Clinical Trial Protocol

	Document Number:	**c26426667-03**
EudraCT No.	2018-003603-19	
BI Trial No.	1402-0010	
BI Investigational Medicinal Product	BI 1358894	
Title	Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)	
Lay Title	A study in healthy men to test if taking different formulations of BI 1358894 with or without food influences the amount of BI 1358894 in the blood	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 02 April 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 January 2019
Revision date	02 April 2019
BI trial number	1402-0010
Title of trial	Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	Results from the first-in-human study with BI 1358894 using TF1 showed a limited bioavailability under fasted conditions while the intake of food increased the exposure and bioavailability of BI 1358894. Two additional formulations were subsequently developed, TF2 , to investigate the adequate formulation with no or negligible food effect and higher exposure under fasted conditions for further clinical development.
Trial objectives	To investigate the relative bioavailability of TF2 under fasted conditions vs. TF1 under fed conditions. To investigate the food effect on the exposure of BI 1358894 with TF2 .
Trial design	Randomised, open-label, single-dose, incomplete blocks crossover design.
Trial endpoints:	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1358894 Secondary endpoints: AUC_{0-72} and $AUC_{0-\infty}$ of BI 1358894
Number of subjects total entered	24 (20 evaluable subjects)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product 1	Tablet formulation 2; TF2 of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast when fed (treatment B), or after an overnight fast of at least 10 h when fasted (treatment C).
Test product 2	Tablet formulation 2; TF2 of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast when fed (treatment D), or after an overnight fast of at least 10 h when fasted (treatment E).
Reference product	Tablet formulation 1; TF1 of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast (treatment A).
Duration of treatment	One day (single dose) for each treatment.
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [8]	Suicidality assessment (C-SSRS)[10]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x		x	x	x	
1-3 (three periods separated by a wash-out of at least 17 days)	2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x					x
	2/3/4	1	-1:30	06:30	Admission to trial site	x[5]					x
			-1:00	07:00	Allocation to treatment sequence (visit 2 only)	x[2, 9, 13]	x[2]		x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (for treatments A, B and D)[12]						
			0:00	08:00	**Drug administration**						
			0:10	08:10			x				
			0:20	08:20			x				
			0:30	08:30			x			x	x
			1:00	09:00			x		x	x	x
			1:30	09:30			x			x	
			2:00	10:00	240 mL fluid intake		x				x
			3:00	11:00			x			x	
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x		x	x	x
			5:00	13:00			x			x	x
			6:00	14:00			x			x	x
			7:00	15:00			x				
			8:00	16:00	Snack (voluntary)[3]		x			x	x
			10:00	18:00	Dinner[3]		x				
			12:00	20:00			x		x	x	x
		2	24:00	08:00	Breakfast[3]	x	x		x	x	x
			34:00	18:00			x			x	x
		3	48:00	08:00	Breakfast[3]		x		x	x	x
		4	72:00	08:00	Breakfast (voluntary)[3], Discharge from trial site[11]		x	x	x	x	x
		5	96:00	08:00	Ambulatory visit		x		x	x	x
		7	144:00	08:00	Ambulatory visit	x	x		x	x	x
		9	192:00	08:00	Ambulatory visit		x		x	x	x
		11	240:00	08:00	Ambulatory visit	x	x		x	x	x
		14	312:00	08:00	Ambulatory visit	x	x		x	x	x
FU	5	17 to 22			End of trial (EoTrial) examination[4]	x		x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath test, 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, neurological examination and suicidality assessment (C-SSRS).
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, concomitant therapies, neurological examination 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 times 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 between Day -3 and Day -1.
8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
9. One blood sample for pharmacogenomics will be taken on Visit 2. If not feasible at Day 1, the sample may also be drawn at any later day.
10. Suicidality assessment will be performed at screening, at discharge from trial site for each period and at end of trial.
11. Confirmation of fitness includes physical examination, vital signs, ECG, suicidality assessment (C-SSRS), and recordings of AEs and concomitant therapies assessed on Day 4 as well as evaluation of safety laboratory assessed on Day 2.
12. High fat, high calorie breakfast will be administered only for treatment A (TF1), treatment B (TF2 fed) and treatment D (TF2 fed). Subjects in treatments C (TF2 fasted) and E (TF2 fasted) will not receive any breakfast. All subjects will be admitted to the trial site after an overnight fast of at least 10 h for all treatments.
13. Only for visit 2. For visit 3 and 4, predose values for safety laboratory will be derived from the Day 14 of the preceding visit.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
AUC_{0-72}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline Personality Disorder
CA	Competent authority
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Contract research organisation
CRP	C-reactive protein
C-SSRS	Columbia Suicidal Severity Rating scale
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol

CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
DRF	Dose range finding
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electro-convulsive therapy
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-foetal development
EoTrial	End of trial
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and drug administration
FE	Food effect
FIH	First in Human
FST	Forced swim test
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
GLDH	Glutamate deshydrogenase
GLP	Good Laboratory Practice
gMean	Geometric mean
hERG	Human ether-a-go-go related gene
HR	Heart rate
IB	Investigator's brochure
IC_{50}	Half maximum inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry

LVSP	Left ventricular systolic pressure
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body, extravascular
NIMH	National institute of mental health
NOAEL	No observed adverse effect level
NRS	Numeric ranking scale
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PT	Preferred term
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
RBC	Red blood cell
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOC	System organ class
SOP	Standard operating procedure
SRD	Single-rising dose
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TF1/2	Tablet formulation 1/2
TRP	Transient receptor potential
TRPC 4/5	Transient receptor potential cation channel, subfamily C, members 4 and 5
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual analog scale

	administration
WBC	White blood cell
XTC	Ecstasy

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).

MDD is a debilitating disease characterised by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the 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 residual symptoms [R16-5475] that 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 severely impaired 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, 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, treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in patients with MDD and BPD.

1.2 DRUG PROFILE

1.2.1 BI 1358894

For a more detailed description of the BI 1358894 profile, please refer to the current Investigator's Brochure (IB) [c10354149].

1.2.1.1 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.

BI 1358894 was profiled using patch clamp electrophysiology and was shown to be a highly potent inhibitor of TRPC4 and TRPC5 without species selectivity. In cells expressing human TRPC4 and TRPC5 and stimulated with carbachol, the IC_{50} was 1.2 nM (hTRPC4) and 0.2 nM (hTRPC5), respectively.

BI 1358894 was investigated in several standard behavioural tests in rodents, such as Forced Swim Test (FST) [n00252903], Marble Burying Test [n00252207] and Elevated Plus Maze Test [n00252277]. The *in vivo* pharmacology studies demonstrated consistent pharmacological effects in line with anxiolytic and/or antidepressant efficacy. In the FST, half maximal efficacy was demonstrated at a plasma exposure of 77 nM, indicating that at this plasma exposure, free brain levels are in the range of the in vitro IC_{50} [n00253628].

BI 1358894 is highly selective against more than 10 ion channels (including other TRPs, potassium channels, calcium channels and sodium channels) with more than 1000-fold selectivity for TRPC4 and at least 200-fold selectivity for TRPC5 [n00248384]. The effect of BI 1358894 on more than 120 targets was evaluated at 1 µM [n00252179]. BI 1358894 was shown to be highly selective.

1.2.1.2 Safety pharmacology

General and safety pharmacology studies have been conducted with BI 1358894 to address the core battery of the central nervous system (CNS) [n00253725], cardiovascular [n00253723, n00253727, n00254034], renal and hepatic [n00253732], respiratory [n00253732], and GI function [n00253729]. The results demonstrated an acceptable profile for clinical trials in healthy volunteers.

BI 1358894-related effects on the CNS of rats were limited to an early and transient increase of motility at dose levels of 10, 30, and 100 mg/kg (nocturnal motility test). This was considered to reflect an increased arousal or decreased anxiety in a novel environment associated with the intended efficacy (anti-depressive and anxiolytic effect). The absence of detectable locomotor effects in the two Modified Irwin studies might be due to differences in the study design.

In the cardiovascular (CV) rat study, long-lasting decreases in arterial blood pressure (10 mmHg) were present at ≥10 mg/kg. Additionally, BI 1358894 induced dose-dependent

and long-lasting increases in heart rate (15 – 20 bpm) in rat and dog at ≥30 mg/kg after single oral dose in the general pharmacology studies. However, increase in heart rate was no longer detectable after 4-day repeat-dosing in rats at 30 mg/kg. In rat telemetry at 100 mg/kg, transient increases in PR duration and body temperature were noted. None of the cardiovascular findings could be confirmed in dog safety pharmacology or toxicity studies. Other ECG parameters, including QT and QTc intervals, and left ventricular pressure parameters (LVSP and dP/dt_{max}) were not affected by BI 1358894.

Transient effects of BI 1358894 on the respiratory function (increases in respiratory rate and minute volume) were seen in male rats treated with 1000 mg/kg.

Altered electrolyte (Cl^-, Na^+, Ca^{2+}) and urea urinary excretion at ≥10 mg/kg was regarded to be indicative of a change in rat renal function. Increases in total and conjugated bilirubin levels were not reproduced after repeated dosing for 4 weeks. Rat kidney and liver injury biomarkers were not altered. No structural degenerative correlates were present in the microscopic examination in toxicity studies.

Dose-dependent decreased gastric emptying was noted at 30 mg/kg (-22%) and 100 mg/kg (-29%). No effects on consistency of intestinal contents and intestinal transit were noted at any dose level.

The influence of BI 1358894 on human ether-a-go-go related gene (hERG)-mediated potassium current in stably transfected CHO cells (Chinese hamster ovary) was determined to evaluate the potential proarrhythmic risk [n00253752]. The IC_{50} for tail current inhibition was 1.15 µM, suggesting a selectivity ratio of about 200 against hERG-encoded channel [hTRCP 1/5 = 5 nM]. These preclinical data do not suggest a proarrhythmic risk.

1.2.1.3 Toxicology

The nonclinical safety program investigating the in vivo toxicological profile of BI 1358894 comprised repeat-dose studies up to 4 weeks of once daily oral (gavage) treatment and a complete battery of in vitro and in vivo studies assessing the genotoxic potential of the compound. Additionally, a 4-week oral repeat-dose (non-GLP) study in mice was performed.

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.

1.2.1.3.1 Repeat-dose toxicity studies

Repeat dose non-GLP toxicity study in mice, rats and dogs revealed toxicologically relevant effects on the skin, Harderian glands, and hepatic function in mice, the vascular system in rats, the CNS function in dogs, and the digestive tract in all three species. In addition, haematology evaluation revealed increases of white blood cell (WBC) counts in all species.

A 4-week toxicity testing in mice identified skin, Harderian glands, and gastrointestinal tract as main target organs in this species at doses ≥500 mg/kg QD. Clinical pathology evaluation indicated a slight to moderate increase in plasma total bilirubin, but without any microscopic

degenerative correlate. Administration of BI 1358894 was clinically well tolerated up to 1500 mg/kg. Minimal to slight epidermal hyperplasia was observed in the skin. In the Harderian glands, crystal deposits (mainly a carboxylic acid metabolite of BI 1358894) induced minimal to severe degeneration and necrosis of the glandular tissue. A metabolite of BI 1358894 was the major compound-related constituent as shown by mass spectrometry analysis. Due to the species-specific metabolism, this mouse finding was considered to be of limited toxicological relevance. Multifocal erosion/ulceration, graded minimal to slight in severity, affected the mucosa of the stomach and the intestine and minimal to moderate epithelial vacuolation of the villi and minimal villous atrophy were present in the duodenum. Other BI 1358894-related pathological findings in the hematopoietic and lymphoid organs (at ≥7 mg/kg) associated with increased reticulocyte and WBC counts in blood, the liver (at ≥30 mg/kg), and the heart (at 1500 mg/kg) were regarded as non-adverse due to their adaptive character.

Repeat-dose toxicity testing in rats revealed no serious clinical signs of toxicity, no toxicologically relevant effects on body weight and food and water consumption, and no ophthalmology findings were noted. The main findings in clinical pathology were indicative of a minimal inflammatory response starting at 200 mg/kg, characterised by leukocytosis, hyperproteinaemia, and hyperglobulinemia. On Day 5 after the start of treatment, minimal to moderate periarterial inflammation was present in the mesentery, pancreas, and/or liver at ≥30 mg/kg, with dose-related increases in incidence and severity. In a few animals given ≥200 mg/kg, arterial inflammation and necrosis focally affected the pancreas and the serosa of the intestine. In a 4-week DRF 'reversibility' study where animals were sacrificed and microscopically examined on Day 5 and at the end of the treatment period (Day 28), perivascular/mesenteric inflammation induced by BI 1358894 occurred early after start of dosing and resolved over 4 weeks despite continued treatment, indicating the transient character of the inflammation. Other BI 1358894-related pathological findings in the kidneys (at ≥7.5 mg/kg), the heart and the liver (at ≥30 mg/kg), and the mandibular glands (at ≥1000 mg/kg) were considered to be non-adverse due to their adaptive character, low magnitude, and/or absence of pathological correlates. All changes were fully reversible or greatly ameliorated over a 4-week off-treatment recovery period.

In repeat-dose toxicity testing in dogs, no spontaneous deaths occurred up to 1000 mg/kg, the highest tested dose, administered for 11 days. Decreased body weight, reduced food consumption and faecal alterations occurred at ≥150 mg/kg. Distinct clinical signs of toxicity were present at ≥500 mg/kg, starting on the 3rd day of treatment (gait abnormalities, decreased motor activity, one episode of convulsions, trembling). In addition, a territorial behaviour was shown by dogs administered 150 mg/kg over 4 weeks. Pathology and clinical pathology investigations did not reveal any pertinent findings which could have explained the clinical signs. Administration of BI 1358894 did not result in any pertinent changes in ophthalmology and cardiovascular investigation. Clinical pathology evaluation revealed a limited number of changes at ≥500 mg/kg: moderate decreases in reticulocyte counts, minimal increases in WBC and neutrophil counts, slight increases in phosphate and minimal decreases in calcium levels in the blood, and slightly to moderately reduced urinary sodium and chloride excretion. Few relevant BI 1358894-related histopathological findings were noted at ≥500 mg/kg, namely (multi)focal minimal to slight erosion/ulceration in the oral cavity, esophagus and duodenum. Changes observed in the thymus (decreased weight,

reduced size, lymphoid depletion), the spleen (decreased weight), the liver (decreased glycogen content), and the salivary glands (secretory depletion) were regarded as unspecific response to stress or secondary to reduced food consumption. No BI 1358894-related findings were observed during a 4-week recovery period.

An overview of estimated safety margins (exposure multiples) is presented in Table: 1.2.1.3.1: 1 below. The comparison revealed safety margins of ≥9 for C_{max} and for AUC_{0-24}.

Table: 1.2.1.3.1: 1 Overview of estimated safety margins (exposure multiples) for BI 1358894 based on the NOAELs of the 4-week oral toxicity studies in rats and dogs and the 4-week oral DRF study in mice

Species	**NOAEL [mg/kg]**	**Mean C_{max} at NOAEL [nM] in m/f**	**Mean AUC_{0-24} at NOAEL [nM.h] in m/f**	**Human to Animal Safety Margin in m/f**	
				Based on multiples of C_{max}	Based on multiples of AUC_{0-24}
Rat	30	1960 / 3600	26300 / 53900	9 / 17	9 / 19
Dog	30	7190 / 4240	137000 / 57300	34 / 20	49 / 20
Mouse	30	7750 / 6270	89400 / 101000	37 / 30	32 / 36

m: male; f: female; safety margins related to predicted human exposure at estimated therapeutic dose (35 mg QD)

1.2.1.3.2 Reproductive and developmental toxicity

Data from two dose range finding studies for effects of BI 1358894 on embryo-foetal development (EFD) have been recently conducted in rats and rabbits. The results in rats showed no maternal nor embryofetal toxicity at exposures corresponding to 29- (C_{max}) and 33-fold (AUC_{0-24}) of an estimated human efficacious plasma level of 210 nM and an AUC_{0-24} of 2800 nM/h. The EFD study in rabbits resulted in maternal toxicity, most strikingly evidenced by a decrease of food intake to approximately 10% of control animals. Embryo- and fetotoxicity, in form of spontaneous abortions and/or uterine deaths, occurred also at all dose levels and were considered to be secondary to the overt maternal toxicity. At the lowest dose level the corresponding C_{max} was 1.24-fold and the AUC_{0-24} 1.53-fold of the estimated human efficacious plasma level. Details can be found in the Investigator's Brochure [c10354149].

Based on these data, a benefit-risk assessment of BI 1358894 was conducted with regards to healthy male participants and concluded that the poor tolerability of BI 1358894 in rabbits does not negatively affect the safety data derived from the repeat-dose toxicity studies in mice, rats, and dogs. The safety profile with regard to general toxicity has not changed and the new data do not change the risk-benefit profile of BI 1358894 with regard to conduct of the present trial.

1.2.1.3.3 Phototoxicity

BI 1358894 is unlikely to cause phototoxicity. For more detailed information, please refer to the Investigator's Brochure [c10354149].

1.2.1.4 Nonclinical pharmacokinetics

Drug Absorption and Disposition

The disposition of BI 1358894 is characterized in rats by low clearance and moderate volume of distribution. High oral bioavailability (81.9 %) in rats suggests an at least moderate bioavailability in humans. The plasma protein binding of BI 1358894 was high in all investigated species, with unbound fractions of 0.26 % (mouse), 0.42 % (rat), 0.31 % (dog), and 0.25 % (human).

In a quantitative whole body autoradiography study, the extent of distribution of [^{14}C] BI 1358894 from plasma into tissues was considered to be moderate [n00252628]. Highest concentrations of radioactivity were found in the Harderian gland (up to 27 times higher than in plasma), the liver (up to 14 times), and the walls of the gastrointestinal tract (up to 9.4 times higher than in plasma). Lowest tissue-to-plasma ratios were found in total eyeball (1% of plasma level), nasal mucosa (3%), and CNS (11% to 23%). While the total eyeball was exposed to drug-related radioactivity throughout the entire timeframe of investigation, drug-related radioactivity in the skin was below the limit of quantification. Qualitative evaluation of the autoradiograms, however, revealed discernible photo-luminescence signals in lipid-rich parts of the skin until the last time-point of investigation.

The terminal half-lives for BI 1358894 in rats were 6.21 h (male) and 7.91 h (female) and longer for [^{14}C] BI 1358894 – related radioactivity with 14.0 h (male) and 14.2 h (female). The fraction of total exposure for BI 1358894 ([^{14}C] BI 1358894 – related radioactivity) was 31% (males) and 49% (females). Similar proportions of parent compound and drug-related radioactivity after oral and intravenous administration indicated a low first pass effect. After intravenous (short term infusion) administration, 0.8% of the total administered radioactive dose was excreted in the urine within 24 h. In faeces, 55.7% (males) or 45.4% (females) of the total dose was recovered within 24 h. Excretion was slow, with a faecal excretion of 81.4% (mean of males and females) within 168 h. The biliary excretion in anesthetized rats was 12.4% (males) or 16.5% (females) of the dose within 6 h.

Potential pharmacokinetic interactions

The inhibition potential of BI 1358894 was investigated for human CYP enzymes CYP1A1/2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 [n00253492]. BI 1358894 was a competitive in vitro inhibitor of CYP2C9, 2C8, 2D6, 2C19 and 2B6 with Ki values of 3.71 µM (CYP2C9), 4.82 µM (CYP2C8), 5.51 µM (CYP2D6), 10.1 µM (CYP2C19) and 13.6 µM (CYP2B6). Due to binding of BI 1358894 to plastic surfaces and microsomal protein, the actual concentrations of BI 1358894 in incubations were lower than the nominal concentrations. Therefore, it has to be taken into account that the actual Ki data could be slightly lower than the measured values. Irreversible inhibition by BI 1358894 was not observed for any of the CYP enzymes under investigation. Depending on the level of exposure during drug therapy, in vivo inhibition of multiple CYP enzymes by BI 1358894 may be possible.

The in vitro potential of BI 1358894 and the metabolite BI 1361608 to induce rat CYP enzymes (CYP1A1, 2B1, 2C7, 2C11, 2D1, 2E1, 3A1/2, 4A) in rat hepatocytes was investigated [n00253490]. An induction potential towards CYP3A1 mRNA was seen with BI 1358894 concentration-dependent at high concentrations of ≥5 µM, and to a lesser extent with BI 1361608 at 20 µM.

The potential for BI 1358894 to induce human CYP enzymes was investigated in vitro at BI 1358894 concentrations up to 100 µM using sandwich cultured human hepatocytes prepared from three donors. BI 1358894 was not an inducer of CYP1A2 but might be a weak inducer for both CYP2B6 and CYP2C8. BI 1358894 was an inducer of CYP3A4 mRNA and enzyme activity up to 25 µM [n00256526].

1.2.1.5 Clinical experience in humans

A First-in-Human (FIH) trial (Trial 1402-0001 [c13880029]) is currently being conducted to explore the safety, tolerability, and pharmacokinetics (PK) of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and to evaluate the effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over design). The SRD part of the study has been completed involving 55 subjects in 7 dose groups with single oral doses of 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 100 mg or 200 mg of BI 1358894 administered under fasted conditions. In each of the 7 dose groups 6 subjects were assigned to BI 1358894 and 2 subjects to placebo. At a dose level of 200 mg, the SRD part was stopped because of a less than dose proportional increase in exposure (C_{max} and AUC_{0-24}), which was considered to be possibly related to a reduced solubility of the film-coated tablets under fasting conditions. The further dose escalation in the SRD part was not stopped because of safety issues. Up to a single dose of 200 mg administered under fasting conditions, BI 1358894 was safe and well tolerated in all doses. There were no serious adverse events (SAEs) or dose limiting adverse events (AEs). In accordance with the trial protocol, the study continued with the FE food effect (FE) part at a dose level of 50 mg and 100 mg of BI 1358894 administered under fasted and fed conditions, according to an open-label, two-period crossover design. Since in this dose group no dose limiting no safety signals precluding a further dose escalation of BI 1358894.

With 100 mg of BI 1358894 tested under fed conditions, a geometric mean exposure of AUC_{0-24} of 6780 nmol*h/L and C_{max} of 517 nmol/L was observed, i.e. close to the exposure limit (AUC_{0-24} = 9500 nmol*h/L, C_{max} = 980 nmol/L) specified in the former trial protocol. A further dose escalation such as 200 mg of BI 1358894 administered under fed conditions was expected to exceed the former exposure limit. The exposure threshold was increased based on available clinical data up to 200 mg fasted and 100 mg fed in 1402-0001 to the current exposure threshold of 1960 nM for C_{max} and 26300 nM/h for AUC_{0-24}.

At the time of CTA submission of the current trial, the multiple rising dose (MRD) study (Trial 1402-0002) has been initiated. This double-blind, randomized and placebo-controlled within dose groups, parallel-group comparison study will evaluate the safety, tolerability, and PK of multiple rising oral doses of BI 1358894. In addition, this study will investigate the interaction with midazolam in a nested, open, fixed-sequence, intra-individual comparison

study. Overall, 50 healthy male subjects are planned to enter the study and the doses of BI 1358894 investigated will range from 10 to 200 mg once daily over 14 days. Midazolam will be administered as an oral microdose on Day -1 and concomitantly with BI 1358894 on Day 1 and Day 14.

Safety evaluations of Trial 1402-0001 included physical examination, vital signs, ECG, laboratory tests, and adverse events. Data analysis from this study is currently on-going. In the tested dose range, BI 1358894 was well tolerated with a low frequency of AEs in all dose groups. There were no AEs considered to be dose limiting and no SAEs; all subjects completed the study per protocol.

Adverse Events

There were no AEs considered to be dose limiting and no SAEs. All subjects completed the study per protocol. All AEs were of mild to moderate intensity; no AE of severe intensity was reported.
The following results were observed (see also Table 1.2.1.5: 1 and Table 1.2.1.5: 2 for a more detailed overview of AEs):

- In the SRD part, 22 of 42 subjects on BI 1358894 and 3 of 13 subjects on placebo reported at least one AE.
- In the FE part, 16 of 20 subjects (all on BI 1358894) reported at least one AE. The higher prevalence of AEs in the FE part compared to the SRD part might be related to the two treatment periods and the longer period of safety monitoring.
- SRD: The frequency of subjects with at least one AE in the highest dose group (200 mg fasted) was comparable to the 50 mg and 100 mg fasted dose groups.
- Food Effect: The frequency of subjects with at least one AE in the 50 mg dose group (fasted and fed period) was higher compared to the SRD part. In contrast, the frequency of subjects with at least one AE in the dose group 100 mg (fasted and fed period) was similar to the SRD part. The subjects with the highest exposure (100 mg fed period) had a slightly lower frequency of adverse events compared to the fasted period.
- At the System Organ Class (SOC) level, the most frequently reported AEs were nervous system disorders, reported in 21 subjects in the SRD part (19 of 42 subjects on BI 1358894 and 2 of 13 subjects on placebo) and 16 of 20 subjects in the FE part (all on active).
- At the Preferred Term (PT) level, the following AEs were observed in more than one subject:
    - Headache in 18 subjects in the SRD part (17 of 42 subjects on active and 1 of 13 subjects on placebo) and in 15 of 20 subjects in the FE part (all on active),
    - Dizziness in 3 subjects in the SRD part (2 of 42 subjects on active and 1 of 13 subjects on placebo) and 7 of 20 subjects in the FE part (all active),
    - Fatigue in 3 subjects in the FE part (all on active), and
    - Disturbance in attention in 2 subjects in the FE part (all on active).

- No dose dependent increase in frequency was observed for any of these AEs.

- AEs of moderate intensity were mainly observed in subjects on BI 1358894:
  - Injury due to a cycling accident in one subject 6 days after dosing (6 mg SRD);
  - Syncope because of a vasovagal reaction during blood drawing in one subject on placebo (25 mg dose group, SRD);
  - Back pain in one subject 2 days after dosing, resolved in 11 hours (50 mg SRD);
  - Nasopharyngitis in one subject 4 days after dosing (100 mg, FE, fasted);
  - Headache in 10 subjects (2 SRD, 8 FE, all on active) with an onset mostly 4-7 hours after dosing and resolved mainly within a few hours.

There were no protocol-specified AEs of special interest (AESI) and no other significant AEs according to ICH E3. Per protocol AESI was hepatic injury, as defined by AST and/or ALT ≥ 3-fold ULN combined with total bilirubin ≥2-fold ULN, and/or aminotransferase elevations ≥ 10 fold ULN.

There were isolated events of apathy, auditory disorder and abnormal dreams in 3 subjects treated with either 3 mg or 6 mg of BI 1358894. Since no comparable events were reported for the remaining dose groups up to a single dose of 200 mg of BI 1358894 and due to the lack of a temporal relationship between dosing and event, these events are considered as chance findings and not drug related. Further, no changes in the Bowdle-VAS were seen for these subjects.

Additional Safety Assessments

There were no clinically relevant changes of laboratory values. In particular there were no changes of ESR or CRP suggesting an inflammatory event.

Explorative analysis of the Bowdle-VAS scores showed a comparable pattern between subjects across all dose groups. There were in particular no abnormalities for the score ‘feeling high’ and ‘changes of perception’, which may indicate psychedelic effects. The occasional occurrence of ‘drowsy’ was evenly distributed between active and placebo.

The suicidality assessment based on C-SSRS did not reveal an individual subject who developed suicidal ideation by end of the study.

ECGs recorded from Day 1 pre-dose until Day 2/34h post-dose were analyzed centrally. After each dose group absolute values and changes in ECG parameters were reported by the ECG core lab to the sponsor and CRO. No dose dependent trend of a possible QTcF prolongation was observed (the maximum individual QTcF interval across all dose groups of the SRD part was 432 ms, and for the FE part 450 ms).

Based on the prespecified criteria in 1402-0001 orthostatic testing did not reveal a subject with a positive test after dosing, i.e. no reduction in systolic blood pressure (BP) of ≥20 mmHg or in diastolic BP of ≥10 mmHg within 3 minutes of standing, no orthostatic symptoms and no increase of heart rate > 100/min during orthostatic testing. Monitoring of vital signs and adverse events conducted in the further course of the study did also not reveal

findings suggesting orthostatic effects of BI 1358894. The data on treatment emerging adverse events in the SRD part covering dose groups 1 to 7 are displayed in Table 1.2.1.5: 1 as well as the adverse events in the FE part are depicted in Table 1.2.1.5: 2.

Table 1.2.1.5: 1 Preliminary frequency [N (%)] of subjects with adverse events treated with BI 1358894 or placebo - FIH Trial 1402-0001

System Organ Class, Preferred Term	**Placebo (N=13)**	**BI 3mg (DG1) (N=6)**	**BI 6mg (DG2) (N=6)**	**BI 10mg (DG3) (N=6)**	**BI 25mg (DG4) (N=6)**	**BI 50mg (DG5) (N=6)**	**BI 100mg (DG6) (N=6)**	**BI 200mg (DG7) (N=6)**
Total with adverse events	**3 (23.1)**	**3 (50.0)**	**6 (100.0)**	**0 (0.0)**	**2 (33.3)**	**4 (66.7)**	**4 (66.7)**	**3 (50.0)**
Nervous system disorders	**2 (15.4)**	**2 (33.3)**	**5 (83.3)**	**0 (0.0)**	**2 (33.3)**	**3 (50.0)**	**4 (66.7)**	**3 (50.0)**
Headache	1 (7.7)	2 (33.3)	4 (66.7)	0 (0.0)	2 (33.3)	3 (50.0)	3 (50.0)	3 (50.0)
Dizziness	1 (7.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Head discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Syncope	1 (7.7)	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (33.3)**	**0 (0.0)**	**0 (0.0)**
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**1 (16.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Auditory disorder	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**2 (15.4)**	**1 (16.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)
Oral discomfort	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (16.7)**	**0 (0.0)**
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Injury, poisoning and procedural complications	**1 (7.7)**	**0 (0.0)**	**1 (16.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Limb injury	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular procedure complication	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**1 (16.7)**	**1 (16.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Abnormal dreams	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Apathy	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**1 (7.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Decreased appetite	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1.2.1.5: 2 Frequency [N (%)] of subjects with adverse events treated with BI 1358894 – 1402-0001 FE part

System Organ Class, Preferred Term	**BI 50mg (fast) (N=8)**	**BI 50mg (fed) (N=8)**	**BI 100mg (fast) (N=12)**	**BI 100mg (fed) (N=12)**
Total with adverse events	**7 (87.5)**	**7 (87.5)**	**8 (66.7)**	**6 (50.0)**
Nervous system disorders	**7 (87.5)**	**7 (87.5)**	**8 (66.7)**	**5 (41.7)**
Headache	7 (87.5)	6 (75.0)	7 (58.3)	4 (33.3)
Dizziness	3 (37.5)	2 (25.0)	3 (25.0)	2 (16.7)
Disturbance in attention	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Head discomfort	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Paraesthesia	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**2 (25.0)**	**0 (0.0)**	**1 (8.3)**
Pruritus generalised	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Rash macular	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Skin reaction	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
General disorders and administration site conditions	**1 (12.5)**	**0 (0.0)**	**0 (0.0)**	**2 (16.7)**
Fatigue	1 (12.5)	0 (0.0)	0 (0.0)	2 (16.7)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (12.5)**	**2 (16.7)**	**0 (0.0)**
Musculoskeletal chest pain	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Gastrointestinal disorders	**1 (12.5)**	**1 (12.5)**	**0 (0.0)**	**0 (0.0)**
Flatulence	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Nausea	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**1 (8.3)**	**0 (0.0)**
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)

Dose Groups 2, 3 and 6 already have sample results available up to 192 h and, therefore, were used to calculate PK parameters dependent on the terminal rate constant (lambda z). Half-life as calculated from these 3 DGs is around 45 to 52 h (gMean) and appears to be independent of dose.

Table 1.2.1.5: 3 Summary of gMean (gCV %) PK parameters of 3, 6, 10, 25, 50, 100 and 200 mg BI 1358894 administered under fasted conditions [SRD part; clinical trial 1402-0001]

Dose Group:	**DG1**	**DG2**	**DG3**	**DG4**	**DG5**	**DG6**		**DG7**
Dose [mg], formulation	**3 mg, tablet**	**6 mg, tablet**	**10 mg, tablet**	**25 mg, tablet**	**50 mg, tablet**	**100 mg, tablet**	**100 mg, tablet**	**200 mg, tablet**
	fasted	fasted	fasted	fasted	fasted	fasted	fasted	fasted
							Without #	
	N=6	N=6	N=6	N=6	N=6	N=6	N=5	N=6
AUC_{0-24} [nmol*h/L]	166 (15.7)	269 (28.9)	400 (13.9)	937 (43.4)	1670 (32.8)	919 (1130)	2210 (58.4)	4130 (30.4)
AUC_{0-24}/D [nmol*h/L/mg]	55.5 (15.7)	44.8 (28.9)	40.0 (13.9)	37.5 (43.4)	33.4 (32.8)	9.19 (1130)	22.1 (58.4)	20.7 (30.4)
AUC_{0-72} [nmol*h/L]	261 (17.9)	445 (31.6)	651 (14.5)	1780 (31.1)	3040 (27.7)	2000 (1320)	5010 (40.4)	8720 (32.1)
AUC_{0-72}/D [nmol*h/L/mg]	87.1 (17.9)	74.1 (31.6)	65.1 (14.5)	71.2 (31.1)	60.9 (27.7)	20.0 (1320)	50.1 (40.4)	43.6 (32.1)
AUC_{0-tz} [nmol*h/L]	288 (18.5)	569 (32.7)	861 (17.7)	2380 (29.7)	4170 (26.2)	2520 (2670)	7120 (37.9)	12600 (42.0)
$AUC_{0-\infty}$ [nmol*h/L]	353* (25.1)	603 (33.6)	930 (20.4)	2580 (30.2)	4530 (24.5)	3000 (1570)	7730 (39.8)	13900 (44.8)
$AUC_{0-\infty}$/D [nmol*h/L/mg]	118* (25.1)	100 (33.6)	93.0 (20.4)	103 (30.2)	90.6 (24.5)	30.0 (1570)	77.3 (39.8)	69.7 (44.8)
C_{max} [nmol/L]	27.6 (30.0)	35.9 (33.8)	59.7 (13.4)	84.2 (44.2)	183 (56.3)	94.3 (735)	206 (72.8)	385 (26.8)
C_{max}/D [nmol/L/mg]	9.20 (30.0)	5.99 (33.8)	5.97 (13.4)	3.37 (44.2)	3.66 (56.3)	0.943 (735)	2.06 (72.8)	1.92 (26.8)
t_{max} [h][1]	2.0 (1-4)	2.5 (1-5)	1 (1-3)	5 (1-6)	1 (0.5-2.5)	2.25 (1-6)	3 (1-6)	5 (1-8)

[1]tmax median (range), D Dose-normalized, DG dose group,
[2]sensitivity analysis without subject who had substantially lower BI 1358894 plasma concentrations
* values are based on planned sampling time points up to 96 h only

Table 1.2.1.5: 4 Summary of gMean (gCV %) PK parameters of 50 mg and 100 mg BI 1358894 administered under fasted conditions and after a high calorie, high fat meal [relative BA food effect part; clinical trial 1402-0001]

Dose [mg]/ condition	**50 mg Fasted (N=8)**	**50 mg Fed (N=8)**	**100 mg Fasted (N=12)**	**100 mg Fed (N=12)**
AUC_{0-24} [nmol*h/L]	1570 (36.7)	2980 (25.1)	2350 (40.6)	6780 (12.2)
AUC_{0-24}/D [nmol*h/L/mg]	31.4 (36.7)	59.6 (25.1)	23.5 (40.6)	67.8 (12.2)
AUC_{0-72} [nmol*h/L]	3120 (20.9)	5110 (28.9)	4600 (49.2)	11600 (14.8)
AUC_{0-72}/D [nmol*h/L/mg]	62.4 (20.9)	102 (28.9)	46.0 (49.2)	116 (14.8)
AUC_{0-tz} [nmol*h/L]	4440 (23.5)	6940 (36.2)	6320 (53.4)	15500 (19.3)
$AUC_{0-\infty}$ [nmol*h/L]	5060 (29.3)	7900 (42.9)	6930 (54.6)*	17200 (21.8)
$AUC_{0-\infty}$/D [nmol*h/L/mg]	101 (29.3)	158 (42.9)	69.3 (54.6)*	172 (21.8)
C_{max} [nmol/L]	149 (59.4)	237 (24.9)	210 (38.8)	517 (8.61)
C_{max}/D [nmol/L/mg]	2.99 (59.4)	4.74 (24.9)	2.10 (38.8)	5.17 (8.61)
t_{max} [h][1]	5 (1-5)	5 (2.98-6)	2.5 (1-6)	6 (0.5-7)

*N=11 due to drop out of subject # PK samples of this subject up to 96 hours available only

Table 1.2.1.5: 5 Summary of preliminary statistical evaluation of food effect [FE part] – adjusted by-treatment geometric means and relative bioavailability

Dose	**PK Parameter**	**Fasted adjusted gMean**	**Fed adjusted gMean**	**Ratio fed/fasted**	**90 % Confidence Interval**	
50 mg (n = 8)	C_{max}	149 nmol/L	237 nmol/L	1.59	1.14	2.21
	AUC_{0-24}	1570 nmol*h/L	2982 nmol*h/L	1.90	1.46	2.47
	AUC_{0-72}	3121 nmol*h/L	5112 nmol*h/L	1.64	1.38	1.94
	$AUC_{0-\infty}$	5059 nmol*h/L	7904 nmol*h/L	1.56	1.32	1.85
100 mg (n = 12)	C_{max}	210 nmol/L	517 nmol/L	2.46	2.03	2.98
	AUC_{0-24}	2353 nmol*h/L	6777 nmol*h/L	2.88	2.36	3.51
	AUC_{0-72}	4601 nmol*h/L	11598 nmol*h/L	2.52	2.04	3.12
	$AUC_{0-\infty}$	6966 nmol*h/L	17232 nmol*h/L	2.47	2.00	3.06

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of BI 1358894 is approximately 14 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Results from the FIH study with BI 1358894 using the reference tablet formulation 1 (TF1) showed a limited bioavailability under fasted conditions while the intake of food increased the exposure and bioavailability of BI 1358894 (see Section 1.2.1). Two additional formulations were subsequently developed, to investigate the adequate formulation with no or negligible food effect and higher exposure under fasted conditions for further clinical development.

1.4 BENEFIT - RISK ASSESSMENT

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

1.4.1 Procedure-related risks

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

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

1.4.2 Drug-related risks and safety measures

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. In addition, recent EFD studies in rats and rabbits were also conducted.

As summarised in Section 1.2.1, potential risks observed in non-clinical studies are a long lasting decrease in the 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 the 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 the start of dosing and resolved despite continued treatment, indicating its transient character. The non-clinical

safety data support clinical Phase I trials in non-childbearing humans with daily oral administration for up to 4 weeks. The conclusion drawn from the EFD studies corroborated the statement from the general toxicity and concluded that the safety profile and subsequent benefit-risk profile was not changed. Furthermore available safety data from healthy volunteers in the SRD did not raise any significant safety concerns related to BI 1358894.

Risks related to the mode of action and nature of the target:

The TRP family members 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 [R18-0249]. 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. In preclinical studies, inhibition of these receptors by BI 1358894 has resulted in 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 [R15-3888]. This supports 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.

The human safety and tolerability profile in healthy male subjects from the FIH SRD study was satisfactory for single doses up to 200 mg under fasted conditions (Trial 1402-0001).

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 mg/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.

Risk minimization:

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

- The dose selected for the current study was already investigated in the FIH SRD study. A higher dose was also investigated and was well tolerated.
- Adequate safety monitoring will be performed (e.g. vital signs (including blood pressure and pulse rate), ECGs, safety laboratory tests including CRP, ESR, hormone parameters, suicidality assessment and assessment of adverse events)
- Subjects will be hospitalized from Day 1 up to Day 4 of each treatment period and will be discharge only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During the in-clinic stay, the subjects will be under medical observation and thoroughly monitored for both expected and unexpected events.

Drug induced liver injury:

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

1.4.3 Overall statement

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

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of a single dose of 100 mg BI 1358894 administered as the tablet formulation 2 (TF2) conventional and TF2 non-conventional under fasted conditions compared with the tablet formulation 1 (TF1) of 100 mg of BI 1358894 under fed conditions following oral administration. In addition, this trial will investigate the food effect on the exposure of BI 1358894 with TF2 conventional and TF2 non-conventional.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1358894:

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

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for BI 1358894:

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- $AUC_{0\text{-}72}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, single-dose, incomplete blocks crossover trial in healthy male subjects in order to compare the test treatments TF2 in fasted state (C and E) to the reference treatment TF1 in fed state (A) to investigate the relative bioavailability of tablet formulation. Additionally, it will evaluate the food effect on test treatments. The test treatments will be one single dose of 100 mg BI 1358894 of the TF2 in a fed state (B) and in the fasted state (C) and TF2 in the fed state (D) and in the fasted state (E). The reference treatment to compare the bioavailability of tablet formulations will be one single dose of 100 mg BI 1358894 of the TF1 (A) administered to subjects in the fed state.

Twenty-four subjects will be randomly allocated to 12 treatment sequences. For details, refer to Section 4.1.

The planned 24 subjects to be included in the study will be assigned to three cohorts, each consisting of eight subjects. The cohorts will be treated at least one week apart. The second and third cohort will be dosed after a careful review by the Investigator of the safety data from all subjects in the preceding cohort(s).

Table 3.1: 1 Treatment sequences

Blocks/Sequences	1	2	3	4	5	6	7	8	9	10	11	12
Period 1	A	D	E	C	A	E	B	C	B	D	C	A
Period 2	B	A	B	A	E	D	C	E	D	C	B	E
Period 3	C	B	A	D	C	A	D	B	E	E	A	D

There will be a washout period of at least 17 days between the treatments, i.e. the dose in the first treatment period and the dose in the second treatment period are separated by at least 17 days. In each subject, an assessment of safety laboratory, vital signs, ECG and AEs will be conducted on the last day of the preceding period prior to next dosing. These data will be reviewed by the Investigator to confirm the eligibility of the subject before the following dosing.

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.

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

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations [R94-1529]. The incomplete blocks design was chosen for this study

instead of a full 5x5 crossover design due to the long apparent terminal half-life of BI 1358894 (between 54.8 and 82.5 h) resulting in a long washout period (17 days).

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of BI 1358894, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

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

Only healthy male subjects will be included in the study which is a standard population in early clinical development.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests.
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

5. Male subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception of the female partner, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device (IUD) that started at least 2 months prior to first study drug administration, or barrier method (e.g. diaphragm with spermicide)
   - Sexually abstinent
   - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success)
   - Surgically sterilised female partner (including hysterectomy, bilateral tubal occlusion or bilateral oophorectomy)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. C-Reactive Protein (CRP) > upper limit of normal (ULN), erythrocyte sedimentation rate (ESR) ≥15 millimeters/h, liver or kidney parameter above ULN, or any other laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy 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) (Lists of excipients are provided in the Investigator's Brochure Section 4.2 for Tablet Formulation 1 and in Appendix 10.2 for Tablet Formulation 2 conventional and Tablet Formulation 2 non-conventional.)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)

14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

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

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment or trial participation, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject shows a raised CRP level of >3.00 mg/dL or an ESR of ≥20 millimetres/hour
6. 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.
7. The subject has an elevation of AST and/or ALT ≥3-fold ULN and 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
8. The subject experiences a serious adverse reaction which is considered at least possibly related to the IMP administration

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported
3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product
5. Occurrence of severe non-serious adverse reactions (i.e., severe non-serious adverse events considered as possibly related to the drug administration) in at least two subjects in the same cohort.

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

3.3.5 Replacement of subjects

In case more than 4 subjects stopped the trial/treatment prematurely due to safety reasons and/or due to poor tolerability further inclusion of new subjects will only be possible after approval of a substantial amendment.

In case subjects do not complete the trial for reasons other than safety and/or poor tolerability (e.g., personal reasons), the Clinical Trial Leader (CTL) together with the Principal Investigator, the Trial Pharmacokineticist and the Trial Statistician are to decide on a case-by-case basis, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Tablet Formulation 2
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	single dose

The characteristics of the reference product are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Tablet Formulation 1
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	single dose

4.1.2 Selection of doses in the trial and dose modifications

The dose selected for this trial, 100 mg of BI 1358894, has been evaluated in the ongoing first-in-human SRD trial (see Section 1.2), in which the highest dose tested was 200 mg and was well tolerated.

4.1.3 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by the method first come first served. Subjects are then assigned to a treatment sequence according to the randomisation list.

Within the treatment sequence, numbers of the randomisation list will be allocated to subjects in their order of registration for the study (that is, the first subject registered will be the first treated and will receive the first number of the respective treatment sequence in the randomisation list).

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is an incomplete blocks crossover study. All subjects will receive three out of the five treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
B (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fed	100 mg
C (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fasted	100 mg
D (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fed	100 mg
E (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fasted	100 mg
A (Reference)	BI 1358894	Tablet	100 mg	1 tablet (100 mg), single dose, fed	100 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In three out of the five treatment periods (treatment A, B and D), a high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

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

Ingredients	kcal
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 was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 72 h after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless lower or supine position is required for trial-related measurements (e.g., recording of 12-lead ECG) or medical reasons (e.g., adverse events).

The treatments will be separated by a wash-out phase of at least 17 days.

4.1.5 Blinding and procedures for unblinding

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.

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

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

4.1.6 Packaging, labelling, and re-supply

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

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

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 authorise symptomatic therapy.

In case of alterations of blood pressure (hypotension) and heart rate (tachycardia), which were reported in nonclinical toxicology studies (see Section 1.2.1.3), first physical

interventions will be the treatment of symptoms. If unsuccessful, appropriate drug therapy will be initiated according to common guidelines and algorithms of emergency trainings. Dependent on individual symptoms, for the treatment of tachycardia this may include intravenous administration of beta blockers or appropriate antiarrhythmic drugs. For the treatment of hypotension, in addition to volume substitution, administration of vasopressors may be a further step. The entire staff of the trial site assuming medical responsibility during the 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 will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water 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 containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the last study period is collected.

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

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 while admitted to the trial site.

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

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 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, recordings of AEs and concomitant therapies, and a physical examination including determination of weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, 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 or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes count	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	Erythrocyte Sedimentation Rate (ESR)	X	X	X
Automatic WBC differential, relative and absolute	Neutrophils; Eosinophils; Basophils; Monocytes; Lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrolphils (segs); band neutrophils (stabs); eosinophils; basophils; monocytes; lymphocytes			
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	X
	Free T3 - Triiodothyronine	X	--	X
	Free T4 – Thyroxine	X	--	X
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	Albumin (Protein Electrophoresis)	X	--	--
	Alpha-1-Globulin (Protein Electrophoresis)	X	--	--
	Alpha-2-Globulin (Protein Electrophoresis)	X	--	--
	Beta-Globulin (Protein Electrophoresis)	X	--	--
	Gamma-Globulin (Protein Electrophoresis)	X	--	--
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -3 to Day -1, unless screening examination is performed between Day -3 and Day -1, and at Visits 2/3/4 on Day 1, Day 2, Day 7, Day 11 and Day 14 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 5 (end of trial examination)

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at Medizinisches Versorgungszentrum Dr. Klein Dr. Schmitt & Partner, Kaiserslautern, Germany, with the exception of drug screening tests. These tests will be performed at the trial site using Multidrogen Pipettiertest (Diagnostik Nord GmbH, Schwerin), or comparable test systems.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if

assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

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

The original C-SSRS is shown in Appendix 10.1.

5.2.5.2 Neurological examinations

As a general additional safety measure, 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).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported

as described in 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.1.7 Suicidal risk assessed by the C-SSRS (paper version)

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

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

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

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

If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1358894 concentrations in plasma, approximately 3 mL of blood will be drawn from an antecubital or forearm vein into a K-EDTA (potassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

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

All plasma samples will be stored at approximately -20°C or below until transfer to the analytical laboratory and analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

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

completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 1358894 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.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKER

Not applicable.

5.5 BIOBANKING

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 10 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 venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood 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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Day 1 to 14 in each period). At least 17 days will separate two consequent drug administration in-between the treatment periods.

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 72 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness on Day 4. On all other study days (Day 5, 7, 9, 11 and 14), the study will be performed in an ambulatory fashion.

If the subject reports headaches during the treatment period the following information and data should be collected daily until the headache is resolved:

- Onset after medication intake (hhh:min)
- Headache severity on a Numeric Ranking Scale (NRS) ranging from 0 - 10
- Quality of headache (New type of headache vs. similar to previous experienced episodes of known headaches)
- Headache characteristics (pressing or tightening vs. burning vs. pulsating vs. aggravated by routine physical activity (such as walking or climbing stairs)
- Location (all of the following that apply: unilateral, bilateral, holocephal, frontal, temporal, occipital, facial)
- Any acompanying symptoms like (all of the following that apply: nausea and/or vomiting, photophobia, phonophobia, lacrimation, other)
- If Headache is resolved: Overall duration of headache episode (start time and end time)

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

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

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the relative bioavailability of a single dose of 100 mg of BI 1358894 administered as the tablet formulation 2 (TF2) fasted conditions compared with the reference tablet formulation 1 (TF1) of 100 mg of BI 1358894 under fed conditions following oral administration, on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. In addition, this trial will investigate the food effect on the exposure of BI 1358894 with TF2

The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics and are specified in Section 2.2.2.1.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of TF2 under fasted conditions compared with TF1 under fed conditions and the relative BA of TF2 under fed conditions compared to TF2 under fasted conditions will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he

contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 1358894 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

Plasma 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),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-

transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence or block, 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. 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 or block effect, i = 1, 10,

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

π_j = the j^{th} period effect, j = 1, 2, 3

τ_k = the k^{th} treatment effect, k = 1, 2, …, 5

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

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1.2) and their two-sided 90% confidence intervals (CIs) will be provided.

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

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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 the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised to one of the 12 treatment sequences in a 1:1:1:1:1:1:1:1:1:1:1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 24 subjects in the trial to have at least 20 evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

As shown in Section 3.1 the trial design is an incomplete crossover with 5 treatments, 12 sequences and 3 periods. To ensure optimal statistical properties, the trial was initially designed in a balanced manner with 10 sequences (see Blocks 1-10 in Section 3.1). The required sample size for a balanced incomplete crossover design is given by $n = \frac{M \times s \times p}{t \times \lambda}$, where M is the sample size for the corresponding complete crossover design with s sequences, t treatments and p periods and λ shows how many times any given pair of treatments (e.g. A and B) appears in the sequences. For a 5×10×3-balanced incomplete crossover, the required sample size is therefore n=2M. This means that the precision for this design with 20 subjects will be equivalent to the precision of a complete crossover design with 10 subjects (e.g. 5×10×5). For a given set of parameters, the number of subjects required for a complete crossover is the same to a first approximation regardless of its order (higher order complete crossovers have slightly higher power due to increased degrees of freedom). Therefore, a 20-subject 5×10×3 design is similar to (but slightly more powerful than) a 10-subject 2×2×2, and this standard, simpler, design will therefore be used to estimate properties of the more complex design. The two additional blocks (CBA and AED) presented in Section 3.1 are considered to provide additional data in favour of planned comparisons.

The total gCVs calculated in trial 1402-0001 and listed in Table 1.2.1.5: 3 are from 17.7% to 42.0% for $AUC_{0\text{-}tz}$ and from 13.4% to 72.8% for C_{max}. The corresponding intra-individual gCV will then be between 8.8% to 20.4% for $AUC_{0\text{-}tz}$ with the intra correlation ρ=0.75, and between 8.5% to 43.1% with the intra correlation ρ=0.6. Therefore, various assumptions around the gCV of 25%, are considered for this trial. Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs approximated by a 2x2 crossover trial *(N=12)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
20.0	1.22	50	41.01	60.96
20.0	1.22	100	82.01	121.93
20.0	1.22	150	123.02	182.89
25.0	1.28	50	39.08	63.98
25.0	1.28	100	78.15	127.95
25.0	1.28	150	156.31	255.91
30.0	1.34	50	37.27	67.08
30.0	1.34	100	74.54	134.16
30.0	1.34	150	149.07	268.33

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

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/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 Julious [R11-5230] using R Version 3.4.2.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

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

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

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

Measures are in place to comply with the applicable rules for the collection and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

Samples and/or data may be transferred to third parties and other countries as specified in the ICF.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

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

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

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

The EC/competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of Clinical Trial Manager (CTM), Clinical Research Associates, and investigators of participating trial sites

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

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

Analyses of BI 1358894 concentrations in plasma will be performed at
.

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

Data management and statistical evaluation will be done 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.

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n00253723 . Influence of BI 1358894 (10, 30 and 100 mg/kg PO) on cardiovascular function (systolic and diastolic arterial pressure, heart rate and ECG) and body temperature in conscious rats. GP2014/0251/PH5. 29 November 2016.

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n00253729 Effects of BI 1358894 (10, 30 and 100 mg/kg p.o.) on gastrointestinal function in the conscious rat. GP2014/0277/PH4. 12 December 2016.

n00253732 . Effects of BI 1358894 (10, 30 and 100 mg/kg p.o.) on urine- and serum-derived parameters in conscious rats. GP2014/0274/PH4. 29 November 2016.

n00253752 . Selectivity test of HC-122608 on TRPV1, TRPV3, TRPM8, TRPC6, TRPA1, hERG, Kv1.3, Cav1.2, Nav1.2, Nav1.7 and Nav1.5. Report #: 155. 11 January 2013.

n00254034 BI 1358894: Telemetric Evaluation of Cardiovascular Effects in the Conscious Dog (Single Oral Administration). WX28PL.10 July 2017.

n00256526 . Evaluation of Induction Potential of Cytochrome P450 Isoforms by BI 1358894 in Cultured Human Hepatocytes. 19 May2017.

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

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**	**Past 12 Months**
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 ☐	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 ☐	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 ☐	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 ☐	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 ☐	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). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past 6 Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	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	___	___

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:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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* _____

10.2 LIST OF INACTIVE INGREDIENTS IN THE TF2

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		01 March 2019
EudraCT number **EU number**		2018-003603-19
BI Trial number		1402-0010
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)

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. Flowchart and associated footnotes 2. Section 1.4.1 Procedure-related risks 3. Section 3.1 Overall trial design and plan 4. Section 3.3.3 Exclusion criteria 5. Section 3.3.4.3 Discontinuation of the trial by the Sponsor 6. Section 3.3.5 Replacement of subjects 7. Section 5,2,1 Physical examination 8. Section 5.3.2 Methods of sample collection 9. Section 8.7 Administrative structure of the trial 10. Section 10.1 Columbia-suicide severity rating scale 11. Section 10.2 List of inactive ingredients in the TF2
Description of change		1. Flowchart and associated footnotes Minor changes were corrected in the flowchart.

		2. Section 1.4.1 Procedure-related risks A procedure-related risk (syncope) due to venous catheter or venepuncture was added to the list. 3. Section 3.1 Overall trial design and plan A description on the planned group sizes and planned dosing interval was added. The subjects will be dosed in three cohorts of eight subjects each, and the cohorts will be separated by one week. Furthermore, confirmation of subject's eligibility with regards to safety prior to further dosing was implemented. 4. / 11. Section 3.3.3 Exclusion criteria / Section 10.2 List of inactive ingredients in the TF2 The list of excipients for the TF2 conventional and non-conventional was added as an appendix and was referenced in the corresponding exclusion criterion. 5. Section 3.3.4.3 Discontinuation of the trial by the Sponsor A discontinuation criterion was added to describe that severe non-serious drug-related AEs in at least 2 subjects in the same cohort will lead to discontinuation of the trial. 6. Section 3.3.5 Replacement of subjects Replacement of subjects was further described to assure that if more than 4 subjects discontinue the trial due to safety and/or poor tolerability, the inclusion of further subjects would require a substantial amendment. Furthermore subjects who drop out for reasons unrelated to safety and/or poor tolerability could be replaced on a case-by-case basis. 7. Section 5.2,1 Physical examination Minor addition in the list of assessments at EOT to include the recording of AEs and concomitant therapies in alignment with the flowchart. 8. Section 5.3.2 Methods of sample collection Information regarding the PK blood sample collection (blood volume and collection tube) was amended.

		9. Section 8.7 Administrative structure of the trial Name and address of the PK laboratory was amended. 10. Section 10.1 Columbia-suicide severity rating scale Discrepancy regarding the suicidality questionnaire was amended. The correct C-SSRS to be used is the "screening / baseline".
Rationale for change		The majority of changes were done based on the request of regulatory authorities. In the context of this amendment, minor changes due to discrepancies or administrative aspects were corrected throughout the document.

11.2 GLOBAL AMENDMENT 2

Date of amendment		02 April 2019
EudraCT number **EU number**		2018-003603-19
BI Trial number		1402-0010
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)
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. Section 3.1 Overall trial design and plan 2. Section 6.2.2 Treatment periods
Description of change		1. Minor inconsistency regarding the timeframe between last safety assessment and start of next period was corrected. 2. The measurement of headache intensity was added in the list.
Rationale for change		Minor inconsistencies and omission were corrected in the document.

APPROVAL / SIGNATURE PAGE

Document Number: c26426667 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy malesubjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		02 Apr 2019 15:06 CEST
Author-Clinical Trial Leader		02 Apr 2019 15:41 CEST
Author-Trial Statistician		02 Apr 2019 16:44 CEST
Approval-Team Member Medicine		02 Apr 2019 18:34 CEST
Author-Trial Clinical Pharmacokineticist		03 Apr 2019 14:47 CEST
Verification-Paper Signature Completion		05 Apr 2019 08:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**

Clinical Trial Protocol

	Document Number:	**c26426667-03**
EudraCT No.	2018-003603-19	
BI Trial No.	1402-0010	
BI Investigational Medicinal Product	BI 1358894	
Title	Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)	
Lay Title	A study in healthy men to test if taking different formulations of BI 1358894 with or without food influences the amount of BI 1358894 in the blood	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 02 April 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 January 2019
Revision date	02 April 2019
BI trial number	1402-0010
Title of trial	Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	Results from the first-in-human study with BI 1358894 using TF1 showed a limited bioavailability under fasted conditions while the intake of food increased the exposure and bioavailability of BI 1358894. Two additional formulations were subsequently developed, TF2 conventional and TF2 non-conventional, to investigate the adequate formulation with no or negligible food effect and higher exposure under fasted conditions for further clinical development.
Trial objectives	To investigate the relative bioavailability of TF2 conventional and TF2 non-conventional under fasted conditions vs. TF1 under fed conditions. To investigate the food effect on the exposure of BI 1358894 with TF2 conventional and TF2 non-conventional.
Trial design	Randomised, open-label, single-dose, incomplete blocks crossover design.
Trial endpoints:	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1358894 Secondary endpoints: AUC_{0-72} and $AUC_{0-\infty}$ of BI 1358894
Number of subjects **total entered**	24 (20 evaluable subjects)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product 1	Tablet formulation 2; TF2 conventional of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast when fed (treatment B), or after an overnight fast of at least 10 h when fasted (treatment C).
Test product 2	Tablet formulation 2; TF2 non-conventional of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast when fed (treatment D), or after an overnight fast of at least 10 h when fasted (treatment E).
Reference product	Tablet formulation 1; TF1 of BI 1358894
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast (treatment A).
Duration of treatment	One day (single dose) for each treatment.
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [8]	Suicidality assessment (C-SSRS)[10]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x		x	x	x	
1-3 (three periods separated by a wash-out of at least 17 days)	2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x					x
	2/3/4	1	-1:30	06:30	Admission to trial site	x[5]					x
			-1:00	07:00	Allocation to treatment sequence (visit 2 only)	x[2, 9, 13]	x[2]		x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (for treatments A, B and D)[12]						
			0:00	08:00	**Drug administration**						
			0:10	08:10			x				
			0:20	08:20			x				
			0:30	08:30			x			x	x
			1:00	09:00			x		x	x	x
			1:30	09:30			x			x	
			2:00	10:00	240 mL fluid intake		x				x
			3:00	11:00			x			x	
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x		x	x	x
			5:00	13:00			x			x	x
			6:00	14:00			x			x	x
			7:00	15:00			x				
			8:00	16:00	Snack (voluntary)[3]		x			x	x
			10:00	18:00	Dinner[3]		x				
			12:00	20:00			x		x	x	x
		2	24:00	08:00	Breakfast[3]	x	x		x	x	x
			34:00	18:00			x			x	x
		3	48:00	08:00	Breakfast[3]		x		x	x	x
		4	72:00	08:00	Breakfast (voluntary)[3], Discharge from trial site[11]		x	x	x	x	x
		5	96:00	08:00	Ambulatory visit		x		x	x	x
		7	144:00	08:00	Ambulatory visit	x	x		x	x	x
		9	192:00	08:00	Ambulatory visit		x		x	x	x
		11	240:00	08:00	Ambulatory visit	x	x		x	x	x
		14	312:00	08:00	Ambulatory visit	x	x		x	x	x
FU	5	17 to 22			End of trial (EoTrial) examination[4]	x		x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath test, 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, neurological examination and suicidality assessment (C-SSRS).
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, concomitant therapies, neurological examination 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 times 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 between Day -3 and Day -1.
8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.

10. Suicidality assessment will be performed at screening, at discharge from trial site for each period and at end of trial.
11. Confirmation of fitness includes physical examination, vital signs, ECG, suicidality assessment (C-SSRS), and recordings of AEs and concomitant therapies assessed on Day 4 as well as evaluation of safety laboratory assessed on Day 2.
12. High fat, high calorie breakfast will be administered only for treatment A (TF1), treatment B (TF2 conventional fed) and treatment D (TF2 non-conventional fed). Subjects in treatments C (TF2 conventional fasted) and E (TF2 non-conventional fasted) will not receive any breakfast. All subjects will be admitted to the trial site after an overnight fast of at least 10 h for all treatments.
13. Only for visit 2. For visit 3 and 4, predose values for safety laboratory will be derived from the Day 14 of the preceding visit.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{0-72}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline Personality Disorder
CA	Competent authority
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Contract research organisation
CRP	C-reactive protein
C-SSRS	Columbia Suicidal Severity Rating scale
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol

CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
DRF	Dose range finding
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electro-convulsive therapy
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-foetal development
EoTrial	End of trial
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and drug administration
FE	Food effect
FIH	First in Human
FST	Forced swim test
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
GLDH	Glutamate deshydrogenase
GLP	Good Laboratory Practice
gMean	Geometric mean
hERG	Human ether-a-go-go related gene
HR	Heart rate
IB	Investigator's brochure
IC_{50}	Half maximum inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry

LVSP	Left ventricular systolic pressure
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body, extravascular
NIMH	National institute of mental health
NOAEL	No observed adverse effect level
NRS	Numeric ranking scale
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PT	Preferred term
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
RBC	Red blood cell
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOC	System organ class
SOP	Standard operating procedure
SRD	Single-rising dose
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TF1/2	Tablet formulation 1/2
TRP	Transient receptor potential
TRPC 4/5	Transient receptor potential cation channel, subfamily C, members 4 and 5
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
VAS	Visual analog scale
V_{ss}	Apparent volume of distribution at steady state after intravascular

	administration
WBC	White blood cell
XTC	Ecstasy

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).

MDD is a debilitating disease characterised by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the 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 residual symptoms [R16-5475] that 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 severely impaired 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, 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, treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in patients with MDD and BPD.

1.2 DRUG PROFILE

1.2.1 BI 1358894

For a more detailed description of the BI 1358894 profile, please refer to the current Investigator's Brochure (IB) [c10354149].

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of BI 1358894 is approximately 14 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Results from the FIH study with BI 1358894 using the reference tablet formulation 1 (TF1) showed a limited bioavailability under fasted conditions while the intake of food increased the exposure and bioavailability of BI 1358894 (see Section 1.2.1). Two additional formulations were subsequently developed, TF2 conventional and TF2 non-conventional, to investigate the adequate formulation with no or negligible food effect and higher exposure under fasted conditions for further clinical development.

1.4 BENEFIT - RISK ASSESSMENT

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

1.4.1 Procedure-related risks

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

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

1.4.2 Drug-related risks and safety measures

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. In addition, recent EFD studies in rats and rabbits were also conducted.

As summarised in Section 1.2.1, potential risks observed in non-clinical studies are a long lasting decrease in the 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 the 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 the start of dosing and resolved despite continued treatment, indicating its transient character. The non-clinical

safety data support clinical Phase I trials in non-childbearing humans with daily oral administration for up to 4 weeks. The conclusion drawn from the EFD studies corroborated the statement from the general toxicity and concluded that the safety profile and subsequent benefit-risk profile was not changed. Furthermore available safety data from healthy volunteers in the SRD did not raise any significant safety concerns related to BI 1358894.

Risks related to the mode of action and nature of the target:

The TRP family members 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 [R18-0249]. 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. In preclinical studies, inhibition of these receptors by BI 1358894 has resulted in 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 [R15-3888]. This supports 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.

The human safety and tolerability profile in healthy male subjects from the FIH SRD study was satisfactory for single doses up to 200 mg under fasted conditions (Trial 1402-0001).

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.

Risk minimization:

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

- The dose selected for the current study was already investigated in the FIH SRD study. A higher dose was also investigated and was well tolerated.
- Adequate safety monitoring will be performed (e.g. vital signs (including blood pressure and pulse rate), ECGs, safety laboratory tests including CRP, ESR, hormone parameters, suicidality assessment and assessment of adverse events)
- Subjects will be hospitalized from Day 1 up to Day 4 of each treatment period and will be discharge only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During the in-clinic stay, the subjects will be under medical observation and thoroughly monitored for both expected and unexpected events.

Drug induced liver injury:

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

1.4.3 Overall statement

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

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of a single dose of 100 mg BI 1358894 administered as the tablet formulation 2 (TF2) conventional and TF2 non-conventional under fasted conditions compared with the tablet formulation 1 (TF1) of 100 mg of BI 1358894 under fed conditions following oral administration. In addition, this trial will investigate the food effect on the exposure of BI 1358894 with TF2 conventional and TF2 non-conventional.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1358894:

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

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for BI 1358894:

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- $AUC_{0\text{-}72}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, single-dose, incomplete blocks crossover trial in healthy male subjects in order to compare the test treatments TF2 conventional and TF2 non-conventional in fasted state (C and E) to the reference treatment TF1 in fed state (A) to investigate the relative bioavailability of tablet formulation. Additionally, it will evaluate the food effect on test treatments. The test treatments will be one single dose of 100 mg BI 1358894 of the TF2 conventional in a fed state (B) and in the fasted state (C) and TF2 non-conventional in the fed state (D) and in the fasted state (E). The reference treatment to compare the bioavailability of tablet formulations will be one single dose of 100 mg BI 1358894 of the TF1 (A) administered to subjects in the fed state.

Twenty-four subjects will be randomly allocated to 12 treatment sequences. For details, refer to Section 4.1.

The planned 24 subjects to be included in the study will be assigned to three cohorts, each consisting of eight subjects. The cohorts will be treated at least one week apart. The second and third cohort will be dosed after a careful review by the Investigator of the safety data from all subjects in the preceding cohort(s).

Table 3.1: 1 Treatment sequences

Blocks/Sequences	1	2	3	4	5	6	7	8	9	10	11	12
Period 1	A	D	E	C	A	E	B	C	B	D	C	A
Period 2	B	A	B	A	E	D	C	E	D	C	B	E
Period 3	C	B	A	D	C	A	D	B	E	E	A	D

There will be a washout period of at least 17 days between the treatments, i.e. the dose in the first treatment period and the dose in the second treatment period are separated by at least 17 days. In each subject, an assessment of safety laboratory, vital signs, ECG and AEs will be conducted on the last day of the preceding period prior to next dosing. These data will be reviewed by the Investigator to confirm the eligibility of the subject before the following dosing.

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.

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

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations [R94-1529]. The incomplete blocks design was chosen for this study

instead of a full 5x5 crossover design

resulting in a long washout period (17 days).

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of BI 1358894, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

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

Only healthy male subjects will be included in the study which is a standard population in early clinical development.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests.
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

5. Male subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception of the female partner, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device (IUD) that started at least 2 months prior to first study drug administration, or barrier method (e.g. diaphragm with spermicide)
   - Sexually abstinent
   - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success)
   - Surgically sterilised female partner (including hysterectomy, bilateral tubal occlusion or bilateral oophorectomy)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. C-Reactive Protein (CRP) > upper limit of normal (ULN), erythrocyte sedimentation rate (ESR) ≥15 millimeters/h, liver or kidney parameter above ULN, or any other laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy 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) (Lists of excipients are provided in the Investigator's Brochure Section 4.2 for Tablet Formulation 1 and in Appendix 10.2 for Tablet Formulation 2 conventional and Tablet Formulation 2 non-conventional.)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)

14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

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

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment or trial participation, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject shows a raised CRP level of >3.00 mg/dL or an ESR of ≥20 millimetres/hour
6. 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.
7. The subject has an elevation of AST and/or ALT ≥3-fold ULN and 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
8. The subject experiences a serious adverse reaction which is considered at least possibly related to the IMP administration

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported
3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product
5. Occurrence of severe non-serious adverse reactions (i.e., severe non-serious adverse events considered as possibly related to the drug administration) in at least two subjects in the same cohort.

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

3.3.5 Replacement of subjects

In case more than 4 subjects stopped the trial/treatment prematurely due to safety reasons and/or due to poor tolerability further inclusion of new subjects will only be possible after approval of a substantial amendment.

In case subjects do not complete the trial for reasons other than safety and/or poor tolerability (e.g., personal reasons), the Clinical Trial Leader (CTL) together with the Principal Investigator, the Trial Pharmacokineticist and the Trial Statistician are to decide on a case-by-case basis, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Tablet Formulation 2 conventional / Tablet Formulation 2 non-conventional
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	single dose

The characteristics of the reference product are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Tablet Formulation 1
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	single dose

4.1.2 Selection of doses in the trial and dose modifications

The dose selected for this trial, 100 mg of BI 1358894, has been evaluated in the ongoing first-in-human SRD trial (see Section 1.2), in which the highest dose tested was 200 mg and was well tolerated.

4.1.3 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by the method first come first served. Subjects are then assigned to a treatment sequence according to the randomisation list.

Within the treatment sequence, numbers of the randomisation list will be allocated to subjects in their order of registration for the study (that is, the first subject registered will be the first treated and will receive the first number of the respective treatment sequence in the randomisation list).

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is an incomplete blocks crossover study. All subjects will receive three out of the five treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
B (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fed	100 mg
C (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fasted	100 mg
D (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fed	100 mg
E (Test)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fasted	100 mg
A (Reference)	BI 1358894	Tablet	100 mg	1 tablet (100 mg), single dose, fed	100 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In three out of the five treatment periods (treatment A, B and D), a high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

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

Ingredients	kcal
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 was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 72 h after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless lower or supine position is required for trial-related measurements (e.g., recording of 12-lead ECG) or medical reasons (e.g., adverse events).

The treatments will be separated by a wash-out phase of at least 17 days.

4.1.5 Blinding and procedures for unblinding

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.

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

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

4.1.6 Packaging, labelling, and re-supply

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

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

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 authorise symptomatic therapy.

In case of alterations of blood pressure (hypotension) and heart rate (tachycardia), which were reported in nonclinical toxicology studies (see Section 1.2.1.3), first physical

interventions will be the treatment of symptoms. If unsuccessful, appropriate drug therapy will be initiated according to common guidelines and algorithms of emergency trainings. Dependent on individual symptoms, for the treatment of tachycardia this may include intravenous administration of beta blockers or appropriate antiarrhythmic drugs. For the treatment of hypotension, in addition to volume substitution, administration of vasopressors may be a further step. The entire staff of the trial site assuming medical responsibility during the 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 will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water 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 containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the last study period is collected.

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

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 while admitted to the trial site.

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

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 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, recordings of AEs and concomitant therapies, and a physical examination including determination of weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, 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 or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes count	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	Erythrocyte Sedimentation Rate (ESR)	X	X	X
Automatic WBC differential, relative and absolute	Neutrophils; Eosinophils; Basophils; Monocytes; Lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrolphils (segs); band neutrophils (stabs); eosinophils; basophils; monocytes; lymphocytes			
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	X
	Free T3 - Triiodothyronine	X	--	X
	Free T4 – Thyroxine	X	--	X
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	Albumin (Protein Electrophoresis)	X	--	--
	Alpha-1-Globulin (Protein Electrophoresis)	X	--	--
	Alpha-2-Globulin (Protein Electrophoresis)	X	--	--
	Beta-Globulin (Protein Electrophoresis)	X	--	--
	Gamma-Globulin (Protein Electrophoresis)	X	--	--
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -3 to Day -1, unless screening examination is performed between Day -3 and Day -1, and at Visits 2/3/4 on Day 1, Day 2, Day 7, Day 11 and Day 14 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 5 (end of trial examination)

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at with the exception of drug screening tests. These tests will be performed at the trial site using Multidrogen Pipettiertest (Diagnostik Nord GmbH, Schwerin), or comparable test systems.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if

assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

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

The original C-SSRS is shown in Appendix 10.1.

5.2.5.2 Neurological examinations

As a general additional safety measure, 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).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported

as described in 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.1.7 Suicidal risk assessed by the C-SSRS (paper version)

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

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

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

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

If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1358894 concentrations in plasma, approximately 3 mL of blood will be drawn from an antecubital or forearm vein into a K-EDTA (potassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

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

All plasma samples will be stored at approximately -20°C or below until transfer to the analytical laboratory and analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

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

completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 1358894 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.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKER

Not applicable.

5.5 BIOBANKING

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 10 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 venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood 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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Day 1 to 14 in each period). At least 17 days will separate two consequent drug administration in-between the treatment periods.

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 72 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness on Day 4. On all other study days (Day 5, 7, 9, 11 and 14), the study will be performed in an ambulatory fashion.

If the subject reports headaches during the treatment period the following information and data should be collected daily until the headache is resolved:

- Onset after medication intake (hhh:min)
- Headache severity on a Numeric Ranking Scale (NRS) ranging from 0 - 10
- Quality of headache (New type of headache vs. similar to previous experienced episodes of known headaches)
- Headache characteristics (pressing or tightening vs. burning vs. pulsating vs. aggravated by routine physical activity (such as walking or climbing stairs)
- Location (all of the following that apply: unilateral, bilateral, holocephal, frontal, temporal, occipital, facial)
- Any acompanying symptoms like (all of the following that apply: nausea and/or vomiting, photophobia, phonophobia, lacrimation, other)
- If Headache is resolved: Overall duration of headache episode (start time and end time)

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

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

Genotyping will be performed at visit 2 in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the relative bioavailability of a single dose of 100 mg of BI 1358894 administered as the tablet formulation 2 (TF2) conventional and TF2 non-conventional under fasted conditions compared with the reference tablet formulation 1 (TF1) of 100 mg of BI 1358894 under fed conditions following oral administration, on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. In addition, this trial will investigate the food effect on the exposure of BI 1358894 with TF2 conventional and TF2 non-conventional.

The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics and are specified in Section 2.2.2.1.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of TF2 (conventional and non-conventional) under fasted conditions compared with TF1 under fed conditions and the relative BA of TF2 under fed conditions compared to TF2 under fasted conditions will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he

contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 1358894 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

Plasma 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),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-

transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence or block, 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. 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 or block effect, i = 1, 10,

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

π_j = the j^{th} period effect, j = 1, 2, 3

τ_k = the k^{th} treatment effect, k = 1, 2, …, 5

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

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1.2) and their two-sided 90% confidence intervals (CIs) will be provided.

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

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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 the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised to one of the 12 treatment sequences in a 1:1:1:1:1:1:1:1:1:1:1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 24 subjects in the trial to have at least 20 evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

As shown in Section 3.1 the trial design is an incomplete crossover with 5 treatments, 12 sequences and 3 periods. To ensure optimal statistical properties, the trial was initially designed in a balanced manner with 10 sequences (see Blocks 1-10 in Section 3.1). The required sample size for a balanced incomplete crossover design is given by $n = \frac{M \times s \times p}{t \times \lambda}$, where M is the sample size for the corresponding complete crossover design with s sequences, t treatments and p periods and λ shows how many times any given pair of treatments (e.g. A and B) appears in the sequences. For a 5×10×3-balanced incomplete crossover, the required sample size is therefore n=2M. This means that the precision for this design with 20 subjects will be equivalent to the precision of a complete crossover design with 10 subjects (e.g. 5×10×5). For a given set of parameters, the number of subjects required for a complete crossover is the same to a first approximation regardless of its order (higher order complete crossovers have slightly higher power due to increased degrees of freedom). Therefore, a 20-subject 5×10×3 design is similar to (but slightly more powerful than) a 10-subject 2×2×2, and this standard, simpler, design will therefore be used to estimate properties of the more complex design. The two additional blocks (CBA and AED) presented in Section 3.1 are considered to provide additional data in favour of planned comparisons.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

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

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

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

Measures are in place to comply with the applicable rules for the collection and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

Samples and/or data may be transferred to third parties and other countries as specified in the ICF.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

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

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

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

The EC/competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of Clinical Trial Manager (CTM), Clinical Research Associates, and investigators of participating trial sites

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

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

Analyses of BI 1358894 concentrations in plasma will be performed at
.

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

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

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

9. REFERENCES

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9.2 UNPUBLISHED REFERENCES

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

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**	**Past 12 Months**
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 ☐	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 ☐	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 ☐	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 ☐	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 ☐	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). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past 6 Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	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	___	___

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:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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)

11.1 GLOBAL AMENDMENT 1

Date of amendment		01 March 2019
EudraCT number **EU number**		2018-003603-19
BI Trial number		1402-0010
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)

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. Flowchart and associated footnotes 2. Section 1.4.1 Procedure-related risks 3. Section 3.1 Overall trial design and plan 4. Section 3.3.3 Exclusion criteria 5. Section 3.3.4.3 Discontinuation of the trial by the Sponsor 6. Section 3.3.5 Replacement of subjects 7. Section 5,2,1 Physical examination 8. Section 5.3.2 Methods of sample collection 9. Section 8.7 Administrative structure of the trial 10. Section 10.1 Columbia-suicide severity rating scale
Description of change		1. Flowchart and associated footnotes Minor changes were corrected in the flowchart.

		2. Section 1.4.1 Procedure-related risks A procedure-related risk (syncope) due to venous catheter or venepuncture was added to the list. 3. Section 3.1 Overall trial design and plan A description on the planned group sizes and planned dosing interval was added. The subjects will be dosed in three cohorts of eight subjects each, and the cohorts will be separated by one week. Furthermore, confirmation of subject's eligibility with regards to safety prior to further dosing was implemented. 4. / 11. Section 3.3.3 Exclusion criteria / 5. Section 3.3.4.3 Discontinuation of the trial by the Sponsor A discontinuation criterion was added to describe that severe non-serious drug-related AEs in at least 2 subjects in the same cohort will lead to discontinuation of the trial. 6. Section 3.3.5 Replacement of subjects Replacement of subjects was further described to assure that if more than 4 subjects discontinue the trial due to safety and/or poor tolerability, the inclusion of further subjects would require a substantial amendment. Furthermore subjects who drop out for reasons unrelated to safety and/or poor tolerability could be replaced on a case-by-case basis. 7. Section 5.2,1 Physical examination Minor addition in the list of assessments at EOT to include the recording of AEs and concomitant therapies in alignment with the flowchart. 8. Section 5.3.2 Methods of sample collection Information regarding the PK blood sample collection (blood volume and collection tube) was amended.

		9. Section 8.7 Administrative structure of the trial Name and address of the PK laboratory was amended. 10. Section 10.1 Columbia-suicide severity rating scale Discrepancy regarding the suicidality questionnaire was amended. The correct C-SSRS to be used is the "screening / baseline".
Rationale for change		The majority of changes were done based on the request of regulatory authorities. In the context of this amendment, minor changes due to discrepancies or administrative aspects were corrected throughout the document.

11.2 GLOBAL AMENDMENT 2

Date of amendment		02 April 2019
EudraCT number **EU number**		2018-003603-19
BI Trial number		1402-0010
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability and food effect of a single dose of different solid formulations of BI 1358894 compared to a single dose of the reference tablet formulation of BI 1358894 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, single-dose, randomised, incomplete blocks crossover design study)
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. Section 3.1 Overall trial design and plan 2. Section 6.2.2 Treatment periods
Description of change		1. Minor inconsistency regarding the timeframe between last safety assessment and start of next period was corrected. 2. The measurement of headache intensity was added in the list.
Rationale for change		Minor inconsistencies and omission were corrected in the document.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		02 Apr 2019 15:06 CEST
Author-Clinical Trial Leader		02 Apr 2019 15:41 CEST
Author-Trial Statistician		02 Apr 2019 16:44 CEST
Approval-Team Member Medicine		02 Apr 2019 18:34 CEST
Author-Trial Clinical Pharmacokineticist		03 Apr 2019 14:47 CEST
Verification-Paper Signature Completion		05 Apr 2019 08:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**