Clinical Trial Protocol

	Document Number:	**c33746782-07**
EudraCT No.	2021-001717-36	
BI Trial No.	1447-0002	
BI Investigational Medicinal Product	BI 1569912	
Title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects	
Lay Title	A study in healthy men to test how well different doses of BI 1569912 are tolerated	
Clinical Phase	I	
Trial Clinical Leader	[redacted] Phone: [redacted] Fax: [redacted]	
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 6))	
Version and Date	Version: 7.0	Date: 24 Jan 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	28 May 2021
Revision date	24 Jan 2024
BI trial number	1447-0002
Title of trial	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	As a transition from preclinical investigations to clinical development and after first experiences in humans with single rising doses, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 1569912 will be assessed in healthy male subjects using multiple rising oral doses to provide a basis for the further clinical development in the indication of major depressive disorder (MDD)
Trial objectives	To investigate (1) safety, tolerability, pharmacokinetics and pharmacodynamics following multiple rising doses of BI 1569912; (2) tolerability of BI 1569912 in an up-titrating dosing scheme
Trial endpoints	Primary endpoint: Safety and tolerability of BI 1569912 is the percentage of subjects with drug-related adverse events Secondary endpoints: After first dose: $AUC_{0\text{-}24h}$, C_{max} of BI 1569912 in plasma After last dose: $AUC_{\tau, ss}$ and $C_{max, ss}$, $C_{min, ss}$, accumulation ratio $(R_A)_{, AUC}$, and $R_{A, Cmax}$ of BI 1569912 in plasma
Trial design	Single-blind, partially randomized within dose groups, placebo-controlled parallel-group design

Number of subjects	
total entered	96* (84 in multiple rising dose (MRD)-part and 12 in optional posology (POSO)-part)
each treatment	12 per dose group (9 on BI 1569912 and 3 on placebo)
	* Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g., preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 96, but is not to exceed 120.
Diagnosis	Not applicable
Main criteria for inclusion	MRD- & POSO-part: Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive) ELDERLY-part: Healthy male subjects, age of 65 to 80 years (inclusive), BMI of 18.5 to 29.9 kg/m^2 (inclusive)
Test product	BI 1569912 tablets of 0.5mg, 2.5 mg or 5 mg strength
dose	MRD-part: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg once daily POSO-part (optional): The starting dose will be a fraction of the selected target dose and will be applied over 7 days and then increased to the target dose until the end of the treatment period. The chosen dose will be based on previous experience and will not exceed the so far tested highest dose. Each dose will be applied once daily ELDERLY-part: The starting dose will be 10 mg over 7 days and then increased to the target dose of 20 mg until the end of the treatment period. Each dose will be applied once daily (POSO-scheme No. 4)
mode of admin.	Oral with 240 mL (340 mL in the 30 mg- and 40 mg dose group) of water after an overnight fast of at least 10 h
Comparator product	MRD-, POSO- & ELDERLY-part: Matching placebo to BI 1569912 tablets
dose	Not applicable
mode of admin.	Oral with 240 mL (340 mL in the 30 mg- and 40 mg dose group) of water after an overnight fast of at least 10 h
Duration of treatment	MRD-, POSO- & ELDERLY-part: Once daily, multiple doses over 14 days
Statistical methods	MRD-, POSO- & ELDERLY-part: Descriptive statistics will be calculated for all endpoints

FLOW CHART

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[10]	PK urine[10, 11] – MRD-part only	6-Beta-OH-Cortisol/ Cortisol urine[7] – MRD-part only	4-Beta-OH-Cholesterol – MRD-part only	Physical/ Neurological Examination	CADSS	C-SSRS	SMWQ	BAC[19]	Safety EEG/ qEEG	ERP	Eyetracking – MRD-part only	12-lead ECG	Holter – ELDERLY-part only	Vital signs (BP, PR, T)	Questioning for AEs and concomitant therapy[6,
1	-21 to -4	-504:00	08:00	Screening (SCR)[1]	A					x	x	x			x[13, 14]			x	x[23]	x	
	-3	-72:00	08:00		x[21]																
2	-2	-38:00	18:00	***Admission to trial site***	x[5]																
		-35:30	20:30	Snack (voluntary)																	
	-1	-25:00	07:00		B			x	x									x		x	x
		-24:00	08:00							x	x	x									
		-23:00	09:00												x	x	x				
		-18:00	14:00											x							
	1	-1:00	07:00	Allocation to treatment[2]		x[2, 15]	x[2]	x	x									x[12]		x[2]	x[2]
		-0:45	07:15							x											
		0:00	**08:00**	**First drug administration[17, 18]**			▲														
		0:15	08:15			x	|											x[9]		x	x
		0:30	08:30			x	|											x[9]		x	x
		0:45	08:45			x	|											x[9]		x	x
		1:00	09:00			x	|				x							x[9]		x	x
		1:15	09:15			x	|											x[9]		x	x
		1:30	09:30			x	|											x[9]		x	x
		2:00	10:00	240 mL fluid intake		x	|												x[9]		x	x
		2:30	10:30			x	|											x[9]		x	x
		3:00	11:00			x	|											x[9]		x	x

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 $_{blood}$[10]	PK $_{urine}$[10, 11] – MRD-part only	6-Beta-OH-Cortisol/ Cortisol $_{urine}$[7] – MRD-part only	4-Beta-OH-Cholesterol – MRD-part only	Physical/ Neurological Examination	CADSS	C-SSRS	SMWQ	BAC [19]	Safety EEG/ qEEG	ERP	Eyetracking – MRD-part only	12-lead ECG	Holter – ELDERLY-part only	Vital signs (BP, PR, T)	Questioning for AEs and concomitant therapy [6,
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	┼				x							x[9]		x	x
		6:00	14:00			x	│											x[9]		x	x
		8:00	16:00	Snack (voluntary)[3]		x	┼											x[9]		x	x
		10:00	18:00	Dinner[3]		x	│											x[9]		x	x
		12:00	20:00			x	┼				x							x[9]		x	x
	2	23:00	07:00		B	x	│								x			x[9]		x	x
		24:00	08:00	Drug administration			▼														
		25:00	09:00												x[16]	x 16	x			x	x
		27:00	11:00												x						
		30:00	14:00											x							
		32:00	16:00												x						
	3	47:00	07:00			x				x		x			x					x	x
		48:00	08:00	Drug administration																	
		49:00	09:00								x						x				
		50:00	10:00															x			
	4	71:00	07:00		B	x		x	x						x					x	x
		72:00	08:00	Drug administration																	
		73:00	09:00												x[16]	x 16				x	x
	5	95:00	07:00			x												x		x	x
		96:00	08:00	Drug administration																	
		97:00	09:00								x						x				
		98:00	10:00															x			
	6	119:00	07:00			x									x					x	x

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 $_{blood}$[10]	PK $_{urine}$[10, 11] – MRD-part only	6-Beta-OH-Cortisol/ Cortisol $_{urine}$[7] – MRD-part only	4-Beta-OH-Cholesterol – MRD-part only	Physical/ Neurological Examination	CADSS	C-SSRS	SMWQ	BAC [19]	Safety EEG/ qEEG	ERP	Eyetracking – MRD-part only	12-lead ECG	Holter – ELDERLY-part only	Vital signs (BP, PR, T)	Questioning for AEs and concomitant therapy [6,]
		120:00	08:00	Drug administration																	
		121:00	09:00												x[16]	x [16]				x	x
	7	143:00	07:00			x		x		x		x								x	x
		144:00	08:00	Drug administration																	
		145:00	09:00								x						x				
		150:00	14:00											x				x		x	x
	8	167:00	07:00		B	x			x						x					x	x
		168:00	08:00	**Drug administration[17, 18]**																	
		169:00	09:00												x[16]	x [16]				x	x
	9[20]	191:00	07:00			x				x								x		x	x
		191:30	07:30	***Light breakfast[22]***																x[22]	x[22]
		192:00	08:00	Drug administration																	
		192:15	08:15			x[22]														x[22]	x[22]
		192:30	08:30			x[22]														x[22]	x[22]
		192:45	08:45			x[22]														x[22]	x[22]
		193:00	09:00			x[22]					x									x[22]	x[22]
		193:30	09:30			x[22]														x[22]	x[22]
		194:00	10:00	240 mL fluid intake[22]		x[22]														x[22]	x[22]
		194:30	10:30			x														x[22]	x[22]
		195:00	11:00			x[22]														x[22]	x[22]
		196:00	12:00	240 mL fluid intake, thereafter lunch[3, 22]		x[22]														x[22]	x[22]
		198:00	14:00			x[22]														x[22]	x[22]
		200:00	16:00	Snack (voluntary)[3, 22]		x[22]														x[22]	x[22]

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[10]	PK urine[10, 11] – MRD-part only	6-Beta-OH-Cortisol/ Cortisol urine[7] – MRD-part only	4-Beta-OH-Cholesterol – MRD-part only	Physical/ Neurological Examination	CADSS	C-SSRS	SMWQ	BAC[19]	Safety EEG/ qEEG	ERP	Eyetracking – MRD-part only	12-lead ECG	Holter – ELDERLY-part only	Vital signs (BP, PR, T)	Questioning for AEs and concomitant therapy[6,
		202:00	18:00	Dinner[3, 22]		x[22]														x[22]	x[22]
		204:00	20:00			x[22]														x[22]	x[22]
	10	215:00	07:00			x		x		x		x						x		x	x
		216:00	08:00	Drug administration																	
		217:00	09:00								x						x				
		218:00	10:00															x		x	x
	11	239:00	07:00			x			x						x					x	x
		240:00	08:00	Drug administration																	
		241:00	09:00												x[16]	x 16				x	x
	12	263:00	07:00			x				x		x						x		x	x
		264:00	08:00	Drug administration																	
		265:00	09:00								x						x				
		266:00	10:00															x		x	x
	13	287:00	07:00			x												x		x	x
		288:00	08:00	Drug administration																	
		289:00	09:00								x						x				
		290:00	10:00															x		x	x
		294:00	14:00											x							
	14	311:00	07:00		B	x[8]		x	x	x					x			x[9]		x	x
		312:00	08:00	**Last drug administration**			▲														
		312:15	08:15			x[8]	|											x[9]		x	x
		312:30	08:30			x[8]	|											x[9]		x	x
		312:45	08:45			x[8]	|											x[9]		x	x
		313:00	09:00			x[8]	|				x				x[16]					x	x

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 $_{blood}$[10]	PK $_{urine}$[10, 11] – MRD-part only	6-Beta-OH-Cortisol/ Cortisol $_{urine}$[7] – MRD-part only	4-Beta-OH-Cholesterol – MRD-part only	Physical/ Neurological Examination	CADSS	C-SSRS	SMWQ	BAC [19]	Safety EEG/ qEEG	ERP	Eyetracking – MRD-part only	12-lead ECG	Holter – ELDERLY-part only	Vital signs (BP, PR, T)	Questioning for AEs and concomitant therapy [6,
		313:30	09:30			x[8]	┼											x[9]		x	x
		314:00	10:00	240 mL fluid intake		x[8]	┼											x[9]		x	x
		314:30	10:30			x[8]	┼											x[9]		x	x
		315:00	11:00			x[8]	┼											x[9]		x	x
		316:00	12:00	240 mL fluid intake, thereafter lunch[3]		x[8]	┼											x[9]		x	x
		318:00	14:00			x[8]	┼											x[9]		x	x
		320:00	16:00	Snack (voluntary)[3]		x[8]	┼											x[9]		x	x
		322:00	18:00	Dinner[3]		x[8]	┼											x[9]		x	x
		324:00	20:00			x[8]	┼						x					x[9]		x	x
	15	335:00	07:00			x[8]	┼				x		x					x[9]		x	x
		336:00	08:00				┼														
		337:00	09:00				┼								x	x					
	16	359:00	07:00			x[8]	┼						x					x[9]		x	x
		360:00	08:00				▼														
		366:00	14:00											x							
	17	383:00	07:00		B	x[8]		x	x	x	x	x	x				x	x[9]		x	x
		385:00	09:00	Breakfast (voluntary), ***Discharge from trial site***											x	x					x
3	17 to 27			End of trial (EoT) examination[4]	B					x		x						x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, EEG, safety laboratory (including drug 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.
2. The time is approximate; the procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.

3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Urine sample will be taken after the first morning void collected as spot urine sample.
8. **MRD-part** only: At this time, an additional blood sample for metabolite identification will be taken at every dose level (refer to Section 5.3.2.2).
9. The ECG recording has to be performed in triplicate at this time. ECG recording will always precede all other study procedures scheduled for the same time point (e.g., blood sampling, measurement of vital signs) to avoid compromising ECG quality.
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits as long as the total blood volume removed does not exceed 500 mL per subject.
11. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24 (and 312:00-316:00, 316:00-320:00, 320:00-324:00, 324:00-336:00, 336:00-360:00 h at Days 14 and 15).
12. At baseline (i.e., Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately 1h. The recordings should be separated by at least 15 minutes.
13. The EEG performed at the Screening Visit is to identify and exclude subjects with an unknown susceptibility for epileptiform abnormalities and/ or seizures. Therefore, Screening EEG will include spontaneous EEG activity in resting condition as well as provocation maneuvers (intermittent photic stimulation and hyperventilation). All EEGs will be reviewed by neurologists experienced in EEG reading.
14. qEEG not to be registered at SCR.
15. In addition, a phramacogenomic sample will be taken.
16. Registration time points may be adapted based on information obtained during the trial (e.g., due to preliminary PK data, clinical symptoms) including the addition of registration time points at the discretion of the investigator.
17. During the (optional) **POSO-part**, the starting dose will be a fraction of the target dose and will be applied over 7 days and then increased to the target dose until the end of the treatment period. Each dose will be applied once daily.
18. During the **ELDERLY-part**, the starting dose will be 10 mg and will be applied over 7 days and then increased to the target dose of 20 mg until the end of the treatment period. Each dose will be applied once daily.
19. BAC = Brief Assessment of Cognition: Verbal Memory and Learning, and Symbol Coding Test.
20. PK-profile and light breakfast.
21. SARS-CoV-2 PCR or Antigen Rapid Test.
22. **MRD-part** only.
23. **ELDERLY-part** only: Holter ECG devices will be installed at the site and brought back by the subjects the day after for analysis by the central ECG reader. The recording time will be at least 24h.

TABLE OF CONTENTS

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
$Ae_{t1\text{-}t2}$	Amount of analyte eliminated in urine over the time interval t_1 to t_2
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time zero to 24 h
$\%AUC_{tz\text{-}\infty}$	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
$AUC_{t1\text{-}t2,ss}$	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2 at steady state
$AUC_{\tau,ss}$	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
β	Slope parameter associated with the power model used to evaluate dose proportionality
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CADSS	Clinician Administered Dissociative States Scale
C_{avg}	Average concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CI	Confidence interval
CK	Creatine kinase
CL	Total clearance of the analyte in plasma after intravascular administration
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 t_1 to t_2
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
C_{min}	Minimum measured concentration of the analyte in plasma

$C_{min, ss}$	Minimum 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')
C-SSRS	Columbia Suicide Severity Rating Scale
CTL	Clinical Trial Leader
CTM	Clinical Trial Monitor
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
EoTrial	End of trial
ERP	Event-related potential
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration
FE	Food effect
fe_{t1-t2}	Fraction of administered drug excreted unchanged in urine over the time interval from t_1 to t_2
FST	Forced swim test
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLDH	Glutamate dehydrogenase
GLP	Good laboratory practice
gMean	Geometric mean
gRT	Global Randomization Team
hERG	Human ether-a-go-go related gene
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
Holter	Ambulatory long term ECG recording
HR	Heart rate
HSA	Human serum albumin
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviations

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
LDH	Lactic dehydrogenase
LI	Linearity index
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in safety testing
MRD	Multiple-rising dose
$MRT_{,ex,ss}$	Mean residence time of the analyte in the body, extravascular at steady state
NAM	Negative allosteric modulator
NDA	New drug application
NMDA	Ketamine, a glutamate N-methyl-D-aspartate
NOAEL	No observed adverse effect level
NR2B	Negative allosteric modulator of subunit 2B
PD	Pharmacodynamic(s)
PE	Polyethylene
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
POSO	Posology
PP	Polypropylene
PQ	Time between start of the P-wave and the start of the Q(R)-wave in an electrocardiogram
PR	Pulse rate
PTF	Peak-trough fluctuation
PTS	Peak-trough swing
qEEG	Quantitative EEG
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QT_c	QT interval corrected for heart rate using the method of Fridericia (QT_cF) or Bazett (QT_cB)
$R_{A,AUC}$	Accumulation ratio based on $AUC_{0-\tau}$
$R_{A,Cmax}$	Accumulation ratio based on $C_{max,ss}$

REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	Steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Temperature
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TMF	Trial master file
$t_{1/2}$	Terminal half-life 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_{ss}	Apparent volume of distribution at steady state after intravascular administration
$V_z/F_{,ss}$	Apparent volume of distribution during the terminal phase λ_z at steady state following extravascular administration
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite numerous antidepressant treatment strategies, there is still significant unmet need in the treatment of major depressive disorder (MDD). First-line antidepressants targeting the monoamine system alleviate symptoms in only 50% of patients after 12 weeks [R06-0086], and the overall cumulative remission rate with multiple treatment trials including drug switch, combination, and/ or augmentation is only 67% after up to 1 year of treatment [P06-11895]. Moreover, current treatments have a long onset of action, usually 3 to 4 weeks.

Ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor channel blocker, has demonstrated efficacy in multiple exploratory trials in patients with treatment-resistant depression (responder rate of approximately 50%), with a fast onset and an antidepressant effect of 1 week on average after a single infusion [R19-0553]. Meanwhile, the intranasal S-enantiomer esketamine received NDA approval by the FDA [R19-0829]. However, transient perceptual disturbances (dissociative reaction), sedation, blood pressure increase, and abuse potential (being a scheduled drug) require controlled distribution as well as cardiovascular and behavioral monitoring after drug application. Those unwanted effects may stem, at least in part, from ketamine's lack of selectivity, as ketamine blocks the ion channel across all NMDA subtypes.

BI 1569912 is an orally administered, small-molecule negative allosteric modulator (NAM) of NMDA receptors containing the subunit 2B (NR2B). These receptors are localized in the forebrain areas including the hippocampus which are associated with the pathophysiology of major depression. Negative allosteric modulation of NR2B causes an acute enhancement of glutamatergic neurotransmission in the medial prefrontal cortex which triggers synaptic strength and thus relieving depression symptoms. In animals, BI 1569912 was shown to have a larger therapeutic window than ketamine according to the doses required for efficacy in the forced swim test (FST) and for the induction of psychotomimetic effects. Clinical results of another negative allosteric modulator of NR2B administered by infusion (i.e., traxoprodil) indicated that this mode of action indeed lead to rapid antidepressant effect at a dose free of dissociative side effects. [redacted].

The key target for BI 1569912 development is achieving an improvement in treatment of depression, assessed by regulatory accepted depression rating scales such as Montgomery-Åsberg Depression Rating Scale (MADRS) on top of standard-of-care antidepressants.

For further information, please refer to current Investigator's Brochure (IB) [c29289852].

1.2 DRUG PROFILE

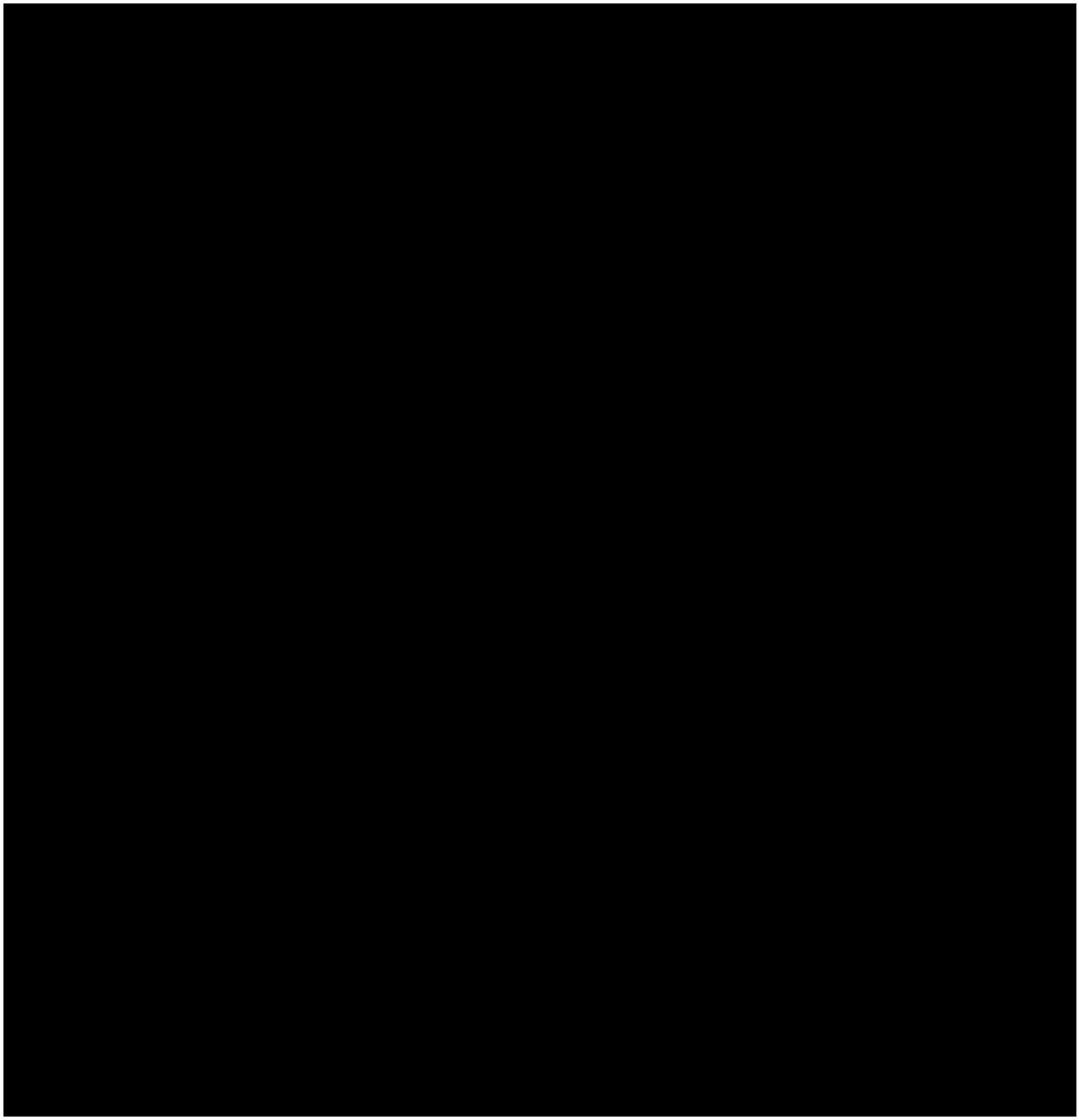
1.2.1 Nonclinical pharmacology

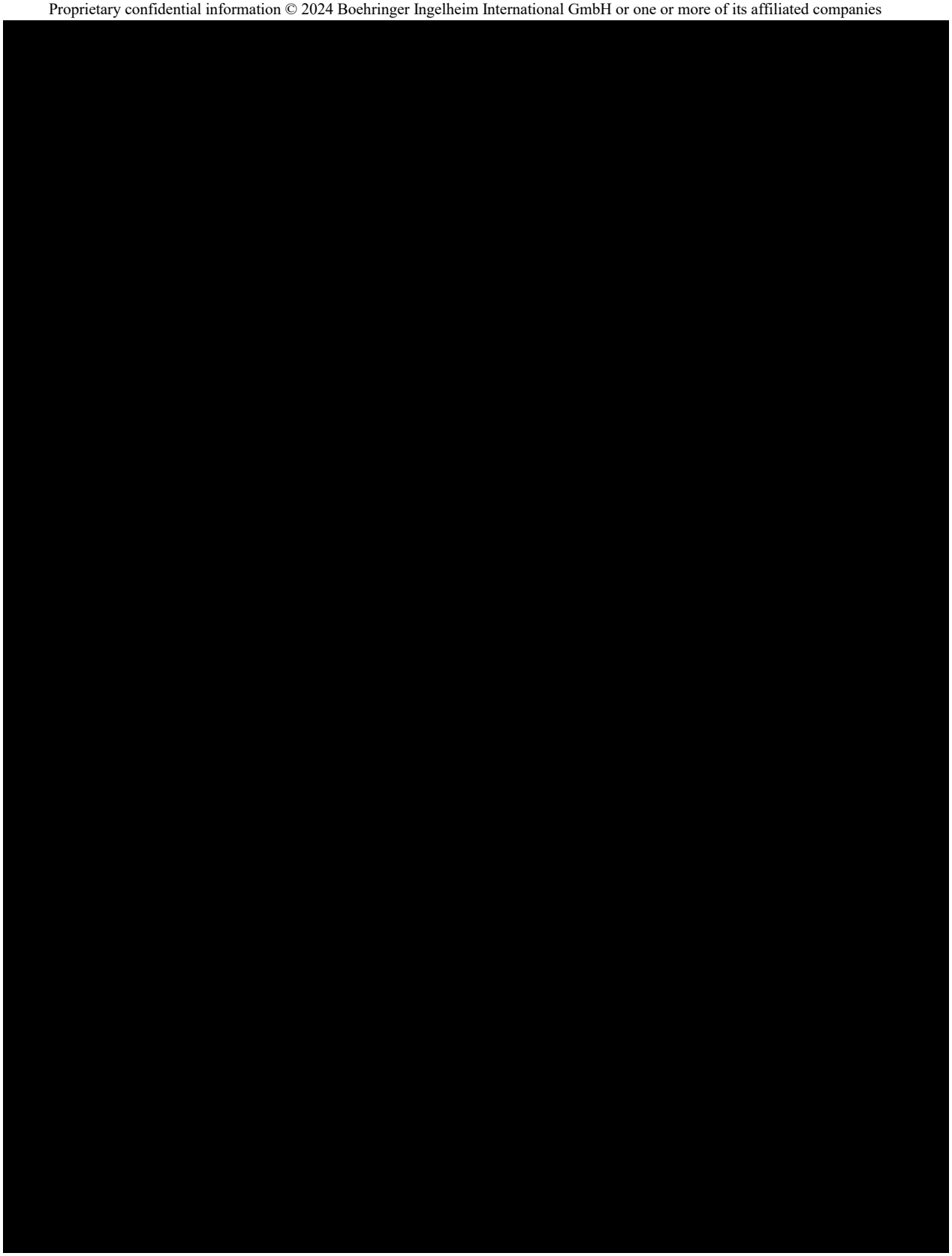
BI 1569912 is a potent negative allosteric modulator (NAM) of NR2B containing NMDA receptors with an EC_{50} of 16 nM [n00272786]. BI 1569912 is similarly potent at human,

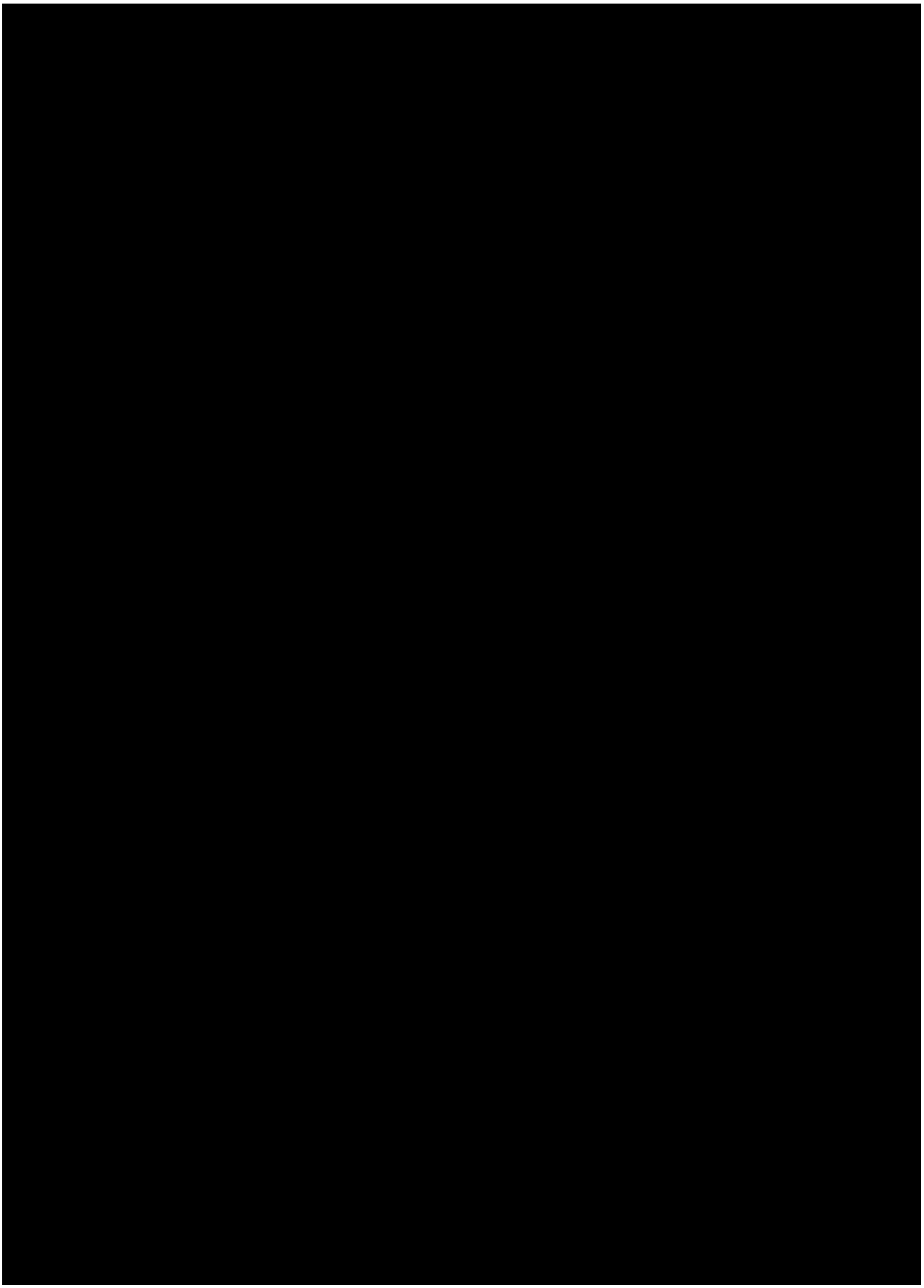
rodent and canine channels [n00272786]. Receptor binding indicates also that BI 1569912, like other known NR2B NAMs, interacts with the prodil-binding site on the NR2B subunit [n00273070]. In vivo, BI 1569912 leads to a modulation of the electroencephalography (EEG) signature in rats, indicating a physiological brain response to the treatment [n00273097].

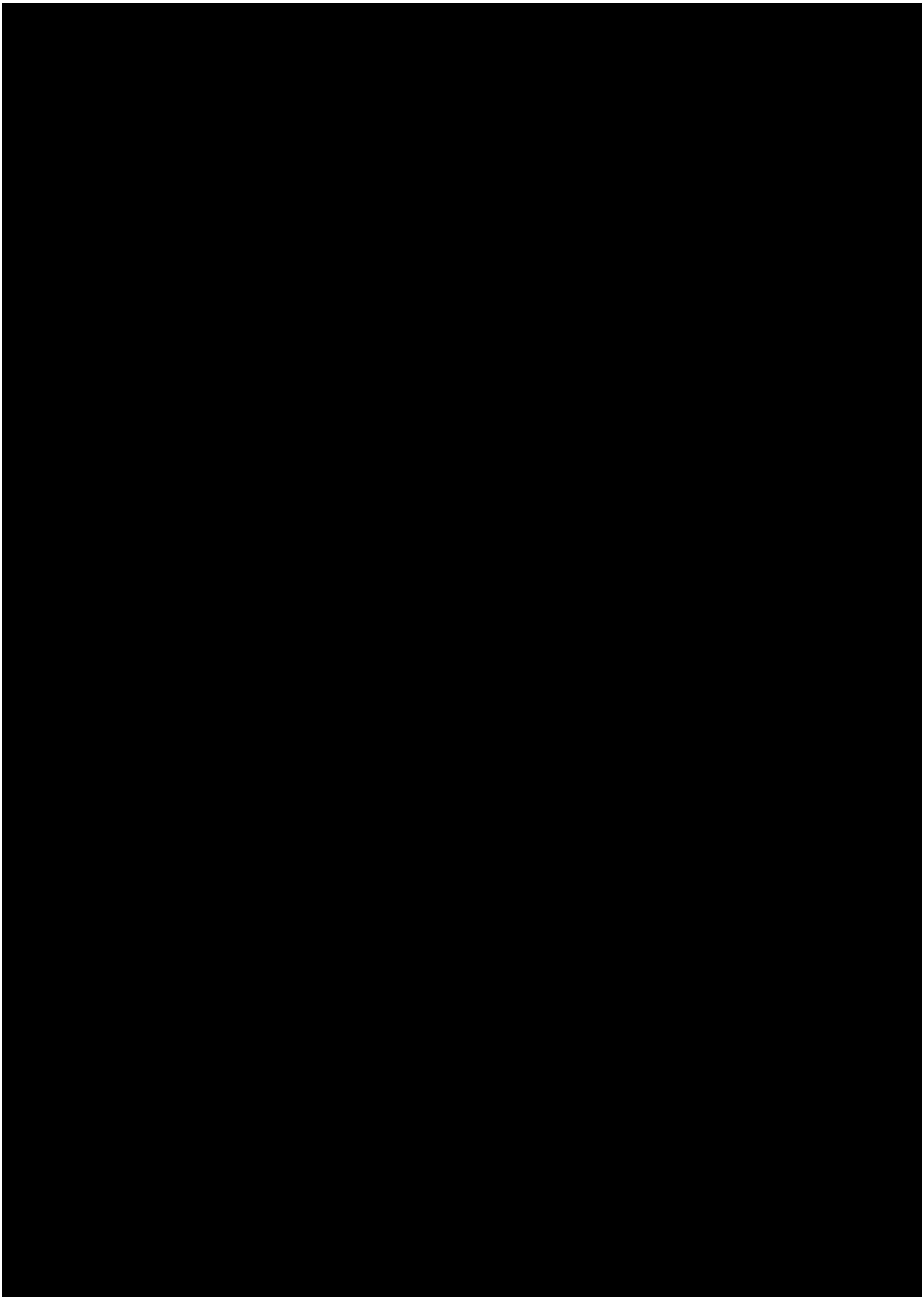
In the forced swim test (FST) in mice BI 1569912 demonstrated efficacy with a comparable effect size as the technical control ketamine [n00273364] at a minimal effective concentration (MEC) of 52 nM. Repeated dosing over 3 days did not indicate any pharmacodynamics drug tolerance with respect to effects observed in the FST. When examined for psychotomimetic-like behaviour in mice [n00273367], it could be demonstrated that pre-treatment with a single lower dose of BI 1569912 was sufficient to prevent psychotomimetic behaviour at a higher dose on the following day.

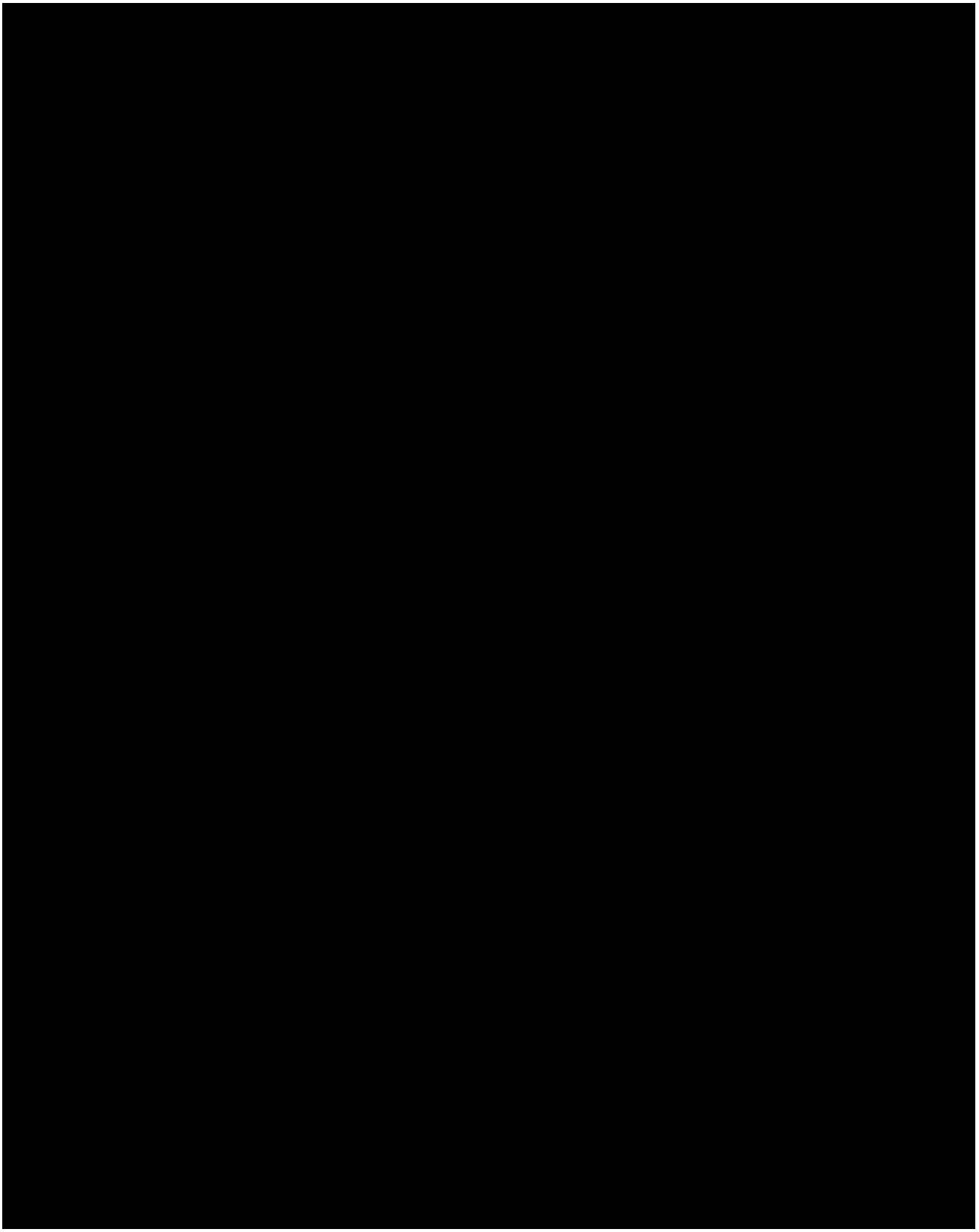
For further information, refer to current IB [c29289852].

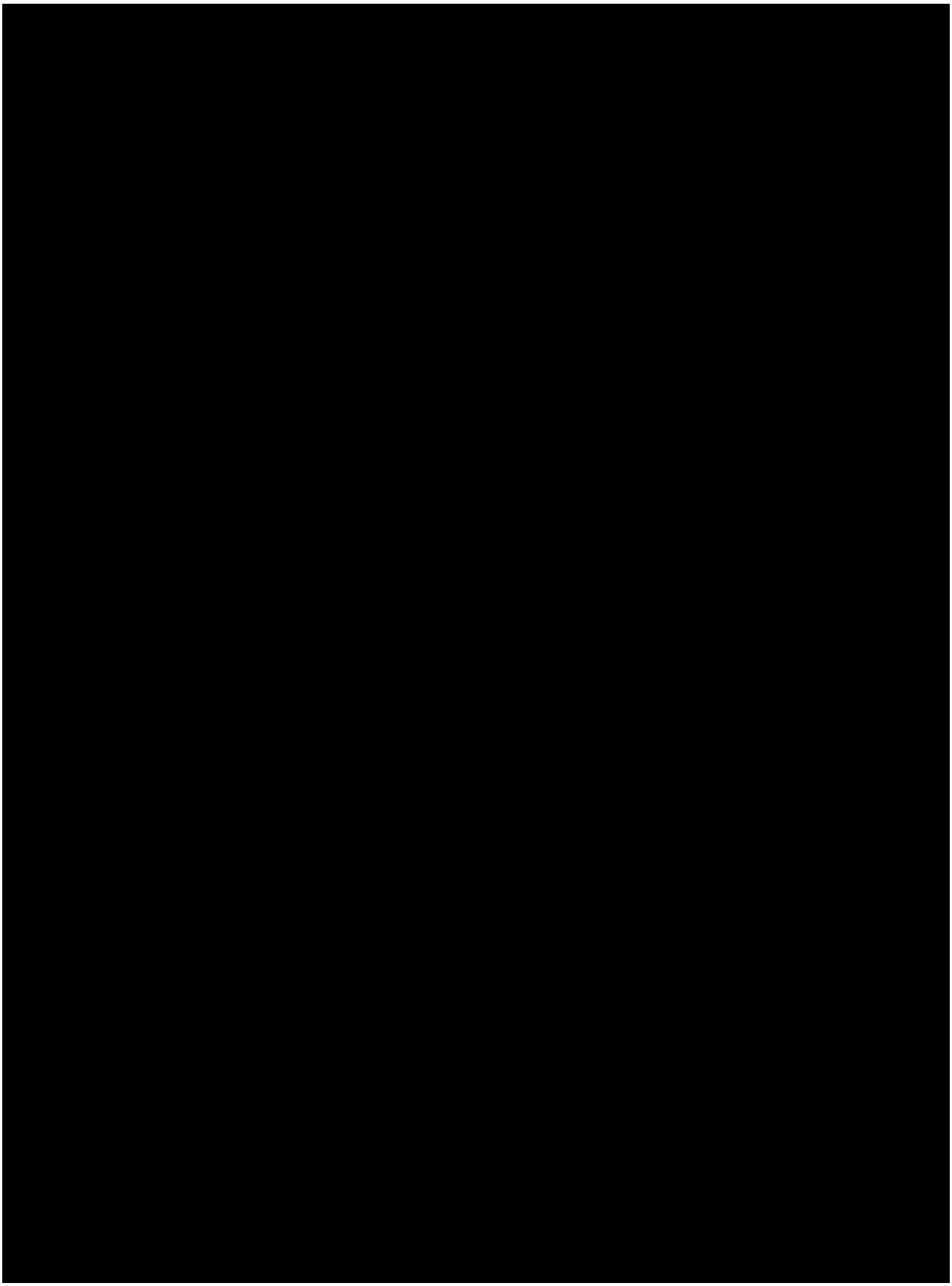


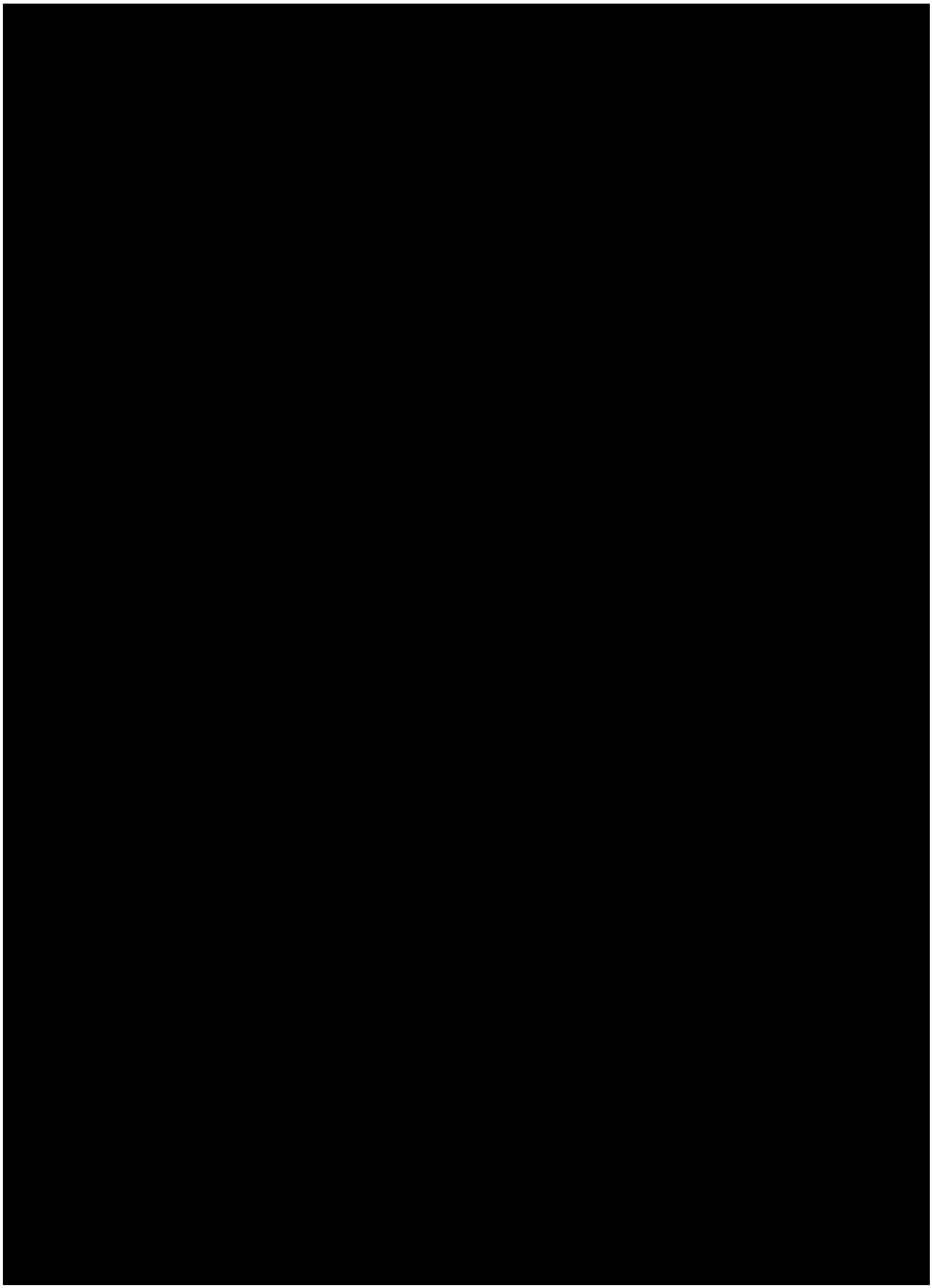


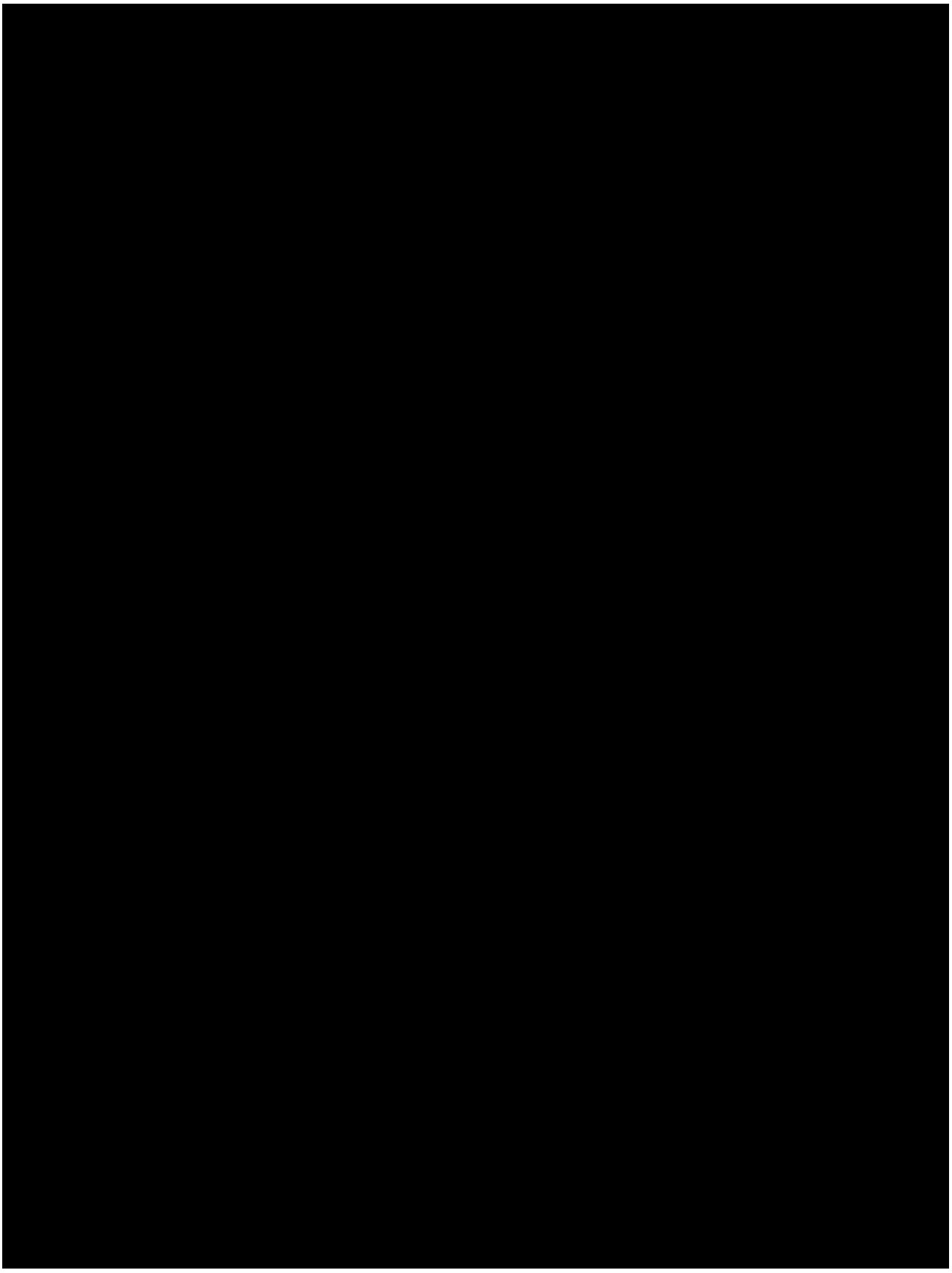


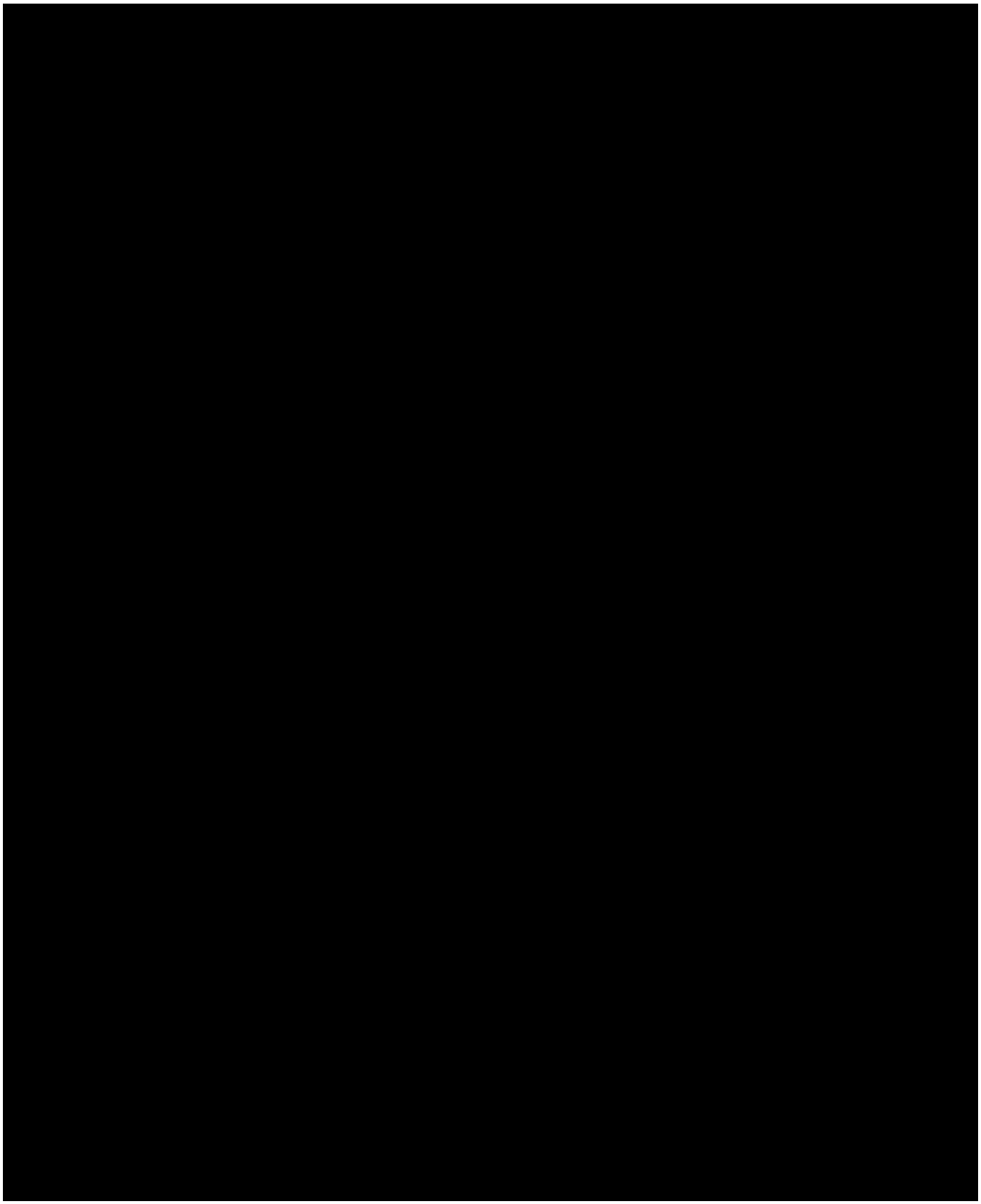












[redacted]

1.2.6 Clinical experience in humans

Results of the single rising dose study 1447-0001

The first-in-human (FIH) study 1447-0001 was performed from 31 August 2020 to 10 September 2021 and consisted of a single-rising dose (SRD)- and a relative bioavailability/ food effect (BA/FE) part in healthy volunteers, evaluating safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BI 1569912.

In the SRD part, a total of 55 subjects in 7 dose groups (DGs) (0.25 mg, 0.75 mg, 2 mg, 5 mg, 10 mg, 20 mg, or 30 mg) received trial medication under fasted conditions; 41 subjects received BI 1569912 and 14 subjects received placebo. Of those, 54 subjects completed the trial as planned. One subject (placebo) prematurely discontinued the trial due to personal reasons. No important protocol deviations were reported. Of the 55 treated male subjects, 51 subjects were White, 1 subject (1.8%) was an American Indian or Alaska Native, and 3 subjects were Asians. The mean age of subjects was 32.7 years, ranging from 19 to 45 years. The mean BMI was 24.7 kg/m^2 , ranging from 18.5 to 29.9 kg/m^2.

In the BA/FE part, a total of 13 subjects were treated in 3 treatment periods (oral solution fasted/ tablet fasted/ tablet fed). Of those, 13 subjects completed Period 1, 10 subjects completed Period 2, and 8 subjects completed Period 3. Five subjects discontinued the trial, but only 2 of them prematurely terminated their planned treatment period of a visit. One subject discontinued due to personal reasons, and 4 subjects due to other (temporary hold of the trial) reasons. Four subjects were reported with at least one important protocol deviation, all related to unplanned meal consumption. The mean age of subjects was 32.2 years , ranging from 19 to 44 years. The mean BMI was 24.8 kg/m^2 , ranging from 19.4 to 29.9 kg/m^2.

Demographic data were similar across treatments in both parts of the study.

[redacted]

Clinical pharmacology results

For the SRD-Part, pharmacokinetic results are summarised in Table 1.2.6: 1. Over the entire dose range, a dose-proportional increase of C_{max} and $AUC_{0-\infty}$, was seen.

Table 1.2.6: 1 SRD part - plasma PK parameter as gMean (gCV%) of BI 1569912 after single administration of BI solution of 0.25 to 30 mg

Parameter	0.25 mg (N=6)	0.75 mg (N=6)	2 mg (N=6)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	30 mg (N=5)
$AUC_{0-\infty}$ (h·nmol/L)							
	32.9 (18.6)	85.1 (18.9)	252 (27.8)	539 (17.4)	1110 (13.8)	2540 (17.1)	2900 (16.9)
C_{max} (nmol/L)							
	11.9 (26.4)	33.1 (36.7)	105 (41.6)	228 (26.9)	361 (30.9)	1090 (32.1)	1100 (27.1)

In the BA/FE part, gMean ratios of $AUC_{0-\infty}$ and AUC_{0-tz} for the tablet vs. solution were within 80 to 125% (an interval usually used for reference); thus, no effect of the formulation on the PK of BI 1569912 AUCs was seen. On average, C_{max} was slightly higher under the tablet as compared to the solution.

After single administration of 5 mg BI 1569912, the gMean ratios of $AUC_{0-\infty}$ and AUC_{0-tz} for the tablet under fed vs. fasted conditions, were within the interval of 80 to 125%; thus, no effect of food on the PK of BI 1569912 AUCs was seen. However, C_{max} was on average 33% lower under fed conditions as compared to fasted conditions.

Safety results

A summary of subjects with investigator-defined drug-related AEs (the primary endpoint in the SRD part of the trial) by dose group is given in Table 1.2.6: 2.

Table 1.2.6: 2 SRD part - Summary of drug-related adverse events

Treatment	Pbo	0.25 mg	0.75 mg	2 mg	5 mg	10 mg	20 mg	30 mg	Total BI	Total on-Trt
SOC/PT	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	14 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	41 (100)	55 (100)
Subjects with related on-treatment AE	1 (7.1)			2 (33.3)			1 (16.7)	2 (40.0)	5 (12.2)	6 (10.9)
Gastrointestinal disorders								1 (20.0)	1 (2.4)	1 (1.8)
Faeces soft								1 (20.0)	1 (2.4)	1 (1.8)
Musculoskeletal and connective tissue disorders				1 (16.7)				1 (20.0)	2 (4.9)	2 (3.6)
Muscle twitching								1 (20.0)	1 (2.4)	1 (1.8)
Myalgia				1 (16.7)					1 (2.4)	1 (1.8)
Psychiatric disorders				1 (16.7)			1 (16.7)	1 (20.0)	3 (7.3)	3 (5.5)
Euphoric mood								1 (20.0)	1 (2.4)	1 (1.8)
Abnormal dreams							1 (16.7)		1 (2.4)	1 (1.8)

Table 1.2.6: 2 SRD part - Summary of drug-related adverse events (cont.)

Treatment	Pbo	0.25 mg	0.75 mg	2 mg	5 mg	10 mg	20 mg	30 mg	Total BI	Total on-Trt
Illusion				1 (16.7)					1 (2.4)	1 (1.8)
Nervous system disorders	1 (7.1)									1 (1.8)
Headache	1 (7.1)									1 (1.8)

Investigator-defined drug-related AEs occurred in 6 subjects (10.9%) overall. Of those, 5 out of 41 subjects (12.2%) reported AEs under treatment with BI 1569912 and 1 out of 14 subjects (7.1%) under treatment with placebo. No dose-dependency was observed.

The most frequently reported drug-related AEs were psychiatric disorders (3 subjects, 5.5%) and musculoskeletal and connective tissue disorders (2 subjects, 3.6%). Psychiatric disorders were euphoric mood, abnormal dreams, and illusion (1 subject each, 1.8%). Musculoskeletal and connective tissue disorders were muscle twitching and myalgia (1 subject each, 1.8%), All other AEs were reported for 1 subject (1.8% of overall subjects) only.

One AE (headache) of moderate intensity was reported for 1 subject (7.1%) in the placebo group, all other AEs were of mild intensity.

In the BA/FE part, no AEs at all were reported.

In both parts of the trial, no deaths, SAEs, protocol-specified AESIs or other significant AEs (according to ICH-E3) were reported. No AE led to discontinuation of trial drug.

No clinically relevant findings were reported from physical and neurological examinations, safety laboratory tests, vital signs measurement, ECG -and EEG assessments. There was no indication of potential suicidality or suicidal ideations, or dissociative symptoms under trial medication at any time point or dose as confirmed by C-SSRS and CADDS questionnaires.

Preliminary results of the multiple rising dose study 1447-0002

At the time of this amendment, this multiple rising dose study was still ongoing. Until16-Jan-2024, 45 healthy male subjects were exposed to BI 1569912 with doses of up to 30 mg QD over 14 days, and 14 to placebo. Three subjects dropped out during the course of the study for personal reasons. So far, 59 subjects, receiving BI 1569912 or placebo, were included in the preliminary safety assessment.

Clinical pharmacology results

Preliminary pharmacokinetic results are summarised in Table 1.2.6: 3.

Table 1.2.6: 3 MRD-part – preliminary plasma pharmacokinetic parameters as gMean (gCV%) of BI 1569912 after multiple administrations of doses up to 30 mg QD over 14 days

	t_{max}* [h]	C_{max} [nmol/L]	AUC_{0-24h} [nmol·h/L]	$t_{1/2}$ [h]	$t_{max,ss}$* [h]	$C_{max,ss}$ [nmol/L]	$AUC_{\tau,ss}$ [nmol·h/L]	$t_{1/2,ss}$ [h]	RA_C_{max}	RA_{AUC}
2.5 mg (N=8)	0.875 (0.500-2.00)	91.0 (20.7)	297 (17.5)	3.67 (30.7)	0.625 (0.250-1.50)	101 (14.5)	313 (18.3)	3.55 (26.9)	1.11 (28.7)	1.05 (6.50)
5 mg (N=8)	0.500 (0.500-1.25)	187 (28.8)	615 (19.7)	3.86 (19.7)	0.75 (0.25-1.00)	205 (21.3)	705 (17.0)	4.68 (41.6)	1.09 (26.7)	1.15 (7.20)
10 mg (N=9)	1.00 (0.500-1.50)	405 (33.0)	1140 (18.5)	3.77 (21.1)	0.75 (0.500-1.5)	396 (22.1)	1270 (19.1)	4.44 (29.7)	0.978 (24.9)	1.11 (6.45)
20 mg (N=9)	0.75 (0.25 - 1.25)	882 (20.3)	2330 (20.3)	3.67 (15.2)	0.5 (0.25 - 2.5)	911 (33.8)	2400 (16.1)	3.78 (17.8)	1.03 (51.0)	1.03 (10.6)
30 mg (N=9)	0.75 (0.25 - 1.5)	1130 (37.6)	3510 (21.6)	3.85 (23.0)	0.5 (0.25 – 1.5)	1300 (31.3)	3850 (21.8)	3.84 (22.7)	1.15 (51.5)	1.1 (6.48)

*median (min-max)

After repeated administrations of BI 1569912, for C_{max} and $AUC_{\tau, ss}$, little accumulation was seen for doses up to 30 mg.

Safety results

A preliminary listing of subjects (on active or placebo) with adverse events after doses of up to 30 mg QD over 14 days is given in Table 1.2.6: 4.

Table 1.2.6: 4 MRD-part – preliminary listing of subjects with adverse events (reported term) after the application of BI 1569912 doses of up to 30 mg QD or placebo over 14 days

Subject	Reported term	Intensity	Outcome	Causality	Comment
2.5 mg dose or placebo					
[redacted]	Headache	Mild	Recovered/Resolved	Yes	
	Tiredness	Mild	Recovered/Resolved	Yes	[redacted] watched Netflix too long the evening or the night before

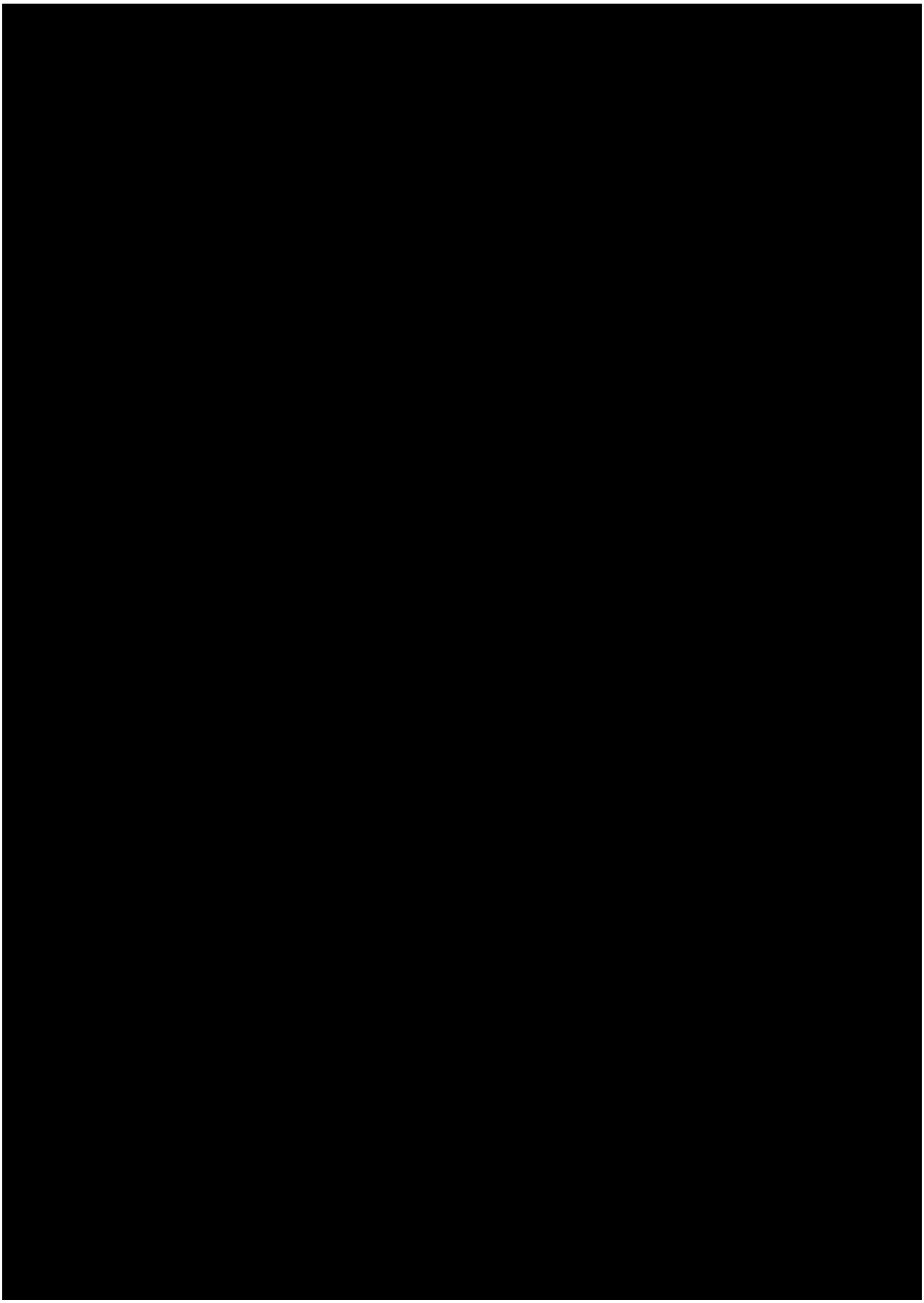
Table 1.2.6: 4 MRD-part – preliminary listing of subjects with adverse events (reported term) after the application of BI 1569912 doses of up to 30 mg QD or placebo over 14 days (cont.)

Subject	Reported term	Intensity	Outcome	Causality	Comment
5 mg dose or placebo					
[redacted]	Rhinorrhea	Mild	Recovered/Resolved	No	
	Headache	Mild	Recovered/Resolved	Yes	
	Headache	Mild	Recovered/Resolved	No	
	Headache	Mild	Recovered/Resolved	Yes	
10 mg dose or placebo					
[redacted]	Phlebitis on the right elbow	Mild	Recovered/Resolved	No	
	Neck pain	Moderate	Recovered/Resolved	No	
	Eczema lower back right	Mild	Recovered/Resolved	No	
	Heartburn	Mild	Recovered/Resolved	No	
	Common cold	Mild	Recovered/Resolved	No	
	Hordeolum	Mild	Recovered/Resolved	No	
	Exanthema	Mild	Recovered/Resolved	No	
20 mg dose or placebo					
[redacted]	Headache	Mild	Recovered/Resolved	Yes	
	Dizziness	Mild	Recovered/Resolved	Yes	
	Headache	Moderate	Recovered/Resolved	No	
30 mg dose or placebo					
[redacted]	Intermittent tiredness	Mild	Recovered/Resolved	Yes	
	Tooth pain (left third molar down)	Moderate	Recovered/Resolved	No	

Eightteen adverse events (AEs) were observed in 15 out of 59 subjects. Neither serious adverse events nor severe AEs related to study drug administration were observed. Seven AEs were judged by the investigator as study drug related. All AEs were mild to moderate in intensity and were resolved at the end of the study. Only symptomatic treatment was needed.

There were no clinically relevant changes from baseline of the physical/ neurological examination, vital signs, ECG- and safety laboratory parameters, as well as of the safety EEG-, the CADSS-, the C-SSRS-, SMWQ- and BAC-assessment.

[redacted]



1.2.6.1 Overall conclusions

Single oral administrations of BI 1569912 ranging from 0.25 mg to 30 mg as oral solution under fasted conditions were safe and well tolerated by healthy male subjects in the SRD part of the trial. Also, BI 1569912 oral solution (fasted) and 5 mg tablets (fasted or fed) were safe and well tolerated, in the BA/FE part of the trial. Following administration of BI 1569912, the mean systemic and peak exposures increased dose proportionally with a median t_{max} of about 0.5 h and a gMean elimination half life of about 4 h. PK parameters AUC_{0-tz} and $AUC_{0-\infty}$ showed that a high-calorie meal did not significantly modify the bioavailability of BI 1569912, but that C_{max} was reduced.

Applicable as of CTP Version 6.0

Multiple, once daily oral administrations of BI 1569912 for 14 days ranging from 2.5 mg to 20 mg as tablets under fasted and fed conditions were safe and well tolerated by healthy male subjects. After a preliminary descriptive statistical analysis across all dose groups as

compared to placebo, an initial suspicion of a dose-dependent QT_cF-interval prolongation was raised. However, no individual stopping criteria were met. Following the repeated administration of BI 1569912, the gMean systemic and peak exposures of BI 1569912 increased dose proportionally with a median t_{max} of ~1 h and a gMean elimination half-life between 4 and 5 h. A minimal food effect was seen at steady state with a decrease in C_{max} (about 500 kcal breakfast prior to drug), while AUC was not affected.

Applicable as of CTP Version 7.0 (ELDERLY-part)

Multiple, once daily oral administrations of BI 1569912 for 14 days ranging from 2.5 mg to 30 mg as tablets under fasted and fed conditions were safe and well tolerated by healthy male subjects. Following the repeated administration of BI 1569912, the gMean systemic and peak exposures of BI 1569912 increased dose proportionally with a median t_{max} of ~1 h and a gMean elimination half-life between 4 and 5 h. A minimal food effect was seen at steady state with a decrease in C_{max} (about 500 kcal breakfast prior to drug), while AUC was not affected.

[redacted]

1.2.8 Drug product

[redacted]

Two oral dosage forms have been developed for clinical use:

- Powder for oral Solution (PfoS) with a co-supplied solvent
- Tablets

BI 1569912 tablets will be applied in this multiple rising dose (MRD)-, posology (POSO) and elderly (ELDERLY)-part. They were developed in 3 dosage strengths: 0.5 mg (approx. 5.5 mm round), 2.5 mg (approx. 10 mm round) and 5 mg (approx. 17.8 x 8.6 mm oval). In addition to the drug substance, [redacted].

The clinical trial supplies will be provided in polypropylene bottles with screw-cap closures.

The tablets should be stored in the containers provided and handled according to the labelled storage instructions and shelf life.

For further information, refer to Section 4.1 and current IB [c29289852].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This is the second trial with BI 1569912 and the first with multiple dose administration, investigating safety, tolerability, pharmacokinetics and pharmacodynamics of BI 1569912 in healthy male subjects. This study population provides a relatively stable physiological, biochemical and hormonal basis for studying drug effects, shows no disease related variations and is not taking regular concomitant medications.

Within each dose group, all actively treated individuals will receive the same BI 1569912 dose. The next higher dose will only be administered to the next group, if the treatment in the preceding dose group was safe and showed acceptable tolerability.

[redacted]

Applicable as of CTP Version 6.0

[redacted]

Justification for dose escalation scheme

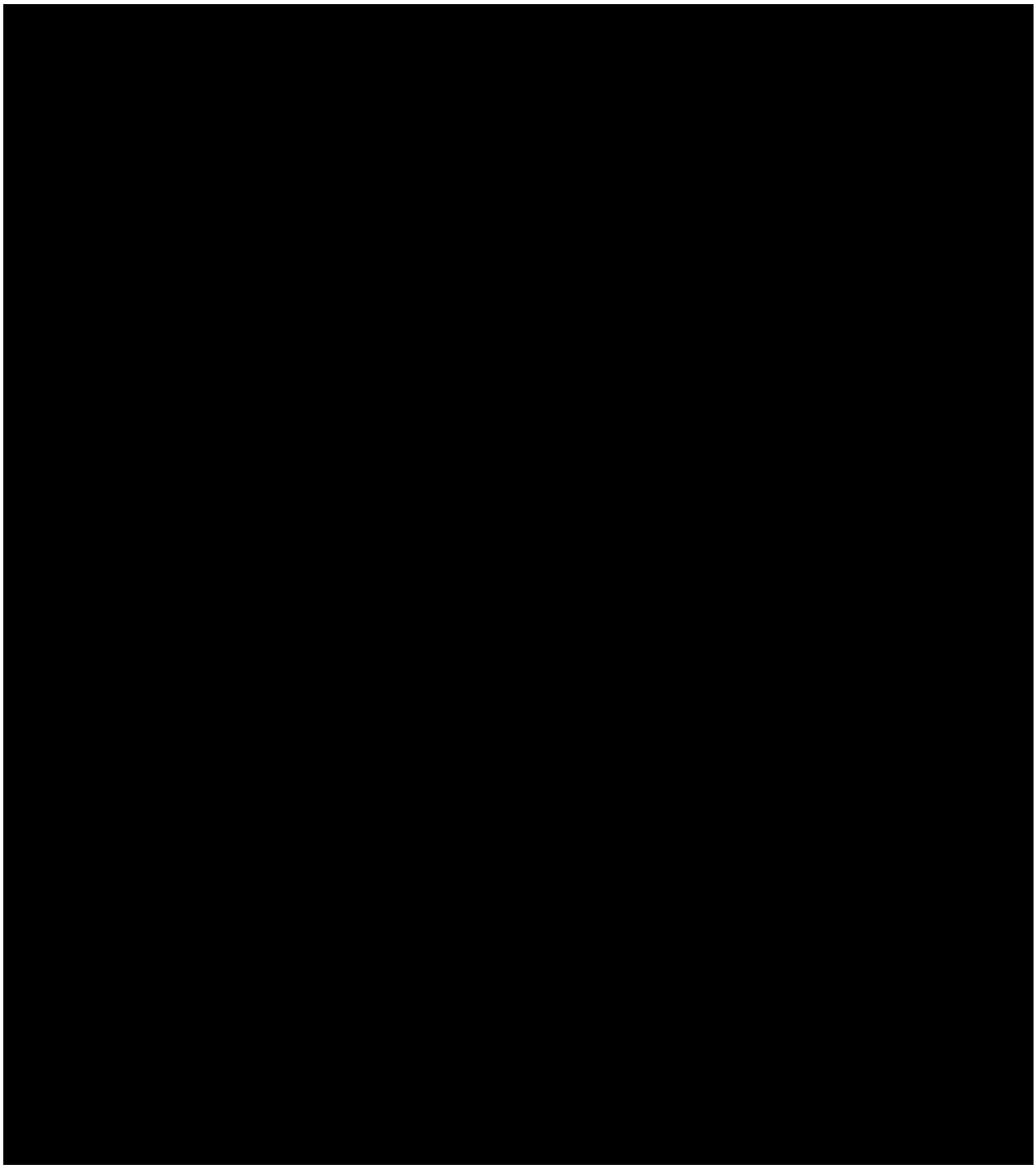
Dose escalation will be guided (besides by safety parameters) by preliminary (monitored and predicted) pharmacokinetic parameters, i.e., $C_{max, ss}$ and $AUC_{\tau, ss}$ on Day 14 in healthy subjects.

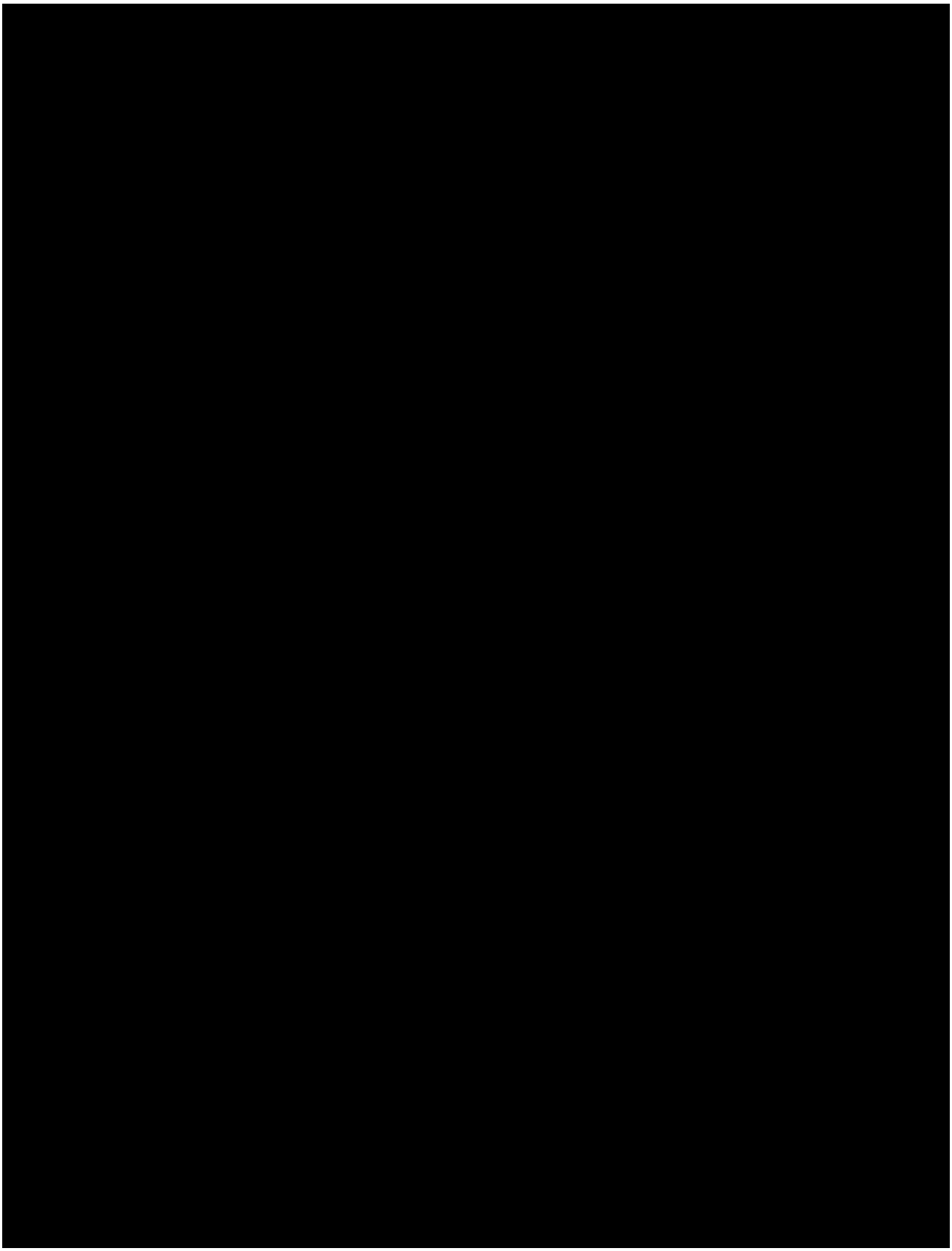
Justification of POSO-part (up-titration)

If subjects of a dose group in the MRD-part experience side effects that would constitute a tolerability issue but would not compromise their safety (e.g., transient dissociative effects), this dose will be tested again in another cohort by starting with a fraction of this dose and then increase it to the target dose according to Table 4.1.4: 1, to examine whether or not this up-titration scheme results in a better tolerability of the target dose. No dose level will be repeated without substantial amendment where any of the dose escalation stopping rules have been met.

Justification of Food Effect Assessment on Day 9 (MRD-part only)

To assess a possible food effect under 'real-life' conditions on the pharmacokinetics of BI 1569912, in all dose groups of the MRD-part at Day 9, subjects will consume a light breakfast, as specified in Table 4.1.4: 2, 30 minutes before drug administration. Day 9 was chosen due to (1) the assumption that drug levels have reached steady state (as demonstrated by preceding trough values) (2) relative few study activities on this day and (3) a long enough time period to Day 14, should there be any food effect on the pharmacokinetics of BI 1569912.





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 to the development of BI 1569912. 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 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

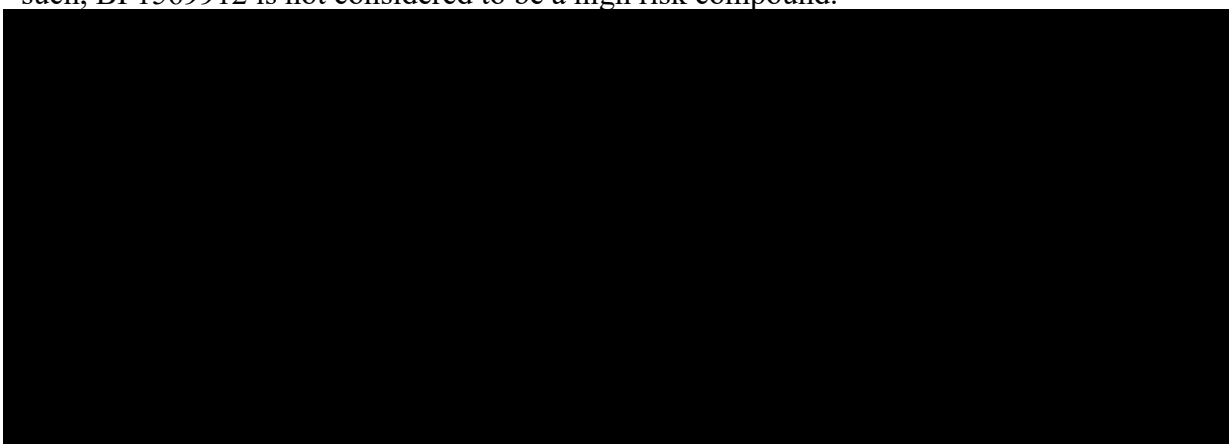
Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models and/ or (4) findings in non-clinical safety studies. Further aspects will be (5) risks resulting from trial medication auxiliaries, and (6) drug induced liver injury, resulting in (7) measures of risk minimization (including safety precautions and stopping rules – refer to Section 1.4.7)

1.4.1 Mode of action

BI 1569912 is a negative allosteric modulator of subunit 2B (NR2B) containing N-methyl-D aspartate (NMDA) receptors which is a therapeutic concept for depression that has been well described [R17-3810]. Clinical information on compounds of the same pharmacological class (NR2B NAMs like traxoprodil and rislenemdaz) or a related pharmacological class (unselective NMDA inhibitors, like esketamine) are available. For NR2B-specific negative allosteric modulators, no serious safety concerns have been identified (refer also to the current version of IB [c29289852]).

1.4.2 Nature of the target

BI 1569912 is a partial, reversible and time-dependent negative allosteric modulator of the human NR2B-subunit contained in NMDA receptors (sodium and calcium channels). As such, BI 1569912 is not considered to be a high risk compound.



[redacted]

1.4.5 Risks resulting from trial medication auxiliaries

Tablets contain lactose.

1.4.6 Drug induced liver injury

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

1.4.7 Measures of risk minimization (including safety precautions and stopping rules)

The following precautionary measures will be taken in this study in order to minimize the risk for healthy subjects:

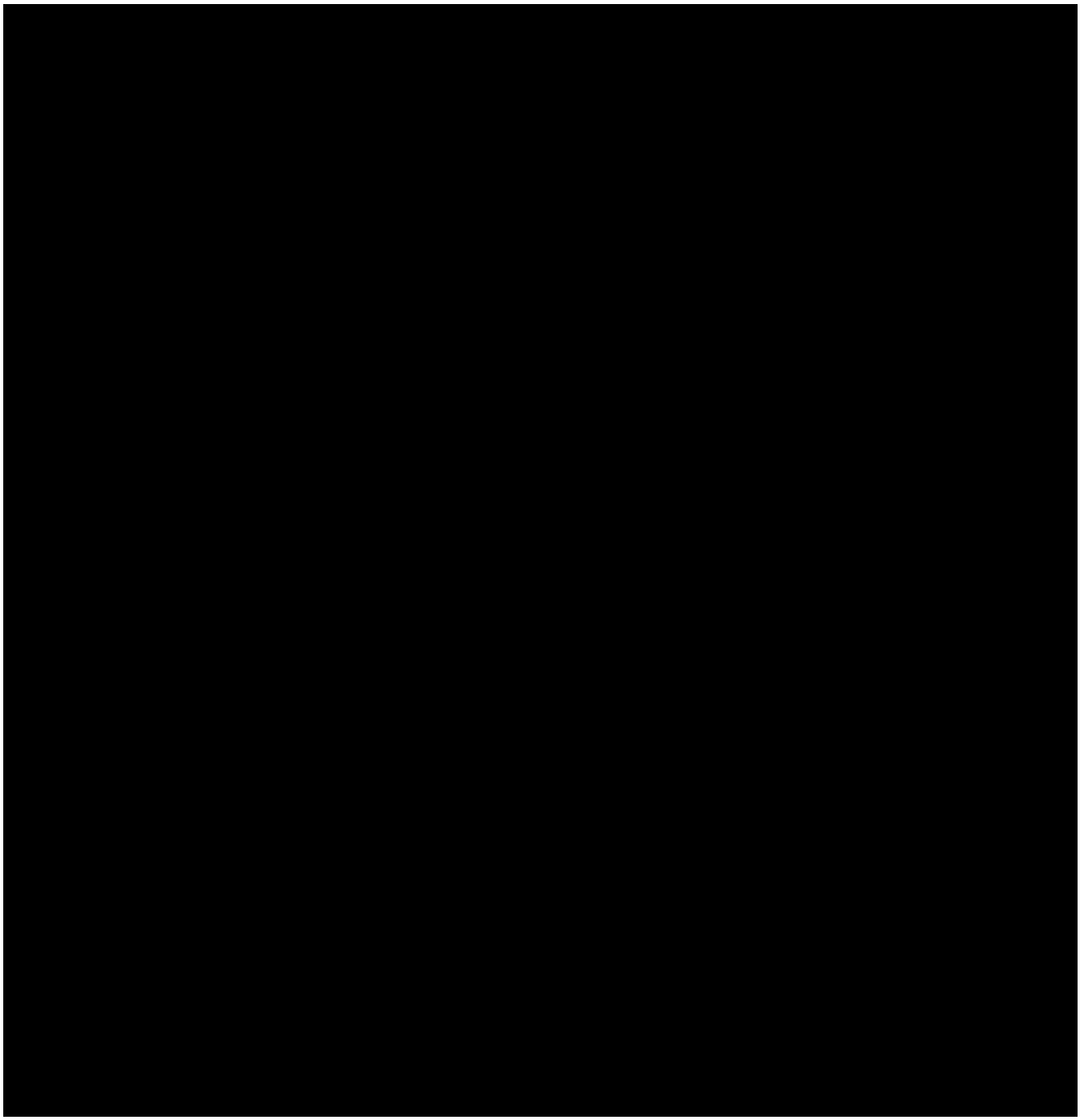
General risk minimization measures

- Careful selection of study subjects according to in- and exclusion criteria (refer to Sections 3.3.2 and 3.3.3).

[redacted]

- Extensive standard safety laboratory measurements will be performed before and after drug administration (refer to Flow Chart and Section 5.2.3).
- Close monitoring of blood pressure (refer to Flow Chart).

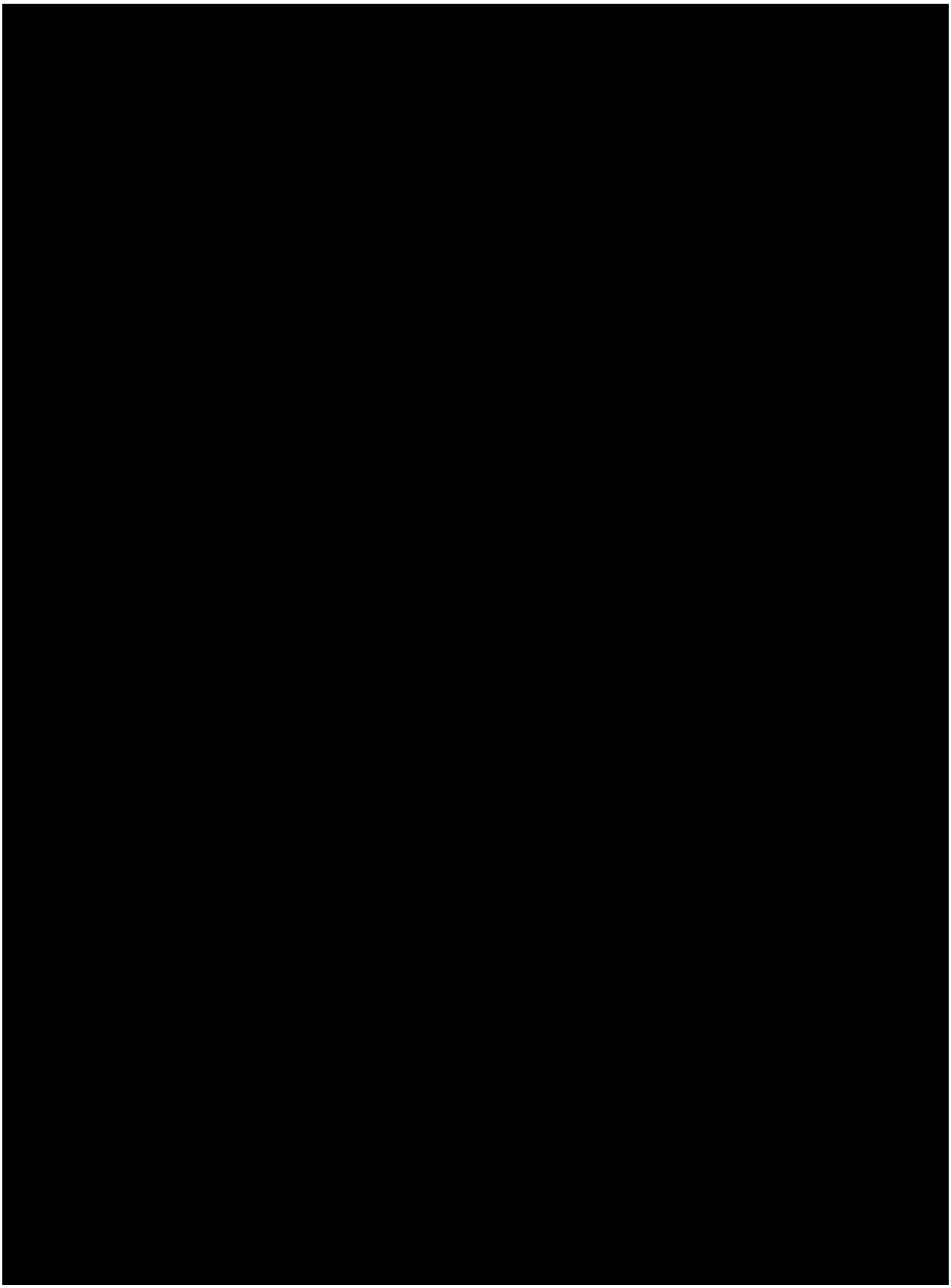
- A thorough ECG and heart rate monitoring will be performed throughout the study. Triplicate ECG-recordings will be done at time points specified in the Flow Chart, with 'rich' sampling on Days 1 and 14 to cover the anticipated period of highest drug exposure. ECG triplets will be recorded to achieve an exemption from Health Authorities for a dedicated QT-study.
- Prior to each dose escalation, a documented safety review will be performed by the Principal Investigator or an authorized deputy and the Clinical Trial Leader or an authorized deputy (refer to Section 3.1).



[redacted]

Stopping rules related to individual subjects

- Occurrence of one adverse event of severe intensity (including but not limited to QT-prolongation, dissociative symptoms or a decrease in vigilance) assessed as related to the study drug by the investigator.
- Occurrence of one serious adverse event assessed as related to the study drug by the investigator.



The clinical trial will also be discontinued when the risk profile deteriorates and a necessary adjustment of the maximum insurance sum is not possible.

1.4.8 Risk and guidance related to Covid-19 infection

No preclinical investigation into distribution and function of BI 1569912 have so far identified any interference with the immune and the cardiovascular system. The investigator 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 trial. 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, wellbeing, and/ or is in the best interest of the subject.

1.4.9 Overall assessment and conclusion

Based on the well-characterized mode of action, nature of target, high relevance of used animal models and the comprehensive non-clinical safety package of BI 1569912, and taking into account specific safety measures, including a close and continuous cardiac-, neurological- and psychiatric monitoring, and resulting from this, the possibility to stop the application of treatment at any point in time, a participation in this multiple dose regimen does not represent an undue risk to healthy subjects. Considering the medical need for a better MDD treatment and taking into account the potential advantage of a highly selective NR2B negative allosteric modulator, the expected benefit of this trial is likely to outweigh the potential risks and justifies the exposure of healthy subjects to BI 1569912.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate (1) safety, tolerability, pharmacokinetics and pharmacodynamics following multiple rising doses of BI 1569912; (2) tolerability of BI 1569912 in an up-titrating dosing scheme.

2.1.2 Primary endpoint

The primary endpoint for the assessment of safety and tolerability of BI 1569912 is the percentage of subjects with drug-related adverse events.

2.1.3 Secondary endpoint

The following pharmacokinetic parameters will be determined if feasible:

After the first dose:

- $AUC_{0\text{-}24h}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 24 h after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma after the first dose)

After the last dose:

- $AUC_{\tau,ss}$ (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)
- $C_{min,ss}$ (minimum concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
- $R_{A,Cmax}$ (accumulation ratio based on $C_{max,ss}$)
- $R_{A,AUC}$ (accumulation ratio based on $AUC_{0\text{-}\tau}$)

[redacted]

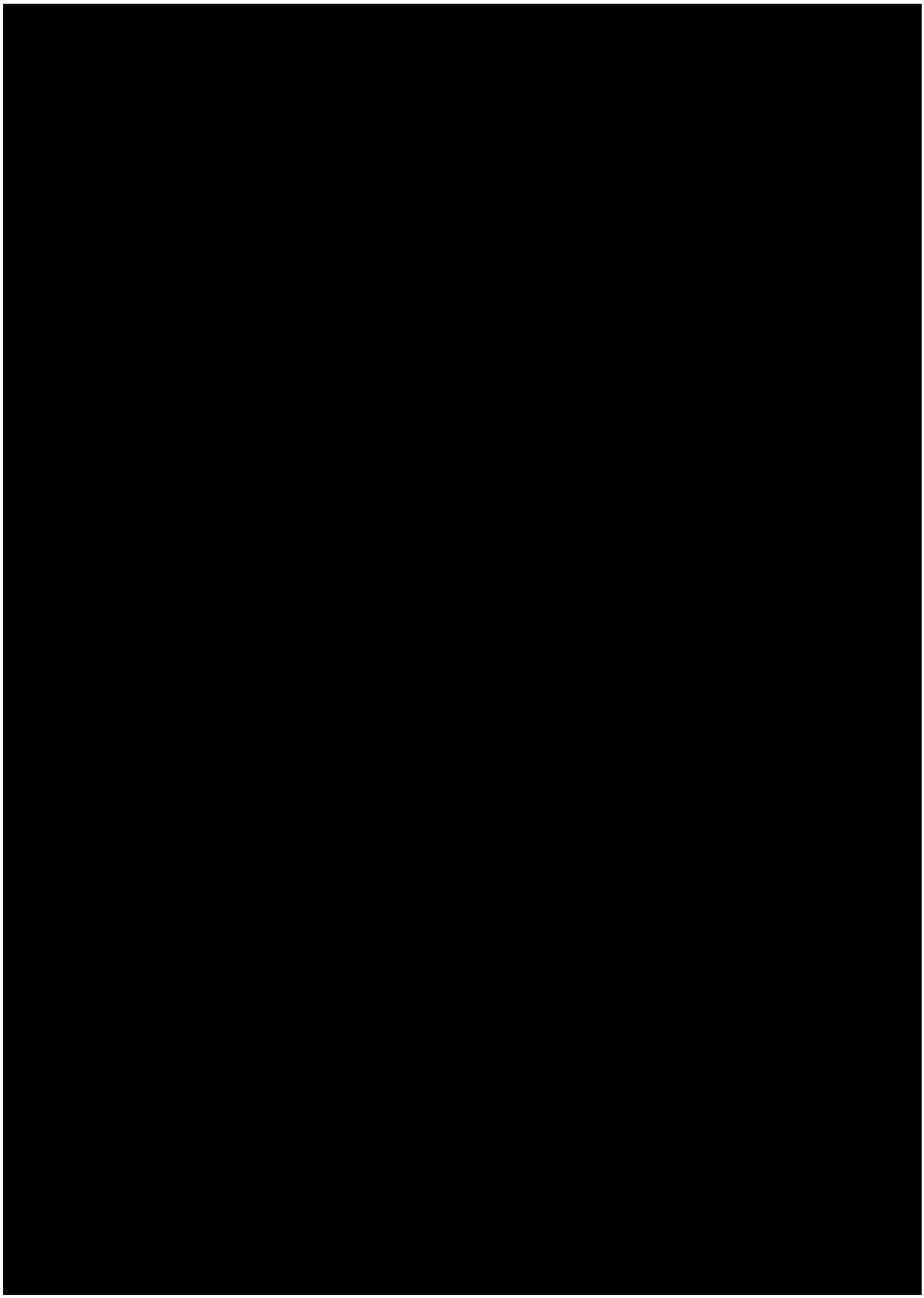
[redacted]

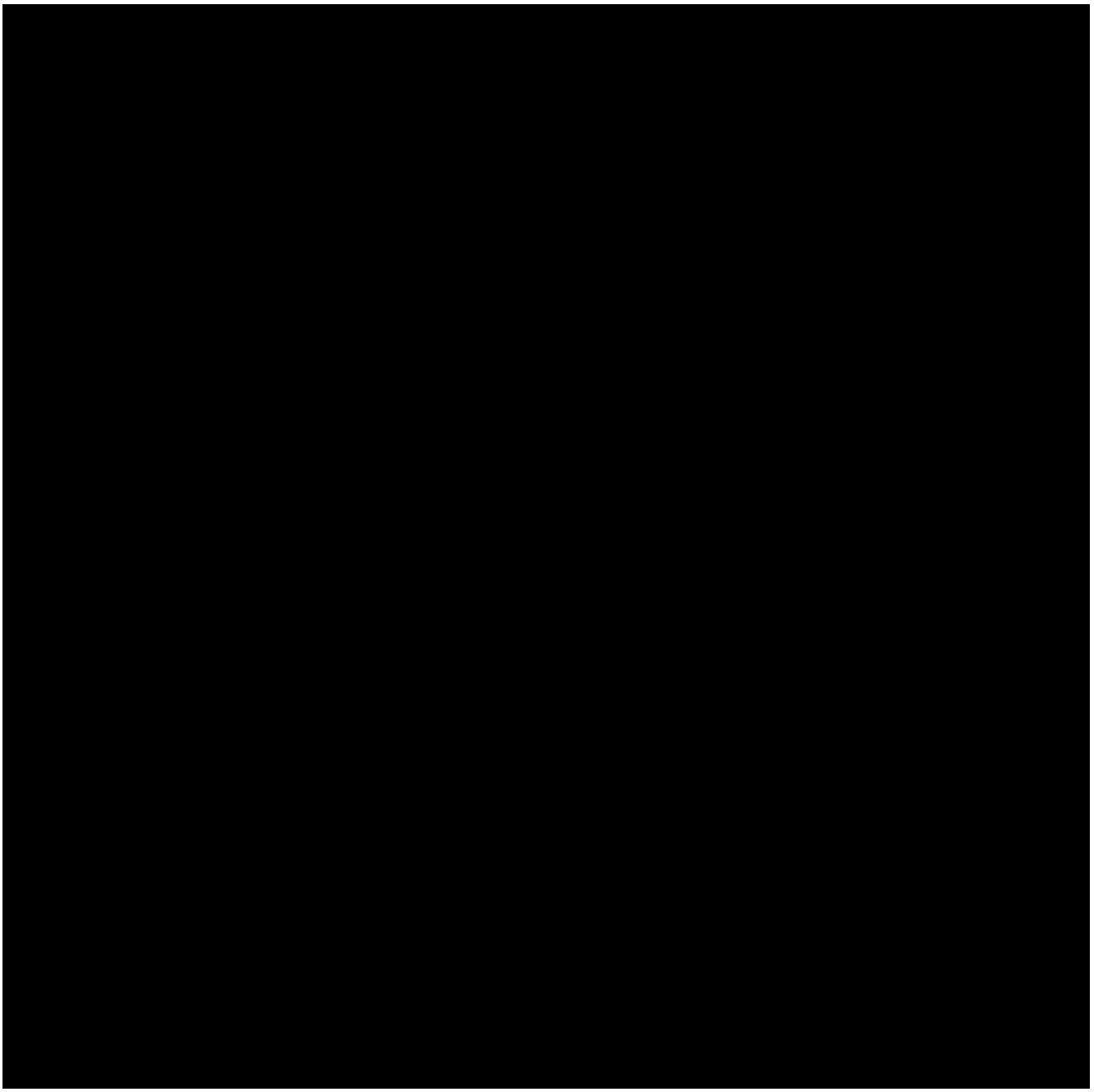
2.2.2.1 Safety and tolerability

Safety and tolerability of BI 1569912 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Standardized physical/ neurological assessment
- Assessment of dissociative symptoms (e.g., CADSS)
- Electroencephalogram (EEG)
- Brief assessment of cognition-BAC (with e.g., Verbal Memory and Learning and Symbol Coding Tasks)
- Assessment of study medication withdrawal symptoms (e.g., SMWQ)

[redacted]

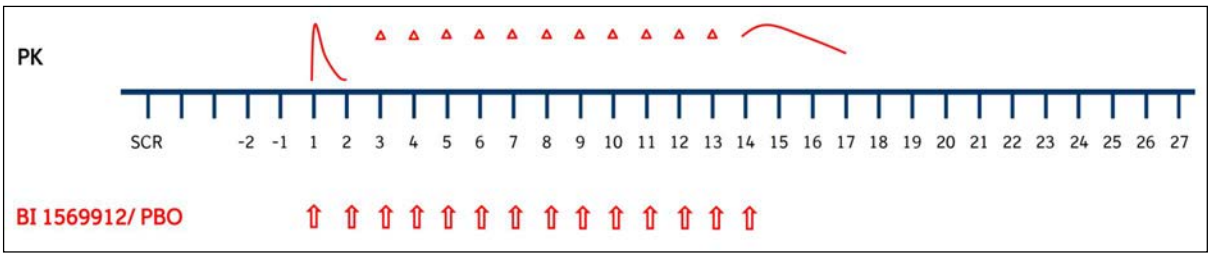




3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The overall study design is depicted in Figure 3.1: 1.



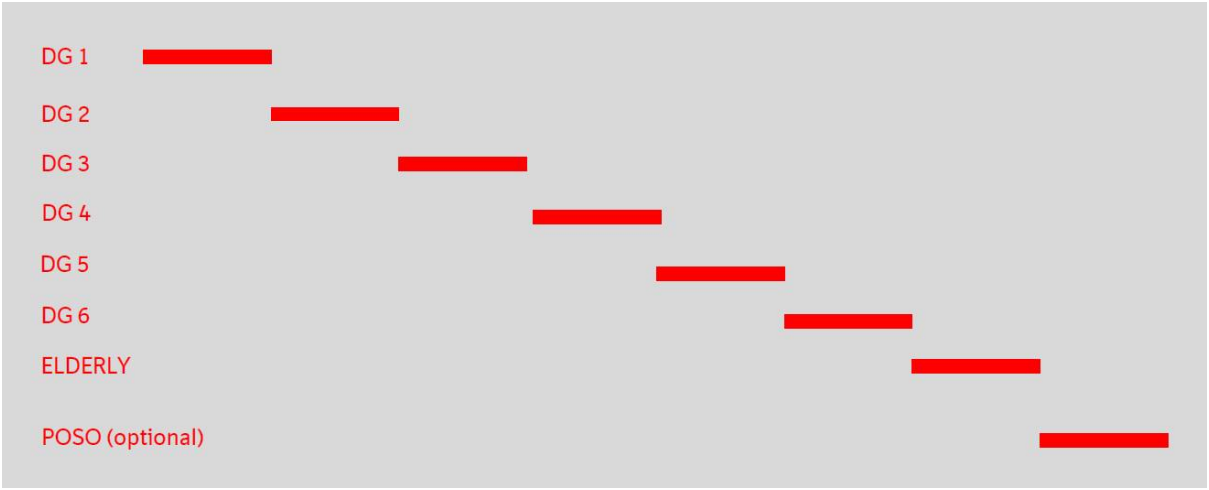


Figure 3.1: 1 Overall study design

This multiple-rising dose trial is designed as single-blind, partially randomized within dose groups, placebo-controlled, parallel group design.

It is planned to include a total of 96 (84 in the Multiple Rising Dose (MRD)-part and 12 in the optional POSO-part) healthy male subjects in the trial. Subjects will be assigned to 6 groups consisting of 12 subjects per group in the MRD-part, to 1 group consisting of 12 subjects in the POSO-part and to 1 group consisting of 12 subjects in the ELDERLY-part; the groups will be dosed sequentially (refer to Table 3.1: 1). The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose groups (e.g., add low and/ or intermediate dose groups) on the basis of experience gained during the study (for instance, based on preliminary PK data), provided, the planned and approved highest dose is not exceeded. Thus, the actual number of subjects entered may be more than 96, but is not to exceed 120. Such changes may be implemented via non-substantial CTP amendments.

In the MRD-part, within each dose group, 9 subjects will receive BI 1569912 and 3 will receive placebo. Only one dose is tested within each dose group.

For safety reasons, at each dose group of 12 subjects (9 on active, 3 on placebo), a sentinel cohort of 2 subjects (1 on active and 1 on placebo) will be dosed at least 72 h prior to the remaining 10 subjects (8 active, 2 placebo). While drug administration can be performed simultaneously in this sentinel cohort, it will be separated by at least 60 minutes in the remaining subjects which is expected to be sufficient to detect relevant acute effects of BI 1569912.

A continuous safety evaluation, including results of safety laboratories, ECG and EEG readings, recordings of vital signs and adverse events will be performed before the individual subject and the subsequent cohort is dosed.

The dose groups to be evaluated are outlined in Tables 3.1: 1.

Table 3.1: 1 Dose groups of MRD-part

Dose Group	1	2	3	4	5	6	ELDERLY
Dose (mg)	2.5	5	10	20	30	40	10/ 20
Number of subjects	12	12	12	12	12	12	12
Subjects receiving placebo	3	3	3	3	3	3	3
Subjects receiving BI 1569912	9	9	9	9	9	9	9

The groups will be dosed consecutively in ascending order, and a time interval of at least 7 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety, tolerability and pharmacokinetic data of all the preceding dose groups. The next dose group will only be treated, if, in the opinion of the Principal Investigator (or an authorised deputy) and the Clinical Trial Leader (or an authorised deputy), no safety concerns have arisen in the preceding dose groups (i.e., no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2).

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime by the Principal Investigator (or an authorised deputy) or the sponsor of the study (for instance, due to the occurrence of any unforeseen adverse events).

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e., no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2).

At minimum, data from at least 9 subjects need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 48 h of the last dose applied, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)

- Results from 12-lead ECG in the current and preceding dose groups up to at least 48 h of the last dose applied
- Vital signs in the current and preceding dose groups up to at least 48 h of the last dose applied
- Clinical laboratory tests in the current and preceding dose groups up to at least 24 h of the last dose applied
- EEG reports up to at least 24 h of the last dose applied
- Preliminary pharmacokinetic data of at least 6 subjects on active treatment for up to at least 24 h of the last dose applied, as per Section 7.4, and exposure predictions ($AUC_{\tau, ss}$ and $C_{max, ss}$) for subsequent dose groups, to make it unlikely that the next applied dose regimen will exceed the predefined exposure limits.
- Check of criteria for stopping subject treatment as per Section 3.3.4.1.

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). In addition and depending on the results and findings, suitable experts from the sponsor or external institutions (e.g., Charité) may be consulted on an as needed basis. In these cases, expert recommendations will be documented in the minutes of the Safety Review and considered for the decision making. Dose escalation will only be permitted, if no safety concerns exist, neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Trial Clinical Monitor (or an authorised deputy).

Safety Reviews can be conducted face-to-face or by video/ telephone conference. The Trial Clinical Monitor is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and Trial Clinical Monitor (or an authorised deputy), and will be filed in the ISF and TMF.

In the POSO-part, the starting dose will be a fraction of the selected target dose and will be applied over 7 days and then increased to the target dose until the end of the treatment period. The chosen dose will be based on previous experience and will not exceed the so far tested highest dose. Each dose will be applied once daily. Refer also to Table 4.1.4: 1.

In the EDERLY-part, the starting dose will be 10 mg and will be applied over 7 days and then increased to the target dose of 20 mg until the end of the treatment period (POSO-scheme No. 4 - refer also to Table 4.1.4: 1). The chosen dose is based on previous experience in young healthy subjects and on the expected therapeutic dose needed for the treatment of MDD patients. Each dose will be applied once daily. Refer also to Table 4.1.4: 1.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

For multiple-rising dose trials, the sequential rising dose design described in Section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks.

At least single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. For details, refer to Sections 4.1.5.1 and 7.6. Subjects and investigators will be aware of the dose level administered. The disadvantage of the trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in single or multiple rising dose trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication. Each dose group consists of 12 subjects, with 9 on active treatment, and 3 on placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 96 healthy male subjects will enter the study (72 in MRD-, 12 in POSO- and 12 in the ELDERLY-part). The actual number of subjects entered may exceed the total of 96, if additional intermediate doses are tested (refer to Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy 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. MRD- and POSO-part: Age of 18 to 45 years (inclusive); ELDERLY-part: Age of 65 to 80 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)

4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception, e.g., any of the following methods (of female partners) plus condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
   - Sexually abstinent
   - Surgically sterilised (including hysterectomy of female partner)
   - Postmenopausal female partner, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the (age-adapted) reference range that the investigator considers to be of clinical relevance, in particular, hepatic parameters (ALT, AST, total bilirubin) or renal parameters (creatinine) exceeding the ULN after repeated measurements
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures/ convulsions or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or unexplained blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients, e.g., known lactose intolerance)
11. Use of drugs within 14 days (or within five times of their respective elimination half-lives – whatever is longer) of planned administration of trial medication that might reasonably

influence the results of the trial (including drugs that cause QT/ QT_c interval prolongation or vaccination of any kind requiring re-vaccination during the course of the trial)

12. Intake of an investigational drug in another clinical trial within 60 days (or within five times of the respective elimination half-live – whatever is longer) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Sperm donation from the time of drug administration until 30 days thereafter
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/ QT_c interval (such as QT_c 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 (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) in the past year prior to randomization
26. History or presence of epilepsy, history of more than one febrile seizure in childhood or a family history of seizures/ convulsions
27. Epileptiform- or other EEG abnormalities at Screening which are not norm variants, or which are indicating a pathological state, or which are associated with an increased risk for seizures, according to investigator's judgement
28. History of clinically relevant head injury or trauma (e.g., associated with loss of consciousness)

29. Subject is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
30. Subject is an employee of the sponsor or investigator or otherwise dependent on them

In addition, the following SARS-CoV-2/ COVID-19-specific exclusion criteria apply:

31. A positive PCR or Antigen Rapid test for SARS-CoV-2/ COVID-19 indicating an ongoing infection with SARS-CoV-2/ COVID-19 and/ or any clinical symptom suggestive for this disease at screening (including Day -3) at the discretion of the investigator

Applicable as of CTP Version 6.0

32. A marked prolongation of PQ-interval greater than 240 ms

Applicable as of CTP Version 7.0 (ELDERLY-part only)

33. Findings from screening Holter-ECG judged as being clinically relevant by the investigator or the cardiologist of the ECG core lab.

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. For details, refer to Sections 3.3.4.1 and 3.3.4.2.

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 (refer to Section 1.2.6), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future

3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as, surgery, adverse events [AEs], or diseases)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
7. The subject is diagnosed with an acute SARS-CoV-2/ COVID-19 infection

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. Refer also to Section 3.3.4.1.

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.
3. Violation of GCP, the CTP impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product
5. Dose escalation will be stopped, if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e., a QT_c increase of greater than 60 ms from baseline in connection with absolute QT or QT_c greater than 500 ms, as confirmed by a repeat ECG recording.

6. Dose escalation will be stopped, if the $C_{max,ss}$ or $AUC_{\tau, ss}$ on Day 14 of at least 1 subject of one dose group increases above the following exposure thresholds or, if the estimated gMean exposure is expected to exceed a $C_{max, ss}$ of 1560 nM or an $AUC_{\tau, ss}$ of 2490 nM*h. Estimation will be done based on preliminary PK results of preceding dose groups (refer to Section 7.4).

   Applicable as of CTP Version 5.0

   Dose escalation will be stopped, if the $C_{max,ss}$ or $AUC_{\tau,ss}$ on Day 14 of at least 1 subject of one dose group increases above the following exposure thresholds or, if the predicted gMean exposure is expected to exceed a $C_{max,ss}$ of 2770 nM or an $AUC_{\tau,ss}$ of 4990 nM*h. Predictions will be done based on preliminary PK results of preceding dose groups (refer to Section 7.4).

   Applicable as of CTP Version 6.0

   The next higher dose level will only be administered, if the predicted gMean values of $C_{max,ss}$ or $AUC_{\tau,ss}$ do not exceed the defined exposure limits of 4490 nM for $C_{max,ss}$ or 7850 nM*h for $AUC_{\tau,ss}$ (see Section 1.2.3) or, if no individually observed value of the current dose group exceeds the defined exposure limits of 4490 nM for $C_{max,ss}$ or 7850 nM*h for $AUC_{\tau,ss}$.

7. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of the same dose group (9 subjects).

The sponsor will stop or terminate the study, if the favourable opinion or the approval is revoked.

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

No subject will be replaced who discontinued the trial for safety and/ or tolerability reasons.

If some subjects do not complete the trial for other reasons, e.g., personal, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician can decide to replace up to 4 subjects. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

The data of all subjects in a dose group, those of ‘replaced subjects’ and ‘replacement subjects’, will be considered for the dose escalation decision.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG. Refer also to current IB [c29289852].

4.1.1 Identity of the investigational medicinal products

For the MRD-part, the characteristics of the test (BI 1569912) and reference (placebo) product are given below:

Table 4.1.1: 1 Test product

Substance	**BI 1569912**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	2.5 mg
Posology	1-0-0 (DG 1)
Route of administration	Oral
Duration of use	Days 1 to 14

Table 4.1.1: 2 Test product

Substance	**BI 1569912**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	5 mg
Posology	1-0-0 (DG 2), 2-0-0 (DG 3), 4-0-0 (DG 4), 6-0-0 (DG 5), 8-0-0 (DG 6)
Route of administration	Oral
Duration of use	Days 1 to 14

Table 4.1.1: 3 Reference product

Substance	**Placebo**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	N/A (equivalent in appearance to the 2.5 mg tablet)
Posology	1-0-0 (DG 1)
Route of administration	Oral
Duration of use	Days 1 to 14

Table 4.1.1: 4 Reference product

Substance	**Placebo**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	N/A (equivalent in appearance to the 5 mg tablet)
Posology	1-0-0 (DG 2), 2-0-0 (DG 3), 4-0-0 (DG 4), 6-0-0 (DG 5), 8-0-0 (DG 6)
Route of administration	Oral
Duration of use	Days 1 to 14

For the POSO-part, the characteristics of the test (BI 1569912) and reference (placebo) product are given below:

Table 4.1.1: 5 Test product

Substance	**BI 1569912**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	0.5 mg
Posology	2-0-0 (POSO 1-A)
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

Table 4.1.1: 6 Test product

Substance	**BI 1569912**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	2.5 mg
Posology	1-0-0 (POSO 1-B), 1-0-0 (POSO 2-A),
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

Table 4.1.1: 7 Test product

Substance	**BI 1569912**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	5 mg
Posology	1-0-0 (POSO 2-B), 1-0-0 (POSO 3-A), 2-0-0 (POSO 3-B), 2-0-0 (POSO/ ELDERLY 4-A), 4-0-0 (POSO/ ELDERLY 4-B), 4-0-0 (POSO 5-A), 6-0-0 (POSO 5-B), 6-0-0 (POSO 6-A), 8-0-0 (POSO 6-B)
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

Table 4.1.1: 8 Reference product

Substance	**Placebo**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	N/A (equivalent in appearance to the 0.5 mg tablet)
Posology	2-0-0 (POSO 1-A)
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

Table 4.1.1: 9 Reference product

Substance	**Placebo**
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	N/A (equivalent in appearance to the 2.5 mg tablet)
Posology	1-0-0 (POSO 1-B), 1-0-0 (POSO 2-A),
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

Table 4.1.1: 10 Reference product

Substance	Placebo
Pharmaceutical formulation	Tablet
Source	BI Pharma GmbH & Co. KG, Germany
Unit strength	N/A (equivalent in appearance to the 5 mg tablet)
Posology	1-0-0 (POSO 2-B), 1-0-0 (POSO 3-A), 2-0-0 (POSO 3-B), 2-0-0 (POSO/ELDERLY 4-A), 4-0-0 (POSO/ELDERLY 4-B), 4-0-0 (POSO 5-A), 6-0-0 (POSO 5-B), 6-0-0 (POSO 6-A), 8-0-0 (POSO 6-B)
Route of administration	Oral
Duration of use	A: Days 1 to 7; B: Days 8 to 14

4.1.2 Selection of doses in the trial and dose modification

MRD-part

The doses selected for this trial cover the assumed sub-therapeutic, therapeutic and supra-therapeutic range and include a safety margin (refer to Section 1.2).

POSO-part (up-titration)

If subjects of a dose group in the MRD-part experience side effects that would constitute a tolerability issue but would not compromise their safety (e.g., transient dissociative effects), this dose can be tested again in another cohort by starting with a fraction of this dose and then increase it to the target dose according to Table 4.1.4: 1, in order to examine whether or not the tolerability is improved. No dose level will be repeated without substantial amendment where any of the dose escalation stopping rules have been met. For non-clinical pharmacology findings, refer also to Section 1.2.1.

ELDERLY-part

The doses selected for this part are based on favourable safety and tolerability data in young healthy subjects treated with up to 30 mg QD over 14 days and the expected therapeutic doses of 20 mg QD needed to treat MDD patients. To account for potential pharmacodynamics and pharmacokinetic particularities in a potentially more vulnerable elderly population, POSO-scheme No. 4 was chosen (refer to Table 4.1.4: 1).

4.1.3 Method of assigning subjects to treatment groups

Subject is screened after the study information and after the subject has given orally and written the informed consent. If the subject is eligible to enter the study, it is invited for the Visit 2. The subject is informed about the planned visit dates in advance as a part of the study information session. The allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomization list will be provided to

the trial site in advance. Numbers of the randomization list will be allocated by the unblinded pharmacist in ascending, sequential order to eligible subjects. Subjects are then assigned to treatment according to the randomization list.

The randomization procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the corresponding dose level.

Table 4.1.4: 1 BI 1569912 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1	BI 1569912	tablet	2.5 mg	1 tablet (2.5 mg) q.d. for 14 days	2.5 mg
2	BI 1569912	tablet	5 mg	1 tablet (5 mg) q.d. for 14 days	5 mg
3	BI 1569912	tablet	5 mg	2 tablets (5 mg) q.d. for 14 days	10 mg
4	BI 1569912	tablet	5 mg	4 tablets (5 mg) q.d. for 14 days	20 mg
5	BI 1569912	tablet	5 mg	6 tablets (5 mg) q.d. for 14 days	30 mg
6	BI 1569912	tablet	5 mg	8 tablets (5 mg) q.d. for 14 days	40 mg
POSO 1	BI 1569912	tablet	A: 0.5 mg	2 tablets (0.5 mg) q.d. for 7 days	1 mg
			B: 2.5 mg	1 tablet (2.5 mg) q.d. for 7 days	2.5 mg
POSO 2			A: 2.5 mg	1 tablet (2.5 mg) q.d. for 7 days	2.5 mg
			B: 5 mg	1 tablet (5 mg) q.d. for 7 days	5 mg
POSO 3			A: 5 mg	1 tablet (5 mg) q.d. for 7 days	5 mg
			B: 5 mg	2 tablets (5 mg) q.d. for 7 days	10 mg
POSO4/ ELDERLY			A: 5 mg	2 tablets (5 mg) q.d. for 7 days	10 mg
			B: 5 mg	4 tablets (5 mg) q.d. for 7 days	20 mg
POSO 5			A: 5 mg	4 tablets (5 mg) q.d. for 7 days	20 mg
			B: 5 mg	6 tablets (5 mg) q.d. for 7 days	30 mg
POSO 6			A: 5 mg	6 tablets (5 mg) q.d. for 7 days	30 mg
			B: 5 mg	8 tablets (5 mg) q.d. for 7 days	40 mg
1-6 & POSO 1-6	Placebo*	tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups
A: Days 1 to 7; B: Days 8 to 14

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL (340 mL in the 30 mg- and 40 mg dose group) of water to subjects who are in a sitting/ standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should

witness the administration of trial medication, and – if applicable – its preparation (e.g., reconstitution), if correct dosage cannot be ensured otherwise. To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

Subjects will be kept under close medical surveillance from the evening of Day -2 to the morning of Day 17. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture except for medical examination) or to sleep.

In each dose group of the **MRD-part**, at Day 9, subjects will start to consume a light breakfast 30 minutes before drug administration. The subjects must completely consume the meal prior to drug intake. If the patients are not able to eat or eat almost nothing, the information should be recorded in the eCRF. The composition of the light breakfast is detailed in Table 4.1.4: 2.

Table 4.1.4: 2 Composition of the light (standard continental) breakfast

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

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

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial will be performed according to a single-blind design to limit any bias which might be caused by the knowledge of treatment allocation (active or placebo/ not to dose level). A summary of the masking/ blinding level of individual functions involved in the trial is provided in Table 4.1.5.1: 1.

Table 4.1.5.1: 1 Masking/ blinding level of individual functions

Role/ function	**Timing of unblinding/ receiving access to the treatment information (including rationale)**
Subject/ participant	Not blinded to dose level. Blinded until data ready for final analysis.
Investigator/ site staff	Not blinded to dose level. Unblinded to the first 4 subjects of each dose group. Blinded to the following 8 subjects until data ready for final analysis.
Unblinded pharmacist/ pharmacy site staff	Prior to first subject entered.

Table 4.1.5.1: 1 Masking/ blinding level of individual functions (cont)

Role/ function	Timing of unblinding/ receiving access to the treatment information (including rationale)
Sponsor (e.g., clinical trial leader, clinical trial manager, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated CRO personnel, if not involved in the clinical conduct of the trial)	As requested during trial conduct, e.g., for the analysis of bioanalytical samples/ drug metabolites or preliminary analysis of pharmacokinetic data/ pharmacometric modelling. The database will be handled open-label, meaning that the trial functions of the sponsor are unblinded. This is acceptable because they are neither in contact with subjects nor with site staff. The objective of the trial is not expected to be affected.
ECG laboratory staff ([redacted])	Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to subject, treatment , recording date and time as well as planned time points of the ECGs. For quality control of the measurements, certain members of the ECG evaluation team will be unblinded to subject. If a preliminary analysis of ECG data is required during the trial, a part of the staff of the central ECG lab (different from the ECG evaluation team) may be unblinded. This part of the staff will receive the necessary information, which will be stored with no access to the ECG evaluation team.
EEG laboratory staff ([redacted]	EEG assessments will be conducted under blind condition (regarding treatment) for neurologist review and EEG signal processing.
Eye tracking laboratory staff ([redacted]	Eyetracking assessments will be conducted under blind conditions. Blinded until data ready for final data analysis.

During the time in which a role/ function is blinded, the randomization schemes and medication kit lists (i.e., the treatment information) are kept restricted by the Global Randomization Team (gRT) per Sponsor SOP. However, due to the fixed order of the trial medication administration in cohort 1 and 2 of each study arm (refer to Section 7.6), the respective roles and functions might be aware of the treatment allocation of these subjects.

Access to the randomization schedule will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

4.1.5.2 Unblinding and breaking the code

The investigator or designee will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomization scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for breaking the code must be documented on the envelope and/ or appropriate CRF page along with the date and the initials of the person who broke the code.

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

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

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 from the sponsor when the following requirements are fulfilled:

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after the first and last drug intake (Days 1 and 14). On the remaining days (Days -1 and 2 to 13), food is not allowed for at least 2 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Days 1 and 14 at 2 h and 4 h post-dose (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 4 h before until 4 h after each administration of trial medication.

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

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

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

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Subjects will be instructed not to perform any tasks or physical activity that may influence the 24-hour ECG Holter recordings at screening.

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, refer to Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

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, and a physical/ neurological examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical (including body weight) and neurological examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g., Dinamap V 100 or Dash 4000, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 minutes in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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

PCR or Antigen Rapid test for SARS-CoV-2 will be performed at Screening (including Day -3) at the discretion of the investigator.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	**BI test name [comment/ abbreviation]**	**A**	**B**
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/ Erythrocytes	X	X
	Reticulocytes, absol.	X	X
	Reticulocytes/ Erythrocyte	X	X
	White Blood Cells/ Leucocytes	X	X
	Platelet Count/ Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/ Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (*if automatic differential WBC is abnormal*)	Neut. Poly (segs)/ Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/ Leukocytes; Neutrophils Bands, absol.; Eosinophils/ Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/ Leukocytes; Lymphocytes, absol		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
	Fibrinogen	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Glutamate Dehydrogenase (GLDH)	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	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
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
	Hb_{A1c} – ELDERLY-part only	X	--

A: parameters to be determined at Visit 1 (screening examination)

B: parameters to be determined at Visit 2 on Days -1, 2, 4, 8, 14 and 17 (and EoT) (for time points refer to Flow Chart)

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	**BI test name [comment/ abbreviation]**	**A**	**B**
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment[1] (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 on Days -1, 2, 4, 8, 14 and 17 (and EoT) (for time points refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/ database and will not be reported in the CTR. It is planned to perform these tests at screening only. Drug screening will be performed at screening.

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

Table 5.2.3: 2 Exclusionary laboratory tests (cont.)

Functional lab group	Test name
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 restrictions, a breath alcohol test (e.g., Alcotest® 6510 or 6820, [redacted] will be performed prior to each treatment period, and ma [redacted] ng 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

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 to V6) will be recorded using a computerised electrocardiograph (e.g., MAC VU360, [redacted]) at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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-second duration after subjects have rested for at least 5 minutes in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

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

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 seconds applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons.

Storing

All ECGs will be stored electronically on the Muse Cardiology Information System ([redacted]).

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab [redacted] for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (refer to TMF).

Evaluation

a) Central ECG lab

Central ECG lab evaluation will be performed for the first of three replicate ECGs at each time point on Days 1 to 17. The remaining second and third ECGs of each triplicate ECG will be stored for additional analyses if required.RR and QT intervals will be determined semi-automatically, whereas PR interval, QRS duration and QRS-axis are measured automatically by a validated GE 12-SL-algorithm or equivalent.

For the statistical analyses, heart rate (HR) and the QT interval corrected for HR (QT_c e.g., QT_cF and QT_cB) will be determined by the sponsor (refer to TSAP for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided.

For blinding arrangements refer to Section 4.1.5. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/ her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/ or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

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

b) Trial site

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

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

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

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening), if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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Holter ECG recording

At screening, a Holter recording, using a digital 7-lead (3 channel) ECG recorder (e.g., CardioMem® CM-3000, [redacted]) will be installed for each eligible subject. After the subject has returned to the clinic on the next day, and after a recording duration of at least 24 h, ECGs will be downloaded to a laptop and sent to the ECG core lab for central evaluation by a cardiologist.

The results of the evaluation will be posted on a secure web site within 24 h after receipt of the ECGs. The respective personal will be informed by email that the results can be downloaded as 3 separate PDF files:

- A Holter Worksheet with a summary of findings, and a judgement by the cardiologist whether or not a particular subject should be excluded from the trial.
- A detailed Holter report with graphs and statistical descriptions containing the most prominent findings.
- Full disclosure of ECG signals (two channels only).

The equipment (recorders, laptop) and consumables (batteries, electrodes) will be supplied by the core lab. A detailed manual will also be provided containing instructions for the use of recorders and transfer of the data. An online training will be performed prior to the first use at screening.

5.2.5 Other safety parameters

5.2.5.1 Standardized mental and neurological assessment

At the time points, specified in the Flow Chart, a neurological examination will be performed. The mental and neurological examination will include the following assessments:

- General level of arousal (vigilance)
- Attention and concentration
- Orientation
- Memory

- Eye movement
- Pupil size and pupil reactivity
- Deep tendon 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 mental and neurological examination will be reported as adverse events (during the trial) or as baseline conditions (at screening). Case narratives may be written, if necessary.

For further information, refer to Appendix 10.1.

5.2.5.2 Suicidality assessment (C-SSRS)

At the time points, specified in the Flow Chart, potential suicidality or suicidal ideations will be assessed using the 'Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a semi-structured interview which was developed to assess both, suicidal behaviour and suicidal ideation in order to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials. Two versions of the C-SSRS will be used in this study: the 'Baseline/ Screening' version and the 'Since-last-visit' version. The 'Baseline/ Screening' questionnaire will be used at the Screening visit, and the 'Since-last visit' questionnaire will be used at Days -1, 3, 7, 10, 12 and 17 before discharge from the trial site. The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of 5 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 questions related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.

The investigator has to directly evaluate the scale and write a report considering plausibility and clinical relevance of results. Doubtful outcomes may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behaviour or suicidal ideation Type 2, 3, 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit. If the investigator did not administer the C-SSRS leading to the positive report, he/ she has to consult a psychiatrist, if considered necessary. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

For each report of suicidal ideation Type 1, 2 or 3 after start of the trial, the investigator has to decide, based on his/ her clinical judgment, whether it represents an AE as defined in the protocol, and, if it is considered to be an AE, reported it accordingly.

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

For further information, refer to Appendix 10.2.

5.2.5.3 Assessment of dissociative symptoms (CADSS)

Dissociative symptoms will be assessed via the 'Clinician Administered Dissociative States Scale' (CADSS) at time points indicated in the Flow Chart. The CADSS is a clinician administered measure of perceptual, behavioral and attentional alterations during active dissociative experiences. The scale contains 23 subjective items, each rated from 0 ('not at all') to 4 ('extremely'). This scale provides a validated assessment of dissociative states sensitive to change over time and amenable to repeated measures [R20-0052]. This instrument, for the purpose of the study, has a here-and-now (current) lookback timeframe.

Additional (unscheduled) CADSS assessments may be performed for safety reasons. These CADSS are assigned to the prior scheduled time point in the Flow Chart.

For further information, refer to Appendix 10.3.

5.2.5.4 Assessment of psychological dependence after treatment termination (SMWQ)

The Study Medication Withdrawal Questionnaire (SMWQ) is a patient reported outcome questionnaire with 10 items which will be used after the last drug administration. The scale is modified from the AWQ (amphetamine withdrawal questionnaire) to monitor psychological dependence after termination of a drug. This questionnaire will be used exploratory to monitor whether BI 1569912 which inhibits specific NMDA receptors in a different way than the known unspecific NMDA inhibitors has signs or symptoms for psychological dependence. As peak times of occurrence of symptoms are not known, it will be applied in the time range of about 12 to 48 h after the last drug administration where drugs with psychological dependence typically show a peak of symptoms.

5.2.5.5 Electroencephalography (EEG) and Event related potentials (ERP)

Electroencephalography (EEG) is an electrophysiological, non-invasive method for the recording of electrical activity arising from the human brain cortex with electrodes placed on the scalp. Preferably, EEG recordings are carried out with the subject sitting in a half-reclined position. For further details about EEG data capture, please also refer to the EEG user manual.

Recording

Safety EEG (as well as qEEG and ERP testing, please refer to Section 5.4.2) will be conducted in an environmentally controlled quiet room. EEGs will be captured through a EEG cap with a minimum of 19 recording electrodes (plus ground and reference electrodes) and will be recorded using an EEG amplifier at the time points given in the Flow Chart. Electrode placement follows the international 10-20 system.

EEGs may be repeated for quality reasons, e.g., due to alternating current artefacts, muscle movements, or electrode dislocation. The repeat EEGs are assigned to the respective scheduled time point.

Additional (unscheduled) EEGs may be recorded for safety reasons. These EEGs are assigned to the prior scheduled time point in the Flow Chart.

The screening EEG is a standard EEG recording of approximately 20 minutes in total, including provocation procedures (photic stimulation and hyperventilation).

Three periods will be included as follows:

(1) 10 minutes of spontaneous EEG: during the first minute, the technician asks the subject to alternate between open eyes and closed eyes every 10 seconds. Then, after the first minute, to keep eyes closed for the next 9 minutes in resting conditions.

(2) 5 minutes of EEG with photic stimulation: a photic lamp is placed in front of the subject's face. In total, 20 incremental frequency flash periods of 20-second duration, separated by 20 seconds periods of no flash. The flash frequency increases automatically from 1Hz to 20 Hz. During the photic stimulation, the subject's eyes are open only for 5 seconds per flash stimulation period.

(3) 5 minutes of EEG with hyperventilation: During the first 3 minutes, the EEG technician asks the subject to keep the eyes closed and to hyperventilate (deep and accelerated breathing). After 3 minutes, the subject is asked to breathe normally for 1 minute. During the last minute, the technician asks the subject to alternate between open eyes and eyes closed every 15 seconds.

For further details, please refer to the EEG user manual Screening.

For all further EEGs during the course of the study (safety EEG and qEEG, refer to Section 5.4.2.1), at time points indicated in the Flow Chart, each EEG sample will last 10 minutes in total and will be performed without photic stimulation or hyperventilation. Two sequences will be included: (1) a ***resting EEG*** with eyes closed for at least 5 minutes; (2) a resting EEG with ***eyes open*** for about 5 minutes. Time spans of EEG samples after drug administration should approximately match time spans at baseline to allow for comparability of the occurrence of abnormal EEG signals. Safety EEG recordings may be used for analysis of quantitative EEG parameters.

For further details, please refer to the EEG user manual.

Storing

All EEGs will be stored electronically.

Data Transfer

All EEGs, regardless of their quality, will be transferred electronically to the central EEG lab for evaluation.

Data transfer from the central EEG lab to the sponsor is described in the EEG data transfer agreement (refer to TMF).

Evaluation

All EEGs will be independently evaluated by two readers at central EEG lab who evaluate recordings according to the same standards.

Should these readers be in disagreement with each other, an adjudication process at the central EEG lab will be in place. A third reader will consolidate the deviating opinions which then will be reflected in the final report. This EEG report will distinguish between three different outcomes of the evaluation:

- 'normal'
- 'abnormal/ epileptiform'
- 'abnormal/ non-epileptiform'

In case of an abnormal EEG result, an additional external reader with expertise in epilepsy, and with full access to the source data can be consulted for advice. The Principal Investigator and the Clinical Trial Leader will then discuss the clinical relevance and the relatedness to the study drug of this finding.

For the inclusion or exclusion (refer to Section 3.3) of a subject and for the assessment of safety during the study, the reports will be reviewed by the investigator.

While an 'abnormal/ epileptiform' finding will lead to exclusion of the subject at screening (refer also to Section 3.3.3), an 'abnormal/ non-epileptiform' finding at screening will be reported as baseline condition. 'Abnormal/ epileptiform' or 'abnormal/ non-epileptiform' findings during the trial will be reported as AEs, if judged clinically relevant by the investigator.

Any EEG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

EEG Reporting

The EEG safety reading turn-around time will be at most 48 h. For all EEGs, Biotrial will perform an independent safety reading by two Biotrial neurologists with an adjudication process, in case of different interpretations.

A remote connection between the EEG device and the neurologists' terminal might be established (if needed e. g., for unclear EEG findings) following the instructions provided in the Biotrial Core LabEEG User Manual. During the EEG recording, the neurologist can visualize the EEG signal in nearly real time (i.e., with a few seconds delay) and navigate throughout the entire duration of the recording, if necessary. Within about 15 minutes after the end of the recording, the Biotrial neurologist will fill in a simplified EEG safety report and send it to the site investigator. This report will define whether the EEG is normal or abnormal and, in case of an abnormal EEG, provide a description of the identified abnormality.

For all recordings, the site clinical staff will upload the EEG data files together with their corresponding transmittal form file to Biotrial's platform as soon as possible after the recording.

5.2.5.6 Brief Assessment of Cognition (BAC)

The BAC [R17-0578] is a tablet-based cognitive assessment battery which allows standardized presentation of task instructions and stimuli, audio-recording of subject responses, and automatized scoring and data management. Two BAC subtests will be administered at time points indicated in the Flow Chart.

5.2.5.6.1 Verbal Memory and Learning

Verbal Memory and Learning consists of two components: (1) Verbal Memory List Learning, and (2) Delayed Free Recall. In the Verbal Memory List Learning component, subjects are aurally presented with 15 unrelated words and asked to recall as many as possible. This procedure is repeated 5 times. There are seven alternate forms. This component takes approximately 7 minutes to administer. The outcome measure is the total number of words correctly recalled (Trials 1-5). For Delayed Free Recall, following a standardized 20-minute retention interval, subjects are asked to recall as many words as possible from the previous list. Administration takes approximately 2 minutes. The outcome measure is the total number of words correctly recalled (after the delay interval).

5.2.5.6.2 Symbol Coding Task

The Symbol Coding task is a measure of speed of processing in which subjects are provided a key explaining how unique symbols correspond to the individual numbers 1 - 9. Subjects are then given 90 seconds to fill in the corresponding number beneath each symbol in a series as quickly as possible, touching the correct digit on a number pad provided on the screen. Scores are based on the number of correct items. There are 8 alternate forms. The correct symbols and numerical matches are automatically scored, and the timer on the device automatically stops the presentation of materials for the test at 90 seconds.

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, neurological examination including mental status 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 Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

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

5.2.6.1.4 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, refer to Section 5.2.6.2.2.

The following are considered as AESIs:

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

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

No other AESIs have been defined for this trial.

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 signs or symptoms that 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?'. Changes in mental status are also to be assessed with questions such as 'Do you remember all events since last assessment?', 'Does everything go as expected?' Specific questions will be asked wherever necessary in order to more precisely describe an AE.

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

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial

due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 h) 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 send 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 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 h) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner.

The outcome of the pregnancy, associated with the drug exposure during pregnancy, must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g., as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments. If a subject has to be withdrawn from treatment at one of the above mentioned time points and the PK sample was already obtained, this PK sample might be registered as EoT sample instead. It will be collected and analysed accordingly.

5.3.2 Methods of sample collection

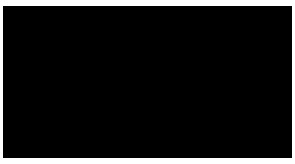
5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1569912 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

EDTA-anticoagulated blood samples will be centrifuged for approximately 10 minutes at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.6 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 minutes with interim storage of blood samples and aliquots in ice water or on ice. The time at which each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20 °C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first one. At the analytical laboratory, plasma samples will be stored at approximately -20 °C or below until analysis.

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

Plasma samples, dedicated to pharmacokinetic analysis, are transferred to:



After completion of the PK analysis of BI 1569912, the plasma remaining samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/ or its metabolites will be

generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

5.3.2.2 Blood sampling for metabolism analysis (MRD-part only)

Additional K_2-EDTA plasma samples for the optional identification of drug metabolites will be investigated in all MRD-dose group. Based on the knowledge gained during the trial conduct, e.g., from preliminary PK results, the dose group may be modified to a different one. The change will be implemented via a non-substantial CTP amendment.

The blood samples will be drawn at the same time points as PK samples on Day 14 (refer to Flow Chart). At each of these times, 3 mL blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples. Plasma samples, dedicated to metabolism investigation, are transferred to:

[redacted]

Only data related to the parent compound and its metabolites will be acquired. Evaluation of drug metabolism will be reported separately and will not be included in the CTR. The study samples will be discarded after completion of the experiments but not later than 5 years after the CTR has been archived.

5.3.2.3 Urine sampling for pharmacokinetic analysis (MRD-part only)

A blank urine sample will be collected before administration of trial medication (within 3 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 3 L polyethylene (PE) containers and stored in the refrigerator during the collection interval. Subjects are told to empty their bladders at the end of each sampling interval. In order to facilitate urine sampling, subjects will be advised to drink at least 100 mL water before the end of each urine sampling interval.

The urine weight/ volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done; i.e., 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurements, with an additional 20 mL aliquot stored for potential metabolite analysis. If more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single polyethylene) (PE)/PP or glass container, and stirring the mixed fractions for about 1 minute (manually or using a stir bar or other stirring device made of PE, PP, Teflon, or glass).

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

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

Urine samples, dedicated to pharmacokinetic analysis, are transferred to:

Urine samples dedicated to metabolite investigations are transferred to:

After completion of the trial, the urine samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/ or its metabolites will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.2.4 Plasma sampling for CYP3A4 biomarker assessment - 4-beta hydroxy-cholesterol (MRD-part only)

For quantification of 4-beta hydroxy-cholesterol concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

EDTA-anticoagulated blood samples will be centrifuged for approximately 10 minutes at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.6 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 minutes with interim storage of blood samples and aliquots in ice water or on ice. The time at which each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -70 °C or below at the trial site. The second aliquot, consisting of the remaining plasma volume, will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first one. At the analytical laboratory, plasma samples will be stored at approximately -70 °C or below until analysis.

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

Plasma samples, dedicated to pharmacokinetic analysis, are transferred to [redacted] Otley Road, Harrogate, HG3 1PY, UK.

5.3.2.5 Urine sampling for CYP3A4 biomarker assessment - 6-beta hydroxy-cortisol and cortisol (MRD-part only)

For quantification of 6-beta hydroxy-cortisol and cortisol concentrations in urine, morning spot urine samples will be collected after the first morning voids into pre-labelled disposable container (Containers for 6β-Hydroxycortisol and Cortisol should be divided) at the times indicated in the Flow Chart.

6β-Hydroxycortisol and Cortisol morning spot urine should be collected in separate urine collection containers than BI 1569912.

Subjects will be advised to drink a glass of water (approx. 200 mL) and to void their bladder completely. Two aliquots (2 mL each), as the spot urine sample, will be stored in polypropylene (PP) tubes for bioanalytical measurements. The first aliquot should contain at least 2 mL of urine. The process from collection until transfer of urine aliquots into the freezer should be completed in less than 60 minutes with interim storage of aliquots in ice water or on ice. The time at which each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -70 °C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first one. At the analytical laboratory, urine samples will be stored at approximately -70 °C or below until analysis.

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

Urine samples, dedicated to pharmacokinetic analysis, are transferred to [redacted]

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER

5.4.1 Eye tracking (MRD-part only)

Eye tracking is a methodology that measures the temporal and spatial accuracy of a subject's gaze while tracking a moving target displayed on a screen. Several assays and read-outs have been established for eye tracking. In this respect, different visual tracking protocols will be implemented to quantitatively characterize smooth pursuit, pro/ anti-saccade, and vestibulo-ocular reflex (VOR) performance at time points indicated in the Flow Chart. An integrated stimulus presentation-eye tracking apparatus with a screen integrated into a goggle-like device (EYE-SYNC, [redacted]) will be used which records eye movements at 60 Hz while the participant is wearing the goggle-based device. Prior to assessments, the system will be calibrated. During this process, the mapping between the pupil image in the eye tracker's camera image and the gaze position on the subject's display screen will be determined using a 5 point primary calibration (4 targets located on a 10 degree circle and 1 located in the centre) and a 9 point secondary calibration stimulus (8 targets are located on a 10 degree circle and 1 target located in the centre). The primary calibration presents targets

counter-clockwise starting in the centre and moving to the upper-left. The secondary calibration is displayed in a random sequence to the subject.

Smooth Pursuit

Circular smooth pursuit evaluates visual synchronization through 0.4 Hz at 10 degree radius with two sets of six cycles separated by central fixation. This test will yield gaze-target synchronization metrics as derived from phase, radial and tangential errors. Data collection duration is approximately 30 seconds.

Pro/ Anti-Saccades

Targets are located ± 8.0 degrees horizontal or vertical from a central indicator. Each trial is switched by blanking the central indicator in a randomized 1.5-3.5 second interval with peripheral target appearing left/ right (horizontal). The stimulus presentation sequence will consist of a block of horizontal prosaccade trials, followed by a block of horizontal antisaccade trials. The administrator will provide instructions to the subject regarding the stimulus prior to each block. This test will yield saccade latency, amplitude and the number or correct responses. Data collection duration is approximately 120 seconds for each pro and antisaccadestimulus.

Vestibulo-Ocular Reflex

A single target is presented at a fixed position in a virtual space, while the patient is instructed to maintain a stable gaze. A clinician manually directs head movement horizontally by holding the patient's head from behind on either side. A ± 10 degree amplitude of motion is maintained at 120 beats per minute with metronome sounds provided by the headset. Data collection duration is approximately 30 seconds.

Including calibration and instructions, the total time for eye tracking assessments is approximately 10 minutes per participant and time point.

5.4.2 Quantitative EEG, event-related potentials (ERP)

EEG is a non-invasive method to measure the electrical activity of large, synchronously firing, populations of neurons in the brain with electrodes placed on the scalp. EEG read-outs will be assessed as potential markers for indirect target engagement and physiological response. The following EEG parameters will be measured prior to drug administration and at selected time points after drug administration (refer to Flow Chart): Quantitative EEG (qEEG) and Event-Related Potential (ERP). The timing of qEEG/ ERPs may be adjusted in consultation with the Principal Investigator and sponsor, based on emerging pharmacokinetics or other data.

When qEEG/ ERP is scheduled for the same time points as blood draws, blood draws will take priority, and the qEEG/ ERP will be obtained shortly thereafter.

qEEG and ERP testing will occur in an environmentally controlled room. Tests will be completed with subjects seated comfortably in front of a computer monitor. EEG electrodes will be affixed to the scalp according to the International 10-20 electrode placement system.

qEEG and ERP records will be collected using a CE Class IIa medically certified and FDA approved amplifier, e.g., Comet AS40 Amplifier from [redacted]. The

sampling rate will be fixed at 400 Hz within a standard range of 0.1-100 Hz. A 50 Hz notch filter will be applied. Tests will occur in series, with qEEG preceding ERP testing, if applicable.

Prior to start of the test, about 30 minutes should be planned to hook up EEG electrodes. After the test, 5 to 10 minutes are required to unhook electrodes.

5.4.2.1 Quantitative EEG (qEEG)

qEEG measures will be recorded during the same recording session as for safety EEG (please refer to Section 5.2.5.4).

Eyes Closed Segment (5 Minutes)

A resting eyes closed recording segment is necessary to assess variations in vigilance over time and acquire pertinent EEG information such as posterior dominant rhythm, standard EEG spectral bands (Delta, Alpha, Beta, etc.), and a number of derived spectral measures (Alpha Slow-Wave Index, Theta-Beta Ratio, etc.). Utmost care should be taken by the technologist to minimize subject eye fluttering, muscle tension, and monitor for drowsiness.

A minimum of 90-120 seconds artefact-free signal is desired.

Eyes Open Segment (5 Minutes)

Eyes open recording segment is necessary as a counterpart to eyes closed segment. Care should be taken by the technologist to minimize subject eye movement, excessive blink frequency, eye fluttering, or muscle tension. Short external interventions for vigilance stimulation (talking to subject, tapping a pen etc.) are permissible, if a decrease in vigilance is observed, for instance in case of intrusion of slow-wave activity in the EEG. A minimum of 90-120 seconds artefact-free signal is desired.

5.4.2.2 Event-related potential (ERP)

In the ERP task, one standard tone (standard tone, probability 0.82, 1000 Hz, 50 ms duration, 5 ms rise/ fall time, 85 dB SPL) will be presented binaurally through headphones with a constant SOA (stimulus onset asynchrony) of 0.4 seconds, randomly interrupted by three types of deviant tone bursts (deviant tone, probability 0.06 each): a duration deviant (1000 Hz, 125 ms duration, 5 ms rise/ fall time, 85 dB SPL), a pitch deviant (1500 Hz, 50 ms duration, 5 ms rise/ fall time, 85 dB SPL) and an double deviant (1500 Hz, 125 ms duration, 5 ms rise/ fall time, 85 dB SPL). A total of 1800 tones will be presented in three blocks separated by 20-second rest periods. This will produce 108 deviant stimuli of each type and a total of 1476 standards.

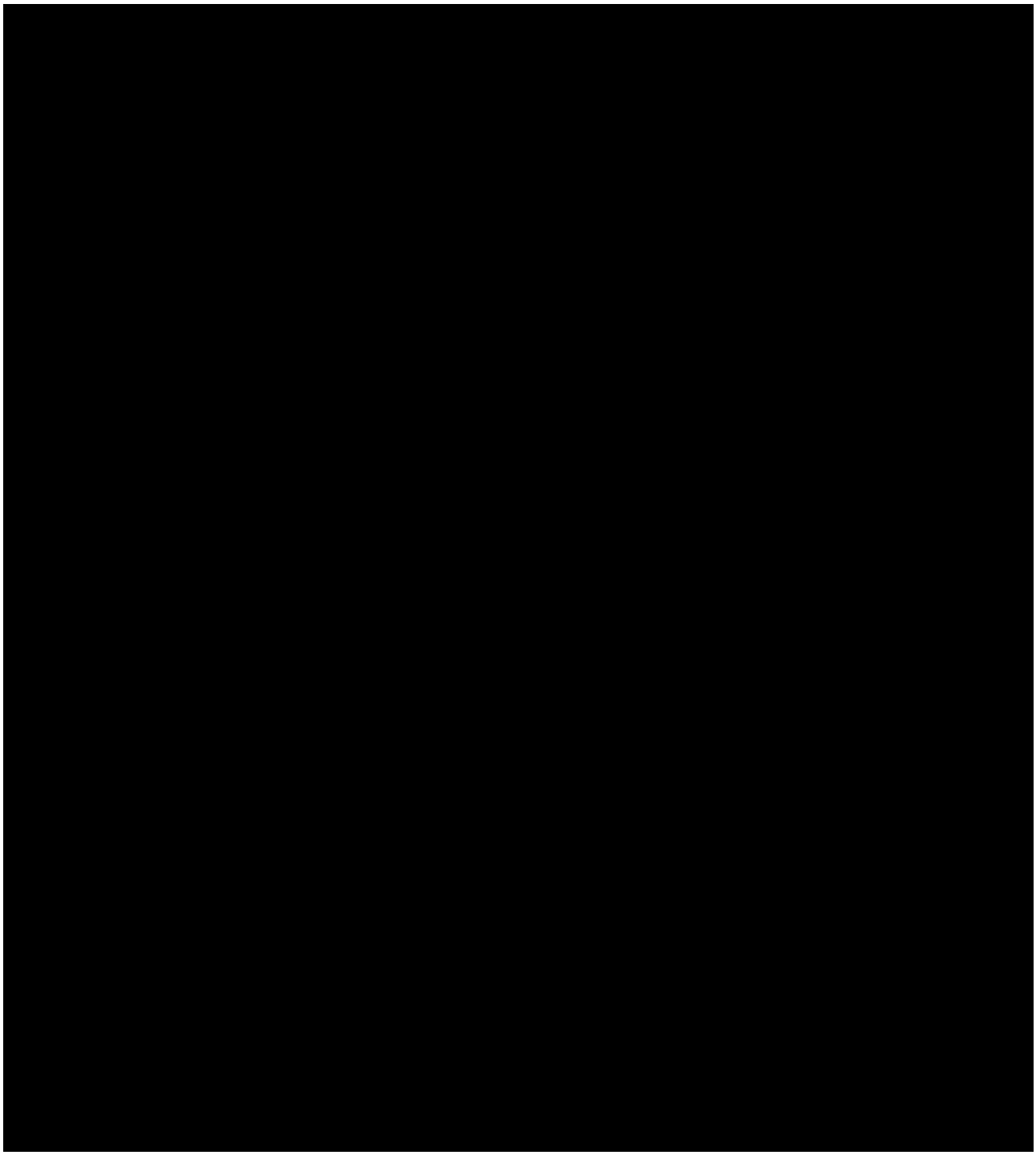
All stimuli will be presented binaurally over headphones. Subjects will be seated comfortably facing a monitor and viewing a slowly changing slide show of nature scenes (landscapes, animals). Subjects will be instructed to ignore the tones and silently count the number of different nature scenes shown. No responses are required during the ERP task. However, subjects will be asked to report the number of slide show scenes they count and this number will be recorded on the transmittal form. No judgement of accuracy will be made concerning the scene count, as the task serves merely to keep the subjects alert and attentive. The total task duration will be 12.67 minutes (3 * 4 minutes + 2 * 0.33 minutes).

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation



5.7 APPROPRIATENESS OF MEASUREMENTS

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

Since, in pre-clinical studies, seizures/ convulsions were detected in dogs at higher exposure levels, a routine EEG is included in order to detect suspect EEG signals as early as possible. The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.4 are of exploratory nature.

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 EoT examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for pharmacokinetics and biomarkers).

On Days 1, 9 and 14, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 5 minutes for the first 4 h, 10 minutes thereafter up to 24 h after trial drug administration, and ± 30 minutes thereafter.

The tolerance for drug administration will be ± 1 minute on Days 1, 9 and 14.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. 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. However, the PK sample collection should have priority in the sense that it should be performed at the exact planned clock time which means that other measurements scheduled at the same time point, e.g., ECG and vital signs, have to be taken a bit earlier. 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/ Holter ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment period

Each subject will receive a single dose of BI 1569912 or placebo from Day 1 to Day 14 at Visit 2.

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be admitted to the trial site in the evening of Day -2 and kept under close medical surveillance for at least 72 h following the last drug administration. Subjects

will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.

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

The safety measurements performed during the treatment period are specified in Section 5.3 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, refer to Sections 5.2.1 to 5.2.5. Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoT 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 EoT Visit must be followed until they have resolved, have been sufficiently characterized, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial will be assessed by calculating descriptive statistics for safety as well as for PK and PD parameters which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality. Linear modelling will be used for analysing whether steady state has been attained and for estimation of the linearity index. The food effect will be assessed descriptively. The POSO- and ELDERLY-part will only be statistically described/ explored with regards to safety and tolerability.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this study.

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the study, i.e., confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.
- Additional analyses sets, e.g., sets including only subjects from the MRD-part or the POSO-part or ELDERLY-part only, may be defined in the TSAP, as appropriate.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (iPD) categories will be suggested in the iPD specification file. iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Sections 2.1 and 2.2.2.2 for drug BI 1569912 will be calculated according to the relevant BI internal procedures.

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

Relevant protocol violations may be

- Incorrect trial medication taken, i.e., the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Incorrect intake of meal (on Day 9) – MRD-part only
- Use of restricted medications

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

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

Plasma/ urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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

Biomarkers

Biomarker data and parameters of a subject will be included in the statistical biomarker analyses, if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability (as revealed during data analysis).

Exclusion of a subject's data will be documented in the CTR.

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature.

7.3.2 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

Further exploratory analyses

Dose proportionality will be explored via graphical checks and, if applicable, via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints $AUC_{\tau, ss}$ and $C_{max, ss}$ at steady state, and potentially also at Day 1 with $AUC_{0\text{-}24h}$ and C_{max}, as specified in Section 2.1.3.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

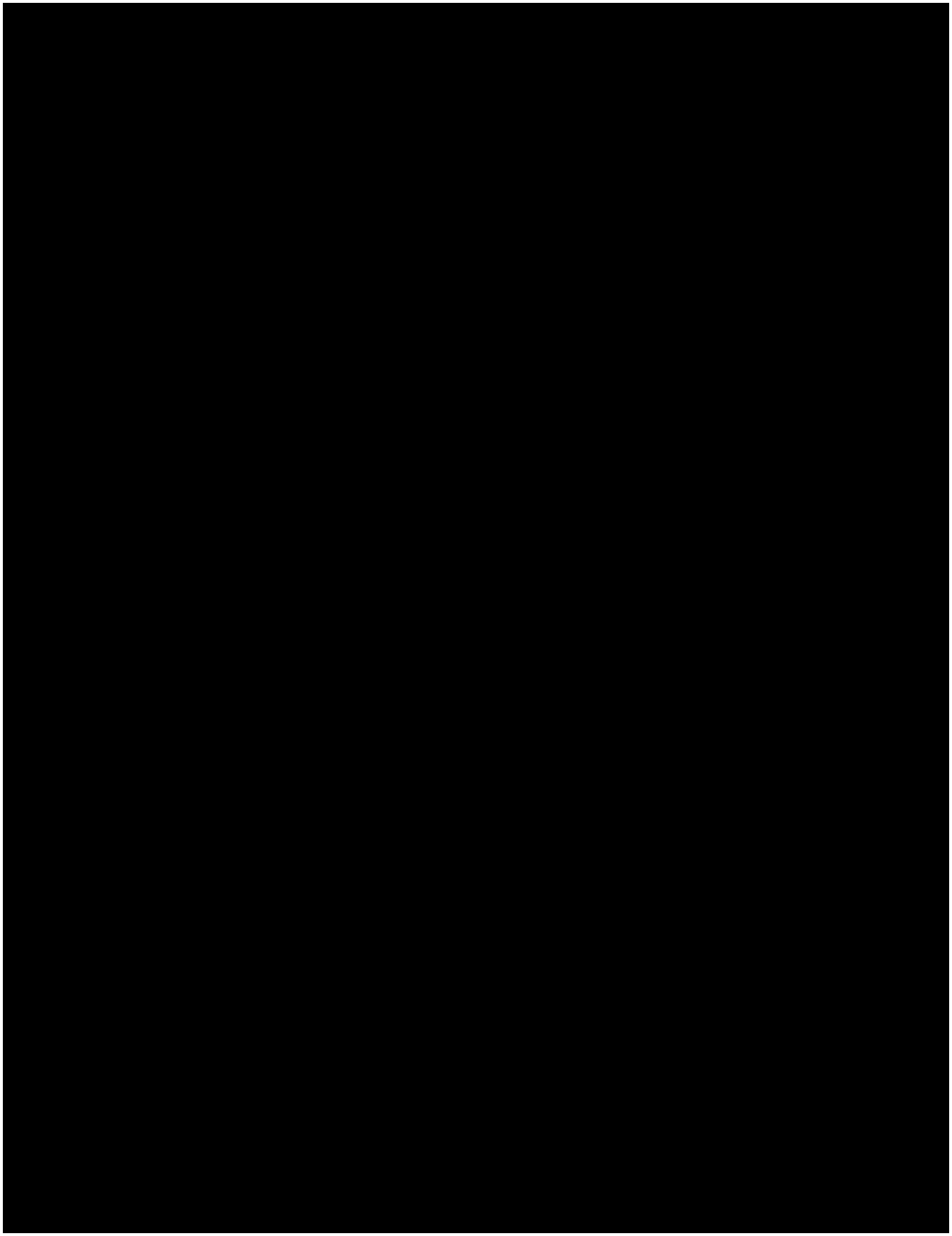
$$y_{km} = \log(x_{km}) = \mu + \beta \cdot \log(D_k) + e_{km},$$

where

- y_{km} logarithm of response (PK parameter) measured on subject m receiving dose k,
- μ the overall mean,
- β slope parameter of linear regression line,
- D_k level of dose k, k=1,…,I,
- e_{km} the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{\beta-1}$ together with its 90% CI will be derived.

As some small doses at the beginning and/ or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire dose range investigated might not be shown. In that case, an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.



7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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

Treatments will be compared in a descriptive way. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the dose group in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. In addition, the POSO and ELDERLY-group will be compared to the corresponding treatment group receiving the same final dose level, again in a descriptive way. Tabulations of frequencies/ proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (refer to 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 the first trial medication intake and end of REP (refer to Section 1.2.7) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study 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 (refer to 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 possibly clinically significant values 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.

The ECG variables QT, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints regarding QT/ QT_c interval, HR, PR interval and QRS duration. These endpoints and their analyses will be described in the TSAP.

EEG changes will be assessed with regard to possible on-treatment changes from baseline.

The assessment of the results of the physical/ neurological examination, CADSS, C-SSRS. SMWQ and BAC will be specified in the TSAP.

7.3.5 Pharmacokinetic - pharmacodynamic analysis

No formal analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial (for exploratory analysis, refer to Section 5.3.4).

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

Prior to each dose escalation, a documented safety review will be performed as described in Section 3.1.

A preliminary analysis of PK parameters (e.g., $AUC_{\tau, ss}$ and $C_{max, ss}$ of BI 1569912), provided as individual values and geometric means per dose level, will always be performed before escalating to the next dose group. The pharmacokinetic parameters of BI 1569912 will be calculated according to relevant BI internal procedures. Available information on dose linearity from preceding dose groups will be considered when estimating $AUC_{\tau, ss}$ and $C_{max, ss}$ values to be expected for the next higher dose to be administered.

In contrast to the final PK/ PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration/ effect-time profiles and summary statistics of individual values without subject identification information. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK/ PD analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses) and additional PK/ PD preliminary analysis may be performed, if requested by the Clinical Trial Leader, the investigator, or Trial Clinical Pharmacokineticist. Preliminary PK/ PD results will not be reported in the CTR.

No inferential statistical interim analysis is planned. However, after completion of each dose group the investigator (or his or her deputy) is allowed to postpone further dose progression until a preliminary analysis of the data has been performed.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.5.3 Biomarkers

It is not planned to impute missing values for biomarker data, i.e., pharmacodynamic parameters.

7.6 RANDOMIZATION

In the MRD- as well as the POSO- and ELDERLY- part, subjects will be randomised within cohort 3 of each dose group in a 3:1 ratio (test treatment to placebo). Trial medication in cohorts 1 and 2 of each study arm will be administered in a fixed order (active - placebo - active - active; refer to Section 3.1).The sponsor will arrange for the randomization as well as

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 96 subjects in this trial, 72 in the MRD-part, 12 subjects in the (optional) POSO- and 12 subjects in the ELDERLY-part. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group (9 on active treatment, and 3 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g., preliminary PK data), provided the planned and approved highest dose will not be exceeded and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 96, but will not exceed 120 subjects entered.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/ 20/ EC, 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 responsible Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each.

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. Refer to Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first subject in the whole trial signs informed consent.

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 local clinical monitors (CTM), Clinical Research Associates, and investigators of participating trial sites.

The trial medication will be provided by the [redacted]

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

Analyses of BI 1569912 concentrations in plasma and urine will be performed at [redacted]

Plasma samples for investigation of metabolism (MIST-samples) will be sent to [redacted]

Analyses of 6-beta hydroxy cortisol/ cortisol (urine) and 4-beta hydroxy cholesterol (plasma) will be performed by [redacted].

The digitally recorded 12-lead and Holter ECGs will be sent to [redacted], for evaluation.

Pharmacogenomic samples will be sent to [redacted], for evaluation.

The digitally recorded EEGs will be sent to [redacted], for evaluation.

The digitally recorded eye-tracking measurements will be sent to [redacted], for evaluation.

The Verbal Memory and Learning Assessment and Symbol Coding Task will be provided by [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 or a contract research organisation appointed by the sponsor, 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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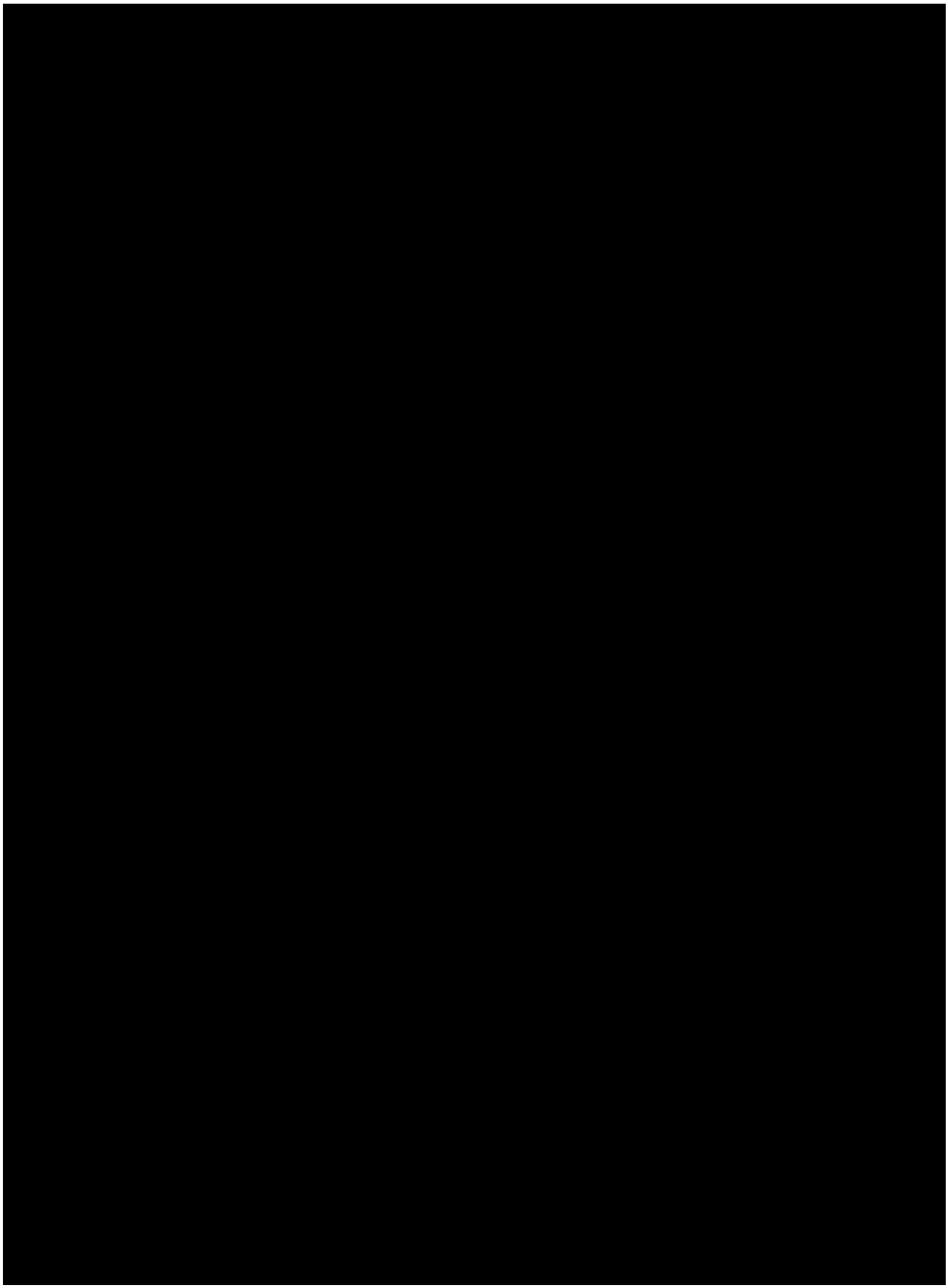
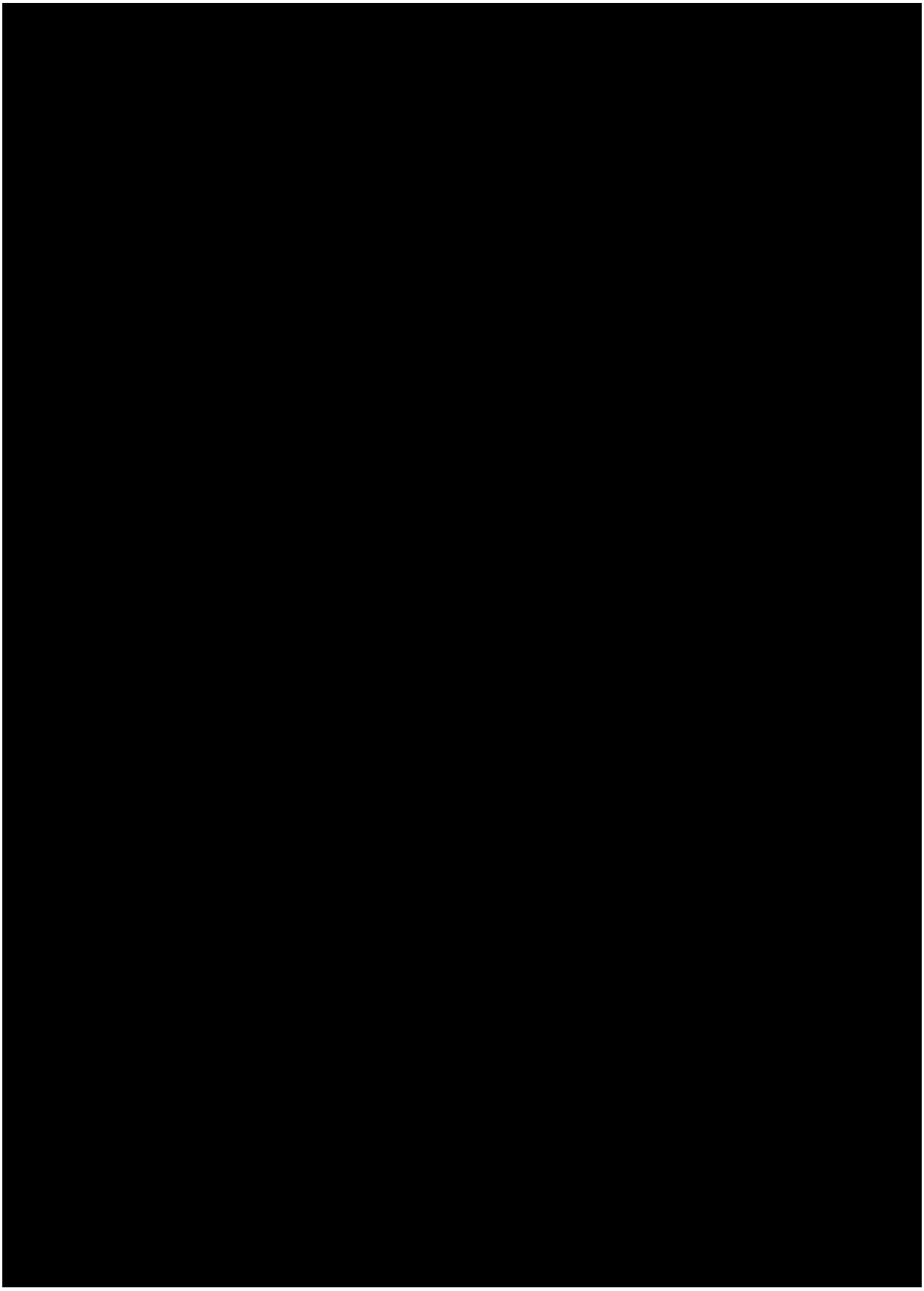




10. APPENDICES

10.1 STANDARDIZED NEUROLOGICAL ASSESSMENT FORM

STANDARDIZED NEUROLOGICAL ASSESSMENT FORM

SID: <SID>		RND:		
Last name: <Lastname>		First name: <Firstname>		
Planned time: *(corresponds to flow chart)*	☐ SCR ☐ Day-1 ☐ Day 7 (143h post-dose) ☐ Day 12 (263h post-dose)	☐ EOT ☐ Day 1 (pre-dose) ☐ Day 9 (191h post-dose) ☐ Day 14 (311h post-dose)	☐ Other: ☐ Day 3 (47h post-dose) ☐ Day 10 (215h post-dose) ☐ Day 17 (383h post-dose)	
Date: *(DD-MMM-YYYY)*		Actual time: *(hh:mm / Start of examination)*		

No.	**Test range** (Minimum set of tests / assessments) **ncs**: not clinically significant: Description in the comment box **cs**: clinically significant: Description must be documented in the comment box and additionally as **AE** or **Baseline Condition**	**Normal**	**Abnorm. ncs**	**Abnorm. cs**
1.	**General level of arousal** *(Attention, wakefulness, mood)* (Explicit ["How do you feel?"] and implicit [behaviour, eye contact, speech, comprehension, posture] assessment)			
2.	**Orientation** (Orientation to time, place, situation and person)			
3.	**Eye movement** (Gaze straight ahead [crossed eyes? Symmetrical deviation? Eyelid fissure symmetrical?], 6 cardinal positions of gaze [palsy? saccades?])			
4.	**Pupil size and pupil reactivity** (Direct and consensual response to light, pupil size; comparison of both sides)			
5.	**Gait** (Walking in a straight line: gait, posture, arm swing present, motion symmetry; dyskinesia? tendency to fall?)			
6.	**Assessment of muscle strength** *(muscle strength; pareses?)* (Elbow flexion against resistance, standing on the balls of the foot on one leg)			
7.	**Romberg test** *(test for gait ataxia including arm extension test)* (Swaying? tendency to fall? Arm extension test [20-30 sec. Holding the position with eyes closed, hands supine])			
8.	**Tremor** (Postural tremor, resting tremor, intention tremor; please document increased physiological tremor)			
9.	**Reflexes** *(autonomic and polysynaptic reflexes)* (Biceps brachii reflex, quadriceps reflex, plantar skin reflex)			
10.	**Sensitivity** (Sensitivity to touch [upper arm, lower arm, thigh, lower leg, insole and sole of the foot] sharp/blunt, cold/warm)			
11.	**Point-to-point movements** (Finger-nose test, heel-knee-shin test)			
	Comment box ("ad X" + comment; incl. normal version, if applicable) ☐ no comment ☐ See back for further explanations			
	Examiner: *Name* *Signature*			

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

10.2.1 Columbia-Suicide Severity Rating Scale (C-SSRS) 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* [redacted] *and* [redacted] *Conte* [redacted] *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 [redacted] *; inquiries and training requirements contact* [redacted]

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_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.	**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

10.2.2 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* [redacted] *and* [redacted] *Conte* [redacted] *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 [redacted] *inquiries and training requirements contact* [redacted]

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

10.3 CLINICIAN ADMINISTERED DISSOCIATIVE STATES SCALE (CADSS)

This is the English version of the questionnaire for illustration purposes only. During the study, the validated German version will be used.

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____
Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

this room.

4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   - 0= Not at all.
   - 1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   - 2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
   - 3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   - 4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   - 0= Not at all.
   - 1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   - 2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   - 3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   - 4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
   - 0= Not at all.
   - 1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   - 2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   - 3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   - 4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
   - 0= Not at all.
   - 1= Mild, things seem slightly different than normal, although it is barely perceptible.
   - 2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   - 3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   - 4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
    - 0= Not at all.
    - 1= Mild, things seem slightly paler than usual if I think about it.
    - 2= Moderate, colors are somewhat diminished, but still recognizable.
    - 3= Severe, colors are extremely pale, in no way as vivid as they usually are.

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

person, or if I am many people.

4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
    - 0= Not at all.
    - 1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
    - 2= Moderate, I feel like I have different parts which don't quite fit together.
    - 3= Severe, there are two or more sides to myself which have unique characteristics.
    - 4= Extreme, I have two or more parts to myself with unique personality characteristics.
22. Do you have gaps in your memory?
    - 0= Not at all.
    - 1= Mild, there are some recent things which I cannot remember.
    - 2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
    - 3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
    - 4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.
23. Do you feel like you have more than one identity?
    - 0= Not at all.
    - 1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
    - 2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
    - 3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
    - 4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

10.4 STUDY MEDICATION WITHDRAWAL QUESTIONNAIRE (SMWQ)

This is the English version of the questionnaire for illustration purposes only. During the study, the validated German version will be used.

THE STUDY MEDICATION WITHDRAWAL QUESTIONNAIRE (SMWQ)

DURING THE PAST 24 HOURS

CHECK ONE BOX PER QUESTION

	Not at all (0)	*Very little* (1)	*A little* (2)	*Quite a lot* (3)	*Very much* (4)
1. Have you been craving the study medication?	☐	☐	☐	☐	☐
2. Have you felt sad?	☐	☐	☐	☐	☐
3. Have you lost interest in things or no longer take pleasure in them?	☐	☐	☐	☐	☐
4. Have you felt anxious?	☐	☐	☐	☐	☐
5. Have you felt as if your movements are slow?	☐	☐	☐	☐	☐
6. Have you felt agitated?	☐	☐	☐	☐	☐
7. Have you felt tired?	☐	☐	☐	☐	☐
8. Has your appetite increased, or have you eaten too much?	☐	☐	☐	☐	☐
9. Have you had any vivid or unpleasant dreams?	☐	☐	☐	☐	☐
10. Have you been craving for sleep or sleeping too much?	☐	☐	☐	☐	☐

Modified from: Srisurapanont M, et al. Aust N Z J Psychiatry 1999;33:89-93.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		13 July 2021
EudraCT number **EU number**		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects
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		Synopsis Flow Chart Section 1.4.7 Section 3.1 Section 3.2 Section 3.3.3 Section 3.3.4.1 Section 3.3.4.3 Section 3.3.5 Section 4.1.2 Section 4.1.3 Section 4.1.5.1 Section 5.2.3 Section 7.6 Section 8.1 Section 8.7 Throughout the document
Description of change		Synopsis: Modification of study title (the posology part is optional) and study design (single-blind,

		partially randomized). Flow Chart: Inclusion of a blood samples for a safety lab on Day 4. Section 1.4.7: Inclusion of a sentinel cohort in each dose group; the statement that the posology part will be performed without a substantial amendment was taken out. Section 3.1: Inclusion of a sentinel cohort in each dose group; the minimum data set needed for a dose escalation decision was change from 4 to 9. Section 3.2: Modification of study design. Section 3.3.3: Inclusion of 2 additional exclusion criteria. Section 3.3.4.1: Inclusion of an 'acute SARS-CoV-2/ COVID-19 infection, as an additional reason to discontinue trial treatment. Section 3.3.4.3: Inclusion of the statement that 'the sponsor will stop or terminate the study, if the favourable opinion or the approval is revoked'. Section 3.3.5: Additional stipulations how to handle replacement of subjects. Section 4.1.2: Inclusion of the statement that 'no dose level will be repeated without substantial amendment where any of the dose escalation stopping rules have been met. Section 4.1.3: Inclusion of an unblinded pharmacist. Section 4.1.5.1: Modification of study design and description of treatment allocation. Section 5.2.3: Adaptation of foot note of Table 5.2.3: 1 (inclusion of a blood samples for a safety lab on Day 4). Section 7.6: Description of treatment allocation. Section 8.1: Deletion of 'or the subject's legally accepted representative' Section 8.7: Name Change of [redacted] to [redacted] Troughout the document: Minor editorial changes were performed.
Rationale for change		Synopsis: A consequence of the request of BfArM/ EC Berlin Flow Chart: Upon request of BfArM/ EC Berlin Section 1.4.7: Upon request of BfArM/ EC Berlin Section 3.1: Upon request of BfArM/ EC Berlin Section 3.2: A consequence of the request of BfArM/ EC Berlin Section 3.3.3: Upon request of BfArM/ EC Berlin

		Section 3.3.4.1: Upon request of BfArM/ EC Berlin Section 3.3.4.1: Upon request of BfArM/ EC Berlin Section 3.3.5: Upon request of BfArM/ EC Berlin Section 4.1.2: Upon request of BfArM/ EC Berlin Section 4.1.3: A consequence of the request of BfArM/ EC Berlin Section 4.1.5.1: A consequence of the request of BfArM/ EC Berlin Section 5.2.3: Upon request of BfArM/ EC Berlin Section 7.6: A consequence of the request of BfArM/ EC Berlin Section 8.1: Upon request of BfArM/ EC Berlin Section 8.7: Laboratory [redacted] changed their Name to [redacted] Troughout the document: For reasons of consistency and orthographic correctness

11.2 GLOBAL AMENDMENT 2

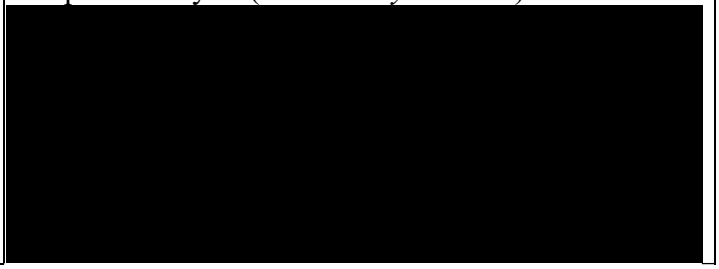
Date of amendment		18 July 2022
EudraCT number **EU number**		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects

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		Synopsis Flow Chart Abbreviations [redacted] 1.2.6 1.2.6.1 1.3 1.4.7 [redacted] 2.2.2 [redacted] 3.1 4.1.1 4.1.2 4.1.3 4.1.4 4.1.5 4.1.6 5.2.1 5.2.3 5.2.5.2

		5.2.5.3 5.2.5.4 5.2.5.5 5.2.5.6 5.3.2.1 5.3.2.3 5.3.2.4 5.3.2.5 5.4.2 5.4.2.2 5.6.1 6.1 7 7.3 7.3.2 [redacted] 7.3.4 7.4 7.5.3 7.6 7.7 8 8.7 9.1
Description of change (*Rationale for change*)		Synopsis: Address change of CTL (*BI internal administrative reason*). Editorial changes (*consistency reasons*). Flow Chart: Inclusion of Brief Assessment of Cognition (BAC) questionnaire (*quantification of possible adverse events – reason for CTP amendment*). Inclusion of a light breakfast and an additional PK sampling schedule at Day 9 (*reason for CTP amendment*). Addition of time points for ECG registrations and vital signs measurements (*consistency reasons*). Editorial changes (*consistency reasons*). Abbreviations: Deletion of not used and inclusion of used abbreviations (*consistency reasons*). [redacted] 1.2.6: Inclusion of the SRD/ BA/ FE- study (1447-0001) safety and PK results (*update of safety and PK information*). 1.2.6.1: Inclusion of the SRD/ BA/ FE- study (1447-0001) safety and PK results (*update of safety and PK*

		information). 1.3: Inclusion of 'justification of dose range' (*correction of a previous oversight*). Inclusion of 'justification of POSO-part (up-titration)' (*correction of a previous oversight*). Inclusion of 'justification of food effect assessment on Day 9' (*reason for CTP amendment*). 1.4.7: Specification of interim measurements (*consistency reasons*). Inclusion of BAC (*quantification of possible adverse events – reason for CTP amendment*). Editorial changes (*consistency reasons*). [redacted] 2.2.2.1: Addition of BAC (*reason for CTP amendment*). Inclusion of SMWQ (*consistency reasons*). [redacted] 3.3.4: Specification of preliminary pharmacokinetic data (*consistency reasons*). 4.1.1: Editorial changes (*consistency reasons*). 4.1.2: Editorial changes (*consistency reasons*). 4.1.3: Description of assigning subjects to treatment groups (*adaptation to* [redacted] *processes*). 4.1.4: Inclusion of the 0.5 mg tablet (*correction of a previous oversight*). Exchange of 'slice of meat' against 'curd cheese' as part of the light breakfast (*adaptation to CRO-processes*). Editorial changes (*consistency reasons*). 4.1.5: Specification of blinding level of individual functions (*consistency reasons*). 4.1.6: A resupply of study medication is planned (*logistic adaptation*). 5.2.1: Specification of the physical examination (*consistency reasons*). 5.2.3: Addition of Day -1 in the foot note of tables (*correction of a previous oversight*). Editorial changes (*correction of orthographic errors*). 5.2.5.2: Editorial changes (*consistency reasons*). 5.2.5.3: Editorial changes (*consistency reasons*). 5.2.5.4: Editorial changes (*consistency reasons*). 5.2.5.5: Specification of screening EEG procedures

		(*clarification*). Inclusion of 'expedited' EEG assessment and reporting (*additional safety measures to provide EEG results prior to the next drug application – reason for CTP amendment*). Editorial changes (*consistency reasons*). 5.2.5.6: Description of BAC (*additional safety measure – reason for CTP amendment*). 5.3.2.1: Specification of sample handling after PK analysis (*consistency reasons*). Editorial changes (*consistency reasons*). 5.3.2.3: Change of volume of urine collection container (*adaptation to CRO processes*). 5.3.2.4: Change of laboratory name (*change of legal name*). 5.3.2.5: Change of laboratory name (*change of legal name*). 5.4.1: Editorial changes (*correction of orthographic errors*). 5.4.2: Editorial changes (*consistency reasons*). 5.4.2.2: Correction of a technical detail (*correction of factual error*). 5.6.1: Specification of laboratory for pharmacogenomic evaluation (*logistic reasons*). Specification of sample destruction (*consistency reasons*). 6.1: Inclusion of Day 9 (*additional PK assessment – reason for CTP amendment*). 6.2.2: Editorial changes (*correction of orthographic errors*). 7.1: Inclusion of food effect part (*reason for CTP amendment*). Specification of POSO-part (*consistency reasons*). 7.3: Specification of handling of 'important protocol deviations' (*adaptation to BI processes*). Inclusion of 'biomarkers' (*consistency reasons*). Editorial changes (*consistency reasons*). 7.3.2: Editorial changes (*correction of orthographic errors and consistency reasons*). Specification of PK endpoint analysis (*consistency reasons*). 

		7.3.4: Inclusion of the statistical assessment of the physical/ neurological examination, CADSS, C-SSRS. SMWQ and BAC (*consistency reasons*). Editorial changes (*consistency reasons*). 7.4: Specification of PK analysis (*consistency reasons*). 7.5.3: Specification of biomarker handling (*consistency reasons*). 7.6: Editorial changes (*consistency reasons*). 7.7: Editorial changes (*consistency reasons*). 8: Reference to directive 2001/20/EC (*adaptation to BI processes*). 8.7: Inclusion of 'VeraSci' as the provider of BAC (*reason for CTP amendment*). Editorial changes (*consistency reasons*). 9.1: Addition of 'BAC' reference (*reason for CTP amendment*).
Rationale for change		Refer to the above

11.3 GLOBAL AMENDMENT 3

Date of amendment		05 Sep 2022
EudraCT number **EU number**		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects
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		5.4.2.2
Description of change (*Rationale for change*)		5.4.2.2: Additional electrode on the nose (Nz) was take out *(not needed for the accurate identification of the ERP topography)* Throughout the document: Minor editorial changes were performed *(for reasons of consistency and orthographic correctness)*
Rationale for change		Refer to the above

11.4 GLOBAL AMENDMENT 4

Date of amendment		05-April-2023
EudraCT number		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects
To be implemented only after approval of the IRB/ IEC/ Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB/ IEC/ Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/ IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2.6 1.3 1.4.7
Description of change (*Rationale for change*)		1.2.6: Preliminary safety and pharmacokinetic results of dose groups 1 to 3 (*supporting safety and pharmacokinetic evidence for increasing the exposure limits*) 1.3 and 1.4.7: Modification of stopping rules (*by the increase of exposure limits*). Throughout the document: Minor editorial changes *(for reasons of consistency and orthographic correctness)*
Rationale for change		Refer to the above

11.5 GLOBAL AMENDMENT 5

Date of amendment		30 Aug 2023
EudraCT number		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects
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		Refer to the below
Description of change (*Rationale for change*)		Synopsis: Increase of sample size *(to account for additional dose groups)*, addition of 30- mg and 40 mg dose group *(rational for this amendment)* and allowance of 340 mL water together with the tablet application in the 30 mg- and 40 mg dose group (*to facilitate the tablet intake*) Flow Chart: Addition of an ECG at 7:00 on Day -1 (*to reliably exclude subjects with abnormal ECG-parameters before dosing*); addition of an Antigen Rapid Test for SARS-CoV-2 (*to provide to the study site a further diagnostic option*) [redacted] 1.2.6: Preliminary safety and pharmacokinetic results of dose groups 1 to 4 *(supporting safety and pharmacokinetic evidence for increasing the exposure limits)*; inclusion of a preliminary systematic review of ECG-parameters (*to critically*

		assess ECG-parameters) 1.3: Rational for the addition of 30 mg- and 40 mg dose group *(rational for this amendment);* increase of exposure limits (*prerequisite for a higher dose*) 1.4.7: Reiteration of safety measures (*to maintain consistency*); modification of stopping rules (*to maintain consistency*) 1.4.9: Reiteration of risk mitigation measures (*to maintain consistency*) 3.1: Adaptation of study design depiction (*to maintain consistency*); increase of sample size *(to account for additional dose groups);* addition of 30 mg- and 40 mg dose group *(rational for this amendment)* 3.3: Increase of sample size *(to account for additional dose groups)* 3.3.3: Addition of exclusion criterion 31 – exclusion of subjects with a marked prolongation of PQ-interval greater than 240 ms (*to exclude subjects with an extensive first degree AV-block*); modification of exclusion criterion 32 – addition of an Antigen Rapid Test for SARS-CoV-2 (*to provide to the study site a further diagnostic option*) 3.3.4.3: Increase of exposure limits (*prerequisite for a higher dose*) 4.1.1: Addition of 30 mg- and 40 mg dose group in the MRD-part *(rational for this amendment)*; adaptation of the POSO-part *(to maintain consistency)* 4.1.2: Adaptation of wording (*to maintain consistency*) 4.1.4: Adaptation of Table 4.1.4:1 (*to maintain consistency*) and allowance of 340 mL water together with the tablet application in the 30 mg- and 40 mg dose group (*to facilitate the tablet intake*)

		4.1.5.1: Modification of wording of sponsor-un-blinding (*to maintain consistency with BI-standard*) 5.2.3: Addition of an Antigen Rapid Test for SARS-CoV-2 (*to provide to the study site a further diagnostic option*); address change of [redacted] (*to adapt to logistical change*) 7.7: Increase of sample size *(to account for additional dose groups)* 8.7: Address change of [redacted] (*to adapt to logistical change*) Throughout the document: Minor editorial changes *(for reasons of consistency and orthographic correctness)*
Rationale for change		Refer to the above

11.6 GLOBAL AMENDMENT 6

Date of amendment		24 Jan 2024
EudraCT number		2021-001717-36
BI Trial number		1447-0002
BI Investigational Medicinal Product		BI 1569912
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects

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		Refer to the below
Description of change (*Rationale for change*)		Synopsis: Increase of sample size *(to account for additional dose groups)*, addition of an ELDERLY-part – age: 65 to 80 years; treatment: POSO-scheme No. 4 *(rational for this amendment)* Flow Chart: Restriction of samplings and measurements to the MRD-part: 'PK in urine', '6-Beta-OH-Cortisol/ Cortisol' and '4-Beta-OH-Cholesterol in urine', 'eye tracking'; Addition of Holter ECG (*to better characterise the cardiovascular risk in the ELDERLY study population*). Modification of footnote 8: restriction of MIST sampling in plasma at PK time points on Day 9 to MRD-part (*to ease the operational burden for the ELDERLY study population*). Addition of footnote 18: specification of POSO-scheme No. 4 (*as a mitigation measure to avoid possible toxicity in the ELDERLY study population*). Addition of footnote 22: restriction of breakfast on Day 9 to MRD-part (*to ease the operational burden for the ELDERLY study population*). Addition of

		footnote 23: description of Holter ECG procedures at the screening examination (*to better characterise the cardiovascular risk in the ELDERLY study population*) [redacted] 1.2.6: Preliminary safety and pharmacokinetic results of dose group 5 *(supporting safety and pharmacokinetic evidence for the inclusion of the ELDERLY-part)* 1.3: Rational for the addition of the ELDERLY-part *(rational for this amendment)* 1.4.4: Summary of added results from toxicity studies (*to maintain consistency*) 1.4.7: Additional risk mitigation measures in the ELDERLY study population - POSO-scheme No. 4 (*to maintain consistency*) 3.1: Adaptation of study design depiction (*to maintain consistency*); increase of sample size *(to account for additional ELDERLY-part);* description of POSO-scheme No. 4 (*to maintain consistency*) 3.3: Increase of sample size *(to account for additional ELDERLY-part)* 3.3.2: Specification of the age (65 to 80 years) of the ELDERLY-study population (*to maintain consistency*) 3.3.3: Addition of 'age-adapted' in exclusion criterion 3 (*to highlight that 'age-adapted' reference ranges will be used for laboratory values*); addition of exclusion criterion 33 (*to exclude subjects with clinically relevant Holter-ECG findings*) 4.1.1: Addition of the ELDERLY-part *(rational for this amendment)*; adaptation of the POSO-part *(to indicate that POSO-scheme No. 4 will be applied to*

		the ELDERLY study population) 4.1.2: Adaptation of wording (*to maintain consistency*) 4.1.4: Adaptation of Table 4.1.4:1 (*to maintain consistency*); Restriction of meal on Day 9 to MRD-part (*to maintain consistency*) 4.2.2: Addition of restrictions while recording an Holter-ECG at screening (*to ensure best recording results*) 5.2.3: Addition of Hb_{A1C} in Table 5.2.3: 1, as an additional screening parameter (*to better characterise the cardiovascular risk of the ELDERLY-study population*) 5.2.4: Additional description of the Holter ECG-recording (*to better characterise the cardiovascular risk of the ELDERLY study population*) 5.3.2.2: Restriction of 'blood sampling for metabolism analysis' (MIST) to the MRD-part (*to ease the operational burden for the ELDERLY study population*) 5.3.2.3: Restriction of 'urine sampling for pharmacokinetic analysis' to the MRD-part (*to ease the operational burden for the ELDERLY study population*) 5.3.2.4: Restriction of 'plasma sampling for CYP3A4 biomarker assessment - 4-beta hydroxy-cholesterol' to the MRD-part (*to ease the operational burden for the ELDERLY study population*) 5.3.2.5: Restriction of 'urine sampling for CYP3A4 biomarker assessment - 6-beta hydroxy-cortisol and cortisol' to the MRD-part (*to ease the operational burden for the ELDERLY study population*) [redacted]

		[redacted] 5.4.1: Restriction of 'eye tracking' to MRD-part (*to ease the operational burden for the ELDERLY study population*) 6.2.1: Addition of Holter ECG (*to maintain consistency*) 7.1 Adaptation of wording (*to maintain consistency*) 7.3 Adaptation of wording (*to maintain consistency*) [redacted] 7.3.4 Adaptation of wording (*to maintain consistency*) 7.6 Adaptation of wording (*to maintain consistency*) 7.7: Increase of sample size *(to account for the additional ELDERLY-part)* 8.7: Inclusion of Holter ECG (*to maintain consistency*) Throughout the document: Minor editorial changes *(for reasons of consistency and orthographic correctness)*
Rationale for change		Refer to the *(above)*

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Signatures (obtained electronically)

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Approval-Clinical Program [redacted]		26 Jan 2024 12:25 CET
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Meaning of Signature	Signed by	Date Signed