Clinical Trial Protocol

	Document Number:	**c29880107-02**
EudraCT No.	2020-000351-13	
BI Trial No.	1402-0016	
BI Investigational Medicinal Product	BI 1358894	
Title	Investigation of pharmacokinetics and absolute bioavailability of BI 1358894 administered orally as tablet co-administered with an intravenous microtracer dose of [C-14]-BI 1358894 in healthy male volunteers via a non-randomised, open-label, fixed-sequence trial (part 1) followed by a randomised, open-label, single-dose, two-period, two-sequence cross-over relative bioavailability trial in BI 1358894 oral suspension (part 2)	
Lay Title	A study in healthy men to test how BI 1358894 is taken up in the body and how food influences the amount of BI 1358894 in the blood	
Clinical Phase	I	
Trial Clinical Monitor	[redacted] Phone: Fax:	
Principal Investigator	[redacted] Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 1))	
Version and Date	Version: 2.0	Date: 26 Jun 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	20 May 2020
Revision date	26 Jun 2020
BI trial number	1402-0016
Title of trial	Investigation of pharmacokinetics and absolute bioavailability of BI 1358894 administered orally as tablet co-administered with an intravenous microtracer dose of [C-14]-BI 1358894 in healthy male volunteers via a non-randomised, open-label, fixed-sequence trial (part 1) followed by a randomised, open-label, single-dose, two-period, two-sequence cross-over relative bioavailability trial in BI 1358894 oral suspension (part 2)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This trial is intended to examine the absolute oral bioavailability of BI 1358894 as tablet formulation for oral administration and the relative bioavailability of BI 1358894 administered as an oral suspension. The data are considered necessary to further support the understanding of the pharmacokinetics of BI 1358894.
Trial objectives	To determine the absolute oral bioavailability of BI 1358894. To investigate the relative bioavailability of an oral suspension of BI 1358894.
Trial design	Part 1: Period 1: non-randomized, open-label, single period, single arm Part 2: Period 2 and 3: randomized, open label, two-period, two-sequence cross-over Part 1 and 2 are designed in a fixed sequence.

Trial endpoints:	Part 1: Primary endpoints: $AUC_{0-\infty}$ of [C-14]-BI 1358894 i.v. $AUC_{0-\infty}$ of BI 1358894 p.o. Secondary endpoints: Oral route: C_{max} of BI 1358894 p.o. Part 2: Primary endpoints: AUC_{0-312} of BI 1358894 p.o Secondary endpoints: C_{max} of BI 1358894 p.o. $AUC_{0-\infty}$ of BI 1358894 p.o
Number of subjects	
total entered	12* (all on active drug) *Screening may include more than 12 healthy subjects who will be exposed to BI 1358894
each treatment	12 (all to receive active treatment in period 1-3)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Trial product 1 **Part 1 (Period 1)**	BI 1358894 film-coated tablet (Treatment Test (T1))
dose	100 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 2 **Part 1 (Period 1)**	BI 1358894 (C-14) as intravenous solution (Treatment Reference (R1))
dose	100 µg BI 1358894 consisting of 90 µg unlabelled BI 1358894 mixed with 10 µg labelled [C-14]-BI 1358894 in 10 mL intravenous solution (10 µg BI 1358894 [C-14] /mL) The radioactive dose per infusion will be ~0.039 MBq.

mode of admin.	Intravenous infusion of 15 min at ~ t_{max} (5 h)
Trial product 3 **Part 2 (Period 2/3)**	BI 1358894 oral suspension under fasted (Treatment Reference (R2)) or fed (Treatment Test (T2)) conditions
dose	100 mg
mode of admin.	Oral with 240 mL of water following a high fat, high calorie breakfast when fed (T2) or after an overnight fast of at least 10 h when fasted (R2).
Duration of treatment	Part 1: Oral dose (Treatment T1): Single oral dose, Day 1 Intravenous dose (Treatment R1): Single intravenous infusion of microtracer over 15 min, Day 1 Part 2: Oral dose (Treatment T2, R2) : Single oral dose, Day 1 of each Period (separated by a washout period of at least 17 days between drug administrations)

Statistical methods	Part 1: Absolute bioavailability (F) will be estimated by the ratios of the geometric means (test/reference) for the primary endpoints AUC0-∞ (dose normalized). Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Part 2: Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART (PART 1)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma} [7]	PK_{plasma} [C-14] BI 1358894	Suicidality assessment (C-SSRS)[9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
SCR	1	-21 to -2			Screening (SCR)[1]	x			x	x	x	
	2	-1	-22:00	10:00	Admission to trial site[11]	x[4, 13]						
			-14:00	18:00	Dinner							
			-10:30	21:30	Light voluntary snack[12]							
		1	-1:00	07:00			x[2]			x[2, 6]	x[2]	
			0:00	08:00	**Drug administration (BI 1358894, 100 mg tablet, oral)**							
			0:15	08:15			x					
			0:30	08:30			x				x	
			1:00	09:00			x			x[8]	x	
			1:30	09:30			x				x	
			2:00	10:00	240 mL fluid intake		x					
			3:00	11:00			x				x	
			4:00	12:00	Light snack[3]	x	x			x[8]	x	
			5:00	13:00	**Start of IV infusion containing [C-14]-BI 1358894** 240 ml fluid intake		x				x	
			5:05	13:05			x	x				
			5:10	13:10			x	x				
			5:15	13:15	**Stop of IV infusion containing [C-14]-BI 1358894**		x	x				
			5:30	13:30			x	x				
			5:45	13:45			x	x				
			6:00	14:00	240 mL fluid intake, thereafter lunch[3]		x	x			x	
			6:30	14:30			x	x				
			7:00	15:00			x	x				
			8:00	16:00			x	x		x[8]	x	
			10:00	18:00	Dinner[3]		x	x				
			12:00	20:00			x	x		x[8]	x	
		2	24:00	08:00	Breakfast[3]	x[13]	x	x		x[8]	x	
			34:00	18:00			x	x			x	
		3	48:00	08:00	Breakfast[3]		x	x		x	x	
		4	72:00	08:00	Breakfast[3]		x	x			x	
		5	96:00	08:00	Breakfast (voluntary)[3], Discharge from trial site[10]		x	x	x	x	x	
		7	144:00	08:00	Ambulatory visit	x	x	x				x
		9	192:00	08:00	Ambulatory visit		x	x				x
		11	240:00	08:00	Ambulatory visit	x	x	x				x
		14	312:00	08:00	Ambulatory visit	x	x	x				x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening, urine alcohol test, hepatitis serology and HIV antibodies), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria, neurological examination and suicidality assessment (C-SSRS).
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. Safety laboratory including urine drug screening and urine alcohol test will be done at this time point.
5. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for twice daily during in-house days.
6. Prior to BI drug administration 3 triplicate ECGs will be recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
7. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
8. ECGs taken at these time points should be performed as triplicate and will be sent out for external evaluation.
9. Suicidality assessment will be performed at screening, at discharge from trial site for each period and at end of trial.
10. Confirmation of fitness includes physical and neurological examination, vital signs, ECG, suicidality assessment (C-SSRS), recordings of AEs and concomitant therapies assessed on Day 5 as well as evaluation of safety laboratory assessed on Day 2.
11. All subjects will be admitted to the trial site after an overnight fast of at least 10 h for all treatments.
12. Light voluntary snack to be consumed within 30 min to allow 10 h fasting prior to oral drug administration.
13. A PCR testing for SARS-CoV-2/COVID-19 will be performed at admission on Day – 1 and on Day 2.

FLOW CHART (PART 2)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma} [8]	Suicidality assessment (C-SSRS)[9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
Period 2/3 (two periods separated by a wash-out of at least 17 days)	3/4	-1	-22:00	10:00	Admission to trial site[11]	x[5, 12]					↓
			-12:00	18:00	Dinner						
		1	-1:00	07:00	Allocation to treatment sequence		x[2]		x[2, 7]	x[2]	
			-0:30	07:30	High fat, high calorie breakfast or overnight fast (for T2 only)						
			0:00	08:00	**Drug administration**						
			0:15	08:15			x				
			0:30	08:30			x			x	
			1:00	09:00			x		x[1]	x	
			1:30	09:30			x			x	
			2:00	10:00	240 mL fluid intake		x				
			3:00	11:00			x			x	
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x		x[1]	x	
			5:00	13:00			x			x	
			6:00	14:00			x			x	
			7:00	15:00			x				
			8:00	16:00	Snack (voluntary)[3]		x			x	
			10:00	18:00	Dinner[3]		x				
			12:00	20:00			x		x[1]	x	
		2	24:00	08:00	Breakfast[3]	x[12]	x		x[1]	x	
			34:00	18:00			x			x	
		3	48:00	08:00	Breakfast[3]		x		x	x	
		4	72:00	08:00	Breakfast[3]		x		x	x	
		5	96:00	08:00	Breakfast (voluntary)[3], Discharge from trial site[10]		x	x	x	x	
		7	144:00	08:00	Ambulatory visit	x	x				x
		9	192:00	08:00	Ambulatory visit		x				x
		11	240:00	08:00	Ambulatory visit	x	x				x
		14	312:00	08:00	Ambulatory visit	x	x				x
FU	5	52 to 57			End of trial (EOT) examination[4]	x[12]		x	x	x	x

1. ECGs taken at these time points should be performed as triplicate and will be sent out for external evaluation
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, concomitant therapies, neurological examination and suicidality assessment (C-SSRS).
5. Safety laboratory including urine drug screening and urine alcohol test will be done at this time point.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for twice daily during in-house days.
7. Prior to BI drug administration 3 triplicate ECGs will be recorded within approximately one hour. The recordings should be separated by at least 15 minutes.

8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
9. Suicidality assessment will be performed at screening, at discharge from trial site for each period and at end of trial.
10. Confirmation of fitness includes physical and neurological examination, vital signs, ECG, suicidality assessment (C-SSRS), and recordings of AEs and concomitant therapies assessed on Day 5 as well as evaluation of safety laboratory assessed on Day 2.
11. All subjects will be admitted to the trial site after an overnight fast of at least 10 h for all treatments.
12. A PCR testing for SARS-CoV-2/COVID-19 will be performed at admission on Day – 1, on Day 2 and at Follow-up.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
[redacted]	
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	
AUC_{0-312}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 312 h
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline personality disorder
bpm	Beats per minute
CA	Competent authority
CCK-4	Cholecystokinin tetrapeptid
CI	Confidence interval
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical Trial Manager

CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP3A4	Cytochrome P450 3A4
DG	Dose group
DILI	Drug induced liver injury
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
e.g.	exempli gratia (for example)
EoTrial	End of trial
EU	European Union
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FIM	First in man
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HIV	Human immunodeficiency virus
[redacted]	
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICRP	International commission on radiological protection
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
i.v.	Intravenous
[redacted]	

LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
p.o.	Oral
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory disease Coronavirus 2
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or treatment
[redacted]	
TMF	Trial master file
[redacted]	
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

[redacted]

XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

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

Major depressive disorder is a debilitating disease characterised by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the National Institute of Mental Health funded STAR*D trial of >4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residual symptoms [R16-5475] that significantly impacted the patients' quality of life [R06-2872]. When monotherapy is insufficient, clinicians employ different augmentation strategies including add-on treatment with lithium or atypical antipsychotics. When augmentation strategies also fail, convulsive therapies such as electro-convulsive therapy may be used.

Borderline personality disorder (BPD) is a chronic mental disorder with an estimated prevalence of around 2% in the general community [R16-5476] and severely impaired quality of life [R16-5474]. The main symptom clusters of BPD include impulsive-behavioural dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations, and affective instability. Patients with BPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times higher than in the general population [R16-5477]. Even the presence of a single diagnostic feature of BPD is predictive for poor functioning and psychiatric illness burden [R16-5483]. Treatment guidelines recommend psychotherapy as the mainstay of treatment, but pharmacotherapy is commonly used as an adjunctive, symptom-targeted component of treatment. However, no drug is approved for the treatment of BPD.

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

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

1.2 DRUG PROFILE

1.2.1 BI 1358894

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

Pharmacokinetics in Humans

Human PK data are currently available from the FIM study 1402-0001, which consisted of an SRD part (tested doses: 3 mg – 200 mg BI 1358894) and a food effect part (tested doses: 50 mg and 100 mg BI 1358894 under fasted and fed conditions) [report in preparation].

Following oral administration of film-coated tablets in fasted state BI 1358894 reached maximum plasma concentrations after 1 to 5 hours. Thereafter BI 1358894 plasma concentrations declined in a multiphasic fashion implying multi-compartmental distribution and exhibited a long terminal phase, which seems to be dose-independent.

C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ of BI 1358894 increased in a dose dependent way. Preliminary statistical evaluation showed that the increase in C_{max} and AUC_{0-72} was less than dose proportional. $AUC_{0-\infty}$ increased slightly less than dose proportional when given without food.

Also the food effect was dependent on the administered dose. While the exposure of BI 1358894 increased by factor 1.6 for the 50 mg dose, a food effect of factor 2.5 was observed for the 100 mg dose.

After completion of the food effect assessment, a dose of 200 mg BI 1358894 has been given after a high-calorie, high-fat meal in the SRD part of 1402-0001. Compared to the cohort receiving 200 mg under fasted conditions, food increased exposure by about 2.4-fold (exposure of 200 mg BI 1358894, fed conditions: C_{max} = 857 nM, AUC_{0-24} = 11640 nM*h).

Based on PK data of previous dose groups (DGs) in the 200 mg fed DG PK blood sampling was extended to 672 h. Sampling from 240 h to 672 h revealed another phase with low plasma concentrations and long terminal half-life of about 200 h. The proportion of AUC beyond 192 h is less than 20% of total AUC. Hence, it is not expected that this phase markedly contributes to accumulation or steady state attainment.

Preliminary PK data from the ongoing MRD study 1402-0002 support this observation. In the first dose groups (10 mg and 25 mg), an accumulation ratio (based on AUC_{0-24}) of 2.5 was observed. Steady state seems to be achieved after about a week. Both accumulation ratio and approximation of steady state attainment are in line with an effective half-life of ~33h.

Safety and tolerability in healthy subjects

At the time of preparing this trial protocol, four Phase I trials with administration of BI 1358894 to approximately 140 healthy subjects have been conducted. Preliminary data on safety and tolerability observed in these trials are given below:

1402-0001, SRD part: In the SRD part of 1402-0001 study safety, tolerability, PK and PD of rising single doses of BI 1358894 has been investigated in 8 DGs (3 mg – 6 mg – 10 mg – 25 mg – 50 mg – 100 mg – 200 mg fasted – 200 mg fed) with planned 8 subjects (6 on active, 2

on placebo). The most frequent drug related AE was headache, which has been reported by 18 of 48 subjects on active treatment. While headache occurred in 50% of subjects on active treatment in DG 2 and in DG 5-8, it was reported by only 1 subject in DG 1 and by 2 subjects in DG 4. The intensity of headache was mild (16 x) to moderate (2 x). The two cases of moderate headache have been observed in DG 5 and 7.

Beyond headache the following drug-related AEs have been observed (each in 1 subject only): delayed auditive perception, dizziness, head pressure, back pain, lightheadedness, tiredness and loss of concentration. These AEs were of mild to moderate intensity.

1402-0001, food effect part: This part of the 1402-0001 study investigated the effect of food on the kinetics of 50 mg (N=8) and 100 mg (N=12) BI 1358894, given as a single dose in two trial periods. The most frequent drug related AE was headache, which has been reported by 15 of 20 subjects (in nine subjects drug related headache occurred in both trial periods).

Beyond headache the following drug-related AEs have been observed: dizziness (5 subjects), tiredness (3 subjects), lightheadedness (2 subjects), loss of concentration (2 subjects), and meteorism, back pain, intermittent hip pain, head pressure, exacerbation of face acne and skin irritation with itching at the whole body (1 subject each). All drug related AEs were of mild or moderate intensity.

1402-0002, MRD-study: Trial 1402-0002 investigates safety, tolerability, PK and PD of rising multiple doses BI 1358894 (administered over 14 days) in a double-blinded fashion. At the time point this protocol is written, the clinical performance of four DGs (10 mg, 25 mg, 50 mg and 100 mg) with a total of 40 subjects (32 on active, 8 on placebo) has been already finished. The highest dose group of 200 mg is currently ongoing.

In course of the first four dose groups the most frequent drug related AE is headache which has been reported by 16 of 40 subjects. Frequency of drug related headache was not dose-dependent. With three and two affected subjects it was even less frequent in the higher DGs (50 mg, 100 mg). Drug related headache was mainly of mild intensity. Moderate intensity has been reported only for three subjects in DG 2 (2 x) and DG 4 (1 x).

In the 25 mg DG seven from ten subjects reported drug related headache. In four cases the affected subjects suffered from intermittent headache that lasted over 9-12 days. In one subject this was accompanied by drug related nausea on Day 6 and 9. Due to this continuous impairment the subject withdrew informed consent prior to dosing on Day 10.

Beyond headache the following drug-related AEs have been observed: orthostatic dysregulation (8 subjects), dizziness (4 subjects), tiredness (3 subjects), heartburn (2 subjects) and stomach cramps, blurred vision, acneiform skin (face), nausea, loose stool, flatulence, decreased concentration, head pressure, fasciculation (finger), and pressure on both eyes (1 subject each). These AEs were of mild intensity and did not follow a specific pattern of distribution.

1402-0003: Trial 1402-0003 investigated the effect of a single dose of BI 1358894 compared to placebo on BOLD responses in modulation brain processing of emotional and cognitive stimuli on the amygdala and related brain structure using fMRI in unmedicated patients with depression in a randomized, placebo-controlled, parallel-group study.

Overall, 73 patients with MDD (males and females) were treated either with BI 1358894 (25 patients), with citalopram (24 patients) used as a positive control, or placebo (24 patients). The overall summary showed that there were no deaths and SAEs. There were also no reports of AESIs, severe AEs, AEs leading to discontinuation of trial drug, or other significant AEs. The frequency of patients with any AEs was higher in the BI 1358894 treatment group (23 patients) than in the citalopram (15 patients) and placebo (14 patients) groups. The most common AE was headache. In the BI 1358894 treatment group, headache was reported by 17 patients compared with 13 patients in the citalopram and 10 patients in the placebo groups. Overall safety results from trial 1402-0003 are in line with the safety results of Phase I trials.

1402-0005: Trial 1402-0005 investigated the pharmacodynamic effects of a single dose of BI 1358894 on CCK-4 induced anxiogenic/panic-like symptoms using the Panic Symptom Scale (PSS) in preselected CCK-4 sensitive healthy volunteers in a double-blind, randomized, placebo-controlled, crossover study. In this trial, 20 patients were treated with a single dose of 100 mg BI 1358894 and placebo (10 patients in the sequence BI 1358894, placebo; 10 patients in the sequence placebo, BI 1358894).

The overall summary showed that there were no deaths and SAEs. There were also no reports of AESIs, AEs leading to discontinuation of trial drug, or other significant AEs. The most common AE was headache and was most frequently reported in the BI 1358894 treatment group (10 subjects) than in the placebo group (1 subject). Overall, the results of Trial 1402-0005 are in line with the pooled safety analysis of Phase I trials.

1402-0007: Trial 1402-0007 investigated the effect of the CYP3A4 inhibitor itraconazole on the kinetics of the CYP3A4 substrate BI 1358894 in 16 healthy subjects. A single dose of 10 mg BI 1358894 has been given alone and together with multiple doses of itraconazole. The most frequent drug related AE was headache reported by five subjects. In one case headache was of severe intensity. All subjects completed the trial.

1402-0009: Trial 1402-0009 investigated the relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1358894 in 28 healthy male subjects (14 in each part). Final results are not yet available at the time of CTA, however no safety findings in conflict with previous observations were reported.

1402-0010: Trial 1402-0010 investigated the relative bioavailability of different trial formulations of BI 1358894. The 24 participating subjects had to undergo three treatment periods. In each trial period a single dose of 100 mg BI 1358894 has been administered. The most frequent drug related adverse event was headache, that has been reported by about 50% of subjects. Drug related dizziness and tiredness was reported by two subjects each. All drug related adverse events were of mild or moderate intensity.

1.2.2 Residual Effect Period

Based on an effective half-life of 33 h the Residual Effect Period (REP) of BI 1358894 is 11 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

This trial is intended to examine the absolute oral bioavailability of BI 1358894 as tablet formulation for oral administration using an intravenous (i.v.) [C-14] microtracer approach (Part 1) and to investigate the relative bioavailability of the oral suspension (Part 2). The data are considered necessary to further support the understanding of the pharmacokinetics of BI 1358894.

1.4 BENEFIT - RISK ASSESSMENT

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

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 solvent for the intravenous infusion containing a mixture of labelled and unlabelled BI 1358894 is isotonic sodium chloride solution (0.9%). Therefore, in case of inadvertent paravenous drug administration apart from local swelling no tissue damage is expected.

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

The single dose administration of up to 200 mg BI 1358894 under fasted and fed conditions has been well tolerated by healthy subjects in the single rising dose trial [c28907328] as well as the single dose administration of 100 mg under fasted and fed administration in the relative bioavailability trial 1402-0010 [c28907328]. Therefore no undue risk is expected from the single dose administration of 100 mg BI 1358894 to healthy subjects planned for this trial. A more detailed description of BI 1358894 tolerability in healthy subjects can be found in Section 1.2.1.

Drug-induced liver injury (DILI):

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.

Administration of ^{14}C-labelled BI 1358894

BI 1358894 is labelled with the isotope [^{14}C] which is necessary for the purposes of this microtracer trial to distinguish the i.v. drug from the unlabelled oral drug. The radioactive dose per infusion has been calculated to be 0.039 MBq which does not exceed the threshold of 0.1 MBq, and thus falls into the ICRP 1 category (negligible radio burden) that is considered acceptable.

Overall assessment

In a previous trial, single oral doses up to 200 mg BI 1358894 administered in fed and fasted state as tablets were safe and well-tolerated. In the current trial, single oral dose of 100 mg BI 1358894 will be administered to healthy male subjects which will give an appropriate safety margin to the highest dose safely tested in the SRD (1402-0001). Each participant will be receiving a single i.v. infusion of a microtracer [C-14] BI 1358894 containing a radioactive dose <0.1 mSv (ICRP 1 category, negligible radioburden).

The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 1358894 without exposing participating volunteers to undue risk. However, there is always the potential of serious adverse events (SAEs) occurring with intake of trial medication. Risks to subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and verbal communication concerning AEs.

If the investigator should have any clinical concern, the safety of the subjects will be of paramount importance. The investigator has the discretion to remove subjects from the study should there be any safety concerns or if the subject's wellbeing is at jeopardy.

The risk associated with the expected maximal radiation burden falls in ICRP category 1 with minor level risk. This is considered to be acceptable.

The risk to participating subjects is minimized and justified when compared to the potential benefit that a successful clinical development of BI 1358894 could provide to the treatment of major depressive disorder and borderline personality disorder.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Part 1

The main objective of Part 1 of this trial is:

- To investigate the absolute bioavailability of 100 mg of BI 1358894 (Test 1, T1) with an intravenous microdose formulation containing labelled [C-14] BI 1358894 and an unlabelled oral tablet formulation of BI 1358894 in healthy male subjects.

Part 2

The main objective of Part 2 of this trial is:

- To investigate the relative bioavailability of BI 1358894 administered as an oral suspension.

2.1.2 Primary endpoints

Part 1

The following pharmacokinetic parameters will be determined for BI 1358894:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 to infinity after i.v. administration) for (C-14) BI 1358894 i.v.
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 to infinity after oral administration) for BI 1358894 p.o.

Part 2

The following pharmacokinetic parameter will be determined for BI 1358894:

- AUC_{0-312} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 312 h)

2.1.3 Secondary endpoints

Part 1

The following pharmacokinetic parameter will be determined for BI 1358894:

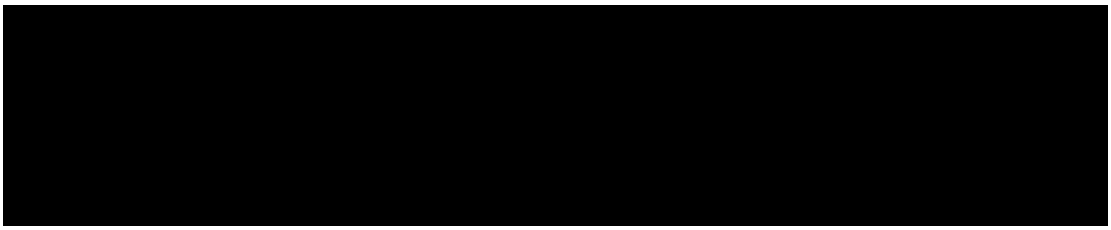
- C_{max} (maximum measured concentration of the analyte after oral administration)

Part 2

The following pharmacokinetic parameters will be determined for BI 1358894:

- C_{max} (maximum measured concentration of the analyte after oral administration)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity after oral administration)

[redacted]



2.2.2.2 Safety and tolerability

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

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

Part 1 of the study will be performed as a non-randomised, open-label trial in healthy male subjects in order to investigate the pharmacokinetics and absolute bioavailability of BI 1358894 as an oral tablet co-administered with an i.v. microtracer dose of [C-14]-BI 1358894. The reference treatment in Part 1 (Reference 1 – R1) will be 10 mL intravenous infusion of 100 µg BI 1358894 using a mixture of 90 µg unlabelled and 10 µg [C-14] labelled BI 1358894. The oral treatment (Test 1 – T1) will consist of two 50 mg BI 1358894 tablets administered on Day 1 to subjects in the fasting state. The i.v. infusion will start 5 hours after oral drug administration, i.e. at the time of the expected t_{max}.

This will be followed by Part 2 of the study which will be performed as a randomised, open-label, single-dose, two-period, two-sequence cross-over trial to investigate the relative bioavailability of BI 1358894 administered as an oral suspension. In Part 2, the treatments will consist of a single dose of 100 mg BI 1358894 administered as an oral suspension either in the fasted state (Reference 2 – R2) or in the fed state (Test 2 – T2). In Part 2, the subjects will be randomly allocated to the 2 treatment sequences (T2-R2 or R2-T2).

Part 1 and Part 2 are designed in a fixed sequence.

For details, refer to Section 4.1.

There will be a washout period of at least 17 days between the treatments, i.e. the dosing in Part 1 and the dosing in the first treatment period of Part 2, as well as the dosing in the first treatment period of Part 2 and the dosing in the second treatment period of Part 2 are separated by at least 17 days.

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

For the absolute bioavailability, the same subject will receive a ^{14}C-labelled microtracer infusion on Day 1 after a single oral dose of BI 1358894. Thus the oral bioavailability will be calculated for each subject.

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations [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 that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 12 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only healthy male subjects will be included in the study because they are an ideal population for the objectives of this trial since they provide relatively stable physiological biochemical and hormonal conditions, i.e. in the absence of disease-related variations and relevant concomitant medications.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 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 who meet any of the following criteria from at least 30 days before the first administration of trial medication until 90 days after trial completion:
   - Use of adequate contraception of the female partner, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device that started at least 2 months prior to first study drug administration or barrier method (e.g. diaphragm with spermicide) or,
   - Sexually abstinent or
   - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success) or
   - Surgically sterilised female partner (including hysterectomy, bilateral tubal occlusion or bilateral oophorectomy) or
   - Postmenopausal female partner, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 40 to 100 bpm
3. C-reactive protein (CRP) > upper limit of normal (ULN), liver or kidney parameter above ULN
4. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
5. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
6. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
7. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
8. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
9. History of relevant orthostatic hypotension, fainting spells, or blackouts
10. Chronic or relevant acute infections
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (average consumption of more than 21 units per week)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within 4 days prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

24. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
25. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
26. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column) in the period of 1 year prior to screening

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject 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

6. The subject shows a raised CRP level of >3.00 mg/dL
7. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP<90/50 mmHg) or hypertension (BP>180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
8. The subject experiences a serious adverse reaction which is considered at least possibly related to the IMP administration

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

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 subjects do not complete the trial, the Clinical Trial Leader together with the Principal Investigator, 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

Radiolabelled BI 1358894 (C-14) (R1) is administered as an intravenous solution. The powder used for intravenous solution containing [C-14] BI 1358894 and unlabelled BI 1358894 has been manufactured by BI Pharma GmbH & Co. KG. The mixture of [C-14] BI 1358894 and unlabelled BI 1358894 and the solution from this mixture are made by [redacted]

Tablet formulation and oral suspension of BI 1358894 have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product 1 (T1) are given below:

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

The characteristics of the reference product 1 (R1) are given below:

Name:	BI 1358894 (C-14) intravenous solution
Substance:	BI 1358894 mixed with [C-14] BI 1358894
Pharmaceutical formulation:	Intravenous solution
Source:	[redacted]
Unit strength:	100 µg BI 1358894 consisting of o 90 µg unlabelled BI 1358894 mixed with 10 µg labelled [C-14] BI 1358894 o in 10 mL intravenous solution (10 µg BI 1358894 (C-14) /mL)
Posology:	1-0-0
Route of administration:	i.v.
Duration of use:	One single infusion on Day 1 of Part 1, infused over 15 minutes

The characteristics of the test product 2 (T2) and reference product 2 (R2) are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	Oral suspension
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg/mL
Posology:	1-0-0
Route of administration:	oral
Duration of use:	single dose on Day 1 of Period 2 and Period 3

4.1.2 Selection of doses in the trial

The dose selected for this trial is one of the standard clinical doses (see Section 1.2).

The oral dose of 100 mg BI 1358894 is below the already tested highest oral dose of 200 mg of BI 1358894 in the SRD in healthy subjects. In healthy volunteers, this dose was safe and well-tolerated (Section 1.2). An oral dose of 100 mg, administered as single dose, is considered adequate for the objectives of the current trial.

The oral dose (100 mg BI 1358894) is ~1000-fold higher than the intravenously infused dose (100 µg). Therefore, exposure of BI 1358894 resulting from the infusion is considered negligible.

The i.v. dose on Day 1 of Part 1 administered as an infusion will include ^{14}C radiolabelled BI 1358894. The radiolabelled dose has been selected to provide sufficient analytical sensitivity, (Accelerator Mass Spectrometry), in this microtracer study while not exceeding the threshold of negligible radioactive burden, see Section 1.4.

4.1.3 Method of assigning subjects to treatment groups

Part 1 of the trial is open-labelled, single arm, therefore all subjects will receive the same treatments. Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2.

Part 1 and Part 2 will be conducted in a fixed-sequence design.

Part 2 of the trial follows a randomized, two-treatment, two-sequence study design. The randomisation list for Part 2 will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the administration of trial medication in the morning of Day 1 (Visit 3). For this purpose, numbers of the randomisation list will be allocated to the subjects in order of screening (the subject who was screened and approved first will be the first subject on the subject list). Subjects are then assigned to a treatment sequence according to the randomisation list.

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

Part 1 of the trial follows a non-randomized, open-label, single arm, single period design. Part 2 of the trial is a randomized, open-label, two-period, two-way crossover study. In Part 2, all subjects will receive the 2 treatments in randomised order. Part 1 and Part 2 of the study are designed in a fixed sequence. 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
T1 (Test 1)	BI 1358894	Tablet	50 mg	2 tablets (50 mg), single dose, fasted	100 mg
R1 (Reference 1)	BI 1358894 (C-14)	i.v. infusion	10 µg/mL	10 mL (10 µg), single dose	100 µg
T2 (Test 2)	BI 1358894	Oral suspension	25 mg/mL	100 mg, single dose, fed	100 mg
R2 (Reference 2)	BI 1358894	Oral suspension	25 mg/mL	100 mg, single dose, fasted	100 mg

Administration of trial medication will be performed after subjects have fasted overnight for T1 and R2; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting position.

For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

For T2, a high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance ‘Food-Effect Bioavailability and Fed Bioequivalence Studies’ [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

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

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

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 96 h after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments in Part 1 and Part 2, as well as between Period 2 and Period 3 of Part 2 will be separated by a wash-out phase of at least 17 days.

4.1.5 Blinding and procedures for unblinding

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

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

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

4.1.6 Packaging, labelling, and re-supply

Unlabelled drug supplies will be provided by BI. Radiolabelled drug supplies manufacturing will be provided by [redacted].

The Investigational Medicine products will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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 oral drug intake.

From 1 h before oral drug intake until lunch (or light snack for Part 1), fluid intake is restricted to the milk served with breakfast if applicable (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, in Part 2) post-dose (mandatory for all subjects).

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

Poppy-seed containing products should not be consumed starting 3 days prior to first trial drug administration until after the last PK sample of the trial.

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

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

Excessive physical activity (such as competitive sport) should be avoided from 96 h (4 days) before the first administration of trial medication until the end of trial examination.

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma 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, a physical examination and a neurological examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of weight and a neurological examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (e.g. Dinamap WC 150) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 4 h at the screening and EOT visits, and at least 10 h for all other time points. 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.

SARS-CoV-2 / COVID-19 specific test will be conducted at admission on Day – 1 and on Day 2 for each treatment period, and at Follow-up. For further details refer to Appendix 10.2.

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

Table 5.2.3: 1 Routine laboratory tests

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

Table 5.2.3: 1 Routine laboratory tests (cont.)

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

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

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a urine alcohol and drug test (e.g. ADVIA Chemistry XPT system) will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted]., with the exception of drug screening. Urinalysis stix and drug screening tests will be performed using e.g. Clinitek Novus test and ADVIA Chemistry XPT system, respectively, or comparable test systems.

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

5.2.4 Electrocardiogram

Recording and storing

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. Mortara Eli 250 C) at the times provided in the Flow Chart.

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

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

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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

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

Data transfer

For time points specified in the Flow Chart, i.e. time points on Day 1 up to 24 h post-dose, ECGs will be transferred electronically to the central ECG lab ([redacted]) for evaluation.

In case of repeat ECGs due to quality reasons, all recordings will be transferred to the central ECG lab and the repeated ECGs will be flagged in the database.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab and evaluated but will not be included into the statistical analysis of interval lengths. Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation by the central ECG laboratory

Central ECG lab evaluation will be performed for the first of three replicate ECGs per time point with ECG recordings as specified in the Flow Chart (i.e., Day 1 up to 24 h post-dose for each Period). The remaining second and third replicate ECGs will be stored for additional analyses, if required, e.g. by authorities at a later time point. For baseline, where 3 triplicate ECGs are recorded, only the first of the triplicate ECGs (i.e. 3 single ECGs) will be evaluated.

Central evaluation will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. The remaining second and third replicate ECG will be stored for additional analysis if required, e.g. by authorities at a later time point.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details). All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study. For blinding arrangements see Section 4.1.5. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by single reader.

For quality assurance and control of measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/ her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

Evaluation by Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used.

In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment using the C-SSRS (paper version)

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

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

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

After the baseline visit the assessment ‘since last visit’ will be performed at each clinic or phone visit (‘since last visit’ version). The investigator is to review positive and negative

reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist.

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

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

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

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

The original English version can be found in Appendix 10.1.

5.2.5.2 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. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

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

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

5.2.6.1.5 Intensity (severity) of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Sufficient discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 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 by the investigator:

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

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

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

5.2.6.3 Collection and reporting of the adverse event headache

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

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

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, a blood sample 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.

For quantification of [C-14] BI 13588945 plasma concentrations, an additional K2-EDTA tube needs to be collected as indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

For detailed description of blood sampling, sample handling, sample preparation, sample storage, tube labelling and sample shipment please refer to the laboratory manual.

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

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

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic 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 each treatment period are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 10 min for the first 4 h following the trial drug administration (on Day 1 of each treatment period) and ± 30 min thereafter until discharge on Day 5. During the ambulatory visits, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 120 min.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Part 1 of the trial and Period 2 and 3 of Part 2). At least 17 days will separate drug administrations in the first and second Part of the trial as well as in the second and third treatment periods of Part 2 of the trial.

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 96 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 Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

Part 1:

The main objective of this study part 1 is to investigate absolute bioavailability of an unlabelled oral tablet formulation of BI 1358894 (Test 1, T1) compared to BI 1358894 [C-14] as intravenous solution (Reverence 1, R1) in healthy male subjects on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3.

Part 2:

The main objective of this study part 2 is to investigate the relative bioavailability of 100 mg BI 1358894 administered as an oral suspension in fed healthy male subjects (Test 2, T2) compared with 100 mg BI 1358894 administered as an oral suspension in fasted healthy male subjects (Reverence 2, R2) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3.

[redacted]

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 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Part 1:

The absolute bioavailability of 100 mg BI 1358894 with an intravenous microdose formulation containing labelled [C-14] BI 1358894 compared with an unlabelled oral tablet formulation 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.

Part 2:

The relative bioavailability of 100 mg BI 1358894 administered as an oral suspension under fed conditions compared with 100 mg BI 1358894 administered as an oral suspension under fasted conditions will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

In both parts of the trial, confidence intervals and p-values will be computed, but have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects, while p-values are considered as an exploratory measure of evidence for effects in the present data.

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 violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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

Pharmacokinetics

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

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

Relevant protocol violations may be:

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

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

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

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

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

7.3.1 Primary endpoint analyses

Primary analyses

Part 1:

The statistical model of study part 1 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 ‘formulation’. The effect 'subjects' will be considered as random, whereas ’formulation’ 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 formulation k,

μ = the overall mean,

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

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

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

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

Part 2:

The statistical model of study part 2 used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence or block, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

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

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

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

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

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

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

For study part 1 and part 2, 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.

[redacted]

7.3.2 Secondary endpoint analyses

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

[redacted]

7.3.4 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake (test

treatment) and beginning of reference treatment will be assigned to the test treatment period. Those between the start of infusion until the end of REP (see Section 1.2.2) will be assigned to the combined test/reference treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. 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.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further qualitative and quantitative ECG endpoints, including the calculation of heart rate corrected QT intervals. The TSAP will provide further details.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Part 1:

Randomization is not applicable in this open-label and single group clinical study part. All subjects will receive the same treatment. Consecutive subject numbers will be assigned via the EDC system.

Part 2:

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

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 12 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (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.

Trial 1402-0010 used the same tablet formulation as the tablet formulation that will be used in this trial [c28907328]. The observed intra-individual coefficient of variation (gCV) for BI 1358894 in that trial was roughly 18% for C_{max} and 8% for $AUC_{0-\infty}$.

For various assumptions around the gCV of 18-20%, Tables 7.7: 1, 7.7: 2, 7.7: 3 provide 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% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2x2 crossover trial (N=10).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
16.000	1.202	40.000	33.275	48.085
16.000	1.202	50.000	41.593	60.106
16.000	1.202	60.000	49.912	72.127
16.000	1.202	70.000	58.231	84.148
16.000	1.202	80.000	66.549	96.169
16.000	1.202	90.000	74.868	108.190
16.000	1.202	100.000	83.187	120.212
18.000	1.230	40.000	32.529	49.187
18.000	1.230	50.000	40.661	61.484
18.000	1.230	60.000	48.793	73.781
18.000	1.230	70.000	56.926	86.077
18.000	1.230	80.000	65.058	98.374
18.000	1.230	90.000	73.190	110.671
18.000	1.230	100.000	81.322	122.968
20.000	1.258	40.000	31.804	50.309
20.000	1.258	50.000	39.755	62.886
20.000	1.258	60.000	47.705	75.463
20.000	1.258	70.000	55.656	88.040
20.000	1.258	80.000	63.607	100.618
20.000	1.258	90.000	71.558	113.195
20.000	1.258	100.000	79.509	125.772
22.000	1.286	40.000	31.099	51.449
22.000	1.286	50.000	38.873	64.312
22.000	1.286	60.000	46.648	77.174
22.000	1.286	70.000	54.422	90.036
22.000	1.286	80.000	62.197	102.899
22.000	1.286	90.000	69.972	115.761
22.000	1.286	100.000	77.746	128.623

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

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

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
16.000	1.173	40.000	34.114	46.902
16.000	1.173	50.000	42.642	58.627
16.000	1.173	60.000	51.171	70.353
16.000	1.173	70.000	59.699	82.078
16.000	1.173	80.000	68.228	93.803
16.000	1.173	90.000	76.756	105.529
16.000	1.173	100.000	85.285	117.254
18.000	1.196	40.000	33.452	47.830
18.000	1.196	50.000	41.815	59.788
18.000	1.196	60.000	50.178	71.745
18.000	1.196	70.000	58.541	83.703
18.000	1.196	80.000	66.904	95.660
18.000	1.196	90.000	75.267	107.618
18.000	1.196	100.000	83.630	119.575
20.000	1.219	40.000	32.806	48.772
20.000	1.219	50.000	41.007	60.965
20.000	1.219	60.000	49.209	73.158
20.000	1.219	70.000	57.410	85.351
20.000	1.219	80.000	65.612	97.543
20.000	1.219	90.000	73.813	109.736
20.000	1.219	100.000	82.015	121.929
22.000	1.243	40.000	32.176	49.726
22.000	1.243	50.000	40.220	62.158
22.000	1.243	60.000	48.264	74.590
22.000	1.243	70.000	56.308	87.021
22.000	1.243	80.000	64.352	99.453
22.000	1.243	90.000	72.396	111.884
22.000	1.243	100.000	80.440	124.316

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

Table 7.7: 3 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2x2 crossover trial (N=14).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
16.000	1.152	40.000	34.713	46.093
16.000	1.152	50.000	43.391	57.616
16.000	1.152	60.000	52.069	69.139
16.000	1.152	70.000	60.747	80.662
16.000	1.152	80.000	69.426	92.185
16.000	1.152	90.000	78.104	103.708
16.000	1.152	100.000	86.782	115.231
18.000	1.173	40.000	34.112	46.904
18.000	1.173	50.000	42.640	58.630
18.000	1.173	60.000	51.168	70.356
18.000	1.173	70.000	59.696	82.082
18.000	1.173	80.000	68.224	93.808
18.000	1.173	90.000	76.752	105.534
18.000	1.173	100.000	85.280	117.260
20.000	1.193	40.000	33.525	47.726
20.000	1.193	50.000	41.906	59.657
20.000	1.193	60.000	50.287	71.589
20.000	1.193	70.000	58.668	83.520
20.000	1.193	80.000	67.050	95.452
20.000	1.193	90.000	75.431	107.383
20.000	1.193	100.000	83.812	119.315
22.000	1.214	40.000	32.951	48.557
22.000	1.214	50.000	41.189	60.696
22.000	1.214	60.000	49.426	72.836
22.000	1.214	70.000	57.664	84.975
22.000	1.214	80.000	65.902	97.114
22.000	1.214	90.000	74.140	109.253
22.000	1.214	100.000	82.377	121.393

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

The calculation was performed as described by Julious [R11-5230] using R Version 3.5.1.

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

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in 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, storage and future use of biological samples and clinical data, in particular

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [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 trial manager (CTM), Clinical Research Associates, and investigators of participating trial sites

The non-labelled trial medication will be provided by the [redacted].

The radiolabelled trial medication will be provided by [redacted]

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

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

Analyses of radioactive [C-14] BI 13588945 concentrations in plasma will be conducted using [redacted]

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ([redacted]) for evaluation.

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

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 C-SSRS (ENGLISH VERSION)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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.)*

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
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	___

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

10.2 COVID-19 RELATED ASSESSMENT AND RISK MITIGATION

This section contains a risk assessment for study 1402-0016 with BI 1358894 due to the circumstances created by the coronavirus disease-19 (COVID-19) pandemic. In addition, the document summarizes the mitigation approaches to be followed to minimize the risk of spreading severe acute respiratory syndrome coronavirus 2 (SARS CoV-2).

Risk Assessment

BI 1358894 is a TRPC4/5 inhibitor in development for treatment of Major Depressive Disorder and for the treatment of Borderline Personality Disorder (BoPD). It is expected that treatment with BI 1358894 has the potential to improve affective symptoms and emotion control, especially in patients with MDD who inadequately respond to the current standard of care (SSRI; SNRI) and in patients with BoPD, where no approved drug treatment is currently available

Relevant information on the product

BI 1358894 is a highly potent and selective TRPC4/5 Inhibitor (transient receptor potential cation channel, subfamily C, members 4 and 5). It has the potential to address core symptoms of MDD and BoPD as it targets TRPC4/5 ion channels. TRPC4 and TRPC5 are highly expressed in pyramidal neurons of the amygdala in the frontal cortex, hippocampus, and hypothalamus, brain areas that are involved in circuits contributing to emotional control. BI 1358894 is thought to decrease neuronal excitability leading to normalization of the activation state of limbic circuits, which are known to be important for emotional control.

BI 1358894 is characterised by high bioavailability after oral intake, moderate volume of distribution, low clearance and long terminal half-life. Excretion occurs almost exclusively via faeces. After administration of BI 1358894 tablets, maximum plasma concentrations of BI 1358894 occurred around 1 to 5 hours after dosing. The terminal half-life was 41 to 52 hours for blood. Steady state was reached after 11 to 14 days of BI 1358894 dosing.

Currently, repeat dose toxicity studies up to 13 weeks revealed toxicologically relevant effects on the skin (mice), Harderian glands (mice), hepatic function (mice), the vascular system (rats), male genital tract (rats), the Central Nervous System (CNS) function (dogs), and the digestive tract, renal function, and white blood cell parameters (mice, rats and dogs).

Minimal to moderate subacute perivascular inflammation was observed in animals dosed at ≥30 mg/kg/day. The inflammation was centred around arterioles and small- to medium-sized muscular arteries of the mesentery and sometimes extended into the serosa of the digestive tract. In few animals dosed at 200 or 1000 mg/kg/day, diffuse slight inflammation and minimal to moderate focal necrotizing vasculitis were also noted. Vascular findings were no longer present after continued dosing at the same dose level for 4 or 13 weeks.

Minimally to moderately increased extramedullary hematopoiesis (EMH) in the spleen correlated with increased spleen weights at all dose levels. At ≥30 mg/kg/day, minimally to slightly increased myelopoiesis was present in the bone marrow (sternum) and minimal to

slight extramedullary myelopoiesis was also observed in the axillary, mandibular, and mesenteric lymph nodes. These findings correlated also with increases in reticulocytes and WBC noted in hematology at all dose levels. These findings were considered to be a physiologic adaptive response of hematopoietic and lymphoid organs to increased demand in context with perivascular inflammation.

In summary, toxicological investigations for BI 1358894 did not show any relevant effect on the function of the cardio-vascular system, the respiratory system or immune system so far. At this time point (16 Apr 2020) the toxicological investigation did not show any evidence that BI 1358894 may alter the susceptibility for a SARS-CoV2 infection or may facilitate the development of severe COVID-19.

Clinical safety was analysed for 7 completed Phase I clinical trials with 217 healthy volunteers and 73 patients with MDD so far (DLP 01 April 2020). There were no deaths or SAEs in any of these trials. Overall, BI 1358894 was well tolerated in healthy male subjects and in male and female patients with MDD.

In general, there were no clinically relevant findings in the clinical laboratory evaluation, including no treatment-emergent signs of inflammation based on erythrocyte sedimentation rate (ESR), C-reactive proteins (CRP), and faecal laboratory tests (faecal occult blood and faecal calprotectin). No evidence of significant changes in blood pressure, heart rate and ECG were observed so far.

Considerations around drug-drug-interactions are not included in this benefit-risk assessment – for those it should be referred to the protocol, Investigator's Brochure and the most recent label of the respective medication(s) used for treatment of COVID-19.

Benefit and risk conclusions and recommendations

BI 1358894 is a highly specific inhibitor of the TRPC 4/5 channels. TRPC 4/5 channels 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. A modulatory impact on the patient's immune system for TRPC 4/5 inhibitor is so far not expected so that susceptibility to vis-à-vis infections should not be affected. Therefore, subjects participating in Phase I trials are at this time point not considered to be at a higher risk for a SARS-CoV2 infection due to BI 1358894 intake than currently posed by the ordinary environment.

For the upcoming Phase I trial, the benefit-risk for the trial participants treated with BI 1358894 remain unchanged in relation to the COVID-19 pandemic since:

- The mode of action does not appear to have a substantial effect on clinically relevant organs (e.g. respiratory or cardiovascular system) critically affected by COVID-19.
- There is currently no evidence that intake of BI 1358894 leads to immunosuppression.
- The healthy volunteers are relatively young (18 – 55 years for the current trial) and in general without common co-morbidities associated with severe course of COVID-19.

Since every subject will be assessed thoroughly and individual benefit-risk assessments are made prior to study entrance by the investigator also in respect of potential COVID-19, the risk for subjects participating in these studies will not differ from the current general risk of COVID-19 with all its consequences.

The investigators will take the totality of information related to each single subject and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each subject's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, well-being and/or is in the best interest of the patient.

Study design key points

The study population for this study consists of healthy subjects with minimized COVID 19 infection risk (free of COVID-19 symptoms, negative PCR test(s) before investigational medicinal product [IMP] administration) and with minimized impact of COVID-19, if contracted during the study (eg, during the COVID-19 pandemic the upper age is 55 years (inclusive), upper body mass index [BMI] ≤29.9 kg/m2).

Subjects will stay in-house from Day – 1 until Day 5 of each treatment period (following a single dose administration on Day 1). Subjects will come back for ambulatory visits on Day 7, 9, 11 and 14. At the time of the follow-up examination (Day 52 – Day 57) BI 1358894 is expected to be eliminated.

SARS-CoV-2 containment measures to the CTP

The following SARS-CoV-2 containment measures will be taken during the study:

- The study will be conducted in accordance with guidance from the Central Committee on Research Involving Human Subjects (CCMO [Centrale Commissie Mensgebonden Onderzoek]) on conducting Phase 1 trials in Clinical Research Units in The Netherlands during the COVID 19 pandemic.
- During the entire study, the clinical research unit will implement all recommendations issued by the Dutch Government, including specific guidelines related to clinical research executed in clinical research units with respect to minimizing the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of personal protection equipment by study staff. Details on specific procedures are described in the Site Specific Manual.
- Polymerase chain reaction (PCR) testing for SARS-CoV-2 will be performed at the following time points:
    - 1 nasopharyngeal PCR test directly before admission to the unit on Day - 1 and 1 additional nasopharyngeal PCRs on Day 2 for confirmatory purpose for each treatment period.

    - Repeated nasopharyngeal PCR test at follow-up visit.
- Physical exams will be limited to the necessary visits (screening, discharge and follow-up).
- In cases where subjects are not able to attend study visits due to the presence of a SARS-CoV 2 infection, the Investigator will discuss with the Sponsor potential mitigation approaches (including, but not limited to, extending the visit window, conducting evaluations via video link or phone call, allowing for safety procedures to be conducted at a local facility). The rationale (e.g., the specific limitation imposed by the SARS-CoV-2 infection that led to the inability to perform the protocol-specified assessment) and outcome of the discussion will be documented in the electronic case report form (eCRF).
- A subject should not be admitted if there was any contact with a COVID-19 patient within the last 2 weeks prior to admission to the clinical research unit.
- If a subject is tested to be SARS-CoV-2 positive on Day -1, the subject will be excluded from participation with reference to exclusion criterion #4, and referred for treatment.
- If a subject becomes ill and/or is tested to be SARS-CoV-2 positive after the first administration of study treatment, dosing will be stopped. The subject will be isolated from other study participants and referred for treatment. The subject will be followed up in quarantine in the clinical research unit until complete elimination of the study compound or will be asked to quarantine at home according to guidelines of the Dutch government.

<u>Conclusion of COVID-19 risk containment</u>

Given the profile of the compound and given the study design, the COVID-19 risk minimization strategy as summarized above is considered adequate. The BI trial team and the [redacted] Principal Investigator and supporting staff recommend study continuation as per latest version of the protocol and with implementation of the measures detailed in this appendix to the protocol.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		26 June 2020
EudraCT number **EU number**		2020-000351-13
BI Trial number		1402-0016
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Investigation of pharmacokinetics and absolute bioavailability of BI 1358894 administered orally as tablet co-administered with an intravenous microtracer dose of [C-14]-BI 1358894 in healthy male volunteers via a non-randomised, open-label, fixed-sequence trial (part 1) followed by a randomised, open-label, single-dose, two-period, two-sequence cross-over relative bioavailability trial in BI 1358894 oral suspension (part 2)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow Chart Part 1 Flow Chart Part 2 Section 5.2.3 Safety laboratory parameters Appendix 10.2 COVID-19 related assessment and risk mitigation
Description of change		1. <u>Flow Chart Part 1/Flow Chart Part 2</u> Minor inconsistency regarding day of discharge was corrected in the footnotes. PCR testing was added on Day – 1 and Day 2 for each treatment period and at Follow-up. 2. <u>Section 5.2.3 Safety laboratory parameters</u> PCR testing was added on Day – 1 and Day 2 for each treatment period and at Follow-up. 3. <u>Appendix 10.2 COVID-19 related assessment and risk mitigation</u> This Appendix was added to provide additional information regarding the benefit-risk assessment with regards to COVID-19 infection and the risk mitigation in the context of this study.

Rationale for change		The changes were implemented to provide information for the trial on benefit-risk and mitigation measures with regards to the COVID-19 global pandemic. In the context of this amendment, minor inconsistencies were corrected throughout the document.

11.2 GLOBAL AMENDMENT 2

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

APPROVAL / SIGNATURE PAGE

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Title: Investigation of pharmacokinetics and absolute bioavailability of BI 1358894 administered orally as tablet co-administered with an intravenous microtracer dose of [C-14]-BI 1358894 in healthy male volunteers via a non-randomised, open-label, fixed-sequence trial (part 1) followed by a randomised, open-label, singledose,

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Verification-Paper Signature Completion	[redacted]	26 Jun 2020 11:15 CEST
Author-Trial Clinical Pharmacokineticist		26 Jun 2020 13:18 CEST
Approval-Team Member Medicine		26 Jun 2020 18:13 CEST
Author-Clinical Trial Leader		29 Jun 2020 07:44 CEST
Author-Trial Statistician		29 Jun 2020 10:30 CEST
Approval-[redacted] Medicine		29 Jun 2020 11:53 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed