Clinical Trial Protocol

	Document Number:	**c25765859-01**
BI Trial No.	1402-0008	
BI Investigational Medicinal Product	BI 1358894	
Title	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled parallel dose group design)	
Lay Title	A study about how different doses of BI 1358894 are taken up in the body and how well they are tolerated in healthy Japanese men	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol	
Version and Date	Version: 1.0	Date: 17 Jan 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	17 Jan 2019
Revision date	Not applicable
BI trial number	1402-0008
Title of trial	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled parallel dose group design)
Principal Investigator	
Trial site	
Clinical phase	I
Trial rationale	The objective of this trial is to investigate the safety, tolerability, and pharmacokinetics of BI 1358894 in healthy Japanese male subjects. The chosen population of healthy male volunteers using single rising oral doses is considered adequate to provide the basis for the clinical development program of BI 1358894 in Japan.
Trial objectives	To investigate safety, tolerability and pharmacokinetics following single rising doses of BI 1358894
Trial endpoints	Primary endpoint The number [N(%)] of subjects with drug related adverse events Secondary endpoints: AUC_{0-tz}, C_{max}, $AUC_{0-\infty}$ (if evaluable) of BI 1358894
Trial design	Double-blind, randomised, placebo-controlled within parallel dose groups
Number of subjects **total entered** **each treatment**	 24 8 per dose group (6 on BI 1358894 and 2 on placebo)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy Japanese male subjects, age of 20 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)
Test product(s)	BI 1358894 film-coated tablet (25 mg, 100 mg)

dose	50 mg, 100 mg, and 200 mg
mode of admin.	Oral with 240 mL of water after a high-calorie, high-fat breakfast
Comparator product(s)	Matching placebo(s)
dose	Not applicable
mode of admin.	Oral with 240 mL of water after a high-calorie, high-fat breakfast
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Dose Group 1 and 2 (50 mg and 100 mg)

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[13]	PK blood	PK urine[9]	Orthostatic testing	Visual analogue scale	C-SSRS	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR, RR)	Questioning for AEs and concomitant therapy[6]
1	-28 to -1			Screening (SCR)[1]	x			x	x	x	x		x	
2	-1	-24:00[7]	09:00	Ambulatory visit	x[7]									x
		-12:00	21:00	Admission to trial site	x[5]									
	1	-1:00	08:00	Allocation to treatment[2]	x[2]	x[2]	x[12]	x[2]	x[2]		x[2,8]		x[2]	x[2]
		-0:30	08:30	High-calorie, high-fat breakfast										
		0:00	**09:00**	**Drug administration**[10]			▲					▲		
		0:10	09:10			x	|					|		
		0:20	09:20			x	|					|		
		0:30	09:30			x	|				x[8]	|	x	x
		1:00	10:00			x	|				x[8]	|	x	x
		1:30	10:30			x	|				x[8]	|	x	x
		2:00	11:00	240 mL fluid intake		x	|		x		x[8]	|	x	x
		2:30	11:30			x	|					|		
		3:00	12:00			x	|	x			x[8]	|	x	x
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]	x	x	+		x		x[8]	▼	x	x
		5:00	14:00			x	|				x[8]		x	x
		6:00	15:00			x	|				x[8]		x	x
		7:00	16:00			x	|							
		8:00	17:00			x	+		x			x[8]		x	x
		10:00	19:00	Dinner[3]		x	|							
		12:00	21:00			x	+					x[8]		x	x
	2	16:00	01:00			x	|				x[8]		x	
		24:00	09:00	Breakfast[3]	x	x	+		x			x[8]		x	x
		34:00	19:00			x	|		x		x[8]		x	x
	3	48:00	09:00	Breakfast[3]		x	+		x			x[8]		x	x
	4	72:00	09:00	Breakfast[3]		x	+					x		x	x
	5	96:00	09:00	Breakfast[3], confirmation of fitness[11], Discharge from trial site		x	| ▼		x	x		x		x	x
	6	120:00	09:00	Ambulatory visit		x								x	x
	7	144:00	09:00	Ambulatory visit		x								x	x
	8	168:00	09:00	Ambulatory visit		x								x	x
	9	192:00	09:00	Ambulatory visit		x								x	x
3	10 to 14			End of trial (EOT) examination[4]	x				x	x	x			x	x

PK: pharmacokinetics, ECG: electrocardiogram, AE: adverse event

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs (including orthostatic testing), ECG, safety laboratory (including drug screening, hepatitis serology, HIV antibodies and syphilis), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, Bowdle visual analogue scales and suicidality assessment (C-SSRS).
2. The time is approximate; the respective procedure is to be performed and completed within 2 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, Bowdle visual analogue scales and suicidality assessment (C-SSRS).
5. Only urine drug screening and alcohol breath test will be done at this time point.
6. 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.
7. Safety laboratory to be taken and to be medically evaluated on Day -1; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. The ECG recording has to be performed as triple at this time point
9. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 h.
10. One blood sample for pharmacogenomics analyses will be taken at any time after administration on Day 1.
11. Confirmation of fitness includes physical examination, vital signs, ECG, recording of AEs and concomitant therapies, Bowdle visual analogue scales and suicidality assessment (C-SSRS).
12. A blank urine sample for PK is to be obtained within 3 h prior to drug administration.
13. Safety laboratory samples will be collected after the subjects have fasted for at least 10 h except 4h on Day 1.

Dose Group 3 (200 mg)

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[13]	PK_{blood}	PK_{urine}[9]	Orthostatic testing	Visual analogue scale	C-SSRS	Neurological Examination	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR, RR)	Questioning for AEs and concomitant therapy[6]
1	-28 to -1			Screening (SCR)[1]	x			x	x	x	x	x		x	
2	-1	-24:00[7]	09:00	Ambulatory visit	x[7]										x
		-12:00	21:00	Admission to trial site	x[5]										
	1	-1:00	08:00	Allocation to treatment[2]	x[2]	x[2]	x[12]	x[2]	x[2]			x[2,8]		x[2]	x[2]
		-0:30	08:30	High-calorie, high-fat breakfast											
		0:00	**09:00**	**Drug administration**[10]			▲						▲		
		0:10	09:10			x	|						|		
		0:20	09:20			x	|						|		
		0:30	09:30			x	|					x[8]	|	x	x
		1:00	10:00			x	|					x[8]	|	x	x
		1:30	10:30			x	|					x[8]	|	x	x
		2:00	11:00	240 mL fluid intake		x	|		x			x[8]	|	x	x
		2:30	11:30			x	|						|		
		3:00	12:00			x	|	x				x[8]	|	x	x
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]	x	x	+		x			x[8]	▼	x	x
		5:00	14:00			x	|					x[8]		x	x
		6:00	15:00			x	|					x[8]		x	x
		7:00	16:00			x	|								
		8:00	17:00			x	+		x				x[8]		x	x
		10:00	19:00	Dinner[3]		x	|								
		12:00	21:00			x	+						x[8]		x	x
	2	16:00	01:00			x	|					x[8]		x	
		24:00	09:00	Breakfast[3]	x	x	+		x				x[8]		x	x
		34:00	19:00			x	|		x			x[8]		x	x
	3	48:00	09:00	Breakfast[3]		x	+		x				x[8]		x	x
	4	72:00	09:00	Breakfast[3]		x	+						x[8]		x	x
	5	96:00	09:00	Breakfast[3]	x	x	| ▼						x[8]		x	x
	6	120:00	09:00	Breakfast[3]		x							x[8]		x	x
	7	144:00	09:00	Breakfast[3], confirmation of fitness[11], Discharge from trial site		x			x	x	x	x[8]			x	x
	9	192:00	09:00	Ambulatory visit		x									x	x
	11	240:00	09:00	Ambulatory visit		x									x	x
	15	336:00	09:00	Ambulatory visit		x									x	x
	22	504:00	09:00	Ambulatory visit		x									x	x
	29	672:00	09:00	Ambulatory visit		x									x	x
3	29 to 33			End of trial (EOT) examination[4]	x				x	x	x	x			x	x

PK: pharmacokinetics, ECG: electrocardiogram, AE: adverse event

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, neurological examination, check of vital signs (including orthostatic testing), ECG, safety laboratory (including drug screening, hepatitis serology, HIV antibodies, and syphilis), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, Bowdle visual analogue scales and suicidality assessment (C-SSRS).
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8. The ECG recording has to be performed as triple at this time point
9. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 h.
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11. Confirmation of fitness includes physical examination, neurological examination, vital signs, ECG, recording of AEs concomitant therapies and Bowdle visual analogue scales and suicidality assessment (C-SSRS).
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13. Safety laboratory samples will be collected after the subjects have fasted for at least 10 h except 4h on Day 1.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
Ae_{t1-t2}	Amount of analyte eliminated in urine over the time interval t1 to t2
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve of the analyte in plasma
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$\%AUC_{tz-\infty}$	The percentage of $AUC_{0-\infty}$ obtained by extrapolation
β	Slope parameter associated with the power model used to evaluate dose proportionality
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	borderline personality disorder
C_{16h}	Concentration of the analyte in plasma at 16h after dosing
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R,\ t1-t2}$	Renal clearance of the analyte in plasma from the time point t1 to t2
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
CRF	Case report form
CRO	Contract Research Organization
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Cardiovascular
DMET	“drug metabolizing enzymes and transporters
DILI	Drug induced liver injury
DMET	drug metabolizing enzymes and transporters
DRF	Dose Range Finding
ECG	Electrocardiogram

eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
FDA	Food and Drug Administration
FE	Food Effect
fe_{t1-t2}	Fraction of administered drug excreted unchanged in urine over the time interval from t_1 to t_2
FIH	First in human
GCP	Good Clinical Practice
hERG	human ether-a-go-go related gene
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LVSP	left ventricular pressure parameters
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MRTpo	Mean residence time of the analyte in the body after oral administration
nM	Nanomolar
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QD	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)
$RAUC_{t1-t2,M/P}$	Ratio of the AUC value of the metabolite versus AUC value of the mother compound over time interval t1-t2
$RC_{max,t1-t2,M/P}$	Ratio of the Cmax value of the metabolite versus Cmax value of the mother compound after single dose
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening

SRD	Single-rising dose
SOP	Standard Operating Procedure
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TRPC	transient receptor potential cation channel
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual analogue scale
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White blood cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 1358894, an oral,

adjunct for the treatment

is a debilitating disease characterised by and often by and . It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the trial of patients with , about of the patients did not reach different medications and continued to experience residuals symptoms which significantly impacted the patients' quality of life When is insufficient, clinicians employ different strategies including add-on treatment with or When strategies also fail, therapies such as may be used.

with an estimated prevalence of around in the general community and severe impaired quality of life . The main symptom clusters of

Patients with have and a rate of that is 5 higher than in the general population Even the presence of a single diagnostic feature of is predictive for poor functioning and psychiatric illness burden Treatment guidelines recommend as the mainstay of treatment, but pharmacotherapy is commonly used as an adjunctive, symptom-targeted component of treatment. However, no drug is approved for the treatment of

are involved in the regulation of They are most highly expressed in and which are involved in modulation and processing of Pre-clinically, treatment with BI 1358894 has shown diminished and and increased without impairing other brain functions such as

It is hypothesized that in patients with disorders, an is a major contributor to and there is growing evidence supporting the role of in the emotion processing observed in patients with Therefore, treatment with BI 1358894 has the potential to improve in patients with

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

channels are
channels implicated in diverse physiological functions, including

1.2.2 Safety pharmacology

1.2.3 Toxicology

1.2.4 Nonclinical pharmacokinetics

e

p
ll

1.2.5 Clinical experience in humans

A FIH (first-in-human) trial [Trial 1402-0001; c13880029] is currently being conducted to explore the safety, tolerability and pharmacokinetics (PK) of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and to evaluate the effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over design).

In accordance with the trial protocol, the study continued with the food effect (FE) part at a dose level of 50 mg and 100 mg of BI 1358894 administered under fasted and fed conditions, according to an open-label, two-period crossover design. Twenty healthy male subjects aligned to the FE part have completed the study.

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of BI 1358894, the time interval when measurable drug levels or pharmacodynamics (PD) effects are still likely to be present after the last administration, .

1.2.7 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 1358894 profile, please refer to the current IB

1.3 RATIONALE FOR PERFORMING THE TRIAL

form ion channels that are involved in the regulation of . They are highly expressed in involved in modulation and processing of It is hypothesized that in patients with disorders, an is a major contributor to

BI 1358894 may therefore have the potential to improve symptoms and in patients with

The objective of this trial is to investigate the safety, tolerability, and pharmacokinetics of BI 1358894 in healthy Japanese male subjects. The chosen population of healthy male volunteers using single rising oral doses is considered adequate to provide the basis for the clinical development program of BI 1358894 in Japan.

The pharmacokinetic and safety data obtained in the current study will help to define appropriate doses for further studies with this compound.

Dose Selection

In this trial it is intended to investigate the safety and tolerability of 50 mg, 100 mg, and 200 mg single dose under the fed condition. The background for this dose selection is described in the following.

The dose range in this trial is expected to cover the potential highest dose in Phase II. The safety, tolerability and pharmacokinetic data will provide further insight on the integration of Asian population into global Phase II.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1358894. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g., blood sampling may result in mild bruising and, in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

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

1.4.2 Drug-related risks and safety measures

Risk factors were derived from (1) observations in nonclinical studies, (2) the mode of action and nature of the target, and (3) the relevance of animal models.

Risks derived from observations in non-clinical studies

Rats and dogs were employed as the animal species for general toxicology investigations on BI 1358894, because *in vitro* and *in vivo* profiling supported the suitability of both species for nonclinical safety profiling of BI 1358894.

As summarised in potential risks observed in non-clinical studies are a long lasting in rats, an in rats and dogs, and signs of a in rats. All findings were observed within 5 days after the start of treatment. The observed in rodents and non-rodents can be easily monitored in a Phase I study induced by BI 1358894 occurred early after the start of dosing and resolved despite continued treatment, indicating its transient character. The non-clinical safety data support clinical Phase I trials in non-childbearing humans with daily oral administration for up to 4 weeks.

Mode of action and nature of the target

The members are considered to play a crucial role in physiological processes such as to act as a cellular sensor or to support signal transmission The subtypes form that are involved in the regulation of . They are highly expressed in which are involved in modulation and processing of Preclinically, of these receptors by BI 1358894 has resulted in diminished and increased without impairing other brain functions such as and . In accordance with these findings, deficient mice display an phenotype This supports the assumption that in healthy subjects due to an inhibition of are limited to a . However, clinical data with compounds inhibiting this target have yet to be published.

Relevance of animal models

Human proteins show high homology with the rat, mouse, and dog proteins and the potency of BI 1358894 to the target is comparable across species. In addition, expression at the protein level is similar across different species, including human. Rat and dog had good oral bioavailability, significant systemic exposure, and good tolerability after oral dosing of a nanosuspension of BI 1358894. Finally, all known metabolites formed after incubation of human hepatocytes with BI 1358894 were covered with the combination of rat and dog. Overall, pharmacodynamic activity, pharmacokinetics, and metabolism all indicate that rat and dog were suitable species for nonclinical safety profiling of BI 1358894.

It should be highlighted that toxicity study in rats did not reveal any toxicologically relevant effects of BI 1358894 on the immune system up to the highest tested dose of . Furthermore, the pharmacological effects of BI 1358894 are dose dependent and no evidence for irreversible effects has been observed. Therefore, despite the novelty of the target, BI 1358894 is not considered a high-risk compound.

Risk minimization (safety precautions and stopping rules)

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

- Careful dose selection
- Shallow dose escalation using a factor 2 for all rising steps
- For safety reasons, Dose Group 3 will be divided into 2 cohorts of 4 subjects each (3 on active drug, 1 on placebo). The dosing of the cohorts will be separated by at least 48h.
- If one dose level was safe and showed acceptable tolerability and if no stopping criterion was met (see Section 3.3.4), the next higher dose will be given, maintaining a time interval of at least 6 days (referring to the first subject of each dose group)
- An extensive safety laboratory will be performed with special focus on full blood exam (see Flow Chart)
- A thorough ECG monitoring including continuous ECG monitoring for at least 15 min pre dose and over 4 hours post dose to cover the anticipated period of highest drug exposure and additional repeated, with frequency indicated in the Flowchart, single 12-lead ECGs over 96 hours for Dose Groups 1 and 2 or over 144 hours for Dose Group 3 following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.3 for details).
- In this study, blood pressure and heart rate will be closely monitored (see Flow Chart). Dose escalation will be stopped if at least 2 subjects at one dose level show a sustained decrease in systolic blood pressure of ≥20 mmHg for at least 2 hours after drug administration compared to baseline (Day 1, predose). Orthostatic testing will be performed to detect whether potential hemodynamic effects of BI 1358894 might interfere with daily life activities. Dose escalation will be stopped if orthostatic

dysregulation (see Section 5.2.2 for definition) is observed in more than 1 subject (severe) or more than 3 subjects (moderate) per dose group

- Adequate safety monitoring will be performed (e.g., vital signs including ECGs, safety laboratory tests including hormone parameters, adverse events including Bowdle visual analogue scales).
- Subjects will be hospitalised throughout the study from Day -1 to Day 5 for Dose Groups 1 and 2 or from Day -1 to Day 7 for Dose Group 3 and will be discharged only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During the in-house stay, the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events

Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.5, adverse events of special interest.

1.4.3 Overall assessment

In summary, although not therapeutically tested in humans to date, BI 1358894 has the potential to become an oral treatment for as an adjunct to therapy and for the treatment of . Based upon preclinical data for BI 1358894, the preliminary clinical data from the on-going FIH study, as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in the clinical trial with BI 1358894, as is the usual case in such Phase I trials. Considering the medical need for the development of a safer and more effective treatment for patients with disorders, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate safety, tolerability and pharmacokinetics (PK) of BI 1358894 in healthy male subjects following oral administration of single rising doses.

2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 1358894 is the number [N(%)] of subjects with drug related adverse events.

2.1.3 Secondary endpoint

The following pharmacokinetic parameters will be determined for BI 1358894 if feasible:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data time point t_z)
- $AUC_{0\text{-}\infty}$ (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)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

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

It is planned to include a total of 24 healthy male subjects in the trial. The subjects will be assigned to 3 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1).

The trial design is depicted in Figure 3.1: 1.

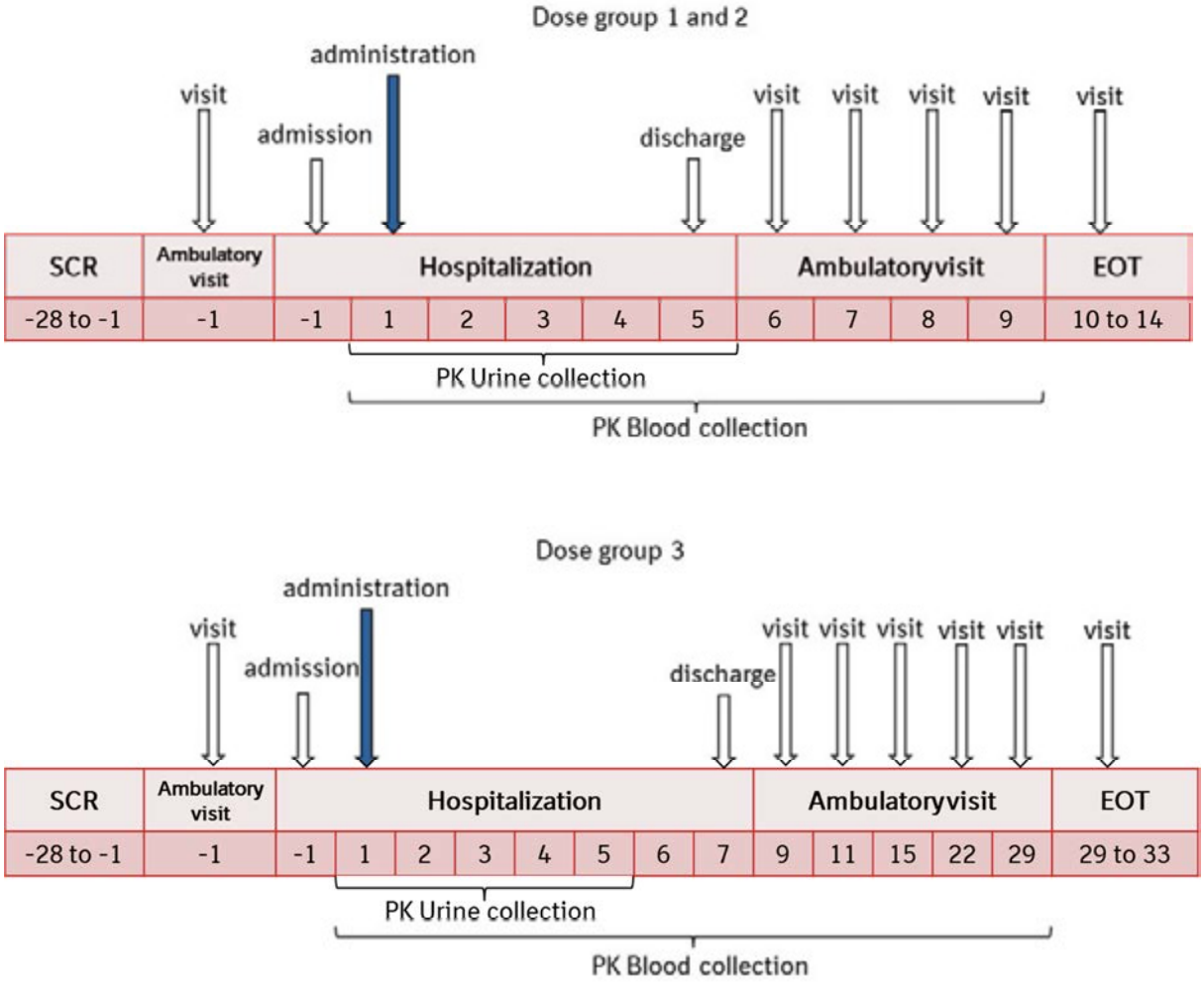

Figure 3.1: 1 Overview of trial design

Within each dose group, 6 subjects will receive BI 1358894 and 2 will receive placebo. Only one dose is tested within each dose group.

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3
Dose (mg)	50	100	200
Number of subjects	8	8	8
Subjects receiving placebo	2	2	2
Subjects receiving active drug	6	6	6

The groups will be dosed consecutively in ascending order, and a time interval of at least 6 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety, and tolerability data of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the investigator, no safety concerns have arisen in the preceding dose groups (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4). For safety reasons, Dose Group 3 will be divided into 2 cohorts (per cohort: 3 subjects on active and 1 subject on placebo, treated in parallel). Both cohorts will be dosed in a randomised fashion.

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime by the Principal Investigator (or an authorised deputy) or the sponsor of the study (for instance, due to the occurrence of any unforeseen adverse events).

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4).

The minimum data set for review consists of the following:

- 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 ECG 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
- 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 authorised deputy) and the Clinical Trial Leader (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). Dose escalation will only be permitted

if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Leader (or an authorised deputy).

Safety Reviews can be conducted face-to-face or by video/telephone conference. The Clinical Trial Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and Clinical Trial Leader (or an authorised deputy), and will be filed in the investigator site file (ISF) and trial master file (TMF).

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

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

For single-rising dose trials, the sequential rising dose design described in Section 3.1 is viewed favourably 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 1358894.

With the rising dose design, double-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of drug administered. The disadvantage of the trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such 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 single or multiple rising dose trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication. Each dose group consists of 8 subjects, with 6 on active treatment, and 2 on placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. Six subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

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

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who are Japanese
3. Age of 20 to 45 years (inclusive) at screening
4. BMI of 18.5 to 25.0 kg/m^2 (inclusive) at screening
5. Signed and dated written informed consent prior to admission to the study, in accordance with Good Clinical Practice (GCP) and local legislation
6. Willingness to comply with contraception requirements. Subjects who are sexually active must use with their female partner, adequate contraception throughout the study and until three months after the last administration of trial medication. Adequate methods are:
   - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success) or
   - Surgical sterilisation (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner or
   - The use of condoms, if the female partner uses an adequate contraception method in addition, e.g., intrauterine device (IUD), hormonal contraception (e.g., implants, injectables, combined oral or vaginal contraceptives) that started at least 2 months prior to first drug administration, or barrier method (e.g., diaphragm with spermicide)

   Unprotected sexual intercourse with a pregnant female partner is not allowed throughout the study and until three months after the last administration of trial medication.

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. C-Reactive Protein (CRP) > upper limit of normal (ULN), erythrocyte sedimentation rate (ESR) ≥ 15 millimeters/hour, liver and kidney parameter above ULN, other laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)

7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections including viral hepatitis, human immunodeficiency virus (HIV) and/or syphilis. (Subject with positive Hepatitis B core antibody will not be allowed to participate in this trial)
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 400 mL within 12 weeks or 200 mL within 30 days or plasma donation within 2 weeks prior to administration or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the 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 *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
24. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF 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 CRF. If the discontinuation occurs before End of Trial (EOT) visit, the discontinued subject should if possible be questioned for AEs and concomitant therapies in order to ensure collection of AEs and concomitant therapies until the planned EOT visit date, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
6. The subject has 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), or ALT and/or AST elevations ≥10 fold ULN and/or needs to be followed up according to the DILI checklist provided in the ISF
7. The subject shows a raised CRP level of >3.00 mg/dL or an Erythrocyte Sedimentation Rate (ESR) of ≥ 20 millimeters/hour.

In addition to these criteria, the investigator 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.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
3. Violation of GCP, or the CTP (clinical trial protocol), or the contract with BI impairing 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 if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording
6. Dose escalation will be stopped if at least 2 subjects at one dose level showed a sustained decrease in systolic blood pressure of ≥ 20 mmHg for at least 2 hours after drug administration compared to baseline (Day 1, predose) which will be measured after 15 min in supine position (to avoid false positive signals because of the required prolonged resting period after drug intake).

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

3.3.5 Replacement of subjects

If some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg, 100 mg
Posology:	2-0-0 (50 mg), 1-0-0 (100 mg), and 2-0-0 (200 mg)
Route of administration:	oral
Duration of use:	Single dose

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

Substance:	Matching placebo
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	2-0-0 (50 mg), 1-0-0 (100 mg), and 2-0-0 (200 mg)
Route of administration:	oral
Duration of use:	Single dose

4.1.2 Selection of doses in the trial

The dose range of BI 1358894 for this trial was selected on the basis of the data obtained in the ongoing FIH SRD Trial 1402-0001. So far, dose levels up to 200 mg in fasting status and 100 mg in fed status were well tolerated.

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

4.1.3 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 are allocated to 1 of the 3

dose cohorts, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomization list will be allocated to subjects by the method 'first come first served'. Subjects are then assigned to treatment according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 BI 1358894 and placebo treatments, oral administration

Dose	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total dose
1	BI 1358894	Film-coated tablet	25mg	2 tablet	50 mg
2	BI 1358894	Film-coated tablet	100 mg	1 tablets	100 mg
3	BI 1358894	Film-coated tablet	100 mg	2 tablet	200 mg
1-3	Placebo*	Film-coated tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee in the morning of Day 1. For drug administration, the so-called four-eye principle (two-person rule) should be applied.

After an overnight fast of at least 10 hours, a high-fat, high-calorie breakfast will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the Food and Drug Administration (FDA) guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
102g roll	322
105g sausage	337
36g process cheese	122
50g boiled egg (whole content)	76
12g tomato ketchup	14
6g mayonnaise	40
150 mL water	0
Sum[1]	911

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 96 h for Dose Groups 1 and 2 and 144 h for Dose Group 3 after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination) or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind. The treatments administered (active or placebo) will be blinded to the subjects and the investigators (outcome assessors) in order to limit the occurrence of any bias which the knowledge of treatment may have.

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

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

4.1.5.2 Unblinding and breaking the code

The investigator or designee will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed

immediately. The reason for breaking the code must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory authority, e.g., competent authority (CA)
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor of unused products.These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the

sponsor, the investigator or designee 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

No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

In case of alterations of blood pressure (hypotension) and heart rate (tachycardia), which were reported in toxicology studies (see section 1.2.3), physical interventions will be the first treatment of symptoms. If unsuccessful, appropriate drug therapy will be initiated according to common guidelines and algorithms trained in emergency trainings. Dependent on individual symptoms, for the treatment of tachycardia this may include intravenous administration of beta blockers or appropriate antiarrhythmic drugs. For the treatment of hypotension, in addition to volume substitution, administration of vasopressors may be a further step. The entire staff of the trial site assuming medical responsibility during conduct of the study is routinely trained in emergency procedures.

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 will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water served on Day 1 at 2 h and 4 h post-dose (mandatory for all subjects).

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

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

Poppy-seed containing products should not be consumed starting 4 days before first trial drug administration until last PK sampling of the trial.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 4 h before until 4 h after each administration of trial medication.

Smoking is not allowed during in-house confinement while admitted to the trial site.

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

4.3 TREATMENT COMPLIANCE

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

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Medical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, a physical examination, Bowdle visual analogue scales and suicidality assessment (C-SSRS). At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of weight, Bowdle visual analogue scales and suicidality assessment (C-SSRS).

5.2.2 Vital signs

Systolic and diastolic BP as well as PR will be measured by a blood pressure device at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Respiratory rate (RR) will be measured after 5 minutes of rest in supine position for at least 1 minute.

Orthostatic tests will be performed at the time points indicated in the Flow Chart. Subjects should have spent at least 5 min in the supine position before blood pressure and pulse rate are measured the first time. A further 2 measurements will be performed immediately after standing up and after 3 min in a standing position. The term “Orthostatic dysregulation” will be used to describe adverse events that occur during orthostatic testing. Orthostatic hypotension is defined as a reduction in systolic BP of ≥20 mm Hg or in diastolic BP of ≥10 mm Hg within 3 minutes of standing and will be recorded as an AE. Orthostatic hypotension may be accompanied by symptoms of dizziness, diaphoresis, a decline in blood pressure, tachycardia (PR >100 bpm), or even fainting (which is reflected in the assessment of AE intensity).

At the time points given in the Flow Chart, the following sequence of measurements should be adhered to: 12 lead-ECG and vital signs will be done before blood sampling; orthostatic testing will be done after blood sampling. While standing up, subjects will be accompanied by staff.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h except 4h on Day 1. For retests, at the discretion of the investigator or designee, overnight

fasting is not required. The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count Erythrocyte Sedimentation Rate (ESR)
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic 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) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase Amylase
Hormones[1]	Thyroid stimulating hormone (TSH) fT3, fT4
Substrates[1]	Plasma glucose Creatinine Total bilirubin Direct bilirubin Total protein Protein electrophoresis (only at screening examination) Albumin Alpha-1-Globulin Alpha-2-Globulin Beta-Globulin Gamma-Globulin C-Reactive Protein (CRP) Uric acid Total cholesterol Triglycerides

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Electrolytes	Sodium Potassium Calcium
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
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] Protein electrophoresis only at screening. Hormones only at screening and end of trial.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infectious serology is planned at screening only. Drug screening will be performed at screening and after admission to the trial site.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening and upon admission to the trial site, 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 Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site or/and at a CRO designated by the sponsor.

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 computerised electrocardiograph (MAC 2000 ECG machines, GE Healthcare) 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-second duration after the subjects have rested for at least 5 minutes 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.

Triple ECGs will be recorded (within 180 sec) at all-time points on Day 1 to Day 3 (48 h) for Dose Groups 1 and 2 or on Day 1 to Day 7 (144h) for Dose Group 3. At all remaining time points, single ECGs will be recorded.

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 QTcF 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 centralised 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 centralised evaluation (during study or post study) of all 12-lead ECGs recorded on Day 1 to Day 3 (48h) for Dose Groups 1 and 2 or on Day 1 to Day 7 (144h) for Dose Group 3 will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis (automatic evaluation based on a validated GE-12-SL-algorithm or equivalent) 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 drug administration), only the first of the three replicate ECGs at a single assessment time will be evaluated. The remaining second and third replicate ECGs will be stored for additional analyses if required, e.g., by authorities at a later time point.

For each QT interval, the RR interval preceding the QT will be measured to calculate the respective frequency corrected QTc intervals 'QTcF' according to Fridericia's formula ($QTcF = QT/ RR^{1/3}$) and 'QTcB' according to Bazett's formula ($QTcB = QT/ RR^{1/2}$). The QTcF correction will be used for evaluation and reporting. Abnormalities detected during centralised 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.

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

5.2.4.2 Continuous ECG monitoring

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

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

5.2.5 Other safety parameters

5.2.5.1 Visual Analogue Scale (VAS)

Possible psychedelic effects will be monitored and evaluated as safety measurement by analogue scales developed by Bowdle along with PK sampling. From these measurements, following factors are derived - external and internal perception, alertness, mood and calmness.

The VAS assessments 2 hours before drug administration will be considered as baseline. At each measuring time point indicated in the Flow Chart, the subjects will assess their subjective impression by themselves by means of a visual analogue scales. The subjects will be asked to mark an adequate position on a line between the two limits characteristics. The length of the line will be exactly 100 mm, and will ascertain a score number (values between

0 and 100) by measuring the distance in mm from the beginning of the line to the position marked by the subject. The score will be documented in the electronic case report form.

The original English version is shown in Appendix 10.1.

5.2.5.2 Suicidality assessment

Suicidality assessment to further evaluate the psychological status of the subject will be performed at screening using the Columbia Suicidal Severity Rating scale C-SSRS.
The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behaviour and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

The original Columbia Suicidal Severity Rating scale is shown in Appendix 10.2.

5.2.5.3 Neurological examinations

As a general additional safety measure in the Dose Group 3, a physical neurological examination will be performed at the time points specified in the respective Flow Chart.

The neurological examination will include the following assessments:

- General level of arousal
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Reflexes
- Assessment of muscle strength
- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

Documentation, Assessment, and Reporting

Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator or sub-investigator. Clinically relevant findings of the neurological examination will be reported as Adverse Events (during the trial) or as baseline conditions (at screening). Case narratives may be written if necessary.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

The following events will be handled as ‘deemed serious for any other reason’. An AE which possibly leads to disability will be reported as an SAE.

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, 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 (electronic Data Capture) system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Suicidal risk assessed by the C-SSRS

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening / baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behavior will also be recorded.

After the baseline visit the assessment 'since last visit' will be performed ('since last visit' version). The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

For 'Self-injurious behaviour, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.

For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6.1.5 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The AESI for this trial is 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, or
- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

5.2.6.1.6 Intensity (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.7 Causal relationship of AEs

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

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure

- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial:

- All AEs (serious and non-serious) and all AESIs
- The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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.

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood and urine samples will be collected for the purpose of pharmacokinetic analysis. Further information about sampling is provided in Section 5.3.2.

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1358894 and BI 1361608 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into a K-EDTA (potassium 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 venepuncture with a metal needle.

Sample handling will be described in detail in a separate lab manual.

Until transfer on dry ice to the analytical laboratory, all sample will be stored upright at approximately -20°C or below at the trial site.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g., for stability testing 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 after the CTR is archived.

5.3.2.2 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (within 3 hours before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in polypropylene (PP) containers and stored in the refrigerator at 4-8°C. Subjects are told to empty their bladders at the end of each sampling interval. To avoid adsorption effects of BI

1358894, suitable volume of 10% Tween 20 solution will be added to the collection container before sampling.

The handling of urine sampling is described in a lab manual.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned collection time. Further information, such as matrix and analyte may also be provided.

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -20°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After completion of the trial, the urine samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

BI 1358894 and BI 1361608 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

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

5.3.3.2 Analytical determination of analyte urine concentration

BI 1358894 concentrations in urine will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

5.4 OTHER ASSESSMENTS

5.4.1 Pharmacogenomic evaluation

Pharmacogenomics investigates genetic variations to explain and to predict an individual's response to drugs. Therefore, a blood sample for pharmacogenomic testing will be taken from each subject. In case of unexplainable variability in pharmacokinetic parameters, DNA might be extracted from these samples and used for exploratory analysis of variants of genes involved in Absorption, Distribution, Metabolism and Excretion (ADME) of drugs. It is not intended to include these data in the final report. However, the data may be part of the report if necessary. All remaining samples will be destroyed no later than three years after the end of the trial.

5.4.1.1 Methods and timing of sample collection

One blood sample of about 8.5 mL will be taken from an arm vein in a PAXgene blood DNA drawing tube after the study drug administration on 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. Further details of sample processing will be described in a study-specific laboratory manual.

5.4.1.2 Analytical determinations

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analysed by drug metabolizing enzymes and transporters (DMET) analysis or other standard genotyping technologies.

5.5 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration except PK urine sample. A blank urine sample for PK will be collected within 3 h before drug administration.

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

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

The acceptable deviation from the scheduled time for standardized neurological tests (conducted in Dose Group 3) is ± 90 min on Day 7.

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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study. If the subject has not fasted for at least 10 h at screening visit, laboratory test will be done another day after the subject has fasted for at least 10 h. For information regarding laboratory tests (including drug and virus screening), ECG, vital signs including orthostatic testing, physical examination, Bowdle visual analogue scales and suicidality assessment (C-SSRS), refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment period

Each subject will receive one dose of trial medication (BI 1358894 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 96 h for Dose Groups 1 and 2 and 144 h for Dose Group 3 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, subjects will be treated 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 5.3.2.

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 times of 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, physical examination, Bowdle visual analogue scales and suicidality assessment (C-SSRS) during the end of trial period, see Sections 5.2.
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 assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's End of Trial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial will be assessed by calculating descriptive statistics for safety as well as for PK parameters, which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this study.

Any confidence intervals (CIs) computed are to be interpreted in the perspective of the exploratory character of the study; i.e., CIs are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- 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. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (IPD) categories will be specified in the IQRMP, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2 for BI 1358894 and BI 1361608 will be calculated according to the relevant Standard Operating Procedure (SOP) of the Sponsor (001-MCS-36-472). Pharmacokinetic analyses will be performed using validated software programs, normally. Phoenix Winnonlin (Pharsight®) with applications validated for the respective purpose. Graphs and tables will be generated using validated customised SAS®

macros or appropriate graphic software. A reference to the software used, e.g., name, will be indicated in the CTR.

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 deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be:

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

Plasma 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.

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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 as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature.

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

Further exploratory analyses

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints ($AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max}) specified in Section 2.1.3.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = \log(x_{km}) = \mu + \beta \cdot \log(D_k) + e_{km},$$

where

y_{km} logarithm of response (PK parameter) measured on subject m receiving dose k,
μ the overall mean,
β slope parameter of linear regression line,
D_k level of dose k, k=1,…,3,
e_{km} the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

The slope parameter β together with its two-sided 90% confidence interval will be estimated.

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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

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

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 5.2) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs).

Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between trial medication intake until the trial termination date will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the trial statistical analysis plan (TSAP). Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, 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 5.2.6.1) and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods. Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

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

7.4 INTERIM ANALYSES

No formal interim analysis is planned. If considered necessary, an exploratory PK analyses will be performed based on planned sampling times.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo).

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

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

7.7 DETERMINATION OF SAMPLE SIZE

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

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH GCP, relevant BI SOPs, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the responsible 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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. 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

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by

The trial will be conducted at , under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs

- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of Clinical Trial Managers, Clinical Research Associates, and investigators of participating trial sites

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

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

Analyses of BI 1358894 and BI 1361608 concentrations in plasma and BI 1358894 concentrations in urine will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany or by a specialised contract research organisation appointed by BI.

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

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

Data management and statistical evaluation will be done by BI or a CRO appointed by BI according to BI SOPs.

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

9. REFERENCES

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10. APPENDICES

10.1 VISUAL ANALOGUE SCALE (VAS)

Bowdle VAS-score (English version):

My body or body parts seemed to change their shape or position

Not at all _____ Extremely

My surroundings seemed to change in size, depth, or shape

Not at all _____ Extremely

The passing of time was altered

Not at all _____ Extremely

I had feelings of unreality

Not at all _____ Extremely

It was difficult to control my thoughts

Not at all _____ Extremely

The intensity of colors changed

Not at all _____ Extremely

The intensity of sound changes

Not at all _____ Extremely

I heard voices or sounds that were not real

Not at all _____ Extremely

I had the idea that events, objects, or other people had particular meaning that was specific for me

Not at all _____ Extremely

I had suspicious ideas or the belief that others were against me

Not at all _____ Extremely

I felt high

Not at all _____ Extremely

I felt drowsy

Not at all _____ Extremely

I felt anxious

Not at all _____ Extremely

10.2 COLUMBA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

Version 1/14.09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

11. DESCRIPTION OF GLOBAL AMENDMENT

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
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		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c25765859 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled parallel dose group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		17 Jan 2019 12:11 CET
Author-Trial Statistician		17 Jan 2019 12:27 CET
Approval-Therapeutic Area		17 Jan 2019 17:56 CET
Approval-Team Member Medicine		18 Jan 2019 11:11 CET
Author-Trial Clinical Pharmacokineticist		18 Jan 2019 14:41 CET
Verification-Paper Signature Completion		21 Jan 2019 15:35 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed