Clinical Trial Protocol

	Document Number:	**c34402516-04**
EudraCT No.	2020-006052-40	
BI Trial No.	1402-0018	
BI Investigational Medicinal Product	BI 1358894	
Title	An open-label, two-period fixed sequence trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers	
Lay Title	A study in healthy men and women to test whether BI 1358894 influences the amount of bupropion in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 3))	
Version and Date	Version: 4.0	Date: 29 July 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	06 April 2021
Revision date	29 Jul 2021
BI trial number	1402-0018
Title of trial	An open-label, two-period fixed sequence trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers
Principal Investigator:	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	To investigate the influence of BI 1358894 on the activity of CYP2B6 by using probe drug bupropion, recommended as sensitive substrate for the CYP2B6 enzyme.
Trial objectives	To assess the influence of BI 1358894 on the pharmacokinetics of CYP2B6 probe drug bupropion when given as an oral single dose together with multiple oral doses of BI 1358894 (Test, T), as compared to when given alone as oral single dose (Reference, R).
Trial design	Open-label, two-period, fixed sequence
Trial endpoints:	Primary endpoints: AUC_{0-tz} and C_{max} of Bupropion Secondary endpoints: $AUC_{o-\infty}$ of Bupropion
Number of subjects **total entered** **each treatment**	 18 18
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male/female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 **dose** **mode of admin.**	BI 1358894 50 mg tablets; 100 mg q.d. over 19 days in treatment T Oral administration under fed conditions with 240 mL of water

Test product 2	Bupropion SR tablet (Elontril®)
dose	150 mg sustained release tablet, 2 single doses in Treatments T and R
mode of admin.	Oral administration under fed conditions with 240 mL of water
Duration of treatment	Reference Treatment (R): Bupropion alone in Period 1 (Visit 2) Single dose of 150 mg bupropion hydrochloride (Day 1). Test Treatment (T): Bupropion plus BI 1358894 in Period 2 (Visit 3) Multiple doses of 100 mg BI 1358894 administered once daily on 19 days (Day -14 to Day 5) combined with a single dose of 150 mg bupropion hydrochloride (Day 1) on the 15th day of BI 1358894 treatment
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, the two-sided 90% confidence interval (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subjects' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART PERIOD R

Visit	Day	Planned Time [h:min] relative to Bupropion	Approximate clock time of actual day[1] [h:min]	Event and comment	PK_{plasma} for Bupropion and metabolites[6]	Clinical laboratory tests [2]	Vital signs (BP, PR), ECG[3]	Physical /Neurological Examination	Questioning for AEs and concomitant therapy[7]
1	-21 to -1			Informed consent, screening [9]		A[12]	X	X	X
2	-1	-24:00		Admission to trial site		B[12,13,14]			X
	1	-3:00			X[11]		X	X	X
		0:00	**08:00**	**Administration of 150 mg Bupropion[4]**					
		1:00	09:00		X				
		2:00	10:00	240 mL fluid intake	X				
		3:00	11:00		X				
		4:00	12:00	240 mL fluid intake thereafter Lunch[8]	X				X
		5:00	13:00		X				
		6:00	14:00		X				
		7:00	15:00		X				
		8:00	16:00	Snack (voluntary) [8]	X				
		10:00	18:00		X				
		11:00	19:00	Dinner					
		12:00	20:00		X				X
	2	24:00	08:00	Breakfast[8]	X	B	X	X	X
		24:30	08:30	Discharge from trial site					
	3	48:00	08:00	Ambulatory visit	X				X
	4	72:00	08:00	Ambulatory visit	X				X
	5	96:00	08:00	Ambulatory visit	X				X
	6	120:00	08:00	Ambulatory visit	X	B[12]			X

FLOW CHART PERIOD T

Visit	Day	Planned Time [h:min] relative to Bupropion	Approximate clock time of actual day[1] [h:min]	Event and comment	PK (plasma) for BI 1358894 [6]	Clinical laboratory tests [2]	PK (plasma) for Bupropion and metabolites[6]	Vital signs (BP, PR) ECG[3]	Physical /Neurological Examination	Questioning for AEs and concomitant therapy[7]
3	-14	-336:00	08:00	**Administration of 100 mg BI 1358894[4],[5]**	X[15]	X[13, 14,15, 16]		X[15]	X[15]	X
			10:00	**Discharge**					X	
	-13	-312:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-12	-288:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-11	-264:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-10	-240:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-9	-216:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-8	-192:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-7	-168:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X
	-6	-144:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**	X[15]	B				X
	-5	-120:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894[4]**						X

Visit	Day	Planned Time [h:min] relative to Bupropion	Approximate clock time of actual day[1] [h:min]	Event and comment	PK (plasma) for BI 1358894 [6]	Clinical laboratory tests [2]	PK (plasma) for Bupropion and metabolites[6]	Vital signs (BP, PR) ECG[3]	Physical /Neurological Examination	Questioning for AEs and concomitant therapy[7]
	-4	-96:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]					X
	-3	-72:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]					X
	-2	-48:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]					X
	-1	-24:00	08:00	Admission to trial site **Administration of 100 mg BI 1358894**[4]	X[15]	B[12]			X	X
	1	-0:30	07:30		X		X	X		X
		0:00	**08:00**	**Administration of 150 mg Bupropion[4] and Administration of 100 mg BI 1358894**[4]						
		1:00	09:00				X			
3		2:00	10:00	240 mL fluid intake			X			
		3:00	11:00				X			
		4:00	12:00	240 mL fluid intake, thereafter Lunch[8]			X			X
		5:00	13:00				X			
		6:00	14:00				X			
		7:00	15:00				X			
		8:00	16:00	Snack (voluntary) [8]			X			
		10:00	18:00				X			X
		11:00	19:00	Dinner						
		12:00	20:00				X			X
	2	24:00	08:00	**Administration of 100 mg BI 1358894**[4] Discharge	X[15]		X	X	X	

Visit	Day	Planned Time [h:min] relative to Bupropion	Approximate clock time of actual day[1] [h:min]	Event and comment	PK (plasma) for BI 1358894 [6]	Clinical laboratory tests [2]	PK (plasma) for Bupropion and metabolites[6]	Vital signs (BP, PR) ECG[3]	Physical /Neurological Examination	Questioning for AEs and concomitant therapy[7]
	3	48:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]		X			X
	4	72:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]		X			X
	5	96:00	08:00	Ambulatory visit **Administration of 100 mg BI 1358894**[4]	X[15]		X			X
	6	120:00	08:00	Ambulatory visit	X	B	X	X		X
4	19			End-of-study examination[10]		C[13]		X	X	X

1 Actual clock time depends on the time of dosing
2 As specified in Section 5.2.3 of this protocol
3 As specified in Section 5.2.2 and 5.2.4 of this protocol
4 Within 30 min following continental breakfast
5 First BI 1358894 administration followed by a 2 hour post-administration in-house observation period
6 As specified in Section 5.3 of this protocol
7 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
8 If several actions are indicated at the same time point, the intake of meals will be the last measure
9 Screening includes subject information, informed consent, physical and neurological examination, check of vital signs, ECG, safety laboratory (including drug and virus screening, and including serum pregnancy test in female subjects of childbearing potential), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy, review of inclusion/exclusion criteria and suicidality assessment (C-SSRS).
10 End-of-trial (EOT) examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, neurological examination and suicidality assessment (C-SSRS). The EOT assessments will be performed on Day 19 at earliest.
11 Including one blood sample for pharmacogenetic analyses (section 5.6.1)
12 SARS-CoV-2 PCR test will be performed at screening, and shortly (within 72 hours) before admission to the site
13 Urine pregnancy for WOCBP
14 Urine drug screening and alcohol breath test
15 Before study drug administration
16 At this timepoint, no safety lab B taken.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALDH	Aldehyde dehydrogenase
ANOVA	Analysis of variance
AO	Aldehyde oxidase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline personality disorder
bpm	Beats per minute
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRP	C-reactive proteins
C-SSRS	Columbia-Suicidal Severity Rating Scale
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture

EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLP	Good Laboratory Practice
gMean	Geometric mean
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus infection
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observed adverse effect level
PCR	Polimerase chain reaction
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PT	Preferred Term
q.d.	Quaque die
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
$RAUC_{0-\infty}$, M/P	Ratio of metabolite $AUC_{0-\infty}$ to parent $AUC_{0-\infty}$
$RAUC_{0-tz}$, M/P	Ratio of metabolite AUC_{0-tz} to parent AUC_{0-tz}
REP	Residual effect period
SAE	Serious adverse event

SIB	Suicidal Ideation and Behavior
SmPC	Summary of Product Characteristics
SOC	System Organ Class level of MedDRA
SOP	Standard operating procedure
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TRPC	Transient receptor potential canonical
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
UGT	UDP-Glucuronosyltransferase
ULN	Upper limit of normal
VAS	Visual Analogue Scale
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of Childbearing Potential
XTC	Ecstasy

1. INTRODUCTION

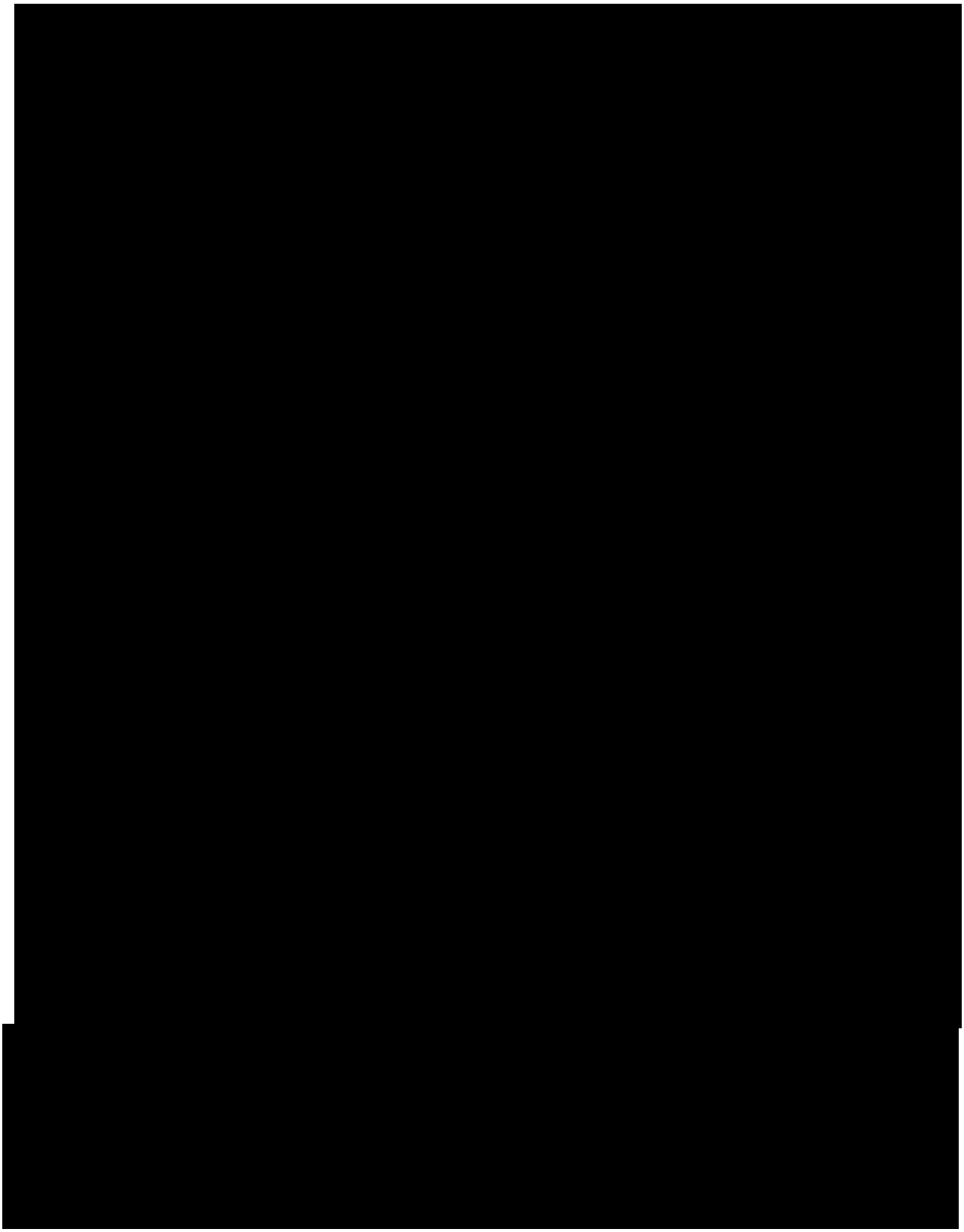
BI 1358894, an oral, small-molecule inhibitor of a transient receptor potential cation channel, subfamily C, members 4 and 5 (TRPC 4/5) is being developed for major depressive disorder (MDD) and borderline personality disorder (BPD).

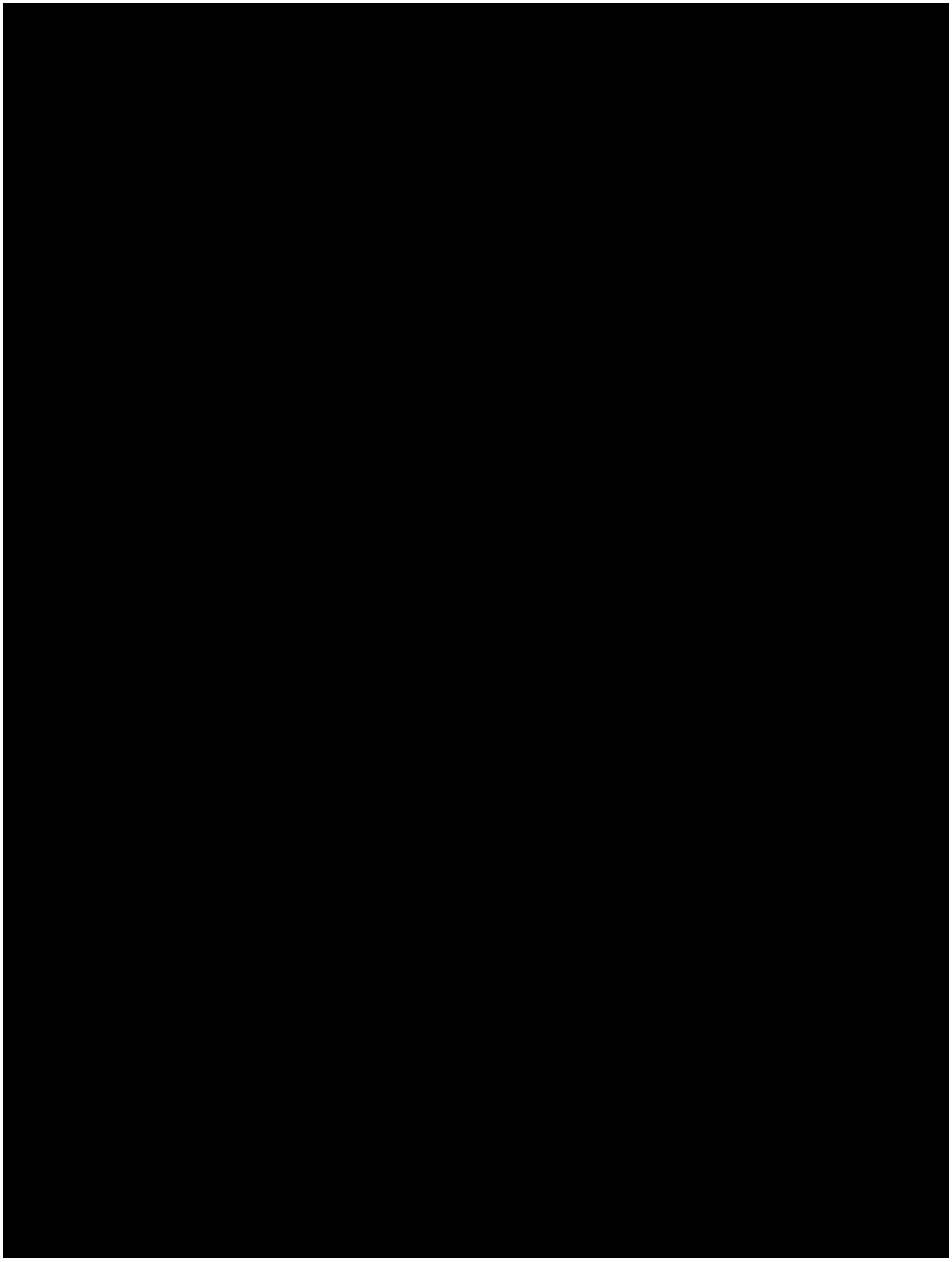
1.1 MEDICAL BACKGROUND

Major depressive disorder is a debilitating disease characterized by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the National Institute of Mental Health funded STAR*D trial of >4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residual symptoms [R16-5475] that significantly impacted the patients' quality of life [R06-2872].
Borderline personality disorder (BPD) is a chronic mental disorder with an estimated prevalence of around 2% in the general community [R16-5476] and severely impaired quality of life [R16-5474]. The main symptom clusters of BPD include impulsive-behavioural dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations, and affective instability. Patients with BPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times higher than in the general population [R16-5477]. Even the presence of a single diagnostic feature of BPD is predictive for poor functioning and psychiatric illness burden [R16-5483]. Treatment guidelines recommend psychotherapy as the mainstay of treatment, but pharmacotherapy is commonly used as an adjunctive, symptom-targeted component of treatment. However, no drug is approved for the treatment of BPD.
TRPC4 and TRPC5 form ion channels that are involved in the regulation of neuronal excitability. They are most highly expressed in the amygdala, frontal cortex, hippocampus, and hypothalamus [R15-3888, R16-5350], which are involved in modulation and processing of emotion and affect. Pre-clinically, treatment with BI 1358894 has shown diminished fear and anxiety and increased social interaction without impairing other brain functions such as learning and memory behaviours.
It is hypothesized that in patients with affective disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts, and anxiety [R16-5473] and there is growing evidence supporting the role of amygdala in the emotion processing disturbances observed in patients with BPD [R16-5472]. Therefore, treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in patients with MDD and BPD.

1.2 DRUG PROFILE

1.2.1 BI 1358894





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

1.2.2 Bupropion

Potential inductive effects of BI 1358894 on CYP2B6 will be investigated using the probe substrate bupropion.
Bupropion is used as antidepressant and smoking cessation aid. It acts as selective inhibitor of neuronal reuptake of noradrenalin and dopamine. The mechanism by which it helps in smoking cessation is unknown.
After oral administration of a 150 mg bupropion extended release tablet (as used in this trial), t_{max} was observed at approximately 2.5-3 h. Bupropion is extensively metabolised with only 0.5% excreted unchanged in either faeces or urine. Hydroxybupropion, threohydrobupropion and erythrohydrobupropion are active metabolites. Only the formation of hydroxybupropion is catalysed via CYP2B6.
Based on a mouse antitetrabenazine model, hydroxybupropion is approximately 50% as active as bupropion, and threohydrobupropion and erythrohydrobupropion are approximately 20% as active as bupropion [P06-00643]. Plasma Cmax and AUC of the main metabolite hydroxybupropion are approximately 3- and 14-fold higher than for bupropion, respectively. t_{max} of hydroxybupropion is reached approximately 6 h after administration of a single dose of bupropion [R21-0979].
Clinically, bupropion is used as a racemate, and disposition is stereoselective. CYP2B6 catalyzes hydroxylation of both enantiomers, R-bupropion and S-bupropion, to R,R-hydroxybupropion and S,S-hydroxybupropion, respectively. The rate of S-bupropion hydroxylation has been reported to exceed R-bupropion hydroxylation by approximately 1.5- to 3-fold. Interestingly, S,S-hydroxybupropion plasma concentration is formation-rate limited, whereas R,R-hydroxybupropion is elimination-rate limited [R14-3843]. Therefore, both plasma concentration of S,S-hydroxybupropion and the metabolite-to-parent ratio of S,S-hydroxybupropion to S-bupropion may be used as parameters for CYP2B6 activity in addition to plasma concentrations of bupropion or S-bupropion.
Mean plasma $t_{1/2}$ of bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion is approximately 20, 20, 37, and 33 h, respectively [R21-0979].
Maximal daily dose of bupropion is 300 mg. Recommended treatment duration is 7-9 weeks for smoking cessation or >6 months for treatment of depression.
The most frequent side effects of bupropion are psychiatric or neurologic reactions such as sleep disorders (especially when taken in the evening), agitation, anxiety, depression, concentration disorders, headache or dizziness, moreover hypersensitivity reactions such as urticaria, skin reactions such as exanthema, pruritus or increased sweating, or fever, or gastrointestinal symptoms such as dry mouth, nausea, vomiting, or obstipation. Moreover, bupropion dose-dependently increases the risk of cerebral seizures (at doses of up to 300 mg bupropion hydrochloride the frequency of cerebral seizure is reported as 0.1%).
Use of bupropion is contraindicated in patients with cerebral seizure, bulimia, anorexia, or a bipolar mood disorder in the medical history.
Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the use of bupropion as in vivo probe drug for CYP2B6 in DDI trials [P12-05791, P15-06991]. The EMA guideline specifically recommends the investigation of

S-bupropion (hydroxylation) as in vivo marker for CYP2B6 activity.
For further details, see the current version of SmPC [R21-0979].

1.2.3 Residual Effect Period

Based on an effective half-life of 50 to 70 h the Residual Effect Period (REP) of BI 1358894 is 14 days. The Residual Effect Period (REP) of bupropion is 5 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on in vitro data, BI 1358894 is a potential inducer of CYP2B6 at anticipated human therapeutic exposure levels. However, the predictive value of in vitro data is limited, and the probability of DDIs can be entirely assessed only with in vivo data in humans. Therefore, this trial is aimed to investigate the influence of BI 1358894 on the activity of CYP2B6 by using drug recommended by both the FDA [P12-05791] and EMA [P15-06991] as in vivo probes. Results of this DDI trial will provide a general signal of potentially important DDI upon which further exploration can be based.

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. The assessment of the drug-drug-interaction (DDI) potential of BI 1358894 will contribute to a safe clinical use of this TRPC 4/5-inhibitor in patients with MDD or BPD that often have to use multiple co-medications.

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

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.

Drug-related risks and safety measures

In a comprehensive package of safety pharmacology, genetic toxicology, general toxicology,

and nonclinical studies, BI 1358894 was demonstrated to be safe in humans for up to 13 weeks. Based on the mode of action, the pharmacological target, non-clinical toxicology data and clinical data, BI 1358894 is not considered a high risk compound for clinical studies. The single and multiple dose administrations of up to 200 mg BI 1358894 under fasted and fed conditions has been well tolerated by healthy subjects.
For details on treatment related risks, refer to CTP section 1.2 and the IB, version 6 [c10354149].

While there are no precedent clinical data implicating association between TRPC4/5 antagonism and Suicidal Ideation and Behavior (SIB), in the interest of ensuring participant safety, trial participants will be proactively screened and monitored for SIB in accordance with available regulatory guidance.
Because psychoactive drugs may impair thinking, judgment, and/or motor skills, participants should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities. It is recommended that participants should exercise caution when driving or operating machinery.
Participants will be closely monitored during the trial participation (including safety laboratory, AE monitoring, physical and neurological examinations) to ensure that any occurring events are detected and any necessary actions taken.
BI 1358894 is a highly specific inhibitor of TRPC 4/5 channels, which are predominantly located in the CNS. All investigation into distribution and function of TRPC 4/5 (preclinical and clinical) so far have not identified any interference with the immune system, the respiratory system or the cardio-vascular system.
Therefore, no undue risk is expected from the multiple dose administration of 100 mg BI 1358894 over 19 days to healthy subjects planned for this trial.

Risks related to bupropion administration

The dose of bupropion administered in the current trial (two single doses of 150 mg extended release tablets separated by a bupropion free interval of 21 days) corresponds to the starting dose given in therapy. AEs will be appropriately monitored and could be adequately treated if necessary because the subjects will be hospitalized at the trial site under close medical surveillance for 24 h after bupropion administration. Subjects with contraindications for the use of bupropion will be excluded from participation (see Section 3).
Single doses of 150 mg bupropion have been well tolerated by healthy volunteers in previous DDI trials. Due to the supposed CYP2B6 induction mediated by BI 1358894, plasma concentrations of bupropion and its metabolites may be decreased. Thus no undue risk is expected to healthy subjects from the combined administration of BI 1358894 and bupropion in this trial.

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

If the investigator should have any clinical concern, the safety of subjects will be of upmost importance. The Investigator has the discretion to remove subjects from the trial should there be any safety concerns, or if the subjects wellbeing is at jeopardy.
Taken together, the risk of study participation is considered to be minimal and justified when compared to the potential benefit of a successful clinical development of BI 1358894 for patients with MDD and BPD.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of a single dose of bupropion when given alone (Reference) compared with co-administration (Test) on the 15th day of a 19-day treatment with BI 1358894 (100 mg once daily) following oral administration in healthy volunteers.
The assessment of safety and tolerability will be additional objectives of this trial.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for bupropion when administered alone and co-administered at BI 1358894 steady state:

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

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for bupropion when administered alone and co-administered at BI 1358894 steady state:

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

2.2.1.2 Safety and tolerability

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

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial is designed to assess effects of BI 1358894 on CYP2B6 activity after achievement of steady-state concentrations of BI 1358894.
The trial will be performed as an open-label, two period fixed sequence trial in healthy male and female volunteers enrolled at a single site. Eighteen subjects will receive the following oral treatments (for details refer to Section 4.1.):

- 150 mg bupropion hydrochloride as single dose on Day 1 of Visits 2 and 3
- 100 mg BI 1358894 as daily doses over 19 days from Day -14 to Day 5 of Visit 3

There will be an interval of 21 days between the single-dose administrations of the CYP2B6 probe, bupropion (Day 1 of Visits 2 and 3).

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

Because of the long (50-70 hours) half-life of BI 1358894, a fixed-sequence design was selected, in which BI 1358894 is administered in the second study period only.

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

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

Dosing durations are long enough to reliably achieve steady-state drug exposures.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 healthy male and female will enter the study. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male or female 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. Male subjects, or female subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Sexually abstinent
   - Use of adequate contraception, e.g. any of the following methods plus condom: implants, injectables, intrauterine device
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

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 safety laboratory, 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 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections

10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation, or vaccination of any kind requiring re-vaccination during the course of the trial)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

Female subjects will not be allowed to participate, if any of the following apply:

23. Positive pregnancy test
24. Lactation

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

25. A history of cerebral seizure
26. A history of bipolar mood disorder, bulimia or anorexia
27. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
28. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), 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:

- The subject wants to discontinue trial treatment, without the need to justify the decision
- 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.
- The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases). The subject will discontinue trial treatment if he or she shows one drug-related adverse event of severe intensity or one drug-related serious adverse event.
- 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
- In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

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

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be

involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see section 3.3.4.1 above

3.3.4.3 Discontinuation of the trial by the sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- 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
- Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial-
- The sponsor decides to discontinue the further development of the investigational product

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

3.3.5 Replacement of subjects

In case more than 2 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 or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Product 1:

Substance:	BI 1358894
Pharmaceutical formulation:	Film coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	Multiple doses from Day -14 to Day 5 of Visit 3 (19 days in total)

The characteristics of the reference product are given below:

Name:	Elontril
Substance:	Bupropion hydrochloride
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	150 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	Single doses on Days 1 of Visit 2 and Visit 3

Bupropion will be obtained from a public pharmacy.

4.1.2 Selection of doses in the trial

In this trial, multiple daily doses of 100 mg of BI 1358894 are planned, and are considered to be safe for administration to healthy subjects. Doses of 100 mg are on the upper end of the expected efficacious dose-range likely to be used in clinical practice.

The doses of bupropion are standard clinical doses. Single doses of 150 mg have been used in previous DDI trials with healthy volunteers [P10-12978, U07-1865, c03050404].

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a study subject number by first come first serve prior to first administration of trial medication in the morning of Day 1 of Visit 2. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each subject

This is an open-label, two-period, fixed-sequence trial. All subjects will receive the 2 treatments in fixed order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1358894[1]	Tablet	50 mg	2 tablets (100 mg) doses on days-14 to Day 5 (19 days) of Visit 3	1900 mg
	Bupropion[1]	Tablet	150 mg	1 tablet (150 mg) single dose on day 1 Visit 3	150 mg
R (Reference)	Bupropion[1]	Tablet	150 mg	1 tablet (150 mg) single dose on day 1 Visit 2	150 mg

[1] Drug administration after a standard continental breakfast

The trial medications will be administered to the subjects as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. Administration of BI 1358894 will be performed in the morning of Days -14 to day 5 of Visit 3, and administration of Bupropion will be performed on Days 1 of Visits 2 and 3 following a standard continental breakfast.
The consumption of the continental breakfast should occur within 30 minutes prior to dosing. PK blood samples should be taken before the study drug administration, whereas the safety laboratory samples should be taken as the first morning sample after an overnight fast.
To ensure a dosing interval of 24 hours (treatment T, Visit 3), the administration of BI 1358894 should take place at the same time every day. For BI 1358894 administration on Days -1 and 2, a deviation of no more than +/-15 min is allowed, whereas on ambulatory visits, a deviation of no more than +/- 60 min is allowed. The first BI 1358894 administration will be followed by a 2-hour post administration in-house observation period.

Table 4.1.4: 2 Composition of the standard continental breakfast as an example

Ingredients	kcal
1 bread roll	164
15 g butter	113
1 slice of Gouda cheese (approximately 40g)	146
1 slice of meat (approximately 20g)	33
1 cup of decaffeinated coffee or tea (without sugar)	2
Sum[1]	458

[1] The total caloric content is supplied approximately as following: approx. 88 kcal as protein, approx. 133 kcal as carbohydrate, and approx. 237 kcal as fat.

Subjects will be kept under close medical surveillance until 24 h following drug administration of Bupropion. During the first 5 h after Bupropion administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The single dose Bupropion in Period Reference and the single dose of Bupropion in Period Test are to be separated by a washout period of at least 7 days. There will be 14 days follow-up period after the last BI 1358894 administration.

4.1.5 Blinding and procedures for unblinding

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

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

4.1.6 Packaging, labelling, and re-supply

BI 1358894 will be provided by BI. It 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.
Bupropion tablets will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.
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 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 locally by the trial site upon written authorisation of the clinical trial leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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 fluid 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 on day 1 Visits 2 and 3.

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 on Visits 2 and 3.

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

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in order to avoid false-positive results in the drug screen.

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.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, suicidality assessment and a physical examination including neurological exam. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, suicidality assessment and a physical 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 (Dinamap, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes, absol.	X	--	--
	Reticulocytes/Erythrocyte	X	--	--
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	--
	Prothrombin time – INR (International Normalization Ratio)	X	--	--
	Fibrinogen	X	--	--
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Lactic Dehydrogenase	X	--	X
	Creatine Kinase [CK]	X	--	--
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--
	Follicle Stimulating Hormone[1]	X	--	--
Substrates	Glucose (Plasma)	X	--	X
	Creatinine	X	X	X
	eGFR (CKD-EPI for creatinine)	X	--	--
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	--	--
	C-Reactive Protein (Quant)	X	--	--
	Uric Acid	X	--	--
	Cholesterol, total	X	--	--
	Triglyceride	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

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

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visits 2 and 3 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 4 (end of trial examination)

1 Only for post-menopausal females if needed

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results might not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. 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)
COVID 19 infection[1]	SARS-CoV-2 virus PCR test
Pregnancy test (urine)[3]	Beta human chorionic gonadotropin (beta-HCG)
Pregnancy test (serum at screening only)[2]	

1 Will be performed at screening, and shortly (within 72 hours) before admission to the site as per Flow Chart.

2 Only for female subjects of childbearing potential.

3 Only for female subjects of childbearing potential. Before start of the study drugs, on Day -1 Visit 2, and day -14 Visit 3 and EOT.

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 6820, [redacted]) 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 [redacted], with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using SureStepTM Multi-Drug Test ([redacted]) and hcG urine test ([redacted]), respectively, or comparable test systems.

SARS-CoV-2 testing will be performed at the local lab mentioned above or at site. Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.2.4 Electrocardiogram

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

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

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

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

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

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

The original C-SSRS is shown in Appendix 10.1.

5.2.4.2 Neurological examination

As a general additional safety measure, a physical neurological examination will be performed at the time points specified in the respective Flow Chart.
The neurological examination will include the following assessments:

- General level of arousal
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Reflexes
- Assessment of muscle strength

- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

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

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. Adverse events of special interest

5.2.6.1.4 Adverse events of special interest

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

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

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the eDC. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain,

etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

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

5.2.6.2 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 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

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1358894 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 2 h, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

For quantification of bupropion (and relevant bupropion metabolite) plasma concentrations, 4.9 mL of blood will be taken into K2-EDTA-Gel blood drawing tubes per time point.
The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C.
Two plasma aliquots will be obtained from each blood sample and stored in polypropylene tubes. For analysis of bupropion (and bupropion metabolite) plasma concentrations, the first aliquot should contain at least 0.8 mL of plasma.
The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min for bupropion samples, with interim storage of blood samples in ice water before centrifugation. Centrifugation of bupropion samples should start within 45 min after blood withdrawal. In the time interval between centrifugation and storage in the freezer, bupropion samples should be cooled, e.g. by use of cryo blocks, to avoid conversion between the S- and R-enantiomers.
The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, bupropion aliquots will be stored upright at approximately -70°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.

At the analytical laboratory, the plasma samples will be stored appropriately until analysis.

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

After completion of the trial, the plasma samples may be used for further methodological investigations. However, only data related to the study will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSEMENT OF BIOMARKER

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

[redacted]

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 2 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 on Day 1, ± 45 min from 24 hours onwards, and ± 60 min from 119 hours onwards.

For ambulatory administration of BI 1358894 of Visit 3, a time window of ± 60 min will be allowed, whereas for BI 1358894 administrations on Days -1 and 2 of Visit 3, a deviation of no more than +/- 15 min is allowed.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, physical examination and neurological examination including suicidality assessment, refer to Section 5.2.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days 1 to 6 in period 1, day –14 to 6 in period 2). At least 6 days will separate drug administrations in the first and second treatment periods.

On Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On 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 5.3 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 Section 5.2.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit, at least 14 days after last administration of BI 1358894 or 5 days after last administration of Bupropion (as applicable).

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objective of this trial is to investigate whether there is a drug-drug interaction between BI 1358894 (as the perpetrator) and the CYP2B6 probe drug bupropion. Hence, the relative bioavailability of bupropion given as single dose without BI 1358894 (Reference R) and given as single dose at steady state of BI 1358894 (Test T) is analysed on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

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 2.2.1.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of bupropion given alone and at steady state of BI 1358894 will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug Bupropion will be calculated according to the to the relevant BI internal procedures.

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

Relevant protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose bupropion concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

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

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

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

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with 'subjects' considered as fixed effects.

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.1.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) 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 previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but

entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

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

7.6 RANDOMISATION

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 18 subjects in the trial, accounting for up to 2 non-PK evaluable subjects. This sample size is not based on a power calculation but is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for bupropion in a previous trial [c03050404] was about 19% for total bupropion, for both C_{max} and $AUC_{0\text{-}tz}$.
For various assumptions around this gCV, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

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

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
15.0	1.127	50	44.38	56.34
15.0	1.127	75	66.56	84.51
15.0	1.127	100	88.75	112.68
15.0	1.127	125	110.94	140.84
20.0	1.172	50	42.67	58.58
20.0	1.172	75	64.01	87.88
20.0	1.172	100	85.35	117.17
20.0	1.172	125	106.68	146.46
25.0	1.218	50	41.06	60.89
25.0	1.218	75	61.59	91.33
25.0	1.218	100	82.12	121.77
25.0	1.218	125	102.65	152.22

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

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

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

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.0.1.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

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

Samples and/or data may be transferred to third parties and other countries as specified in the biobanking 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 [redacted], [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

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

The trial medication BI 1358894 will be provided by the [redacted]. Bupropion will be obtained by the clinical trial site from a public pharmacy.

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]).

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

Analyses of Bupropion, S-Bupropion, R-Bupropion and metabolites S,S-Hydroxybupropion and R,R-Hydroxybupropion-concentrations in plasma will be performed at [redacted], [redacted].

Pharmacogenomic samples will be sent to and analysed by [redacted], [redacted].

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 COLUMBA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past 6 Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

Version 1/14/09

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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

Version 1/14/09

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		27 May 2021
EudraCT number		2020-006052-40
BI Trial number		1402-0018
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, two-period fixed sequence trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers

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

Section to be changed		1. Title page 2. Flow Chart 3. Section 3.3.3 4. Section 3.3.4.1
Description of change		1. CT Leader change from [redacted] to [redacted] implemented 2. Formatting corrected: In Flow Chart "Period T" header is now formatted as header to ensure it is displayed on all pages of this flow chart 3. Content and format: • Content: Exclusion limit for alcohol consumption in exclusion criterion 15 lowered to more than 24 or 12 g/d in men or women, respectively • Format: "Female subjects will not be allowed to participate, if any of the following apply:" is not an independent exclusion criterion but, as indicated by the ":" a header/explanation for the subsequent two criteria 4. Treatment discontinuation criterion for individual subjects for medical reasons specified that a drug-related severe or serious AE in a subject requires treatment discontinuation in the respective subject

Rationale for change		1. CT Leader has changed 2. Formatting correction avoids mistakes 3. Content change requested by IEC/CA. Formatting correction needed for implementation. 4. Specification of treatment discontinuation criterion requested by IEC/CA.

11.2 GLOBAL AMENDMENT 2

Date of amendment		23 Jun 2021
EudraCT number		2020-006052-40
BI Trial number		1402-0018
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, two-period fixed sequence trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Flow Chart 2. Section 4.1.4 3. Section 5.2.3 4. Section 6.1 5. Section 8.7
Description of change		1. Flow Chart: 1.1. Explanation added to footnote 9 that screening includes serum pregnancy test in females of childbearing potential 1.2. Addition of footnote 13 to Visit 2, Day -1; deletion of footnote 13 at Visit 2, Day 6, and addition of footnote 13 to Visit 3, Day -14 1.3. New footnote 14 “Urine drug screening and alcohol breath test”; added to Visit 2, Day -1 and Visit 3, Day -14 1.4. New footnote 15 “Before study drug administration”; added to Visit 3, Day -14,

		08:00 (PK sample BI 1358894, clinical laboratory, vital signs, physical/neurological examination), and to Visit 3, Days -6, -4, -3, -2, -1, 2, 3, 4, and 5 (PK sample BI 1358894) 1.5. Addition of "Ambulatory visit" to ambulatory appointments at Visit 3 and addition of "Discharge" to timepoint +24 h at Visit 3 1.6. Combination of the two rows at identical timepoint Visit 3, -24:00 h to one single row and deletion of the redundant AE questioning 1.7. Deletion of the two timepoints without activities (Visit 3, planned time 0:15 and 0:30) and deletion of the empty rows (Visit 3, between planned times 1:00 and 2:00 and between planned times 3:00 and 4:00) 1.8. Addition of 240 mL fluid intake at planned times +2:00 and +4:00 h at Visit 3 and Lunch moved from planned time +5:00 h to planned time +4:00 h at Visit 3 1.9. Correction of links in footnote 3 from Sections 5.2.1 and 5.2.2 to 5.2.2 and 5.2.4 1.10. New footnote 16 "At this timepoint, no safety lab B taken" added to newly introduced "X" in clinical laboratory column at Visit 3, Day -14 2. Section 4.1.4: 2.1. Table 4.1.4: 1: Already available footnote 1 ("drug administration after a standard continental breakfast") added also to "Bupropion" (previously only with BI 1358894). 2.2. Section 4.1.4, text part: Clarification that the described time window of +/- 15 min applies to BI 1358894 administration on Days -1 and 2, and added that for ambulatory administration of BI 1358894 a time window of +/- 60 min applies. 3. Section 5.2.3: 3.1. Table 5.2.3: 1: Addition of "--" when parameter is not measured in the respective laboratory set 3.2. Table 5.2.3: 2: Specification that urine pregnancy test applies only to female

		subjects of childbearing potential 3.3. Section 5.2.3, text (2nd paragraph): Deletion of hyperlink to Section 10 4. Section 6.1: Clarification that a time window of +/- 60 min applies to ambulatory BI 1358894 administration, and that for administration of BI 1358894 on Days -1 and 2, a time window of +/- 15 min applies. [redacted]
Rationale for change		1. Changes to Flow Chart: 1.1. Serum pregnancy test in women of childbearing potential at screening is described in Section 5.2.3; has now been added to Flow Chart for consistency 1.2. Urine pregnancy test prior to each treatment period is described in Section 5.2.3 including exact timepoints; has now been corrected in / added to Flow Chart for consistency 1.3. Alcohol breath test and urine drug screening are planned prior to each treatment period as per Section 5.2.3; has now been added to Flow Chart for consistency 1.4. New footnote 15 to describe order of events for clarity and consistency with Section 4.1.4 1.5. Clarification of ambulatory appointments and discharge timepoints for consistency with Sections 1.4, 4.1.4, and 6.2.2 1.6. Formatting at Visit 3 timepoint -24:00 h has been corrected for clarity; at this timepoint there were two AE questionings, the duplicate was deleted because illogical. 1.7. Deletion of timepoints without activities and of empty rows because these activity-empty lines are not needed (meaningless) and deletion makes Flow Chart clearer 1.8. Fluid intake on Day 1 of Visit 3 added and lunch moved from +5:00 to +4:00 h at Visit 3 for consistency with Day 1 of Visit 2 and for consistency with Section 4.2.2 1.9. Links in Flow Chart footnote 3 referred to wrong Sections. This has now been

		corrected. 1.10. Footnote 16 added to clarify that the newly introduced "X" in clinical laboratory column does not introduce a new safety lab B at Visit 3 Day -14. 2. Changes to Section 4.1.4: 2.1. Table 4.1.4: 1: Footnote 1 was missing for Bupropion and has now been added; administration of all study drugs after food is described as such in the Flow Chart and in the text of Section 4.1.4. 2.2. Section 4.1.4, text part: Specification of time windows for BI 1358894 administrations for clarification and alignment between conflicting statements in Sections 4.1.4 and 6.1. 3. Section 5.2.3: 3.1. Table 5.2.3: 1: Addition of "--" when the parameter is not a part of the respective set to improve readability of the table. 3.2. Table 5.2.3: 2: Specification that urine pregnancy test applies only to females of childbearing potential for consistency with Flow Chart footnote 13 and for consistency with text in Section 5.2.3. 3.3. Section 5.2.3, text, 2nd paragraph: Deletion of hyperlink to the appendix because text refers to ISF Section 10 and not to Section 10 of the protocol 4. Section 6.1: Specification of time windows for BI 1358894 administrations for clarification and alignment between conflicting statements in Sections 4.1.4 and 6.1. [redacted]

11.3 GLOBAL AMEDNMENT 3

Date of amendment		29 Jul 2021
EudraCT number		2020-006052-40
BI Trial number		1402-0018
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, two-period fixed sequence trial to

		evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers
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		Title Page
Description of change		Clinical Trial Leader change from [redacted] to [redacted] implemented
Rationale for change		Change in Clinical Trial Leader

APPROVAL / SIGNATURE PAGE

Document Number: c34402516 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: An open-label, two-period fixed sequence trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of bupropion in healthy volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	29 Jul 2021 21:38 CEST
Author-Trial Statistician		30 Jul 2021 10:41 CEST
Approval-Clinical Trial Leader		30 Jul 2021 13:00 CEST
Verification-Paper Signature Completion		04 Aug 2021 08:13 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed