Clinical Trial Protocol

	Document Number:	**c31118084-01**
EudraCT No.	2020-002054-25	
BI Trial No.	1402-0015	
BI Investigational Medicinal Product	BI 1358894	
Title	A phase I, open-label trial to investigate metabolism and pharmacokinetics of a single dose of [^{14}C] BI 1358894 administered as oral solution (Part 1) and multiple doses of BI 1358894 administered as film-coated tablets (Part 2) in healthy male volunteers	
Lay Title	A study in healthy men to test how BI 1358894 is taken up and handled by the body	
Clinical Phase	I	
Trial Clinical Monitor	[redacted] Phone: [redacted] Fax:	
Principal Investigator	[redacted] Phone: [redacted] Fax:	
Status	Final Protocol	
Version and Date	Version: 1.0	Date: 21 August 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	21 August 2020
Revision date	Not applicable
BI trial number	1402-0015
Title of trial	A phase I, open-label trial to investigate metabolism and pharmacokinetics of a single dose of [^{14}C] BI 1358894 administered as oral solution (Part 1) and multiple doses of BI 1358894 administered as film-coated tablets (Part 2) in healthy male volunteers
Principal Investigator:	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The trial is intended to investigate the basic pharmacokinetics, excretion pathways and metabolism of BI 1358894 and its metabolites.
Trial objective	To investigate the basic pharmacokinetics after a single dose of BI 1358894 and its metabolites, total radioactivity including mass balance, excretion pathways and metabolism following a single oral dose of 100 mg [^{14}C] BI 1358894 given to healthy male subjects. To investigate the pharmacokinetics of BI 1358894 and its metabolite(s) following treatment with 100 mg BI 1358894, once daily over 21 days.
Trial design	Open-label, single period and single arm design with 2 treatment parts (Part 1 single dose with radiolabelled compound and Part 2 multiple doses with non-radiolabelled compound).

Trial endpoints:	• Part 1: Primary endpoints: - Mass balance recoveries of total radioactivity in urine and faeces - Amount of radioactivity excreted as a percentage of the administered dose (fe_{0-t2}) for urine and faeces Secondary endpoints: Assessment of the oral pharmacokinetics of [^{14}C] BI 1358894 by calculating the following parameters: - for total radioactivity and for BI 1358894: C_{max} and AUC_{0-tz} • Part 2: Secondary endpoints: - Pharmacokinetics of BI 1358894 • AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24h) • C_{max} (maximum measured concentration of the analyte in plasma) • $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ) • $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
Number of subjects **total entered** **each treatment**	 16 8 (per Part)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 **dose** **mode of admin.**	Carbon 14 labelled BI 1358894 ([^{14}C] BI 1358894) as oral solution 100 mg on Day 1 (Part 1) - in 10 mL oral solution (10 mg/mL) containing a radioactive dose of 3.7 MBq (100 µCi) Oral

Test product 2 **dose** **mode of admin.**	BI 1358894 film-coated tablet formulation 100 mg (2x50 mg) QD (Part 2) Oral with 240 mL of water
Duration of treatment	Treatment Part 1: On Day 1, a single dose of radiolabelled oral solution (Test product 1) Treatment Part 2: Non-radiolabelled film-coated tablets (Test product 2) from Day 1 to Day 21.
Statistical methods	Descriptive statistics and graphical displays.

FLOW CHART

Flow Chart: Part 1 (Single dose)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood/plasma}$ [2, 9]	PK $_{urine}$ [5]	PK $_{faeces}$ [4]	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	A					x	x	
2	-1	-21:00	11:00	Admission to trial site	B[13,17]							x
	1	-2:00	06:00		x[3,8,16]	x[3]	x[3]	x[14]		x[3]	x[3]	▲
		0:00	08:00	Drug administration (labelled compound)			▲ |	▲ |				|
		0:20	08:20			x	|	|				|
		0:40	08:40			x	|	|				|
		1:00	09:00		x[16]	x	|	|		x	x	|
		2:00	10:00	240 mL water intake		x	|	|				|
		3:00	11:00			x	|	|				|
		4:00	12:00	Lunch, 240 mL water intake[6]	x[16]	x	+	|		x	x	|
		6:00	14:00			x	|	|				|
		8:00	16:00		x[16]	x	+	|				|
		10:00	18:00	Dinner[6]		x	|	|				|
		12:00	20:00	Snack[6]		x	+	|		x	x	|
	2	24:00	08:00		x[16,17]	x	+	+		x	x	|
		36:00	20:00			x	|	|				|
	3	48:00	08:00			x	+	+				|
	4	72:00	08:00			x	+	+				|
	5	96:00	08:00			x	+	+				|
	6	120:00	08:00			x	+	+				|
	7	144:00	08:00			x	+	+				|
	8	168:00	08:00		B[8]		+	+		x	x	|
	9	192:00	08:00			x	+	+				|
	10	216:00	08:00				+	+				|
	11	240:00	08:00			x	+	+				|
	12	264:00	08:00				+	+				|
	13	288:00	08:00			x	+	+				|
	14	312:00	08:00				+	+				|
	15	336:00	08:00	Discharge from trial site[15]	B[8]	x	▼	▼		x	x	▼

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood/plasma [2, 9]	PK urine [5]	PK faeces [4]	Vital signs (BP, PR), ECG	Questioning for AEs & concomitant medication
2	20	461:00	13:00	Start home collection[10, 11]				▲		▲
	21	485:00	13:00	Admission to trial site[10]	x[16, 17]	x	▲	┼		┼
	22	509:00	13:00	Discharge from trial site[10]			▼	▼	x	┼
	27	629:00	13:00	Start home collection[10, 11]				▲		┼
	28	653:00	13:00	Admission to trial site[10]	x[16, 17]	x	▲	┼		┼
	29	677:00	13:00	Discharge from trial site[10]			▼	▼	x	┼
	34	797:00	13:00	Start home collection[10, 11]				▲		┼
	35	821:00	13:00	Admission to trial site[10]	x[16, 17]	x	▲	┼		┼
	36	845:00	13:00	Discharge from trial site[10]			▼	▼	x	┼
	41	965:00	13:00	Start home collection[10,11]				▲		┼
	42	989:00	13:00	Admission to trial site[10]	x[16, 17]	x	▲	┼		┼
	43	1013:00	13:00	Discharge from trial site[10]			▼	▼	x	┼
	48	1133:00	13:00	Start home collection[10. 11]				▲		┼
	49	1157:00	13:00	Admission to trial site[10]	x[16, 17]	x	▲	┼		┼
	50	1181:00	13:00	Discharge from trial site[10]			▼	▼	x	▼
3	16-50			End of trial (EOT) examination[7,12,15]	C[17]				x	x

A, B & C: safety laboratory sets (see Table 5.2.3: 1)

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug and virus screening), 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. Pharmacokinetics (PK): BI 1358894 and metabolites in plasma; [^{14}C]-radioactivity in whole blood and plasma. At all time points, samples for [^{14}C]-radioactivity in whole blood and plasma will be taken. Samples for PK assessment of cold BI 1358894 will be collected for al PK samples taken and for its metabolites in plasma which will be collected at the metabolite PK time points in the Flow Chart, after intake of radiolabelled drug on Day 1. PK sampling for the metabolites will continue as long as radioactivity in plasma is above LLOQ (< 30 dpm/mL)
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration.
4. All stools (for [^{14}C]-radioactivity assessment [redacted] will be collected quantitatively from Day 1 in sampling intervals as defined in the Flow Chart after intake of [C] BI 1358894. Thereafter, if warranted, 24 h collections are to be performed on days 21-22, 28-29, 35-36, 42-43, and 49-50. A blank sample will be collected before drug administration on Day 1. Collection of the predose faeces sample will start from approximately -48 h before drug administration. Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 15). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity.
5. Urine collection intervals (for PK/[^{14}C]-radioactivity assessment [redacted] (planned time): on Day -1 or Day 1 predose (blank) sample, on Day 1 prior to start of urine collection voiding of the bladder, and at the intervals defined in the Flow Chart up to 336 h after drug administration. Thereafter, if warranted, 24 h collections are to be performed on days 21-22, 28-29, 35-36, 42-43, and 49-50. Urine sampling for PK will be stopped when release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 15). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity, BI 1358894 and its metabolites. [redacted]
6. If several actions are indicated at the same time point, the intake of meals will be the last action.

7. End-of-trial (EOT) examination to be performed within 1 to 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 50. EOT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, neurological examination and suicidality assessment (C-SSRS).
8. Subjects are to be fasted for at least 10 h before sample is taken.
9. Blood sampling for an individual subject can be stopped if [^{14}C]-radioactivity in plasma is below limit of detection (<LLOQ 30 dpm/mL) at two consecutive sampling time points for this subject.
10. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.
11. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, 41-42, and 48-49. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
12. For definition of the individual subject's end of trial see Section 6.2.3
13. Urine drug and alcohol screening will be done at this time point.
14. Subjects will collect a pre-dose faeces sample at home in specific containers provided by [redacted]
15. Confirmation of fitness includes physical and neurological examination, vital signs, ECG, suicidality assessment (C-SSRS) only at Day 15 and EOT, recordings of AEs and concomitant therapies as well as evaluation of safety laboratory assessed on Day 8.
16. At this time point, only a sample for haematocrit measurement is taken.
17. PCR testing for SARS-CoV-2 will be performed at admission on Day – 1, on Day 2, at each admission to the trial site for the 24-h visits and at EOT.

Flow Chart: Part 2 (Multiple dose)

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} [2, 9]	PK_{urine} [5]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant medication
1	-21 to -2			Screening (SCR)[1]	A			x	x	x
2	-1	-21:00	11:00	Admission to trial site	B[10, 11]					x
	1	-2:00	06:00			x[3]	x[3]	x[3]	x[3]	
		-0:30	07:30	Standard continental breakfast						
		0:00	08:00	Drug administration						
		0:30	08:30			x				
		1:00	09:00			x				
		2:00	10:00			x				
		4:00	12:00	Lunch[6]		x				
		5:00	13:00			x				
		6:00	14:00			x				
		7:00	15:00			x				
		8:00	16:00			x				
		10:00	18:00	Dinner[6]		x				
		12:00	20:00	Snack[6]		x				
		14:00	22:00			x				
	2	24:00	08:00	Drug administration[12]	x[11]	x[3]	x[3]			
	3	48:00	08:00	Drug administration[12]						
	4	72:00	08:00	Drug administration[12]						
	5	96:00	08:00	Drug administration[12]						
	6	120:00	08:00	Drug administration[12]						
	7	144:00	08:00	Drug administration[12]	B[8]	x[3]	x[3]	x[3]	x[3]	
		144:30	08:30			x				
		145:00	09:00			x				
		146:00	10:00			x				
		148:00	12:00	Lunch[6]		x				
		149:00	13:00			x				
		150:00	14:00			x				
		151:00	15:00			x				
		152:00	16:00			x				
		154:00	18:00	Dinner[6]		x				
		156:00	20:00	Snack[6]		x				
		158:00	22:00			x				
	8	168:00	08:00	Drug administration[12]		x[3]				
	9	192:00	08:00	Drug administration[12]		x[3]	x[3]			
	10	216:00	08:00	Drug administration[12]						
	11	240:00	08:00	Drug administration[12]		x[3]	x[3]			
	12	264:00	08:00	Drug administration[12]						
	13	288:00	08:00	Drug administration[12]						
	14	312:00	08:00	Drug administration[12]	B[8]	x[3]	x[3]	x[3]	x[3]	
		312:30	08:30			x				
		313:00	09:00			x				
		314:00	10:00			x				
		316:00	12:00	Lunch[6]		x				
		317:00	13:00			x				

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} [2, 9]	PK_{urine} [5]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs & concomitant medication
		318:00	14:00			x				
		319:00	15:00			x				
		320:00	16:00			x				
		322:00	18:00	Dinner[6]		x				
		324:00	20:00	Snack[6]		x				
		326:00	22:00			x				
	15	336:00	08:00	Drug administration[12]		x[3]	x[3]			
	16	360:00	08:00	Drug administration[12]						
	17	384:00	08:00	Drug administration[12]		x[3]	x[3]			
	18	408:00	08:00	Drug administration[12]						
	19	432:00	08:00	Drug administration[12]		x[3]	x[3]			
	20	456:00	08:00	Drug administration[12]						
	21	480:00	08:00	Drug administration[12]	B[8]	x[3]	x[3]	x[3]	x[3]	
		480:30	08:30			x				
		481:00	09:00			x				
		482:00	10:00			x				
		484:00	12:00	Lunch[6]		x				
		485:00	13:00			x				
		486:00	14:00			x				
		487:00	15:00			x				
		488:00	16:00			x				
		490:00	18:00	Dinner[6]		x				
		492:00	20:00	Snack[6]		x				
		494:00	22:00			x				
	22	504:00	08:00			x				
	23	528:00	08:00			x				
	25	576:00	08:00			x				
	27	624:00	08:00	Breakfast[6] (voluntary), Discharge from trial site after confirmation of fitness[4]	B[8]	x		x	x	
	30	696:00	08:00	Ambulatory visit		x				x
	34	792:00	08:00	Ambulatory visit		x				x
	37	864:00	08:00	Ambulatory visit		x				x
	41	960:00	08:00	Ambulatory visit		x				x
	44	1032:00	08:00	Ambulatory visit		x				x
	48	1128:00	08:00	Ambulatory visit		x				x
	51	1200:00	08:00	Ambulatory visit		x				x
	55	1296:00	08:00	Ambulatory visit		x				x
	58	1368:00	08:00	Ambulatory visit		x				x
3	62			End of trial (EOT) examination[7,9]	C[11]	x		x	x	x

A, B & C: safety laboratory sets (see Table 5.2.3: 1)

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug and virus screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy, review of inclusion/exclusion criteria, neurological examination and suicidality assessment (C-SSRS).
2. Pharmacokinetics (PK): BI 1358894 and metabolite(s) in plasma.

3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration.
4. Confirmation of fitness includes physical and neurological examination, vital signs, ECG, suicidality assessment (C-SSRS), recordings of AEs and concomitant therapies as well as evaluation of safety laboratory assessed on Day 21.
5. Urine collection (for PK assessment [redacted] planned time): A predose urine sample collected and stored on Day -1 or Day 1 predose will serve as blank sample. Urine collection is to be performed as described in the Flow Chart.
6. If several actions are indicated at the same time point, the intake of meals will be the last action.
7. End-of-trial (EOT) examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, neurological examination and suicidality assessment (C-SSRS). The EOT assessments will be performed after the last PK sample on Day 62 has been taken.
8. Subjects are to be fasted for at least 10 h before sample is taken.
9. For definition of the individual subject's end of trial see Section 6.2.3
10. Urine drug and alcohol screening will be done at this time point.
11. PCR testing for SARS-CoV-2 will be performed at admission on Day – 1, on Day 2 and at EOT.
12. A standard continental breakfast will be provided approx. 30 min prior to each daily drug administration from Day 1 to Day 21.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
$Ae_{faeces,\ t1\text{-}t2}$	Amount of analyte eliminated in faeces over the time interval t_1 to t_2
$Ae_{faeces,\ 0\text{-}t2}$	Amount of analyte eliminated in faeces from time 0 to the last quantifiable timepoint
$Ae_{urine,\ t1\text{-}t2}$	Amount of analyte eliminated in urine over the time interval t_1 to t_2
$Ae_{urine,\ 0\text{-}t2}$	Amount of analyte eliminated in urine from time 0 to the last quantifiable timepoint
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz\text{-}\infty}$	Percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation
$AUC_{t1\text{-}t2}$	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0\text{-}24}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
$AUC_{0\text{-}72}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h
BCRP	Breast cancer resistance protein
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline Personality Disorder
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R,\ t1\text{-}t2}$	Renal clearance of the analyte in plasma from the time point $_{t1}$ to $_{t2}$
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady-state over a uniform dosing interval τ
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTM	Clinical Trial Manager
CTP	Clinical trial protocol

CTR	Clinical trial report
Cum Ae	Cumulative recovery of [^{14}C]-radioactivity
Cum %Ae	Cumulative recovery of [^{14}C]-radioactivity expressed as a percentage of the dose
CYP3A4	Cytochrome P450 3A4
DG	Dose Group
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
$fe_{faeces,\ t1\text{-}t2}$	Fraction of administered drug excreted unchanged in urine over the time interval from t_1 to t_2
$fe_{urine,\ t1\text{-}t2}$	Fraction of administered drug excreted unchanged in the faeces over the time interval from t_1 to t_2
FIM	First-in-Man
FU	Follow-up
GCP	Good Clinical Practice
GI	Gastro-intestinal
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDD	Major Deperessive Disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)

PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QD	Once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
XTC	Ecstasy

1. INTRODUCTION

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) and borderline personality disorder (BPD). BI 1358894 has been characterised to be an inhibitor of P-glycoprotein (P-gp), Breast cancer resistance protein (BCRP) and of the Organic anion transporting polypeptides (OATP) 1B1 and 1B3 in-vitro. This trial should investigate the basic pharmacokinetics, excretion pathways and metabolism of BI 1358894 and its metabolites.

1.1 MEDICAL BACKGROUND

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 of a food effect part (tested doses: 50 mg and 100 mg BI 1358894 under fasted and fed conditions) [c24903142].

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 [c24903142]. 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 MRD study 1402-0002 [c28667517] 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 2 weeks. Both accumulation ratio and approximation of steady state attainment are in line with an effective half-life of ~ 50 to 70 h.

Safety and tolerability in healthy subjects

At the time of preparing this trial protocol, seven Phase I trials with administration of BI 1358894 to approximately 217 healthy subjects and 73 MDD patients 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 the 1402-0001 study [c24903142], 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 [c24903142] 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 [c28667517] investigated safety, tolerability, PK and PD of rising multiple doses BI 1358894 (administered over 14 days) in a double-blinded fashion in a total of five DGs (10 mg, 25 mg, 50 mg, 100 mg and 200 mg) with a total of 50 subjects (40 on active, 10 on placebo) has been already finished.

Overall, the most frequent drug related AE is headache which has been reported by 17 of 40 subjects. Frequency of drug related headache was not dose-dependent and was even less frequent in 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 (6 subjects), dizziness (5 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 [c28123801] 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 [c28123801] are in line with the safety results of Phase I trials.

1402-0005: Trial 1402-0005 [c28698771] 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 [c28698771] are in line with the pooled safety analysis of Phase I trials.

1402-0007: Trial 1402-0007 [c28714279] 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 [c28907328] 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.

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

1.2.2 Residual Effect Period

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

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 1358894 and its metabolites, total radioactivity in blood, plasma, urine and faeces and the resulting PK parameters after single dosing. Major tasks involve the structure elucidation of metabolites as well as the [^{14}C]-radioactivity in blood cells, plasma, urine and faeces. This study will also help to determine the metabolic pathways following oral administration of [^{14}C] BI 1358894 and BI 1358894. The second part of the study is intended to investigate the pharmacokinetics of BI 1358895 and its metabolite(s) following multiple oral administration of 100 mg BI 1358894 in healthy volunteers.

The data are necessary for in-depth understanding of the pharmacokinetics of BI 1358894 including quantitative determination of elimination pathways and drug metabolites and are required for submission to regulatory authorities.

1.4 BENEFIT - RISK ASSESSMENT

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

Procedure-related risks

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

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

Drug-related risks and safety measures

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 1402-0010 [c28907328] as well as the single dose administration of 100 mg under fasted and fed administration in the relative bioavailability trial 1402-0010 [c28907328]. In addition, the multiple dose administration of up to 200 mg BI 1358894, once daily for 14 days was also well tolerated [c28667517]). There were no deaths or other serious adverse events. Adverse events, mostly reported as mild, had no apparent dose or exposure relationship. In view of the non-proportional increase of exposure there is an acceptable safety margin between the

highest exposure observed in preceding phase I studies and the exposure at 100 mg of BI 1358894 q.d. in the planned study. Therefore no undue risk is expected from the single dose and multiple 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-marked BI 1358894 in Part 1

[^{14}C] BI 1358894 is labelled with the isotope [^{14}C] which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective dose that each subject receives from one administration of 3.7 MBq is approximately 0.51 mSv (see Appendix 10.2). For biomedical investigations in small groups of healthy volunteers, an effective dose ≤ 1.0 mSv is considered acceptable.

Summary of benefit-risk assessment

In a previous trial in healthy volunteers, single oral doses up to 200 mg BI 1358894 and multiple oral doses up to 200 mg BI 1358894 administered once daily over 14 days were safe and well-tolerated. In the current trial, either a single oral dose or multiple oral doses of 100 mg BI 1358894, once daily over 21 days, will be administered to healthy male subjects which will provide an appropriate safety margin to the highest dose safely tested in the MRD [c28667517]. In addition, the subjects will stay at the trial site under close medical surveillance until Day 15 in the single dose part and until Day 27 in the multiple dose part.

In Part 1, each participant will receive a single dose of [^{14}C]-radiolabelled BI 1358894.The risk associated with the expected maximal radiation burden falls in ICRP category 2a with minor level risk. This is considered to be acceptable.

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 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

The main objective of this trial is to investigate the basic pharmacokinetics of BI 1358894 and its metabolites, total radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 100 mg [^{14}C] BI 1358894 in Part 1 and to investigate the pharmacokinetics of BI 1358894 and its metabolite(s) following multiple-dose treatment over 21 days with non- radiolabelled compound at a dose of 100 mg of BI 1358894 QD in Part 2.

2.1.2 Primary endpoints

Part 1:

The following pharmacokinetic parameters will be determined for BI 1358894:

- Mass balance recoveries of [^{14}C] BI 1358894 total radioactivity in urine and faeces after single oral dose
- Amount of radioactivity excreted as a percentage of the administered dose (fe_{0-t2}) for urine and faeces

2.1.3 Secondary endpoints

Part 1:

The following pharmacokinetic parameters will be determined for total [^{14}C] BI 1358894 and BI 1358894 after single dose administration:

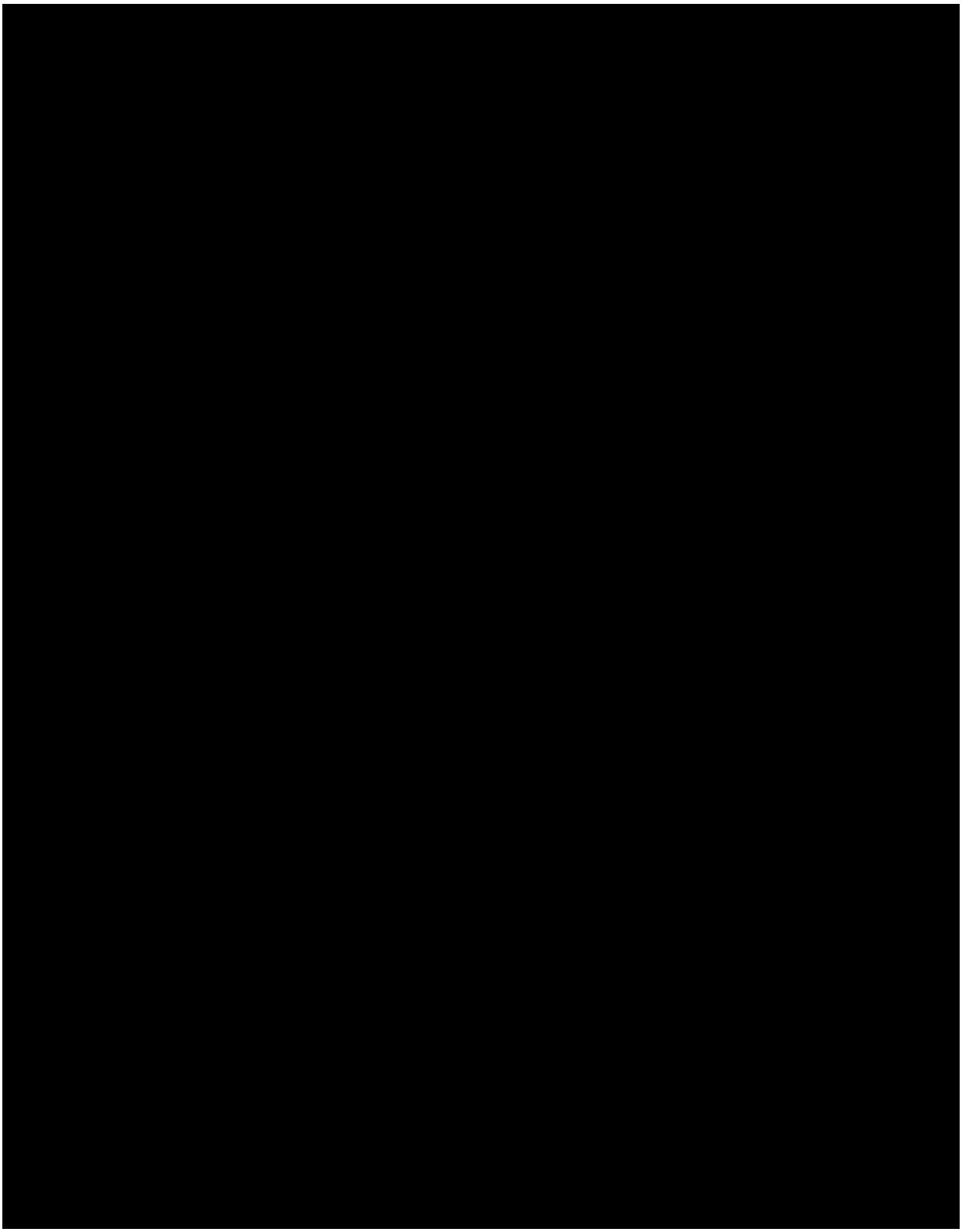
- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

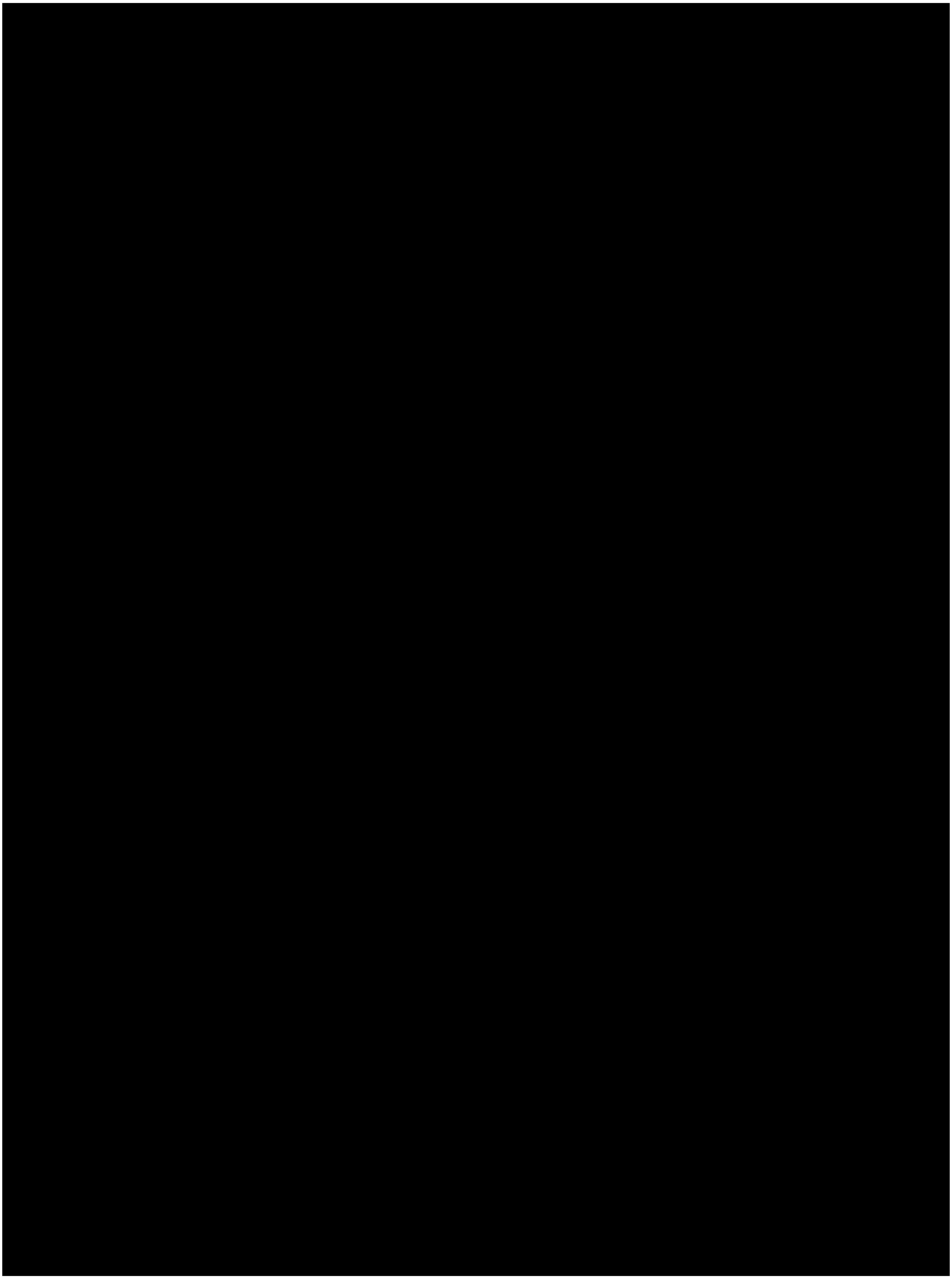
Part 2:

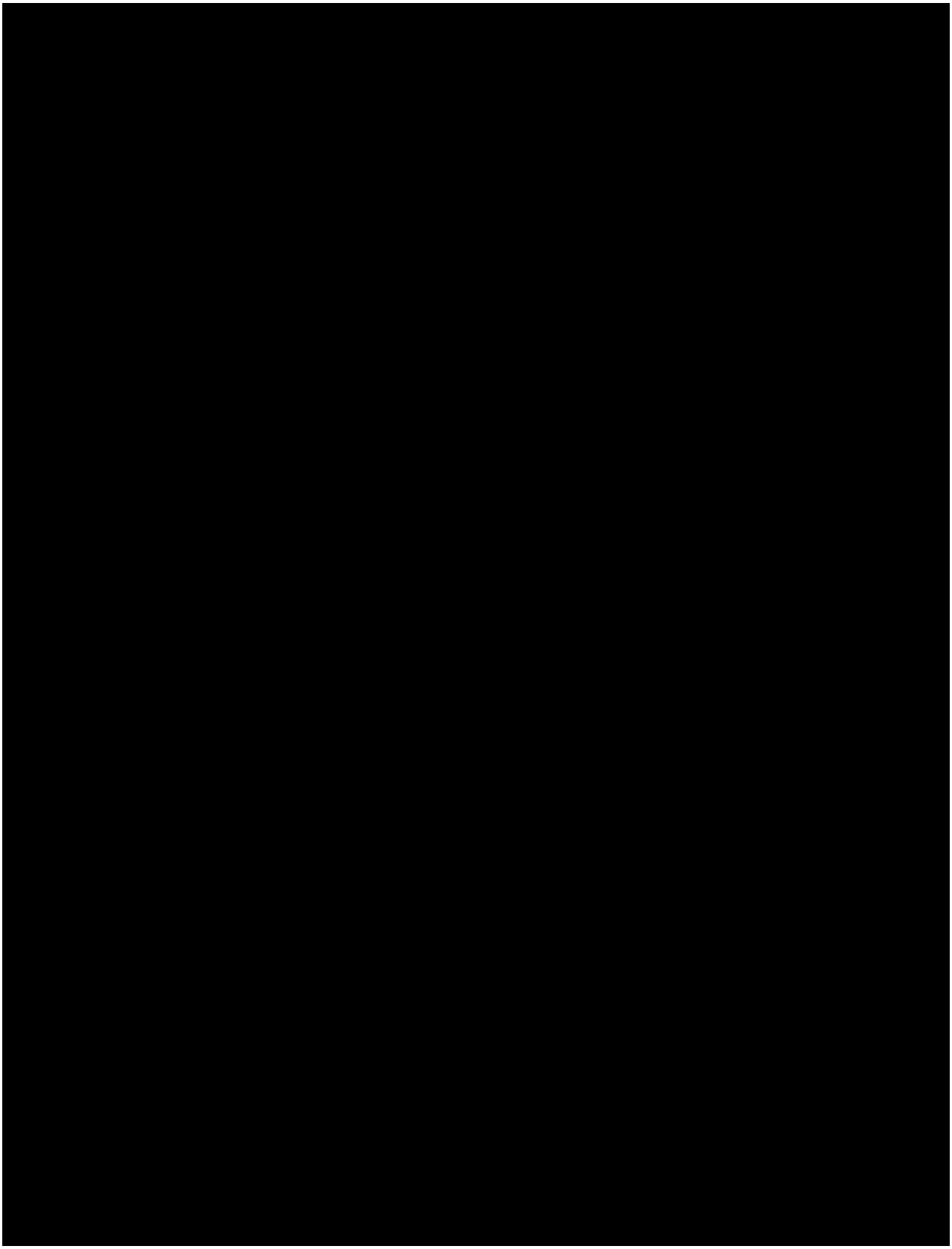
The following pharmacokinetic parameters will be determined for BI 1358894:

- AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24)
- C_{max} (maximum measured concentration of the analyte in plasma)
- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)







[redacted]

2.2.2.4 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

The study will be performed as an open-label, single arm and single- or multiple dose trial in healthy male subjects in order to investigate the basic pharmacokinetics of BI 1358894, [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of [^{14}C] BI 1358894 in Part 1 and to investigate the pharmacokinetics of BI 1358894 and its metabolite(s) following multiple oral doses of 100 mg BI 1358894 administered as film-coated tablets in Part 2.

Part 1:

The planned radioactive dose per subject is 3.7 MBq (100 µCi).The [^{14}C] labelled drug will be administered on Day 1. Subjects will remain at the study site from admission on Day – 1 up to discharge on Day 15 following the fulfilment of release criteria. Subjects will then be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 21, 28, 35, 42 and 49, if release criteria have not been met. Within 24 h before each of these once weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval.

For determination of whether release criteria have been reached for individual subjects, [^{14}C]-radioactivity will be measured in excreta (urine and faeces). The actual recovery results will be reported as a percentage of the administered dose.

If one of the following release criteria is true (i.e., release criteria have been met), 24 h collection intervals after Day 15 will not be performed any longer/will be stopped:

- Greater than or equal to 90% of the administered dose has been recovered in urine and faeces combined over the investigational period, or
- If <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h intervals, and
- Concentration of total radioactivity in plasma <5% of C_{max} of total radioactivity in plasma

If the mass balance recovery is less than 90% on Day 15, subjects will still be asked to return to the clinic for 24 h collection of urine and faeces on Days 21, 28, 35, 42 and 49 or until the recovery is deemed to be sufficient for mass balance purposes. If a subject is unable to attend one of these visits, they may be allowed to reschedule the visit if needed.

Irrespective of whether release criteria have been met or not after collection interval Day 49-50, no further collections are planned.

Part 2:

Non-radiolabelled compound will be administered at the site from Day 1 to Day 21. Subjects will remain at the study site from admission on Day – 1 up to discharge on Day 27.

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

This is a standard design for a [^{14}C]-human study for investigation of absorption, distribution, metabolism, and excretion including determination of mass balance. Inclusion of a control groups is not required for this investigation.

The elimination of BI 1358894 is multiphasic, therefore it cannot be excluded that prolonged sampling is necessary in humans. Hence, following in-house excreta collection after radioactive dosing on Day 1, subjects will return on a weekly basis for in-house 24 h collection intervals for up to 7 weeks after last dosing as long as release criteria are not met (Section 3.1).

Part 2 is a standard design for a multiple dose study in order to characterise the pharmacokinetics of BI 1358894 and its metabolite(s) with validated LC-MS methods over a longer time period and under well controlled conditions in healthy volunteers.

Blinding is not necessary, because all subjects receive the same dose per study part.

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects (8 in each Part) will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via external databases and advertisements.

Only healthy male subjects will be included in this trial because they are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. 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 65 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 screening 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 two 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 levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including 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. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. C-reactive protein (CRP) > upper limit of normal (ULN), liver or kidney parameter above ULN
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)

For Part 1 only:

26. Participation in another ADME study with a radiation burden of >0.1 mSv in the period of 1 year prior to screening
27. 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
28. Irregular defecation pattern (less than a mean of one bowel movement every 1 or 2 days)

In addition, the following SARS-CoV-2 specific exclusion criterion apply:

29. A positive test indicating an ongoing infection with SARS-CoV-2 and clinical symptoms suggestive of the disease.

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 >30.0 mg/L
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 some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist, the Trial Statistician and the Principal Investigator 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 (test product 1) is administered as oral solution. The oral solution contains a mixture of [^{14}C]-radiolabelled BI 1358894 and non-radiolabelled BI 1358894 and is manufactured by BI Pharma GmbH & Co. KG. The solution from this mixture is made by [redacted]

Non-radiolabelled film coated tablets of BI 1358894 (test product 2) have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Test product 1

Name:	[^{14}C] BI 1358894 oral solution
Substance:	BI 1358894 mixed with [^{14}C] BI 1358894
Pharmaceutical formulation:	Oral solution
Source:	[redacted]
Unit strength:	100 mg - Containing [^{14}C]-radiolabelled BI 1358894 corresponding to a radioactive dose of 3.7 MBq (100 µCi) - In a solution of 10 mL volume (concentration of BI 1358894 10 mg/mL)
Posology:	1-0-0
Route of administration:	oral
Duration of use:	Single dose

Test product 2

Substance:	BI 1358894
Pharmaceutical formulation:	Film-coated tablet (Tablet Formulation 2)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	21 days

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 dose of 100 mg BI 1358894 is below the already tested highest dose of 200 mg of BI 1358894 for 2 weeks in healthy subjects. In healthy volunteers, this dose was safe and well-tolerated (Section 1.2). A dose of 100 mg, administered as multiple dose, is considered adequate for the objectives of the current trial.

The dose on Day 1, Part 1 administered as oral solution will include 3.7 MBq (100 µCi) of [^{14}C]-radiolabelled BI 1358894. The radiolabelled dose of 3.7 MBq is required to provide sufficient analytical sensitivity to enable metabolite quantification in a sufficiently low range. The total effective dose (radiation burden) amounts to 0.51 mSv. This is below the limit of 1.0 mSv and considered acceptable. Radiation burden calculations are presented in Appendix 10.2. For the benefit-risk assessment, see Section 1.4.

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, phase I, single- or multiple-dose study. All subjects in each Part receive the same dose. Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2.

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is an open-label, single period and single arm with 2 treatment parts. 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 per day
T1 (Test product 1)	BI 1358894	Oral solution	10 mg/mL	10 mL (100 mg) on Day 1	100 mg
T2 (Test product 2)	BI 1358894	Film-coated tablet	50 mg	2 tablets x 50 mg, q.d. (Day 1 to Day 21)	100 mg

In Part 1, in the morning of Day 1, following an overnight fast of at least 10 h, all subjects will receive one single oral dose of the radiolabelled trial drug ([^{14}C] BI 1358894 oral solution 10 mg/mL (10 mL; 3.7 MBq)) followed by the administration of about 200 mL of water.

[redacted] will determine both the weight of drug product and the total dose of [C]-radioactivity administered for each volunteer.

In Part 2, subjects will receive a multiple-dose treatment of non-radiolabelled 100 mg BI 1358894 as film-coated tablets once daily from Day 1 to Day 21 following a standard

continental breakfast administered approximately 30 minutes prior to each dosing. The investigator (or authorised designee) will administer the trial medications as an oral dose together with about 240 mL of water to subjects who are in a sitting position.

Part 1 and Part 2:

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.

Subjects will be kept under close medical surveillance until Day 15 for Part 1 and until Day 27 for Part 2. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except for medical examination or if necessary for any medical reasons (e.g. AEs).

4.1.5 Blinding and procedures for unblinding

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

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

4.1.6 Packaging, labelling, and re-supply

Non-radiolabelled drug supply will be provided by BI. Radiolabelled drug supplies manufacturing will be provided by [redacted]

They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PRODECURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake on Day 1, Part 1.

On Day 1 of Part 1, fluid intake is restricted from 1 h before drug intake until lunch to the 200 mL of water following the drug administration and to the 240 mL at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 48 h before the first administration of trial medication until after the last PK sample 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 and/or urinary excretion 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 [redacted] at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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.

For each Part, SARS-CoV-2 specific test will be conducted at admission on Day – 1, on Day 2, at each admission to the trial site for the 24-h visits (Part 1 only) and at EOT.

[redacted]

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); Neutrophils Bands; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/Leukocytes;.			
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
PCR	SARS-CoV-2	--	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 Hemoglobin (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (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. It is planned to perform these tests during screening only. Drug screening will be performed at screening and at admission on Day – 1.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic and drug restrictions, a urine alcohol and drug test (e.g. ADVIA Chemistry XPT system) will be performed at admission on Day – 1, 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]

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

5.2.4 Electrocardiogram

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

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

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

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

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

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

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

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 the time points indicated in the Flow Chart. 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:
  - o An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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 accompanying symptoms like (all of the following that apply: nausea and/or vomiting, photophobia, phonophobia, lacrimation, other)
- If Headache is resolved: Overall duration of headache episode (start time and end time)

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection for Part 1

5.3.2.1 Sampling of whole blood and plasma

Whole blood and plasma will be collected at time points shown in the Flow Chart:

- To determine [^{14}C]-radioactivity concentrations in whole blood and plasma
- To determine concentrations of BI 1358894 in plasma
- To identify metabolites of BI 1358894 in plasma

[redacted]

Blood for pharmacokinetics of BI 1358894 and for quantification of its metabolites will be taken from an antecubital or forearm vein into a K2-EDTA (dipotassium ethylenediaminetetraacetic acid)- anticoagulant blood drawing tube at the times indicated in the Flow Chart. Withdrawal of blood will be done via an indwelling cannula or by direct venepuncture.

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

Premature stopping of blood sampling

In case [^{14}C]-radioactivity in plasma samples is not detectable (<LLOQ 30 dpm/mL) at two consecutive time points for a subject, blood sampling can be stopped for this subject.

However, all samples until 24 h after the last drug administration have to be taken.

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

5.3.2.4 Sampling of urine

During the trial urine will be collected at time points or in intervals as indicated in the Flow Chart:

- to determine [^{14}C]-radioactivity concentrations in urine
- to determine concentrations of BI 1358894 in urine

[redacted]

A blank sample will be taken prior to drug administration. For urine collection, the weight of the containers has to be determined prior to and at the end of the collection interval. The urine volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All samples after intake of [^{14}C] BI 1358894 are planned to be used for determination of [^{14}C]-radioactivity.

On Day 1 of Part 1, samples until and including the collection interval 12-24 h are planned to be used for analysis of BI 1358894. [redacted]

For a detailed description of urine sampling, preparation of collection containers, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

5.3.2.5 Sampling of faeces

Faeces will be collected for the analysis of [^{14}C]-radioactivity [redacted] in intervals as indicated in the Flow Chart. A blank sample will be taken prior to drug administration.

All faeces samples after intake of [^{14}C] BI 358894 are planned to be used for determination of [^{14}C]-radioactivity.

[redacted]

For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.3.2.6 Collection of vomit

If after trial drug administration vomiting occurs in a volunteer within 12 h after radioactive drug administration, the vomit will be collected for determination of weight and [^{14}C]-radioactivity.

[redacted]

5.3.3 Methods of sample collection for Part 2

5.3.3.1 Sampling of plasma

Plasma will be collected at time points shown in the Flow Chart:

- To determine concentrations of BI 1358894 in plasma

[redacted]

Blood for pharmacokinetics of BI 1358894 [redacted] will be taken from an antecubital or forearm vein into a K2-EDTA (dipotassium ethylenediaminetetraacetic acid)- anticoagulant blood drawing tube at the times indicated in the Flow Chart.

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

5.3.3.2 Sampling of urine

During Part 2 of the trial urine will be collected at time points as indicated in the Flow Chart:

- To determine concentrations of BI 1358894 in urine

[redacted]

A blank sample will be taken prior to first drug administration. For urine collection, the weight of the containers has to be determined prior to and at the end of the collection. The urine volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection will be documented.

For a detailed description of urine sampling, preparation of collection containers, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

5.3.3.3 [redacted]

After completion of the trial, the plasma and urine samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/ or its metabolite(s) 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 final study report has been signed.

[redacted]

5.3.5 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKER

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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 Part are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1 of Part 1 and ± 90 min for the other days in Visit 2.

In Part 1, the planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.

In Part 2, the acceptable deviation from the planned times for blood sampling during the ambulatory visits (from Day 30 to Day 62) will be ± 180 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, 12-lead ECG recordings and urine/faeces collection 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 and urine/faeces collection intervals, 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 beginning or end of a urine/faeces collection interval and a blood sample are scheduled for the same time point, urine/faeces collection should be done first, with withdrawal of the blood sample as closely to the planned time point as possible.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

6.2.2 Treatment periods

On Day – 1, all study participants will be admitted to the trial site and kept under close medical surveillance as indicated in the Flow Chart.

In Part 1, subjects will receive a single dose of [^{14}C] BI 1358894 in the morning of Day 1. Subjects will be readmitted to the trial site for 24 hours collection intervals of urine and faeces on Days 21, 28, 35, 42 and 49, if release criteria have not been met on Day 15. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collections will be used for analysis in case no defecation occurs in the subsequent 24-h in-house collection interval. Otherwise it will be discarded.

Once release criteria are reached, home collections will be stopped.

If a subject is unable to attend one of these visits, they may be allowed to reschedule the visit, if needed.

Irrespective of whether release criteria have been met or not after the last collection interval on Day 50, no further collections are planned.

In Part 2, subjects will receive a single daily dose of BI 1358894 from Day 1 up to Day 21.

For Part 1 and Part 2:

For details on time points and procedures for collection of plasma, urine and faeces samples for PK analysis, refer to Flow Chart and Sections 5.3.2 and 5.3.3.

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 5.2.1 to 5.2.6.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the basic pharmacokinetics of BI 1358894 and its metabolites, total radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 100 mg [^{14}C] BI 1358894 in Part 1 and to investigate the pharmacokinetics of BI 1358894 and its metabolite(s) following multiple-dose treatment over 21 days with non-radiolabelled compound at a dose of 100 mg of BI 1358894 QD in Part 2.

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

No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the iQRMP prior to trial initiation, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

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

Relevant protocol deviations may be:

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

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

- A pre-dose concentration is >5% of the C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve.

The following analysis sets will be defined for this trial:

- Treated set (TS)

  This subject set includes all subjects who entered the study who were documented to have received at least one dose of study drug

- Pharmacokinetic set (PKS)

  This subject set includes all subjects in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment.

7.3.1 Primary endpoint analyses

The primary endpoints (refer to Section 2.1.2) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472). All parameters will be calculated and analysed descriptively.

7.3.2 Secondary endpoint analyses

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

7.3.4 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

Exploratory data analysis will be performed during the conduct of the trial, using the subject data as it is being collected. This analysis will involve descriptive and graphical presentation of primary, secondary and further endpoints. It will be performed to evaluate the mass balance and metabolism of BI 1358894, as well as enable the review of safety data. The information collected during the ongoing review of subject data will also enable further project planning. This analysis is not foreseen to lead to changes to the planned study.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, no prospective calculations of statistical precision or power have been made. The planned sample size of 8 evaluable subjects per study part, 16 subjects in total, has been selected for practical reasons and is judged as being adequate to get reliable results regarding the trial objectives.

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, biobanking and future use of biological samples and clinical data, in particular

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], 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 Trial Clinical Monitor, responsible for coordinating all required trial activities, in order to

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

The non-radiolabelled 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 non-radiolabelled BI 1358894 concentrations in plasma will be performed at the Department of [redacted]

Analyses of [^{14}C] radioactivity concentrations in plasma, urine and faeces will be performed at the [redacted]

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

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

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

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10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USori.doc

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

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

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

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

10.2 RADIATION BURDEN CALCULATION

[redacted]

Radiation Burden Calculation Report [redacted]

Title:	BI 1358894 hADME - Radioburden Calculation
Sponsor:	Boehringer Ingelheim
Protocol No:	BI 1358894
PRA Project Id:	TBD
Version Date:	27 Feb 20

Calculation of Radiation Burden (Dosimetry)

BI 1358894 is an inhibitor of 2 transient receptor potential canonical (TRPC) channels, which are TRPC4 and TRPC5. BI 1358894 is being developed for the treatment of major depressive disorder (MDD) and borderline personality disorder (BoPD).
Excretion and pharmacokinetic studies using BI 1358894 were conducted on rats[1,2], and quantitative tissue distribution studies on pigmented and non-pigmented rats[3]. A radiation dose assessment was made based on these studies. In addition, data from studies in human patients[4] were taken into consideration.
The following assumptions, based on the data from these experiments, and taking the worst-case scenario, were made to be able to estimate the effective radiation dose:

- After oral dosing, BI 1358894 and possible metabolites are considered to be distributed more or less homogeneously throughout the body, with the exception of higher exposure of the liver and brain, which are calculated separately.
- The major part of the administered amount of ^{14}C-radiolabeled BI 1358894 and possible metabolites show reasonably fast elimination from the body, almost completely via fecal excretion.
- Using the data of the BI 1358894 study in rats a half-life of total ^{14}C-activity of 120 hours is estimated, in humans a terminal phase half-life of BI 1358894 of approximately 960 hours is assumed[4].
- The absorbed fraction is 0.8, based on rat data[1].
- Based on the excretion study in rats ^{14}C-radiolabeled BI 1358894 is found to be excreted both in feces and in urine. For the calculation is assumed:100% of the administered radioactivity is excreted via the gastrointestinal tract in feces.

Based on these assumptions the estimated effective radiation burden after a single oral radioactivity dose of 3.7 MBq ^{14}C-radiolabeled BI 1358894 is approximately 0.51 mSv. For biomedical investigations in small groups of human volunteers an effective dose of 0.1 – 1.0 mSv is considered acceptable [5].

References:

1: preclinical report A117/16SMB (B5853) Excretion of radioactivity in urine, faeces and bile after oral and intravenous administration of [14C]BI 1358894 to rats, (dated 15 November 2016)
2.: preclinical report A054/16BOB (B5984) Metabolism of BI 1358894 in rats (dated 22Jun 2018)
3.: QWBA report. A130/19JS (B6838) Quantitative whole-body autoradiography in male pigmented rats after single intravenous or oral administration of [^{14}C]BI 1358894 (not dated)
4.: Investigator's brochure BI 1358894 Nr.c10354149-06 Version 06 (Dated 22jan2020).
5.: Handboek Radionucliden; A.S. Keverling Buisman, second edition, August 2007.
6.: Recommendations of the International Commission on Radiological Protection. User's ICRP publication 60, Pergamon Press 1992 and update from ICRP 103.

[redacted]

Appendix A1: Radiation burden of the gastrointestinal tract after oral administration of 3.7 MBq ^{14}C BI 1358894

Using SEE-values, an organ-specific radiation burden can be estimated. The SEE-value is dependent, among other factors, on the mass of the target organ and the type of radiation.
With these SEE-values and the number of disintegrations U in the target organ, the organ dose equivalent H_t is calculated:
H_t= constant x U x SEE (mSv); using a target organ-related weight factor, the contribution of the organ burden to the body burden is translated as: $H_{wb,t}$ = H_t x weight factor (mSv)

In order to be able to calculate the radiation burden of the GI tract, this has been divided in five sections, i.e., the stomach (st), the small intestines (si), the right part of the large intestines, the left part of the large intestines (lc) and the rectum / sigmoid (rs)..
The SEE-values for these organs are:

ST:	1.0 x 10 -5,	(weight factor = 0.12)
SI:	3.2 x 10 -7,	(weight factor = 0.01)
RC:	2.3 x 10 -10,	(weight factor = 0.048)
LC:	2.9 x 10 -10.	(weight factor = 0.045)
RS:	9.2 x 10 -10.	(weight factor = 0.027)

The number of disintegrations U in each target organ depends on the amount of radioactivity excreted, or any metabolites that are eliminated via the gall bladder that is standardised for the various compartments of the GI tract (constant). I_0 = 3.7 MBq; Excretion via GI tract: 100% of the dose, excretion via urine: 0% of the dose. These assumptions give:

H_{st}=	0.0030 mSv
H_{si}=	0.0000 mSv
H_{RC}=	0.0000 mSv
H_{LC}=	0.0000 mSv
H_{RS}=	0.0000 mSv
total GI:	0.0030 mSv

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to **0.0030 mSv**.

Appendix A2: Radiation burden of the central compartment after oral administration of 3.7 MBq ^{14}C BI 1358894

Average body weight = 70 kg; SEE = 7.1905 x 10^{-7}; 70% of the dose administered oral is excreted with a half-life of **120 h**; total number of disintegrations in the central compartment after oral administration of 3.7 MBq [^{14}C] BI 1358894 is 1.5984 x 10^{12} with a tissue weighting factor of 0.8 giving a Htw of 0.1432 mSv. and with a half-life of **960 hours**. adds 1.27872 x 10^{13} with a tissue weighting factor of 0.2 giving a Htw of **0.2864** mSv. This gives a total of **0.4296** mSv

Appendix A3: Radiation burden of the liver and brain after oral administration of 3.7 MBq ^{14}C BI 1358894

For the Liver SEE = 2.72 x 10^{-7}; 4% of the dose administered and excreted by the liver with a half-life of 600 h and with a tissue weighting factor of 0.04 gives a contribution to the radiation burden of 0.0795 mSv

For the Brain SEE = 5.80 x 10^{-10}; 26% of the dose administered and excreted from the brain with a half-life of 70 h and with a tissue weighting factor of 0.05 gives a contribution to the radiation burden of 0.0000 mSv

[redacted] Radiation Burden Calculation Report [redacted]
BI 1354149

Conclusion:

The total effective dose (radiation burden), based on the above-mentioned worst-case scenario amounts to 0.0030 + 0.4296 + 0.0795 + 0.0000 = 0.51 mSv.

Name and Date:	**Signature:**
[redacted]	Signed by: [redacted] Senior Research Physician Reason: I am the author of this document. Date & Time: 27 Feb 2020 04:54 PM +01:00 DocuSign

EDSEXE 010 T 16 A Page 3 of 3

10.3 COVID-19 SITE SPECIFIC MEASURES

This section contains a risk assessment for study 1402-0015 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 toslight 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 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 70 years (inclusive), upper body mass index [BMI] ≤29.9 kg/m^2).

Subjects will stay in-house from Day – 1 until Day 15 for Part 1 (following a single dose administration on Day 1). Subjects will then come back for 24-h in-house stay at several time points if they did not reach the release criteria (see Flow Chart). For subjects enrolled in Part 2, they will stay in-house from Day – 1 until Day 27 (following multiple doses administration of 100 mg BI 1358894, once daily over 21 days) and will return for ambulatory visits from Day 30 to Day 62 (see Flow Chart).

At the time of the follow-up examination (Day 16 – Day 50 for Part 1 and Day 62 for Part 2) 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.
    - 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 #29, 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.

Conclusion of COVID-19 risk containment

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)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

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

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-01

Title: A phase I, open-label trial to investigate metabolism and pharmacokinetics of a single dose of [14C] BI 1358894 administered as oral solution (Part 1) and multiple doses of BI 1358894 administered as film-coated tablets (Part 2) in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	21 Aug 2020 12:06 CEST
Author-Clinical Trial Leader		21 Aug 2020 14:04 CEST
Verification-Paper Signature Completion		21 Aug 2020 14:59 CEST
Approval-[redacted] Medicine		21 Aug 2020 16:07 CEST
Approval-Team Member Medicine		21 Aug 2020 21:14 CEST
Author-Trial Statistician		24 Aug 2020 09:16 CEST

(Continued) Signatures (obtained electronically)

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