Clinical Trial Protocol

	Document Number:	**c21630258-01**
EudraCT No.	2018-000057-41	
BI Trial No.	1402-0005	
BI Investigational Medicinal Product	BI 1358894	
Title	A double-blind, randomised, two-way cross-over, single-dose, placebo-controlled trial to investigate the effects of BI 1358894 on cholecystokinin tetrapeptide (CCK-4) induced panic symptoms in healthy male subjects	
Lay Title	A study in healthy men to test whether BI 1358894 reduces drug-induced panic symptoms	
Clinical Phase	I	
Trial Clinical Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol	
Version and Date	Version: 1.0	Date: 13 March 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	13 March 2019
Revision date	Not applicable
BI trial number	1402-0005
Title of trial	A double-blind, randomised, two-way cross-over, single-dose, placebo-controlled trial to investigate the effects of BI 1358894 on cholecystokinin tetrapeptide (CCK-4) induced panic symptoms in healthy male subjects
Principal Investigator	
Trial site	
Clinical phase	I
Trial rationale	Inhibition of ion channels by BI 1358894 may potentially improve affective symptoms and emotion control in patients with affective disorders. The pharmacodynamic data obtained in this study will help to detect the pharmacological principle of the BI 1358894 compound by demonstrating indirect target engagement via downstream pharmacodynamic measures.
Trial objective	To investigate the pharmacodynamic effects of a single dose of BI 1358894 on CCK-4 induced anxiogenic/panic-like symptoms using the Panic Symptom Scale (PSS) in preselected CCK-4 sensitive healthy volunteers.
Trial design	Single dose, placebo-controlled, double-blind, randomised, two-way cross-over
Trial endpoint	Primary endpoint: maximum change from baseline of PSS sum intensity score after CCK-4 injection
Number of subjects **total entered** **each treatment**	 20* *Screening may include more than 60 healthy subjects who will be exposed to CCK-4 to identify subjects with an anxiogenic and panic induced effect in response to CCK-4 as until 20 eligible subjects have been identified 20 (all to receive both active treatment and placebo)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male CCK-4 sensitive subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Challenging agent	CCK-4 (CCK B receptor agonist)
dose	50 µg
mode of admin.	iv bolus injection
Test product	BI 1358894 film-coated tablet, strength 25 mg (inhibitor)
dose	100 mg (4 film-coated tablets)
mode of admin.	Oral with 240 mL of water after a standard high-fat meal
Reference product	Matching placebo as film-coated tablet
dose	Not applicable
mode of admin.	Oral with 240 mL of water after a standard high-fat meal
Duration of treatment	2 single doses of CCK-4 and BI 1358894 or placebo (separated by a washout period of at least 17 days between drug administrations), 1 single dose of the provoking agent for the preselection of CCK-4 sensitive healthy subjects
Statistical methods	Descriptive statistics will be calculated for all endpoints. The statistical model to assess the primary pharmacodynamic endpoint PSS sum intensity score will be a mixed effects model including effects for 'treatment', 'period' and 'subject', as well as covariates 'period baseline' and 'subject baseline'. Two sided 90% confidence intervals (CIs) will be calculated based on the residual error from the mixed model.

FLOW CHART FOR THE SINGLE DOSE CCK-4 CHALLENGE

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory			CCK-4 challenge[8]	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Suicidality assessment[7]		PSS/	Questioning for AEs and concomitant therapy[5]
SCR	1	-28 to -7			Screening (SCR)[1]	x				x		x	x			
	2	-6 to -2	-0:15	08:00	Screening CCK-4-challenge visit[8,13]	x					▲	x			x	x
			0:00	08:15					x		|					
			0:05	08:20							|				x	
			0:10	08:25							|				x	
			0:20	08:35							|				x	
			0:30	08:45							▼				x	x[10]
			4:45	13:00	lunch, discharge from trial site[14]			x				x	x			x[10]
two identical treatment periods separated by a wash-out of at least 17days	3/4	-1	-18:00	14:00	Admission to trial site	x		x					x			x
		1	-2:00	06:00	allocation to treatment[2]		x[2, 9]			x[2]	▲	x[2]				x[2]
			-0:30	07:30	Breakfast											
			0:00	**08:00**	**BI 1358894 drug administration or placebo**						|				x[2]	
			0:30	08:30			x			x	┃	x				x
			1:00	09:00			x			x	┃	x				x
			1:30	09:30			x				┃					x
			2:00	10:00	240 mL fluid intake					x	┃	x				x
			2:30	10:30			x				┃					x
			3:00	11:00			x			x	┃	x				x
			4:00	12:00	240 mL fluid intake[3]		x			x	┃				x	x
			4:30	12:30							┃					
			4:45	12:45			x	x		x	┃	x		x	x	
			5:00	13:00	CCK-4 challenge[8]				x		┃					
			5:05	13:05				x			┃				x	x[10]
			5:10	13:10				x			┃				x	x[10]
			5:20	13:20				x			┃				x	x[10]
			5:30	13:30			x	x			┃	x			x	x[10]
			6:00	14:00	Lunch[3]		x	x		x	▼	x				x[10]
			7:00	15:00			x	x								
			8:00	16:00	Snack (voluntary)[3]		x	x		x		x				
			10:00	18:00	Dinner[3]		x	x								
			12:00	20:00			x			x		x				
		2	24:00	08:00		x	x			x		x				x[10]
			34:00	18:00			x			x		x				x
		3	48:00	08:00			x			x		x				x
		4	72:00	08:00			x			x		x				x

		5	96:00	08:00		x	x			x		x				x
		6	120:00	08:00			x			x		x				x
		7	144:00	08:00			x			x		x				x
		8	168:00	08:00			x			x		x				x[10]
		9	192:00	08:00	Discharge from trial site[11]	x	x			x		x	x	x	x	x
		13	288:00	08:00	Ambulatory visit[12]		x									
EOT	5	35 to 40			End of trial (EOT) examination[4]	x				x		x	x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG (including rhythm strip of at least 10 sec), safety laboratory (including drug screening and alcohol urine test), demographics (including determination of body height and weight, smoking status and alcohol history), neurological examination, relevant medical history, concomitant therapy, review of inclusion/exclusion criteria and suicidality assessment (C-SSRS).
2. The time is approximate; the respective procedure is to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, concomitant therapies, suicidality assessment (C-SSRS), neurological examination, and PSS
5. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
6. Sampling times and periods may be adapted based on information obtained during the trial including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject
7. Suicidality assessment only at screening, admission to trial site, discharge from trial site and end of trial.
8. CCK-4 challenge test (CCK-4 injection (50 µg)) is to be performed after subjects have had a standard high-fat meal except Visit 2, no breakfast is needed at Visit 2. Injection time must be recorded. PSS assessments will be determined 5 ± 1, 10±1, 20±1 and 30 ±1 minutes after the injection. The CCK-4 will be administered to the subjects as a bolus injection over 5 seconds (maximum of 8 seconds) via a venous cannula.
9. One additional blood sample for pharmacogenomics analyses will be taken either at Visit 3 or at Visit 4.
10. Standardized assessment of local tolerability using the criteria swelling, induration, heat, redness, pain or other findings.
11. Discharge on Day 9 includes physical examination, vital signs, ECG, safety laboratory, recording of AEs, concomitant therapies, suicidality assessment (C-SSRS), PSS and a neurological examination.
12. For ambulatory visit examinations, a time window of 3 hours is acceptable.
13. The time is approximate and could start between 8:00 to 12:00
14. Discharge after screening CCK-4 challenge after confirmation of fitness by PI or designee

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC5-5.5	area under the concentration-time curve of the analyte in plasma over the time interval 5h to 5:30h
AUC0-24	Area under the concentration-time curve of the analyte in plasma during 24 hours
AUC0-72	Area under the concentration-time curve of the analyte in plasma during 72 hours
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	borderline personality disorder
b.p.m.	Beats per minute
CA	Competent authority
CCK-4	Cholecystokinin tetrapeptide
CHO	Chinese hamster ovary
CI	Confidence interval
Cmax	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
CRF	Case report form
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury

DNA	Desoxyribonucleic acid
DRF	Dose Range Finding
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	electro-convulsive therapy
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
E_{max}	maximum PSS sum intensity score after CCK-4
EOT	End of trial
ES	Entered Set
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
FE	Food Effect
FIH	First in Human
FST	Forced Swim Test
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
hERG	human ether-a-go-go related gene
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IPD	Important Protocol Deviation
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
i.v.	Intravenous
LVSP	left ventricular pressure parameters
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NIMP	Non-investigational medicinal product
nM	Nanomolar

NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
p.o.	Oral
PR	Pulse rate
PSS	Panic Symptom Scale
q.d.	*Quaque die*, once daily
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
SRD	Single-rising dose
Ss	(at) steady state
SOP	Standard Operating Procedure
T	Test product or treatment
TMF	Trial master file
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White Blood Cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

1.2 DRUG PROFILE

1.2.1 BI 1358894

1.2.1.1 Nonclinical pharmacology

1.2.1.2 Safety pharmacology

1.2.1.3 Toxicology

1.2.1.3.1 Single dose toxicity

1.2.1.3.2 Repeat-dose toxicity studies

1.2.1.3.3 Genotoxicity

1.2.1.3.4 Reproductive and developmental toxicity

1.2.1.3.5 Phototoxicity

1.2.1.4 Nonclinical pharmacokinetics

1.2.1.5 Clinical experience in humans

Pharmacokinetics

1.2.1.6 Drug product

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

1.2.2 Cholecystokinin-tetrapeptide (CCK-4)

Administration of the neuropeptide cholecystokinin-tetrapeptide (CCK-4) induces panic attacks both in patients with panic disorder and healthy volunteers in a dose-dependent fashion [R19-0565]. No habituation was observed after repeated administration of CCK-4 as a provoking agent. It has been shown that panic disorder patients are much more sensitive to CCK-4 administration than healthy controls [R19-0564]. Therefore, it has been suggested that CCK-4 might be involved in the pathophysiology of panic disorder.

When rechallenged without any treatment, panic disorder patients did not show any change in the behavioral effects of CCK-4 [R19-0625]. In contrast, it has been demonstrated that administration of agents that are effective in the treatment of panic disorder reduce CCK-4-induced panic. [R19-0626] investigated the effect of treatment with imipramine on CCK-4-induced panic in panic disorder patients in an open-label design. They found a marked reduction in the number and intensity of panic symptoms when patients were rechallenged after the treatment period [R19-0626]. Similarly, Shlik [R19-0560] showed a marked reduction of intensity and number of panic symptoms after citalopram treatment [R19-0560].

In a placebo-controlled study with fluvoxamine, significant treatment effects on CCK-4-induced panic attacks were found in panic disorder patients compared to placebo [R19-0628].

An interaction of CCK-4 with several other neurotransmitter systems has been discussed. Apart from the serotonergic and noradrenergic system, the gamma-amino-butyric-acid (GABA) system also seems to be involved in the pathophysiology of CCK-4-induced panic [R19-0627]; [R19-0626].

Administration of 50 µg CCK-4 was well-tolerated in numerous clinical research trials (see Section 4.1.2). The CCK-4 related anxiety symptoms show a rapid increase followed by a fast decline within a period of 5 minutes. There may be some residual anxiety symptoms after 10 minutes, but these are usually mild and disappear without any residual symptoms within 30 minutes. Changes in vital signs (blood pressure, pulse rate, respiratory rate) occur during the CCK-4 challenge test. Short lasting changes in pulse rate and blood pressure have been observed together with changes in anxiety-status [R18-2695].

The panic symptoms induced by CCK-4 may be expressed by the following potential symptoms (all symptoms are covered by the assessment of the Panic Symptom Scale *(*PSS), vital signs and will be thoroughly monitored):

- Dyspnea
- Dizziness
- Faintness
- Trembling
- Sweating
- Nausea
- Abdominal stress
- Tachycardia
- Chest pain or discomfort

- Hot flushes
- Anxiety, fear or apprehension
- Fear of dying, losing control, of going crazy

1.2.3 Residual Effect Period

1.3 RATIONALE FOR PERFORMING THE TRIAL

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1358894.

Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

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

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (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 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.

1.4.2.1.1 Risks derived from observations in non-clinical studies

1.4.2.1.2 Mode of action and nature of the target

1.4.2.1.3 Relevance of animal models

1.4.2.1.4 Risk minimization (safety precautions and stopping rules)

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

- For safety reasons, each treatment period will be divided into 4 cohorts of 5 subjects. Each drug administration will be separated by at least 10 minutes and the dosing of the cohorts will be separated by at least 2 days. Adequate continuous safety monitoring (see below) will be performed before the subsequent cohort is dosed.
- An extensive safety laboratory will be performed with special focus on full blood exam, including CRP and ESR to monitor for potential perivascular/mesenteric inflammation (see Flow Chart)
- Adequate safety monitoring will be performed (e.g. vital signs (including blood pressure, pulse rate, respiratory rate), ECGs, safety laboratory tests including hormone parameters, visual analogue scales, suicidality, and assessment of adverse events)
- Subjects will be hospitalised throughout the study from Day -1 to Day 9 of each period and will be discharged only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During the in-house stay, the subjects will be under medical observation and thoroughly monitored for adverse events, which may be reported in an expedited manner if they match the criteria for expedited reporting
- As reproductive toxicity studies have not yet been conducted, only male subjects will be enrolled in this study

1.4.2.1.5 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 5.2.6.1.6, adverse events of special interest.

1.4.2.2 CCK-4

The CCK-4 challenge test is well-tolerated, based on numerous clinical studies (see Section 1.2.2). CCK-4 induced effects are transient (5 minutes) and include changes in vital signs (blood pressure, pulse rate, respiratory rate) and panic symptoms (increased anxiety, tremors, sweating, dry mouth, derealization, mild nausea, and a strange feeling in stomach).

Safety precautions will include thorough monitoring of panic symptoms (via the PSS), vital signs, and continuous ECG. Subjects will be hospitalised and kept under close medical surveillance for at least 4 hours following CCK-4 administration.

1.4.2.3 Overall assessment

Based upon preclinical data for BI 1358894, the preliminary clinical data from the on-going FIH study, the well-known safety profile of CCK-4, as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks from BI 1358894 or CCK-4 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 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 pharmacodynamic effects of a single dose of BI 1358894 (4 x 25 mg film-coated tablet in the fed state) on CCK-4- induced anxiogenic/ panic-like symptoms using the PSS in preselected CCK-4 sensitive healthy volunteers.

2.1.2 Primary endpoint

The following pharmacodynamic parameter will be determined:

Maximum change from baseline of Panic symptom scale (PSS) sum intensity score after CCK-4 injection.

2.1.3 Secondary endpoints

Not applicable.

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 and neurological examinations)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate)
- Suicidality assessment (C-SSRS)

2.2.2.3 Local tolerability

Local tolerability of CCK-4 injections will be assessed by the investigator or designee on the basis of swelling, induration, heat, redness, pain, and other findings.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, double-blind, placebo-controlled, two-way crossover trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The subjects will be randomly allocated to the two treatment sequences (T-R or R-T). The treatments will be 4 x 25 mg BI 1358894 film-coated tablet in the fed state (T) and four placebo film-coated tablets in the fed state (R) administered prior to CCK-4 injection. For this trial CCK-4 will be used as a provoking agent. For details refer to Section 4.1.

There will be a washout period of at least 17 days between the treatments.

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 experimental challenge studies, the crossover design is preferred due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes intersubjective variability from the comparison between treatments and the overall number of subjects enrolled can be minimized [R94-1529].

3.3 SELECTION OF TRIAL POPULATION

It is planned that 20 healthy male subjects will enter the study; a minimum of 15 subjects must be evaluable for the analysis of the primary endpoint (see Section 3.3.5 for replacement of subjects). They will be recruited from the volunteers' pool of the trial site. For the selection of the 20 healthy male subjects it is planned to screen up to about 60 healthy male subjects to identify 20 CCK-4 sensitive subjects by exposing them to a CCK-4 challenge during Screening. Sufficient CCK-4 sensitivity is defined as achievement of the following after a CCK-4 i.v. bolus injection:

- A sudden onset of panic and
- Presence of at least 4 symptoms in the PSS and
- A score of 2 or higher on PSS item 15: “Anxiety and Fear for Apprehension”

Or:

- Achievement of a total PSS sum intensity score > 20 after CCK-4 i.v. bolus injection.

Only male subjects will be included in the study because limited data on reproductive toxicology are available at this time.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy male 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 55 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 one month after the last administration of trial medication. Adequate methods are:
    - Sexual abstinence or
    - A vasectomy performed at least 1 year prior to screening (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
    - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with FSH above 40 U/L and estradiol below 30 ng/L is confirmatory) 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 one month after the last administration of trial medication

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. C-Reactive Protein >ULN, erythrocyte sedimentation rate (ESR) ≥15 millimeters/h, liver or kidney parameter above ULN,

4. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
5. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
6. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
7. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
8. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
9. History of relevant orthostatic hypotension, fainting spells, or blackouts
10. Chronic or relevant acute infections
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication, CCK-4 or its excipients)
12. 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)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 5 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Average intake of more than 21 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

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. Insufficient response to the CCK-4 challenge in Screening Visit 2 (see Section 3.3 above).

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 surgery, adverse events [AEs], or diseases)
5. 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

6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
7. The subject shows a raised CRP level of >3.00 mg/dL or an ESR of ≥20 millimeters/hour if these results are confirmed by a second sample.

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

1. Failure to meet expected enrolment goals
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. 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 serious adverse event is reported
3. Violation of GCP, or the CTP, or the contract with BI, impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product
5. The trial will be stopped if at least 2 subjects show relevant individual QT prolongation (absolute QT or QTc greater than 500 ms), which has been confirmed by a repeat ECG recording
6. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of the same dose group

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 some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects

will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces. A minimum of 15 subjects evaluable for the analysis of the primary endpoint have to be enrolled.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 1358894 was manufactured by

The provoking agent solution containing 50 µg CCK-4 acetate is manufactured by

.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Film-coated tablet
Source:	
Unit strength:	25 mg
Posology:	4-0-0
Route of administration:	p.o.
Duration of use:	1 single dose

The characteristics of the reference product are given below:

Substance:	Placebo
Pharmaceutical formulation:	Film-coated tablet
Source:	
Unit strength:	n.a.
Posology:	4-0-0
Route of administration:	p.o.
Duration of use:	1 single dose

The characteristics of the provoking agent (NIMP) are given below:

Substance:	CCK-4 (cholecystokinin tetrapeptide)
Pharmaceutical formulation:	injection solution

Source:

Unit strength:	50 µg
Posology:	1-0-0
Route of administration:	i.v. bolus injection
Duration of use:	3 single dose

4.1.2 Selection of doses in the trial

The CCK-4 dose selected for this trial reflects standard doses for clinical trials (see Section 1.2). The administration of 50 µg CCK-4 has been performed in numerous clinical research trials in healthy subjects, elderly subjects, and patients with anxiety disorders. It has proven to be well-tolerated, even in patients with anxiety disorders who are highly sensitive to such challenges [P98-0035], [R18-2694], [R18-2695], [R18-2696].

In this single dose CCK-4 challenge study a higher inhibition of about 90 % (EC90) is intended to be achieved during PSS evaluation in order to ensure adequate target inhibition during the short lasting CCK-4 related stimulus.

4.1.3 Method of assigning subjects to treatment groups

Prior to start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. According to the planned sample size, at least 4 cohorts are planned. After assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups in the morning of Day 1 (Visit 2) prior to first administration of trial medication and the appropriate medication number will be assigned. The randomisation will be provided by the sponsor to the trial site in advance.

Once a subject number has been assigned, it cannot be reassigned to any other subject. Subject Numbers are automatically pre-populated via the BRAVE system (during data entry, in an ascending order).

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 2-way crossover study. All subjects will receive the 2 treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1358894	Tablet	25 mg	4 tablets (25 mg) q.d for 1 day	100 mg
R (Reference)	Placebo	Tablet	n.a. mg	4 tablets (n.a. mg) q.d for 1 day	n.a. mg

The investigator (or authorised designee) will administer the trial medication as a single 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.

CCK-4 will be provided in vials containing 50 µg lyophilized CCK-4. Immediately prior to use, 5 mL of sterile normal saline (0.9% NaCl) for injection will be added to the vial containing lyophilized CCK-4 powder and mixed to produce a solution for injection. Before CCK-4 administration, 5 mL (50 µg CCK-4) of the solution is withdrawn from the vial into a syringe. Then the CCK-4 will be administered to the subjects as a bolus injection over 5 seconds (maximum of 8 seconds) via a venous cannula.

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

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

Ingredients	kcal
2 fried eggs *(in 15 g butter/margarine) (approximately 100 g)*	220
40 g fried bacon[2]	151
2 toasted slices of whole-wheat bread	154
15 g margarine for buttering toast slices	112
115 g fried potatoes	130
240 mL whole milk (3.5% fat)	151
Sum[1]	918

1 The total caloric content was supplied approximately as following: 156 kcal as protein, 235 kcal as carbohydrate, and 500 to 600 kcal as fat.

2 Vegetarians may replace bacon with 40 g brie 60+ (148 Kcal)

Subjects will be kept under close medical surveillance for 8 days after drug administration as described in the Flow Chart.

During the first 2 h after drug administration, subjects will only be allowed to lie down if supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG).

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

4.1.5 Blinding and procedures for unblinding

The trial is designed double-blind. Neither subject nor investigator will be aware of the trial treatments. The investigator will be supplied with a set of sealed envelopes containing the medication codes. The envelopes will be kept unopened at the study site until the end of data collection or, in an emergency requiring the investigator to know a subject's treatment allocation, opened with appropriate documentation. At the trial close-out visit, all envelopes will be collected.

Access to the randomisation schedule is restricted to the randomisation operators, the Clinical Trial Support group and the Pharmaceutics Department.

Persons directly involved in the conduct of the trial will be blinded to trial treatments. The trial medication will be packed blinded. The trial will only be unblinded after locking of the database, which takes place only after the trial is clinically completed and all queries have been clarified. Access to the randomisation codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

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

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4.1.6 Packaging, labelling, and re-supply

4.1.6.1 BI 1358894

Drug supplies will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator’s possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the 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

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

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

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

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

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 under supervision of the investigating physician or a designee. The measured plasma and serum concentrations will provide additional confirmation of compliance.

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, a physical examination, and a neurological examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight, and a neurological examination.

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 (e.g. Dinamap VC 150,) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

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

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leucocytes Urine pH
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Protein electrophoresis only at screening. Hormones only at screening and end of trial; for time points of assessment of , refer to Flow Chart.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infectious serology will be performed during screening only. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic and drug restrictions, a urine alcohol and drug test (e.g. ADVIA Chemistry XPT system) 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

Urinanalysis stix and drug screening tests will be performed using e.g. Clinitek Novus test and ADVIA Chemistry XPT system, respectively.

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

5.2.4 Electrocardiogram

5.2.4.1 Twelve-lead ECGs

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. Mortara Eli 250 C) 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. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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.

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 12-lead ECG recording at visit 2 for at least 15 min before CCK-4 challenge until 30 min after the challenge and at visit 3 and 4 for at least 2 h before the BI 1358894 administration (for baseline assessment), and 6 h following drug administration using patient monitors (e.g. Mortara Telemetry System). Abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator but no other data will be transferred to the database.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator or designee on the basis of swelling, induration, heat, redness, pain, and other findings.

5.2.5.2 Suicidality assessment

Suicidality assessment to further evaluate the psychological status of the subject will be performed at screening using the Columbia Suicidal Severity Rating scale (C-SSRS). The C

SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behaviour and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

The original English version is shown in Appendix 10.2.

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.

The provoked panic symptoms in response to CCK-4 injection (as documented by the PSS score), which are prerequisite for demonstrating a potential effect of the investigational compound, will be considered PD parameters. Since they are an expected and desired response in the context of this trial (even though they constitute an untoward medical occurrence), they will not be recorded as AEs. All other observations not included on the PSS questionnaire occurring during the standard AE reporting time period (see Section 5.2.6.2.1) are to be documented as AEs.

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 Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

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

5.2.6.1.4 Detailed assessment of the adverse advent headache

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

- Onset after medication intake (hhh:min)
- Headache severity on a Numeric Ranking Scale (NRS) ranging from 0 - 10
- Quality of headache (new type of headache vs. similar to previous experienced episodes of known headaches)
- Headache characteristics (pressing or tightening vs. burning vs. pulsating vs. aggravated by routine physical activity (such as walking or climbing stairs))
- Location (all of the following that apply: unilateral, bilateral, holocephal, frontal, temporal, occipital, facial)
- Any 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)

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

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

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

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

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

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

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

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

5.2.6.1.6 Adverse events of special interest

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

The following is considered an AESI:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o 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
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

5.2.6.1.7 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

5.2.6.1.8 Causal relationship of AEs

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

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

Once a male subject has been enrolled in the clinical trial and has taken trial medication, and if the 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

5.3.2 Methods of sample collection

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

5.3.4 Pharmacokinetic - pharmacodynamic relationship

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Methods of sample collection

5.4.2 Assessment of pharmacodynamic parameters

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTSS

5.6.1 Pharmacogenomic evaluation

5.6.2 CCK-4 challenge test

CCK-4 challenge tests (CCK-4 bolus iv injection of 50 µg) will be performed at the time points indicated in the Flow Chart. The CCK-4 injection time, 5 h after drug administration, must be recorded. PSS assessments will be determined -15±1, 5 ± 1, 10±1, 20±1 and 30 ±1 minutes after the injection to ensure a detailed compilation of potential changes in psychological conditions of the subjects. The time for the post CCK-4-injection blood samples must be recorded.

5.6.3 Pharmacodynamic parameters

The following pharmacodynamic parameters will be evaluated within this study:

- Panic Symptom Scale (PSS, see Appendix 10.4)

PSS:
The PSS is a patient reported outcome measurement from which the following factors are derived: physical symptoms of fear and the perception of alertness, anxiety, fear, and pain. The PSS assessments conducted on Day 1 15 min before drug administration will be considered as period baseline. At each measuring time point indicated in the Flow Chart, the subjects will assess their subjective impression of themselves by means of the panic symptom scale. The subjects will be asked to mark an adequate position on a scale from 0 (absent) to 4 (very strong) of the characteristic 18 questions to be measured. The sum of the scale over all items will constitute the PSS sum intensity score. In addition to this sum intensity score, the number of positively rated PSS symptoms (total number of symptoms) will be also recorded. The score will be documented in the electronic case report form. It is anticipated that the highest PSS sum intensity score will be reached approximately 5 minutes after CCK-4 injection and will decrease thereafter.

The original English version is shown in Appendix 10.4.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic 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 5.4 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Sections 5.5 and 5.6 are of exploratory nature only.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

Study measurements and assessments scheduled to occur at ambulatory visits as indicated in the Flow Chart are to be performed and completed within a 3 h-period latest at 11:30 a.m.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening periods

In Screening Visit 1, 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 5.2.3 to 5.2.5.

In Screening Visit 2 (on one day between Days -6 and -2), subjects will undergo a CCK-4 challenge test. Only subjects with sufficient CCK-4 sensitivity (see Section 3.3) will enter the treatment periods.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days 1 till 9 in each period). The treatment periods will be separated by at least 17 days between drug administrations.

On Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for 8 days after drug administration. On Day 9, 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 samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart.

For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.2 to 5.2.6.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This is a double-blind, randomised, two-way cross-over, single-dose trial, including a washout period of at least 17 days between the treatments (Section 3.1).

The main objective of this trial is to investigate the pharmacodynamic effects of a single dose of BI 1358894 (Test, T) on CCK-4 induced anxiogenic/ panic-like symptoms using the PSS compared to placebo (Reference, R) on the basis of the primary pharmacodynamic endpoint as listed in Section 2.1.2. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear mixed effects model.

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

It is not planned to test any statistical hypotheses with regard to any of the variables listed in Section 2 in a confirmatory sense. Two sided 90% confidence intervals (CIs) will be computed and will have to be interpreted in the perspective of the exploratory character of the study.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Enrolled set (ES):
  This subject set includes all enrolled subjects that underwent screening procedures.
- Entered set (ENTS):
  This subject set includes all enrolled subjects that underwent screening procedures and entered the trial, whether treated or not.
- Treated set (TS):
  This subject set includes all subjects from the ENTS who were documented to have received at least one dose of study drug.
- Pharmacodynamic set (PDS)
  This subject set includes all subjects in the TS who provide at least one primary PD parameter that was not excluded according to the description below.
- Pharmacokinetic set (PKS)
  This subject set includes all subjects in the TS who provide at least one PK parameter

that was not excluded according to the description below.

All individual data will be listed.

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

Pharmacokinetics

Pharmacodynamics

PSS data of a subject will be included in the statistical analysis if they are not flagged for exclusion. Reasons for exclusion of single PSS parameters may be:

- The subject experiences emesis at or before two times median t_{max} or before the subject completes PSS assessments on study day 1 according to Flow Chart. Median t_{max} is to be determined excluding the subjects experiencing emesis
- Time deviations
- Use of restricted medications
- If a predose concentration value is greater than 5% of C_{max} of the subjects´ pharmacokinetic data, the respective PD assessments in the respective period may be excluded from statistical assessments

7.3.1 Primary endpoint analyses

The derivation of the primary endpoint PSS sum intensity score per time point is outlined in Section 5.6.3. The maximum CfB is defined as the maximum of the differences of the PSS sum intensity score measured at each time point after the CCK-4 challenge minus the PSS sum intensity score measured at baseline. Further details on the calculation will be given in the TSAP. The primary endpoint analysis will be performed on the PDS (refer to Section 7.3).

Primary analyses

The statistical model used for the investigation of the primary endpoint PSS sum intensity score will be a mixed effects model given by

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b_i' + s_i + e_{imj},$$

where

y_{imj}	Maximum CfB (absolute change from period baseline) in PSS sum intensity score for the ith subject and the mth period, receiving randomised treatment j,
μ	overall intercept,
π_m	mth period effect, m = 1,2,
τ_j	jth treatment effect, j = 1,2,
b_{im}	baseline value for subject i in period m (period baseline),
γ	associated covariate effect of period baseline,
b_i'	the subject baseline value (mean of the 2 period baselines) for subject i,
γ'	associated covariate effect of subject baseline,

s_i the random effect of subject i,

e_{imj} the random error associated with subject i who received treatment j in period m.

The last value before administration of the CCK-4 challenge in each period is considered as the corresponding period baseline measurement. The PSS sum intensity score mean value of the two period baseline values is considered as the subject baseline.

The treatment comparison will be the difference between active treatment and placebo. Adjusted means (Least Squares Means) as well as 2-sided 90% CIs will be calculated. Additionally, the difference in adjusted means relative to placebo will be provided. To support this analysis, listings and graphical displays may be generated if appropriate.

As a sensitivity analysis, the same statistical model as stated above will be repeated for the primary endpoint but with all sources of variation considered as fixed effects.

Further details will be presented in the TSAP.

7.3.2 Secondary endpoint analyses

Not applicable.

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 7.3) 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 Blinded Report Planning Meeting).

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the immediately preceding treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

For a description of PK and PD analyses, please see Section 7.3.1 and Section 7.3.3.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.5.3 Pharmacodynamics

For the PD endpoints PSS if the period baseline value is missing in treatment period 1, it will be imputed by the corresponding value measured in treatment period 2. If the period baseline value is missing in treatment period 2, it will be imputed by the corresponding value measured in treatment period 1. If a value is missing after CCK-4 injection, this value will not be imputed. If all four assessments after CCK-4 injection are missing for a subject, this subject is not evaluable for this endpoint in this period.

7.6 RANDOMISATION

Subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 20 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. At least 15 subjects need to be evaluable for the primary objective of this trial.

Based on this sample size, the probability to observe a meaningful reduction in PSS sum intensity score after a single dose of BI 1358894 when compared to placebo is given in Table 7.7: 1 for N=20 subjects and in Table 7.7: 2 for N=15 subjects.

For these calculations, the following assumptions are made. A total of N subjects are evaluable in this cross-over study. The standard deviation of the maximum change from baseline of the treatment contrast of PSS relative to placebo is 20%. The maximum change from baseline for PSS sum intensity score relative to placebo is 0% after the placebo treatment. Six different scenarios are displayed.

Table 7.7: 1 Probability to observe a difference in the primary endpoint ≤ 20%, 20% - 40% and > 40% relative to placebo for different scenarios and a sample size of N=20 evaluable subjects.

True maximum change from baseline relative to placebo		Probability to observe a relative mean difference (BI 1358894 vs. Placebo)		
BI 1358894	Placebo	≤ 20%	20% - 40%	> 40%.
10%	0%	70.9	23.6	5.5
18%	0%	54.4	33.9	11.7
28%	0%	33.0	41.5	25.5
33%	0%	23.8	41.2	35.0
46%	0%	8.2	28.9	62.9
52%	0%	4.5	21.0	74.5

Table 7.7: 2 Probability to observe a difference in the primary endpoint ≤ 20%, 20% - 40% and > 40% relative to placebo for different scenarios and a sample size of N=15 evaluable subjects.

True maximum change from baseline relative to placebo		Probability to observe a relative mean difference (BI 1358894 vs. Placebo)		
BI 1358894	Placebo	≤ 20%	20% - 40%	> 40%.
10%	0%	68.2	23.3	8.6
18%	0%	53.8	30.9	15.4
28%	0%	35.3	36.1	28.6
33%	0%	27.1	35.9	37.0
46%	0%	11.6	27.3	61.2
52%	0%	7.3	21.3	71.4

The calculations were performed using R version 3.3.2. The R code for the sample size calculations will be documented in a separate file and stored in the Trial Master File (TMF).

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 the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject 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.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or 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. Relevant documentation on the participating Principal Investigator (e.g. curricula vitae) will be filed in the ISF.

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local clinical trial manager (CTM), Clinical Research Associates, and the participating trial site

The trial medication BI 1358894 will be provided by the Clinical Trial Supplies Unit (CTSU),

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

The analyses of BI 1358894 concentrations in plasma will be performed at the Department of Drug Metabolism and Pharmacokinetics,
or a contract research organisation appointed by BI.

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

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

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

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10. APPENDICES

10.1 PREPARATION INSTRUCTIONS FOR CCK-4

The CCK-4 will be prepared as follows:

- A vehicle will be prepared with citrate buffer pH4, 1% polysorbate 80 and 10% mannitol in WFI
- 10 mg CCK-4 will be dissolved into 100 mL of this vehicle
- The solution will be diluted to 1000 mL using normal saline solution (final concentration 10 µg/mL, dose will be 50 µg in 5 mL)

CCK-4 solution for injection will be prepared as follows:

- 10 mL vials with 6 mL fills of a sterile CCK-4 solution will be manufactured by and stored at -20°C.
- Shortly before use the vial will be thawed; 5 mL of the solution will be drawn into a 5 mL syringe and closed with a stopper.

10.2 COLUMBA-SUICIDE SEVERITY RATING SCALE

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

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	___	___

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* _____

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.

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

Version 1/14/09

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

10.4 PANIC SYMPTOM SCALE

The Panic Symptom Scale
English Version

item	Symptom	Absent	Intensity			Very Strong
1	dyspnea /difficulty breathing	0	1	2	3	4
2	dizziness	0	1	2	3	4
3	unsteadiness	0	1	2	3	4
4	faintness	0	1	2	3	4
5	palpitations	0	1	2	3	4
6	trembling	0	1	2	3	4
7	sweating	0	1	2	3	4
8	choking	0	1	2	3	4
9	nausea	0	1	2	3	4
10	abdominal distress	0	1	2	3	4
11	feeling unreal or detached	0	1	2	3	4
12	paresthesia/ numb or tingling feelings	0	1	2	3	4
13	hot flushes	0	1	2	3	4
14	chest pain or discomfort	0	1	2	3	4
15	anxiety, fear or apprehension	0	1	2	3	4
16	fear of dying	0	1	2	3	4
17	fear of losing control	0	1	2	3	4
18	fear of going crazy	0	1	2	3	4

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		
Description of change		
Rationale for change		

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐

To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c21630258 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: A double-blind, randomised, two-way cross-over, single-dose, placebo-controlled trial to investigate the effects of BI 1358894 on cholecystokinin tetrapeptide (CCK-4) induced panic symptoms in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		14 Mar 2019 11:25 CET
Approval-Therapeutic Area		14 Mar 2019 12:11 CET
Approval-Team Member Medicine		14 Mar 2019 14:44 CET
Author-Trial Statistician		14 Mar 2019 15:15 CET
Author-Clinical Trial Leader		14 Mar 2019 15:27 CET
Verification-Paper Signature Completion		18 Mar 2019 10:17 CET

(Continued) Signatures (obtained electronically)

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