Clinical Trial Protocol

	Document Number:	**c44069281-01**
Trial Sponsor	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein, Germany	
Boehringer Ingelheim Trial No.	1447-0012	
Boehringer Ingelheim Investigational Medicinal Product(s)	BI 1569912	
Title	A 6-week, multi-centre, randomised, double-blind (participant and investigator), placebo-controlled, dose-finding trial to evaluate the efficacy, tolerability, and safety of different doses of oral BI 1569912 in patients with major depressive disorder	
Lay Title	A study to test different doses of BI 1569912 in people with depression	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Email: [redacted]	
Current Version and Date	Version 1.0, 15 Apr 2024	
Original Protocol Date	Version 1.0, 15 Apr 2024	Page 1 of **103**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date **Latest revision date**	15 Apr 2024 Not applicable
BI trial number	1447-0012
Title of trial	A 6-week, multi-centre, randomised, double-blind (participant and investigator), placebo-controlled, dose-finding trial to evaluate the efficacy, tolerability, and safety of different doses of oral BI 1569912 in patients with major depressive disorder
Coordinating Investigator	[redacted] Phone: [redacted] Email: [redacted]
Trial site(s)	Multi-centre trial conducted at approximately 45 trial centres in 2 countries (USA and Japan)
Clinical phase	II
Trial rationale	Major depressive disorder (MDD) is a common, severe, and frequently recurrent mental illness with an estimated global point prevalence of approximately 5%. Despite the array of available treatment options, there remains significant unmet medical need for patients who do not respond or tolerate current treatment options. Medications that offer rapid sustained relief from depressive symptoms with limited side effect burden would constitute a major medical advance and fulfil a high unmet medical need for patients suffering from MDD. Following Phase I studies in healthy volunteers and a proof of clinical principle trial in participants with MDD, the present trial is designed to assess dose-range finding data, provide proof of clinical concept, and confirm the safety and tolerability of BI 1569912 compared with placebo when administered for 6 weeks.

Benefit-risk assessment and ethical considerations	BI 1569912 has the potential to address core symptoms of MDD faster than standard treatments as it targets the NR2B subunit of NMDA receptors. Non-selective NMDA antagonists such as ketamine and esketamine have demonstrated rapid and robust antidepressant effects. Preclinical data have shown a larger therapeutic window for BI 1569912 compared with ketamine according to doses required for efficacy in behavioural tests and for the induction of psychotomimetic effects. Clinical data have shown preliminary efficacy signals after a single dose of BI 1569912 and a favourable safety profile after single and multiple doses. However, BI 1569912 is an experimental drug at an early stage of testing and therefore an individual benefit for participants cannot be guaranteed. It is important to have a placebo control to address potential confounding factors. This is considered to be acceptable as participants will be closely monitored throughout the trial and treatment duration is limited to 6 weeks.
Trial objective(s)	The overall objectives of this trial are to assess dose-range finding data of BI 1569912 compared with placebo in patients with MDD, provide proof of clinical concept (PoCC), and to support dose selection for pivotal studies.
Trial endpoints	Primary endpoint: • Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6
Trial design	A 6-week, multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial in patients with MDD.
Total number of trial participants randomised	Approximately 222 participants will be randomised, in order to have approximately 180 participants evaluable for the primary analysis.
Number of trial participants per treatment group	Placebo: approx. 74 participants BI 1569912 (5 mg): approx. 37 participants BI 1569912 (10 mg): approx. 37 participants BI 1569912 (20 mg): approx. 74 participants
Diagnosis, main inclusion and exclusion criteria	Main Inclusion Criteria/Diagnosis: • Male and female participants, 18 to 65 years of age • Women who are of childbearing potential (WOCBP) must be able and willing, to use two methods of contraception • Established diagnosis of MDD, single episode or recurrent with a duration of current depressive episode ≥8 weeks and ≤24 months at the time of randomisation • Hamilton Depression Rating Scale-17 (HDRS-17) – Severity score ≥20 • Clinical Global Impression Severity Scale (CGI-S) score ≥4

	Main Exclusion Criteria: • Have ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, or delusional disorder • Diagnosis with antisocial, paranoid, schizoid or schizotypal personality disorder, or MDD with psychotic features at the time of screening visit. Any other personality disorder that significantly affects current psychiatric status and likely to impact trial participation, as per the judgement of investigator • Diagnosis of any other mental disorder that was the primary focus of treatment within 6 months prior to screening, as per clinical discretion of the investigator • Treatment failure to 2 or more antidepressants in the current episode • A current or recent history of clinically significant suicidal ideation with intent within the past 3 months or a suicidal attempt within the past year • Participants with a body mass index (weight [kg]/height [m]^2) lower than 18 kg/m² or greater than 40 kg/m^2 at screening • Diagnosis of a moderate to severe substance related disorder within 6 months prior to screening visit (with exception of caffeine and tobacco) • Frequent use of benzodiazepines • Positive drug screen (amphetamines, opiates, cocaine, barbiturates, phencyclidine) at screening. Participants with positive cannabis and benzodiazepine tests can be included if the investigator confirms that there is no moderate to severe substance related disorder or chronic benzodiazepine use • Have started psychotherapy or other non-drug therapies (e.g. acupuncture, hypnosis) within 3 months prior to screening or plan to start at any time during the study • Use of NMDA inhibitors (including ketamine/esketamine) for the current ongoing depressive episode or any past treatment failure with ketamine • Use of psychotropic medication (including antidepressant and antipsychotic therapy) which was not discontinued at least 5 half-lives prior to randomisation • Prior use of any investigational product within 6 months prior to randomisation • Have failed a 3rd party eligibility assessment within the 6 months prior screening • Known history of HIV infection and/or a positive result for an active Hepatitis B or C infection

Test product	BI 1569912
Dose and mode of administration	5 mg, 10 mg, 20 mg once per day, orally
Comparator	Placebo
Dose and mode of administration	Matching; once per day, orally
Duration of treatment	6 weeks
Statistical methods	To demonstrate proof of concept of clinical activity and to evaluate the dose response relationship for BI 1569912, a multiple comparison procedure with modelling techniques (MCPMod) approach is planned to be used for the primary analysis. As a basis for the MCPMod analysis and to assess quantitative treatment benefit, a mixed model for repeated measure (MMRM) analysis will be used to generate covariate adjusted estimates of mean change from baseline in MADRS total score at Week 6 and associated covariance matrices.

SCHEDULE OF ASSESSMENTS (SOA)

Trial Periods	Screening[1]	Randomised Treatment					End of Study[2]	Comments
[redacted]								
Informed consent	X							Signing of main ICF is mandatory prior to any study-related procedure. Consent for data tokenisation, biobanking, and feedback questionnaires is optional.
Demographics	X							
Medical history/baseline conditions	X							
Participant duplicate check	X	X				X		If local regulatory approval has been obtained. See Section 5.6.3
Physical/Neurological examination	X	X	X	X	X	X	X	Physical/Neurological exam can be performed before or after IMP administration. See Section 5.2.1
Height	X							See Section 5.2.1
Weight/BMI	X					X		See Section 5.2.1
Vital signs	X	X	X	X	X	X	X	See Section 5.2.2
12-lead ECG[1]	X	X	X		X	X	X	If screening visit is conducted over multiple days, ECG should be done on the first day. ECGs should be captured after IMP administration during Visits 2 and 5. See Sections 5.2.4 and 6.2
Review of in-/exclusion criteria	X	X						See Section 3.3

Trial Periods	Screening[1]	Randomised Treatment					End of Study[2]	Comments
[redacted]								
MINI[1]	X							If the screening visit is conducted over multiple days, MINI should be done on the first day.
ATRQ[1]	X							If screening visits are conducted over multiple days, ATRQ should be done on first day.
HDRS-17[1]	X							PCRS to be read before HDRS-17 during screening. If screening visits are conducted over multiple days, HDRS-17 should be done on first day.
Interactive response technology use	X	X	X	X	X	X		IRT registration only at Visit 1
[redacted]								
C-SSRS	X	X						
All AEs/SAEs/AESIs	X	X	X	X	X	X	X	See Section 5.2.6
Concomitant therapy	X	X	X	X	X	X	X	See Section 4.2.2.1
Placebo control reminder script (PCRS)	X	X	X	X	X	X		To be read by the rater to each subject immediately before administering the MADRS and HDRS-17
MADRS		X	X	X	X	X		PCRS to be read just before MADRS. MADRS, [redacted] should be assessed in this order prior to IMP intake at all visits, with the exception of Visit 5, where they should be assessed after IMP intake, with MADRS specifically assessed 1 to 2 h after IMP. See Section 6.2.2
[redacted]								

Trial Periods	Screening[1]	Randomised Treatment					End of Study[2]	Comments
[redacted]								
Safety laboratory tests[1]	X	X	X	X	X	X	X	If screening visits are conducted over multiple days, blood sampling should be done on first day. See Section 5.2.3
Urine drug screen	X	X	X	X	X	X	X	
Pregnancy test	X	X			X	X		Women of childbearing potential only. If urine test is positive, serum pregnancy test is to be performed for confirmation.
[redacted]								
Optional sampling for biobanking (serum, plasma)		X				X		Two serum and two plasma samples will be taken, sample collection should adhere to the schedule, i.e. taken at Visit 2 and EoT; see Section 5.5
Optional DNA Biobanking		X						In total one sample will be taken, preferably at Visit 2. Collection at later visits is permitted as long as the ICF for biobanking remains valid. See Section 5.5

Trial Periods	Screening[1]	Randomised Treatment					End of Study[2]	Comments
[redacted]								
Placebo informational video	X							See Section 6.2.1
Randomisation		X						
Dispense IMP		X	X	X	X			
Administer trial IMP		X[3]	X	X	X			Participants should not take IMP in the morning of Visits 3, 4, and 5 as they will be dosed at the site. The final dose of IMP should be taken the day before the EoT Visit. Participants should fast for 2 h prior to and 1 h after every IMP intake (both at the trial site and at home). The fasting schedule for Visit 5 is described in Appendix 10.2. See also Sections 4.1.4 and 6.2.2.
IMP return/accountability			X	X	X	X		Participants must bring trial medication (used/unused blister and covering packages) to site visits for compliance checks. Accountability, reconciliation, and returns will be registered in IRT. See Section 4.1.8.
Completion of participant's participation							X	See Section 3.3.4 for discontinuation details. See Section 5.6.6 and Appendix 10.1 for optional trial feedback questionnaires to be given at the start and end of the trial.

1 Screening visit can be split if required due to logistical reasons. Blood sampling, ECG, MINI, ATRQ, HDRS-17, and CGI-S should be done at the beginning of the screening period. The first day of screening will be the starting point for the screening period calculation. See Section 6.2.1 for further details.

2 For participants who permanently discontinue (DC) the IMP prior to the scheduled Week 6 EoT Visit, an EoT Visit must be completed as soon as possible after IMP discontinuation. If early DC participants do not agree to continue regularly scheduled visits after the EoT Visit, a EoS Visit should be scheduled (8 days after IMP discontinuation date [+ 6 day window]). See Section 3.3.4 for further details. An EoS Visit must be completed for all randomised participants. EoS = individual participant's end of trial.

3 Day of randomisation/Day of first intake of randomised IMP – all activities must be done before IMP administration, except for ECG and the collection of AEs/SAEs. It is recommended to monitor participants for 2 h post IMP administration on Day 1 to record any potential AEs.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criteria
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATRQ	Antidepressant treatment response questionnaire
$AUC_{0\text{-}24\ h}$	Area under the plasma concentration-time curve from time zero to 24 h
BI	Boehringer Ingelheim
[redacted]	[redacted]
CA	Competent Authority
CGI-S	Clinical Global Impression of Severity
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CNS	Central nervous system
COA	Clinical outcome assessment
CRA	Clinical research associate
CRF	Case report form, paper or electronic (normally referred to as "eCRF")
CRO	Contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical trial protocol
CTR	Clinical trial report
DBL	Database lock
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram

eCOA	Electronic clinical outcome assessment
ED_{50}	Effective dose required to achieve 50% of the desired response
EDC	Electronic data capture
EEG	Electroencephalography
eGFR	Estimated glomerular filtration rate
E_{max}	Maximal efficacy
EoS	End of study (corresponds with end of trial)
EoT	End of treatment
ePRO	Electronic patient reported outcome
[redacted]	[redacted]
FST	Forced swim test
[redacted]	[redacted]
GCP	Good clinical practice
GGT	Gamma glutamyl transpeptidase
gMean	Geometric mean
GMP	Good manufacturing practice
HDRS-17	Hamilton Depression Rating Scale-17
HDRS-SIGH-D	Structured Interview Guide for the Hamilton Depression Rating Scale
HIV	Human immunodeficiency virus
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalised ratio
iPD	Important protocol deviations
IRB	Institutional review board
IRT	Interactive response technology
ISF	Investigator site file
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IUD	Intrauterine device

IUS	Intrauterine hormone-releasing system
LCMS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactic dehydrogenase
LPLT	Last participant last treatment
LPLVPE	Last participant last visit primary endpoint
MADRS	Montgomery Åsberg Depression Rating Scale
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare (Japan)
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed-effect model for repeated measures
MoA	Mode of action
MRD	Multiple rising dose
NAM	Negative allosteric modulator
NDA	New drug application (FDA)
NMDA	N-methyl-D-aspartate
NR2B	N-methyl-D-aspartate receptor subtype 2B
p.o.	Per os (oral)
PAS	Primary analysis set
PCP	Phencyclidine
PCRS	Placebo-Control Reminder Script
[redacted]	[redacted]
PFC	Prefrontal cortex
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
PoCC	Proof of clinical concept
PoCP	Proof of clinical principle
PRO	Patient-reported outcome

PSPV	Patient safety pharmacovigilance
PT	Prothrombin time
qd	Quaque die (once a day)
[redacted]	[redacted]
RBC	Red blood cell
RDW	Red blood cell distribution width
REML	Residual maximum likelihood method
REP	Residual effect period
SAE	Serious adverse event
SDTM	Study data tabulation model
[redacted]	[redacted]
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate-pyruvate transaminase
SIGMA	Structured Interview Guide for the MADRS
SMDDS	Symptoms of Major Depressive Disorder Scale
[redacted]	[redacted]
SNRI	Serotonin and norepinephrine reuptake inhibitor
SoA	Schedule of assessments
SOP	Standard operating procedure
SRD	Single rising dose
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TMS	Transcranial magnetic stimulation
TRD	Treatment-resistant depression
TS	Treated set
TSAP	Trial statistical analysis plan
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential

Terms synonymous with those used in this CTP are listed below.

Term	**Synonymous term**
Trial participant *or* participant	Subject *or* patient
End of study	End of trial
Investigational medicinal product	Trial medication (*or* medication), *or* trial drug (*or* drug), *or* trial treatment (*or* treatment), *or* trial intervention, *or* intervention, *or* investigational product
MADRS	Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (MADRS-SIGMA)
HDRS-17	Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS-SIGH-D)

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Major depressive disorder (MDD) is a common, severe, and frequently recurrent mental illness with an estimated global point prevalence of approximately 5% [R14-3147]. MDD poses a serious social and economic threat to modern societies, as it is a major cause of disability according to the Global Burden of Disease Study [R19-0778]. 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]. Current treatments options with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) require 6 to 8 weeks of treatment before treatment effects can be fully assessed. Therefore, a treatment with the potential to provide more rapid relief from depressive symptoms would be significantly beneficial for patients and carers.

The antidepressant effects of non-specific N-methyl-D-aspartate (NMDA) glutamate receptor antagonists are well established [R19-0681, R19-0772]. Ketamine has demonstrated antidepressant efficacy in multiple exploratory clinical trials in treatment-resistant depression (TRD). The responder rate in these trials was approximately 50%, the onset was fast, and the average antidepressant effect lasted for approximately 1 week after a single infusion [R19-0553]. Meanwhile, the intranasal S-enantiomer esketamine received new drug application (NDA) approval by the FDA for treatment-resistant depression in conjunction with an oral antidepressant [R19-0829]. However, transient perceptual disturbances (dissociative reaction), sedation, blood pressure increases, and abuse potential (being a scheduled drug) require controlled distribution as well as cardiovascular and behavioural monitoring after drug application. Those unwanted effects may, at least in part, derive from ketamine's lack of selectivity, as ketamine blocks the cation channel across all NMDA subtypes [R19-0555].

Based on genetic mouse models, the NR2B subunit was identified as a key mediator of ketamine's efficacy [R19-0549].

1.2 DRUG PROFILE

BI 1569912 is a NR2B NAM to be developed for the treatment of MDD. [redacted]

A summary of the BI 1569912 profile is briefly described below, for a more detailed description, please refer to the current IB [c29289852].

Mode of action

[redacted]

[redacted]

Key Pharmacokinetic characteristics

The analysis of pharmacokinetic (PK) parameters in humans have shown an overall good fit with predictions based on animal models. A dose-proportional increase was observed for the PK endpoints AUC and C_{max} in the single rising dose (SRD) trial 1447-0001 (completed) [redacted] After administration of a [redacted] in the fasted state, BI 1569912 reached rapid maximum plasma concentrations within a median t_{max} of about 0.5 h. After reaching the maximum concentration, there was a fast decline with a parallel terminal phase for all dose groups with a short terminal half-life of about 4 h.

[redacted]

Urinary PK analysis revealed that the amount excreted in urine increased with increasing dose. The gMean fraction of dose excreted in urine was very low and ranged from 0.100% to 0.205%.

Preliminary PK parameters (gMean [%gCV]) after single and multiple oral administrations of BI 1569912 as a tablet in healthy volunteers in MRD trial 1447-0002 are summarised in the current IB [c29289852] and Table 5. [redacted]

[redacted] Food intake instructions for this trial are described in Section 4.1.4.

Drug interactions

[redacted]

[redacted]

[redacted], according to the basic models from the FDA [R20-0261], EMA [P21-11010], and MHLW [P19-01288] DDI guidelines, [redacted] The induction potential of [redacted] BI 1569912 were predicted using the software DDI risk calculator v2.0 from PharmaPendium. This tool contains the official equations provided by the above-mentioned FDA guidance [R20-0261].

[redacted]

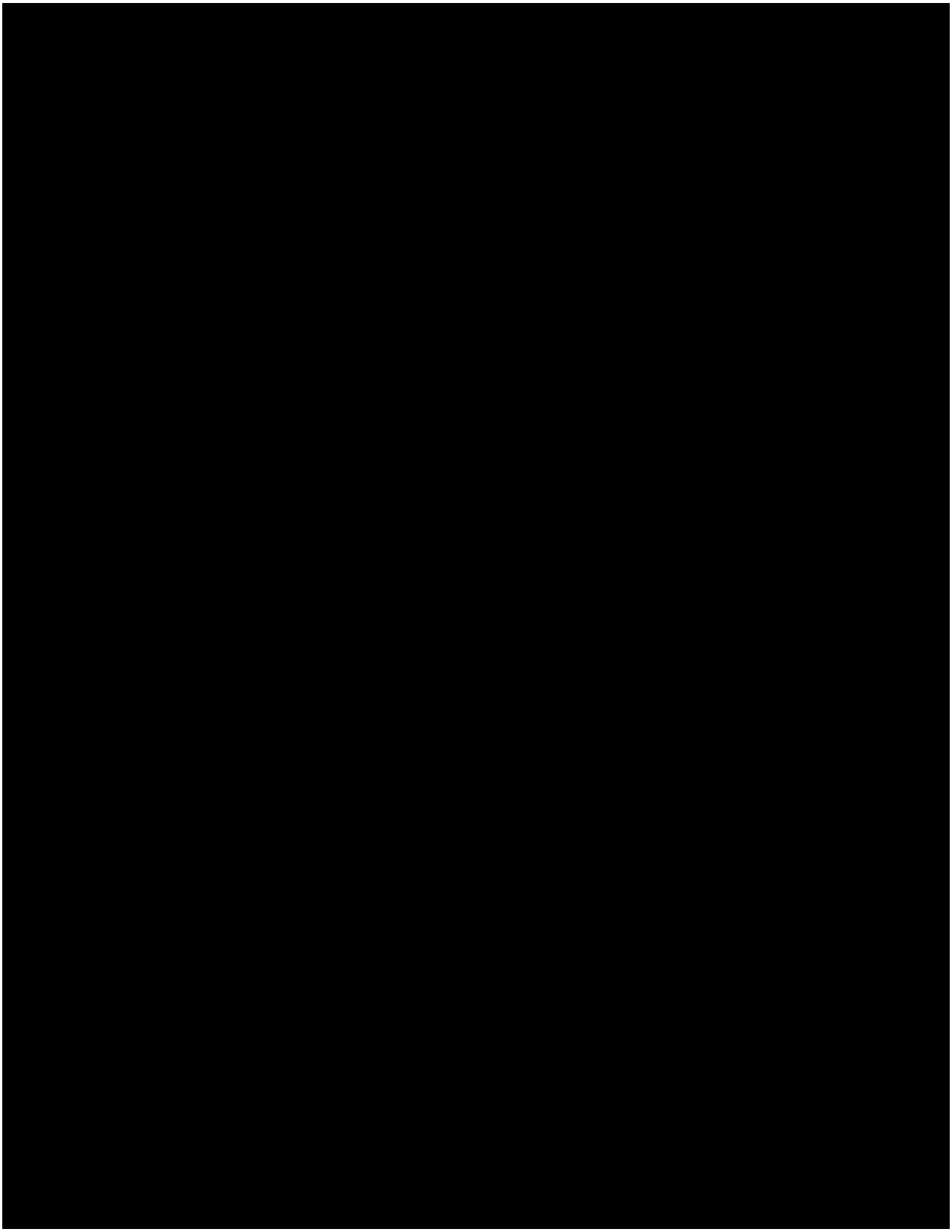
Consequential restricted medications of all described drug interactions are described in Section 4.2.2.1 and listed in the ISF.

Residual Effect Period

[redacted]

Data from non-clinical studies

[redacted]



Safety data from clinical studies

In clinical trials to date, BI 1569912 has been well tolerated with a low frequency of adverse events (AEs) in all dose groups. Across observed AEs, no dose-dependent increase in

frequency has been observed for any of these AEs. None of the observed AEs were of severe intensity; there were no AEs considered to be dose limiting and no serious AEs (SAEs).

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

Despite the array of available treatment options, there remains a significant unmet medical need for patients with MDD who either do not respond to or do not tolerate current treatment options. Medications that act rapidly with improved efficacy but without the side effects and/or resource requirements of last-line treatment options (i.e. a monitored setting for esketamine) would constitute a major medical advance and fulfil a high unmet medical need for patients suffering from MDD.

Disruption of complex mood-related circuitry has been implicated in depression. Among the findings of altered brain structure and function in depression, the most consistent finding is the hypoactivity in the medial prefrontal cortex (PFC). Ketamine [R19-0550, R19-0556] as well as NR2B NAMs [R19-0855] cause a burst of glutamate in the PFC that is understood to occur via a biased inhibition of GABA-ergic interneurons thus disinhibiting glutamatergic neurons [R19-0556]. This transient increase in glutamate triggers neuronal activation and enhances synaptic plasticity [R19-0548, R19-0549, R19-0554, R19-0552].

Following Phase I studies in healthy volunteers and a proof of clinical principle trial in participants with MDD, the present trial is designed to assess dose-range finding data, provide proof of clinical concept, and confirm the safety and tolerability of BI 1569912 compared with placebo when administered for 6 weeks. These results will be used to characterise the dose-response relationship within the therapeutic range, and to select the target dose(s) for pivotal studies.

In order to be able to address future scientific questions, trial participants will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the trial participant agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of the product's effects and thereby better match patients with therapies.

1.4 BENEFIT– RISK ASSESSMENT

1.4.1 Benefits

BI 1569912 has been given to healthy volunteers in a single dose escalation study (1447-0001) and in a Japanese dose escalation study (1447-0004) at up to [redacted] which were assessed as safe and well tolerated showing no dose limiting effects, including those [redacted]. Single doses of BI 1569912 in an ongoing blinded trial in participants with MDD (1447-0003) have not presented any safety signals. [redacted]. Doses selected for the current study in MDD participants (refer to Section 4.1.2) had a favourable safety profile and were well tolerated in both the SRD and MRD healthy volunteer studies.

Participants with MDD receiving oral BI 1569912 may experience relief of symptoms related to depression during the study. However, BI 1569912 is an experimental drug at an early stage of testing and therefore an individual benefit for participants cannot be guaranteed. Nevertheless, participation in this trial is of major importance for the development of a new orally available treatment with the potential to relieve depressive symptoms faster than standard treatments in MDD patients.

1.4.2 Risks

Table 1 provides an overview of the potential risks related to exposure to the trial investigational medicinal product (BI 1569912), known risks related to the compound class, known risks related to psychoactive drugs, and trial procedure-related risks. For further details on treatment-related risks, refer also to Section 1.2 of the current clinical trial protocol (CTP) and the current version of the IB [c29289852].

Table 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product – BI 1569912		
Nonclinical data:		
[redacted]		

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		
Healthy volunteer data:		
• Phase I SRD Up to [redacted], no AE occurred more than once across all 7 dose groups. • [redacted] Therefore, no specific AE risk associated with BI 1569912 has been identified. There might be compound-related unknown risks at the same dose levels in participants with a psychiatric disorder.	All reported AEs were transient and a majority were of mild intensity. None of the participants experienced any serious adverse events (SAEs) or relevant alterations in laboratory parameters, vital signs, or ECG. Whether participants with MDD show a different sensitivity to BI 1569912 compared with healthy volunteers is not known, although a higher sensitivity is not expected. However, the doses required for efficacy might be higher than expected based on animal data using the forced swim test as a sign of potential antidepressant activity. In the first [redacted] participants with MDD in the ongoing PoCP clinical trial (1447-0003), no SAEs, AESIs, or adverse events of severe intensity have been observed.	Extensive standard safety laboratory measurements, ECG measurements, monitoring of vital signs, and physical examinations will be performed before IMP administration and at every site visit thereafter. Management of symptoms, evaluation, and follow-up will be conducted as needed to ensure participant safety, per the investigator's clinical judgement.
[redacted]		

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure the safety of trial participants.
General risks of psychoactive drugs		
Occurrence or increase of suicidality	Some patients with MDD have an increased risk of suicidality. Some studies have shown a correlation of increased suicide risk with the use of certain antidepressants. Although there is no precedent from clinical data implicating an association between NR2B negative allosteric modulation and suicidal ideation and behaviour, this risk cannot be ruled out completely.	Participants with a recent history of clinically significant suicidal ideation are to be excluded from the current trial (refer to Section 3.3.3). In the interest of ensuring participant safety, trial participants will be proactively screened and monitored throughout the trial for suicidal ideation and behaviour in accordance with regulatory guidance.

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Sedation, combined with impaired thinking, judgement, and/or motor skills	Psychoactive drugs are known to potentially cause unwanted side effects on brain function.	It is recommended to monitor participants for 2 h after first dose. During site visits, participants will be continuously monitored for AEs and neurological examinations will be performed throughout the trial. While no AEs involving somnolence, vision impairment, or psychomimetic effects associated with BI 1569912 have been observed in clinical trials, participants should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the IMP does not adversely affect their ability to engage in such activities. It is recommended that participants should exercise caution when driving or operating machinery.
Potential compound class effects:		
Dissociative symptoms	NMDA antagonists, in particular ketamine, and some NR2B-specific modulators such as traxoprodil, are associated with the occurrence of dissociative symptoms which would be expected to occur in a dose-dependent manner.	Participants with a history of psychotic episodes or positive drug screening are to be excluded from the current clinical trial (See Section 3.3). IMP should be administered in quiet ambient conditions. Clinical assessment of psychiatric symptoms associated with dissociation will be assessed during the course of the study via the [redacted] AE reporting to monitor and assess the severity of specific symptoms.
Blood pressure increase	Same risk and rationale as dissociative symptoms	Monitoring of arterial blood pressure at site visits
Potential for drug abuse	Some drugs, including ketamine, are associated with a risk of abuse. While the potential for abuse liability with BI 1569912 appears low based on the currently available nonclinical data, specific clinical abuse liability studies have not yet been performed with BI 1569912.	Participants with a history of substance use disorders are to be excluded from the current clinical trial, clinical assessments of psychiatric symptoms will be conducted throughout the trial [redacted]

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Matching placebo to BI 1569912		
Worsening of depression and/or the occurrence or increase in suicidality	Even though mitigation measures are applied, this risk cannot be ruled out completely.	Participants will remain on stable psychotherapy, where applicable. Participants will be monitored during the treatment and follow-up periods to ensure that worsening of pre-existing conditions or any newly occurring events are detected and any necessary actions taken according to stopping criteria.
Trial procedures		
General discomfort	Participants might experience some general discomfort due to the procedural nature of clinical trial conduct	Management of discomfort, evaluation, and follow-up will be conducted as needed to ensure participant safety.
Blood draw	The potential risks of a blood draw include fainting, pain, bruising, swelling, or infection (rarely) where the needle is inserted. In rare cases, a nerve may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch, and persistent pain. The total volume of blood withdrawn during the entire study per participant will not exceed the volume of a normal blood donation (approximately 500 mL).	No health-related risk is expected from blood withdrawal.
Other risks		
Hypersensitivity and allergic reactions	As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration with BI 1569912 administration.	First dosing of BI 1569912 will be conducted on site with a recommendation of at least 2 h of post-administration surveillance; monitoring and management of symptoms and treatment as needed throughout the course of the trial, including discontinuation of trial participation as per the investigator's clinical judgement.

1.4.3 Discussion

Major depressive disorder was ranked as the third highest cause of the burden of disease worldwide in 2008 by the WHO, which has projected that MDD will rank first by 2030. Both patients, caregivers, and healthcare providers are seeking more effective therapies that address the core symptoms of MDD, with a faster onset of action, a higher response rate, higher remission rate, and a more tolerable safety profile than what is currently available. NR2B-specific negative allosteric inhibitors have shown rapid efficacy in reducing depressive symptoms in multiple exploratory trials with no serious safety concerns [R17-3810, R19-0986, R22-0355, c42998816]. In contrast to other compounds with a similar mode of action, which are delivered intravenously or intranasally under medical supervision, BI 1569912 is an oral medication that allows for non-monitored, home administration. This means that BI 1569912 could be given in [redacted] than NMDA receptor antagonists such as esketamine.

The nature of the target and the mechanism of action of BI 1569912 is well understood. The preclinical safety package has shown a favourable profile of BI 1569912 at doses in the range of the expected human exposure. [redacted] Close monitoring was conducted in Phase I trials for signs indicative of these events, with no reported occurrences.

In view of the patient population expected for the current trial and the need to adequately monitor suicidality; frequent clinic visits, [redacted] are planned to monitor participants. In addition to the standard situations, treatment should be discontinued if there are signals consistent with disease worsening as listed in Section 3.3.4.1. With regard to the mechanism of action of BI 1569912 and the AEs reported in clinical trials to date, there is no undue risk related to stopping the IMP during the treatment period or at the end of the treatment period. Considering the medical need for the development of a better tolerated and more effective treatment for patients with MDD, the expected benefit outweighs the potential risks.

In the context of the unmet medical need, anticipated benefit of BI 1569912, and available non-clinical and clinical information, the benefit-risk evaluation of the compound is favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

The main aims of this trial are to assess dose-range finding data of BI 1569912 compared with placebo in participants with MDD, and to provide proof of clinical concept (PoCC) to support dose selection for pivotal studies.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary trial objectives are to demonstrate a non-flat dose response curve, to evaluate the dose response relationship, and to assess the quantitative treatment effect size.

The trial will be performed to characterise the dose-response curve for BI 1569912 in participants with moderate to severe MDD by assessing 3 active doses and placebo. Response is defined as the change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6 summarised per arm by the adjusted mean. The multiple comparison procedure with modelling (MCPMod) approach will be used to characterize the dose-response curve.

The primary characterisation will be on treatment which will assume all participants took randomised treatment for the duration of the trial.

Assessments of further efficacy, pharmacokinetic, and safety parameters will further support the selection of a dose (range).

2.1.2 Primary endpoint(s)

- Change from baseline in MADRS total score at Week 6

2.1.3 Secondary endpoint(s)

No secondary endpoints have been defined for this trial.

[redacted]

2.2.3 Safety

There are no specific safety endpoints defined for this trial, however, safety (e.g. AEs, SAEs, AESIs, [redacted], physical examination, vital signs, ECG, and safety laboratory tests) will be analysed descriptively in participants who receive at least 1 dose of IMP.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-centre, randomised, double-blind (participant and investigator), placebo-controlled parallel group Phase II trial to examine the efficacy and safety of oral BI 1569912 once daily over a 6-week treatment period in adult patients with moderate to severe MDD. Participants will be enrolled into the trial once informed written consent has been obtained.

Participants suitable after screening will be randomised to the 6-week double-blind treatment period and will be assigned to placebo or one of 3 doses of active BI 1569912 drug (low to high dose) in a 2:1:1:2 ratio.

Once treatment is completed, participants will have an 8-day follow-up period and complete study participation (EoS Visit). Individual participation is concluded when the participant has completed their last planned visit. The overall trial design is depicted in Figure 1.

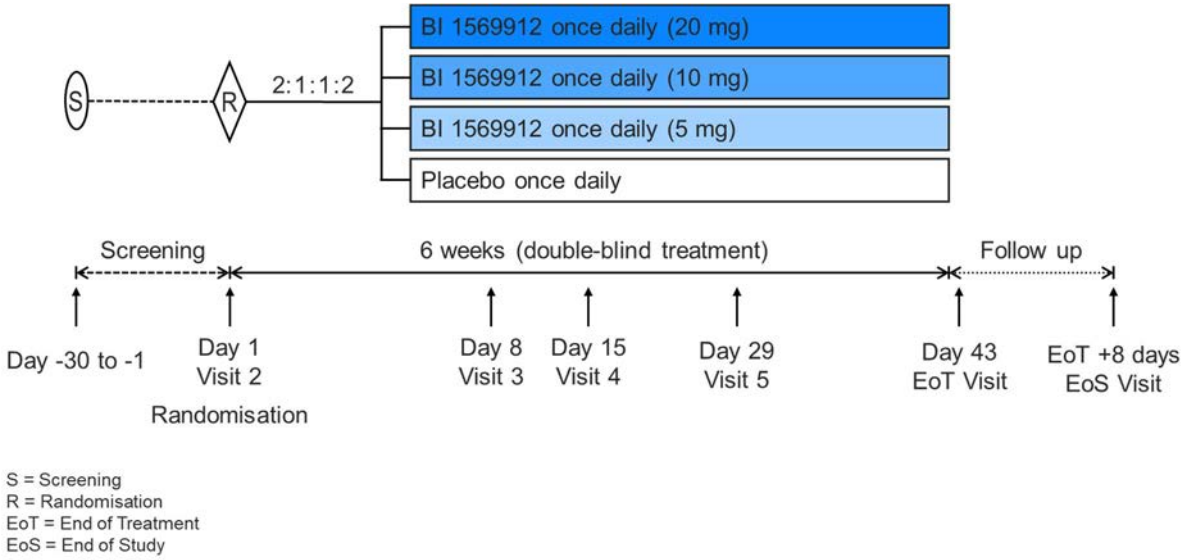


Figure 1 Study Design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This is a randomised double-blind, placebo-controlled, parallel-design trial. This design is appropriate for providing proof-of-concept/dose-range finding and assessing the safety and efficacy of BI 1569912 compared with placebo in participants with MDD. Implementation of a placebo control is crucial to address potential confounding factors; a practice that is required per regulatory guidelines, but also driven by methodological considerations. This approach has been standard practice in recent clinical development and is deemed acceptable as participants will have regular visits, extra safety visits are allowed as needed, participants will remain on psychotherapy, where applicable, and the duration of the placebo treatment will be limited to 6 weeks including the right to stop participation by the subject or investigator if necessary.

The design of the trial will provide efficacy, safety, and dosing information to support PoCC. In order to achieve both aims in an efficient way, the generalised MCPMod approach has been implemented as the statistical design. This approach is widely accepted [R15-1961], [R19-1647] and is able to incorporate potential relationships between the different doses into the evaluations via optimal test contrasts and uses the available data better than the commonly applied pairwise comparisons.

The trial design and schedule of assessments was put through a trial simulation. The trial simulation objective was to engage with patients and trial sites early in the development of the trial. Trial simulations were conducted with MDD trial nurses, coordinators, and patients living with MDD. Key learnings around insights and potential challenges should lead to solutions to ensure a positive clinical trial experience by sites and patients.

A total of 3 active BI 1569912 doses will be administered to provide reasonable coverage for most monotonic shapes of the dose-response relationship. A sufficiently broad set of candidate shapes for this relationship has also been chosen. In addition, an unequal allocation ratio (2:1:1:2) has been selected for the treatment and placebo groups. In general, an allocation of a higher proportion of participants to the placebo and active dose of interest versus other treatment arms will lead to better precision which then leads to a higher power. In addition, increasing the proportion of participants in the placebo group compared with other treatment arms may lead to the observation of a greater separation between the placebo and active treatment arms [P09-01434]. Details of the statistical approach including the set of candidate models as well as a sample size justification are given in Section 7.5.

Data at Week 6 will provide evidence of a sustained effect. [redacted] In addition, we will also obtain safety data through the end of observation period (early IMP discontinuation date/EoT +8 days [+6 days]). Collectively, this information will help facilitate the design of pivotal studies.

This trial will include an option for participants to complete questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Appendix 10.1).

3.3 SELECTION OF TRIAL POPULATION

Approximately 222 participants are planned to be randomised into the trial, in order to have approximately 180 participants evaluable for the primary analysis. It is planned that about 45 trial centres in 2 countries (USA and Japan) will be participating in this trial to ensure a sufficient number of participants are randomised.

It is expected that approximately 4-8 participants will be randomised at each trial centre. If enrolment is delayed, additional sites may be recruited. To avoid differential centre influence on trial results, permission to randomise more than 15 participants per site must be obtained from the sponsor, CTL or designee. This will only be allowed after a careful review of the enrolment status and the site.

Screening of participants for this trial is competitive, i.e. screening for the trial will stop at all centres when such a number of participants have been screened that it can be anticipated that a sufficient number of participants will be randomised to trial treatment. Investigators will be notified about screening completion and will then not be allowed to screen additional participants for this trial. Participants already in screening at this time will be allowed to continue to randomisation if eligible.

A log of all participants screened for the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether or not IMP was administered to the participant.

The following information, at minimum, will be collected, including for participants who are determined to be ineligible for randomisation: participant number, visit date, demographics, eligibility criteria, information on AEs (if applicable), and concomitant treatment relevant for the AE.

If retrospectively it is found that a trial participant has been randomised in error (i.e. did not meet all the inclusion criteria or met one of more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made as to whether continued trial participation is possible.

3.3.1 Main diagnosis for trial entry

Participants meeting diagnostic criteria of MDD per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and diagnosis confirmed at time of screening by Mini-International Neuropsychiatric Interview (MINI) will be screened for suitability for the trial. In addition, participants must meet criteria for moderate to severe depression as assessed and confirmed by the Hamilton Depression Rating Scale-17 (HDRS-17) and the Clinical Global Impression- Severity Scale (CGI-S).

Please refer to Section 5.6.1 for further details regarding the confirmation of diagnosis and Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

For inclusion in the randomised trial, all inclusion criteria must be satisfied prior to randomisation.

1. Male and female participants, 18 to 65 years of age, both inclusively at the time of consent
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
3. Women of childbearing potential (WOCBP) must be ready and able to use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly plus one additional barrier method. A list of contraception methods meeting these criteria and instructions on the duration of use is provided in the participant information and in Section 4.2.2.3

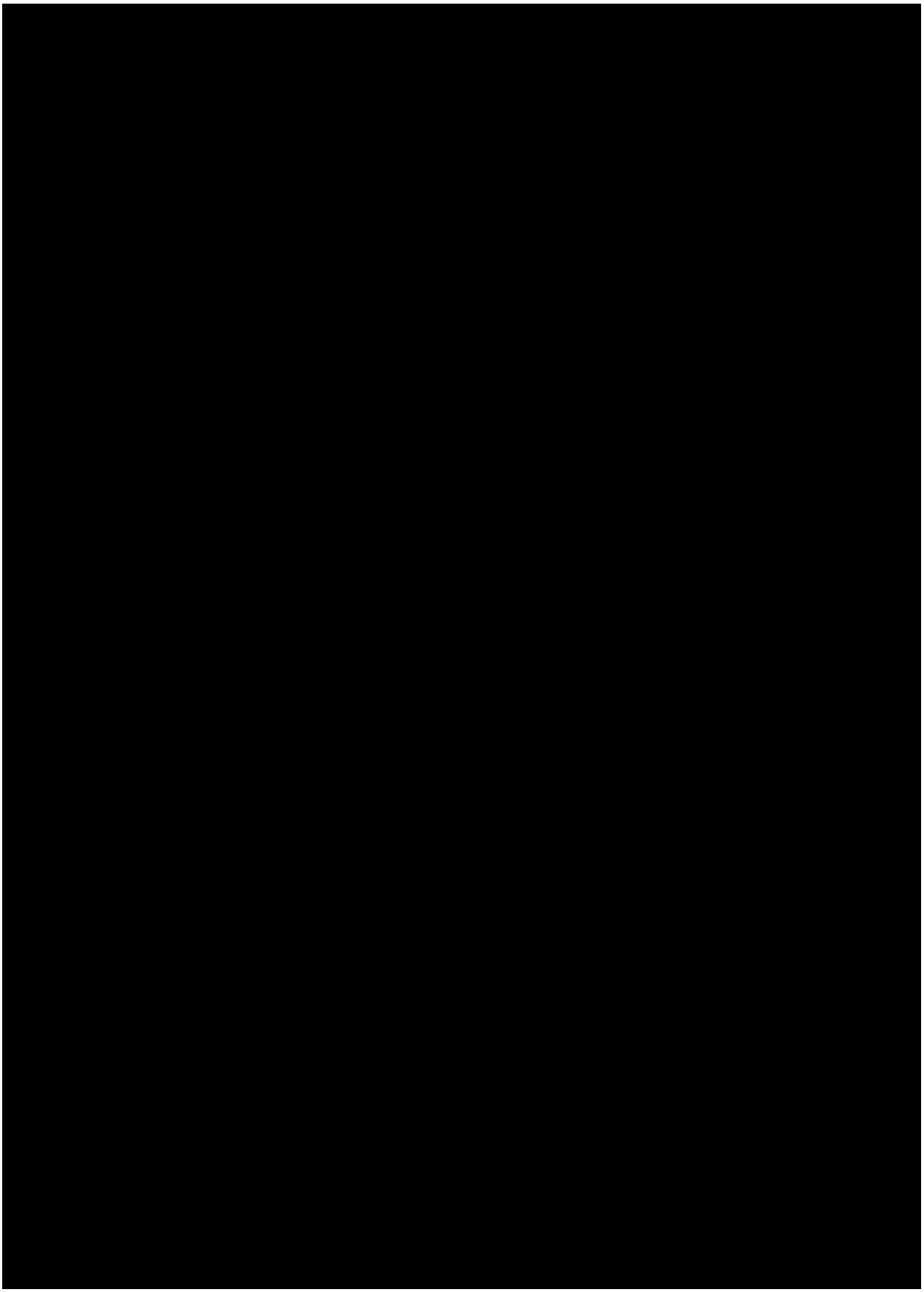
4. Established diagnosis of MDD, single episode or recurrent, as confirmed at the time of screening by the MINI with a duration of the current depressive episode ≥8 weeks AND ≤24 months at the time of randomisation
5. Hamilton Depression Rating Scale-17 (HDRS-17) – Severity scale score ≥20
6. Clinical Global Impression- Severity Scale (CGI-S) score ≥4

3.3.3 Exclusion criteria

All exclusion criteria must be assessed during the screening visit (Visit 1).

1. Per MINI, have ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, or delusional disorder
2. Diagnosis with antisocial, paranoid, schizoid or schizotypal personality disorder, or MDD with psychotic features as per DSM-5 criteria, at the time of screening visit. Any other personality disorder at screening visit that significantly affects current psychiatric status and likely to impact trial participation, as per the judgement of investigator
3. Diagnosis of any other mental disorder that was the primary focus of treatment within 6 months prior to screening (as per clinical discretion of the investigator)
4. Treatment failure to 2 or more antidepressants in the current episode, defined as less than 50% response to treatments administered at an adequate dose and duration as evaluated by the ATRQ
5. History or presence (upon clinical examination) of seizure disorders or an increased risk of seizures (first degree relative with epilepsy), stroke, brain tumour, or any other major neurological illness that could impact participation in the trial
6. A current or recent history of clinically significant suicidal ideation with intent within the past 3 months, corresponding to a score of 4 or 5 for ideation on the C-SSRS or a suicidal attempt within the past year, as indicated by the C-SSRS at screening visit
7. Participants with a body mass index (weight [kg]/height [m]²) lower than 18 kg/m² or greater than 40 kg/m^2 at screening
8. Diagnosis of a moderate to severe substance related disorder as defined by DSM-5 criteria within 6 months prior to screening visit (with exception of caffeine and tobacco)
9. Frequent use of benzodiazepines defined as use on ≥4 days per week within the 4 weeks prior to screening
10. Positive drug screen (amphetamines, opiates, cocaine, barbiturates, phencyclidine) at screening. Participants with positive cannabis and benzodiazepine drug tests can be included if the investigator confirms that there is no moderate to severe substance related disorder or chronic benzodiazepine use

[redacted]



3.3.4 Discontinuation of trial participants from treatment or assessments

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

Measures to control the withdrawal rate include careful trial participant selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal. Every effort should be made to collect data on all randomised participants. This includes randomised participants who never took the IMP and participants who permanently discontinued the IMP.

The decision to discontinue trial IMP or withdraw consent to trial participation and the reason (if provided) must be documented in the trial participant files and eCRF. If applicable, consider the requirements for AE collection and reporting (see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial IMP if:

- The trial participant wants to discontinue trial IMP. The trial participant will be asked to explain the reasons but has the right to refuse to answer.
- The trial participant has been repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the trial participant cannot be guaranteed as they are not willing or able to adhere to the trial requirements in the future.
- The trial participant needs to take concomitant medication that interacts with the IMP, see Section 4.2.2.1.
- If it is found that a trial participant took restricted medication, used electroconvulsive therapy, TMS, other non-drug therapies (e.g. acupuncture, hypnosis), or initiated/discontinued psychotherapy during the trial, the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made as to whether the trial participant can continue the IMP or should be discontinued.

- The trial participant can no longer receive trial IMP for medical reasons such as surgery, AEs, other diseases, or pregnancy. In case of a temporary reason, trial IMP should be restarted if medically justified (i.e. there is no safety concern, in the opinion of the investigator) and the maximum interruption period is less than 2 weeks.
- Pregnancy occurs during the trial. Once a participant has been randomised in the clinical trial and has taken the IMP, the investigator must report any IMP exposure during pregnancy which occurred in a female trial participant to the Sponsor immediately (within 24 h) by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point.
- The participant must discontinue treatment with the IMP if:
    - The participant develops suicidal ideation [redacted] or suicidal behaviour [redacted]
    - In the event of worsening of MDD which requires medical treatment which is on the list of restricted medications (refer to Restrictions Section 4.2.2.1 and ISF), the IMP has to be discontinued.

If a participant permanently discontinues the IMP, an EoT Visit must be performed as soon as possible after the last dose of IMP, ideally 24 h after final IMP intake. It is extremely important that participants are encouraged to complete at least the MADRS, [redacted] assessments. [redacted] EoT. The reason for discontinuation of treatment must be recorded in the eCRF, if given. Participants who discontinue IMP prematurely should ideally be observed as if they were still receiving blinded trial treatment.

If it is not possible to attend all regularly scheduled visits after the EoT Visit, at least phone contacts should occur at the scheduled visit time points. It is vital to explain to these participants the importance of continued trial participation. If the participant is not willing to continue to attend regularly scheduled visits after the EoT Visit, an EoS Visit should be scheduled for 8 days (+6 days) after discontinuation of the IMP. Additional information will be provided in the ISF.

When discussing options for continued trial participation, sites must present the first option outlined in Table 2 to the participant and discuss this option thoroughly before presenting the next option for follow-up.

Table 2 Follow-up of participants who prematurely discontinue the IMP

Early DC Option 1	EoT Visit performed as soon as possible, ideally 24 h after last IMP intake. Continue to conduct regularly scheduled trial visits as per protocol [redacted]
If participant does not agree to Option 1, present: **Early DC Option 2**	EoT Visit as soon as possible and attend the EoS Visit in person; other in person visits can be replaced with teleconference visits. Focus on key efficacy and safety endpoints MADRS, [redacted] (at minimum MADRS should be completed) and safety assessments per Section 5.2.6.2.1
If participant does not agree to Option 2, present: **Early DC Option 3**	EoT Visit and proceed to EoS Visit (8 + 6 days after last intake of IMP)

Participants should be encouraged to choose the most rigorous follow-up schedule they are willing and able to comply with. The investigators should inform these participants that they will be allowed to change this schedule later if needed. If the patient refuses any further follow-up after treatment discontinuation, this will be considered as "withdrawal of consent" by the patient and must be recorded as such in the eCRF.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the IMP for all trial participants or take any other appropriate action to guarantee the safety of the trial participants. Even if the IMP is discontinued, the trial participants will remain in the trial and, given their agreement, undergo the procedures for early treatment discontinuation and follow-up as outlined in the SoA and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Trial participants may withdraw their consent to trial participation at any time without the need to justify the decision.

If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant and explain the difference between IMP discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after IMP discontinuation (see 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 overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New efficacy or safety information invalidating the earlier positive benefit-risk assessment; please see Section 3.3.4.1
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial

Further treatment and follow up of trial participants affected will occur as described in Section 3.3.4.1.

The investigator/trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 1569912 tablets and matching placebo are provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

See Section 1.2 and the current IB [c29289852] for more details regarding BI 1569912.

4.1.1 Identity of the Investigational Medicinal Products

Table 3 BI 1569912

Substance:	BI 1569912
Pharmaceutical formulation:	Tablets
Unit strength:	2.5 mg and 10 mg
Posology:	qd
Mode of administration:	p.o.

Table 4 Placebo matching BI 1569912

Substance:	Placebo matching in size and weight to BI 1569912 tablets
Pharmaceutical formulation:	Tablet
Unit strength:	Not applicable
Posology:	qd
Mode of administration:	p.o.

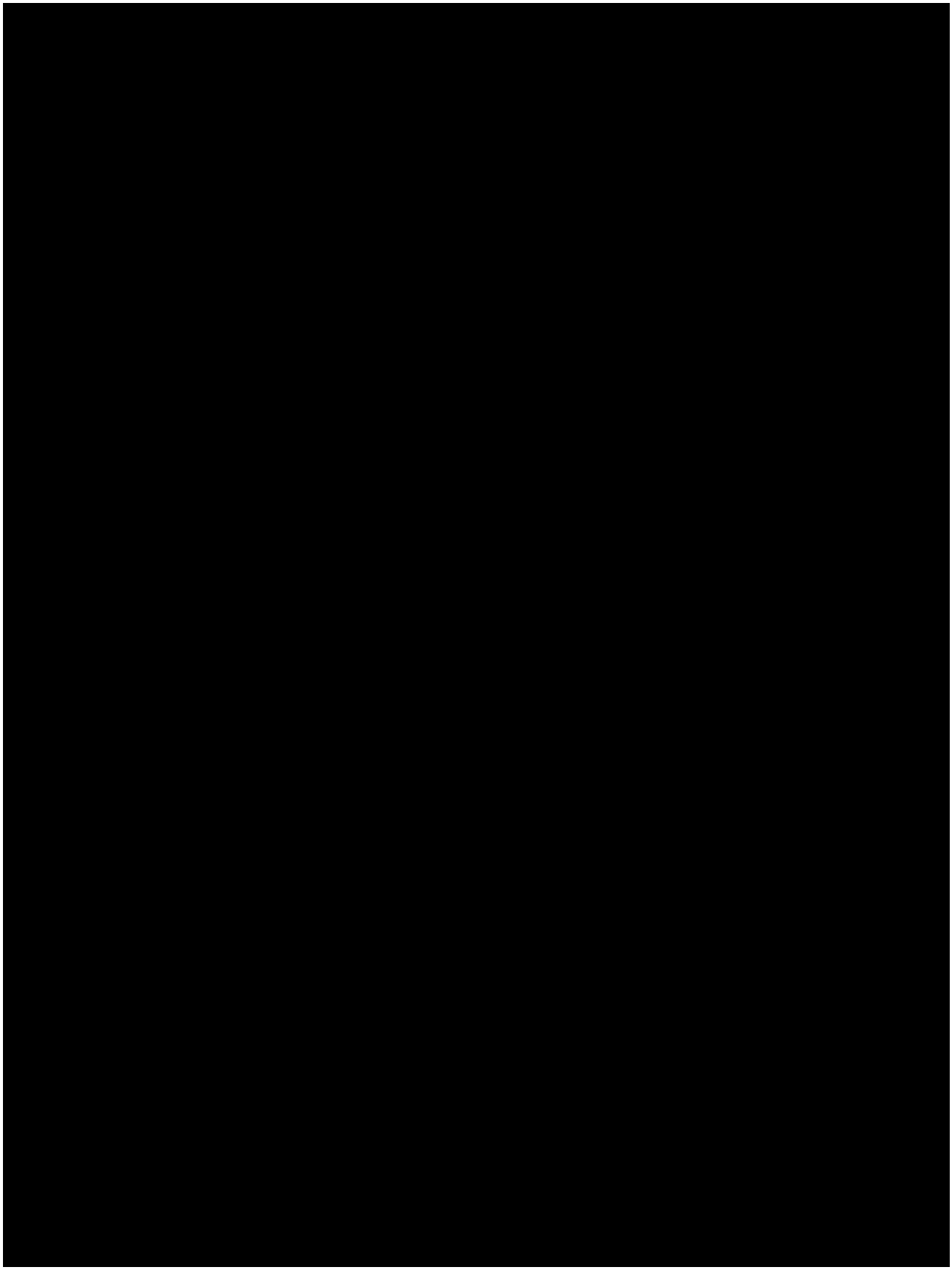
4.1.2 Selection of doses in the trial and dose modifications

The following doses of BI 1569912 have been selected for this trial:

- 5 mg, qd
- 10 mg, qd
- 20 mg, qd

The criteria for dose selection are based on preclinical and clinical data of BI 1569912 gathered during research and development (See Section 1.2). Doses from 5 to 20 mg BI 1569912 once daily were selected based on the following considerations:

Safety and tolerability of BI 1569912 have been evaluated in healthy volunteers for up to 14 days for doses ranging from 2.5 to 20 mg and in single doses from 0.25 to 30 mg. Across all observed AEs, there has been no dose dependent-increase in frequency for any AEs. There were no AEs considered to be dose limiting and no SAEs. In the first 42 randomised participants of a double-blinded, single dose trial in patients with a similar profile to those expected in the current trial, there were no reports of SAEs, AESIs, or AEs of severe intensity.



[redacted]

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all inclusion and exclusion criteria during Visit 2, each eligible trial participant will be randomised to a treatment group according to a randomisation scheme described in Section 7.4. Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites, and trial participants. Access to the codes will be controlled and documented. An Interactive Response Technology (IRT) system will be used to screen participants, create a participant number, perform treatment assignment, manage initial/re-supply ordering of IMP supplies, and handle emergency unblinding. Instructions for the use of IRT are provided in the ISF.

4.1.4 Drug assignment and administration of doses for each trial participant

The IMP assignment will be provided through IRT. The assigned medication numbers must be entered in the eCRF and the corresponding medication kits must be given to the participant. The duration of treatment is 6 weeks. The final dose of IMP should be taken on the day before the EoT Visit.

Participants should be instructed to swallow the IMP in its entirety (without chewing) with water, every day at approximately the same time (ideally in the morning). The ideal time between intake of IMP is 24 h. Participants should not eat (i.e. fast) for 2 h prior to and 1 h post every IMP intake. There are no restrictions for water intake. On Visit 5, participants should be instructed not to eat [redacted] The time of IMP and food intake should be recorded in the eCRF as described in Section 5.3.1. If a daily dose is missed by more than 12 h, that dose should be skipped and the next dose should be taken as scheduled. On days prior to a visit, the daily dose should be taken approximately 24 h before the planned dose at the visit. Site visits should be scheduled according to the usual IMP intake time, which is ideally in the morning.

After randomisation during Visit 2, patients will receive their first medication kit. A dose of IMP consists of 2 tablets to be taken once daily. The first dose of IMP will be taken at the study site under supervision of the investigator or site staff. It is recommended to monitor participants for 2 h after the first dose. At Visits 2 and 3, participants will receive a medication kit containing supplies for a total of 10 treatment days (7 treatment days plus 3 days reserve). At Visits 4 and 5, kits will contain supplies for a total of 20 treatment days (14 treatment days plus 6 days reserve). Return of the used/unused medication kits will occur at Visits 3, 4, 5, and EoT. After a temporary interruption, trial treatment may be restarted (Section 3.3.4.1).

Participants should be instructed not to take the IMP on the day of Visits 3, 4, and 5 [redacted] before the EoT visit. Participants who have taken a dose of IMP on the day of the EoT Visit should have the visit rescheduled as soon as possible, ideally on the following day.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Trial participants, investigators, central reviewers, and everyone involved in the trial conduct or analysis will remain blinded regarding the randomised treatment assignments until the database is declared ready for final analysis (after database lock after last patient last visit) according to the sponsor's standard operating procedures (SOPs). Further details regarding the timepoint of unblinding the database for analyses are provided in the TSAP.

Access to the randomisation code will be kept restricted until its documented release per sponsor SOP.

[redacted]

Exploratory interim analyses may be performed by an independent team at the sponsor for internal planning purposes. Details are given in Section 7.2.8, including how access to unblinded data and results will be controlled and documented in the Logistics and Access Plans.

The results of ECGs do not represent a risk of unblinding.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must be used only in an emergency when the identity of the trial IMP must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The treatment allocation should not be disclosed to the sponsor/designee unless this is explicitly requested. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page.

Due to the requirements to report suspected unexpected serious adverse reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance

group to access the randomisation code for individual trial participants during trial conduct. The access to the code will only be given to authorised PSPV representatives for processing in the Pharmacovigilance database and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The IMP will be provided by Boehringer Ingelheim or a designated CRO. The IMP will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

IMP supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, immediately contact the CRA (as provided in the list of contacts) and follow the procedures for assessing and reporting temperature excursions provided in the ISF.

4.1.8 Drug accountability

The investigator or designee will receive the IMP delivered by the sponsor or delegate 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 or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority (CA)
- Availability of a signed and dated clinical trial protocol
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572

The IMP is not allowed to be used outside the context of this protocol and must not be forwarded to other investigators or clinics. Trial participants should be instructed to return unused IMP (refer to Section 4.3 for more details regarding compliance).

The investigator or designee must maintain records of the product's delivery to the trial site, inventory at the site, use by each trial participant, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products in alignment with the sponsor, if applicable. If applicable, the sponsor or warehouse/drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry (‘use by’) dates, and the unique code numbers assigned to the IMP and trial participants. The investigator or designee will maintain records that adequately document that trial participants were provided the medication kits specified by this clinical trial protocol and reconcile all IMPs received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used IMP supplies have been returned by the trial participant and that no remaining IMP supplies are in the investigator’s possession. Accountability, reconciliation, and returns will be registered in IRT.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Auxiliary medicinal products

Not applicable.

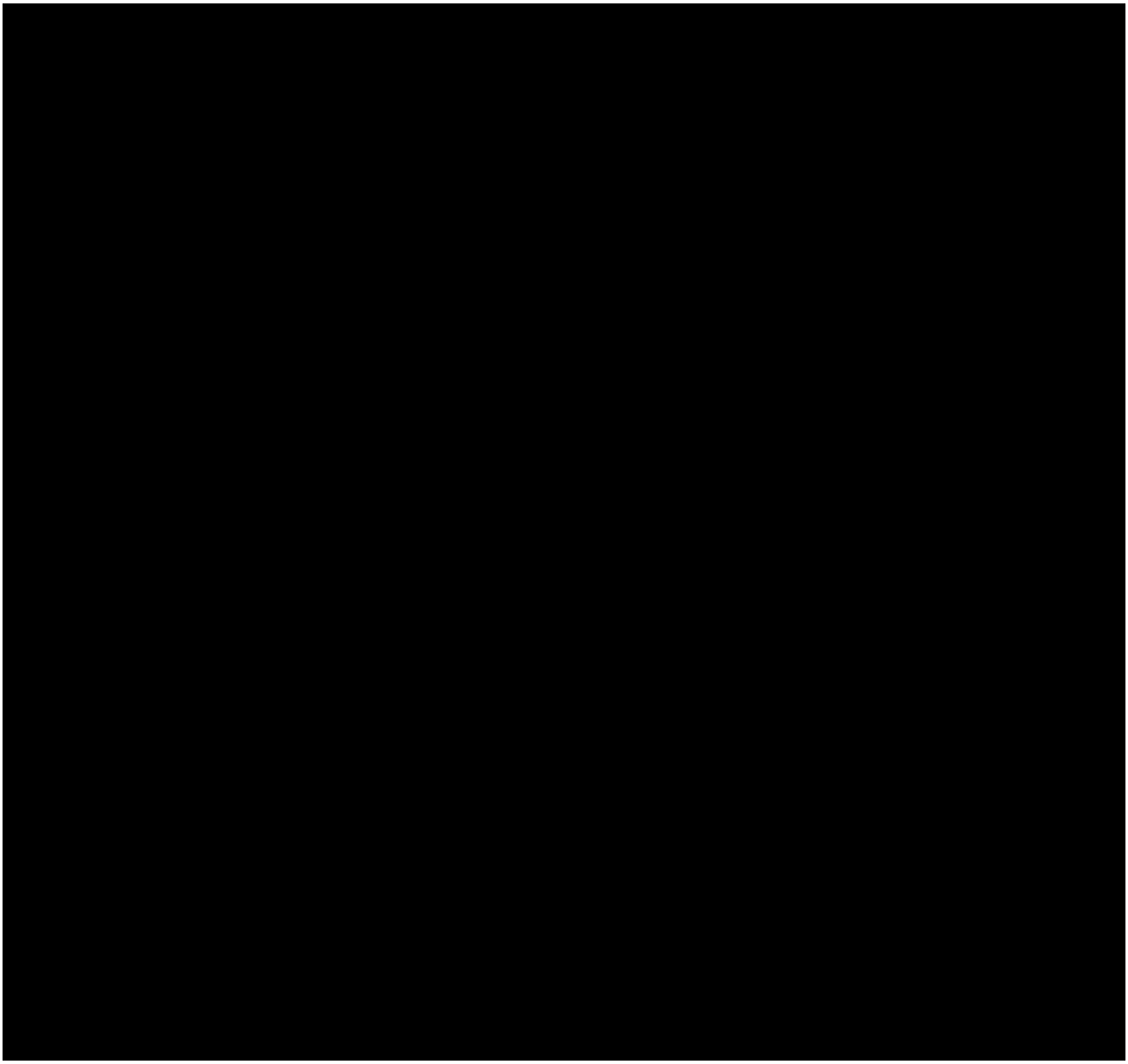
4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed. If AEs require treatment, the investigator can authorise symptomatic therapy. In those cases, site staff will follow SOPs and participants 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 and have returned to normal or values that are considered clinically non-relevant.

For the handling of participants with positive report of suicidal ideation and/or behaviour, please refer to Section 5.2.5.1.

4.2.2 Restrictions

[redacted]



4.2.2.2 Restrictions on diet and lifestyle

In general, participants should keep their usual habits throughout the trial for diet and exercise, as well as nicotine, alcohol, and caffeine intake. These habits should be within acceptable daily amounts (at the discretion of the investigator) and not be drastically changed throughout the trial conduct.

Note the following restrictions:

- Participants should not abuse alcohol or use drugs of abuse during the trial. A urine drug screen will be performed at selected trial visits (see SoA). For a list of drugs assessed by the urine drug screen please refer to Table 7.
- Participants should not enter or modify a smoking-cessation program during the conduct of the trial.

- Patients should not have a change in type, intensity, and/or frequency of allowed psychotherapy or other non-drug therapies (e.g. acupuncture or hypnosis) during the conduct of the trial.
- It is recommended that participants should exercise caution when driving or operating machinery until they are reasonably certain that the IMP does not adversely affect their ability to engage in such activities.

[redacted] There are no restrictions on water intake.

4.2.2.3 Contraception requirements

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Throughout the trial and for a period of at least 28 days after the final dose of IMP, trial participants who are WOCBP must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly, **plus** one barrier method if their sexual partner is a man able to father a child. Systemic hormonal contraceptives must be initiated ≥60 days prior to randomisation.

Acceptable forms of contraception are:

- Combined (oestrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and provided that the partner is the sole sexual partner of the WOCBP clinical trial participant
- Complete sexual abstinence is allowed when this is in line with the preferred and usual lifestyle of the participant. In this specific case the barrier methods, as mentioned below, are not applicable. Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active (i.e. periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception).

Plus one of the following barrier methods:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

There are no contraceptive requirements for male participants. Please see the current IB [c29289852] for details regarding nonclinical reproductive/developmental toxicity studies.

4.3 TREATMENT COMPLIANCE

Investigational medicinal product will be dispensed to the participant at the study site by responsible site personnel. Details regarding dispensing of the IMP to each participating patient, including patient identification, the amount of IMP dispensed, the date the IMP was dispensed, and the numbers of tablets returned to the site, will be recorded in the drug accountability log. All dispensed IMP should be recorded in the drug accountability log of the investigator site file.

Trial participants are requested to bring all remaining trial IMP, including empty package material, with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of doses actually taken} \times 100}{\text{Number of doses that should have been taken as directed by the investigator}}$$

The potential for IMP abuse will be closely monitored. Events including overdose, misuse, lost, and unaccounted for IMP must be thoroughly documented in the participant's source documentation and on the appropriate pages of the eCRF. Furthermore, if the treatment compliance is less than 80% or greater than 100%, site staff should discuss with the trial participant the importance of compliance and document the reasons for non-compliance in the eCRF.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Clinical outcome assessments (COAs)

Data from the COAs described in Section 5.1 will be collected in the eCRF or will be electronically transferred to the sponsor.

5.1.1.1 MADRS - Montgomery-Åsberg Depression Rating Scale

The Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (MADRS-SIGMA) will be used to collect MADRS scores. For the purpose of this document, MADRS is synonymous with MADRS-SIGMA. The MADRS is a clinician-reported interview guide designed to assess the severity of symptoms in depressive illness and to be sensitive to treatment effects [R24-1238]. The MADRS consists of 10 items:

1. reported sadness
2. apparent sadness
3. inner tension
4. reduced sleep
5. reduced appetite
6. concentration difficulties
7. lassitude
8. inability to feel
9. pessimistic thought
10. suicidal thoughts

Symptoms are rated on a 7-point Likert scale from 0 (no symptom) to 6 (severe symptom). Definitions of severity are provided at 2-point intervals. The possible total score could range from 0 to 60 (from normal with absence of symptoms to severe depression). A recall period of 7 days will be used at all visits.

[redacted]

An experienced clinician can administer the MADRS after a training session. The MADRS will be audio recorded for quality assurance. This assessment should take approximately 25 to 30 min. The MADRS score will be captured using a paper questionnaire. The Placebo Control Reminder Script (PCRS) should be read to, and audio recorded, prior to each MADRS assessment at every visit. See Section 5.6.2 for details regarding the PCRS.

5.1.1.2 CGI-S – Clinical Global Impression Severity Scale

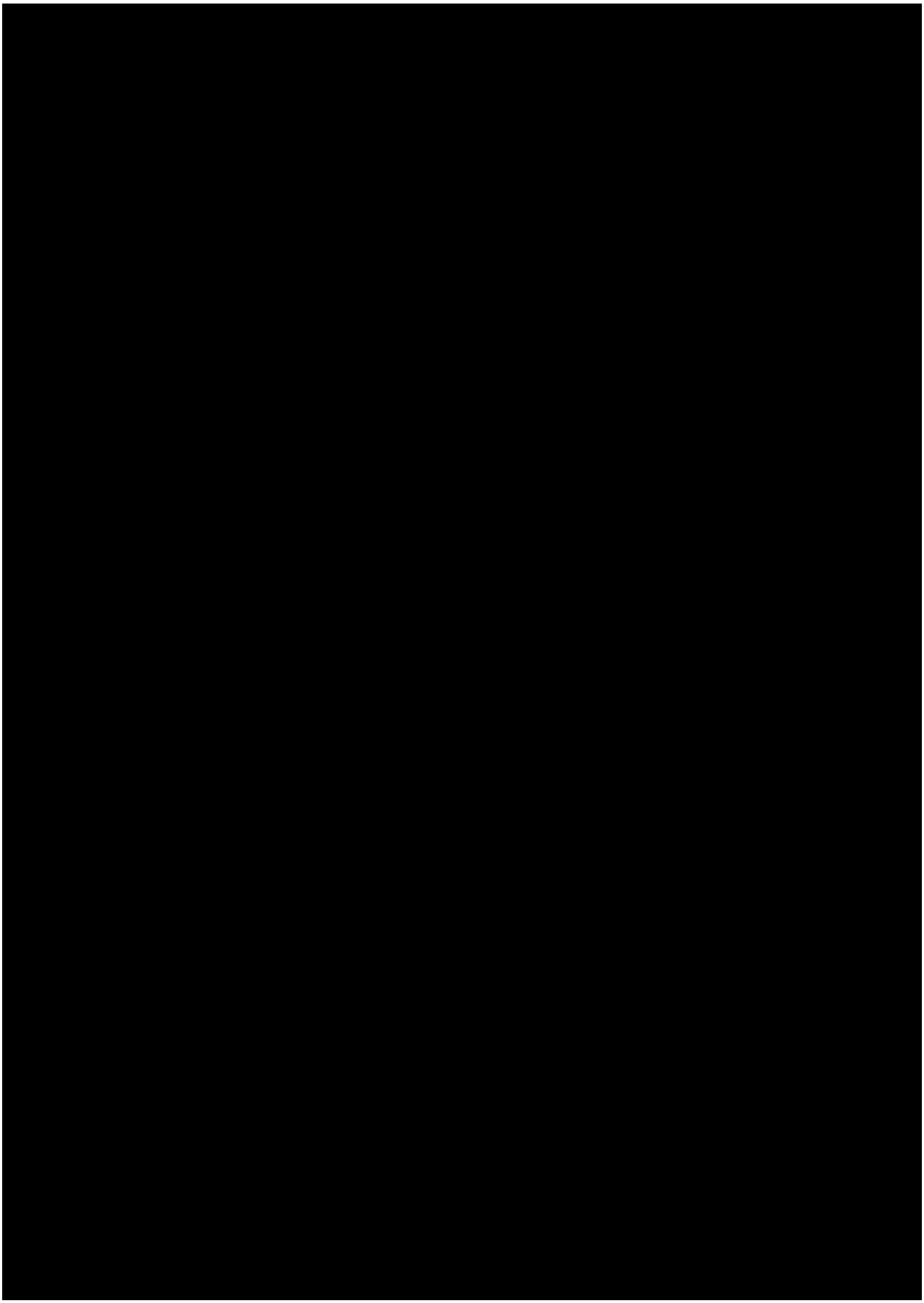
The CGI-S rating scale measures the clinician's impression of the severity of illness exhibited by a participant and takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the participant's ability to function [R03-0520, R19-1932]. The CGI-S

evaluates the severity of psychopathology on a scale of 1 to 7. Higher scores indicate worsening of the patient's illness. This rating is based upon observed and reported symptoms, behaviour, and function over the past seven days.

The CGI-S question states "Considering your total clinical experience with this particular population, please choose the response below that best describes how mentally ill the patient was over the past week?", and is rated on the following seven-point scale:

1. Normal, not at all ill
2. Borderline ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most extremely ill patients

The CGI-S is to be completed by the interviewer and should take approximately 5 min to complete. The CGI-S will be captured using an eCOA device.



[redacted]

5.1.1.8 COA rater training and qualification

Rater training and qualification on COAs will be managed by a vendor as per vendor qualification methodology that has been agreed with the sponsor.

The vendor will manage rater training and qualification by evaluating the rater's experience and scoring performance, tracking required training, and collecting documentation of training and qualification. New raters joining the trial will be trained and qualified with the same defined rater training and qualification program using the vendor learning platform.

The MADRS and CGI-S must be administered by a psychiatrist, psychologist, or other clinician demonstrating adequate experience in patients with MDD and relevant comorbidities. Exceptional situations will be reviewed on a case-by-case basis.

The C-SSRS must be administered by a trained staff member with a valid C-SSRS training certificate (See Section 5.2.5.1).

Each rater will complete a COA-specific training as defined in the rater training and qualification program before being considered qualified for rating a participant on the respective scale in the context of the trial. All raters for the trial will be trained on the handling of all assessments that they will be administering.

For raters handling PROs throughout the trial (i.e. [redacted]), the completion of a PRO administrator training is obligatory.

The vendor will provide a certification indicating the status for all raters who have completed the rater training and qualification program as well as follow-up requirements. No participant is allowed to be assessed/rated before the certification confirming the qualified status for the rater, is filed in the ISF. The C-SSRS certificate will be filed separately.

For each individual participant, the same qualified rater should rate the participant throughout the trial if possible. In case of unforeseen circumstances, a qualified back-up rater must be available throughout the trial. For sites without a back-up rater, rater or site staff should take measures to avoid missing evaluations, such as adjusting the visit date within each window according to the participant's schedule.

5.1.1.9 COA/eCOA handling

Administration of COAs/eCOAs will be handled according to guidance documents from regulatory authorities and international societies (e.g. ISPOR). Participants are to complete

PRO assessments on their own in a quiet area/room at the frequency specified in the SoA, without being influenced by the investigator or other members of the trial team. PRO/ePRO assessments are to be completed by the participant in the same language the participant provided written consent for the trial and without any help from or interpretation/translation by other people. If this is not possible, the PRO assessments are not to be done. Adequately trained and qualified site staff are to be available at any time for general questions and to support the participant, as well as to ensure PRO completion compliance. Whether the participant was able to complete the PRO assessment themselves and the mode of administration will be documented.

For the compilation of paper questionnaires, the site personnel should check questionnaires for completeness prior to the participant leaving the site, but the response to each item will not be tampered with, and a participant should not be influenced in any manner on how to respond to the questions. Scores for paper-based questionnaires will be entered into the eCRF by site personnel.

For COAs and PROs compiled on electronic devices, completeness and consistency checks will be programmed into the application and no further check by site personnel is needed. Data from these assessments will be electronically transferred to a vendor. The data flow for eCOAs is described in the vendor data management plan. A back up device will be provided to sites.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical/Neurological examination

A complete physical examination will be performed at the time points specified in the SoA. This examination includes, at a minimum: general appearance, neck, lungs, cardiovascular system, abdomen, extremities, skin, and a basic neurological assessment.

The neurological assessment includes:

- General level of arousal (vigilance)
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Deep tendon reflexes
- Assessment of muscle strength
- Tremor
- Point-to-point movements
- Romberg test
- Gait
- Sensitivity

Measurement of height and body weight will be performed at the time points specified in the SoA and collected in the eCRF. The BMI (kg/m^2) will then be automatically calculated from the entered results and recorded in the eCRF. 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 physical, mental, and neurological examination will be reported either as baseline conditions (prior to IMP administration) or as AEs (after IMP has been administered).

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the SoA, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 min) in a comfortable seated position after 5 min of rest. Preferably measurements should be taken with the same device at every visit. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

The safety and exclusionary laboratory parameters to be assessed in this trial are listed in Table 6 and Table 7, respectively. The sampling time points are shown in the SoA.

Trial participants do not have to be fasted for the blood sampling for safety laboratory tests. Participants should be asked about fasting/last meal. If the last meal was at least 10 h before the blood sampling, participants should be marked as fasted on the lab requisition form. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the laboratory manual in the ISF.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (after IMP intake) or as baseline conditions (prior to IMP intake). Refer to Section 5.2.6.1.1 for specific AE definitions.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (see Section 5.2.6.1 and the DILI Checklist provided in the ISF). The amount of blood taken from the trial participant concerned will be increased due to this additional sampling.

The results of various drug screens (e.g. cannabis, benzodiazepines, barbiturates, opiates, cocaine, amphetamines, methadone, PCP) will be captured in the clinical database to ascertain the use of drugs in this study population and the impact of use on the recruitment failure rate, to assess the frequency of benzodiazepine use as sleeping aids, and to assess the relevance of occasional cannabis use to facilitate the design of pivotal trials.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

The results of infectious serology tests will be used by the investigator to assess each participant’s eligibility for the trial. Infectious serology laboratory results will not be reported to the sponsor.

Table 6 Safety laboratory tests

Functional laboratory group	Test name
Haematology	Haematocrit Haemoglobin Red blood cells (RBC) Platelet count White blood cells (WBC) Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) Red cell distribution width (RDW) Reticulocyte Count
Automatic WBC differential (relative and absolute)	Neutrophils Eosinophils Basophiles Monocytes Lymphocytes total
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalised ratio (INR)
Enzymes	Alanine aminotransferase (ALT, SGPT) Aspartate aminotransferase (AST, SGOT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactic dehydrogenase (LDH)
Hormones	Thyroid stimulating hormone (TSH)
Substrates	Glucose Creatinine, enzymatic eGFR[1] Urea nitrogen Total bilirubin (fractionated if increased) Total protein Albumin C-reactive protein (CRP) Globulin Albumin / globulin ratio Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Chloride Phosphate Calcium

1 Estimated glomerular filtration rate (eGFR) will be calculated using Chronic Kidney Disease Epidemiology [CKD-EPI] equation for adults

Table 6 (cont'd) Safety laboratory tests

Functional laboratory group	Test name
Urinalysis (qualitative determination)	Urine nitrite Urine protein Urine glucose Urine ketone Urine bilirubin Urine haemoglobin (detects erythrocytes) Urine leukocyte esterase (detects leucocytes) Urine pH Specific gravity
Urine sediment (microscopic examination if erythrocytes, leukocytes, nitrite, or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)
Urine pregnancy test (only for female participants of childbearing potential)	β-human chorionic gonadotropin (β-HCG)
Serum pregnancy test (only if urine pregnancy test is positive)	β-HCG

Table 7 Exclusionary safety laboratory tests

Functional laboratory group	Test name
Drug screening (urine). Use of cannabis and benzodiazepines are not exclusionary in accordance with exclusion criteria (Section 3.3.3).	Amphetamine Barbiturates Buprenorphine Benzodiazepine Cocaine Methadone metabolite Methadone Methamphetamine Ecstasy Morphine Opiates Oxycodone Phencyclidine Tricyclic antidepressants Cannabis
Infectious serology (blood)[1]	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) Hepatitis C vaccine RNA (only if Hepatitis C antibodies are positive)

1 Additional testing for infectious diseases (such as HIV 1 and HIV 2) can be added as required.

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be performed as scheduled in the SoA and recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for a duration of at least 10-seconds after the participants have rested for at least 5 min in a supine position and prior to lab sampling. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all timepoints indicated in the SoA, single ECGs will be recorded. ECG recordings at planned time points may be repeated for quality reasons (i.e. alternating current artefacts, muscle movements, and electrode dislocation). In this case the repeated ECG recordings will be used if quality was better.

The investigator or a designee will evaluate whether the ECG is normal or abnormal and in the latter case, whether it is clinically significant. The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the participant's medical file if there is no validated and certified e-medical record for ECG data.

Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant findings noticed at baseline assessment (Visit 1) should be reported as baseline conditions. Clinically relevant abnormal findings noticed after baseline assessment will be reported as AEs and will be followed up and/or treated as medically appropriate.

All ECGs will be transmitted electronically to the central ECG vendor in order to enable a centralised and independent re-evaluation of all 12-lead ECGs. A centralised and independent re-evaluation will be done. Abnormalities detected during this centralised ECG evaluation will not necessarily qualify as AEs.

Central evaluation on individual ECG level will be performed by the vendor and a report will be provided to the site. The central ECG vendor will transfer the results to the sponsor or delegate. Decisions on eligibility for the trial and treatment or further follow-up of any findings are the responsibility of the investigator.

5.2.5 Other safety parameters

Data from the COAs described in Section 5.2.5 will be collected in the eCRF or will be electronically transferred to the sponsor.

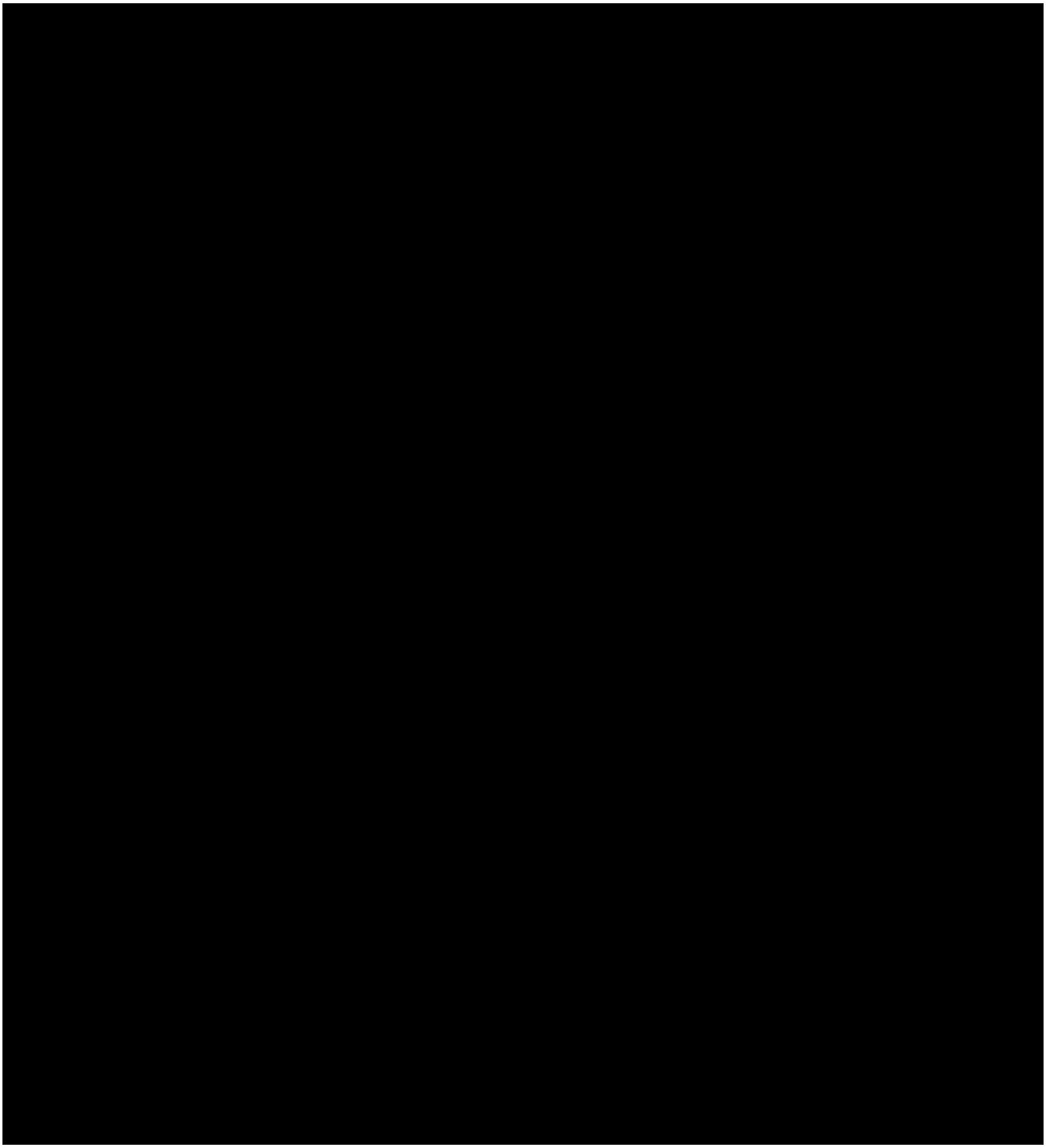
5.2.5.1 C-SSRS – Columbia-Suicide Severity Rating Scale

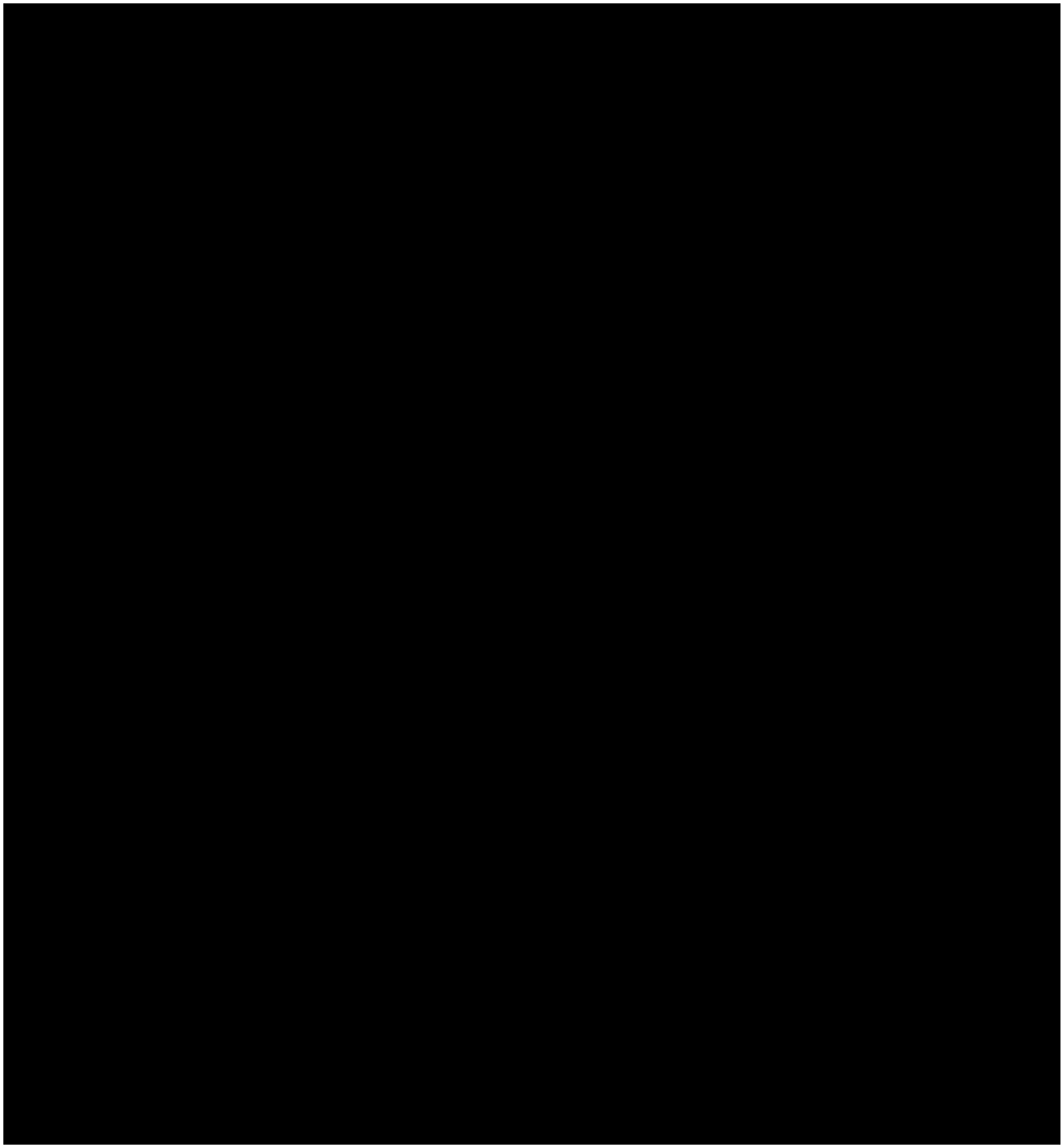
Suicidal risk will be assessed by the C-SSRS. The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behaviour and ideation. C-SSRS responses will be captured using an eCOA device.

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 and a valid C-SSRS certificate. It has a typical duration of 5 min and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal

ideation and 4 related to suicidal behaviour and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.

The C-SSRS will be administered at the screening visit (using the 'baseline/screening' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The lifetime history of suicidal ideation and behaviour will also be recorded.





5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF(s). This may include specific data and information not prospectively specified in this protocol.

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a trial participant 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 considered related or not.

The following should also be recorded on the appropriate eCRF(s) and the Boehringer Ingelheim SAE form:

- Worsening of the underlying disease or of other pre-existing conditions
    - AEs in the context of suicidal risk assessment [redacted] should be adhered to
- Changes in vital signs, ECG, physical/neurological examination findings, and/or laboratory test results, if judged clinically relevant by the investigator

If such abnormalities already 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

An SAE is defined as any AE that fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the participant 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 or 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 on appropriate medical judgement which may jeopardise the participant 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

For Japan only: An event that possibly leads to disability will be handled as “deemed serious for any other reason” and, therefore, reported as an SAE.

5.2.6.1.4 Adverse events of special interest

The term “adverse event 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; see Section 5.2.6.2.2.

The following is considered an AESI:

- Potential severe drug induced liver injury (DILI)

Potential severe DILI

A potential severe drug-induced liver injury (DILI) that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

1. AST or ALT elevation ≥3 × ULN and total bilirubin ≥2 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation ≥3 × ULN and INR ≥1.5 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation ≥3 × ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
4. AST or ALT elevation ≥5 × ULN

These laboratory findings constitute a hepatic injury alert, and participants showing any of these laboratory abnormalities need to be followed up according to the “DILI Checklist” provided in the ISF.

In case of clinical signs or symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure 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.

Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5 × ULN requires repeat testing within 72 h. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

The following events should lead to immediate discontinuation of trial IMP:

- Hepatic injury alert numbers 1, 2, or 3
- Hepatic injury alert number 4, if persists >2 weeks
- AST or ALT elevation >8 × ULN

Following completion of the DILI Checklist, if the IMP cannot be excluded as a possible cause of the DILI event, discontinuation should be made permanent without rechallenge. If an alternate causality, e.g. acute viral hepatitis, is confirmed by the DILI Checklist evaluation, IMP may be re-started, if warranted.

5.2.6.1.5 Intensity (severity) of AEs

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

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

Moderate: Sufficient discomfort to cause interference with usual activity

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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the AE and the IMP, 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 a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the IMP
- 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 IMP exposure
- Evidence that the event is reproducible when the IMP is reintroduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or comedications)
- 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 no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of IMP exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days/weeks of IMP administration, an allergic reaction weeks after discontinuation of the IMP concerned)
- Continuation of the event despite the withdrawal of the IMP, considering 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
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the IMP concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the participant files.

Per default, SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the Boehringer Ingelheim paper SAE form should be used; see Section 5.2.6.2.2.

The following must be collected and documented:

- From signing the informed consent onwards until the individual participant's end of trial (usually the EoS Visit; please see Sections 3.3.4 and 6.2.3):
  - all AEs (serious and non-serious) and all AESIs

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI on the AE eCRF immediately (within 24 h of becoming aware of the event) triggering a data transfer to the sponsor's unique entry point. The country-specific process will be described in the ISF. On specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

With receipt of any further information on these events, follow-up reports must be provided. For follow-up information, the same rules and timelines apply as for initial information. All AEs/SAEs, including those persisting after an individual participant'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.

Should the EDC system not be available for more than 24 h, reporting must occur via the Boehringer Ingelheim paper SAE form.

5.2.6.2.3 Pregnancy

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

The outcome of the pregnancy associated with the IMP exposure during pregnancy must be followed up and reported to the sponsor’s unique entry point on the Pregnancy Monitoring Form for Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Studies (Parts A and B). 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 Studies is to be completed. However, an SAE and/or AESI associated with the pregnancy must be reported as described in Section 5.2.6.2.2.

5.4 ASSESSMENT OF BIOMARKER(S)

Biomarkers will not be assessed in this trial.

5.5 BIOBANKING

Biobanking will be performed only in countries where allowed by local laws and regulations. Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will occur only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage of biobanking samples are provided in the laboratory manual. For sampling timepoints, see the SoA.

In total, approximately 45.5 mL of blood will be drawn for DNA, plasma, and serum for banking purposes.

5.6 OTHER ASSESSMENTS

5.6.1 Confirmation of diagnosis

Eligibility of potential participants will be based on a combination of a neuropsychiatric diagnosis via the MINI and the severity of the current depressive episode as assessed through the HDRS-17 and CGI-S scales. The MINI and HDRS-17 assessments will be administered on paper while audio recorded at the Screening Visit 1. The MINI and HDRS-17 recordings will be reviewed by an independent external clinical reviewer provided by a specialised vendor. The eligibility of potential participants will be confirmed by an external clinical reviewer, in which screening data will be obtained to evaluate psychiatric status.

5.6.1.1 MINI – Mini International Neuropsychiatric Interview

The MINI will be used during screening for confirmation of the diagnosis of MDD and to exclude trial participants with other psychiatric disorders as described in the exclusion criteria (Section 3.3.3). The MINI is a structured interview for making the major DSM-5 diagnoses [R97-1075, R07-1303]. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. Administration of the MINI should take approximately 15 min. Raters will complete the questionnaire with the participants as a paper version. Any diagnoses identified though the MINI must be recorded as baseline conditions.

5.6.1.2 ATRQ – Antidepressant Treatment Response Questionnaire

The Massachusetts General Hospital ATRQ will be used to document antidepressant medication history, or lack thereof, and to determine treatment resistance in MDD. The ATRQ customised for this study provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants. The ATRQ will be completed by the patient with assistance from the clinician/site staff, with required responses collected in the eCRF.

5.6.1.3 HDRS-17 – Hamilton Depression Rating Scale-17

The Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS-SIGH-D) will be used to collect HDRS-17 scores. For the purpose of this document, HDRS-17 is synonymous with HDRS-SIGH-D. The HDRS-17 consists of 17 items that evaluate the multidimensional symptoms of depression. During the HDRS-17 clinicians are to consider the intensity and frequency of the given symptoms based on patient responses and observations [R99-1131]. The HDRS-17 items are rated on a 3 or 5 point Likert scale from 0 (absent/no disturbances) to 2 or 4 (constant/severe). The total score is yielded from the sum of the 17 item ratings and possible scores could range from 0 to 52 (from normal with absence of symptoms to severe depression).

An experienced clinician can administer the HDRS-17 after a training session. It should take approximately 15 to 20 min to administer the HDRS-17. The PCRS (Section 5.6.2) should be read to participants just prior to administering the HDRS-17 during screening. The HDRS-17 score must meet inclusion thresholds (severity scale score ≥20), as described in the

inclusion criteria (Section 3.3.2). Raters will complete the questionnaire with the participant as a paper version.

5.6.2 PCRS – Placebo-Control Reminder Script

Although not an outcome measure, but rather a tool designed to mitigate the placebo and nocebo response, the PCRS © (Version 5.0, R20-4054) educates clinical trial participants of key causes of the placebo and nocebo effects. It does this namely through the tempering of participant study expectations, reminding subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with previous providers. As such, the PCRS informs subjects that they are to be honest about their symptoms, that site staff have no expectations of symptom improvement or worsening and will not be disappointed if they feel better, worse, or the same, and asks participants to explain in their own words its content to ensure comprehension. Per the instructions on the PCRS, the HDRS-17 or MADRS rater will read the script verbatim immediately before administering this scale. The PCRS is read to each subject at each visit (time point) listed on the SoA, typically taking about 3 min to read. The PCRS has been empirically found to manage (reduce) the placebo and nocebo effects in a relevant manner [R20-4054]. Reading of the PCRS to participants will be audio recorded for quality assurance. No data regarding the PCRS will be electronically transferred to the sponsor or collected in the eCRF.

5.6.3 Verification of current and past research study status of the trial participant

Duplicate enrolment and protocol violations are risk factors for poor quality data and safety concerns. These issues may result in increased placebo rates and failed clinical trials. Each participant, in this study, must have their current study status checked by utilizing the system of the vendor “Verified Clinical Trials”. This is a mandatory process where local regulatory approval has been obtained (therefore will not be conducted in Japan).

Following proper informed consent and after issuing a study subject number, the subject’s information will be checked against the Verified Clinical Trials (VCT) database, as indicated in the SoA. Partial identifiers will be utilised. This will include checking a valid form of picture identification when available.

The first 3 letters of the participant’s first and last name will be entered along with the middle initial, date of birth, sex, and last 5 digits of that identification. If the status of the research subject is a “Verification Success” they may proceed in the study. If, however, the status is a “Verification Failure” they will not be permitted to screen without sponsor/designee approval. The duplicate participant check will be performed only after approval is received in accordance with local regulations. No data regarding VCT will be electronically transferred to the sponsor or collected in the eCRF.

5.6.5 Data tokenisation

Data tokenisation is a cutting-edge technology and the most advanced form of pseudonymisation. Data pseudonymisation is the process of replacing personally identifiable information, like birth year or first name, with a pseudonym. In the context of clinical trials, tokens can be used to establish a link between a patient's participation in a BI study and the data collected from the same patient in other health care databases. This type of data is also called real world data. Data tokenisation will be used in this study to allow potential future use of patient data for further research. No tokenisation data will be collected in the eCRF.

The software used for data tokenisation generates a secure token (patient key) which maps to data available in commercial databases which include aggregate medical, claims, and laboratory data. The commercial databases include information on office visits, hospitalisations, laboratory tests, prescriptions, and other health care utilisation data. Once the patient data is tokenised, it is not possible to re-map the tokens to the individual patients.

It is requested, but not required, that all sites in the countries where the data tokenisation can be conducted participate in this initiative. Data tokenisation will be allowed only in countries where approved by local authorities. All participants at participating sites will be invited to provide separate written informed consent to participate in data tokenisation.

If a trial participant provides consent to participate in data tokenisation (participation is voluntary and does not impact their ability to participate in the main trial), patient identifiers will be collected and held by a CRO until data tokenisation is complete. The identifiers to be collected include: first name, last name, gender, birth date, postal/zip code. An independent review (data certification) will be done on the tokenised data to ensure that re-identification of individual patients is not possible.

Any activity using tokenised data will be out of scope of this study (1447-0012) and will be considered a separate observational and non-interventional study to evaluate the utilisation of health care resources and associated costs and to provide empirical evidence to inform market access strategy and decisions.

5.6.6 Optional trial feedback questionnaires

This trial will include an option for participants to complete an anonymised questionnaire, 'Trial Participant Feedback Questionnaire' to provide feedback on their clinical trial experience as detailed in Appendix 10.1. The start survey should be filled out during Visit 2 or 3, and the end survey during EoT or EoS. No data from the optional trial feedback questionnaires will be collected in the eCRF.

5.7 APPROPRIATENESS OF MEASUREMENTS

The measurements performed during this trial are standard measurements in MDD treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way. Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstance (e.g. pandemic, war), the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the participant, the sponsor and investigator may agree on alternative, back-up, or rescue methodology which may include, but will not be limited to, virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-participant shipments of IMP, direct-from-participant shipments of IMP, or biological sample pick up from the participant's home. The implementation of these measures will depend on the participant's consent, operational feasibility, and local laws and regulations. Such alternative measures will be described in the participant information. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

The trial visit schedule is presented in the SoA. Each visit date (with its window) is to be counted from Day 1 (day of randomisation/first intake of IMP, Visit 2). If a participant misses an appointment, it should be rescheduled, if possible. Subsequent visits should follow the original visit date schedule. The trial medication packs contain sufficient IMP to allow for the time windows described in the SoA. Additional visits for the purposes of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures and the order in which they are to be performed at each visit are listed in the SoA. Additional details regarding visit procedures are provided below.

Clinical outcome assessments

The following requirements for the conduct of the clinician administered COAs (C-SSRS, MINI, HDRS-17, MADRS, and CGI-S) need to be followed:

- The site staff must be properly trained on all trial procedures and training documentation filed in the ISF. Qualification, training, and remediation (if needed) of the scales will be provided by a specialised vendor. The training standards and standards for the conduct of the assessments will be defined for each assessment individually and can be found in the ISF; it is the responsibility of the primary investigator at each site to ensure that all members of the site staff involved in the neuropsychological assessments undergo qualification and training by the vendor.
- Each assessment of the site-rater administered scales (C-SSRS, HDRS-17, MADRS, and CGI-S) should preferentially be done by the same members of the site staff for a given participant throughout the trial period.
- All MINI, HDRS-17, MADRS, and PCRS rater performed administrations will be audio recorded for central review by the vendor for quality assurance.
- During the neuropsychological testing, participants are allowed to take short breaks as needed, per the judgement of the rater/investigator.

The baseline/screening scale of the C-SSRS will be administered for eligibility confirmation [redacted]. If there is an unscheduled visit due to suicidal ideation or behaviour, it is up to the investigator's judgement as to what appropriate testing should be completed as part of that evaluation.

Fasting

Participants should fast for 2 h prior to and 1 h after every IMP intake (both at the trial site and at home).

During Visits 2, 3, and 4, IMP intake should occur after all assessments are completed and the final dose of IMP should be taken on the day before the EoT Visit. Therefore, participants are not required to arrive to the trial site fasted for Visits 2, 3 and 4, however it should be ensured that the last meal was at least 2 h prior to IMP intake which will occur close to the end of the visit.

During Visit 5, participants should arrive to the trial site fasted as IMP intake will take place early during the visit to allow for pre and post-dose PK sampling. Participants should remain fasted until after the collection of the final PK sample during Visit 5 (2 h post IMP).

Safety laboratory and other laboratory tests

Trial participants do not have to be fasted for the blood sampling for safety laboratory tests. Participants should be asked about fasting/last meal. If the last meal was at least 10 h before the blood sampling, participants should be marked as fasted on the lab requisition form.

In rare cases where blood sampling for central laboratory is unable to be performed, safety laboratory analyses may be conducted at a local laboratory. The results and local lab standards of the laboratory tests must be transferred to the investigator who ensures medical review and documentation of any clinically relevant safety issue as an AE.

Ideally all parameters listed in Table 6 and Table 7 should be measured. If this is not feasible, the minimum required safety laboratory parameters are:

- Haematology
- Enzymes
- Substrates
- Electrolytes
- Urinalysis
- Pregnancy test
- Drug screening
- Infectious serology (only if clinical signs or symptoms are present)

6.2.1 Screening

No trial procedures should be done unless the participant has consented to taking part in the trial. After the participant has given informed consent in accordance with GCP and local legislation, the screening period will start with the first trial related procedure. The

participants should be recorded on the enrolment log. The participant should be registered in IRT as a screened participant.

At participating sites, participants will be invited to participate in data tokenisation (see Section 5.6.5). A separate informed consent will be required for participation in data tokenisation.

Within the screening period, screening procedures may be extended to more than one physical visit if needed. Blood sampling, ECG, MINI, ATRQ, HDRS-17, CGI-S should be done at the beginning of the screening period. The first day of screening will be the starting point for the screening period calculation. The screening period (i.e. period between Visit 1 and Visit 2) should be kept as short as possible. If screening period needs to be extended, the Clinical Trial Leader or designee should be contacted to discuss further steps.

In addition, a short informational video intended to educate the participant about placebos and why they are used in clinical trials may be available for participants. The video advises the participant not to attempt to guess if they are on active drug or placebo, reminds them that there is always a chance they have been randomly assigned to placebo, and stresses the importance of reporting all symptoms, be they positive, negative, or neutral.

6.2.1.1 Rescreening of participants:

Rescreening of a participant can be done twice, if there is a reasonable explanation and expectation that the participant may have become eligible (at the discretion of the investigator) post discussion with the Clinical Trial Leader or designee. For rescreening, the participant must re-consent to participation in the trial, all screening examinations must be repeated, and a new participant number assigned.

Potential reasons for rescreening could be:

- Positive urine drug screen
- Restricted medications like CYP sensitive drugs/alternative or traditional medicine
- Clinically significant findings per the investigator’s judgement
- Initiation of hormonal contraceptive

6.2.1.2 Retesting

Participants with unexpected lab values at Visit 1 may be retested once within the 30-day screening period if there is a reasonable explanation and expectation that the participant will meet the in- and exclusion criteria during the retest at the discretion of the investigator. This doesn’t apply to the urine drug screen, which must not be retested.

6.2.1.3 Demographics

During the screening visit, demographic information will be collected. This includes:

- Age (in years) on the day of informed consent
- Sex (male or female, in order to describe the trial participant’s sex at birth)

- Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic sex) **if** 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) participants are willing to reply
- For women of childbearing potential, yes/no in order to characterise the participant population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterise the participant population, to support possible subgroup analyses if needed, and to support the calculation of the kidney function via the CKD EPI formula unless not acceptable according to local regulations

6.2.1.4 Baseline conditions

Any diagnoses identified though the MINI must be recorded as baseline conditions.

Vital signs should always be measured before any blood samples are taken. For procedural details see Section 5.2.2. Any abnormal condition of clinical significance identified during physical examination, vital signs, ECG, and/or laboratory assessment should be recorded as a baseline condition.

6.2.1.5 Medical history

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least 1 documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Information related to the history of depression, e.g. age at time of diagnosis, number of antidepressants used for the current episode, duration of current episode, and number of previous episodes, will also be recorded in the eCRF at screening.

Additional details regarding concomitant psychotherapy (e.g. duration of ongoing non-drug therapies) at screening and randomisation need to be recorded in the eCRF. Please refer to the current eCRF for information that needs to be collected. During the treatment period, the question whether there were any significant changes in psychotherapy will be recorded in eCRF during trial site visits.

Substance use, (e.g. nicotine, alcohol, caffeine, cannabis, etc.) will be collected throughout the trial from screening to the EoS Visit. Please refer to the current eCRF for details about substance use to be collected.

Concomitant treatments which are allowed or restricted before and during trial participation, including required washout durations, are listed in the ISF. Participants will be instructed to continue allowed background therapy (e.g. ongoing psychotherapy) without changes.

6.2.1.6 Interactive Response Technology

All potential participants who are screened must be registered with IRT. If the screening results in a screen failure, the participant must be recorded as screen failure in IRT as soon as possible and within the 30-day screening period. Details of IRT procedures can be found in the IRT Manual filed in the ISF.

6.2.1.7 Participant Eligibility Review

Eligibility of potential participants will be confirmed by an external vendor. At screening, participant eligibility will be based on an external clinical review of the HDRS-17 and MINI data as well as their audio recordings. Any uncertainty raised by the external clinical reviewer of these scales related to inclusion/exclusion criteria will be discussed with the investigator/rater in order to establish confidence in the diagnosis and level of symptom severity. The external clinical reviewer will determine whether the participant is eligible to be randomised pending other screening procedures and issue a notification to the site regarding the participant's eligibility status. Participants for whom diagnostic/severity agreement between the investigator/study centre clinician and the vendor clinician(s) cannot be reached, may not be appropriate for study participation and should not be enrolled. Sites will be issued a notification from the vendor regarding eligibility for a potential participant before randomisation can occur.

6.2.2 Treatment period(s)

6.2.2.1 General remarks

After all the screening procedures have been completed and the eligibility of screened patients is confirmed, Visit 2 can be conducted including randomisation via IRT. IRT should not be called in advance of Visit 2 until eligibility is fully confirmed, as randomisation of a patient cannot be reserved. Randomisation should not be performed in case of a positive urine pregnancy test (to be completed locally on-site using kits provided by central lab). In the event of the positive urine pregnancy test, a serum pregnancy test must be performed for confirmation by the central lab.

Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the participant or to perform safety laboratory assessments.

Upon randomisation via the IRT at Visit 2, medication kits will be dispensed. The first dose of IMP should be taken at the clinic after all assessments are completed, with the exception of the ECG assessment and the collection of any AEs. It is recommended to monitor participants for 2 h post IMP administration. ECG readings should also be collected after IMP administration during Visits 2 and 5. Investigators should inform participants to continue daily dosing until their next visit.

Participants should be instructed to bring all IMP supplies (used and unused kits/packaging including blisters) with them to clinic visits.

6.2.2.2 Optional study feedback questionnaires

These questionnaires will be implemented after local regulatory approval, if required, and after consent of the trial participant. The start survey should be filled out during Visit 2 or 3, and the end survey during the EoT or EoS Visit. See Section 5.6.6 and Appendix 10.1 for more details.

6.2.2.3 Optional biobanking samples

Participation in the collection of plasma and serum for biochemical markers and DNA for pharmacogenomic markers is voluntary and only allowed after the participant has given separate consent prior to the collection of the respective blood samples. Samples will be stored at a biobanking facility for future research.

- Serum and plasma biobanking: in total two serum and two plasma samples will be taken, the sample collection should adhere to the schedule (i.e. taken at Visit 2 prior to administration of the IMP and the EoT Visit).
- DNA biobanking: in total one sample will be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.

6.2.2.4 Order of rating scales assessments

[redacted] During all clinic visits, the placebo control reminder script should be performed just prior to the MADRS assessment [redacted] The remaining scales ([redacted]) can be performed in any order.

During Visit 5, MADRS and ECG should be completed between 1 and 2 h post IMP administration followed by other COAs, as feasible. See Table 11 for the schedule of [redacted] MADRS, and ECG capture during Visit 5. During all other visits during the treatment period, COAs should be completed prior to IMP intake.

[redacted]

6.2.2.6 EoT Visit

The EoT Visit (at treatment Week 6) represents the regular end of the treatment period. The final IMP intake should occur one day before the EoT Visit. If it is found that a participant has taken the final dose of IMP in the morning of the EoT Visit, the visit should be rescheduled as soon as possible, ideally on the following day. The overall anticipated treatment duration (first IMP intake to the final IMP intake) should be 42 days; therefore, the EoT Visit is scheduled for Day 43 with a visit window of up to +2 days. See Section 3.3.4.1 for procedures with regard to premature discontinuation of the IMP.

6.2.3 Follow-up period and trial completion

For all participants who had at least one dose of IMP, the EoS Visit will be performed as described in the SoA. The sequence of visit procedures will be the same as in the treatment period. In case of early discontinuation, the procedures detailed in Section 3.3.4.1 should be followed.

EoS Visit is the final scheduled visit and the End of Study eCRF must be entered including termination of IMP and trial completion. If it is not possible for the patient to attend the EoS Visit at the study site as scheduled, a visit outside of the visit window should be performed as soon as possible. If a visit at the site is not possible at all, at least a phone contact should occur at the scheduled EoS Visit time point.

A trial participant is considered to have completed the trial if one of the following applies:

- Completion of planned follow-up period (i.e. EoS Visit completed)
- Lost to follow-up
- Refusal to be followed-up
- Death

If needed, in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

Abnormal assessments or laboratory values judged clinically relevant by the investigator will be monitored until they return to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 1569912 on the primary endpoint change from baseline in MADRS total score at Week 6. An MCPMod approach is applied to detect a statistically significant non-flat dose-response.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis of the MCPMod test is that there is a flat dose response curve comparing placebo and the BI 1569912 dose groups on the primary endpoint of change from baseline in MADRS total score at Week 6. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 1569912 over placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, while protecting the overall probability of Type I error (one-sided, α level of 10%). The pre-specified models and their parameters used for this test are outlined in Section 7.2.3.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Statistical analyses will be based on the following main analysis sets:

- Treated set (TS):
  The TS includes all participants who were randomised and treated with the IMP. The TS will be used for safety and most of the efficacy analyses. Safety analyses will be conducted using actual treatment received. For efficacy analyses, treatment assignment will be as randomised, unless specified otherwise.
- Primary analysis set (PAS)
  The PAS comprises all randomised participants who received at least one dose of IMP during the trial and had a baseline MADRS total score ≥24. The primary analysis will be performed on the PAS and will be based on assigned treatment.

Further analysis sets may be specified in the TSAP.

In general, baseline will be defined as the last available value prior to the first administration of the IMP. Further details will be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (iPDs) categories and how to handle iPDs in the analysis will be specified in the SDTM DV domain specifications, which are stored in the TMF. The iPD categories will be updated as needed. Also, the extent and impact of the receipt of incorrect trial medication will be assessed. Details will be specified in the TSAP.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:

- Death
- Treatment discontinuation
    - due to reasons related to IMP
    - due to reasons unrelated to IMP
- Change in (pharmacological or non-pharmacological) antidepressant treatment
    - Introduction of further antidepressant treatments
    - Change in existing background psychotherapy

The primary treatment effect of interest is the effect obtained at the primary time point if the participant had stayed on randomised IMP, i.e. cases of treatment discontinuation, regardless of reason, will be handled using a hypothetical approach (Table 8). Data collected after treatment discontinuation + REP will be censored and will not be included in the analysis.

Changes in antidepressant treatment will be disregarded in the primary analysis of treatment effect, i.e. they will be handled using the treatment policy approach as defined in ICH E9(R1).

Table 8 Strategies for handling intercurrent events

Intercurrent event	**Primary**	[redacted]
Death	Hypothetical	
Treatment discontinuation related to IMP	Hypothetical	
Treatment discontinuation unrelated to IMP	Hypothetical	
Change in (pharmacological or non-pharmacological) antidepressant treatment	Treatment policy	

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy. The handling of intercurrent events that are not listed will be decided during blinded review and will be documented in the TSAP.

7.2.3 Primary objective analyses

7.2.3.1 Main analyses

As defined in Section 2.1.2, the primary endpoint is the change from baseline to Week 6 in MADRS total score.

MCPMod (multiple comparison and modelling techniques) [R10-1424] is used to evaluate several possible dose response models (patterns). As a basis for the MCPMod analysis, a restricted maximum likelihood estimation (REML) based on a mixed-effect model for repeated measures (MMRM) analysis will be used to generate covariate adjusted estimates of mean change from baseline in MADRS total score at Week 6 and associated covariance matrices. The model will include fixed categorical effects of treatment at each visit and number of antidepressant treatments taken for the current episode (0 versus 1), and fixed continuous effects of baseline MADRS total score at each visit. Participants from the PAS with a baseline and at least one post-baseline value with their MADRS values of all post-baseline visits will be included in the model, according to the considered strategy for handling intercurrent events.

The primary treatment comparisons will be the contrasts between each BI 1569912 treatment arm and placebo at Week 6. Procedures to be followed if the planned analysis fails to converge will be described in the TSAP.

The dose-response relationship of these estimates from the MMRM will then be analysed using MCPMod. Thereby, several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error at 10%, one-sided) to identify the best-fitting model or subset of models.

A monotone dose-response relationship is assumed. For the PoCC testing and for the sample size calculations the following model assumptions (Table 9) and resulting graphs (Figure 2) have been selected to cover both the plausible and a diverse range of potential dose response patterns.

Table 9 Dose response pattern assumptions and rationale

Model	**Description**
Linear	Linear dose response
Emax1	50% of the maximum effect (ED50) is achieved at the 5 mg dose
Emax2	95% of the maximum effect (ED95) is achieved at the 10 mg dose
Exponential	5% of the maximum effect is achieved at the 5 mg dose, i.e. high effect only at a high dose
Sigmoid Emax	20% of the maximum effect (ED20) is achieved at the 5 mg dose, 80% of the maximum effect (ED80) is achieved at the 10 mg dose, i.e. effect of 5 mg and 10 mg are further apart (fixed hill parameter h=4)

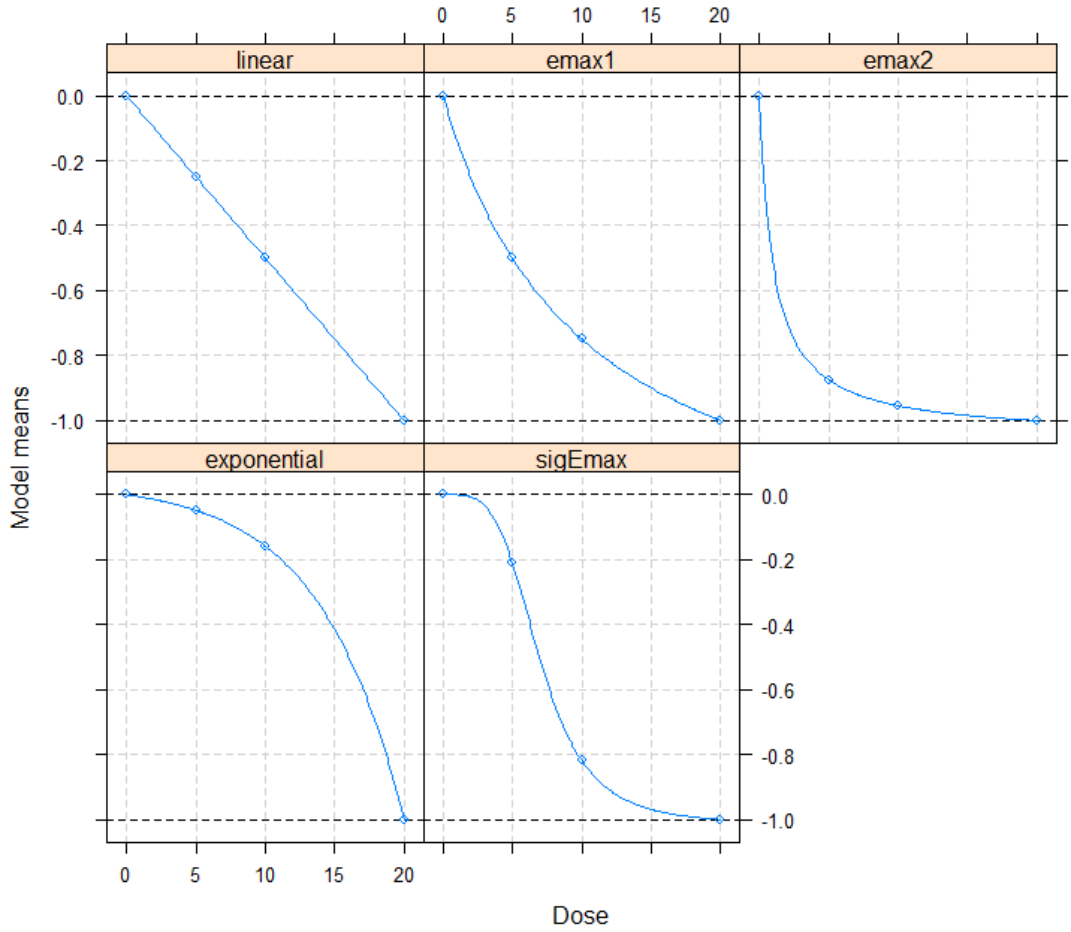


Figure 2 Shape and considered dose response patterns for the MCPMod analysis

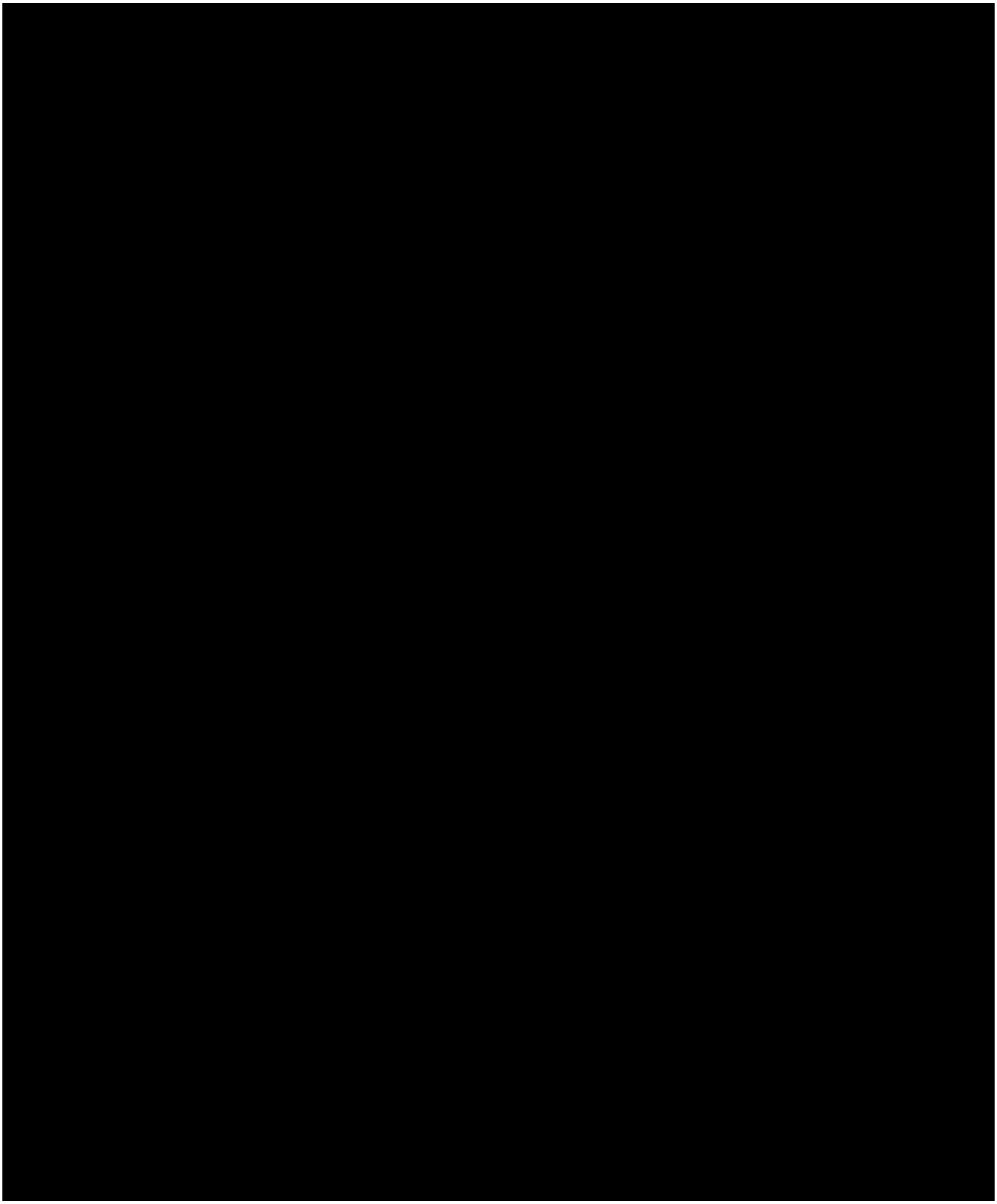
The optimal contrasts corresponding to the candidate models will be shown in the TSAP. For the final evaluation, these contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model.

A non-flat dose response is established if at least one dose response pattern is statistically significant, rejecting the null hypothesis of a flat dose response relationship on change from baseline in MADRS total score at Week 6 jointly for each of the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at a one-sided $\alpha = 10\%$.

If a non-flat dose response is established, the statistically significant model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters. The dose-response curve is then obtained via model averaging across the significant models based on the Akaike Information Criteria (AIC). The target dose(s) for further clinical development can be estimated from each significant model by incorporating information on the minimum clinically relevant effect. The totality of evidence, including further efficacy and safety parameters, will be taken into account in the selection of dose(s) for pivotal studies.

7.2.4 Secondary objective analyses

There are no secondary objectives defined in this clinical trial protocol, and therefore no secondary endpoints have been created.



7.2.6 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard Boehringer Ingelheim summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 8 days after the last dose of trial IMP, will be assigned to the on-treatment period for evaluation.

All treated trial participants will be included in the safety analysis and summarised by the actual trial medication received at randomisation. In general, safety analyses will be descriptive in nature and will be based on Boehringer Ingelheim standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between the start of treatment and the end of the REP. AEs that start before first IMP intake and deteriorate under treatment will also be considered 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of trial participants with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, and other safety-relevant data observed at screening, baseline, during the course of the trial, and at the end-of-trial evaluation will be assessed with regard to possible changes compared with findings before the start of treatment.

[redacted]

7.2.8 Interim Analyses

Exploratory interim analyses (IA) for internal project planning may be performed. The decision to conduct such an IA will be documented in the decision log. In order to support the double-blinded conduct of the trial, the trial team will be kept blinded to the individual participant's treatment group assignment at interim. An independent team will be formed to perform the interim analysis.

Personnel involved with trial conduct at study sites will not have access to unblinded data from the IA. Secure folders with restricted access will be used for the storage of unblinded interim data and results. Further operational details of who will perform the IA, and the steps to be taken to protect the integrity of the ongoing trial, will be specified in a Logistics Plan. Details of the Boehringer Ingelheim personnel who will have access to unblinded interim data or results, and how interim results will be communicated within Boehringer Ingelheim, will be specified in an Access Plan. These documents will be finalised prior to unblinding treatments at interim database lock.

Such an IA will not have an impact on the trial conduct; it will not be used for sample size recalculations or adjustments of enrolment targets.

7.3 HANDLING OF MISSING DATA

For the primary efficacy endpoint, which is continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach in the primary analysis will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model. The same holds true for further continuous endpoints which will be analysed via MMRM.

In case there is a relevant number of missing values (e.g. ≥5% for a visit), a multiple imputation approach will be used to handle missing data in the analysis of the further endpoints response and remission in MADRS.

More details for missing data handling will be included in the TSAP.

7.4 RANDOMISATION

Participants will be randomly assigned in a 2:1:1:2 ratio to one of these treatment groups:

1. Placebo
2. 5 mg BI 1569912 qd
3. 10 mg BI 1569912 qd
4. 20 mg BI 1569912 qd

Randomisation will be stratified by baseline MDD severity, defined as baseline MADRS total score <24 versus ≥24, region (USA versus Japan), and number of antidepressant treatments taken for the current episode (0 versus 1).

Boehringer Ingelheim will arrange for the randomisation and the packaging and labelling of trial IMP. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Specific parameters used for the creation of the randomisation schedule (e.g. block size) will be documented in the CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

The study is intended to show a benefit of BI 1569912 over placebo in terms of the difference in change from baseline in MADRS total score at Week 6.

The aim of this study is to show a significant non-flat dose-response curve across the different doses and placebo. The probability of success of this trial is therefore defined as the probability to obtain a significant test for non-flat dose-response curve.

The sample size calculation is based on an assumed maximum difference in change from baseline in MADRS total score of BI 1569912 vs. placebo of ≤ -4 at Week 6, as well as on the pre-specified models listed in Section 7.2.3.1. The standard deviation of change from baseline in MADRS total score is assumed to be 10 (i.e. the assumed maximum difference of ≤ -4 corresponds to a standardised effect size of ≤ -0.4). For placebo, a fixed rate of -9 change from baseline in MADRS total score at Week 6 will be considered.

The following calculations and presented operating characteristics use a sample size of 180 evaluable patients with a baseline MADRS total score ≥24 (assigned to placebo and low to high dose regimes, respectively, in a 2:1:1:2 ratio). Adjusting for a drop-out rate of approximately 18% (randomised patients not included in the PAS, or without primary endpoint assessment), the total sample size required is then approximately 222 (with 74/37/37/74 per dose group).

Using a total sample size of 180 evaluable patients, the probability for a successful trial (as defined above) was estimated using simulations. For each dose group, samples of the required size were drawn from a normal distribution.

Based on these assumptions, if the maximum difference between active doses and placebo is -4, the success probability is approximately 82% on average across the different considered dose response models. The probability to observe an effect of at least -3.5 in the trial is 65%. If the maximum difference between active doses and placebo is -5, the success probability is approximately 93% on average across the different considered dose response models. In this case, the probability to observe an effect of at least -3.5 in the trial is 83%.

If the difference between active doses and placebo is low, i.e. -1 (which is assumed to be clinically not relevant), the success probability is approximately 23% on average. The probability to observe an effect of at least -3.5 in the trial is 10%. In the case that there is no treatment benefit, the false positive probability is limited by the α-level for the significance testing of the non-flat dose-response curve of 10% (one-sided).

Table 10 provides success probabilities under different scenarios (i.e. different treatment effects and dose-response curves).

Table 10 Success probability given expected change from baseline in MADRS total score at Week 6 and a total sample size of 180 patients (with 60/30/30/60 per dose group) based on MCPMod nominal alpha-level of 10% (one-sided).

Scenario	(Assumed) true model											
Expected max. resp. diff. (BI-Plac)	Linear		Emax1		Emax2		Exponential		Sigmoid Emax		Average	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
-5	92.2	81.5	92.4	81.3	93.8	84.2	93.7	83.7	94.1	84.4	93.3	83.0
-4	81.1	63.9	81.4	63.6	83.5	65.7	82.7	65.8	83.3	66.1	82.4	65.0
-3	62.3	41.6	64.1	42.4	66.2	44.6	63.9	43.8	65.2	44.1	64.3	43.3
-2	42.3	23.1	42.3	23.4	42.4	23.4	42.9	23.7	44.1	23.9	42.8	23.5
-1	22.3	9.2	22.9	10.2	23.6	10.2	22.8	10.1	23.2	9.7	22.9	9.9
0	9.5	3.1	10.2	3.7	9.9	3.4	9.9	3.4	9.8	3.2	9.9	3.3

(1) success probability (%): significant non-flat dose-response achieved based on at least one of the candidate set models (one-sided α-level of 10%),

(2) probability (%) to observe a response difference of at least -3.5 compared with placebo for at least one modelled dose within the considered dose range.

Probabilities have been calculated using R Version 4.0.1 based on simulations (10000 simulations per scenario). Thereby the calculations for the MCPMod step have been performed using DoseFinding R-package 1.0-2.

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 Harmonised Guideline for GCP, relevant Boehringer Ingelheim SOPs, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP, or applicable regulations will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the treating physician of the trial participant.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial participants 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 rule, no trial results should be published prior to finalisation of the clinical trial report.

The certificate of insurance cover is made available to the investigator and the trial participants and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The investigator or delegate must give a full explanation to trial participants based on the participant information form. A language understandable to the trial participant should be chosen, with technical terms and expressions avoided, if possible.

The trial participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial participant's own free will with the informed consent form after confirming that the trial participant understands the contents. The investigator or delegate must sign (or place a seal on) and date the informed consent

form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may be 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.

For participating sites, a separate informed consent form will be required for participation for tokenisation of participant-level medical data (see Section 5.6.5). Consent for tokenisation may be provided at any time during study participation, but preferably during screening.

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 participant protection and reliability of the results, as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH GCP E6, 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 designee, IRB/IEC, or 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.

In order to achieve a high level of standardised processes, data collection of efficacy endpoints is coordinated centrally: a service provider has been selected to support tasks related to the neuropsychological assessments. These services include:

- Necessary rater pre-qualification
- Site rater training for COAs used as primary and further endpoints
- Provision of rater materials
- Central quality review of MINI, HDRS-17, MADRS, and PCRS. For this purpose, the MINI, HDRS-17, MADRS, and PCRS interviews will be audio recorded

Details of rater prequalifications, rater training, rater materials (including assessments), and of the central review procedures will be available in separate documents; qualification methodology document and data analysis methodology filed in the TMF.

8.3 RECORDS

Case Report Forms for individual trial participants will be provided by the sponsor. See 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

A detailed description of the transmission of electronic data (i.e. data flow) is provided in the data management plan.

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial participant. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal, and **a**ccurate. Changes to the data in EDC should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data, or the discrepancies must be explained. Electronic records, i.e. clinician administered assessment data, related audio recordings (for central review), and patient reported outcome data entered into the tablet will be regarded as source data. These may be further analysed by the third-party vendor.

The current medical history of the participant may not be sufficient to confirm eligibility for the trial, and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least 1 documented attempt to retrieve previous medical records. If this fails, a verbal history from the participant, documented in their medical records, would be acceptable.

The electronic version of the ECG is regarded as source documentation. Dated and signed printouts should be stored in the patient's medical file.

Copies of source documents necessary for central clinical review of COAs and ECGs, as applicable, will be provided to the corresponding vendor. Before sending or uploading those copies, the investigator must ensure that all participant identifiers (e.g. participant's name, initials, address, phone number, social security number) have been properly removed or redacted from all copies of the participant's source documents.

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

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

- Participant identification: sex, year of birth (in accordance with local laws and regulations)
- Participant participation in the trial (substance, trial number, participant number, date participant was informed)
- Dates of participant's visits, including dispensing of trial IMP
- 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)
- Completion of participant's participation in the trial (end date; in case of premature discontinuation, document the reason)
- Prior to allocation of a trial participant to a treatment in 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 participant, or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the participant eligible for the clinical trial

8.3.2 Direct access to source data and documents

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

In the event of force majeure or other disrupting circumstance (e.g. pandemic or war; see Section 6), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site, such as source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralised monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage, and processing of participant data in accordance with principles 7 and 12 of the WHO GCP handbook.

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect participants' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- In the event of an accidental or unlawful destruction, loss, alteration, unauthorised disclosure, or access to personal data ("breach"), the sponsor has implemented procedures and measures to promptly address and mitigate any risk to the participant. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the participant(s) in accordance with applicable data protection law
- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access

Individual participant data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

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

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

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

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

8.6 TRIAL MILESTONES

The **first act of recruitment** represents the **start of the trial** and is defined as the date when the first trial participant in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last trial participant in the whole trial ("last participant completed").

The "**last participant last treatment"** (LPLT) date is defined as the date on which the last trial participant in the whole trial is administered the last dose of trial IMP (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial IMP until 30 days after LPLT at their site.

The "**last participant last visit primary endpoint**" (LPLVPE) date is defined as the date on which the last randomised participant reaches the Week 6 Visit (EoT Visit).

Early termination of the trial is defined as the premature termination of the trial due to 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 sponsor will prepare a clinical trial report within 1 year from the end of trial.

A final report of the clinical trial data will be written only after all trial participants have completed the trial to incorporate and consider all data in the report.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their *curricula vitae*) will be filed in the ISF.

The investigators will have access to the Boehringer Ingelheim web portal, Clinergize, to access documents provided by the sponsor.

Boehringer Ingelheim has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to:

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of Clinical Trial Managers, Clinical Research Associates (CRAs), and investigators of participating countries

In the participating countries, the trial will be performed by the respective local or regional Boehringer Ingelheim organisation (Operative Unit [OPU]) in accordance with applicable regulations and Boehringer Ingelheim SOPs.

Data management, statistical evaluation, and reporting of clinical trial results will be done by Boehringer Ingelheim according to Boehringer Ingelheim SOPs.

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

A central laboratory service, a speciality laboratory for ECG, a service provider for data collection and review related to COAs, and an IRT vendor will be used in this trial. Details will be provided in the IRT manual and central laboratory manual, available in the ISF.

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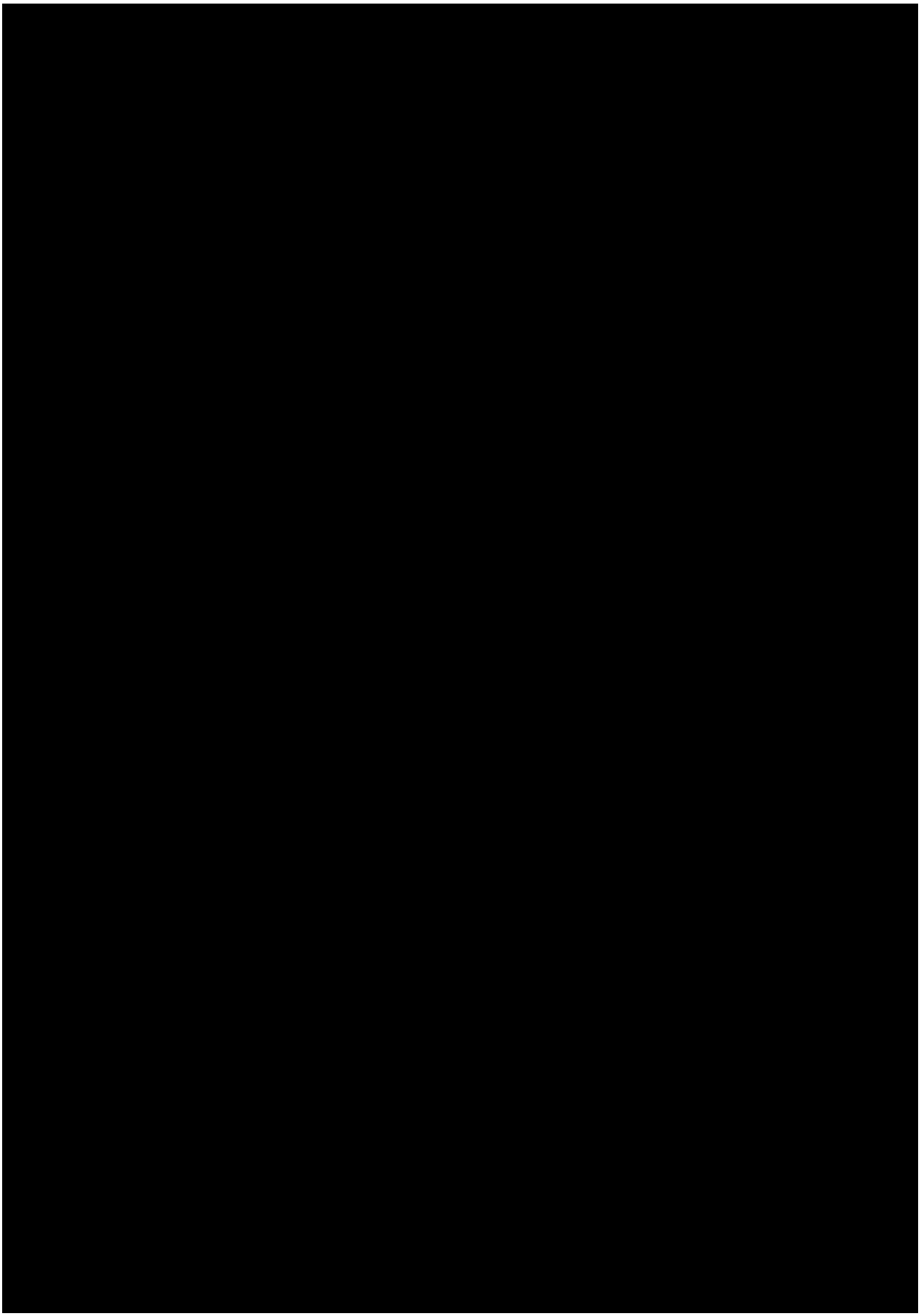
10. APPENDICES

10.1 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaire:

This trial will include an option for participants to complete a 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval, if required, and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.



11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

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

Title: A 6 week, multi centre, randomised, double-blind (participant and investigator), placebo controlled, dose finding trial to evaluate the efficacy, tolerability, and safety of different doses of oral BI 1569912 in patients with major depressive disorder

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	17 Apr 2024 17:00 CEST
Approval-Clinical Program Leaders		17 Apr 2024 17:17 CEST
Approval-Clinical Trial Leader		18 Apr 2024 21:20 CEST
Verification-Paper Signature Completion		25 Apr 2024 11:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed