Clinical Trial Protocol

	Document Number: c13880029-10
EudraCT No.:	2017-000143-40
BI Trial No.:	1402-0001
BI Investigational Product:	BI 1358894
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
Clinical Phase:	I
Trial Clinical Monitor:	Phone Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 9))
Version and Date:	Version: 10.0 Date: 25 September 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1358894			
Protocol date: 23 February 2017	**Trial number:** 1402-0001		**Revision date:** 25 September 2018

Title of trial:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics (PK) following single rising doses including food effect of BI 1358894
Methodology:	- Single rising dose (SRD): single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design - Food effect (FE): randomised, open label, two-way, two-sequence cross-over design
No. of subjects:	
total entered:	*88
each treatment:	SRD: 8 per dose group (6 on active drug and 2 on placebo) FE: 24 (all on active treatment) * The study will be initially conducted with a tablet formulation and 8 dose groups resulting in a planned number of 64 subjects in the SRD part and 24 subjects in the FE part. Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 88, but will not exceed 96 subjects entered. The food effect part will not start before the respective dose has been tested in the SRD part,
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2

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Test product 1:	BI 1358894 film-coated tablet (tablet strength 1 mg, 5mg, 25 mg 100 mg)
dose:	SRD*: 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg (fasted q.d.), FE:, 50 mg, and 100 mg SRD fed: 200 mg (fed)* q.d. * Dose selection based on the assumption to include the potential therapeutic range. In the SRD part doses may be decreased or increased based on the knowledge gained during trial conduct (e.g. safety, exploratory PK analyses). In any case, the selected dose must not exceed the approved dose range. The food effect part will not start before the respective dose has been studied in the SRD part. **The estimated exposure of 200 mg of BI 1358894 administered under fed conditions may exceed the current exposure threshold C_{max} of 980 nM or an AUC_{0-24h} of 9500 nM*h. Since at the time of this 200 mg fed dose group clinical data up to 200 mg fasted and 100 mg fed are available, the exposure threshold for the dose group of 200 mg administered under fed conditions will be further increased to the exposure at NOAEL in rats (i.e. C_{max} of 1960 nM and an AUC_{0-24} of 26300 nM*h). The exposure in previous fed dose groups indicates that the geometric mean of the AUC_{0-24} for the 200mg fed group is predicted to be 15400 nM*h and the geometric mean of C_{max} is predicted to be 1127 nM, i.e. below the new threshold. Even based on the 95% prediction interval the threshold would not be exceeded.
mode of admin.:	SRD: Oral with 240 mL of water after an overnight fast of at least 10 h FE: Oral with 240 mL of water after an overnight fast of at least 10 h and after a standard high fat breakfast SRD fed: Oral after a standardized high fat breakfast
Comparator products:	Matching placebo tablets
dose:	Not applicable
mode of admin.:	SRD: Oral with 240 mL of water after an overnight fast of at least 10 h SRD fed: Oral with 240 mL of water after a standardized high fat breakfast
Duration of treatment:	SRD: 1 single dose FE: 2 single doses [separated by a wash-out period of at least 7 days between drug administrations]
Criteria for pharmacokinetics:	**SRD** Secondary endpoints: $AUC_{0-\infty}$ (if evaluable), C_{max}, AUC_{0-tz} **FE:** Secondary endpoints: $AUC_{0-\infty}$ (if evaluable), C_{max}, AUC_{0-tz}

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Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 1358894 is the number [N (%)] of subjects with drug related adverse events. Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR]), orthostatic test and Bond & Lader and Bowdle visual analogue scales and suicidality assessment (C-SSRS).		
Statistical methods:	Descriptive statistics will be calculated for all endpoints. The PK parameters AUC and C_{max} will be explored for dose proportionality of BI 1358894 using a regression model; a 95% confidence interval (CI) for the slope will be computed. The statistical model to assess relative bioavailability in the food effect part will be an analysis of variance (ANOVA) on the ln-transformed parameters AUC and C_{max} including effects for "sequence", "subjects nested within sequences", "period" and "treatment". Point estimators (geometric means) for the ratios of response under test compared to reference treatment and their two-sided 90% confidence intervals will be calculated. Confidence intervals will be based on the residual error from ANOVA		

FLOW CHART

SRD (3 mg – 200 mg fasted)

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [10, 11]		Orthostatic testing	Visual analogue scale[15]	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR, RR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x			x	x	x		x	
2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x[7]								x
	1	-1:30	06:30	Admission to trial site	x[5]			x					x
		-0:30	07:30	Allocation to treatment[2]	x[13]	x[2]			x[2]	x[2,9]		x[2]	x[2]
		0:00	**08:00**	**Drug administration**							▲		
		0:10	08:10			x					|		
		0:20	08:20			x					|		
		0:30	08:30			x				x[9]	|	x	x
		1:00	09:00			x				x[9]	|	x	x
		1:30	09:30			x				x[9]	|	x	x
		2:00	10:00	240 mL fluid intake		x			x	x[9]	|	x	x
		2:30	10:30			x					|		
		3:00	11:00			x[8]		x		x[9]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x			x	x[9]	▼	x	x
		5:00	13:00			x				x[9]		x	x
		6:00	14:00			x				x[9]		x	x
		7:00	15:00			x							
		8:00	16:00	Snack (voluntary)[3]		x			x	x[9]		x	x
		10:00	18:00	Dinner[3]		x							
		12:00	20:00			x				x[9]		x	x
		16:00	24:00			x				x[9]		x	
	2	24:00	08:00	Breakfast	x	x			x	x[9]		x	x
		34:00	18:00			x			x	x[9]		x	x
	3	48:00	08:00	Breakfast, Discharge from trial site[16]		x			x	x[9]		x	x
	4	72:00	08:00	Ambulatory visit		x				x		x	x
	5	96:00	08:00	Ambulatory visit		x				x		x	x
	6	120:00	08:00	Ambulatory visit		x[14]						x	x
	7	144:00	08:00	Ambulatory visit		x[14]						x	x
	8	168:00	08:00	Ambulatory visit		x[14]						x	x
	9	192:00	08:00	Ambulatory visit		x[14]						x	x
4	10 to 14			End of trial (EOT) examination[4, 14]	x				x	x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening, hepatitis serology and HIV antibodies), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, Bond & Lader and 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 (first) 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, Bond & Lader and 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 within 3 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.

14. Time points optional, may be modified after availability of PK data of each dose, EOT starts one day after the last ambulatory visit
15. Suicidality assessment only at screening and end of trial.
16. Confirmation of fitness includes physical examination, vital signs, ECG, recording of AEs and concomitant therapies. Evaluation of safety lab assessed on Day 2.

Food Effect (FE), 50 mg and 100 mg

Visit	Day	Planned Time [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety Laboratory	Alcohol and drug screening	PK_{blood} [9,12]	12-lead ECG	Vital signs (BP, PR, RR)	AE/CT-Qestioning[6]
1	-21 to -1			Screening examination [1]	x	x		x	x	
2 or 3[8]	-3	-72:00	8:00		x[7]					x[7]
	-1	-12:00	20:00	Admission to trial site	x[5]					
	1	-1:30	6:30	Treatment allocation[10]	x[2,11]	x[2]	x[2]	x[2]	x[2]	x
		-0:30	7:30	Standardized breakfast (only in fed state arm)						
		0:00	**8:00**	**Drug administration**						
		0:10	8:10				x			
		0:20	8:20				x			
		0:30	8:30				x			
		1:00	9:00				x		x	
		1:30	9:30				x			
		2:00	10:00	240 mL fluid intake			x	x	x	x
		2:30	10:30				x			
		3:00	11:00				x			
		4:00	12:00	240 mL fluid intake, Lunch[3]			x	x	x	x
		5:00	13:00				x			
		6:00	14:00				x		x	
		7:00	15:00				x			
		8:00	16:00	Snack[3] (voluntary)			x	x	x	x
		10:00	18:00	Dinner[3]			x			
		12:00	20:00				x		x	x
		16:00	24:00				x		x	
	2	24:00	8:00	confirmation of fitness, discharge from trial site, breakfast[3]	x		x	x	x	x
		36:00	20:00	Ambulatory visit			x		x	x
	3	48:00	08:00	Ambulatory visit	x		x		x	x
	4	72:00	08:00	Ambulatory visit			x		x	x
	5	96:00	08:00	Ambulatory visit			x		x	x
	6	120:00	08:00	Ambulatory visit			x[13]		x	x
	7	144:00	08:00	Ambulatory visit			x[13]		x	x
	8	168:00	08:00	Ambulatory visit			x[13]		x	x
	9	192:00	08:00	Ambulatory visit			x[13]		x	x
4	10 to 14			End-of-trial (EOT)-examination[4,13]	x			x	x	x

1 Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening hepatitis serology and HIV antibodies), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria Bond & Lader and 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 (first) 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, Bond & Lader and 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 AE/CT-Questioning and safety laboratory will take place **once**, prior to first study drug administration between 72 h and 24 h.
8 Two identical treatment periods, separated by a wash-out period of at least 7 days between drug administrations; based on sequence intake of study drug under fasted or fed conditions. The duration of wash-out period may be revised based on the PK exploratory analysis in SRD part of the study. Predose at visit 3 Bond & Lader and Bowdle visual analogue scales and suicidality assessment (C-SSRS) will be performed.
9 The sample collection schedule may be altered based on the results of PK exploratory analyses in the SRD part
10 Treatment allocation only at visit 2

12 Based on preliminary PK evaluations, visit days and blood samples may be modified as long as blood loss will not exceed 500 ml
13 Time points optional, may be modified after availability of PK data of the SRD part, EOT starts one day after the last ambulatory visit

SRD 200 mg fed Dose group

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9]		Orthostatic testing	Visual analogue scale[12]	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR, RR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x			x	x	x		x	
2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x[7]								x
	1	-1:30	06:30	Admission to trial site	x[5]			x					x
		-0:30	07:30	Allocation to treatment[2]	x[11]	x[2]			x[2]	x[2,8]		x[2]	x[2]
		-0:30	7:30	Standardized breakfast									
		0:00	**08:00**	**Drug administration**							▲		
		0:10	08:10			x					|		
		0:20	08:20			x					|		
		0:30	08:30			x				x[8]	|	x	x
		1:00	09:00			x				x[8]	|	x	x
		1:30	09:30			x				x[8]	|	x	x
		2:00	10:00	240 mL fluid intake		x			x	x[8]	|	x	x
		2:30	10:30			x					|		
		3:00	11:00			x		x		x[8]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x			x	x[8]	▼	x	x
		5:00	13:00			x				X[8]		x	x
		6:00	14:00			x				X[8]		x	x
		7:00	15:00			x							
		8:00	16:00	Snack (voluntary)[3]		x			x	X[8]		x	x
		10:00	18:00	Dinner[3]		x							
		12:00	20:00			x				X[8]		x	x
		16:00	24:00			x				X[8]		x	
	2	24:00	08:00	Breakfast	x	x			x	X[8]		x	x
		34:00	18:00			x			x	X[8]		x	x
	3	48:00	08:00			x			x	X[8]		x	x
	4	72:00	08:00			x				X[8]		x	x
	5	96:00	08:00		x	x				X[8]		x	x
	6	120:00	08:00			x				X[8]		x	x
	7	144:00	08:00	Breakfast, confirmation of fitness[13,12], discharge from trial site		x				X[8]		x	x
	9	192:00	08:00	Ambulatory visit		x						x	x
	11	240:00	08:00	Ambulatory visit		x						x	x
	15	336:00	08:00	Ambulatory visit		x						x	x
	22	504:00	08:00	Ambulatory visit		x						x	x
	29	672:00	08:00	Ambulatory visit		x						x	x
4	29 to 33			End of trial (EOT) examination[4]	x				x	x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, neurological examination, check of vital signs, ECG, safety laboratory (including drug screening, hepatitis serology and HIV antibodies), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, Bond & Lader and 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 (first) 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, neurological examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, Bond & Lader and 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 within 3 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.

12. Suicidality assessment at screening, discharge from CPU and end of trial.
13. Confirmation of fitness includes physical examination, neurological examination, vital signs, ECG, recording of AEs and concomitant therapies. Evaluation of safety lab assessed on Day 2 and 5.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
ANOVA	Analysis of variance
AST	Aspartate amino transferase
AUC	Area under the curve
$AUC_{0-\infty}$	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
β	Slope parameter associated with the power model used to evaluate dose proportionality
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BW	Body weight
BPD	borderline personality disorder
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
$C_{pre,N}$	Predose concentration of the analyte in plasma immediately before administration of the Nth dose after N-1 doses were administered
CRF	Case report form
CRO	Clinical Research Organization
CT	Concomitant Therapy

CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
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
FIH	First in Human
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
GMP	Good Manufacturing Practice
hERG	human ether-a-go-go related gene
HIV	Human Immunodeficiency Virus
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
MRD	Multiple rising dose
nM	Nanomolar
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate

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)
R	Reference treatment
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SRD	Single-rising dose
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
TMF	Trial master file
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
$t_{max(,N)}$	Time from (last) dosing to the maximum measured concentration of the analyte in plasma (after administration of N doses)
TRPC	transient receptor potential cation channel
t_z	Time of last measurable concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White Blood Cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 1358894, an oral, small-molecule inhibitor of a transient receptor potential cation channel, subfamily C, members 4 and 5 (TRPC 4/5) for major depressive disorder (MDD) as an adjunct to antidepressant therapy and for the treatment of borderline personality disorder (BPD), that has not yet been tested in humans.

MDD is a debilitating disease that is difficult to treat, even when using systematic antidepressant strategies. In the National Institute of Mental Health (NIMH) funded STAR*D trial of > 4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residuals symptoms [R16-5475] which significantly impacted the patients' quality of life [R06-2872]. When monotherapy is insufficient, clinicians employ different augmentation strategies including add-on treatment with lithium or atypical antipsychotics. When augmentation strategies also fail, convulsive therapies such as electro-convulsive therapy (ECT) may be used.

Borderline personality disorder (BPD) is a chronic mental disorder with an estimated prevalence of around 2% in the general community [R16-5476] and severe impairment of quality of life [R16-5474]. The main symptom clusters of BPD include impulsive-behavioural dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations and affective instability. Patients with BPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times higher than in the general population [R16-5477]. Even the presence of a single diagnostic feature of BPD is predictive for poor functioning and psychiatric illness burden [R16-5483]. Treatment guidelines recommend psychotherapy 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 BPD.

TRPC4 and TRPC5 form ion channels that are involved in the regulation of neuronal excitability. They are most highly expressed in the amygdala, in the frontal cortex, hippocampus, and hypothalamus [R15-3888; R16-5350] which are involved in modulation and processing of emotion and affect. Pre-clinically, treatment with BI 1358894 has shown diminished fear and anxiety and increased social interaction without impairing other brain functions such as learning and memory behaviours.

It is hypothesized that in patients with affective disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts and anxiety [R16-5473] and there is growing evidence supporting the role of amygdala in the emotion processing disturbances observed in patients with BPD [R16-5472]. Therefore, it is expected that treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in patients with MDD and BPD.

The clinical development program will first explore the clinical pharmacology of BI 1358894 in healthy volunteers and subsequently in patients with MDD and BPD.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

Transient receptor potential canonical (TRPC) channels are Ca^{2+}-permeable nonselective cation channels implicated in diverse physiological functions, including smooth muscle contractility and synaptic transmission.

1.2.2 Safety pharmacology

1.2.3 Toxicology

1.2.4 Nonclinical pharmacokinetics

1.2.5 Clinical experience in humans

This is the first-in-man study. No clinical data are available to date for BI 1358894. Inhibition of TRPC4/5 is a novel mechanism of action, with no precedent published clinical data for other drug candidates.

1.2.6 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 1358894 profile please refer to the current Investigator's Brochure [c10354149-01].

1.2.7 Prediction of human pharmacokinetics

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

TRPC4 and TRPC5 form ion channels that are involved in the regulation of neuronal excitability. They are highly expressed in the amygdala and other CNS regions [R15-3888; R16-5350] which are involved in modulation and processing of emotion and affect. It is hypothesized that in patients with affective disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts and anxiety [R16-5473] . Inhibition of TRPC4/5 ion channels by BI 1358894 may therefore have the potential to improve affective symptoms and emotion control in patients with affective disorders.

As a transition from preclinical investigations to clinical development in this first-in-man trial, safety, tolerability, and pharmacokinetics of BI 1358894 will be assessed in healthy male volunteers using single rising oral doses. The study will provide the basis for potential further clinical development of BI 1358894 in patients with MDD and BPD.

Healthy male subjects aged 18 - 45 years will be recruited for this study. They provide a relatively stable physiological and biochemical basis for studying drug effects, they show no disease-related variation and they are not taking concomitant medication.

In the single rising dose (SRD) part, within each dose group, all actively treated individuals will receive the same BI 1358894 dose. The next higher dose will only be administered (to the next group) if the treatment in the preceding dose groups was safe and showed acceptable tolerability.

In the relative bioavailability (BA) part, up to 3 dose groups may be studied in a two-way-crossover fashion. This will help gain information about the effect of food on the exposure of BI 1358894 and will support upcoming clinical studies with respect to better trial designs, and to help if needed in the optimization for future trial-formulation development.

Dose selection

It is intended to investigate the following dose levels of BI 1358894 in the SRD part of this trial: 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 100 mg, and 200 mg. The background for this dose selection is described in the following paragraphs.

In order to cover the anticipated dose range, a stepwise and careful dose increase has been selected for this trial. The escalation schedule has been chosen in a way that a shallow escalation will be applied for the higher dose levels with a factor not greater than 2.5. This dose escalation is considered to be adequate and safe.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 1358894 in healthy male subjects following oral administration of single rising doses of 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 100 mg, and 200 mg.

Secondary objectives are the exploration of the pharmacokinetics (PK), including dose proportionality of BI 1358894 after single dosing.

The objective of the FE part will be to explore the influence of food on the relative bioavailability of BI 1358894.

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

2.3 BENEFIT - RISK ASSESSMENT

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

2.3.1 Procedure-related risks

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

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

2.3.2 Risks related to the intake of BI 1358894

2.3.2.1 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 summarized in Section 1.2.3, potential risks observed in non-clinical studies are a long lasting decrease of blood pressure in rats, an increase in heart rate in rats and dogs, and signs of a short lasting episode of arterial/ perivascular inflammation in rats. All findings were observed within 5 days after start of treatment. The CV effects observed in rodents and non-rodents can be easily monitored in a Phase I study (CV effects). Perivascular/mesenteric inflammation induced by BI 1358894 occurred early after 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.

2.3.2.2 Drug-related risks and safety measures

Mode of action and nature of the target

The TRP family are ion channels considered to play a crucial role in physiological processes such as to act as a cellular sensor or to support signal transmission (Minke 2010). The subtypes TRPC4 and TRPC5 form ion channels that are involved in the regulation of neuronal excitability. They are highly expressed in the amygdala, in the frontal cortex, hippocampus, and hypothalamus [R15-3888; R16-5350], which are involved in modulation and processing of emotion and affect. Pre-clinically, inhibition of these receptors by BI 1358894 has shown diminished fear and anxiety and increased social interaction without impairing other brain functions such as learning and memory behaviours. In accordance with these findings, TRPC5 deficient mice display an anxiolytic-like phenotype (Riccio, 2009). This is considered to support the assumption that CNS effects in healthy subjects due to an inhibition of TRPC 4/5 are limited to a reduced anxiety. However, clinical data with compounds inhibiting this target have yet to be published.

Relevance of animal models

Human TRPC4 and TRPC5 proteins show high homology with the rat, mouse and dog proteins, and 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 indicated that rat and dog were suitable species for nonclinical safety profiling of BI1358894.

It should be highlighted that toxicity study in rats [n00250347] did not reveal any toxicologically relevant effects of BI 1358894 on the immune system up to the highest tested dose of 2000 mg/kg (1000 m/kg twice daily). 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.

2.3.2.3 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 as described in Section 2.1.
- Preliminary measurement of BI 1358894 plasma concentrations and preliminary determination of PK parameters (C_{max}, AUC_{0-24}; see Section 7.3.4). For precautionary reasons, drug plasma concentrations of healthy volunteers in this trial should not exceed the mean C_{max} of 980 nM or mean AUC_{0-24} of 9500 nM*h, which will be considered a preliminary threshold (see Section 2.1). Further dose progression would only be allowed after a safety interim analysis and filing and approval of a substantial CTP amendment. For subjects receiving 200 mg of BI 1358894 under fed conditions that the geometric mean of the AUC_{0-24} is predicted to be 15400 nM*h and the geometric mean of C_{max} is predicted to be 1127 nM. Based on the 95% prediction interval the threshold (NOAEL in rats: C_{max} of 1960 nM or mean AUC_{0-24} of 26300 nM*h) would not be exceeded.
- An extensive safety laboratory will be performed with special focus on full blood exam (see Flow Chart).
- For safety reasons, during the single rising dose part each dose group of 8 subjects (6 on active, 2 on placebo) will be divided into three cohorts: on the first study day of each dose level, only 2 subjects will be treated: one will receive active treatment, the other subject will receive placebo. If BI 1358894 treatment is safe and tolerated in this first cohort, 2 subjects on active will be treated in the second cohort no sooner than on the next day and could be dosed as close as 2 h apart. The remaining 4 subjects (either active or placebo) are the third cohort and will be treated no sooner than after 2 days following the first cohort. This design ensures that between first and second active dose of each dose level there is a time interval of at least 1 day, which covers the Tmax of BI 1358894 and the period of highest risk / peak effect. If BI 1358894 was safe and showed acceptable tolerability in the first two cohorts, the remaining third cohort of the respective dose level could be dosed as close as 10 minutes apart. During the single rising dose part, a thorough ECG monitoring including continuous ECG measurement over 4 hours post dose to cover the anticipated period of highest drug exposure and additional repeated single 12-lead ECGs over 96 hours (for Dose Group 200 mg fed up to 144 h) following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.2 for details).

- In this study, blood pressure and heart rate will be closely monitored (see Flow Chart). 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 5.2.5.2 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 Bond & Lader visual analogue scales and suicidality assessment by C-SSR).
- The subjects will stay at the trial site for at least 48 hours after study drug administration at each dose level. Based on the initially anticipated terminal half-life for BI 1358894 of approximately 15 hours, this is expected to cover the period of highest risk / peak effect.
- The subjects assigned to Dose Group 200 mg fed will stay at the trial site for at least 144 hours after study drug administration. For a period of at least 24 hours after intake of study drugs which is expected to cover the period of highest risk / peak effect, a physician will stay at the study site to allow, if needed, immediate emergency intervention and rescue measures.
- During in house-confinement, the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Only if the respective dose of BI 1358894 is safe, shows acceptable tolerability, and no stopping criterion are met (refer to Section 3.3.4.2), the next higher dose will be given (at least 6 days later, referring to the 1st subject of each dose group).
- The food effect part with 50 mg will only start after the completed SRD part. Further dose levels may be tested based on safety and tolerability of the completed SRD part, as long as predicted exposure will remain below the predefined thresholds (mean C_{max} of 980 nM or mean AUC_{0-24} of 9500 nM*h).As reproductive toxicity studies have not yet been conducted, women of child-bearing potential will not be enrolled in this study.

2.3.2.4 Drug induced liver injury

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

2.3.3 Overall assessment

In summary, although not tested in humans to date, BI 1358894 has the potential to become an oral treatment for major depressive disorder as an adjunct to antidepressant therapy and for the treatment of borderline personality disorder. Based upon preclinical data for BI 1358894, as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a

basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this FIM clinical trial with BI 1358894, as is the usual case in such Phase I trials. Considering the medical need of the development of a safer and more effective treatment for patients with Mood and Borderline Personality disorders, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This FIH study consists of an SRD and an FE part. The SRD part is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups, while the FE part will be conducted according to an open-label, randomised, two-way crossover design.

SRD:

The SRD part will start with a tablet formulation. In case the tablet formulation will be used up to the final dose group, 64 healthy male subjects will be included, according to 8 sequential groups comprising 8 subjects per group. However, based on in vitro data, there is a possibility that due to the low solubility of the drug substance and tablet, the exposure in subjects will be limited and increase may be less than dose proportional (see Section 7.3.4).

Further subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number may exceed 64, but will not exceed 72 subjects entered. Such changes may be implemented via non-substantial CTP Amendments.

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

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

Table 3.1: 1 Dose groups (SRD part)

Test product 1: BI 1358894 tablets (1 mg, 5mg, 25 mg 100 mg)

Trial part	SRD							
Dose Group	1	2	3	4	5	6	7	8*
Dose (mg)	3	6	10	25	50	100	200	200
Number of subjects	8	8	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2	2	2
Subjects receiving active drug	6	6	6	6	6	6	6	6

*Administration under fed conditions

The dose groups of the SRD part will be investigated sequentially in ascending order of doses, maintaining a time interval of at least 5 days between the last drug administration in the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next dose group will be based upon the safety, tolerability, and exploratory pharmacokinetic data (see Section 7.3.4) of the preceding dose groups. The next

dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

FE part

The food effect part will be performed as a randomised, open label, single-dose, two - sequence, two-way cross-over trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The subjects will be randomly allocated to the two treatment sequences (T-R or R-T). The 4 treatments will be two 25 mg tablets and one 100 mg tablet in the fasting state (R) and two 25 mg tablets and one 100 mg tablet after a standardised high fat breakfast (T). The dose strengths to be tested (lowest and maximum dose) will be re-evaluated after explorative safety and PK analysis. For details, refer to Section 4.1. There will be a washout period of at least 7 days between the treatments. A total of 24 healthy male subjects are planned to participate in the FE part. An overview of all relevant trial activities is provided in the Flow Chart.

For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

Table 3.1: 2 Dose groups (FE part)

Test product 1: BI 1358894 (film-coated tablets)

Trial part		FE
Dose Group		
Dose (mg)	50	100
Number of subjects	12	12
Subjects receiving placebo	--	--
Subjects receiving active drug	12	12

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

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

- AEs in the current and preceding dose groups (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)

- Results from 12-lead ECG and continuous ECG monitoring (SRD only) in the current and preceding dose groups.
- Vital signs and results from the orthostatic test in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK data for selected groups as defined in Section 7.3.4.
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

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

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

3.1.1 Administrative structure of the trial

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

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

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

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

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

The analyses of BI 1358894 concentrations in plasma 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

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

Data management and statistical evaluation will be done by BI according to BI SOPs.

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

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

For single-rising dose trials, the design described in Section 3.1 is considered 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, single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to potential dose-dependent effects, as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that up to 64 healthy male subjects will enter the SRD part (8 per dose group, 6 on active and 2 on placebo) and 24 healthy males will enter the FE part (12 per dose group, all on active) of the study. The actual number of subjects entered may exceed the total of 88 if additional intermediate doses will be tested (see Section 3.1), but will not exceed 96 subjects. Subjects will be recruited from the volunteers' pool of the trial site.

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

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 45 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Willingness to comply with contraception requirements. Subjects who are sexually active, must use, with their female partner, adequate contraception throughout the study and until one month after the last administration of trial medication. Adequate methods are:
   - Sexual abstinence or
   - A vasectomy performed at least 1 year prior to screening in combination with a barrier method (condom) or
   - Surgical sterilisation (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subjects female partner or
   - The use of condoms, if the female partner uses in addition an adequate contraception method, 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 one month 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) is deviating from normal
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 > ULN, erythrocyte sedimentation rate (ESR) ≥ 15 millimeters/hour, liver and kidney parameter above ULN, other laboratory values outside the reference range the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 30 g per day for males)
16. Drug abuse as per investigator judgment or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
6. The subject shows at one dose level a raised CRP level of >3.00 mg/dL or an baseline Erythrocyte Sedimentation Rate (ESR) of ≥ 20 millimeters/hour.

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

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments). This is in particular to be checked before second dosing of the FE part.

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
6. Dose escalation will be stopped if the estimated exposure is expected to exceed a C_{max} of 1960 nM or anAUC_{0-24h} of 26300 nM*h. Estimation will be done based on preliminary mean values of AUC_{0-24h} and C_{max} of preceding dose groups (see Section 7.3.4).
7. Dose escalation will be stopped, as soon as at least 2 subjects at one dose level showed a sustained decrease in systolic blood pressure of over ≥ 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 / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product and comparator products

SRD part

The characteristics of the test product 1 for dose group 1-8 are:

Substance:	BI 1358894
Pharmaceutical formulation:	film coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	1mg, 5 mg, 25 mg, 100 mg
Posology:	3-0-0 (3 mg), 6-0-0 (6 mg), 2-0-0 (10 mg, 50 mg, 200 mg), 1-0-0 (25, 100 mg),
Route of administration:	p.o.
Duration of use:	single dose

The characteristics of the reference product (placebo) for dose groups 1-8 are:

Substance:	matching placebo
Pharmaceutical formulation:	film coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	3-0-0 (3 mg), 6-0-0 (6 mg), 2-0-0 (10 mg, 50 mg, 200 mg), 1-0-0 (25, 100 mg),
Route of administration:	p.o.
Duration of use:	single dose

FE part

The characteristics of the test product 1 are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	film coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany

Unit strength:	25 mg and 100 mg
Posology:	2-0-0 (50 mg) 1-0-0 (100 mg), see Flow chart.
Route of administration:	p.o.
Duration of use:	2 single doses

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to one of the dose cohorts (3 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomisation list with study subject numbers and allocated treatments (SRD part) or treatment sequences (FE part) will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

For the SRD part, oral doses in the range of 3 mg to 200 mg have been selected in order to assess the safety and tolerability of BI 1358894 in healthy male volunteers, and to investigate the PK of this novel TRPC 4/5 inhibitor. The doses selected for this trial cover the subtherapeutic, as well as the estimated therapeutic range and potentially supra-therapeutic doses within the levels determined by toxicological investigations (see Section 1.2).

For the FE part, oral doses may range from 25 mg to 100 mg.. The dose strengths to be tested will (lowest and highest dose) be re-evaluated after explorative safety and PK analysis. The FE part will assess the intra-individual food effect, tablet fasted versus tablet fed, of BI 1358894 in healthy male volunteers, with the aim to cover a dose range suitable for the subsequent clinical development.

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 // dose volume for placebo corresponds to the number of units // dose volume of the respective dose level.

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

Dose	Substance	Pharmaceutical form	Unit strength	Number of units / dose volume per administration	Total daily dose
1	BI 1358894	Film-coated tablet	1 mg	3 tablets	3 mg
2	BI 1358894	Film-coated tablet	1 mg	6 tablets	6 mg
3	BI 1358894	Film-coated tablet	5 mg	2 tablets	10 mg
4	BI 1358894	Film-coated tablet	25mg	1 tablet	25 mg
5	BI 1358894	Film-coated tablet	25 mg	2 tablets	50 mg
6	BI 1358894	Film-coated tablet	100 mg	1 tablet	100 mg
7	BI 1358894	Film-coated tablet	100 mg	2 tablet	200 mg
8*	BI 1358894	Film-coated tablet	100 mg	2 tablet	200 mg
1-8	Placebo*	Film-coated tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups, dose group 8 treatment under fed conditions

Table 4.1.4: 2 BI 1358894 film-tablets for the FE part

Treatment	Substance	Pharmaceutical form	Unit strength	Number of units / dose volume per administration	Total Dose
T1 (tablet fed)	BI 1358894	Film-coated tablet	25 mg	2 tablets	50 mg
R (tablet fasted)	BI 1358894	Film-coated tablet	25 mg	2 tablets	50 mg
T1 (tablet fed)	BI 1358894	Film-coated tablet	100 mg	1 tablet	100 mg
R (tablet fasted)	BI 1358894	Film-coated tablet	100 mg	1 tablet	100 mg

The dose strengths to be tested will (lowest and highest dose) be re-evaluated after explorative safety and PK analysis.

The trial medication will be administered to the subjects, while they are in a sitting/standing 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. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured

otherwise. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

In treatment T1, a high-fat, high-calorie breakfast will be served 30 min before drug administration. The breakfast must be completely consumed prior to drug administration. The composition of the standard high-fat, high-calorie breakfast will be in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269] as detailed in Table 4.1.4: 3.

Table 4.1.4: 3 Composition of the high-fat, high-calorie breakfast

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content will be 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 48 h (SRD part) following drug administration. During the first 2 h after drug administration, subjects of the SRD 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. During the first 4 hours after drug administration, subjects of the FE part will only be allowed to lie down if supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG). 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

SRD part

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

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager,

statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist, as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

FE part

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

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single blinded (single rising dose part) and open-label (food effect part), the treatment information will be known to the investigator. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. Smaller bottles/boxes within the clinical trial supply containers will be labelled with:

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

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the

correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol
- Availability of the Form 1572

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

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

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator / pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator / pharmacist must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and 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

In case of adverse events in need of treatment, the investigator can authorize symptomatic therapy.

In case of alterations of blood pressure (hypotension) and heart rate (tachycardia), which were reported in toxicology studies (see section 1.2.2) physical interventions will be the first treatment of symptoms. If not successful, 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, beside volume substitution, administration of vasopressors may be a further step. The whole staff of the trial site assuming medical responsibility during conduct of the study is routinely trained in emergency procedures.

If required, any subject with an adverse event in need of treatment will be kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (FE part Treatment T, 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).

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

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 1358894 is the number [N (%)] of subjects with drug- related adverse event.

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate, respiratory rate) and Orthostatic tests (SRD part only)
- Visual analogue scale (Bond & Lader)

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect, or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

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

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

Intensity of AEs

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

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

Causal relationship of AEs

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

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

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

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

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

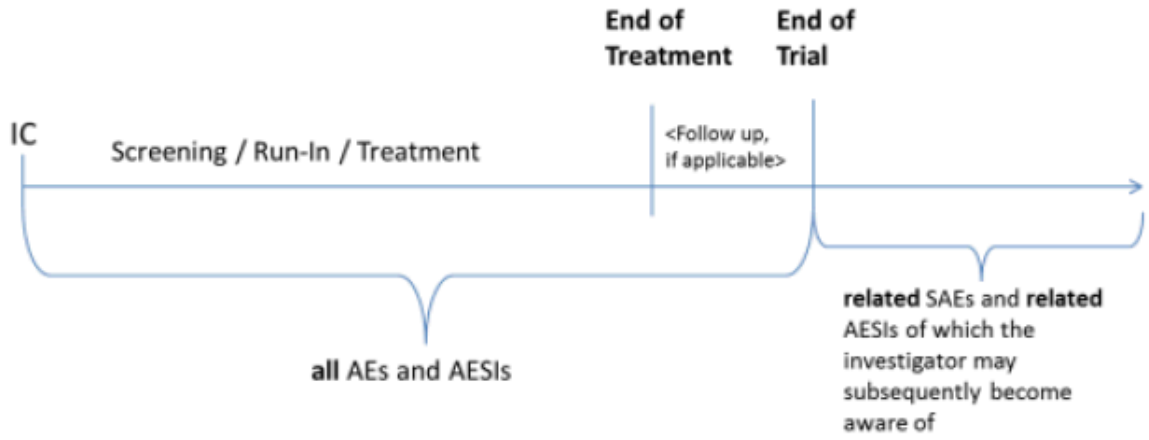
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

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

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

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



The REP for BI 1358894, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment (please see Section 7.3.3).

AE reporting to sponsor and timelines

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

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

Information required

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

The following should also be recorded as an (S)AE in the CRF and 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 eCRFonly.

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

5.2.3 Assessment of safety laboratory parameters

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

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

Manual differential white blood cell count 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) Glutamate dehydrogenase (GLDH) 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
Electrolytes	Sodium Potassium Calcium

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Urinalysis[1] (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment[1] (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 which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening, after admission to the trial site (SRD part) and prior to each treatment period (FE part).

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody/p24-antigen (qualitative)

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed with the exception of the urinalysis stix and drug screening tests. These tests will be performed at the

trial site using Combur9 Test, and AccuSign® DOA 10 test ( ).

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System,) 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.

Single rising dose part: Triple ECGs will be recorded (within 180 sec) at all-time points as specified in the respective Flow Chart. At all remaining time points, single ECGs will be recorded.

Food effect part: Single ECGs will be recorded for all time points. However, the number of ECGs per time point may be increased to three ECGs based on preliminary ECG results obtained during the single rising dose part of the study.

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

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time points with triple ECGs, all three single ECGs will be repeated. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for 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.

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored (only during SRD part) by means of continuous 3-lead ECG recording for at least 15 min before (for baseline assessment), and 4 h following drug administration using patient monitors (e.g. ApexPro Telemetry System).

Abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator but no other data will be transferred to the database.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure device) 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.

5.2.5.2 Orthostatic tests

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 measurements will be performed using the blood pressure device described in Section 5.2.5.1. The term "Orthostatic dysregulation" will be used to describe adverse events that occur during orthostatic testing. Typical symptoms (and findings) of orthostatic dysregulation are 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 (MRD part), 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. The timing of orthostatic testing may be adapted based on information obtained during the trial (e.g. preliminary PK data (t_{max}), including reducing or adding measurements. This would be implemented via a non-substantial CTP amendment.

5.2.5.3 Visual Analogue Scale (VAS)

Possible psychedelic effects will be monitored and evaluated as safety measurement by analogue scales developed by Bond and Lader [R98-0752] and 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.

5.2.5.4 Medical examinations

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

5.2.5.5 Suicidality assessment

Suicidality assessment to further evaluate the psychological status of the subject will be performed at screening, as indicated in the Flow Chart 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 10.3.

5.2.5.6 Neurological examinations

As a general additional safety measure in the planned dose group 200mg fed 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.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Plasma samples will be collected for the purpose of pharmacokinetic analysis

Further information about sampling is provided in Section 5.5.2.

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

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

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

- $AUC_{0\text{-}tz}$ (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)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1358894 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium Ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

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

All samples will be stored at about -20°C or below until transfer to the analytical laboratory.

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

BI 1358894 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.

5.6 BIOMARKER

No biomarker will be detected.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation 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 scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters except for the orthostatic testing.

The acceptable deviation from the scheduled time for standardized neurological tests (conducted in Dose Group 200 mg fed) is ± 45 min on day 1, and ± 90 min from day 2 onwards.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment periods

SRD part

Each subject will receive one dose of the respective 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 morning of Day 1 and kept under close medical surveillance for at least48h following the first drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.

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

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

FE part

In the FE part, each subject is expected to participate in 2 treatment periods. The treatment periods will be separated by at least 7 days between drug administrations. On Day 1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On other study days, the study will be performed in an ambulatory fashion.

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.

6.2.3 End of trial period

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

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

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed

up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1358894 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) of BI 1358894. Endpoints as specified in Section 5.5.1 will be analysed by descriptive statistics. Secondary endpoints as defined in Section 5.5.1.1 will be subjected to analysis of dose proportionality by use of the power model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

SRD part

Safety and tolerability of the different dose groups of BI 1358894 will be determined on the basis of the investigational parameters in comparison with placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

For the evaluation of the dose proportionality, a two-sided 95% confidence interval of the slope will be computed. However, the confidence interval will be interpreted according to the exploratory character of the study, i.e. as an interval estimate for effects in the present data.

BA part (Food effect evaluation)

The relative bioavailability of BI 1358894 to evaluate the food effect given as tablets under fasted conditions (R) compared to BI 1358894 given as tablets under fed conditions (T1) will be estimated by the ratios of the geometric means (T1/R). Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

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

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The PK parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472], current version.

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

Relevant protocol violations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications
- The subject has a protocol deviation relevant to the evaluation of relative bioavailability. (Whether a protocol deviation is relevant, will be decided no later than the Report Planning Meeting.)

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

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

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

Assessment of dose proportionality

Dose proportionality will be assessed using the pharmacokinetic endpoints as specified in Section 5.5.1.1 (AUC and C_{max}). The specific AUC for the analysis will be defined in the TSAP.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …, 8, j = 1, 2, …, 8;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

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

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

Dose proportionality will be assessed separately for film-coated tablet after fasted and fed conditions..

BA part: Investigation of relative bioavailability (food effect evaluation)

Relative bioavailability is primarily to be determined on the basis of the parameters AUC and C_{max} (cf. Section 5.5) for the dose levels as specified in Section 3.1 (currently planned for 50mg, 100mg). The specific AUC for the analysis will be defined in the TSAP. Those parameters will be ln-transformed (natural logarithm) prior to fitting the model.

The statistical model used for the analysis of AUC and C_{max} will be an ANOVA (analysis of variance) model on the logarithmic scale. The specific AUC for the analysis will be defined in the TSAP. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. The model is described by the following equation

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

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., 12

π_j = the j^{th} period effect, j = 1, 2

τ_k = the k^{th} treatment effect, k = 1, 2

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

The difference between the expected means for test treatments (tablets under fed conditions T1) and reference treatment (tablets under fasted conditions R) log(T1)-log(R), will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

7.3.3 Safety analyses

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

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

In the SRD part, the active treatment groups will be compared to the placebo control group in a descriptive way. In the BA part, the two different treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by ‘randomised treatment’.

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

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

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

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

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

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1358894 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472, current version].

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma / concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma / concentrations, pharmacokinetic parameters or other statistical assessment.

Only concentration values within the validated concentration range will be used for the calculation of pharmacokinetic parameters.

Final PK analyses will use actual sampling times.

Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

SRD part
The subjects of the first two cohorts per dose level will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. In the third cohort of each dose level the subjects will be assigned to active or placebo treatment using a 3:1 allocation ratio.

BA part (food effect evaluation)

Subjects will be randomized to one of the two treatment sequences R/T1, T1/R in a 1:1 ratio.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

SRD part

It is planned to include a total of up to 64 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in

general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 64 but will not exceed 72 subjects entered.

BA part (food effect evaluation)

It is planned to enter a maximum of 24 subjects in this part of the trial: 12 subjects receiving 50mg and 100mg of BI 1358894. With this sample size, a certain precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined through the ratio of upper to lower confidence interval limit. Note that the precision is independent of the actual ratio of geometric means.

For this first-in-man study, no information on intra-subject variability is available. Therefore, Table 7.6: 1 provides an overview on the achievable precision for estimating the ratio of geometric means (test/reference) when comparing the formulations for two different gCV.

For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of geometric means ratios T1/R.

Table 7.6: 1 Precision and illustrative two-sided 90% confidence intervals around selected ratios of geometric means (T1/R) for different gCVs in a two way cross-over design trial (N=12)

N	gCV	gMean Ratio [%]	CI of gMean Ratio	Precision w%
12	15%	100	(86.13, 116.11)	15%
		150	(129.19, 174.16)	
		200	(172.26, 232.21)	
	20%	100	(82.01, 121.93)	20%
		150	(123.02, 182.89)	
		200	(164.03, 243.86)	
	25%	100	(78.15, 127.95)	25%
		150	(117.23, 191.93)	
		200	(156.31, 255.91)	
	30%	100	(74.54, 134.16)	29%
		150	(111.80,201.25)	
		200	(149.07,268.33)	

Ratio of the geometric means (test/reference) for a PK endpoint defined by $(\exp\mu_T)/\exp(\mu_R)$

The expected 90% confidence interval limits in the table were derived by CI limitupper, lower = $\exp(\ln(\theta) \pm \omega)$ with θ being the ratio (T1/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by [R12-0972] using R Version 3.2.2.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

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10. APPENDICES

10.1 VISUAL ANALOGUE SCALE (VAS)

Visual Analogue Scales (Bond & Lader) –English version

(As described in : Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol 1974;47:211-18) [R98-0752]

Please rate the way you feel in terms of the dimensions given below.
Regard the line as representing the full range of each dimension.
Rate your feelings as they are at the moment.
Mark clearly and perpendicularly across each line.

1	Alert	_____	Drowsy
2	Calm	_____	Excited
3	Strong	_____	Feeble
4	Confused	_____	Clear-headed
5	Well-coordinated	_____	Clumsy
6	Lethargic	_____	Energetic
7	Contented	_____	Discontented
8	Troubled	_____	Tranquil
9	Mentally slow	_____	Quick-witted
10	Tense	_____	Relaxed
11	Attentive	_____	Dreamy
12	Incompetent	_____	Proficient
13	Happy	_____	Sad
14	Antagonistic	_____	Amicable
15	Interested	_____	Bored
16	Withdrawn	_____	Gregarious

10.2 BOWDLE VAS-SCORE

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

10.3 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 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)*	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(S)

Number of global amendment		1
Date of CTP revision		16 May 2017
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Synopsis and flowchart 2. Section 2.3.2.3; Risk minimization (safety precautions and stopping rules) 3. Section 3.1;Overall Trial Design and Plan 4. Section 3.3.3, Exclusion criteria 5. Section 3.3.4.2, Discontinuation of the trial by the sponsor 6. Section 4.2.1, Other treatments and emergency procedure 7. Section 5.2.5.5, Suicidality assessment

Number of global amendment		1
Description of change		Changes apply to several sections throughout the protocol and are described only once and not repeated for each section: 1. Synopsis and Flow Chart To further evaluate the psychological status of subjects at screening and during the study a further visual analogue scale (Bowdle VAS to screen for psychedelic effects) has been included. In addition a suicidality assessment scores (Columbia-Suicide Severity Rating Scale) will be conducted at screening and at EOT. This applies also for the FE part. 2. Section 2.3.2.3, Risk minimization (safety precautions and stopping rules) Deferred inclusion of subjects and implementation of three cohorts per dose groups taking into account safety, tolerability and preliminary PK data. 3. Section 3.1, Overall Trial Design and Plan The dose strength used in the FE part will be selected based on the data of the completed SRD part. 4. Section 3.3.3, Exclusion criteria Exclusion criteria no. 1 and 3 have been modified to limit the acceptance of selected abnormal values by the investigator as not clinically relevant.Exclusion criteria number 23 and 24 have been added (abnormal suicidality assessment score) 5. Section 3.3.4.2, Discontinuation of the trial by the sponsor Drug related SAEs will lead to discontinuation of the trial, no drug related SAE will be considered. 6. Section 4.2.1, Other treatments and emergency procedure Emergency procedures for cardiovascular events have been specified.

Number of global amendment		1
		7. Section 5.2.5.5, Suicidality assessment Forms of suicidality assessment and Bowdle VAS have been added.
Rationale for change		Based on the feedback by BfArM and Ethics Committee, the respective recommendations were included in a revised protocol. This applies for all major changes as summarized in "Section to be changed", such as deferred inclusion of subjects, increased efforts for psychological testing and modification of exclusion criteria. In context with these changes a few remaining inconsistencies were also corrected.

Number of global amendment		2
Date of CTP revision		19 June 2017
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		- Synopsis and Flow Chart - Section 2.1 Rationale for performing thetrial - Section 2.3.2.3 Risk minimization (safety precautions and stopping rules) - Section 3.1 Overall Trial Design and Plan - Section 3.1 Table 3.1:1 Dose Groups - Section 3.3 Selection of Trial Population - Section 3.3.3 Exlusion Criteria - Section 3.3.4.1 Removal of individual subjects - Section 4.1.1 Identity of BI investigational product + comparator products - Section 4.1.1 Table 4.1.4:1 BI 1358894 and placebo treatments, oral administration for SRD part - Section 5.2.1.1 Routine laboratory tests -

Number of global amendment		2
Description of change		Changes apply to several sections throughout the protocol and are described only once and not repeated for each section: Synopsis and different sections throughout the protocol: The maximum exposure threshold was lowered to mean AUC $_{0\text{-}24\ of}$ 950 nmol*h/L corresponding to 1/10th of the exposure observed in male rats at 7.5 mg/kg/day in the 4-week toxicology study An additional dose group of 6 mg was added. The maximum number of subject may increase to 120 in the SRD part. Section 3.3.3 Exlusion Criteria C-reactive Protein > ULN and erythrocyte sedimentation rate > 15mm/hour are included as strict exlusion criteria Section 3.3.4.1 C-reactive Protein > 3 mg/dl and erythrocyte sedimentation rate > 20mm/hour are included as individual discontinuation criteria
Rationale for change		Based on the feedback by FDA, the respective recommendations were included in this revised protocol. This applies for most of the changes as summarized in “Section to be changed”, such as lowering of the exposure threshold, modification of exclusion criteria and discontinuation criteria for an individual subject. In context with these changes some inconsistencies were also corrected, in particular the addition of psychological assessments prior to the second dosing of the FE part.

Number of global amendment		3
Date of CTP revision		27 July 2017
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		- 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		Changes apply only to the section 3.3.4.2 To avoid false positive blood pressure values
Rationale for change		To avoid false positive signals in blood pressure values because of the required prolonged resting period after drug intake. In context with these changes some inconsistencies were also corrected.

Number of global amendment		4
Date of CTP revision		21 December 2017
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Synopsis 2. Section 2.1 Rational for performing the trial 3. Section 2.3.2.3 Risk minimization 4. Section 3.1 Overall Trial Design and Plan 5. Section 3.3.4.2 Discontinuation of the trial by the sponsor

Number of global amendment		4
Description of change		Changes apply to several sections throughout the protocol and are described only once and not repeated for each section: Synopsis and different sections throughout the protocol: The maximum exposure threshold was increased to geometric mean AUC 0-24 of 9500 nmol*h/L corresponding to the maximum of the exposure observed in male rats at 7.5 mg/kg/day in the 4-week toxicology study Section 3.1 and section 7.3.4 In case of a less than dose proportional increase of exposure with a tablet formulation a switch to an oral suspension for further dose escalations may be considered.
Rationale for change		Oral single doses of up to 25 mg were shown to be well tolerated. There were no SAEs and no AEs considered to be dose limiting. With an oral dose of 25 mg we are approaching the predefined maximum exposure threshold. Since all currently tested dose levels were well tolerated we consider it justified to further increase the exposure threshold which would allow us to test doses beyond 25 mg. We would like to propose an increase of the exposure threshold up to the NOAEL in rats due to the up to now encouraging safety profile in the ongoing Phase I study. We would like to highlight that we continue to stop dose escalation as soon as safety signal as defined in the protocol will be observed. In context with these changes a few remaining inconsistencies were also corrected.

Number of global amendment		5
Date of CTP revision		06 February 2018
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		Synopsis and different sections throughout the protocol:
Description of change		Hospitalisation period will be prolonged to 48 h instead of 34 hours.
Rationale for change		Based on interim PK-data of the ongoing study the preliminary half-life was calculated to be in a range of about 40 hours instead of an initially predicted human half-life of about 15 hours. Because of the longer half-life it is considered necessary to extend the observation period to at least 48 hours.

Number of global amendment		6
Date of CTP revision		12 March 2018
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Flow Chart SRD and FE
Description of change		Additional PK blood samples at 8:10 hour (0:10min) and 8:20 (0:20 min)
Rationale for change		Based on interim PK-data of the ongoing study, dose group 5 (50 mg), the increase of plasma concentrations before C_{max} should be covered adequately by earlier PK sampling. In context with these changes a few remaining inconsistencies were also corrected.

Number of global amendment		7
Date of CTP revision		12 June 2018
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		Synopsis Section 4.1.1 Identity of BI investigational product and comparator products Section 4.1.3 Selection of dose trial Table 4.1.4:2 BI 1358894 film-tablets for the FE part
Description of change		Additional dose group in the food effect part
Rationale for change		The ongoing study has recently completed the first dose group of the food effect part, using 50 mg as the initial dose strength. Since preliminary PK and safety assessments did not prevent further dose escalation the FE part of the study will continue with a dose level of 100 mg. Provided that the FE part with 100 mg does still not reveal dose limiting findings, a further dose group beyond 100 mg may enter the FE part. The maximum planned dose of the tentative group

Number of global amendment		7
		will not exceed the maximum tested dose of the SRD part, i.e. 200 mg, and the predicted exposure for this tentative dose group is required to not exceed the approved exposure threshold (gMean AUC 0-24 of 9500 nmol*h/L). In context with these changes a few remaining inconsistencies were also corrected.

Number of global amendment		8
Date of CTP revision		17 August 2018
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		- Synopsis and Flowchart - 2.1 Rationale for performing the trial - 2.2 Trial objectives - 2.3.2.3 Risk minimization - 3.1 Overall trial design and plan - 3.3.4 Removal from therapy or assessments - 4.1 Treatments to be administered - 5.2.4 Electrocardiogram - 5.2.5.8 Neurological examination - 6.1 Visit schedule
Description of change		Changes applies to several sections of the CTP, therefore it will be described once and not repeated for each section. ***Synopsis and Flowchart, sections 2.2, 3.1, and 4.1*** - Inclusion of a new dose group to receive 200 mg under fed conditions

Number of global amendment		8
		- Dose group of 400 mg and 600 mg deleted, will not be conducted - Additional flow chart for Dose group 200 mg fed, prolongation of in-house period, prolonged ECG monitoring, assessment of C-SSRS at discharge from CPU, inclusion of standardized neurological examination, increase of individual exposure threshold to AUC_{0-24} to 26300 nM*h and C_{max} to 1960 nM. - Oral suspension will not be applied and therefore will be deleted - 25 mg in the FE part was not conducted and therefore will be deleted ***Sections 2.3.2.3, 3.3.4*** - Dose group 200 mg fed will be only conducted, if there is an at least 90% probability that the estimated individual exposure based on PK of preceding dose groups will not exceed the new exposure limit of 26300 nM*h (AUC_{0-24}) ***Section 5.2.4*** - For dose group 200 mg fed, triple ECG recordings up to 144 h ***Section 5.2.5.8*** - For dose group 200 mg fed, physical examination includes standardized neurological assesment ***Section 6.1*** - Definition of time window for neurological examination
Rationale for change		The ongoing study has recently completed the second dose group of the food effect part, using 100 mg as dose strength. Safety assessments from all dose groups including the most recent 100 mg administered under fed conditions did not reveal dose limiting safety findings and the mean exposure (AUC_{0-24}) remained below the current threshold of 9500 nmol*h. A further increase of dose beyond 100 mg administered under fed conditions requires an adjustment of the exposure threshold to the exposure at NOAEL in rats (i.e. C_{max} of 1960 nM and an AUC0-24 of 26300 nM*h), which is considered to be the maximum possible threshold for an individual exposure in healthy subjects. The safety assessments of this final dose group have been intensified and the

Number of global amendment		8
		hospitalisation phase will be extended to Day 7. In context with these changes a few remaining inconsistencies were also corrected, such as the deletion of dose levels beyond 200 mg in the SRD part (i.e. 400 mg, 600 mg) and 25 mg fed in the FE part as well as the oral suspension which will no more be tested in this study to the exposure at NOAEL in rats (i.e. Cmax of 1960 nM and an AUC0-24 of 26300 nM*h), which is considered to be the maximum possible threshold for an individual exposure in healthy subjects.

Number of global amendment		9
Date of CTP revision		25 September 2018
EudraCT number		2017-000143-40
BI Trial number		1402-0001
BI Investigational Product(s)		BI 1358894
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over)
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		- 2.3.2.3 Risk minimization
Description of change		- For a period of at least 24 hours after intake of study medication a physician will stay at the study site to allow, if needed, immediate emergency intervention and rescue measures.
Rationale for change		BfArm request to assure presence of a physician at the study site for at least 24 h after dosing.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		27 Sep 2018 08:22 CEST
Author-Trial Statistician		27 Sep 2018 08:51 CEST
Approval-Therapeutic Area		27 Sep 2018 11:12 CEST
Author-Clinical Trial Leader		27 Sep 2018 14:08 CEST
Verification-Paper Signature Completion		27 Sep 2018 14:12 CEST
Approval-Team Member Medicine		27 Sep 2018 22:00 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed