardiogram (ECG), continuous ECG monitoring (only Part 1), vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR], aural body temperature), body weight (only Part 2), and

Statistical methods:

Descriptive statistics will be calculated for all endpoints.

FLOW CHARTS

PART 1: SRD

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory/Urinalysis		Vital signs[8,12]	12-lead ECG[12]	Surveillance (continuous ECG-monitoring)	In-house	PK blood[9]			Adverse event questioning[7]
1	-14 to -2			Screening examination[1]	x		x	x[3]						x
2	-3 to -1	-72:00	08:00	Ambulatory visit	x[11]									x
	-1	-12:00	20:00	Admission	x[11]									x
	1	-2:00	06:00	Randomization	x[17]		x[14]	x[14,19]		┬	x[14,15]			x
		0:00	08:00	Drug administration					┬	│				x
		0:15	08:15						│	│	x			
		0:30	08:30				x	x[3]	│	│	x			x
		0:45	08:45						│	│	x			
		1:00	09:00				x	x[3]	│	│	x			x
		1:15	09:15						│	│	x			
		1:30	09:30				x	x[3]	│	│	x			x
		2:00	10:00	240 mL fluid intake [10]			x	x[3]	│	│	x			x
		2:30	10:30						│	│				x
		3:00	11:00						│	│	x			x
		4:00	12:00	Lunch[10]	x		x	x[3]	┴	│	x			x
		6:00	14:00							│	x			
		8:00	16:00	Snack (voluntary) [10]			x	x[3]		│	x			x
		10:00	18:00				x	x[3]		│				
		11:00	19:00	Dinner[10]						│				
		12:00	20:00							│	x			x
	2	24:00	08:00	Discharge[5]	x		x	x[3]		┴	x[18]			x
		34:00	18:00	Ambulatory visit							x			x
	3	48:00	08:00	Ambulatory visit			x	x[3]			x			x
	4	72:00	08:00	Ambulatory visit	x		x	x[3]			x			x
	5	96:00	08:00	Ambulatory visit			x	x			x			x
	6	120:00	08:00	Ambulatory visit	x		x	x			x			x
3	8 to 9			End of trial	x		x	x						x

				examination[4]										

1. Screening (14 to 2 days before drug administration) including subject information, informed consent, check of inclusion/exclusion criteria, physical examination, laboratory vital signs, ECG, demographics including body weight and height, drug and virus screening, alcohol breath test, medical history and concomitant therapy (cf. Section 6.2.1)

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

7. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above
8. Blood pressure (BP), pulse rate (PR), body temperature, and respiratory rate.
9. PK blood sampling times may be adapted based on information obtained during trial conduct (e.g. preliminary PK) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
10. If several actions are indicated at the same time point, the intake of meals/fluid will be the last action.
11. Drug screen and alcohol breath test will be performed on admission. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
12. Blood pressure (BP), pulse rate (PR), respiratory rate and ECG after 10 minutes lying in supine position

14. The time is approximate; the respective procedure is to be performed and completed within 2 h prior to drug administration.

17. Only urinalysis

19. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.

PART 2: MRD

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory / Urinalysis			PK blood[9]			12-lead ECG[12]	Vital signs[8,12]		In-house	Adverse event questioning[7]
1	-21 to -2			Screening examination[1]	x						x[3]	x			x
2	-1	-24:00	08:00	Admission[13]	x[11]									⊣	x
	1	-2:00 – 0:00	6:00 – 08:00	Randomisation[14,15]	x[20]			x[15,16]			x[15,22]	x[15]		|	x[15]
		-0:30	07:30	Breakfast[17]										|	
		0:00	08:00	Drug administration										|	x
		0:15	08:15					x						|	
		0:30	08:30					x						|	
		0:45	08:45					x						|	
		1:00	09:00					x			x[3]	x		|	x
		1:15	09:15					x						|	
		1:30	09:30					x						|	
		2:00	10:00	240 mL fluid intake[10]				x			x[3]	x		|	x
		3:00	11:00					x						|	
		4:00	12:00	240 mL fluid intake, lunch[10]				x			x[3]	x		|	x
		6:00	14:00					x						|	
		8:00	16:00	Snack (voluntary)[10]				x						|	
		10:00	18:00											|	
		11:00	19:00	Dinner[10]										|	
		12:00	20:00					x			x[3]	x		|	x
	2	24:00	08:00		x			x			x[3]	x		|	x
		34:00	18:00					x						|	x
	3	47:00	07:00											|	
		47:30	07:30	Breakfast[17]										|	
		47:55	07:55					x						|	
		48:00	08:00	Drug Administration										|	x
		59:30	19:30	Dinner[17]										|	
		60:00	20:00	Drug Administration										|	x
	4	71:00	07:00											|	
		71:30	07:30	Breakfast[17]										|	
		71:55	07:55					x						|	

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory / Urinalysis			PK blood[9]			12-lead ECG[12]	Vital signs[8,12]		In-house	Adverse event questioning[7]
2	4	72:00	08:00	Drug Administration										|	x
		83:30	19:30	Dinner[17]										|	
		84:00	20:00	Drug Administration										|	x
	5	95:30	07:30	Breakfast[17]	x[15]						x[3,15]	x[15]		|	
		96:00	08:00	Drug administration										|	x
		107:30	19:30	Dinner[17]										|	
		108:00	20:00	Drug Administration										|	x
	6	119:00	07:00											|	
		119:30	07:30	Breakfast[17]										|	
		120:00	08:00	Drug administration										|	x
		131:30	19:30	Dinner[17]										|	
		132:00	20:00	Drug Administration										|	x
	7	143:30	07:30	Breakfast[17]	x[15,23]									|	
		144:00	08:00	Drug administration										|	x
		155:30	19:30	Dinner[17]										|	
		156:00	20:00	Drug Administration										|	x
	8	167:00	07:00											|	
		167:30	07:30	Breakfast[17]										|	
		167:55	07:55					x						|	
		168:00	08:00	Drug administration										|	x
		179:30	19:30	Dinner[17]										|	
		180:00	20:00	Drug Administration										|	x
	9	191:30	07:30	Breakfast[17]	x[15]						x[15]	x[15]		|	
		192:00	08:00	Drug administration										|	x
		203:30	19:30	Dinner[17]										|	
		204:00	20:00	Drug Administration										|	x
	10	215:00	07:00											|	
		215:30	07:30	Breakfast[17]										|	
		216:00	08:00	Drug administration										|	x
		227:30	19:30	Dinner[17]										|	
		228:00	20:00	Drug Administration										|	x
	11	239:30	07:30	Breakfast[17]										|	
		239:55	07:55					x						|	
		240:00	08:00	Drug administration										|	x
		251:30	19:30	Dinner[17]										|	
		252:00	20:00	Drug Administration										|	x
	12	263:00	07:00		x[15,23]									|	
		263:30	07:30	Breakfast[17]										|	

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory / Urinalysis			PK blood [9]			12-lead ECG [12]	Vital signs [8,12]		In-house	Adverse event questioning [7]
2	12	263:55	07:55					x							
		264:00	08:00	Drug administration											x
		275:30	19:30	Dinner[17]											
		276:00	20:00	Drug administration											x
	13	287:30	07:30	Breakfast[17]											
		287:55	07:55					x							
		288:00	08:00	Drug administration											x
		299:30	19:30	Dinner[17]											
		300:00	20:00	Drug Administration											x
	14	311:00	07:00		x[15]						x[3,15]	x[15]			
		311:30	07:30	Breakfast[17]											
		311:55	07:55					x							
		312:00	08:00	Drug Administration											x
		312:15	08:15					x							
		312:30	08:30					x							
		312:45	08:45					x							
		313:00	09:00					x			x[3]	x			x
		313:15	09:15					x							
		313:30	09:30					x							
		314:00	10:00	240 mL fluid intake[10]				x			x[3]	x			x
		315:00	11:00					x							
		316:00	12:00	240 mL fluid intake, lunch[10]				x			x[3]	x			x
		318:00	14:00					x							
		320:00	16:00	Snack (voluntary)[10]				x							
		322:00	18:00												x
		323:00	19:00	Dinner[10]											
		324:00	20:00					x			x[3]	x			
	15	336:00	08:00					x			x[3]	x			x
		346:00	18:00					x							x
	16	360:00	08:00	Discharge [5,13]	x			x			x[3]	x			x
	17	384:00	08:00	Ambulatory visit				x			x[3]	x			x
	18	408:00	08:00	Ambulatory visit				x			x	x			x
	19	432:00	08:00	Ambulatory visit				x			x	x			x
	20	456:00	08:00	Ambulatory visit	x			x				x			x
	21	480:00	08:00	Ambulatory visit				x			x	x			x
	22	504:00	08:00	Ambulatory visit				x				x			x
	23	528:00	08:00	Ambulatory visit							x	x			x
	24	552:00	08:00	Ambulatory visit	x							x			x
	25	576:00	08:00	Ambulatory visit							x	x			x
3	26-28			End of trial examination[4]	x						x	x			x

1. Screening (within 21 to 2 days before first drug administration) including subject information, informed consent, demographics including height and weight, smoking and alcohol history, relevant medical history and prior medications, check of inclusion/exclusion criteria, vital signs (BP, PR, respiratory rate, body temperature), 12-lead ECG, clinical laboratory (hematology, clinical chemistry, urinalysis, fecal occult blood and fecal calprotectin testing), drug and virus screening, alcohol breath test, and a physical examination

3. Three 12-lead ECGs (Triple-ECG) will be recorded
4. End-of-study-examination to be performed within 1 to 3 days after last PK sampling; including physical examination, vital signs, ECG, laboratory, concomitant therapy, AE review and
5. Discharge by the investigator or designee after confirmation of fitness of the subject

7. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above
8. Blood pressure (BP), pulse rate (PR), body temperature, respiratory rate
9. PK blood sampling times may be adapted based on information obtained during trial conduct (e.g. preliminary PK) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
10. If several actions are indicated at the same time point, the intake of meals/fluid will be the last action.
11. Drug screen and alcohol breath test will be performed on admission. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
12. Blood pressure (BP), pulse rate (PR), respiratory rate, and 12-lead ECG after 10 minutes of rest in supine position
13. Measurement of body weight on admission and prior discharge
14. On day 1 of visit 2 prior first trial drug administration only
15. The time is approximate; the respective procedure is to be performed and completed within 2 h prior to drug administration and prior to predose meal intake.

17. Moderate fat breakfast and moderate fat dinner i.e 400-500 kcal with fat content of approx. 150 kcal, respectively, starting 30 min. prior to drug administration and has to be consumed completely within 25 minutes.

20. Only urinalysis

22. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
23. Abbreviated safety laboratory (for details refer to Section 5.2.3)

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over an uniform dosing interval τ after the first dose
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma over the dosing interval τ at steady state
BI	Boehringer Ingelheim
b.i.d.	*Bis in die*, twice daily
BLQ	Below the limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
C-SSRS	Columbia Suicidal Severity Rating
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P
DDI	Drug drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

eCRF	electronic Case report form
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
GMP	Good manufacturing practice
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IFP	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
MTD	Maximum tolerated dose
nM	Nanomolar
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PDE	Phosphodiesterase
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set

PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
$R_{A, AUC}$	Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ, expressed as ratio of AUC at steady state and after single dose
$R_{A, Cmax}$	Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ, expressed as ratio of C_{max} at steady state and after single dose
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE(s)	Treatment emergent adverse event(s)
TMF	Trial master file
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

1. INTRODUCTION

BI 1015550 is a selective inhibitor of the Phosphodiesterase 4 B (PDE4 B) with broad anti-inflammatory and anti-fibrotic activities. It is under development for the treatment of This integrated clinical trial is an extension of the previously performed single and multiple rising dose trials 1305.1 and 1305.2 [U13-1792-01 and c02191718-02] to investigate safety, tolerability and pharmacokinetics of single and multiple rising doses of BI 1015550 beyond the ones already investigated.

1.1 MEDICAL BACKGROUND

For further information please refer to the Investigator's Brochure [c02094779-02].

1.2 DRUG PROFILE

1.2.1 Nonclinical Pharmacology

For details on nonclinical pharmacology refer to the nonclinical pharmacology section in the IB [c02094779-02].

1.2.2 Safety pharmacology

For further details on safety pharmacology refer to the IB [c02094779-02].

1.2.4 Nonclinical pharmacokinetics

For further information please refer to the IB [c02094779-02].

1.2.5 Clinical experience in humans

1.2.5.1 Clinical safety

Two clinical trials have been completed with BI 1015550 in healthy male volunteers:

- a single rising dose First-in-Men (FIM) trial (1305.1) [U13-1792-01]
- a multiple rising dose trial (1305.2) [c02191718-02]

1.2.5.1.1 Single-Rising Dose study (1305.1)

BI 1015550 (0.02 mg, 0.06 mg, 0.2 mg, 0.6 mg, 2 mg, 4 mg, 8 mg, 16 mg and 24 mg dose levels) has been tested in 70 healthy male subjects who completed a partially randomised, placebo-controlled within dose groups, partially single-blinded, 2 cohorts with first cohort with defined treatment sequence (active-placebo-active-active), nine dose groups FIM study. Sixteen subjects received placebo and 54 received BI 1015550.

A total of 41 treatment emergent adverse events (TEAEs) were reported by 27 (39%) subjects. Five of these subjects (31%) received placebo. The most frequent TEAEs occurred within the CNS and GI organ classes. In total, 27 out of 70 subjects (38.6%) reported at least 1 TEAE during the treatment period of the trial. Twenty-two subjects were reported with AEs following administration of BI 1015550. In each dose group between 1 and 3 subjects reported at least 1 TEAE. Five subjects reported TEAEs following the administration of placebo. There was no correlation of the administered drug-dose and the number of subjects reporting at least 1 TEAE. Most subjects reported TEAEs of mild intensity (23 of the 27 subjects). Four of the subjects (including one subjects on placebo) reported moderate TEAEs (headache: 1 subject in the 0.2 mg group and 1 subject in the 4 mg group, nausea, vomiting, fatigue and headache: 1 subject in the 8 mg groups). All subjects were reported to have recovered from TEAEs by the end-of-study examination.

Nine subjects (12.9%) reported TEAEs that were considered drug-related by the investigator, most of them of mild-intensity: A total of 3 subjects were reported with drug-related diarrhea (all mild), 2 subjects with abdominal pain (mild), 2 subjects with headache (mild), and 1 subject each with nausea, vomiting, fatigue (all moderate), and oral herpes (mild).

There were no SUSARs, nor any significant (based upon ICH E3), severe, serious or fatal AEs. No subject was discontinued due to AEs.

In addition, no clinically relevant laboratory, vital signs and ECG changes were observed following administration of single doses of BI 1015550.

Global tolerability was assessed as good for all 70 subjects entered.

In summary, single doses from 0.02 mg up to 24 mg BI 1015550 were well tolerated by healthy male subjects. There were no notable differences between the dose groups with respect to safety and tolerability.

Further details can be found in IB [c02094779-02].

1.2.5.1.2 Multiple-Rising Dose study (1305.2)

BI 1015550 (1 mg and 6 mg b.i.d. for two weeks) has been tested in 24 healthy male subjects who completed two out of four planned dose levels in a randomized, double-blind, placebo-controlled within dose groups trial. Six subjects received placebo and 18 received BI 1015550. Dose escalation was stopped after the 2nd dose group as per protocol; interim PK

evaluation predicted that exposure in the 3rd dose group would exceed a pre-defined exposure limit (based on the NOAEL exposure of the 4-week rat repeat-dose toxicity study).

A total of 10 TEAEs were reported by 6 (25%) subjects, 1 subject (16.7%) in the placebo group, 4 subjects (44.4%) in the 1 mg group and 1 subject (11.1%) in the 6 mg group.

The most frequent TEAEs, all of mild intensity, occurred within the CNS and GI organ classes. TEAEs involving the CNS included headache reported by 1 subject on placebo and 1 subject on BI 1015550. GI TEAEs occurred in 3 subjects treated with BI 1015550 including mild diarrhea, abdominal pain and aphtous stomatitis in two subjects (1 mg b.i.d.) and mild constipation and abdominal pain in one subject (6 mg b.i.d.). No GI TEAE occurred in the placebo group.

There were no TEAEs of severe intensity, SUSARS, severe, serious or fatal AEs.

Two subjects were discontinued, one for personal reasons in the 1 mg b.i.d. group and one due to TEAEs in the 6 mg b.i.d. group (see above).

In conclusion, BI 1015550 was well tolerated with headache in both groups (Placebo and BI 1015550) and abdominal pain in the BI 1015550 treated group being the most frequent TEAEs. There was no apparent association between increasing dose and GI TEAEs.

1.2.5.1.3 Clinical experience with other PDE4 inhibitors

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

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

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

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

1.2.6 Drug product

For a more detailed description of the BI 1015550 profile please refer to the current Investigator's Brochure [c02094779-02].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The planned trial 1305-0011 will investigate safety, tolerability and pharmacokinetics of BI 1015550 and thereby provide essential information for a clinical development of BI 1015550 As this trial is an extension of the previously conducted single rising dose First-in-Man trial 1305.1 [U13-1792-01] and multiple rising dose trial 1305.2 [c02191718-02], an integrated clinical trial protocol has been chosen combining 2 parts:

Part 1: single rising dose part (SRD)

Part 2: multiple rising dose part (MRD)

2.2 TRIAL OBJECTIVES

Objectives in this integrated trial vary between trial parts. A description of all 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.

Part 1 (SRD):

The primary objective of this trial part is to investigate the safety and tolerability of BI 1015550 in healthy male subjects following oral administration of single rising doses of 36 mg and 48 mg.

Secondary objectives are the exploration of the pharmacokinetics of BI 1015550 after single dosing.

Part 2 (MRD):

In Part 2, the primary objective is to investigate the safety and tolerability of BI 1015550 in healthy male subjects following oral administration of multiple rising doses of 6 mg b.i.d. and 12 mg b.i.d..

Secondary objectives are the exploration of the pharmacokinetics of BI 1015550 after multiple dosing.

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

ECG electrodes may cause local and typically transient skin reactions.

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

2.3.2 Drug-related risks and safety measures

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

2.3.3 Safety measures

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

- Careful dose selection as described in Section 2.1.
- A maximum acceptable human exposure has been defined based on toxicity findings. Dose escalation within Part 1 (SRD) and Part 2 (MRD) is guided by measurements of BI 1015550 (free C_{max} and free $AUC_{0-\infty}$). The exposure in the next higher dose group in both parts will be estimated based on preliminary data of the preceding dose groups. The next higher dose level will only be administered if estimated gMean values for free C_{max} and free $AUC_{0-\infty}$ do not exceed the maximum acceptable human exposure (see Section 2.1.2; Section 7.3.4 and Section 3.3.4.2).
- For safety reasons, each dose group in Part 1 and Part 2 will be split into 2 cohorts:
  Part 1:
  Each dose group of 9 subjects (6 on active and 3 on placebo) will be divided into two cohorts. The first cohort will consist of 3 subjects who will be dosed in a fixed sequence fashion (active-placebo-active). Drug administration will be separated by at least 55 min between the first three subjects. This design ensures that between first and second active dose of each dose level there is a time interval of at least 110 min.

  If BI 1015550 is safe and well tolerated during in the first cohort, the remaining subjects of the respective dose level (i.e. second cohort) could be dosed as close as 30 minutes apart.

Part 2:
Each dose group of 12 subjects (8 on active and 4 on placebo) will be divided into two cohorts. The first cohort will consist of 3 (2 on active and 1 one placebo) subjects, the second of 9 subjects (6 on active, 3 on placebo).

- For each dose level, the two cohorts will be separated by a pre-defined time interval:
  Part 1:
  at least 48 hours (between 1st subject of each cohort),

  Part 2:
  Dose group 6 mg b.i.d.: at least 48 hours (between 1st subjects of each cohort)
  Dose group 12 mg b.i.d.: at least 72 hours (between 1st subjects of each cohort)

- A documented Safety Review meeting takes place prior to each dose escalation. Dose escalation is only permitted if there are no safety concerns and if none of the prespecified stopping criteria are met. The minimum time interval between last dosing in the first cohort of a given dose group and the first dosing in the next higher dose group is 7 days. For details see Section 3.1 and Section 3.3.4.2.
- After completion of Part 1 (SRD) a documented Safety Review meeting has to be performed before proceeding to Part 2. No subject in Part 2 may be dosed before the last subject in Part 1 has been dosed and the drug was considered safe and well-tolerated. This Safety Review meeting is based on safety and tolerability criteria of Part 1 without PK data of the 48 mg single dose group as this is no further dose escalation step. Further, based on the available human PK data of this dose it is unlikely that the maximum acceptable human exposure will be exceeded with 6 mg b.i.d. However, for the safety review meeting between dose group 1 and 2 of Part 2, PK data of Part 1 have to be available to ensure that expected exposure (C_{max} and AUC_{0-24}) after multiple dosing of 12 mg b.i.d. is covered by exposures reached after single dosing before [R17-1541].
- Safety laboratory examinations including surrogate markers of inflammation/vasculitis will be performed as described above
- A thorough ECG and heart rate monitoring including continuous ECG measurement over 4 hours post dose to cover the anticipated period of highest drug exposure (in Part 1) and additional repeated single and triple 12-lead ECGs in Part 1 and 2
- During in-house confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Subjects have to use adequate contraception as detailed in Section 3.3.3.

2.3.4 Overall assessment

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

The currently available toxicology data suggest that BI 1015550 can be safely administered

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

Part 1:

This single-rising dose part of the trial is designed as single-blind, partially randomized, and placebo-controlled within parallel dose groups.

A total of 18 healthy male subjects is planned to participate in Part 1 of the trial, according to 2 sequential groups comprising 9 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 18, but will not exceed 27 subjects entered. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects will receive the active drug and 3 will receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 2 cohorts which will be treated subsequently for safety reasons.

The design is partially randomized, i.e. the first block of one dose group will be treated according to a fixed sequence (Active-Placebo-Active) the other block will be randomized.

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

Table 3.1: 1 Dose groups

Dose Group	**1A**	**1B**
Dose (mg)	36	48
Number of subjects	9	9
Subjects receiving placebo	3	3
Subjects receiving active drug	6	6

Part 2:

The second part, the multiple-rising dose part, is designed as double-blind, partially randomized, and placebo-controlled within parallel dose groups.

A total of 24 healthy male subjects is planned to participate in this part of the trial, according to 2 sequential groups comprising 12 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 (for details please see end of this Section).

Within each dose group of Part 2, 8 subjects will receive the active drug and 4 will receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 2 cohorts which will be treated subsequently for safety reasons.

The design is partially randomized, i.e. the first block of one dose group will be treated according to a fixed sequence (Active-Placebo-Active) and the other block will be randomized.

The dose groups to be evaluated are outlined in Table 3.1: 2 below.

Table 3.1: 2 Dose groups

Dose Group	**2A**	**2B**
Daily dose (mg)	12 mg	24 mg
Dose regimen	6 mg b.i.d.	12 mg b.i.d.
Posology Day 1 and 14	1-0-0	1-0-0
Posology Day 3 to 13	1-0-1	1-0-1
Number of subjects	12	12
Subjects receiving placebo	4	4
Subjects receiving active drug	8	8

In Part 1 and 2, the two dose groups (Part 1: 1A and 1B, and Part 2: 2A and 2B) will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 7 days between the last drug administration in the previous dose group (i.e. Part 1: dose group 1A (36 mg SD); Part 2: dose group 2A (6 mg b.i.d.)) and the first drug administration of the subsequent dose group (i.e. Part 1: dose group 1B (48 mg SD); Part 2: dose group 2B (12 mg b.i.d.). 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 in Part 1 and 2. Furthermore, unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorized 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 authorized deputy) and the trial clinical monitor (or an authorized deputy).

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) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead EGG and AEs, i.e. abnormal findings judged clinically relevant by the Investigator, from continuous ECG monitoring (only in Part 1) in the current and preceding dose groups
- Vital signs in the current and preceding dose groups

- Clinical laboratory tests in the current and preceding dose groups including fecal occult blood and fecal calprotectin testing and urinalysis
- Preliminary PK data of the preceding dose groups for selected time points, i.e of DG 1A before proceeding to DG 1B and of DG 1A, DG 1B and DG 2A before proceeding to DG 2B (Section 7.3.4).
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorized deputy) and the trial clinical monitor (or an authorized 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 authorized deputy) and filed in the ISF and TMF.

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

Additional dose groups in Part 1 and 2

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) within the approved dose range on the basis of experience gained during the study. This may include PK data suggesting an exposure close or just above predefined thresholds or initial safety signals with open causality (not dose limiting), provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase.

Thus, for Part 1 the actual number of subjects entered may exceed 18, but will not exceed 27 subjects entered. For Part 2 the number of subjects entered may increase but will not exceed 36. Such changes may be implemented via non-substantial CTP Amendments.

The dosing of such an additional dose group will follow the same dosing regimen as described for the planned dose groups of this trial part, including same time intervals between cohorts and dose groups (ref. to Section 2.3.3).

An overview of all relevant trial activities is provided in the Flow Charts. For visit schedules and details of trial procedures at selected visits, refer to Section 6.1 and Section 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
under the supervision of the Principal Investigator.

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

The analyses of BI 1015550 concentrations in plasma and urine will be performed at

Biomarker analyses will be performed by

The digitally recorded 12-lead ECGs will be sent to a specialized contract research organization) for evaluation.

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

The design described in Section 3.1 is viewed favorable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 1015550.

With the rising dose design, single-blind (Part 1) and double-blind (Part 2) 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.

For Part 1, each dose group consists of 9 subjects with 6 on active treatment and 3 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.

In Part 2, each dose group will consist of 12 subjects with 8 on active treatment and 4 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 8 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics. After the first dose (single dose segment), a drug-free time to calculate $AUC_{0-\infty}$ is included before the second dose (first dose of the multiple dose segment) is administered. This will allow for appropriate calculation of the pharmacokinetic parameters after a single dose administration and for comparison with pharmacokinetic parameters at steady state.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 42 healthy male subjects (18 in Part 1, 24 in Part 2) will enter the study. The actual number of subjects entered may exceed the total of 42 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, 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 vital signs 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 55 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)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders, including but not limited to mood disorders and any history of suicidality.
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
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 20 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

23. Male subjects who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until two months after the study completion. Acceptable methods of contraception comprises barrier contraception and a medically accepted contraceptive method for the female partner (intra-uterine device with spermicide, hormonal contraceptive since at least two months)

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

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

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

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after 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. More specifically, dose escalation will be terminated if more than 50% of the subjects of one dose group show drug-related and clinically relevant adverse events of moderate or severe intensity, and the trial will be terminated if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.

Section 7.3.4.

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

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product and reference products

Part 1 (SRD)

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Tablet formulation 1 (TF1)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mg
Posology:	Dose group 1A: 6-0-0
	Dose group 1B: 8-0-0
Route of administration:	p.o.
Duration of use:	Single dose

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

Substance:	Placebo matching in size and weight to 6 mg tablet
Pharmaceutical formulation:	Tablet formulation
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	Dose group 1A: 6-0-0
	Dose group 1B: 8-0-0
Route of administration:	p.o.
Duration of use:	Single dose

Part 2 (MRD)

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Tablet formulation 1 (TF1)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mg
Posology:	Dose group 2A: 1-0-0 (day 1 and 14), 1-0-1 (day 3 - 13)
	Dose group 2B: 2-0-0 (day 1 and 14), 2-0-2 (day 3 - 13)
Route of administration:	p.o.
Duration of use:	2 day single dose (day 1 and 14) and 11 days b.i.d. dosing

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

Substance:	Placebo matching in size and weight to 6 mg tablet
Pharmaceutical formulation:	Tablet formulation
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	Dose group 2A: 1-0-0 (day 1 and 14), 1-0-1 (day 3 - 13)
	Dose group 2B: 2-0-0 (day 1 and 14), 2-0-2 (day 3 - 13)
Route of administration:	p.o.
Duration of use:	2 day single dose (day 1 and 14) and 11 days b.i.d. dosing

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 groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 2 dose cohorts (2 cohorts per dose group) the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts or groups 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.

For Part 1, the randomization list with study subject numbers and allocated treatments and for Part 2, the list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomization procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

Trial 1305-0011 is an extension of the previous single and multiple rising dose trials (1305.1 and 1305.2) and proceeds with dose escalation. The doses selected cover the expected sub-therapeutic as well as the estimated therapeutic range including a safety window. For safety margins and further details on dose selection see Section 2.1.1 and Section 2.1.2.

4.1.4 Drug assignment and administration of doses for each subject

Part 1 (SRD)

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

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

Dose	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1A	BI 1015550	Tablet	6 mg	6 tablets as single dose	36 mg
1B	BI 1015550	Tablet	6 mg	8 tablets as single dose	48 mg
1A-1B	Placebo[1]	Tablet	--	identical to active treatment	--

[1]Subjects receiving placebo are equally distributed across dose groups

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

Subjects will be kept under close medical surveillance until at least 24 h following drug administration. During the first 4 hours after drug administration subjects will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG) or medical reasons (e.g., adverse events). For restrictions with regard to diet see Section 4.2.2.2.

Additional doses

Additional subjects may be entered to allow testing of additional doses on the basis of the experience gained during the conduct of the trial (e.g. preliminary PK data), provided that the planned and approved highest dose will not be exceeded (see Section 3.1). Such changes may be implemented via non-substantial CTP amendments.

Part 2 (MRD)

The treatments to be evaluated are outlined in Table 4.1.4: 2 below. The number of units for placebo corresponds to the number of units of the respective dose level.

Table 4.1.4: 2 BI 1015550 and placebo treatments, oral administration

Dose	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
2A	BI 1015550	Tablet	6 mg	1 tablet as single dose on Day 1 + 14, 1 tablet in the morning and evening on Days 3-13	6 mg (Day 1+14) 12 mg (Day 3-13)
2B	BI 1015550	Tablet	6 mg	2 tablets as single dose on Day 1 + 14, 2 tablets in the morning and evening on Days 3-13	12 mg (Day 1+14) 24 mg (Day 3-13)
2A-2B	Placebo[1]	Tablet	--	identical to active treatment	--

[1] Subjects receiving placebo are equally distributed across dose groups

This trial part will be divided into two segments (single dose and multiple doses). During the single dose segment (Days 1 to 2) subjects will receive one single dose of BI 1015550 (or placebo) on Day 1. The multiple dose segment starts on Day 3 and subjects will receive a dose of 6 mg (dose group 2A) or 12 mg (dose group 2B) of BI 1015550 (or placebo) twice daily (in the morning and in the evening at about 12 hours after the morning dose) for 11 days (Days 3 to 13) and a single dose of 6 mg (dose group 2A) or 12 mg (dose group 2B) of BI 1015550 (or placebo) in the morning of Day 14.

The trial medication will be administered to the subjects, while in a standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorized 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.

After an overnight fast of at least 10 hours, a standard moderate-fat breakfast and a moderate-fat dinner, respectively, will be served 30 minutes before drug administration. The meal should be in compliance with recommendations provided by EMA [R17-1541], i.e. the meal should contain approximately 400-500 kcal with fat contributing to ca. 150 kcal. The meals must be completely consumed within 25 minutes or less; however the medication should be taken 30 minutes after start of the meal.

To ensure a dosing interval of 12 h from Day 3 to Day 14, the administration of trial medication should take place at the same time every morning and evening (no evening administration on Day 14).

Subjects will be kept under close medical surveillance until 48 h following the last drug administration on Day 14. During the first 2 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 medical reasons), or to sleep.

For further restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

In Part 2 only, access to the randomization schedule is restricted to unblinded pharmacists at the trial site. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF. Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to database lock.

At the ECG laboratory all staff will be blinded with respect to treatment. Within the ECG laboratory, the staff involved with interval measurements and assessments will also be blinded with regard to the recording date and time as well as time points of the ECGs. Semi-automatic interval measurements for a given subject will be performed in random and blinded sequence by a single technician.

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

Further, the Human Pharmacology Centre (HPC) deputy of the sponsor will receive the randomization codes prior to official unblinding, so that in case of emergency the HPC physician on duty can perform emergency unblinding. HPC deputy will confirm in writing that the codes will be treated confidentially.

In addition, the drug metabolism scientist will 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.

Part 1 (SRD)

The treatments administered (active or placebo) will be single-blind (blinded to subjects only). However, the current dose level will be known to the subjects.

Part 2 (MRD)

The trial is designed double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators.

4.1.5.2 Procedures for emergency unblinding

Part 1 (SRD)

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

Part 2 (MRD)

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

4.1.6 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
- Subject or medication number (only in Part 2)
- 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.

A re-supply after Part 1 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
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol

Only 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 in all parts of the trial. Further restrictions apply for the different parts:

Part 1 (SRD)

From 1 hour before drug intake until 4 hours post-dose liquid intake is restricted to the fluid administered with the drug and 240 mL of water at 2 hours and 4 hours post-dose (mandatory for all subjects). From 4 hours post-dose until 24 hours post-dose water intake is restricted to 3000 mL. Standardized meals will be served at 4, 8, 11 and 24 hours following drug administration.

During the days of urine collection, total fluid intake should be at least 1.5 liters and should not exceed 3.5 liters.

Part 2 (MRD)

On PK profile days (i.e., Day 1 and Day 14) liquid intake is restricted from 1 hour before administration until lunch with exception to the fluid administered with the breakfast and the drug and 240 mL of water at 2 and 4 hours post-dose (mandatory for all subjects). From lunch until 24 hours post-dose water intake is restricted to 3000 mL. On all other days, fluid intake is restricted from 1h before administration until 2h post-dose with the exception of the fluid administered with the meals and the drug. On PK profile days (i.e., Day 1 and Day 14), standardized meals will be served at 4, 8, and 11 hours following drug administration.

Both parts

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

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

Further criteria of interest:

- TEAEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests, including
  urinalysis
- 12-lead ECG
- Abnormal findings in the continuous ECG monitoring if rated as AE (only Part 1)
- Vital signs (blood pressure, pulse rate, respiratory rate, aural body temperature) and body weight (only Part 2)

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,
- 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 Section 5.2.2.2, subsections 'AE collection' and 'AE reporting to sponsor and timelines'.

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

The latest list of 'Always Serious AEs' can be found in the eDC 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. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.
The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
  - aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the 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 (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).
- 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.

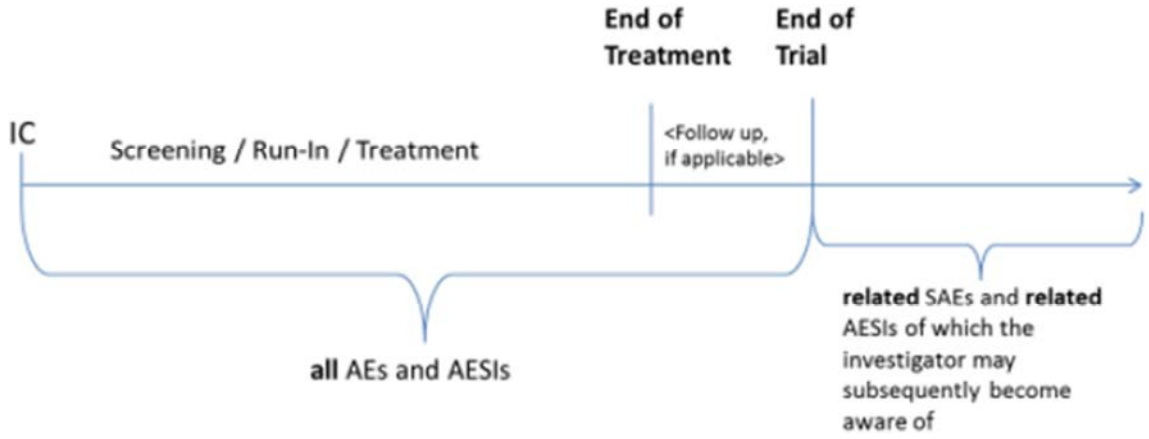
A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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.



The REP for BI 1015550, when measurable drug levels or PD effects are still likely to be present, is defined as after the last administration of BI 1015550. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3. Events which occurred after the REP but prior to the last per protocol contact 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 eCRF 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 the BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

In rare cases, pregnancy might occur in a clinical trial. Once a subject 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 Table 5.2.3: 1 and Table 5.2.3: 2.
Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count will only be performed if there is an abnormality in the automatic blood cell count, i.e. if automatic count is not feasible or differential WBC is abnormal (i.e. pathological or atypical cells) and clinically relevant in the opinion of the investigator. In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein, microscopic examination of the urine sediment will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	D[4]	EOT
Hematology[5]	Hematocrit	x	x	x	x	--	x
	Hemoglobin	x	x	x	x	--	x
	Red blood cell count (RBC)	x	x	x	x	--	x
	Reticulocyte count	x	--	--	x	--	x
	White blood cell count (WBC)	x	x	x	x	x	x
	Platelet count	x	x	x	x	--	x
	Erythrocyte sedimentation rate (ESG)	x	x	x	x	x	x
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x	x	x	x
Manual differential WBC (if automatic count is not feasible or differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes						
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x	--	x
	Prothrombin time (Quick's test and INR)	x	x	x	x	--	x
	Fibrinogen	x	x	x	x	x	x
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x	--	x
	Alanine transaminase (ALT/GPT)	x	x	x	x	--	x
	Alkaline phosphatase (AP)	x	--	x	x	--	x
	Gamma-glutamyl transferase (GGT)	x	x	x	x	--	x
	Glutamate dehydrogenase (GLDH)	x	--	--	x	--	x
	Creatine kinase (CK); CK-MB only if CK is elevated	x	x	--	x	--	x
	Lactate dehydrogenase (LDH)	x	x	x	x	--	x
	Lipase	x	x	--	x	--	x
	Amylase	x	x	--	x	--	x
Hormones	Thyroid stimulating hormone (TSH)	x	--	--	--	--	x
	fT3, fT4	x	--	--	--	--	x
Substrates	Plasma glucose	x	--	--	x	--	x
	Creatinine	x	x	x	x	--	x
	Total bilirubin	x	x	x	x	--	x
	Direct + indirect bilirubin	x	x	x	x	--	x

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	D[4]	EOT
	Total protein	x	x	x	x	--	x
	high sensitivity C-Reactive Protein (hsCRP)	x	x	x	x	x	x
	Uric acid	x	--	--	--	--	x
	Total cholesterol	x	--	--	x	--	x
	Triglycerides	x	--	--	x	--	x
	Albumin	x	x	x	x	--	x
Electrolytes	Sodium	x	x	x	x	--	x
	Potassium	x	x	x	x	--	x
	Calcium	x	--	--	x	--	x
	Chloride	x	--	--	x	--	x
	Inorganic phosphate	x	x	--	x	--	x
Urinalysis (Stix)	Urine nitrite	x	x	-	x	x	x
	Urine protein	x	x	-	x	x	x
	Urine glucose	x	x	-	x	x	x
	Urine ketone	x	x	-	x	x	x
	Urobilinogen	x	x	-	x	x	x
	Urine bilirubin	x	x	-	x	x	x
	Urine erythrocytes	x	x	-	x	x	x
	Urine leukocytes	x	x	-	x	x	x
	Urine pH	x	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 -3 to -1
2 B: post-dose on Day 1 (Part 1 (SRD) only)
3 C: Days 2, 4, 6 (Part 1 (SRD)), days 2, 5, 9, 14, 16, 20, 24 (Part 2 (MRD)
4 D: abbreviated safety lab Days 7 and 12 (Part 2 (MRD)) only
5 In addition to the parameters listed above MCV,MCH and MCHC will be reported by the lab, as due to technical reasons only a complete blood count can be analyzed

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/HIV-1 p24-antigen (qualitative)

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed at screening and 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 Table 5.2.3: 2 will be performed at Medizinisches Versorgungszentrum Dr. Klein Dr. Schmitt & Partner, Kaiserslautern, Germany with the exception of the urinalysis stix and drug screening tests. These tests will be performed at the trial site using Combur9 Test and AccuSign® DOA 10 test, respectively.

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

Twelve-lead resting 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.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 10 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. 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.

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

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

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). For time points with triple ECGs, all three single ECGs will be repeated. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralized evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

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

A post-study centralized evaluation of all 12-lead ECGs recorded after Days 1 (Part 1 and 2) and Days 14 (Part 2 only) up to 72 h after drug administration will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECG at a single assessment time will be evaluated. The remaining second and third replicate ECG will be stored for additional analyses if required, e.g. by authorities at a later time point. HR and QTc (QT interval corrected for HR, e.g. QTcF and QTcB) will be determined in house (see TSAP for details).

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

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

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311], [R13-0801], [R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure device (Dinamap, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 10 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Further, respiratory rate [RR] and oral body temperature as well as body weight (only Part 2) will be monitored.
Body temperature will be determined in the ear at the time points indicated in the Flow Chart using electronic thermometers (Thermoscan, Welch Allyn GmbH, Hechingen, Germany).
Respiratory rate will be counted by trained study personal by observing the chest movements over a period of one minute after the subject has rested in the supine position for 5 minutes.
Recording of the values will be done at the time points indicated in the Flow Chart.

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body temperature, respiratory rate), 12-lead ECG, laboratory tests including fecal occult blood and fecal calprotectin testing, suicidality assessment (C-SSRS, only Part 2) and a physical examination.
At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, suicidality assessment (C-SSRS, only Part 2) and a physical examination with determination of weight.

5.3 OTHER

5.3.1.1 Methods and timing of sample collection

One blood sample of at most 10 mL will be taken from an arm vein in a PAXgene blood DNA drawing tube prior to the first study drug administration (Visit 2, Day 1). The blood sample has to be stored at a temperature of approximately -20°C or below. Once frozen, thawing of the samples should be avoided.
Frozen blood samples should be shipped on dry ice to:

5.3.1.2 Analytical determinations

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analyzed by DMET analysis or other standard genotyping technologies.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values including surrogate markers for gastrointestinal vasculitis, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. 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 in the CRFs.

Times and periods for sampling of PK as well as metabolism analysis 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 for BI 1015550 will be determined if feasible:

5.5.1.1 Primary endpoints

- Not applicable

5.5.1.2 Secondary endpoints

Part 1 (SRD)

- $AUC_{0-\infty}$ (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)

Part 2 (MRD)
After the first dose:

- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)

- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose:

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

Accumulation ratios:

- $R_{A,Cmax}$ (accumulation ratio based on $C_{max,ss}$)
- $R_{A,AUC}$ (accumulation ratio based on $AUC_{0-\tau}$)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis of BI 1015550

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

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

After bioanalysis of BI 1015550, left-over plasma samples may be used for further methodological investigations**,** e.g. for stability testing and/or, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) 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

5.5.3.1 Analytical determination of drug 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 unblinded during sample analysis. The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim

Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization (CRO).

5.6 BIOMARKER

5.7 PHARMACOKINETIC - PHARMACODYNAMIC BIOMARKER RELATIONSHIP

The direct relationship between pharmacokinetic concentrations and biomarker parameters will be explored by a scatter plot. Further analysis might be performed, if deemed reasonable.

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 2 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation on profile days from the scheduled time for vital signs and ECG will be -10 min and for laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter.

Fecal occult blood and calprotectin testing will be done as indicated and described in the Flow Chart.

The tolerance for drug administration will be ± 1 min on Days 1 and 14, ± 10 min on all other treatment days.

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 and urine collection intervals refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including urinalysis), ECG, vital signs, and physical examination, (only Part 2) refer to Section 5.2.3 to Section 5.2.5.

6.2.2 Treatment period

Part 1 (SRD)

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

Study participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 24 h following the drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.
For details on time points and procedures for collection of plasma and urine 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.

Part 2 (MRD)

Each subject will receive a single dose of BI 1015550 or placebo on Day 1 and then daily multiple doses of BI 1015550 of the respective dose strength or placebo for 11 days from Day 3 onwards as described in Section 4.1.

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 48 h following the last drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma 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, recording of ECG and vital signs, and physical examination during the end of trial period, see Section 5.2.2 to Section 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The objectives in this integrated trial vary between trial parts and are described in Section 2.2.

7.1.2 Endpoints

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1. Pharmacokinetics and will be explored based on endpoints and parameters specified in Section 5.5.1 and Section 5.6.1.

7.1.3 Model

The statistical models used for the assessments of
are described in Section 7.3.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 4 different dose groups in 2 trial parts (SRD, MRD) of BI 1015550 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

7.3 PLANNED ANALYSES

All individual data will be listed.

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

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 PK parameter that was not excluded according to the description below.

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

Relevant protocol violations may be

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

Plasma and urine 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.

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.

7.3.3 Safety analyses

Safety will be assessed for the endpoints and parameters of interest listed in Section 5.2.1. Safety analyses will be done based on the treated set (refer to Section 7.3) and 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 for Part 1 and 2 in the safety evaluation will consist of all placebo treated subjects in the respective trial part, regardless of the dose group in which they were treated. For trial Parts 1 and 2, 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 analyze continuous (quantitative) data.

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

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

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake and end of REP will be assigned to the treatment period, and all AEs occurring between the end of REP and trial termination date will be assigned to ’follow-up’. 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 (analyzing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralized evaluation of 12-lead ECG recordings from Part 1 and 2 will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1015550 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472] using validated software programs (preferably Phoenix WinNonlin®).

Subjects who are not included in the PKS (refer to Section 7.3) will be reported with their individual plasma / urine concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma / urine 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).

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

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/urine drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

Subjects will be partially-randomized within each dose group. For each dose group the first block will be treated according to fixed sequence (active-placebo-active), the remaining block will be randomized in a 2:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

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 Section 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

A total of 42 subjects shall be included into this trial.

Part 1 (SRD)
It is planned to include a total of 18 subjects into this part of the trial. The planned sample size is not based on a power calculation. The size of 9 subjects per dose group (6 on active treatment, and 3 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] and enables a balanced analysis of subjects on verum and on different doses of BI 1015550.

Part 2 (MRD)
In this part, it is planned to include a total of 24 subjects. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group (8 on active treatment, and 4 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics [R95-0013] and enables a balanced analysis of subjects on verum and on different doses of BI 1015550.

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 42, but will not exceed 54 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 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.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to 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 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. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:
The trial site must retain the source 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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10. APPENDICES

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		03 July 2017
EudraCT number		2017-002003-10
BI Trial number		1305-0011
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects
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. Flow Chart, Part 2 (MRD) 2. Section 3.3.4.2 Discontinuation of the trial by the sponsor 3. Section 4.1.6: Packaging, labelling, and re-supply
Description of change		1. Flow Chart, Part 2 (MRD), p 8+10: Minor modifications in the Flow chart (PK urine) to be consistent with the foot notes 2. Section 3.3.4.2, p 46: Clarification that the trial will be stopped in case one subject experience a drug-related SAE 3. Section 4.1.6, p 52: A re-supply with IMP is needed due to organizational issues with the updated LTAFs

Number of global amendment		1
Rationale for change		Based on the feedback by BfArM and Ethics Committee, the respective recommendation was included into a revised protocol. In context with this adaptation a few remaining inconsistencies were also corrected and the requirement of a re-supply was added.

Number of global amendment		2
Date of CTP revision		28 August 2017
EudraCT number		2017-002003-10
BI Trial number		1305-0011
BI Investigational Product(s)		BI 1015550
Title of protocol		Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects
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. Flow Chart, Part 1, p. 6 2. Flow Chart, Part 2, p. 10 3. Table 5.2.3.1, p. 62/63 4. Section 5.2.4.1, p. 65 5. Section 5.5.2.1, p. 71 6. Section 6.1, p. 76
Description of change		1. Typo corrected (visit 3 instead of visit 4) 2. Missing visit number 3 added, inconsistency regarding urine collection start between footnote (312:00) and Flow Chart corrected 3. In addition to the parameters listed in the table MCV, MCH and MCHC will be reported by the lab, as due to technical reasons only a complete blood count can be analyzed 4. Clarification of wording regarding timepoints of ECG analysis 5. Clarification that “after completion of the trial” refers to completion of the bioanalysis of BI 1015550 as described in the protocol. Left-over

Number of global amendment		2
		samples may only be used for further analysis after the predefined bioanalysis of the sample has been completed. 6. Correction of an inconsistency between Flow Chart and section 6.1: “before” trial medication corresponds to a 2 h-period.
Rationale for change		Clarification that analysis of left-over plasma samples may only be done after the samples was analyzed for BI 1015550 as predefined in the protocol. In addition some minor inconsistencies were corrected and clarified.

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		28 Aug 2017 12:59 CEST
Author-Trial Statistician		28 Aug 2017 13:02 CEST
Approval-Therapeutic Area		28 Aug 2017 13:55 CEST
Author-Trial Clinical Pharmacokineticist		29 Aug 2017 05:00 CEST
Approval-Team Member Medicine		29 Aug 2017 14:55 CEST
Verification-Paper Signature Completion		29 Aug 2017 15:24 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed