Clinical Trial Protocol

	Document Number:	**c25796375-03**
EudraCT No.	2018-004274-10	
BI Trial No.	1402-0007	
BI Investigational Medicinal Product	BI 1358894	
Title	Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence study)	
Lay Title	A study in healthy men to test how itraconazole influences the amount of BI 1358894 in the blood	
Clinical Phase	I	
Clinical Trial Lead	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 27 Mar 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	18 December 2018
Revision date	27 March 2019
BI trial number	1402-0007
Title of trial	Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence study)
Principal Investigator:	
Trial site(s)	
Clinical phase	I
Trial rationale	This clinical trial will be performed to investigate the effect of multiple doses of itraconazole on the pharmacokinetics of a single dose of BI 1358894 in order to assess if and to which extent the pharmacokinetics of BI 1358894 are affected by co-administration of a drug that inhibits cytochrome P450 3A4 (CYP3A4) and P-glycoprotein.
Trial objective(s)	The main objective of this trial is to investigate the relative bioavailability of BI 1358894 in plasma when given as oral single dose together with multiple oral doses of itraconazole (Test, T) as compared to when given alone as oral single dose (Reference, R).
Trial design	Open-label, two-treatment, two-period, fixed sequence design
Trial endpoints:	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 1358894 Secondary endpoints: AUC_{0-tz} of BI 1358894
Number of subjects **total entered** **each treatment**	 16 16
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 **dose** **mode of admin.**	BI 1358894 film-coated tablets 10 mg Oral with 240 mL of water after an high-fat, high-caloric breakfast

Test product 2 (probe)	Itraconazole oral solution (Sempera® 10 mg/ml oral solution)
dose	200 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	Treatment "Reference" (R, in treatment period 1): - One single dose of 10 mg BI 1358894 on Day 1 Treatment "Test" (T; in treatment period 2): - 200 mg itraconazole once daily (QD) for 14 days on Days -3 to 11 - One single dose of 10 mg BI 1358894 on Day 1 Wash-out interval Administrations of BI 1358894 will be separated by a wash-out interval of at least 17 days
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 'subjects' 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 first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[9]	PK_{blood} BI 1358894 and metabolite	PK_{blood} itraconazole	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]	Physical and neurological examination	C-SSRS
SCR	1	-21 to -1			Screening (SCR)[1]	A[9]			x	x		x	x
Period 1: Treatment R (BI 1358894 alone)[7]	2	-1	-12:00	20:00	Admission to trial site	x[5]					x		
			-11:30	20:30	Snack (voluntary)								
		1	-0:30	07:30	High-fat, high caloric breakfast	A[2, 9, 10]	x[2]		x[2]	x[2]	x[2]		
			0:00	08:00	**BI 1358894 administration**								
			0:30	08:30			x			x	x		
			1:00	09:00			x		x	x	x		
			1:30	09:30			x			x	x		
			2:00	10:00	240 mL fluid intake		x			x	x		
			2:30	10:30			x						
			3:00	11:00			x			x	x		
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x	x		
			6:00	14:00			x			x	x		
			7:00	15:00			x			x	x		
			8:00	16:00	Snack (voluntary)[3]		x			x	x		
			10:00	18:00	Dinner		x						
			12:00	20:00			x		x	x	x		
			16:00	24:00			x			x			
		2	24:00	08:00		B[9]	x		x	x	x		
			34:00	18:00			x			x	x		
		3	48:00	08:00			x		x	x	x		
		4	72:00	08:00	Breakfast (voluntary), discharge from trial site[8]	B[9]	x		x	x	x	x	x
		5	96:00	08:00	Ambulatory visit		x		x	x	x		
		6	120:00	08:00	Ambulatory visit		x			x	x		
		7	144:00	08:00	Ambulatory visit		x			x	x		
		8	168:00	08:00	Ambulatory visit		x			x	x		
		9	192:00	08:00	Ambulatory visit	B[9]	x			x	x		
		11	240:00	08:00	Ambulatory visit		x			x	x		
		14	312:00	08:00	Ambulatory visit	B[9]	x			x	x		

FLOW CHART (continued)

Period	Visit	Day	Planned time (relative to first BI 1358894 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[9]	PK_{blood} BI 1358894 and metabolite	PK_{blood} itraconazole	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]	Physical and neurological examination	C-SSRS
Period 2: Treatment T (BI 1358894 + itraconazole)[7]	3	-3	-72:00	08:00	Ambulatory visit, **itraconazole administration**								
		-2	-48:00	08:00	Ambulatory visit, **itraconazole administration**								
		-1	24:00	08:00	Ambulatory visit, **itraconazole administration**								
			-12:00	20:00	Admission to trial site	x[5]					x		
			-11:30	20:30	Snack (voluntary)								
		1	-2:30	05:30		B[2, 9]	x[2]	x[2]	x[2]	x[2]	x[2]		
			-1:30	06:30	**Itraconazole administration**								
			-0:30	07:30	High-fat, high-caloric breakfast								
			0:00	08:00	**BI 1358894 administration**								
			0:30	08:30			x			x	x		
			1:00	09:00			x		x	x	x		
			1:30	09:30			x			x	x		
			2:00	10:00	240 mL fluid intake		x			x	x		
			2:30	10:30			x						
			3:00	11:00			x			x	x		
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x	x		
			6:00	14:00			x			x	x		
			7:00	15:00			x			x	x		
			8:00	16:00	Snack (voluntary)[3]		x			x	x		
			10:00	18:00	Dinner		x						
			12:00	20:00			x		x	x	x		
			16:00	24:00			x			x			
		2	24:00	08:00	**itraconazole administration**	B[9]	x	x[2]	x	x	x		
			34:00	18:00			x			x	x		
		3	48:00	08:00	**itraconazole administration**		x		x	x	x		
		4	72:00	08:00	**itraconazole administration** Breakfast (voluntary) discharge from trial site[8]	B[9]	x		x	x	x	x	x
		5	96:00	08:00	Ambulatory visit, **itraconazole administration**		x		x	x	x		
		6	120:00	08:00	Ambulatory visit, **itraconazole administration**		x	x[2]		x	x		
		7	144:00	08:00	Ambulatory visit, **itraconazole administration**		x			x	x		
		8	168:00	08:00	Ambulatory visit, **itraconazole administration**		x			x	x		

Period	Visit	Day	Planned time (relative to first BI 1358894 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[9]	PK $_{blood}$ BI 1358894 and metabolite	PK $_{blood}$ itraconazole	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]	Physical and neurological examination	C-SSRS
		9	192:00	08:00	Ambulatory visit, **itraconazole administration**	B[9]	x			x	x		
		10	216:00	08:00	Ambulatory visit, **itraconazole administration**		x			x	x		
		11	240:00	08:00	Ambulatory visit, **itraconazole administration**		x	x[2]		x	x		
		14	312:00	08:00	Ambulatory visit	B[9]	x			x	x		
		21	480:00	08:00	Ambulatory visit		x			x	x		
FU	4	22 - 28			End of trial (EoTrial) examination[4]	C			x	x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include: physical examination, neurological examination, check of vital signs, ECG, safety laboratory (including drug screening, hepatitis serology and HIV antibodies), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, 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 (Period 1) / within 2.5 h prior to BI 1358894 administration (Period 2).
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. End of trial examination (performed 11 to 17 days after last itraconazole and 21 to 27 days after last BI 1358894 administration) includes: physical examination, neurological examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, and suicidality assessment (C-SSRS).
5. Only urine drug screening and alcohol breath test will be done at this time.
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. Headaches will be recorded with the data given in Section 6.2.2.
7. Treatments R and T are to be separated by a wash-out interval of at least 17 days between administrations of BI 1358894.
8. Discharge from trial site fitness assessment includes: physical examination, neurological examination, ECG, vital signs, recording of AEs, suicidality assessment (C-SSRS), and concomitant therapies.
9. Letters A, B, and C define different sets of safety laboratory examinations (see Section 5.2.3). Safety laboratory examination A to be taken and medically evaluated within 3 days before first administration of BI 1358894. This can be omitted if screening examination is performed on Days -3, -2 or -1 of treatment period 1.
10. Blood sample for pharmacogenetic assessment.

TABLE OF CONTENTS

ABBREVIATIONS

δ	Bioequivalence margin
ADH	Alcohol dehydrogenase
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
b.p.m.	Beats per minute
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
CL	Confidence limit
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale

CTL	Clinical Trial Lead
CTM	Clinical Trial Monitor
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
DNA	Desoxyribonucleic acid
DRF	Dose-range finding
e.g.	*exempli gratia* (for example)
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electro-convulsive therapy
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EoTrial	End of trial
ES	Entered Set
ESR	Erythrocyte sedimentation rate
EU	European Union
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
GLP	Good Laboratory Practice
gMean	Geometric mean
GMP	Good Manufacturing Practice
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HPLC-MS/MS	High performance liquid chromatography tandem mass spectrometry
i.d.	Intradermal
i.v.	Intravenous

IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in safety testing
NIMH	National Institute of Mental Health
NOAEL	No observed adverse event level
p.o.	Oral
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PR	Pulse rate
PT	Preferred Term
QD	Once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event

SCR	Screening
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test product or treatment
TCPK	Trial Pharmacokineticist
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
TSTAT	Trial Statistician
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell count

1. INTRODUCTION

1.2 DRUG PROFILE

1.2.1 BI 1358894

1.2.1.1 Nonclinical pharmacology

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

The compound inhibits La3+ activated hTRPC5-channels with an IC50 of 0.2 nM. In addition the compound inhibits TRPC5 and TRPC4, respectively, after activation by Carbachol, with an the half maximal inhibitory concentration (IC_{50}) of 0.8 nM (hTRPC5) and 0.2 nM (hTRPC4).

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 central nervous system (CNS) [n00253725], cardiovascular [n00253723], [n00253727], [n00253734], renal and hepatic [n00253732], respiratory [n00253732], and gastrointestinal 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 rat study, long-lasting decreases in arterial blood pressure (10 mm Hg) were present at ≥10 mg/kg. Additionally, BI 1358894 induced dose-dependent and long-lasting increases in heart rate (15 – 20 b.p.m.) 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 Chinese hamster ovary (CHO) cells 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 Single dose toxicity

No single dose toxicity assessments have been conducted with BI 1358894. Relevant information was obtained from the repeat-dose toxicity studies in mice, rats, and dogs. The maximum tolerated dose was considered to be above 2000 mg/kg in rodents, the highest tested dose. In dogs, oral administration of 500 mg/kg was discontinued after 11 days due to prominent clinical signs. Systemic drug exposure at that dose level was 385-fold for C_{max} and 596-fold for AUC_{0-24h} compared to predicted therapeutic exposure (please see Section 5.3.9 of the Investigator's Brochure [c10354149].

1.2.1.3.2 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 count (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 dose-range finding (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: 1.2.1.3.2: 1 below. The comparison revealed safety margins of ≥9 for C_{max} and for $AUC_{0\text{-}24h}$.

Table: 1.2.1.3.2: 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 $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24h}$
Rat	30	1960 / 3600	26300 / 53900	9 / 17	9 / 19
Rat	7.5	913 / 1440	9439 / 13600	4 / 7	3 / 5
Dog	30	7190 / 4240	137000 / 57300	34 / 20	49 / 20

Predicted human C_{max}: 210 nM, predicted human AUC0-24: 2800 nM.h

1.2.1.3.3 Genotoxicity

The genotoxic potential of BI 1358894 was investigated in an ICH-compliant test battery of in vitro and in vivo studies (for details see Section 5.3.9 of the Investigator's Brochure, [c10354149]. There was no evidence that BI 1358894 is associated with genotoxic activity.

1.2.1.3.4 Reproductive and developmental toxicity

In preliminary studies on embryofoetal development, BI 1358894 was well tolerated in pregnant rats and had no effect on embryofoetal viability, but caused overt maternal toxicity

and embryofoetal lethality at all dose levels tested in rabbits. These effects in rabbits occurred at BI 1358894 plasma levels in the range or at low multiples of estimated efficacious human levels. The poor tolerability of BI 1358894 in rabbits is considered to be related to their known sensitivity to disturbances of the alimentary tract and the embryofoetal lethality as a sequel thereof.
There was no indication from the pivotal (GLP) 4-week toxicity studies in rats and dogs that oral administration of BI 1358894 was associated with morphological changes in reproductive organs of both sexes.

1.2.1.3.5 Phototoxicity

BI 1358894 is unlikely to cause phototoxicity. BI 1358894 did not induce any cytotoxic effect in the in vitro 3T3 NRU phototoxicity test.

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.

Metabolism

The in vitro metabolism of [^{14}C]BI 1358894 was investigated by the use of human liver microsomes, S9 supernatant, cytosol, expressed CYP, UDP-glucuronosyl transferase, aldehyde oxidase, and alcohol dehydrogenase (ADH) enzymes and human hepatocytes [n00258719]. Metabolites were identified by HPLC-MS/MS analysis.

Metabolite M700(1) (BI 1358894-glucuronide) and metabolite M538(1) (BI 1361608) were the predominant metabolites formed in human hepatocytes. Only low amounts of additional metabolites M540(2) and M538(2) were observed. These metabolites were formed at amounts close to the lower limit of the linear detection range. The aldehyde structured intermediate metabolite M522(1) (BI 1361575) was not observed in experiments with human hepatocytes but was found only during in vitro incubations in the absence of cytosolic enzyme sources.

Metabolites in safety testing (MIST) relevant metabolites found in human hepatocytes were also found in rat in vivo, therefore the potential for disproportionate human metabolites was considered to be low [R17-0660].

In order to obtain in vivo information on the metabolic pathways and the routes of excretion the metabolism of BI 1358894 was investigated at a dose of 0.5 mg/kg (i.v.) and 1 mg/kg (p.o./i.d.) in male and female Sprague Dawley rats [n00261794].

After intravenous (i.v.) and oral (p.o.) administration of [^{14}C]BI 1358894, 0.8% and 0.6% of drug-related radioactivity was excreted with urine within 0 – 24 h and the bulk of the radioactivity (about 80%-90%) was excreted with faeces within 0 - 168 h.
Neither BI 1358894 nor a metabolite was excreted > 0.5% of dose in urine. In faeces, the most abundant metabolite was generated by oxidation of the alcohol group to carboxylic acid M538(1) (BI 1361608) which is also present in bile. Great amount of radioactivity was eliminated via faeces as the hydroxylated metabolite M540(1) and N-demethylated M510(1). Lower amounts, about 5% in faeces, were eliminated as parent compound, the hydrogenated and twofold hydroxylated metabolite M558(1) and the both N-methylated metabolites M524(2) and M686(1) which were also detected in bile samples. M542(2) was further oxidated to the carboxylic acid and M686(1) was a glucuronide conjugate. Metabolites which were exclusively found in bile samples were the glucuronide of the parent compound M700(1) and the hydroxylated and further glucuronidated conjugate M716(1). First hydroxylated followed by a glutathione conjugation was the metabolite M847(1) and two additionally metabolites were M689(1) (+$C_4H_{11}O_2N_3S$) and M647(1) (+$CH_5O_2N_3S$).

The main metabolite in plasma, in addition to parent compound, was M538(1) (BI 1361608). In smaller amounts present were the N-demethylated metabolite M510(1), the hydroxylated metabolite M540(2) and the twofold hydroxylated and hydrogenated metabolite M558(1). Two radioactive peak fractions of about 1% could not be assigned. Those were defined as m1 and m2.

Relevant differences of metabolite pattern in plasma, urine, faeces and bile related to application route were not observed. However, the metabolite pattern in faeces and bile showed a higher prevalence of oxidation to the carboxylic acid M538(1) versus demethylation to M510(1) in male compared to female rats.

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 K_i 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 K_i 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 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 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

An FIH (first-in-human) trial [Trial 1402-0001; c13880029] is currently being conducted to explore the safety, tolerability, and pharmacokinetics (PK) of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and to evaluate the effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over design).
The single-rising dose (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 SAEs or dose limiting AEs.
Furthermore, BI 1358894 has been tested in 20 subjects with and without a high calorie, high fat breakfast to evaluate the effect of food on its relative bioavailability (food effect [FE] part: 8 subjects at 50 mg, 12 subjects at 100 mg).

Adverse events

There were no adverse events (AEs) considered to be dose limiting and no serious adverse events (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.

- 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.

- 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.

- 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).

- 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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥3-fold upper limit of normal (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 were considered as chance findings and not drug related.

Additional Safety Assessments

There were no clinically relevant changes of lab values. In particular there were no changes of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) suggesting an inflammatory event.

Explorative analysis of the Bowdle-Visual Analogue Scale (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 Columbia suicide severity rating scale (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 / 34 h 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 study site. 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 pre-specified criteria of the trial protocol orthostatic testing did not reveal a subject with a positive test after dosing, i.e. no reduction in systolic BP of ≥20 mm Hg or in diastolic BP of ≥10 mm Hg 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– 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)

Pharmacokinetics

Following oral administration of film coated tablets in fasted state (SRD part, doses 3 mg to 200 mg), BI 1358894 reached maximum plasma concentrations between 1 and 5 hours (median t_{max}). C_{max}, AUC_{0-24}, AUC_{0-72} and $AUC_{0-\infty}$ increased dependent on dose. However, preliminary statistical analysis of dose proportionality indicates a less than dose-proportional increase in exposure of BI 1358894 formulated as tablet and administered in fasted state over the tested dose range from 3 mg to 200 mg.

Within the Food Effect part of the study, BI 1358894 was administered under fasted conditions and after a high-fat, high-caloric breakfast in a 2-way-crossover design.
A positive food effect (based on AUC and C_{max}, see Table 1.2.1.5: 4) was observed when BI 1358894 was administered as tablet after a high calorie, high fat breakfast in comparison to fasted state. An increase of about a factor of 1.6 was observed at the 50 mg dose whereas an increase of a factor of about 2.5 was observed after 100 mg between fasted and fed state.

After reaching C_{max}, BI 1358894 plasma concentrations declined in a multiphasic fashion implying multicompartmental distribution and exhibited a long terminal phase, which seems to be dose-independent.

The apparent terminal half-life ($t_{1/2}$) after oral dosing was calculated based on available data until 192 h after administration. Considering the last 3 time points for determination of λ_z (and dependent parameters) and extrapolation (96 h to 192 h planned sampling times, all doses apart from 3 mg DG), the percentage of extrapolation beyond the last measured time point was between 2.75% and 26.0% (only 4 subjects above 20%). The resulting $t_{1/2}$ (gMean) was between 50.2 and 74.4 hours. The gMean of mean residence time after oral dosing (MRT_{po}) was between 54.8 and 82.5 hours. $t_{1/2}$ and MRT_{po} appear to be independent of dose based on PK data of BI 1358894 after a single dose oral administration (Table 1.2.1.5: 3 and Table 1.2.1.5: 4).

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 Without #135[2]	fasted
	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)
$AUC_{0-\infty}$ [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)
$t_{1/2}$	46.6* (31.9)	53.1 (14.4)	58.5 (11.5)	60.6 (18.7)	58.4 (13.3)	50.2 (28.0)	54.0 (23.7)	60.2 (39.6)
MRT_{po}	51.5* (33.1)	54.8 (21.2)	61.2 (24.0)	66.9 (16.0)	67.3 (15.1)	66.3 (26.7)	71.3 (21.7)	76.4 (23.8)

[1] t_{max} 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 %) non-compartmental 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 1402.1]

Dose [mg]/ condition	**50 mg**	**50 mg**	**100 mg**	**100 mg**
	Fasted N=8	Fed N=8	Fasted N=12	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)
$AUC_{0-\infty}$ [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)
$t_{1/2}$	71.2 (24.7)	74.4 (27.7)	68.9 (34.6)*	66.7 (25.8)
MRT_{po}	82.5 (24.1)	76.7 (35.9)	78.8 (30.8)*	70.1 (29.4)

[1] t_{max} median (range), D Dose-normalized
* N=11 due to drop out of subject , PK samples of this subject up to 96 hours available only

1.2.1.6 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 1358894 profile, please refer to the current IB [c10354149].

1.2.2 Itraconazole

Absorption of itraconazole solution is fast with maximum plasma concentration being reached within 2.5 h after oral administration in fasting condition. Bioavailability of itraconazole liquid is increased by 30% when given under fasting condition compared to administration together with food [R18-2644]. Mean peak plasma concentrations were 547.7 ng/mL after a single dose of 200 mg itraconazole solution (fasting) and 1965 ng/mL after 15 days of daily treatment with 200 mg itraconazole (solution, fasting). Kinetics of

itraconazole are non-linear. The half-life of itraconazole after multiple doses of 200 mg once daily with solution formulation was about 40 h [R17-3742].

In the liver, itraconazole is metabolised extensively to more than 30 metabolites [R17-3743]. Its main metabolite, OH-itraconazole, accounts for about twice the amount of plasma itraconazole at trough. It has been shown in vitro that CYP3A4 is mainly responsible for the formation of this metabolite [R18-2643]. FDA classifies itraconazole as strong index inhibitor of CYP3A and as inhibitor of P-glycoprotein [R18-0241]. However, not only itraconazole contributes to the in vivo inhibition of CYP3A observed after itraconazole administration but also three of its metabolites (OH-itraconazole, keto-itraconazole and N-desalkyl-itraconazole) [R10-1102].
For a more detailed description of itraconazole please refer to the SmPC [R18-2643].

1.2.3 Residual effect period

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

For the use of itraconazole in this trial, the REP is defined as 6 days.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Results from nonclinical studies indicate that BI 1358894 is metabolized by CYP3A4.

This clinical trial will be performed to investigate the effect of multiple doses of itraconazole on the pharmacokinetics (PK) of a single dose of BI 1358894 in order to assess if and to which extent the PK of BI 1358894 are affected by co-administration of a drug that inhibits CYP3A and P-glycoprotein.

Itraconazole is chosen for this trial as perpetrator drug, as this drug is recommended as strong inhibitor of CYP3A by EMA [P15-06991], as strong index inhibitor of CYP3A and inhibitor of P-glycoprotein by FDA [R18-0241], and as strong inhibitor of CYP3A and typical inhibitor of P-glycoprotein by PMDA [P15-06298]. Moreover, safety and tolerability of itraconazole were acceptable in previous drug-drug interaction trials [c02336088], [c03355329], [c08928447].

1.4 BENEFIT - RISK ASSESSMENT

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

1.4.1 Procedure-related risks

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

ECG electrodes may cause local and typically transient skin reactions.

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

1.4.2.1 Risks related to BI 1358894

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

Risks derived from observations in non-clinical studies

Rats and dogs were employed as the animal species for general toxicology investigations on BI 1358894, because in vitro and in vivo profiling supported the suitability of both species for nonclinical safety profiling of BI 1358894.
As summarised in 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 cardiovascular effects observed in rodents and non-rodents can be easily monitored in a Phase I study (cardiovascular 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.

Mode of action and nature of the target

The transient receptor potential (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. Preclinically, 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.

Relevance of animal models

Human TRPC4 and TRPC5 proteins show high homology with the rat, mouse, and dog proteins and the potency of BI 1358894 to the target is comparable across species. In addition, expression at the protein level is similar across different species, including human. Rat and dog had good oral bioavailability, significant systemic exposure, and good tolerability after oral dosing of a nanosuspension of BI 1358894. Finally, all known metabolites formed after incubation of human hepatocytes with BI 1358894 were covered with the combination of rat and dog. Overall, pharmacodynamic activity, PK, and metabolism all indicate that rat and dog were suitable species for nonclinical safety profiling of BI 1358894.

It should be highlighted that toxicity study in rats [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.

1.4.2.2 Risks related to itraconazole

Multiple dosing of 200 mg itraconazole up to 15 days was of acceptable tolerability in healthy subjects [c02336088], [c03355329], [c08928447], [R17-3742].

1.4.2.3 Risks related to the potential drug-drug interaction between itraconazole and BI 1358894

It is likely that concomitant administration of BI 1358894 with itraconazole may cause an increase of plasma concentrations and $t_{1/2}$ of BI 1358894 (see Section 1.2.1.4).
Therefore, a low dose of 10 mg BI 1358894 has been selected for this trial.

Doses of up to 200 mg BI 1358894 in fasted state, and of 50 and 100 mg in fed state had been shown to be safe and well-tolerated in the FIH trial 1402-0001. C_{max}, AUC_{0-24}, AUC_{0-72} and $AUC_{0-\infty}$ increased dependent on dose, and a higher bioavailability of BI 1358894 was observed when given together with food.
Thus, with a dose of 10 mg BI 1358894 administered in fasted or fed state, even in case of substantial increases of BI 1358894 plasma concentrations by itraconazole, the safety margin was assessed to be sufficient for the current trial.

1.4.2.4 Risk minimisation (safety precautions)

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

- Careful dose selection
- An extensive safety laboratory will be performed with special focus on full blood exam (see Flow Chart).
- Repeated triplet 12-lead ECGs are scheduled throughout the study.
- Blood pressure and heart rate will be closely monitored (see Flow Chart).
- Adequate safety monitoring will be performed (e.g. vital signs including blood pressure, pulse rate), ECGs, safety laboratory tests including CRP, ESR, hormone parameters, suicidality, and assessment of adverse events).
- Subjects will be hospitalised in each treatment period from Day -1 (treatment with oral dose of BI 1358894) to Day 4 and will be discharged only after a formal assessment and confirmation of fitness by an investigator or qualified designee. The hospitalisation may be extended at the investigator's discretion.
- During the in-house stay, the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Only male subjects will be enrolled in this study.
- In order to address the risk of hepatotoxicity, only subjects with normal liver enzyme values will be included into the study (see Section 3.3.3), criterion 3.
- Safety laboratory parameters will be monitored closely. An individual subject will be removed from the trial if the subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample, (see Section 3.3.4.1). Further, most of the reported cases of serious hepatotoxicity during itraconazole treatment occurred in patients that suffered from concomitant liver diseases, had other significant diseases, or took concomitant hepatotoxic drugs. Subjects with liver diseases or a medical history of drug induced liver failure are excluded from trial participation (Section 3.3.3), criteria 5 and 25.

1.4.2.5 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 assessment of benefit-risk ratio

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

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 BI 1358894 in plasma when given as oral single dose together with multiple oral doses of itraconazole (Test, T) as compared to when given alone as oral single dose (Reference, R).

2.1.2 Primary endpoints

The following PK parameters will be determined for BI 1358894:

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

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

2.1.3 Secondary endpoint

The following PK parameter will be determined for BI 1358894:

- 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)

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1358894 will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, two-treatment, two-period, fixed sequence trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be one oral single dose of 10 mg BI 1358894 as tablet formulation (tablet strength: 5 mg) together with multiple oral doses of 200 mg itraconazole as oral solution formulation (concentration: 10 mg/ml) (T) and one oral single dose of 10 mg BI 1358894 as tablet formulation (tablet strength: 5 mg) given alone (R).

The trial design is shown in Figure 3.1: 1.

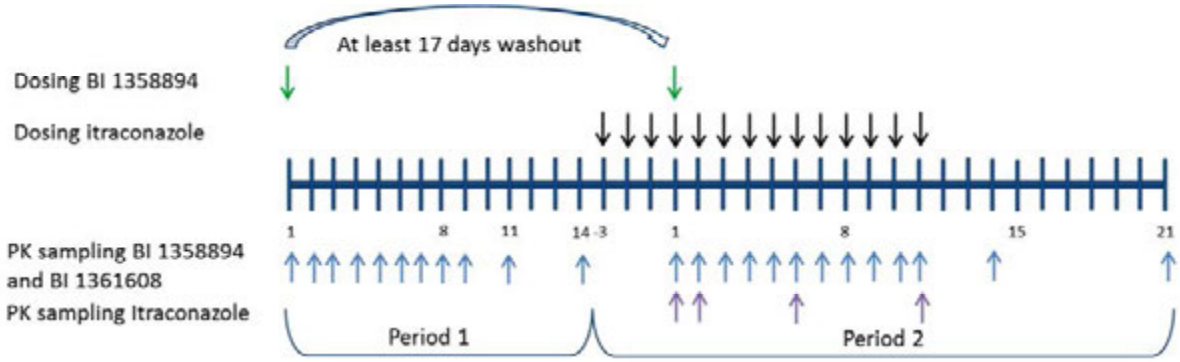

Figure 3.1: 1: Overview of trial design

In both treatments, BI 1358894 is administered after a high-fat, high-caloric breakfast. Itraconazole will be administered in the fasted state.

In the first treatment period (Period 1, Visit 2), all subjects are planned to undergo treatment R, and in the second treatment period (Period 2, Visit 3), all subjects are planned to undergo treatment T. For details, refer to Section 4.1.

There will be a washout period of at least 17 days between the administrations of BI 1358894.

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 GROUP(S)

For relative bioavailability / bioequivalence trials, the crossover design is preferred because of its efficiency: since each subject serves as his/her own control, the comparison between formulations/treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations/treatments [R94-1529].

Because of the long half-life of itraconazole (about 40 hours) and its metabolites and the unknown effect of itraconazole on the half-life of BI 1358894 , a fixed sequence design was selected, with administration of itraconazole in the second study period only. This design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration. For itraconazole studies, this design is recommended by the Innovation and Quality in Pharmaceutical Development's Clinical Pharmacology Leadership Group (CPLG) [R17-3744].

For this PK drug-drug interaction trial, open-label treatment is acceptable, because the primary and secondary endpoints of this trial are PK endpoints derived from measurement of plasma concentrations of BI 135994 and metabolites. These endpoints are not expected to be affected by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because for the purpose of this trial, male healthy volunteers are standard.

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 45 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. Willingness to comply with contraception requirements. Subjects who are sexually active must use adequate contraception with their female partner throughout the study and until 1 month after the last administration of trial medication. Adequate methods are:
   - Sexual abstinence or
   - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success) or

- Surgical sterilisation (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner or

- The use of condoms, if the female partner uses an adequate contraception method in addition, e.g., intrauterine device (IUD), hormonal contraception (e.g. implants, injectables, combined oral or vaginal contraceptives) that started at least 2 months prior to first drug administration, or barrier method (e.g. diaphragm with spermicide)

Unprotected sexual intercourse with a female partner is not allowed throughout the study and until 1 month after the last administration of trial medication.

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) 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. CRP > ULN, 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 or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medications or their excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 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 in males) 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
23. Persons who are committed to an institution by way of official or juridical order will not be enrolled in the study

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

24. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
25. 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)
26. Any history of drug-induced liver failure.
27. History of ventricular dysfunction or congestive heart failure.

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 1.2.3) 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, 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 pregnancy, surgery, adverse events [AEs], or diseases)
5. 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 Investigator Site File (ISF)
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 shows a raised CRP level of >3.00 mg/dL or an ESR of ≥20 mm/h
8. The subject experiences a serious' adverse reaction which is considered at least possibly related to the Investigational Medicinal Product (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 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 (BI) 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 1 drug-related SAE is reported

3. Violation of Good Clinical Practice (GCP), or the clinical trial protocol (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 events considered as drug-related by the investigator in 2 subjects

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 do not complete the trial, the Clinical Trial Lead (CTL) together with the Trial Pharmacokineticist (TCPK) and the Trial Statistician (TSTAT) are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 1358894 has been manufactured by BI Pharma GmbH & Co. KG. Itraconazole oral solution will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the two test products are given below:

Test product 1

Substance:	BI 1358894
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	5 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	1 day (in treatments R and T)

Test product 2

Name:	Sempera® 10 mg/ml oral solution
Substance:	Itraconazole
Pharmaceutical formulation:	Oral solution
Source:	Public pharmacy (obtained by the clinical site)
Holder of marketing authorisation:	Janssen-Cilag GmbH, Neuss, Germany
Unit strength:	10 mg/ml
Posology:	20 ml-0-0
Route of administration:	oral
Duration of use:	14 days (in treatment T only)

4.1.2 Selection of doses in the trial and dose modifications

Perpetrator (itraconazole)

The dose of itraconazole selected for this trial reflects standard clinical doses, is considered sufficient to yield significant CYP3A inhibition and has been used successfully and safely in previous drug-drug interaction trials [c02336088], [c03355329], [c08928447].

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, two-treatment, fixed sequence study. Each subject will be allocated to the same treatment sequence (R-T, see Flow Chart). Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. For safety margin to exposure reached in previous SRD trial 1402-0001 refer to Section 1.4.2.3 and for discussion of study-associated risks and safety measures see Section 1.4.3).

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a two-treatment, two-period, fixed sequence study. All subjects will receive the 2 treatments in fixed 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 period	Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
1	R (Reference)	BI 1358894	Tablet	5 mg	2 tablets on Day 1	10 mg
2	T (Test)	BI 1358894	Tablet	5 mg	2 tablets on Day 1	10 mg
		Itraconazole	Oral solution	10 mg/ml	20 ml (200 mg) on Days -3 to 11	2800 mg

Administration of itraconazole will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing of itraconazole on Day 1 of Period 2 (coadministration of BI 1358894), and on Days 2 to 11 (itraconazole alone) fasting from at least 6 h before until 1 h after intake of itraconazole.

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 each treatment period, a high-fat, high-calorie meal will be served 30 min before BI 1358894 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 administration of BI 1358894. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), except for medical reasons or for recording of 12-lead ECG and vital signs measurements.

The treatments will be separated by a wash-out phase of at least 17 days between BI 1358894 administrations.

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.

4.1.6 Packaging, labelling, and re-supply

BI 1358894 tablets will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice (GMP).

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.

<u>Itraconazole oral solution</u>

Itraconazole oral solution will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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, if the following requirements are fulfilled:

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

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 IMP 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 IMP received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator’s possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the trial clinical monitor. 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 AEs 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 1.2.1.2 and Section 1.4.2.1), 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 i.v. 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 AE 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

Acetylsalicylic acid or other drugs that may inhibit platelet aggregation or coagulation should be avoided during the entire study.

Known inhibitors/inducers of CYP3A and P-glycoprotein activity as well as drugs with a known hepatotoxicity profile should be avoided during the entire study.

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 BI 1358894 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 on PK profile days (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before until 24 h after each administration BI 1358894.

Barbecued meat and broccoli should be avoided during the trial.

Smoking is not allowed from 24 h before until 24 h after each administration of BI 1358894.

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.

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre as medication will be administered by the investigator (or authorised 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

No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

Physical examination performed at screening and updated at end of trial examination includes general condition/psyche, skin, lymph nodes, head (eyes, ears, mouth), neck / thyroid gland, lungs, heart, abdomen, kidney, musculoskeletal system, neurological system, and vascular system.

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 (IntelliVue Patients Monitor MP70, Philips GmbH Market DACH, Hamburg, 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	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, absol.	X	X	X
	Reticulocytes/Erythrocyte	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/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time (aPTT)	X	X	X
	Prothrombin time – International Normalisation Ratio (INR)	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
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	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	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 (CRP) (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	Test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
	Calcium	X	X	X
	Phosphate (as Phosphorus, Inorganic)	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 Erythrocytes/hemoglobin	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) and at Visit 2 Day 1 (if screening had been earlier than 3 days prior)
B: parameters to be determined at Visit 2 on Days 2, 4, 9, 14 and at Visit 3 on Days 1, 2, 4, 9, 14 (for time points refer to Flow-Chart)
C: parameters to be determined at Visit 4 (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 Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis A antibodies (qualitative) Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) HIV-1 p24 antigen

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 6810 und 6820, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in 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 Diagnostika Nord: M10/14PDT-10 test, respectively, 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 Information 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 using the 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 questionnaires are shown in Appendix 10.1.

5.2.5.2 Medical examinations

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

At the end of trial examination, it will include review of AEs and concomitant therapies, vital signs, 12-lead ECG, laboratory tests, suicidality assessment (C-SSRS), and a physical examination including neurological examination with determination of weight.

5.2.5.3 Neurological examinations

As a general additional safety measure, a physical neurological examination will be performed at the time points specified in the 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 AEs. Case narratives may be written if necessary.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the 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 5.2.7.1, 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 5.2.7.1.1.

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 electronic data capture (eDC) system. 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

5.2.7 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 behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, 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 behaviour, 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 behaviour 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 behaviour 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 adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.7.1 Adverse event collection and reporting

5.2.7.1.1 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.

5.2.7.1.2 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.

5.2.7.1.3 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.

5.2.7.1.4 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 / time intervals 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 of BI 1358894 and

For quantification of analyte concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium 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.

The K_2-EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2,000 g to 4,000 g and at 4 to 8°C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma, the second aliquot will contain the remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 2 h, with interim storage of blood samples and aliquots on ice. The time each aliquot was placed in the freezer will be documented.

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

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time, and the analyte “BI 1358894”. Further information, such as matrix, may also be provided.

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

5.3.2.2 Blood sampling for determination of itraconazole

For quantification of itraconazole concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The K_2-EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented.

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

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

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

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte in plasma concentration

BI 1358894, and itraconazole 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.

5.4 BIOBANKING

Not applicable.

5.5 OTHER ASSESSMENTS

5.5.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a blood sample for pharmacogenomic testing will be taken from each subject. In case of unexplainable variability in pharmacokinetic or pharmacodynamic parameters, DNA might be extracted from these samples and used for exploratory analysis of variants of genes related to these parameters, such as genes involved in Absorption, Distribution, Metabolism and Excretion (ADME). It is not intended to include these data in the final report. However, the data may be part of the report if necessary.
All remaining samples will be destroyed no later than three years after the end of the trial.

Methods and timing of sample collection
One blood sample of at most 10 mL will be taken from an arm vein in a PAXgene blood DNA drawing tube on Visit 2 (Day 1). The blood sample has to be stored at a temperature of approximately -20°C or below. Once frozen, thawing of the samples should be avoided.

The sampling tubes will be labelled with study number, subject number, visit, time point, matrix, and "DNA pre-specified".

Frozen blood samples should be shipped on dry ice to:

5.5.1.1 Analytical determinations

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

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, 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' BI 1358894 administration on Day 1 of Period 1 are to be performed and completed within a 2 h-period prior to BI 1358894 administration.

Study measurements and assessments scheduled to occur 'before' itraconazole administration on Days -3 to -1 and 2 to 11 of Period 2 are to be performed and completed within a 2 h-period prior to itraconazole administration. Study measurements and assessments scheduled to occur 'before' BI 1358894 administration on Day 1 of Period 2 are to be performed and completed within a 1.0 h-period prior to itraconazole administration.

In visits 2 and 3, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 45 min on Day 1, ± 60 min on Day 2, and ± 120 min from Day 3 onwards.

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

For planned 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. Starting from 48 hours after BI 1358894 administration (and beyond), a time window of ± 120 min will be allowed for pharmacokinetic blood sampling times.

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 and run-in period(s)

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 5.2.4.

6.2.2 Treatment period(s)

Each subject is expected to participate in 2 treatment periods.

Genotyping will be performed (for details, see Section 5.5.1).

If screening had been earlier than 3 days prior to Day 1 of Visit 2, safety laboratory panel A will be repeated on that day.

At least 17 days will separate administrations of BI 1358894 in the first and second treatment periods.

On Day -1 of each 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 all other study days, subjects will be treated in an ambulatory fashion.

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

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

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

- Onset after medication intake (hh: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 accompanying 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)

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 5.2.2 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 BI 1358894 in plasma when given as oral single dose together with multiple oral doses of itraconazole (Test, T) compared to when given alone as oral single dose (Reference, R) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial will be conducted as a two-treatment, two-period, fixed sequence design, which allows intra-subject comparisons. It will be evaluated statistically by use of a linear model for logarithmically transformed primary and secondary PK endpoints.

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 BI 1358894 in plasma when given with multiple oral doses of itraconazole (T) vs. single oral dose of BI 1358894 alone (R) will be estimated by the ratios of the geometric means (T/R), 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:

- Entered Set (ES): The Entered Set includes all subjects who entered the trial, i.e. who have been assigned to a subject number whether treated or not.
- Treated set (TS): The Treated Set includes all subjects of the Entered Set who were 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.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the Integrated Quality Risk Management Plan (IQRMP), IPDs will be identified no later than in the Blinded Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Sections 2.1 and 2.2 for drug BI 1358894 or will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Further PK parameters may be calculated if considered appropriate.

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 pre-dose 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 'subject' and 'treatment'. The 'subject' effect will be considered as random, whereas the 'treatment' effect will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + \tau_k + s_m + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n

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

e_{km} = the random error associated with the m^{th} subject who received treatment k.

where $s_m \sim N(0, \sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and s_m, e_{km} are independent random variables. The indices 'B' and 'W' correspond to 'between' and 'within' variability, respectively.

Point estimates for the ratios of the geometric means (T/R) for the primary endpoints (see Section 2.1) 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 endpoint (refer to Section 2.1.3) 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 intake of BI 1358894 until end of residual effect period (14 days) in period 1 are attributed to the treatment interval “BI 1358894 alone”. Events after the residual effect period of BI 1358894 but prior to first intake of itraconazole will be assigned to “BI 1358894 follow-up”. Events between first intake of itraconazole in period 2 and administration of BI 1358894 in period 2 are attributed to the treatment interval “itraconazole alone” and those occurring between treatment with BI 1358894 and itraconazole in period 2 and end of residual effect period of itraconazole (6 days) after last intake of itraconazole or end of residual effect period of BI 1358894 (14 days) after BI 1358894 intake, whatever occurs first, are attributed to the treatment interval “BI 1358894 + itraconazole”. Events after the treatment interval “BI 1358894 + itraconazole” but before trial termination date are assigned to “BI 1358894 + itraconazole follow-up”. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the individual subject’s end of trial 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.

Relevant ECG findings and relevant findings from neurological examinations during the trial will be reported as AEs.

7.4 INTERIM ANALYSES

A preliminary, exploratory analysis of the PK parameters ($AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max} of BI 1358894) may be performed based on all evaluable data after last subject out and prior to data base lock. This may be necessary, e. g., in case the information is needed to inform other activities during the development of BI 1358894 such as concomitant treatment restrictions in other studies. In contrast to the final pharmacokinetic calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. Results will be provided as individual values and geometric means as well as the adjusted gMean ratios determined according to the planned primary analysis described in Section 7.3.1. The preliminary, exploratory results will be distributed to the trial team.

No formal preliminary PK report will be written.

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

In this trial all subjects receive both treatments in the same order, thus, no randomisation for the treatment assignment is performed (see also Section 4.1.3).The sponsor will arrange for the packaging and labelling of BI 1358894 trial medication.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (T/R) can be expected with 95% tolerance 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.

The observed intra-individual coefficient of variation (gCV) for BI 1358894 in previous trial 1402-0001 [c10354149] was about 13%-73% for C_{max} and 20%-45% for $AUC_{0-\infty}$. Based on the data obtained in trial 1402-0001 under fasted and fed conditions, sample size estimations were performed assuming %CV of 25% to 35%.

For various assumptions around the gCV of 30% and different samples sizes N=12 and 16 Table 7.7: 1 provides and overview of the achievable precision for estimating the ratio of geometric means (T/R). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios of geometric means (T/R).

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs (N=12 and 16)

N	gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
12	25.000	1.273	100.000	78.550	127.307
12	25.000	1.273	130.000	102.116	165.499
12	25.000	1.273	150.000	117.826	190.960
12	30.000	1.334	100.000	74.988	133.355
12	30.000	1.334	130.000	97.484	173.362
12	30.000	1.334	150.000	112.481	200.033
12	35.000	1.396	100.000	71.654	139.560
12	35.000	1.396	130.000	93.150	181.428
12	35.000	1.396	150.000	107.481	209.340
16	25.000	1.218	100.000	82.119	121.774

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs (N=12 and 16) (cont.)

N	gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
16	25.000	1.218	130.000	106.755	158.306
16	25.000	1.218	150.000	123.179	182.661
16	30.000	1.265	100.000	79.067	126.475
16	30.000	1.265	130.000	102.787	164.417
16	30.000	1.265	150.000	118.601	189.712
16	35.000	1.313	100.000	76.187	131.256
16	35.000	1.313	130.000	99.043	170.633
16	35.000	1.313	150.000	114.280	196.884

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

Assuming a gCV of 25% and given a sample size of 16 subjects the precision of the two-sided 90% confidence interval of the geometric mean ratio will be approximately 1.218 If only 12 patients will be evaluable in both periods, the precision would still be approximately 1.273.

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

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

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 3.5.1.

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), 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 a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to 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. 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, storage 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 (e.g, biomarker proposal, analysis plan and report) ensures compliant usage
- If applicable, 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.

BI has appointed a Clinical Trial Lead, 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 Monitors (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 and concentrations in plasma will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany or by a specialised contract research organisation appointed by BI.

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

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P06-11895 Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163(11):1905-1917.

P15-06298 Ministry of Health, Labour and Welfare. Drug interaction guideline for drug development and labeling recommendations (draft). http://www.solvobiotech.com/documents/Japanese_DDI_guideline_(draft)_2014Jan.pdf (access date: 22 June 2015) ; Ministry of Health, Labour and Welfare (2014).

P15-06991 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions (21 June 2012, CPMP/EWP/560/95/rev. 1 corr. 2). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 8 July 2015) ; London: European Medicines Agency (EMA) (2012).

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

R06-2872 Trivedi MH, Rush AJ, Wisniewski SR, et al. Factors associated with health-elated quality of life among outpatients with major depressive disorder: a STAR*D report. J Clin Psychiatry 2006;67(2):185-195.

R10-1102 Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL, Isoherranen N. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. Clin Pharmacol Ther 83 (1), 77 - 85 (2008).

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

R15-3888 Riccio A, Li Y, Moon J, Kim KS, Smith KS, Rudolph U, Gapon S, Yao GL, Tsvetkov E, Rodig SJ, Veer A van't, Meloni EG, Carlezon WA, Bolshakov VY, Clapham DE. Essential role for TRPC5 in amygdala function and fear-related behavior. Cell 2009;137(4):761-772.

R16-5350 Fowler MA, Sidiropoulou K, Ozkan ED, Phillips CW, Cooper DC. Corticolimbic expression of TRPC4 and TRPC5 channels in the rodent brain. Plos One 2007;2(6):e573.

R16-5472 Koenigsberg HW, Denny BT, Fan J, Liu X, Guerreri S, Mayson SJ, et al. The neural correlates of anomalous habituation to negative emotional pictures in borderline and avoidant personality disorder patients. Am J Psychiatry 2014; 171(1):82-9.

R16-5473 Mandell D, Siegle G, Shutt L, Feldmiller J, Thase ME. Neural substrates of trait ruminations in depression. J Abnorm Psychol 2014;123(1):35-48.

R16-5474 IsHak WW, Elbau I, Ismail A, Delaloye S, Ha K, Bolotaulo NI, et al. Quality of life in borderline personality disorder. Harvard Rev Psychiatry 2013;21(3): 138-150.

R16-5475 McClintock SM, Husain MM, Wisniewski SR, Nierenberg AA, Stewart JW, Trivedi MH, et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. J Clin Psychopharmacol 2011;31(2): 180-186.

R16-5476 Links PS, Heslegrave R, Reekum R van. Prospective follow-up study of borderline personality disorder: prognosis, prediction of outcome, and axis II comorbidity. Can J Psychiatry 1998;43(3):265-270.

R16-5477 Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. Biol Psychiatry 2002;51(12):951-963.

R16-5483 Ellison WD, Rosenstein L, Chelminski I, Dalrymple K, Zimmerman M. The clinical significance of single features of borderline personality disorder: anger, affective instability, impulsivity, and chronic emptiness in psychiatric outpatients. J Personal Disord 2016;30(2):261-270.

R17-0660 Safety testing of drug metabolites: guidance for industry (November 2016, pharmacology/toxicology, revision 1). https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guid ances/ucm079266.pdf (access date: 22 February 2017) ; U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2016.

R17-3742 Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy 18 (2), 295 - 301 (1998).

R17-3743 Willems L, Geest R van der, Beule K de. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J Clin Pharm Ther 26, 159 - 169 (2001).

R17-3744 Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. J Clin Pharmacol 56 (2), 143 - 151 (2016)

R18-0241 Guidance for industry: clinical drug interaction studies - study design, data analysis, and clinical implications (draft guidance, this guidance document is being distributed for comment purposes only) (October 2017, clinical pharmacology). https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf (access date: 19 January 2018); Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2017).

R18-0249 Minke B. The history of the Drosophila TRP channel: The birth of a new channel superfamily. 2010;24(4):216-233.

R18-2643 Sporanox 10 mg/ml oral solution (Janssen-Cilag) (summary of product characteristics, updated 01-Mar-2018). https://www.medicines.org.uk/emc/product/1522/smpc/print (access date: 14 August 2018); 2018.

R18-2644 Sempera Liquid 10 mg/ml, Loesung zum Einnehmen (Janssen-Cilag) (Fachinformation, Stand der Information: Dezember 2017).

R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

9.2 UNPUBLISHED REFERENCES

c02336088 Relative bioavailability of a single oral dose of BI 691751 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, randomised, two-period, two-sequence crossover study). 1334.10. 09 Jan 2015.

c03355329 Relative bioavailability of a single oral dose of BI 425809 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, two-period, fixed-sequence trial) 1346.10. 03 Dec 2015.

c08928447 Effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1026706 in healthy male subjects (an open-label, randomised, two-period, two-sequence crossover study) 1320.20. 29 Sep 2016.

c10354149 Investigator's brochure BI 1358894 in Major Depressive Disorder and Borderline Personality Disorder. 23 November 2018.

c13880029 Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way crossover. Trial 1402.1. 21 Dec 2017.

n00248384 Selectivity Test of BI 1358894 on TRPV1, TRPV3, TRPM8, TRPC6, TRPA1, hERG, Kv1.3, Cav1.2, Nav1.2, Nav1.7 and Nav1.5. Report #: 155. 20 January 2016.

n00250347 BI 1358894: 4-week oral (gavage) toxicity study in Sprague Dawley rats. 16B024. 04 July 2017.

n00252179 Selectivity/ Safety Pharmacology of HC-122608. Report #: 154. 06 September 2012.

n00252207 Effects of HC-122608 on mouse marble burying. Report #: 213. 18 June 2013.

n00252277 Effect of HC-122608 in the mouse elevated plus maze. Report #: 168. 16 January 2013.

n00252628 . [14C]BI 1358894: Distribution Study in the Male Pigmented Rat. HG96MB. 27 September 2016.

n00252903 Effect of BI 1358894 in the mouse forced swimming test. 05 October 2016.

n00253490 Cytochrome P450 Inducibility in SD rat hepatocytes – Effect on in vitro clearance. 18 November 2016.

n00253492 BI 1358894: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions. 8 November 2016.

n00253628 Prediction of BI 1358894 Pharmacokinetics and Therapeutic Dose in Human. 06 December 2016

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.

n00253725 Effects of BI 1358894 on behavior assessed by observation of nocturnal activity or in a modified IRWIN-test after oral administration of 10, 30 and 100 mg/kg. GP2014/0271/0272/PH3. 29 November 2016.

n00253727 Influence of BI 1358894 (10, 30 and 100 mg/kg PO) on hemodynamic and electrocardiographic parameters in conscious dogs. GP2014/0269/PH5. 29 November 2016.

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.

n00253734 Partial validation of an LC-MS/MS method for the quantification of BI 1072668 in rat plasma, calibration range 5.00 - 25000 nmol/L. 16B133. 09 February 2017.

n00253752 Selectivity test of HC-122608 on TRPV1, TRPV3, TRPM8, TRPC6, TRPA1, hERG, $K_v1.3$, $Ca_v1.2$, $Na_v1.2$, $Na_v1.7$ and $Na_v1.5$. Report #: 155. 11 January 2013.

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

n00258719 Investigations on the in vitro metabolism of [14C]BI 1358894 and assessment of the human cytochrome P450 enzymes that are involved. 7 November 2017.

n00261794 Metabolism of BI 1358894 in rats. 28 May 2018.

10. APPENDICES

10.1 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

10.1.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

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

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS.1_eng-USorl.doc

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 __ 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 X 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	___	___

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
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 _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**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 _____	**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 _____	**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** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**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* _____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 2 of 2

10.1.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit

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

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

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	___

 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

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* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		21 Feb 2019
EudraCT number		2018-004274-10
BI Trial number		1402-0007
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence 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, Section 1.4.2.4, Section 6.2.2 2. Section 3.3.3 3. Section 3.3.4.3 4. Section 4.2.2.2 5. Flowchart and Section 5.2.3 6. Section 8
Description of change		1. Hospitalisation phase extended to 72 h, safety laboratory added 2. Exclusion criteria no. 23 added. 3. Discontinuation criteria added. 4. Smoking restrictions updated due to longer in-house confinement. 5. Panel B of safety laboratory markers extended by additional markers and time points in the flowchart. 6. Reference to EU regulation 536/2014 deleted.
Rationale for change		All changes were done based on the request of regulatory authorities.In addition, typos throughout the document were corrected.

11.2 GLOBAL AMENDMENT 2

Date of amendment		27 March 2019
EudraCT number		2018-004274-10
BI Trial number		1402-0007
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence 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, 2. Section 6.2.2
Description of change		1. Adaptation of planned time at Day -3,- 2 and -1 2. Insertion of the intensity measurement for headaches
Rationale for change		In addition, typos and inconsistencies throughout the document were corrected.

APPROVAL / SIGNATURE PAGE

Document Number: c25796375 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-2

Title: Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		27 Mar 2019 16:39 CET
Author-Trial Clinical Pharmacokineticist		27 Mar 2019 17:09 CET
Author-Trial Statistician		28 Mar 2019 09:28 CET
Verification-Paper Signature Completion		28 Mar 2019 14:32 CET
Approval-Team Member Medicine		28 Mar 2019 22:22 CET
Approval-Therapeutic Area		01 Apr 2019 10:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed