Clinical Trial Protocol

	Document Number:	**c30650673-03**
EudraCT No. **EU Trial No.**	NA	
BI Trial No.	1402-0014	
BI Investigational Medicinal Product(s)	BI 1358894	
Title	A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants	
Lay Title	A home-based study using mobile technology to test whether BI 1358894 is effective in people with depression	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Telephone: +[redacted] Fax: +[redacted] Email: [redacted]	
Principal Investigator	[redacted] Phone: +[redacted] Fax: +[redacted] E-mail: [redacted]	
Version and Date	**Version:** 3.0	**Date:** 20-Jul-2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	24-Mar-2020
Revision date	20-Jul-2021
BI trial number	1402-0014
Title of trial	A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants
Principal Investigator	[redacted] Phone: +[redacted] Fax: +[redacted] E-mail: [redacted]
Trial site(s)	[redacted]
Clinical phase	II
Trial rationale	Based on the pre-clinical data and the data from the proof of clinical principle (PoCP), there is reason to believe that BI 1358894 may be efficacious in major depressive disorder (MDD) and that there are no safety signals precluding this assessment. The decentralized clinical trial (DCT) model will be used to conduct this study, bringing the clinical trial to study participants in their homes through deployment of mobile research nurses. This model integrates telemedicine technology into the clinical research process and supports the management of research activities remotely, including data collection. With more advanced technology now available and the understandable desire to reduce participant burden, DCTs allow for a more patient-centric alternative for conduct of clinical trials. The DCT model will be piloted in this trial, offering the opportunity to assess the safety and efficacy of BI 1358894 in participants with MDD with a decentralized approach.
Trial objective(s)	The trial will be performed to compare BI 1358894 with placebo in participants with MDD with inadequate response to antidepressants (selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI). The primary comparison of interest is the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6 summarized per arm by the adjusted mean. The primary trial objective is to assess superiority of BI 1358894 verses placebo in a DCT model.
Trial endpoints	Primary endpoint: • Change from baseline in MADRS total score at Week 6 Secondary endpoints: • Response defined as ≥ 50% MADRS reduction from baseline at Weeks 6 • Change from baseline in State-Trait Anxiety Inventory (STAI) scores at Week 6 • Change from baseline in Clinical Global Impression Severity Scale (CGI-S) score at Week 6

	• Change from baseline in Symptoms of Major Depressive Disorder Scale (SMDDS) total score at Week 6 • Change from baseline in Patient Global Impression Severity Scale (PGI-S) score at Week 6 • Patient Global Impression Severity Scale (PGI-C) score at Week 6
Trial design	This study will be conducted as decentralized clinical trial (DCT). It is a 6-week parallel-group, randomized, double-blinded, placebo-controlled Phase II trial in participants with MDD with inadequate response to ongoing treatment of an SSRI or SNRI. This trial will be conducted in the US, with [redacted] as the single decentralized site enrolling in the study.
Total number of participants randomised	164
Number of participants on each treatment	BI 1358894 125 mg = 82 Placebo = 82
Diagnosis	Participants with an established diagnosis of Major Depressive Disorder confirmed at the time of screening by Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) (SCID-5) Clinical Trials version.
Main in- and exclusion criteria	Inclusion criteria: 1. Established diagnosis of Major Depressive Disorder, single episode or recurrent, as confirmed at the time of screening by the Structured Clinical Interview for DSM-5 (SCID-5), with a duration of current depressive episode ≥ 8 weeks and ≤ 18 months at the time of screening visit. 2. Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 22 at screening, as confirmed by a trained rater. In addition, trial participants must have a score of ≥ 3 on the Reported Sadness item on MADRS. 3. A documented ongoing monotherapy treatment of ≥ 8 weeks at the screening visit, with a protocol specified SSRI or SNRI at adequate dose (at least minimum effective dose as per prescribing information and as confirmed per detectable drug levels in the screening blood or urine sampling). 4. Male and female participants, 18 to 65 years of age, both inclusively at the time of consent. 5. Women of child-bearing potential (WOCBP)[1] able and willing to use two methods of contraception, which include one highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1%, plus one barrier method. Exclusion criteria: 1. Per DSM-5, had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder or MDD with psychotic features as assessed by the SCID-5 at the time of screening. 2. Diagnosis of any other mental disorder (in addition to those as described in Exclusion Criterion #1) that was the primary focus of treatment within 6 months prior to screening or at baseline (as per clinical discretion of the investigator). 3. Diagnosis with antisocial, paranoid, schizoid or schizotypal personality disorder 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. 4. Diagnosis of a substance related disorder within 3 months prior to screening visit (with exception of caffeine and tobacco). 5. History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial. 6. History of 4 or more unsuccessful monotherapy treatments (at adequate dosage

	and duration, per local prescribing information of the product) with an approved antidepressant medication for the current ongoing major depressive episode. These include ongoing monotherapy treatment with a protocol specified SSRI or SNRI as described in Inclusion Criterion #3. 7. Any suicidal behavior in the past 12 months prior to screening (per investigator judgement including an actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour). 8. Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months prior to screening or at screening or baseline visit (i.e. active suicidal thought with method and intent but without specific plan, or active suicidal thought with method, intent and plan).
Test product(s)	BI 1358894
dose	125 mg daily
mode of administration	per os / oral (p.o.)
Comparator product(s)	Placebo
dose	Matching
mode of administration	per os / oral (p.o.)
Duration of treatment	6 weeks
Statistical methods	A two-sided test using the mixed model with repeated measurements (MMRM) model will be carried out to assess the primary endpoint, with an α level of 10%. The primary analysis will be the restricted maximum likelihood (REML) based approach using a MMRM comparing the change from baseline of MADRS score at week 6. Response rate over the 6-week treatment period will be assessed using the MADRS total score. Participants with ≥ 50% reduction in MADRS total score from baseline to Week 6 are considered responders. The proportions of participants achieving response at Week 6 will be summarized as the frequency and percentage of participants in each treatment arm. In addition, if a sufficient number of responders is observed, a logistic regression model adjusted for treatment (BI 1358894 or placebo) will be used to calculate the odds ratio for response between the BI 1358894 arm and placebo and corresponding confidence interval. Change from baseline to Week 6 in STAI, CGI-S and SMDDS scores will be analyzed using an MMRM model similar to the model described for the primary endpoint analysis.

[1] A woman is considered of childbearing potential (WOCBP), 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.

FLOW CHART

Trial Periods	**Screening[a]**	**Randomization[b]**	**Treatment**							**Early D/C**	**Follow-up/End of Study**
Visit[1]	**1**	**1A**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8 / EOT[5]**	**eEOT[5]**	**9 EoStudy[6]**
Week			0	1	2	3	4	5	6		10
Day	-28 to -3	-7 to -1	1[4]	8 ±1	15±1	22 ±1	29 ±1	36 ±1	43 ±2		EOT (early drug d/c date) +28 +4 days
Informed consents [2] (include consents for participant's duplicate check)	X										
Demographics	X										
Medical history	X										
SCID-5	X										
ATRQ	X										
Physical examination[7]	X								X	X	X
Vital signs, incl. body weight	X[7]		X		X		X		X	X	X
Laboratory tests (incl. pregnancy test) [8]	X		X		X		X		X	X	X
12 lead-ECG	X		X		X		X		X	X	X
Review of in-/exclusion criteria	X	X									
Randomization		X									
Assignment (IRT) and dispense of trial drug[9]		X			X		X				
Administration of trial drugs			X		X		X				
Drug Accountability [10]					X		X		X	X	
Sample for confirmation of blood/urine levels SSRI/SNRI[11]	X								X	X	
PK Sampling BI 1358894[12]			X		X		X		X	X	X
Optional sampling for biobanking of serum, plasma and DNA[13]			X[14]						X[14]	X[14]	
MADRS	X		X	X	X		X		X	X	
SMDDS [d]			X	X	X		X		X	X	
PGI-S [d]			X	X	X		X		X	X	

FLOW CHART (cont.)

Trial Periods	**Screening[a]**	**Randomization[b]**	**Treatment**							**Early D/C**	**Follow-up/End of Study**
Visit[1]	**1**	**1A**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8 / EOT[5]**	**eEOT[5]**	**9 EoStudy[6]**
Week			0	1	2	3	4	5	6		10
PGI-C [d]									X	X	
STAI [d]			X	X	X		X		X	X	
[redacted]											
[redacted]											
C-SSRS	X[15]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]
CGI-S			X	X	X		X		X	X	
[redacted]											
[redacted]											
[redacted]											
Medication adherence			↔	↔	↔	↔	↔	↔	←		
Smartphone App training/ set-up [20]		X									
All AEs/SAEs/ AESIs	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Substance Use	X		X	X	X	X	X	X	X	X	X
Termination of trial medication									X[21]	X	
Completion of participant's participation											X
Participant Feedback Questionnaire[22]											X

[a] Screening visit may be completed in multiple days, for example: with first day SCID-5, C-SSRS, demographics (completed via videoconferencing) and second day MADRS, repeat C-SSRS, medical history, patient report questionnaires, physical exams, vitals and laboratory. Note, for safety, C-SSRS needs to be completed on each day that other assessments/procedures are completed, if multiple days are needed for screening. Screening MADRS must be completed within 21 days of randomization (repeat of MADRS is allowed once to maintain within this 21-day window). Physical exams and medical history will be conducted by physician interview and guided assessments through videoconference calls (a method known as telemedicine).

[b] Randomization and assignment of trial drugs via IRT system may occur up to 7 days before Visit 2 to allow for the drug kit assignment in the IRT system, as well as shipment and delivery of trial drugs to the participant's home. Training and set-up of Smartphone App may start at Visit 1 and repeated/continued to this visit, however all must be completed within this time between randomization and Visit 2. All eligibility criteria must be confirmed, including C-SSRS, confirmation of positive blood levels of SSRI/SNRI in the screening lab, before randomization can be registered in IRT.

[c] On day of Visit 2, all assessments, including ClinROs (Clinician Reported Outcomes: MADRS, CGI-S and C-SSRS) and PROs (Patient reported outcomes) assessments need to be completed before dosing, not including [redacted]

[d] PROs = self-reported assessments. All scales, including PROs, are recommended to be completed in the order top down as indicated here on the Flow Chart, most importantly the SMDDS must be completed before the PGI-S and PGI-C. If participant discontinues early, only one PGI-C will be collected at eEOT Visit [redacted]

[1] As part of the Decentralized Clinical Trial (DCT) model, study visits will be conducted in several ways: i) at participant's home by mobile study nurse; ii) by videoconference only (indicated by 💻 symbol); and iii) by telephone contact only (indicated by ☎ symbol). Unless indicated, visits are conducted by mobile study nurse at participant's home.

[2] Informed consent must be completed prior to any trial related procedure, may also be done at an extra visit up to 2 weeks before V1.

[3] ☎ indicates telephonic contact visits. Participant's visits to be conducted by telephone contact, but a videoconference may also be conducted, depending on clinical needs.

[4] Day 1 = Day of first intake of randomised medication.

[5] EOT (end of treatment) for participants who complete the treatment period, Week 6 (Visit 8) will be completed.

Participants who discontinue (D/C) trial drug prematurely should ideally be observed until trial end as if they were still receiving blinded trial treatment. All early D/C participants will complete the FUP visit (early drug discontinuation date + 28 days) for a full trial safety follow-up. There are 2 options for observing participants after premature drug discontinuation. Option 1 is most preferred, and Option 2 is only when Option 1 can't be completed.

Early D/C Participants:

Option 1: An eEOT Visit must be conducted within 7 days of the last dose of trial medication for participants who agree to conduct regularly scheduled visits after premature drug discontinuation. Thereafter, participants will be followed up according to the regular visit schedule for both home and phone visits, including FUP visit. All visit procedures will be completed, with the exception of trial drug procedures and PK samples, Meal intake, and PGI-C collections.

If FUP visit (early drug discontinuation date + 28 days) coincides with and can be completed at a visit prior to the planned Visit 8, no additional FUP visit is needed. Assessments under both FUP and that visit need to be completed without duplicates. If planned FUP is within 7 days prior to planned Visit 8, then no FUP is needed, Visit 8 should be completed.

Option 2: An eEOT Visit must be conducted within 7 days of the last dose of trial medication for participants, FUP visit, and then Visit 8. All FUP and Visit 8 procedures will be completed, with the exception of trial drug procedures and PK samples, Meal intake, and PGI-C collections. If FUP visit (early drug discontinuation date + 28 days) is within 7 days prior to planned Visit 8, then no FUP is needed; V8 should be completed, however, the completion of participation must be completed.

[6] After the EoStudy visit (=individual participant's end of the study) the investigator will report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI Serious Adverse Event (SAE) form. See section 5.3.6.2.1.

[7] Physical examinations will be conducted via telemedicine with the mobile nurse conducting the physician-guided examination through videoconference with study investigator or physician. Vital signs at Visit 1 will include the collection of height. Measurements of vital signs should precede blood sampling.

[8] Urine drug screens will be completed at screening visit only. For WOCBP, a serum pregnancy test will be performed at screening and urine pregnancy tests at all home visits beginning with V2. If a urine pregnancy test is positive, a serum test needs to be performed for confirmation.

[9] Assignment of trial drugs via IRT system and dispensing may occur up to 7 days before actual visit to allow for the drug kit assignment in the IRT system, as well as shipment and delivery of trial drugs to the participant's home. Once trial drug is received at participant's home, site staff will confirm drug fit for use and dosing of (received) trial drugs will be done on day of planned visit with mobile nurse at participants' home.

[10] Drug accountability will be completed for drug compliance by pill counts of the trial medication (used/unused blister and covering packages) returned/shipped back to site. Last regular intake of the trial drug is the day before EOT visit.

[11] Blood sample for confirmation that participants are on SSRIs or SNRIs at Visit 1 and EOT; urine sample only collected at Visit 1 (except for Duloxetine which is serum only).

[12] PK-blood trough samples to be collected pre-dosing, within 30 minutes before drug administration, and will be taken together with safety lab. Meal intake will also be collected at each PK sample collection. No dosing is done at Visit 8/EOT and FUP visit, therefore PK may be completed at any time. If participant discontinues early, only one PK sample will be collected at eEOT Visit.

[13] Collection of biobanking samples is optional. Samples will be collected at Visit 2 (serum, plasma and DNA samples) and Visit 8 (serum, plasma only). If participant discontinues early, the Visit 8 serum and plasma sample will be collected at eEOT Visit. Participants are required to sign a separate informed consent for biobanking. Samples will be stored at a biobanking facility for future research.

[14] One sample for DNA biobanking will be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.

[15] C-SSRS: Columbia Suicide Severity Rating Scale baseline/screening scale.

[16] C-SSRS: Columbia Suicide Severity Rating Scale since-last-visit scale; version to be completed after the first C-SSRS baseline/screening version was completed. At Visit 1A, C-SSRS will be completed before randomization.

[redacted]

[21] For participants who early discontinue treatment and following Option 1, this does not apply at Visit 8 as this would have been completed at eEOT.

[22] At the End of Study, participants will be asked to complete a feedback questionnaire, provided through a separate website (BI's MyStudyWindow website). See section 5.6.5 for details.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Variance
App	(Smartphone) Application
AST	Aspartate Aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
AUC	Area under the Curve
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BI	Boehringer Ingelheim
[redacted]	[redacted]
CA	Competent Authority
CCK-4	Cholecystokinin Tetrapeptide
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
CGI-S	Clinical Global Impression Severity Scale
ClinRO	Clinician Reported Outcome
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CYP	Cytochrome P450
DBL	Database Lock

DCT	Decentralized Clinical Trial
D/C	Discontinue
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, v5
EC	Ethics Committee
EC50	Half maximal effective concentration
eCDF	Empirical Cumulative Distribution Function
ECG	Electrocardiogram
[redacted]	[redacted]
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
eDC	Electronic Data Capture
EGFR	Estimated Glomerular Filtration Rate
EoStudy	End of Study
EOT	End of Treatment
[redacted]	[redacted]
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
FUP	Follow Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GMP	Good Manufacturing Practice
HA	Health Authority
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council on Harmonisation

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine System
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry)
LPLT	Last Patient Last Treatment
LS	Least Square
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at random
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
MGH	The Massachusetts General Hospital
MMRM	Mixed effects model for repeated measurements
MRD	Multiple Rising Dose
nM	Nanomole
NIMH	National Institute for Mental Health
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporter Protein
OPU	Operative Unit
PANAS	Positive And Negative Affect Scales
P-gp	P-Glycoprotein
PGI-C	Patient Global Impression of Change Scale
PCG-S	Patient Global Impression Severity Scale
PK	Pharmacokinetics
p.o	Per Os
PoCP	Proof of Clinical Principle
PRO	Patient Reported Outcomes
PV	Pharmacovigilance

QD	quaque die (once a day)
QIDS-SR (D)	Quick Inventory of Depressive Symptomatology – Self Report Daily
QTcF	Corrected QT interval by Fredericia
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SD	Standard deviation
[redacted]	[redacted]
SIB	Suicidal Ideation and Behavior
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
STAR*D	Sequenced-Treatment-Alternatives to Relieve Depression
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMS	Transcranial Magnetic Stimulation
TRPC	Transient Receptor Potential Channel
TS	Treated Set
TSAP	Trial statistical analysis plan
UGT	UDP-Glucuronosyltransferase
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
VCT	Verified Clinical Trial
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Major Depressive Disorder (MDD) is a debilitating disease that is difficult to treat, even when using systematic antidepressant strategies. In the National Institute for Mental Health (NIMH) funded Sequenced-Treatment-Alternatives to Relieve-Depression (STAR*D) trial in more than 4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residual symptoms [R16-5475] which significantly impacted the patients' quality of life.

Studies have also reported that up to 50% of patients diagnosed with MDD do not respond to an initial antidepressant treatment of adequate dose and duration [R16-5475]. When monotherapy with a Selective Serotonin Reuptake Inhibitor (SSRI) / Serotonin Norepinephrine Reuptake Inhibitor (SNRI) is insufficient, clinicians employ different augmentation strategies including add-on treatment with lithium, thyroid hormones, antiepileptic agents or atypical antipsychotics [R17-0163]. When augmentation strategies fail, somatic therapies such as electroconvulsive therapy (ECT), vagal nerve stimulation or transcranial magnetic stimulation (TMS) can be used.

In clinical practice, telepsychiatry has become an accepted method of managing many psychiatric conditions, and its adoption has improved access to mental health care [R20-0034]. The literature in this field points to substantial growth in evidence to support equivalence of telepsychiatry care when compared to treatment rendered in-person [R20-0034, R19-4127, R19-4092). In clinical trials, preliminary efforts employed various telemedicine technologies (ranging from webcams and telephones to smartphone apps and videoconferencing) that demonstrated how decentralized trials can augment traditional research and development methods and provide data from a broader, more diverse group of patients in real-world practice settings [R20-0033].

Given that many assessments in psychiatric research are interview-based, bringing telepsychiatry to mental health research is an inevitable and logical extension of mental health care. Benefits of telemedicine for clinical research in MDD include diminished patient burden, broadened access to clinical research for the target population by enabling home participation, increased likelihood that the MDD study population represents the demographics of the U.S. population with this condition, and potentially accelerated study conduct, which in turn, can speed patient access to potentially important treatments [R19-4127, R19-4092, P10-04017].

1.2 DRUG PROFILE

Transient Receptor Potential Cation (TRPC) channels 4 and 5 are involved in the regulation of neuronal excitability. They are highly expressed in the amygdala, frontal cortex, hippocampus, and hypothalamus [R15-3888] which are the brain regions involved in modulation and processing of emotion and affect.

BI 1358894 is a TRPC4/5 inhibitor that is being developed for symptomatic treatment of Major Depressive Disorder [redacted]

Therefore, it is expected that treatment with BI 1358894 has the potential to improve affective symptoms and emotion control, especially in patients with MDD who inadequately respond to the current standard of care (SSRI; SNRI) [redacted]

Mode of action

BI 1358894 is a highly potent and selective TRPC4/5 inhibitor (transient receptor potential cation channel, subfamily C, members 4 and 5). It has the potential to address core symptoms of MDD and BoPD as it targets TRPC4/5 ion channels. TRPC4 and TRPC5 are highly expressed in pyramidal neurons of the amygdala in the frontal cortex, hippocampus, and hypothalamus, brain areas that are involved in circuits contributing to emotional control. It is hypothesized that in patients with mood disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts and anxiety [R16-5473].

BI 1358894 is thought to decrease neuronal excitability leading to normalization of the activation state of limbic circuits which are known to be important for emotional control. Therefore, it is expected that augmentation treatment with BI 1358894 has the potential to improve symptoms of patients with MDD who do not adequately respond to monotherapy treatment with SSRIs/SNRIs.

Data from non-clinical studies

[redacted]

[redacted]

Data from clinical studies

Overall, 217 healthy volunteers and 73 participants with MDD had been exposed to BI

[redacted]

Key pharmacokinetic characteristics

[redacted]

[redacted]

Drug interactions

[redacted]

[redacted]

Residual Effect Period
The Residual Effect Period (REP) of BI 1358894 is 28 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For a more detailed description of the BI 1358894 profile, please refer to section 1.4 and the current IB [c10354149]. For the most frequently reported adverse events refer to Table 1.4.2: 1.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Despite the array of available treatment options for patients with MDD, there remains significant unmet medical need in patients who either do not respond to or do not tolerate current augmentation approaches (e.g., atypical antipsychotics, lithium) or in cases where these are either not available or unsuitable. A product that would show similar efficacy to the above-mentioned augmentation treatments, but without the side effects (e.g., weight gain, akathisia, somnolence, abuse potential), would constitute a major medical advance.

Based on the pre-clinical data and the data from the proof of clinical principle (PoCP), there is reason to believe that BI 1358894 may be efficacious in MDD and that there are no safety signals precluding this assessment.

The underlying hypothesis of the therapeutic concept is that stress and emotion dysregulation are core features of MDD and that a reduction of these abnormalities will lead to a decrease of the symptom burden related to the depressive symptomatology, including negative valence, anxiety and rumination. If that is achieved, such a treatment approach will lead to a significant improvement in disease burden and an improvement in overall functioning.

To address future scientific questions, participants will be asked in this trial to voluntarily donate biospecimens for banking (please see section 5.5). If the 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 less likely to experience an adverse event, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

The decentralized clinical trial (DCT) model will be used to conduct this study. This model integrates telemedicine technology into the clinical research process and supports the management of research activities remotely, including data collection. [redacted] will be the site responsible for the conduct of this DCT.

Clinician Reported Outcomes (ClinROs) assessments that are commonly and traditionally used to assess the efficacy of investigational products for MDD will be employed in this DCT but will be administered via telemedicine. Similar to interviews administered in-person, telemedicine-administered ClinROs are administered by an investigator or sub-investigator, occur "live" with the subject (i.e. in real-time, so each party can observe the other), are documented in real-time by the investigator, and can be recorded. The difference in the methodology is that the investigator or sub-investigator administers the ClinRO during a videoconference rather than physically being together with the subject.

In 2011, the REMOTE trial was the first randomized controlled clinical trial to be conducted under a U.S. IND (Investigational New Drug application) that enrolled and managed study participants entirely remotely using the Internet and smartphone technology, with no participant visits to investigator sites [R20-0033, R20-0032]. Though the resulting efficacy observations were consistent with conventional trials, the trial was terminated early due to recruitment challenges [R20-0032]. Following the REMOTE trial, other studies have been conducted using a decentralized model across different therapeutic areas [R20-0033].

For this study, [redacted] will apply a DCT model that will bring the clinical trial to study participants in their homes through telemedicine using a study-issued smartphone and through deployment of mobile research nurses. [redacted] will use its technology platform to support the conduct this study. The [redacted] platform is also utilized as a mobile application downloaded to the participant's study-issued smartphone, enabling remote management of all research activities in this study. Given that participants can participate from their homes, regardless of where they live, the enrolled MDD population is expected to represent the real-world U.S. MDD population more closely.

With more advanced technology now available and the understandable desire to reduce participant burden, DCTs allow for a more patient-centric alternative for conduct of clinical trials. The DCT model will be piloted in this trial, offering the opportunity to assess the safety and efficacy of BI 1358894 in participants with MDD with a decentralized approach.

1.4 BENEFIT - RISK ASSESSMENT

The overall safety profile of BI 1358894 is outlined in the current IB c10354149.

1.4.1 Benefits

This is an experimental drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. Potential efficacy has been demonstrated in pre-clinical and PoCP data.

BI 1358894 is a highly potent and selective TRPC 4/5 inhibitor (transient receptor potential cation channel, subfamily C, members 4 and 5). It has the potential to address core symptoms of MDD as it targets TRPC 4/5 ion channels. TRPC4 and TRPC5 are highly expressed in pyramidal neurons of the amygdala in the frontal cortex, hippocampus, and hypothalamus, brain areas that are involved in circuits contributing to emotional control.

It is hypothesized that in participants with mood disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts and anxiety [R16-5473]. Therefore, it is expected that treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in participants with MDD.

1.4.2 Risks

In a comprehensive package of safety pharmacology, genetic toxicology, general toxicology, and nonclinical studies, BI 1358894 was demonstrated to be safe in humans for up to 13 weeks. Based on the mode of action, the pharmacological target, non-clinical toxicology data and clinical data, BI 1358894 is not considered a high risk compound for clinical studies. As in other clinical trials, trial participants are exposed to the risks related to the exposure to the trial medication and to the risks of the trial procedures.

While there are no precedent clinical data implicating association between TRPC4/5 antagonism and Suicidal Ideation and Behavior (SIB), in the interest of ensuring participant safety, trial participants will be proactively screened and monitored throughout the trial for SIB in accordance with available regulatory guidance.

Because psychoactive drugs may impair thinking, judgment, and/or motor skills, participants should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities. It is recommended that participants should exercise caution when driving or operating machinery.

Participants will be closely monitored during the trial participation (including AE monitoring beyond planned visits and assessment of suicidal ideation during visits) to ensure that worsening of pre-existing conditions or any newly occurring events are detected and any necessary actions taken according to stopping criteria.

BI 1358894 is a highly specific inhibitor of TRPC 4/5 channels, which are predominantly located in the CNS. All investigation into distribution and function of TRPC 4/5 (preclinical and clinical) so far have not identified any interference with the immune system, the respiratory system or the cardio-vascular system.

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

- The mode of action does not appear to have a substantial effect on clinically relevant organs (e.g. respiratory or cardiovascular system) critically affected by COVID-19
- There is currently no evidence that intake of BI 1358894 leads to immunosuppression
- There is currently no evidence that their underlying disease (MDD) makes the patients at higher risk to SARS-CoV-2 infection or to develop severe COVID-19
- The MDD patients are relatively young patients (30 – 50 years) and in general without common co-morbidities associated with severe course of COVID-19

Therefore, the risk for subjects or patients participating in these studies will not differ from the current general risk for humans of SARS-CoV 2 infection with all its potential consequences. A specific SARS-CoV 2 PCR serving as a tool for inclusion or exclusion of trial participants during the screening phase is not foreseen, since it is not believed that study substance implies an elevated risk for the patient to develop COVID-19. It is also not believed that a SARS-CoV2 infection or clinical apparent COVID-19 impacts the activity of the investigational compound.

As part of the screening safety procedures, every participant will be assessed thoroughly, and individual benefit-risk assessments are made prior to study entrance and during the study by the investigator in respect of SARS-CoV2 infection. The investigators will take the totality of information related to each single participant, including but not limited to physical exam, vitals, ECG, safety labs, etc., and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment. Considering all aspects, the investigator will decide upon each participant's inclusion and continued participation in the trial. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the participant and the mobile nurse.

For details on treatment related risks, refer to CTP section 1.2 and the IB, version 6 [c10354149].

Table 1.4.2:1 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 1358894		
Most commonly reported AEs in Phase I were: • Headache • Dizziness • Orthostatic intolerance • Fatigue • Disturbance in attention • Dyspepsia • Nasopharyngitis	All reported AEs were of mild or moderate intensity. None of the participants experienced any serious SAE or relevant alterations in laboratory parameters, vital signs, and Electrocardiogram (ECG). Refer to IB for more details	Management of symptoms, evaluation, and follow-up as needed to ensure participant safety, per investigators clinical judgment.
Concomitant use of: • sensitive substrate of CYP2B6 • Strong inducers of CYP3A4	Based on current non-clinical and BI 1358894 drug-drug interactions data, use of certain concomitant medications may increase or decrease such medications or BI 1358894. Refer to the Investigator Site File (ISF) for more information on restricted medications.	Participants on these medications will be excluded from trial and use of these drugs will be restricted during the treatment period. If such medication is used during the trial for some reason, Investigator should stop either this medication or Investigational Medicinal Product (IMP) per the clinical judgment.

Table 1.4.2:1 Overview of trial related risks (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product - BI 1358894		
Concomitant use of: • Statins	Drug-drug interactions suggest a minor to moderate increase in rosuvastatin levels when concomitantly taken with BI 1358894. This interaction takes place on an OATP transporter level and is expected to affect all statins.	Participants on statins should be monitored for statin related toxicity including signs of myopathy weakness, muscle pain, etc. along with clinical lab results. If statins are concomitantly used during the trial, the highest dose should not be taken together with the investigational compound. If participant in this trial is on the highest recommended statin dose, investigator should consider changing the statin dose to the next lower dose recommended for the respective statin if appropriate.
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 participant safety.

Table 1.4.2:1 Overview of trial related risks (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
BI 1358894 - Placebo		
• Worsening of the depression • Occurrence or increase of suicidality	Even though mitigation measures are applied, this cannot be completely ruled out	Participants will remain on their stable anti-depressive treatment with an SSRI/SNRI and psychotherapy, where applicable. Placebo is adjunctive to this treatment. Frequencies of visits with suicidality assessments are optimized. Suicidal participants will be excluded from trial participation (refer to section 3.3.4.1)
General risk of psychoactive drugs		
• Impair thinking, judgment, and/or motor skills	Psychoactive drugs are known to potentially cause unwanted side effect on brain function.	Participants should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.

Table 1.4.2:1 Overview of trial related risks (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures		
General discomfort • Blood draw	The potential risks of a blood draw include fainting and pain, bruising, swelling, or rarely infection 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 withdrawal per participant during the trial will be approximately up to 83 mL over 14 weeks. This amount may be exceeded if additional unscheduled (in case of necessary safety follow-up) monitoring of laboratory results is needed.	Management of discomfort, evaluation, and follow-up as needed to ensure participant safety. No health-related risk is expected from this 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 when BI 1358894 is administered.	First dose of BI 1358894 administered with mobile nurse oversight and safety videoconference visit at Week 1. Monitoring and management of symptoms and treatment as needed, including discontinuation of trial treatment as per investigators clinical judgment.

1.4.3 Discussion

Considering this population, and the need to adequately monitor suicidality, frequent visits, which include Columbia Suicide Severity Rating Scale (C-SSRS) assessments, are planned in this trial to monitor participants. Participants are able to access the investigator and site staff directly for any concerns or questions through the [redacted] application available on the provisioned smartphone.

Additionally, all participants will be on stable treatment of MDD with an SSRI/SNRI at the time of trial entry and throughout their entire trial participation or until the end of treatment if a change is clinically needed per investigator discretion. Considering the mechanism of action of BI 1358894 and the adverse events reported in clinical trials to date, there is no undue risk related to stopping the trial drug during the treatment period or at the end of the treatment period, nor any major risk related to potential aggravation of the side effect profile/s of the background medication/s.

Given the acceptable and manageable safety profile of BI 1358894 as demonstrated in pharmacology and toxicology studies and the good tolerability in clinical studies performed to date, and the close monitoring planned during the trial visits, the potential risks to the participating participants will be minimized and outweighed by a potential therapeutic benefit of the trial drug.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

The main objectives of this trial are to evaluate the efficacy and safety of oral BI 1358894 compared to placebo over a 6-week treatment period in participants with Major Depressive Disorder (MDD) and with inadequate response to antidepressants (SSRI or SNRI) utilizing a decentralized clinical trial (DCT) model.

2.1.1 Main objectives

The trial will be performed to compare BI 1358894 with placebo in participants with MDD with inadequate response to antidepressants (SSRI or SNRI). The primary comparison of interest is the change from baseline in MADRS total score at Week 6 summarized per arm by the adjusted mean. The primary trial objective is to assess superiority of BI 1358894 versus placebo in a DCT model. A mixed model with repeated measurements (MMRM) method will be used to assess the efficacy.

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

The secondary and further efficacy and safety parameters will be assessed to support the understanding of the efficacy and safety of BI 1358894.

2.1.2 Primary endpoint(s)

- Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6

2.1.3 Secondary endpoint(s)

Montgomery-Asberg Depression Rating Scale (MADRS)
- Response defined as ≥ 50% MADRS reduction from baseline at Week 6

State-Trait Anxiety Inventory (STAI)
- Change from baseline in STAI State and Trait version scores at Week 6

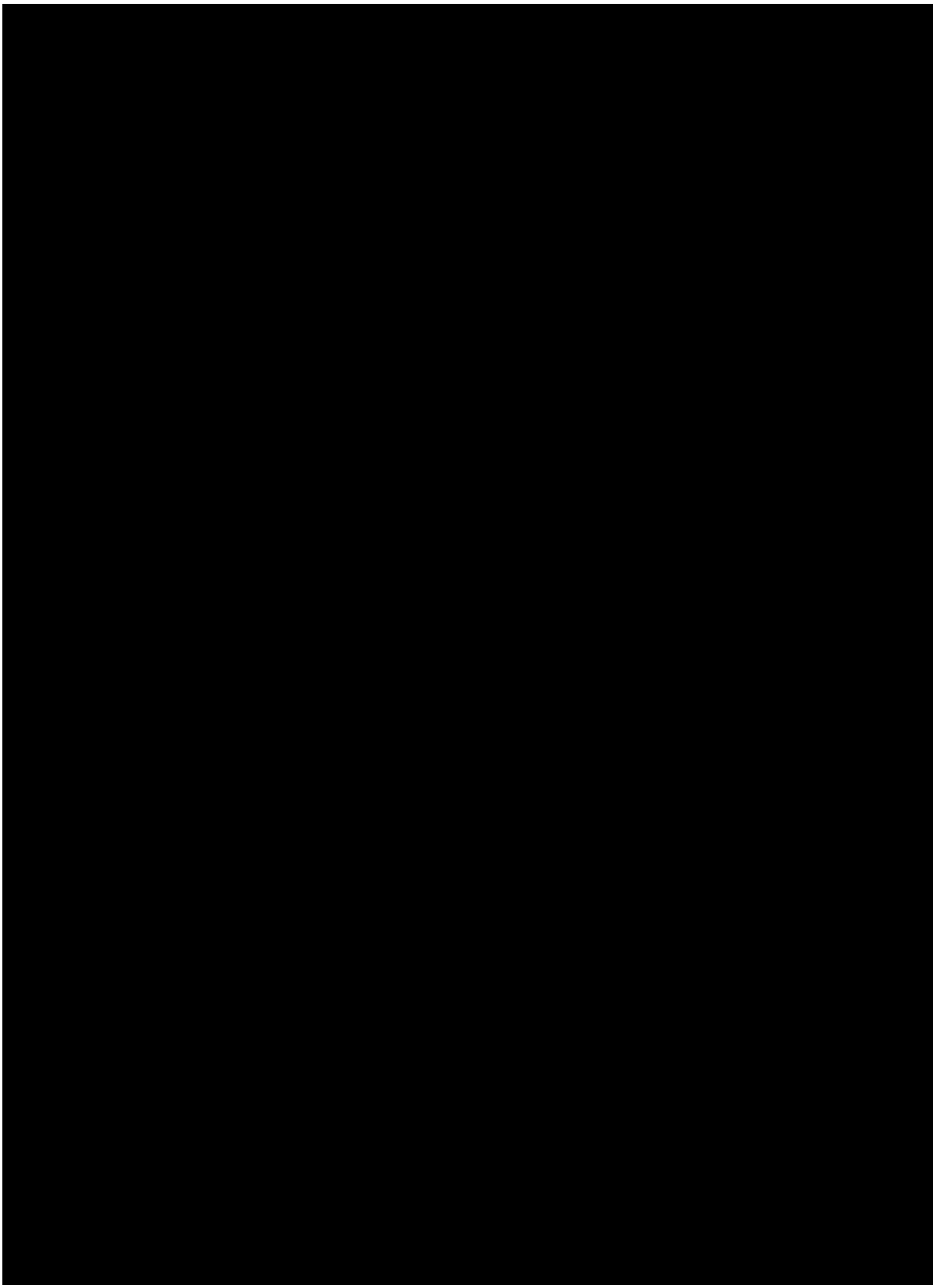
Clinical Global Impression Severity Scale (CGI-S)
- Change from baseline in CGI-S score at Week 6

Symptoms of Major Depressive Disorder Scale (SMDDS)
- Change from baseline in SMDDS total score at Week 6

Patient Global Impression Severity Scale (PGI-S)
- Change from baseline in PGI-S score at Week 6

Patient Global Impression of Change Scale (PGI-C)

- PGI-C score at Week 6



2.2.3 Safety

There are no safety endpoints defined for this trial however safety will be assessed descriptively in participants who received at least one dose of study drug (e.g., AEs, SAEs, AESI, C-SSRS, physical examination, vital signs ECG and laboratory tests).

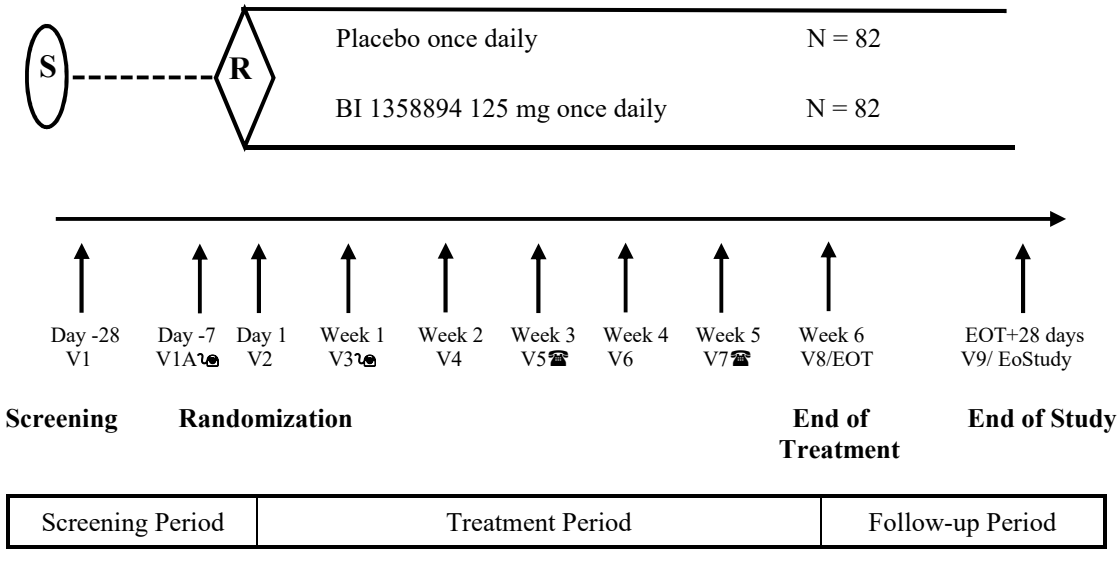
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This study will be conducted as decentralized clinical trial (DCT). It is a 6-week parallel-group, randomized, double-blinded, placebo-controlled Phase II trial in participants with MDD with inadequate response to ongoing treatment of an SSRI or SNRI. This trial will be conducted in the US, with [redacted] as the single decentralized site enrolling in the study.

This DCT will employ telemedicine technology for interactions between the investigator/ trial staff and trial participants. The method of telemedicine allows for practice of medicine using technology to deliver care remotely at a distance. Through Health Insurance Portability and Accountability Act (HIPAA) compliant videoconferencing tools, study physicians and staff will conduct relevant study procedures and assessments. In this trial, clinical and guided assessments will be conducted through videoconference calls, i.e. telemedicine. Additionally, mobile trial personnel will visit each participant's home to complete the designated trial procedures, such as collecting vitals and lab samples, assisting with the study devices, and administering the investigational product. Trial supplies and investigational products will be shipped direct-to-participant in the appropriate shippers, and the [redacted] trial team will perform a fit for use assessment upon the participant's receipt of the investigational drug (see Investigational Product section 4.1.4 for more information).

In total, approximately 164 male and female participants with MDD meeting the entry criteria are planned to be randomized into this trial.



= Videoconferencing visit
☎ = Telephonic contact visit

Figure 3.1: 1 Trial design

Trial participants are enrolled into the trial once consent has been signed. Participants suitable after screening will be randomized to the 6-week double-blind treatment period and will be assigned to placebo or treatment with BI 1358894, refer to Figure 3.1: 1.

After the completion of the 6-week double-blind treatment period, or following early discontinuation of trial medication at any point, participants will complete the 4-week follow-up period at the end of study (EoStudy) visit. All (S)AEs, including those persisting after an individual participant's end of study must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained. Individual participation is concluded when the participant has completed their last planned visit (End of Study visit) (refer to sections 3.3.4.1 and 3.3.4.2).

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

This is a decentralized clinical trial (DCT) of a Phase II, 6-week parallel-group, randomized, double-blinded, placebo-controlled trial in MDD participants with inadequate response to ongoing monotherapy treatment of an SSRI or SNRI. It is important to have a placebo control to address potential confounding factors. This is acceptable as participants will remain on background treatment of standard of care and the duration of the placebo treatment will be limited to 6 weeks. Since participants will remain on their standard antidepressants with either an SSRI or SNRI, no intolerable disease progression is to be expected during this period.

The design of the trial will provide efficacy and safety data for BI 1358894, as well as the proof of concept of the DCT model.

Specifically, data at Week 6 will provide evidence of efficacy and dosing information of BI 1358894 compared to placebo. In addition, we will also obtain safety data through the end of observation period (eEOT + 28 days). [redacted]

3.3 SELECTION OF TRIAL POPULATION

Approximately 164 participants will be randomized into the trial. Participants will be recruited through a highly targeted, multi-channel, adaptive recruitment strategy that covers both digital and conventional forums. Participants who express interest will be contacted via phone where the study staff will complete a pre-screening questionnaire to determine a participant's eligibility to move forward. In addition, trial staff will collect medical records from the participant's primary care physician and/or specialist to further determine eligibility to move forward in the trial. Screening for the trial will stop when the number of participants screened is expected to result in a sufficient number of participants randomized to trial

treatment.

A log of all participants enrolled in the trial (i.e., who have signed informed consent) will be maintained in the [redacted] platform irrespective of whether they have been randomized and treated with investigational drug or not. A final copy of the enrolled patients log will be filed in the ISF after the last trial participant visit.

If a participant is randomized in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Participants with an established diagnosis of Major Depressive Disorder confirmed at the time of screening by Structured Clinical Interview for DSM-5 (SCID-5), Clinical Trial version.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Established diagnosis of Major Depressive Disorder, single episode or recurrent, as confirmed at the time of screening by the Structured Clinical Interview for DSM-5 (SCID-5), with a duration of current depressive episode ≥ 8 weeks and ≤ 18 months at the time of screening visit.
2. Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 22 at screening, as confirmed by a trained rater. In addition, trial participants must have a score of ≥ 3 on the Reported Sadness item on MADRS.
3. A documented ongoing monotherapy treatment of ≥ 8 weeks at the screening visit, with a protocol specified SSRI or SNRI (refer to the ISF) at adequate dose (at least minimum effective dose as per prescribing information and as confirmed per detectable drug levels in the screening blood or urine sampling).
4. Male and female participants, 18 to 65 years of age, both inclusively at the time of consent.

5. Women of child-bearing potential (WOCBP)[1] able and willing to use two methods of contraception, which include one highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1%, plus one barrier method.
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
7. Able to communicate well, and to understand and comply with trial requirements.

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[1]A woman is considered of childbearing potential (WOCBP), 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.

3.3.3 Exclusion criteria

1. Per DSM-5, had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder or MDD with psychotic features as assessed by the SCID-5 at the time of screening.
2. Diagnosis of any other mental disorder (in addition to those as described in Exclusion Criterion #1) that was the primary focus of treatment within 6 months prior to screening or at baseline (as per clinical discretion of the investigator).
3. Diagnosis with antisocial, paranoid, schizoid or schizotypal personality disorder 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.
4. Diagnosis of a substance related disorder within 3 months prior to screening visit (with exception of caffeine and tobacco).
5. History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial.
6. History of 4 or more unsuccessful monotherapy treatments (at adequate dosage and duration, per local prescribing information of the product) with an approved antidepressant medication for the current ongoing major depressive episode. These include ongoing monotherapy treatment with a protocol specified SSRI or SNRI as described in Inclusion Criterion #3.
7. Any suicidal behavior in the past 12 months prior to screening (per investigator judgement including an actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
8. Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months prior to screening or at screening or baseline visit (i.e. active suicidal thought with method and intent but without specific plan, or active suicidal thought with method, intent and plan).

9. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
10. Known history of HIV infection and/or a positive result for ongoing Hepatitis B or C infection.
11. Have initiated psychotherapy or other non-drug therapies (e.g., acupuncture or hypnosis) within 3 months prior to screening or planning to start any time during the trial. The participant should not have a change in type, intensity and/or frequency of psychotherapy within the last 8 weeks prior to screening and it is not anticipated to change during the entire course of trial.
12. Any use of restricted medications within 7 days prior to randomization and during the entire course of the trial (refer to section 4.2.2).

Please note:

- Investigators may use their clinical discretion to wash out (at least 3 half-lives of referenced medication) the restricted medications during the screening period. The participant must adhere to the screening visit dose of the background SSRI/SNRI for the entire duration of the trial or until end of treatment.
- Other uses of antidepressants or quetiapine, at a dose less than indicated for MDD, or at dose less than recommended dose for MDD may be included (see ISF for details on allowed medication and doses restrictions). Use of bupropion is not allowed.
- Participants who are on stable treatment with ongoing benzodiazepines and/or non-benzodiazepine hypnotics (refer to the ISF) for insomnia or anxiety for at least 28 days prior to screening should continue without change for the entire trial duration. For participants who are not on current treatment of insomnia and anxiety symptoms at the time of screening, the protocol will allow short term treatment of these symptoms during the course of trial (see section 4.2.2.1 and ISF for details on allowed medications and permitted dosages).

13. Participants who must or wish to continue the intake of restricted medications (refer to ISF) or any drug considered likely to interfere with the safe conduct of the trial.
14. Use of alternative medicine (e.g. Chinese traditional medicine, herbal medication, St. John's wort, etc.) during the entire course of the trial.
15. Have initiated or discontinued hormone treatment (including hormone replacement therapy) within the 3 months prior to screening (however use of hormonal contraceptives is allowed).
16. Known hypersensitivity to any of the excipients of BI 1358894 or matching placebos.
17. Use of any investigational procedure within 30 days prior to randomization. In case of exposure to an investigational medicinal product, investigator must ensure that it is adequately washed out prior to randomization (at least 5 half-lives of the investigational medicinal product).
18. Positive drug screen at the screening visit. (In case of positive drug screen for benzodiazepines or cannabis, investigator to confirm that there is no active substance related disorder; this also applies to prescribed medications).

19. Have received electroconvulsive therapy and/or administration of Ketamine /S-Ketamine for the current ongoing depressive episode.
20. Have a lifetime history of vagal nerve stimulation, transcranial magnetic stimulation, or psychosurgery
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. Participants not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
23. Considered by the investigator, for any other reason, to be an unsuitable candidate for the trial.

3.3.4 Withdrawal from treatment

Every effort will be made to keep the participants in the trial, if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the options for early discontinuation in case of withdrawals (see section 6.2.2).

Participants may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections below.

If a participant discontinues trial treatment prior to the completion of protocol-specified end of treatment (EOT) visit/Visit 8, every effort will be made by the site staff to encourage participants to remain in the trial if medically safe. Participants who discontinue trial drug prematurely will ideally be observed until the end of the study as if they were still receiving blinded trial treatment. Participants will complete the early End of Treatment (eEOT) procedures as described in the Flow Chart and section 6.2.2. If a participant refuses to participate in completing all further visits after early treatment discontinuation, the participant will be encouraged to complete at least the Week 6/Visit 8 as scheduled and a FUP visit 28 days after early drug discontinuation. If FUP visit (early drug discontinuation date + 28 days) is within 7 days prior to planned Visit 8, then no additional FUP visit is needed.

Participants who refuse all of the above are considered to have fully withdrawn consent to participate in the trial. In this case, the participant does not need to justify the decision and should be withdrawn from the trial and all follow-up assessments (see section 6.2.3).

Withdrawal from the trial of an individual participant may be considered also in case of administrative reasons, such as but not limited to multiple important protocol violations and persistent non-compliance. No participant will be withdrawn from the trial before discussion with the CT Leader.

3.3.4.1 Discontinuation of trial treatment

An individual participant will discontinue trial treatment if:

- The participant wants to discontinue trial treatment, without the need to justify the decision.
- The participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The participant needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment; refer to the ISF
- The participant undergoes an ECT
- Participant receives Ketamine /S-Ketamine treatment during the course of the trial
- The participant can no longer receive trial treatment for serious medical reasons (such as surgery, adverse events, other diseases, or pregnancy), per investigator's clinical judgement. In case of a temporary reason, trial treatment will be restarted if medically justified.
- Pregnancy occurs during the trial. Once a participant has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy which occurred in a female trial participant to the Sponsor immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point (refer to ISF).
- The participant must discontinue treatment with trial medication if:
  - The participant develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e., active suicidal thought with intent but without specific plan, active suicidal thought with plan and intent) or suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt or preparatory acts or behavior).
  - In the event of worsening of MDD which requires medical treatment which is on the list of restricted medications (refer to ISF), the trial drug has to be discontinued.

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

For all participants the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the eCRF. These data will be included in the trial database and reported.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all participants or take any other appropriate action to ensure the safety of the trial participants.

A single episode of an interruption of the trial treatments due to an AE or a concomitant illness, up to a maximum of 3 subsequent days, is permissible in the discretion of the investigator.

3.3.4.2 Withdrawal of consent to trial participation

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

If a participant wants to withdraw consent, the investigator will be involved in the discussion

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of participants affected will occur as described in section 3.3.4.1.
The investigator / the 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 1358894 film-coated tablets have been manufactured by BI Pharma GmbH & Co. KG, Germany. Placebos, matching BI 1358894 film-coated tablets, have been manufactured by BI Pharma GmbH & Co. KG, Germany and [redacted].

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 BI 1358894

Substance:	BI 1358894
Pharmaceutical formulation:	Film-coated Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg, 50 mg
Posology:	QD
Method and route of administration:	Per os

Table 4.1.1: 2 Placebo matching BI 1358894

Substance:	Placebo matching BI 1358894
Pharmaceutical formulation:	Film-coated Tablet
Source:	[redacted] Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	N.A.
Posology:	QD
Method and route of administration:	Per os

As part of this DCT, [redacted]'s designated vendor will receive/store/ship and provide trial treatment and all required trial supplies via direct-to-participant shipments. [redacted]'s designated vendor will receive supply of trial treatment from the Sponsor and store it as required per protocol until ready to send to participant. Storage conditions are temperature-controlled, with continuous temperature monitoring and alarm system. Once randomization

procedures are completed and a unique medication number for the kit to be distributed to the participant is obtained, shipments are prepared and sent out for delivery to participant's home/preferred address; shipments will be confirmed as delivered, with appropriate documentation in the participant's trial records. The trial treatment will be confirmed as received in good condition and within the acceptable temperature range (i.e. fit for use). The appropriate supplies and instructions will be provided to trial subjects for shipment of unused study treatment back to the site's designated vendor. All records of shipments, returns, and drug accountability will be maintained by the site and/or site's designated vendor as required.

Drug compliance will be monitored through drug accountability.

4.1.2 Selection of doses in the trial and dose modifications

The dose of 125 mg BI 1358894, once daily, is selected for this trial [redacted]

4.1.3 Method of assigning participants to treatment groups

After the assessment of all in- and exclusion criteria, each eligible participant will be randomized to treatment groups according to a randomisation sequence at Visit 1A via Interactive Response Technology (IRT). Note that the medication number is different from the participant number (the latter is generated during screening via the IRT System). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

Participants will be randomly assigned by IRT with an allocation ratio of 1:1 to the following treatment groups:

1. Placebo matching BI 1358894
2. 125 mg BI 1358894

Participant assignment to each of the treatment groups will be determined by a computer generated random sequence. Randomization sequence will be generated using validated randomisation software. Access to the randomization code will be controlled and documented.

The kit(s) corresponding to the assigned medication number(s) should be given to the participant and the number of kit(s) that was/were dispensed will be entered in the eCRF. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.4 Drug assignment and administration of doses for each participant

The medication assignment will be provided through IRT. The assigned medication number(s) must be entered in the eCRF, and the corresponding medication kit(s) must be given to the participant. Dosing per treatment assignment is noted in Table 4.1.4: 1. The duration of treatment is 6 weeks. The last dose of trial medication should be taken on the day before the EOT Visit.

Once participant's eligibility has been confirmed, randomization and assignment of trial drugs via IRT system may occur up to 7 days (Visit 1A) before Visit 2 to allow for the drug kit assignment in the IRT system, as well as shipment and delivery of trial drugs to the participant's home. Each trial medication kit contains supplies for 14 days of treatment. For the first trial medication kit supplies, participants will receive two kits (one kit for the 14 treatment days plus a reserve kit), and all following re-supplies will be one kit of BI 1358894 or matching placebo.

Training and set-up of Smartphone apps will also be completed at this time (Randomization Visit 1A). All eligibility criteria must be confirmed, including C-SSRS, before randomization can be registered in IRT.

At Visit 2 with the home visit, the first (preferably in the morning) dose of trial medication will be taken under supervision of the mobile nurse. Thereafter, assignment of trial drugs via IRT system may occur up to 7 days before actual visit (Visit 4, 6) to allow for the drug kit assignment in the IRT system, as well as shipment and delivery of trial drugs to the participant's home. Participants will be instructed to take their medication once a day, in the morning time. Compliance check of medication taken will be completed by mobile nurse at the home visits at Visits 4, 6, and 8 (or eEOT) and returns /shipping back all used and partially used medication kits. The unused kit may be kept as a reserve until V8/eEOT.

Participants will be instructed not to take their trial medication in the morning of Visit 4 and Visit 6, as participants will be dosed under supervision of the mobile nurse after pre-dose PK sampling.

Participants will also be instructed not to take their trial medication at Visit 8/EOT/eEOT Visit. Trough PK sample will be taken at that visit. For participants who complete the treatment period, the last dose of trial medication will be taken on the day before the EOT

Visit. Participants who fail to do so will have the visit rescheduled as soon as possible, ideally on the following day.

Participants will be instructed to take the BI 1358894 tablets or matching placebos orally with water and in a consistent way, i.e. either with or without food every morning at approximately the same time. If a morning dose is missed by more than 12 hours, that dose will be skipped, and the next dose should be taken as scheduled. On days prior to a home visit, the morning dose should be taken approximately 24 hours before the planned morning dose at the home visit. Home visits should be scheduled in the morning, to the extent possible; should this not be possible due to participant's conflict, afternoon or evening visits may occur where the visit dosing is no more than 36 hours from last IMP dose. A dose reduction of BI 1358894 is not possible.

If the participant must temporarily stop trial treatment for medical reasons (such as adverse events), per investigator's clinical judgement, trial treatment may be restarted as soon as possible if medically justified.

Table 4.1.4: 1 Dosage and Treatment Schedule for BI 1358894 / Matching Placebo

	25mg film-coated tablet	**50mg film-coated tablet**	**PBO matching 25mg film-coated tablet**	**PBO matching 50mg film-coated tablet**
Dose group	**Number of tablets to be taken daily – in the morning ☼**			
PBO	0	0	1	2
125 mg	1	2	0	0

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

At each treatment day, all participants will take three tablets of trial medication (either of BI 1358894 or matching placebo). Packaging design is the same for both treatment groups to ensure blinding. Participants, investigators, mobile nurses, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until the time specified in the database lock process, with the exceptions described in this section below.

The access to the randomization code will be kept restricted until its release for analysis.

The randomization codes will be provided to bioanalytics prior to last participant completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo participants. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual participants during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Contract Research Organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the site will be managed via an IRT system, which will also monitor expiry dates of supplies available at the site.

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

4.1.7 Storage conditions

Drug 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, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. Participants will be instructed to return used, partially-used and unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. 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 investigational medicinal product and trial participants. The investigator or designee will maintain records that document adequately that the participants were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products 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 drug supplies have been returned by the clinical trial participant and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Please refer to section 5.3.5.1 for handling participants with positive report of suicidal ideation and/or behavior.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following restrictions for comedications are defined for this trial, until clinical DDI studies are conducted to determine the potential drug interaction:

- Sensitive substrates of CYP2B6
- Strong inducers of CYP3A4

A list of restricted concomitant medications and drugs with potential pharmacokinetic interactions with the trial compound BI 1358894 can be found in the ISF. The list is not comprehensive. For example, drugs that are solely indicated for diseases that are excluded in this trial - like cancer drugs - may not be listed.

Use of ECT and Ketamine/S-Ketamine are restricted during the study, that would lead to study discontinuation (refer to section 3.3.4.1).

Participants on statins should be monitored for statin related toxicity including signs of myopathy, weakness, muscle pain, etc. along with clinical lab results. If statins are concomitantly used during the trial, the highest dose should not be taken together with the investigational compound. If participant in this trial is on the highest recommended statin dose, investigator should consider changing the statin dose to the next lower dose recommended for the respective statin if appropriate.

Please note:

- Concomitant use of benzodiazepines or non-benzodiazepine hypnotics are allowed during study for up to 7 days at dose equivalent to ≤ 1.0 mg lorazepam per day, for management of AEs (e.g. anxiety and/or insomnia). Such drugs should be stopped after the AE is resolved, at the discretion of Investigator. If longer duration of treatment is needed, further re-evaluation is required by investigator for every 7 days per treatment cycle (and possibly more cycles if needed). Refer to ISF for dose equivalence information and comprehensive list of allowed concomitant medications.
- In case of AEs, any treatment deemed necessary per the clinical judgment of investigator for the management of AEs considering participant safety is allowed.

For further guidance investigators are referred to the Investigator´s Brochure [c10354149] or may contact the sponsor.

4.2.2.2 Restrictions on diet and life style

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

Note the following restrictions:
- Use of traditional medicine (e.g. Chinese traditional medicine, herbal medication, St. John's wort, etc.) during treatment period.
- Participants should not abuse alcohol or use drugs of abuse during the trial. Substance use, e.g., nicotine, alcohol, cannabis, caffeine, will be collected throughout the trial from screening to FUP visit. Please refer to the current CRFs for details about substance use to be collected. A urine drug screen will be performed at screening visits (see Flow Chart). For a list of drugs assessed by the urine drug screen please refer to Table 5.3.3: 1.
- Participants should not enter or modify a smoking-cessation program during the conduct of the trial.

It is recommended that patients should exercise caution when driving or operating machinery until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.

Participants do not have to be fasted to any trial visit.

4.2.2.3 Contraception requirements

Women of childbearing potential (WOCBP - for the definition please refer to section 3.3.2) must use two methods of contraception, which include one highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1%, **plus** one barrier method. Contraception must be used during the treatment and follow-up period.

Women of child-bearing potential must agree to periodic pregnancy testing during participation in the trial. If a urine pregnancy test is positive, a serum test needs to be performed for confirmation.

Acceptable forms of contraception for females are:
One of the highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1%:

- Use of hormonal methods of contraception associated with inhibition of ovulation
    a. combined (estrogen and progestogen containing) hormonal contraception:
        - oral
        - intravaginal
        - transdermal
    b. progestogen-only hormonal contraception:
        - oral
        - injectable
        - Implantable

- Placement of intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
- Bilateral tubal occlusion or ligation
- Vasectomy (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that male partner is the sole sexual partner of the WOCBP trial participant)
- Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the patient (note: periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) - (in this specific case the barrier methods, as mentioned below, are not applicable).

Plus with one barrier method:

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

4.3 TREATMENT COMPLIANCE

Upon delivery of study medication shipment, participants are requested to confirm receipt and store at secure place until instructed to use by site staff. Secure place includes out of reach of children, in a place that is not freely accessible to other members of the household. All unused remaining trial medication will be accounted and then collected by mobile nurse at appropriate home visits (as noted in Flow Chart).

Based on non-missing tablet counts, treatment compliance for a visit will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

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

The potential for trial drug abuse will be closely monitored. Events including overdose, misuse, lost and unaccounted for medication must be thoroughly documented in the

participant's source and on the appropriate eCRFs. Furthermore, if the treatment compliance is less than 80% or greater than 100%, site staff will discuss and document the reasons on the eCRFs.

Additionally, as an exploratory approach, the intake of the trial drug will be monitored by the participant with a smartphone [redacted] app (see section 5.6.4). The identification of the tablet shapes and sizes, time and day, the participant face-ID, and the drug intake process will be captured in selfie mode of the smartphone camera, by the participant. The face of the participant will be anonymized by the managing software of the vendor before the data are submitted to the vendor for potential further analysis.

5. ASSESSMENTS

All clinical assessments in this DCT will be conducted via telemedicine (e.g. physician-guided physical exam, adverse events evaluations) and/or videoconference with direct participant-clinician facing calls. Mobile nurse will also be performing safety assessments at home visits. All self-reported (or PROs, patient reported outcome) questionnaires and scales are completed by the participant under the oversight of a trained site staff, [redacted]

5.1 CONFIRMATION OF DIAGNOSIS

The (SCID-5) Structured Clinical Interview for DSM-5 (Clinical Trial version) will be used during screening for confirmation of the diagnosis of Major Depressive Disorder (MDD) and to exclude trial participants with other psychiatric disorders as described in the exclusion criteria. The SCID-5 is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The SCID-5 interview, conducted via videoconferencing, takes approximately 90 minutes to administer.

The Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) will be used to determine treatment history of MDD. The MGH ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants. In this trial, the ATRQ will be used to assess satisfaction with baseline medication. The ATRQ will be administered by a clinician rater; it takes about 10 minutes, one-time during screening.

5.2 ASSESSMENT OF EFFICACY

The current status of MDD will be assessed during the course of the trial by using the MADRS and SMDDS scores and, in a wider perspective, with the outcomes of the STAI, PGI-S, PGI-C, CGI-S, [redacted] (detailed instructions how to administer the assessments can be found in the respective user manuals which will be filed in the ISF).

5.2.1 MADRS - Montgomery–Åsberg Depression Rating Scale

The **MADRS** consists of 10 items:

1. apparent sadness
2. reported 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

The MADRS evaluates core symptoms of depression. Nine of the items are based upon participant reports, and one is on the rater's observation (apparent sadness) during the rating interview. MADRS items are rated on a 0–6 continuum (0=no abnormality, 6=severe). The possible total score could range from 0 to 60 (from normal with absence of symptoms to severe depression).

The administration of MADRS takes about 30 minutes, and is performed by a trained rater to the participant through videoconferencing.

5.2.2 SMDDS - Symptoms of Major Depressive Disorder Scale

The SMDDS is a 16-item, patient-reported outcome (PRO) measure developed to capture the core symptoms of MDD.

The different categories and associated 16 items are:

1. Negative Emotions/Mood: sadness, hopeless/helpless, irritability, anhedonia
2. Anxiety: feeling overwhelmed, worry
3. Low Energy: tiredness
4. Cognition: intrusive thoughts, poor concentration
5. Sleep Disturbances: general sleep adequacy
6. Self Harm/Suicide: life not worth living
7. Low Motivation: lack of drive, no interest in activities
8. Sense of Self: self-blame
9. Eating Behavior: poor appetite, overeating

The SMDDS uses a recall of "over the past 7 days" and participants respond to each question using a rating scale between 0 ("Not at all" or "Never") to 4 ("Extremely" or "Always"). The total score ranges from 0 to 64 with a higher score indicating more severe depressive symptomatology.

The self-reporting of the SMDDS takes about 10 minutes. Participants will be instructed when and how to complete the scale, at visits as specified in the Flow Chart.

5.2.3 STAI - The State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) for adults has been used extensively in research and clinical practice. It comprises separate self-report scales for measuring state and trait anxiety. The S-Anxiety scale (STAI Form Y-1) consists of twenty statements that evaluate how respondents feel "right now, at this moment." The T-Anxiety scale (STAI Form Y-2) consists of twenty statements that assess how people generally feel.

Each STAI item is given a weighted score of 1 to 4. A rating of 4 indicates the presence of a high level of anxiety for ten S-Anxiety items and eleven T-Anxiety items (e.g., "I feel frightened," "I feel upset"). A high rating indicates the absence of anxiety for the remaining ten S-Anxiety items and nine T-Anxiety items (e.g., "I feel calm," "I feel relaxed"). The scoring weights for the anxiety-present items are the same as the chosen numbers on the print inventory form. The scoring weights for the anxiety-absent items are reversed, i.e., responses marked 1, 2, 3, or 4 are scored 4, 3, 2, or 1, respectively. The anxiety-absent items for which the scoring weights are reversed on the S-Anxiety and T-Anxiety scales are:

S-Anxiety: 1, 2, 5, 8, 10, 11, 15, 16, 19, 20
T-Anxiety: 21, 23, 26, 27, 30, 33, 34, 36, 39

To obtain scores for the S-Anxiety and T-Anxiety scales, simply add the weighted scores for the twenty items that make up each scale, taking into account the fact that the scores are reversed for the above items. Scores for both the S-Anxiety and the T-Anxiety scales can vary from a minimum of 20 to a maximum of 80. Higher scores indicate greater anxiety.

The self-reporting of the STAI takes about 10 minutes. Participants will be instructed when and how to complete the scale, at visits as specified in the Flow Chart.

5.2.4 CGI-S - The Clinical Global Impression Severity Scale

The Clinical Global Impression Severity (CGI-S) rating scale measures the clinician's impression of the severity of illness exhibited by a participant that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a participant is assessed on severity of illness at the time of rating according to: 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 participants. Higher scores indicate worsening.

The clinician-reporting of the CGI-S takes about 5-10 minutes, at specific visits as noted in the Flow Chart.

5.2.5 PGI-S - Patient Global Impression Severity Scale

The PGI-S, similar to the CGI-S, will be used to measure the patient's impression of the severity of their illness (R03-0520, R19-1931). It is a single item 4-point scale that asks patients to rate the severity of their illness.

The PGI-S question states "Please choose the response below that best describes the overall severity of your depressioin symptoms over the past week."

1. None
2. Mild
3. Moderate
4. Severe

The PGI-S is completed by the patient and should take a few minutes to complete, to be completed after the SMDDS.

5.2.6 PGI-C - Patient Global Impression of Change Scale

The PGI-C is a one-time assessment at the end of treatment (EoT) to measure the patient's impression of the how their illness has changed over time. It is a single item 7-item scale that asks patients to rate the overall change since the start of treatment.

The PGI-C question states "Please choose the response below that best describes the overall change in your depression symptoms since you started taking the study medication."

Very much improved
Much improved
Minimally improved
No change
Minimally worse
Much worse
Very much worse

[redacted]

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum clinical assessments of general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

The results must be included in the source documents available at the site. Clinically relevant abnormal findings noticed after baseline assessment will be reported as (S)AEs.

5.3.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

Measurement of height (Visit 1 only) and body weight will be performed at the time points specified in the Flow Chart.

5.3.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.3.3:1. For the sampling time points please see the Flow Chart.

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

Participants do not have to be fasted for the blood sampling for the safety laboratory.

Should there be a need for a re-test or repeat lab, participants may be advised to have the lab drawn at a nearby local lab, or if feasible, by mobile nurse or lab technician at home. The coordination and lab kits and lab requisition form for the blood draw will be completed by the study staff, and guidance will be provided to the participant as to when, which local lab to go, and which lab kits to bring. If the participant does not have the available lab kit at home, an appropriate kit will be shipped. Samples collected at the local lab will be sent to central laboratory for analyses.

If taking blood samples for central lab using the provided lab kit is not possible, blood analysis for safety lab can be done in a local lab. The results of the lab tests are to be reported and transferred to the investigator, who has to ensure medical review and proper documentation. Safety lab parameters should at least include liver enzymes and bilirubin, haematology including differential test, blood glucose, sodium, potassium, creatinine, urea (BUN) and eGFR. It is important that the reference values of the local lab are also provided.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual 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 baseline condition (if at screening) or adverse events during study (please refer to section 5.3.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.3.6.1.4 and the DILI Checklist provided in the ISF and electronic data capturing (eDC) system). The amount of blood taken from the participant concerned will be increased due to this additional sampling.

Capturing the results of various drug screens (e.g., Cannabis, Benzodiazepine, Barbiturates, Opiates, Cocaine, Amphetamines, Methadone, PCP) in the clinical database is planned to permit examination of the use in this study population, impact of use on the recruitment failure rate, frequency of benzodiazepine use as sleeping aids and the impact of occasional use of Canabis in light of the planning of Phase III of this development program.

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

Table 5.3.3:1 Safety laboratory tests

Category	Test name
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Red Blood Cell Count/ Erythrocytes Erythrocyte sedimentation rate (ESR) Reticulocyte Count White Blood Cells / Leucocytes Platelet Count/ Thrombocytes MCV, MCH, RDW, MCHC
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils Eosinophils Basophils Monocytes Lymphocytes

Table 5.3.3:1 Safety laboratory tests (cont.)

Category	Test name
Chemistry	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Chemistry Amylase Calcium Sodium Urea (BUN) Potassium Glucose Creatinine Bilirubin Total, fractionated if increased Protein, Total C-Reactive Protein Cholesterol, total Triglycerides TSH Testosterone[3] LH[3] FSH[3] Folate eGFR using the CKD-EPI equation
SSRI/SNRI detectable drug levels[1]	Duloxetine Citalopram/Escitalopram Paroxetine Sertraline and Desmethylsertraline Fluoxetine and Norfluoxetine Venlafaxine and Desmethylvenlafaxine Desvenlafaxine
Urine (dipstick) Pregnancy test (only for female participants of childbearing potential - test done at all home visits beginning with Visit 2)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female participants of childbearing potential) at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin

Table 5.3.3:1 Safety laboratory tests (cont.)

Category	Test name
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Blood (Hemoglobin) and Myoblobin Leukocytes Esterase Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)*	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine	Albumin (quantitative) Creatinine
Drug screening (urine)[2]	Cannabis Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Methadone PCP
Infections screening[2]	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibody (qualitative) Hepatitis C Virus (HCV) RNA – only if Hepatitis C antibodies (qualitative) are positive

[1] At screening and EOT only (at screening, urine samples will also be collected, except for Duloxetine);

[2] At screening only; [3] Males only

* Urine Sediment microscopic analysis, performed only if any of the urinalysis is positive, and reported (any of the following) only what is identified (positive).

RBC	Granular Casts	Ca Carbonate Crystals
WBC	Fatty Casts	Am Biurate Crystals
Sq EPI	Cellular Casts	Bilirubin Crystals
Bacteria	Broad Casts	Uric Acid Crystals
Hyaline Casts	Waxy Casts	Amorphous Crystals
Epithelial Casts	Tri Phos Crystals	Leucine Crystals
WBC Casts	Ca Oxalate Crystals	Tyrosine Crystals
RBC Casts	Ca Phosphate Crystals	Cystine Crystals

For assessment of the kidney function, the formula of the estimated glomerular filtration rate

(EGFR) CDK-EPI (Chronic Kidney Disease Epidemiology Collaboration) will be used. This requires that ethnicity need to be captured.

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for at least 10-second duration after the participants have rested for at least 5 minutes 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 time points indicated in the Flow Chart, single ECGs will be recorded. ECG recordings at planned time points may be repeated for quality reasons like 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 whether it is clinically significant, if abnormal. 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 screening assessment (Visit 1) will be reported as baseline condition. Clinically relevant abnormal findings noticed after baseline assessment will be reported as AEs and followed up and/or treated locally until normal or stable condition.

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

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

5.3.5 Other safety parameters

5.3.5.1 Assessment of Suicidality

Suicidal risk assessed by the Columbia Suicide Severity Rating Scale (C-SSRS, clinician interview version equivalent to the paper-version) shall be administered via videoconference or telephone by trained study staff.

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

The C-SSRS interview may be administered by any physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical

duration of five minutes, and causes only a low burden on participants. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered first at screening (Visit 1) (using the 'Baseline / Screening' version) with the aim to exclude participants with active moderate or severe symptomatology within a specified time prior to screening. The life time history of suicidal ideation and behavior will also be recorded.

After screening (Visit 1) the assessment 'since last visit' will be performed at each visit ('Since Last Visit version'). The investigator is to review/consider the C-SSRS results for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the participant during the visit (if the investigator did not administer the C-SSRS leading to the positive report), and/ or is to consult a psychiatrist if considered necessary. If the positive report is confirmed, appropriate actions for the participant's safety have to be initiated.

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

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

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

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

5.3.6.1.1 Adverse event

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

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

The following will also be recorded as an AE in the eCRF and BI SAE form (if applicable):
- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

Regarding AEs in the context of suicidal risk assessment by C-SSRS, section 5.3.5.1 should be adhered.

5.3.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the 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.

5.3.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.
The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events will always be reported as SAEs as described in section 5.3.6.1.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.3.6.2, subsections “AE Collection” and “**AE reporting to sponsor and timelines”.**

5.3.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from

other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.3.6.2.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the participants showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.3.6.1.5 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.

5.3.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).

- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

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

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

5.3.6.2 Adverse event collection and reporting

5.3.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the participant files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual participant's end of study (the End of Study (EoStudy) visit): all AEs (serious and non-serious) and all AESIs.
- After the individual participant's end of study: the investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.3.6.2.2), but not on the CRF.

5.3.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available.

In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form."

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual participant's end of study must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.3.6.2.3 Pregnancy

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

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part 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 Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Methods of sample collection

For the quantification of BI 1358894 plasma concentrations, blood samples will be collected as indicated in the Flow Chart. The actual sampling times and time of dosings will need to be recorded. Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. Plasma samples will be stored frozen at about -20°C or below at central laboratory and bioanalytical laboratory. The samples will be shipped on dry ice.

If collection of PK samples is scheduled at the visit when local lab is used, PK samples will not be taken.

[redacted]

5.4.3 Assessment of biomarker(s)

Not applicable

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

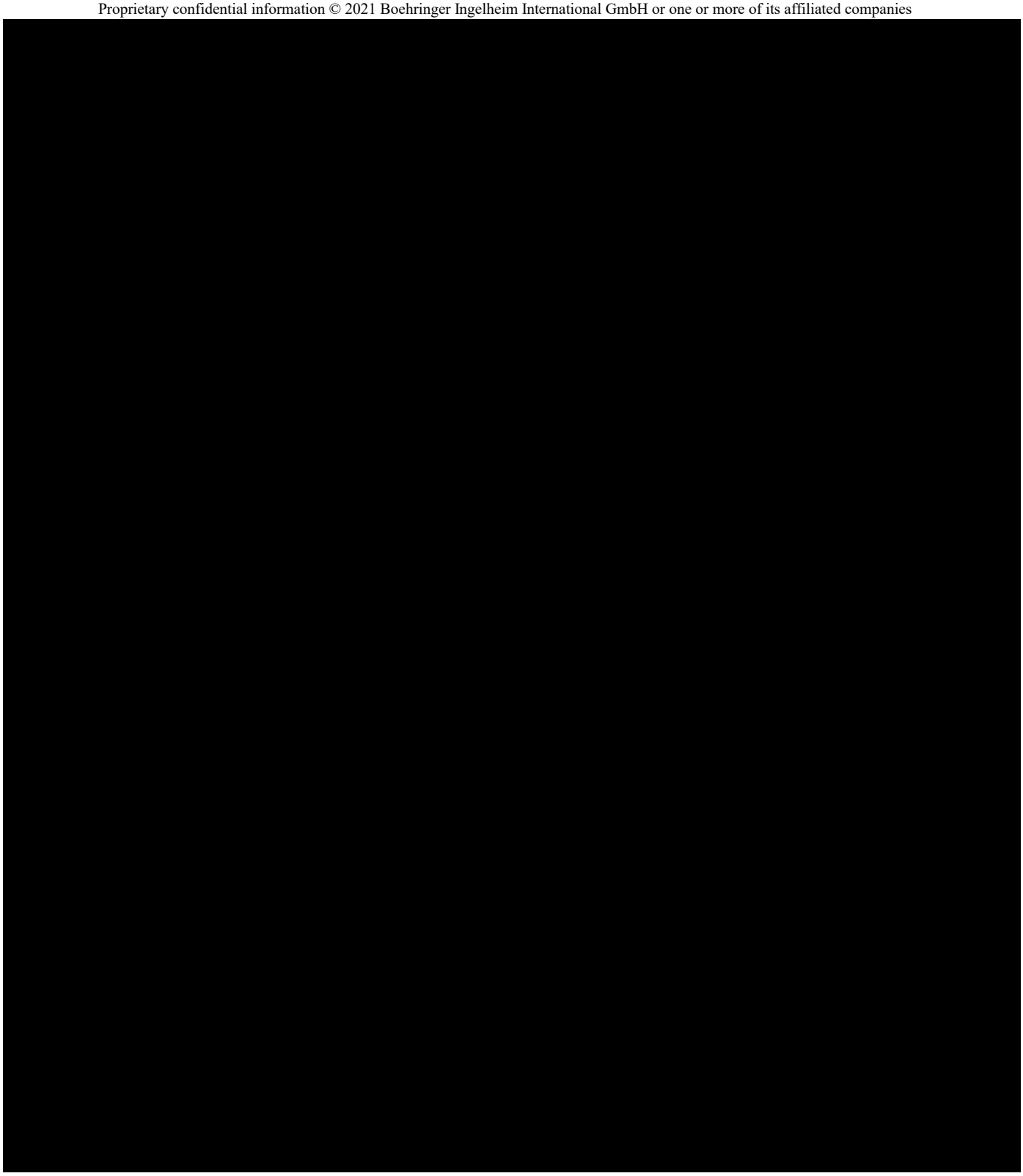
5.5.1 Methods and timing of sample collection

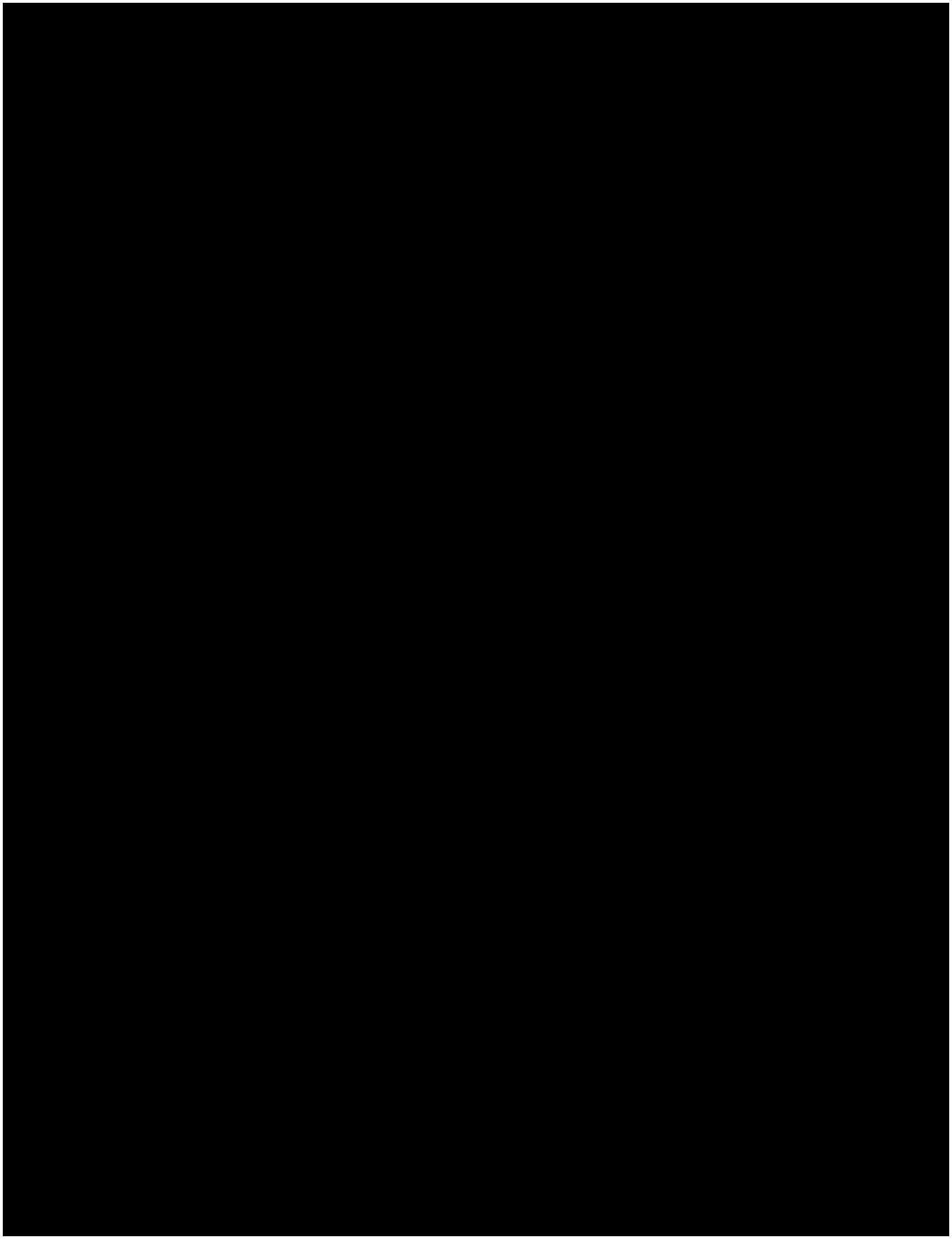
Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling time points, see Flow Chart.

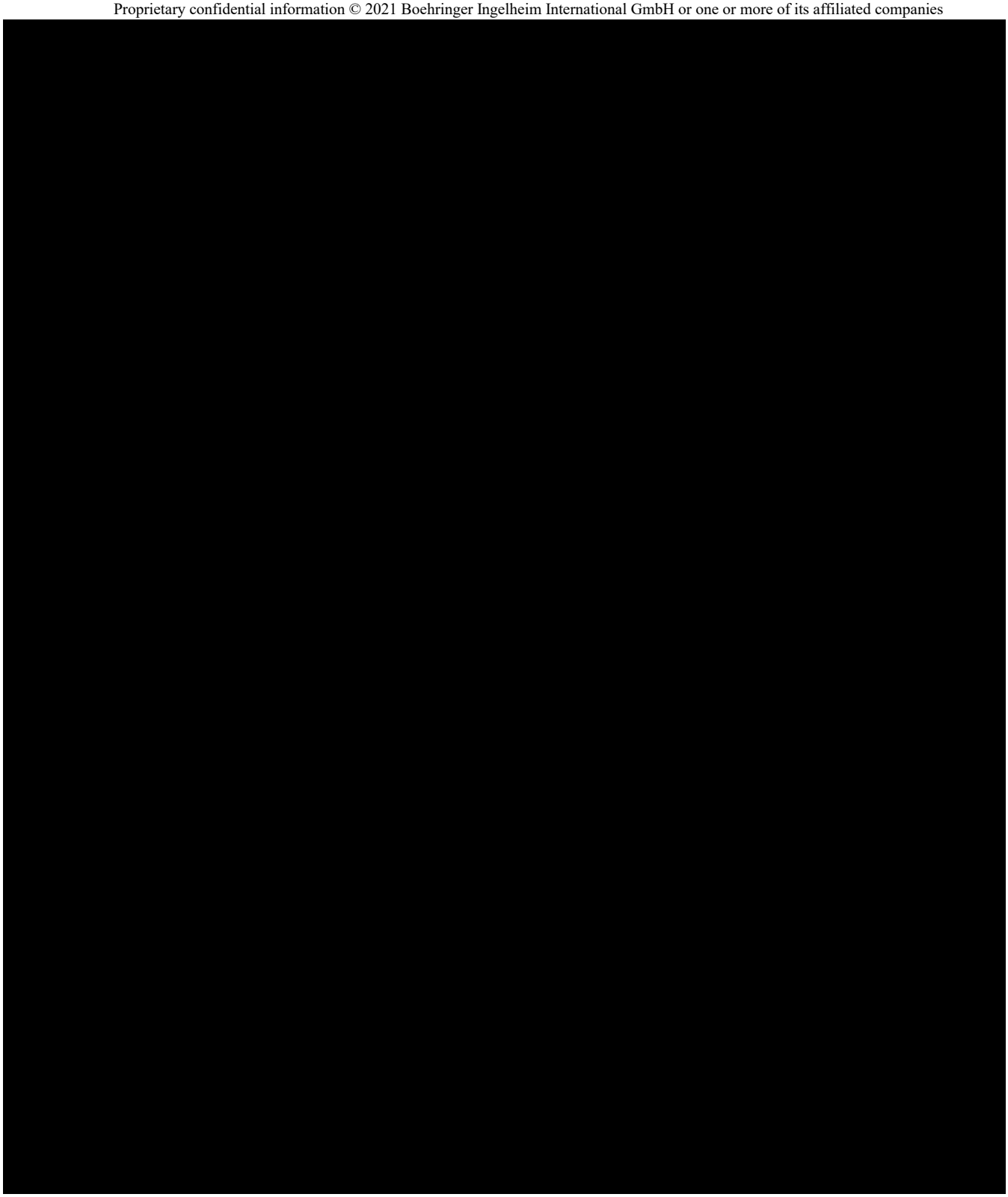
Approximately 45.5 mL blood will be drawn for DNA (1 x 8.5 ml), Plasma (2 x 10 ml) and Serum (2 x 8.5 ml) banking purposes.

[redacted]

[redacted]







5.6.4 Medication Adherence and Reminder System

In addition to the regular calculation of treatment compliance as described in section 4.3, this trial will employ an additional medication adherence monitoring platform ("Platform") for all participants in the trial. The Platform uses artificial intelligence through a smartphone

[redacted] app to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

These measures will not supersede or replace the physician and/or prescribed medication protocol of the participants. The platform encourages adherence to the predefined protocol but does not change the medication protocol of the participants; thus, use of this platform presents minimal risk to the participants. Use of the platform will be required for all participants in the trial.

The monitoring Platform requires that all participants take each dose of the medication while using the smartphone [redacted] app. The [redacted] app will be provided to participants preloaded on the provisional smartphone.

When at home, participants will receive medication reminders for their daily morning dosing. This notification reminds participants to take their medication dose while using their provisional smartphones through the [redacted] app. Participants will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the participant has properly taken their medication at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the participant takes their medication.

5.6.5 End of Study Participant Feedback Questionnaire

This trial will include an option for participants to complete an anonymized questionnaire, 'Study 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. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and therefore would not be part of the trial data or clinical trial report.

5.6.6 Verification of Current and Past Research Study Status of 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" (VCT). This is a mandatory process where local regulatory approval has been obtained.

Following proper informed consent and after issuing a study subject number, the subject's information will be checked against the Verified Clinical Trials database, as indicated in the Flow Chart. Partial identifiers will be utilized. This will include checking a valid form of picture ID when available.

The first 3 letters of the first and last name will be entered along with the middle initial, DOB, Sex, and last 5 digits of that ID. If the status of the research subject is a "Verification

Success" he/she may proceed in the study. If, however, the status is a "Verification Failure" he/she will not be permitted to screen without sponsor approval. The duplicate patient check will be performed only after approval is received in accordance with local regulations.

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

6.1 VISIT SCHEDULE

All participants have to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

During the COVID-19 pandemic, there might be situations when participants might not be able to complete the scheduled study visit. This might be e.g. due to participant not feeling well enough for the telemedicine or telespychiatric procedures, or because the participant is quarantined or showing symptoms that may deem unsafe for mobile nurse's home visit, or because of any particular situation that the investigator judges as being not safe for the participant or mobile nurse.

For such cases, the visit procedures or home visit may be adjusted or rescheduled to maximize opportunities, after evaluation of operational feasibility and minimal required data (i.e. primary /secondary /exploratory endpoints. etc.). Such cases will be documented in eCRFs and/or patient source.

For detailed description of the trial procedures, please refer to the Flow Chart.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

As part of the DCT model, study visits will be conducted in three ways, as indicated in the Flow Chart:

1. Home visits by mobile study nurse at participant's home
2. Videoconference (indicated by 🖳 symbol)
3. Telephone contact (indicated by ☎ symbol).

Unless indicated, visits are home visits, conducted by mobile study nurse at participant's home.

Trial procedures to be performed at each visit are listed in the Flow Chart. In this DCT, all trial visits (e.g. Visits 1, 2, 4, 6, 8, 9) requiring physical exams and/or laboratory testing, will be conducted with home visits by mobile study nurse, and other visits (Visits 1A, 3, 5, 7) will be conducted remotely by a trained trial staff. Additional details regarding visit procedures are provided below.

Procedures and assessments at study visits will be conducted through several methods and are broken down as below:

- Screening procedures including demographics, medical history, ATRQ, inclusion/exclusion criteria interview, will be completed via telephone or videoconference.

- Neuropsychological assessments by qualified rater (SCID-5, MADRS) will be completed via videoconferencing
- Physical examinations will be conducted via telemedicine with the mobile nurse conducting the physician-guided examination through videoconference with study investigator or physician.
- C-SSRS, AEs, and concomitant medications review may also be conducted by telephone or videoconference by trained study staff or by mobile nurse during home visits.
- Vital signs, ECG, blood draws (for PK, laboratory tests, and biobanking), administration of trial medications (at Visits 2, 4, 6), and drug accountability will be conducted by mobile nurse at participant's home.
- PRO questionnaires (SMDDS, PGI-S, PGI-C, STAI, [redacted]) will be completed by participants with guidance from mobile nurse during home visit or by study staff via videoconference (Visit 3) as indicated per Flow Chart.

[redacted]

For study procedures and communications with trial staff during the study, participants will be provided with a smartphone with the [redacted] platform application installed. Most of the patient-reported outcome and procedures will be through this smartphone's [redacted] and [redacted] apps, with the exception of the Beiwe app for the optional Digital Phenotyping which is installed on the participant's personal smartphone. Participants will be instructed on the use and access of the [redacted] app and how to use the installed apps for the study procedures during and between visits.

The following requirements for the conduct of the clinical and neuropsychological assessments need to be followed:

- The site staff must be properly trained on all trial procedures and training documentation filed in the ISF.
- Qualification, training, remediation (if needed) and central reading of the scales will be provided by a specialized 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 Principal Investigator at the site to ensure that all members of the site staff involved in the neuropsychological assessments undergo qualification and training by the vendor.
- All scales are recommended to be completed in the order as indicated at each visit in the Flow Chart (ClinROs [MADRS, CGI-S, C-SSRS], then PROs [SMDDS, PGI-S, PGI-C, STAI, ED-5D-5L, SDS]).
- All neuropsychological assessments are recommended to be completed in the morning. In rare cases where participants are unable to arrange for morning home visits, MADRS must still be completed in the morning via videoconference.

- Each assessment of the site-rater performed scales (MADRS, CGI-S) should preferentially be done by the same member of the site staff for a given participant throughout the trial period.
- Results of the MADRS and SCID-5 assessments at screening are part of the eligibility evaluation (see below).
- During the neuropsychological testing, participants are allowed to take short breaks as needed, in the judgement of the rater/investigator.
- All C-SSRS (baseline/screening and since-last-visit) scales completed during screening will be evaluated for eligibility confirmation, and the since-last-visit C-SSRS scale to be used for all following visits for assessment of suicidality.

In general, the following should be noted for the conduct of trial procedures:

- PRO (self-reported assessments) should be completed before physical exams.
- Vitals and ECG should be completed before blood draws.
- Unscheduled visits/calls will be possible at the discretion of the investigator at any time in order to check the safety of the participant including additional safety laboratory assessments.
- The background antidepressant medications (SSRI/SNRIs) will be taken as usual throughout the study (including on the day of a clinical visit) by the participant, according to the requirements as described in this protocol and in the investigator's recommendations and prescribing guidelines.
- Quality control of MADRS and SCID-5 assessments will be monitored by central reviewer from qualified vendor.

6.2.1 Screening period(s)

Screening Period

No trial procedures should be done unless the participant has consented to taking part in the trial. The participant information and informed consent may be done up to 2 weeks before Visit 1. After the participant has signed the informed consent and completed the first study activity or assessment, the screening period will start. The participant will be registered in IRT as a screened participant and recorded on the enrolment log.

Consenting process in this DCT will be completed electronically (via eConsent) involving several steps within the [redacted] platform eConsent. Before study eConsent is initiated, potential participants will be assessed as preliminarily eligible after review of medical records by the investigator/study team. Once this is confirmed, an informed consent discussion will be scheduled.

During the informed consent discussion, eConsent will present the informed consent materials. The participant will review the documents and discuss them with the investigator by phone call, during which all their questions about the study will be answered and all elements of the informed consent process will be covered. Once the discussion is completed, the participant will be provided with the independent opportunity to consider participation in the study. If agreed, he or she will provide a handwritten signature executed to an electronic record in the designated signature block using a computer mouse, touchscreen, or stylus depending on the capability of their device. The investigator administering the consent will

countersign in the same manner as soon as possible within 3 business days of the participant's signature.

For participants who elect not to sign the informed consent materials, the reason(s) for not signing will be documented in the [redacted] platform and all study related procedures will be stopped. The consent process must be completed prior to initiation of any study procedures.

Visit 1 – Home visit
The screening visit will take place no more than 28 days before Visit 2. Within the 28 days screening period, the screening visit may be completed in multiple days; for example, with first day SCID-5, ATRQ, C-SSRS, demographics (completed via videoconferencing) and second day MADRS, repeat C-SSRS, Medical history, patient-report questionnaires, physical exams, vitals and laboratory (home visit by mobile nurse). Note, for safety, C-SSRS needs to be completed at each day, if multiple days are needed for screening. Screening MADRS however must be completed within 21 days of randomization. Baseline/screening C-SSRS and the most recent C-SSRS results will be used for eligibility.

Visit 1A – Videoconference
This will be scheduled after confirmation of eligibility, including positive blood levels of SSRI/SNRI in the screening lab which may be up to 7 days but not less than 1 day prior to the planned home Visit 2 date. During this visit, the IRT randomization transaction will be registered by the investigator or designee. This allows for the drug kit assignment in the IRT system, shipment and delivery of trial drugs to participant's home. At this visit, participants will be guided through the set-up of all relevant smartphone apps and provided training on usage and navigations. Trainings on smartphone apps may start at Visit 1 and be repeated/continued to this visit, however all trainings must be completed by Visit 2. An assessment of a C-SSRS will also be performed prior to randomization.

All eligibility criteria must be confirmed, including C-SSRS, before randomization can be registered in IRT. The IRT transaction should not take place (or be registered) until eligibility is fully confirmed, as randomization of a participant cannot be reversed. [redacted] he medication adherence assessments will start with the first administration of the trial drug at Visit 2.

Optional
Participation in the sampling of biobanking of plasma and serum for biochemical markers and DNA is voluntary and only allowed after the participant has given separate consent prior to the collection of the respective blood samples.

Participation in the Beiwe Digital Phenotyping is optional and implemented only after the participant has given a separate consent, and to start collection 2 days prior to Visit 2 (first drug administration).

Demographics, Baseline Conditions and Physical Examinations
Information on race will be collected because this demographic information is required for the calculation of eGFR (CKD-EPI formula). Physical examinations will be conducted via telemedicine with the mobile nurse conducting the physician-guided examination through videoconference with study investigator or physician. Blood pressure will always be measured before any blood samples are taken. Any abnormal condition of clinical significance identified during physical examination, vital signs, 12 lead ECG and/or laboratory assessment will be recorded as a baseline condition.

Medical History
It is important to collect previous medical records to document exact dates/diagnoses of relevant medical conditions and prior medications. Three attempts to obtain records on different days should be documented. In the case that medical records cannot be obtained after the minimum of three attempts, a verbal medical history obtained by the investigator will be sufficient. However, at a minimum, medical record confirming use of SSRI/SNRI for diagnosis of MDD should be available.

Additional details regarding headaches need to be recorded in CRFs for all headaches that occurred up to 3 months prior to the screening visit. Please refer to the current CRFs for information that needs to be collected.

Additional details regarding concomitant psychotherapy at screening need to be recorded in CRFs. Please refer to the current CRFs for information that needs to be collected. During the treatment, the question whether there were any significant changes in psychotherapy will be recorded in CRFs only at study visits.

Concomitant treatments which are allowed or restricted before and during trial participation, including required washout durations, are listed in the ISF.

Substance use, e.g., nicotine, alcohol, cannabis, caffeine, will be collected throughout the trial from screening to FUP visit. Please refer to the current CRFs for details about substance use to be collected.

Clinical outcome assessments will also be performed as summarized in the trial Flow Chart. Participants will be instructed to continue allowed/ required background medication without changes and to adhere to their administration algorithm.

Re-testing
Participants with unexpected lab values at Visit 1 may be re-tested once within the 4 week screening period if there is a reasonable explanation and expectation that the participant will meet the in- and exclusion criteria at re-test at the discretion of the investigator. This doesn't apply to the urine drug screen, which must not be repeated.

In case of a need for a lab re-test, participants may be advised to have the lab drawn at a nearby local lab, or if feasible, by mobile nurse or lab technician at home (see section 5.3.3). The coordination and lab kits and requisition form for the blood draw will be completed by

the study staff, and guidance will be provided to the participant as to when, which local lab to go, and which lab kits to bring.

Re-screening of participants
Rescreening of a participant can be done once, 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 CTL. All screening examination must be repeated, and new participant number assigned, in case of re-screening.

Potential reasons for re-screening could be:
- Positive urine drug screen
- Restricted medications like CYPs/ alternative or traditional medicine
- Clinically significant findings per Investigator's judgement

In addition, participants will watch a short informational video intended to educate the participant about placebo, and why they are used in clinical trials. 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 may have been randomly assigned to placebo, and stresses the importance of reporting all symptoms, whether the symptoms are positive, negative or neutral.

6.2.2 Treatment period(s)

Visit 2 (Baseline/Day 1) – Home visit
Before the planned Visit 2 home visit by mobile nurse, all participant trial supplies (e.g. lab kits, etc.) and investigational products (trial medication) must be confirmed delivered at participant's home.

At Visit 2, all ClinRO and PRO assessments need to be completed **before** dosing. In the event of a positive urine pregnancy test, a serum pregnancy test must be performed by the central lab for confirmation, and a negative serum pregnancy test result must be received before the participant can be dosed. In this case, all (baseline) study procedures will be completed as planned for Visit 2, however first dose of study medication will be withheld. Once the result of serum pregnancy test is confirmed negative, first dosing will be conducted via videoconference under the direction of the study staff. If the serum pregnancy test is re-confirmed positive, the participant will be discontinued from study.

The participant will have received sufficient trial drug for 14 days (treatment kit plus a reserve kit). The first dose will be taken under the supervision of the mobile nurse, with further practice using the medication adherence app, after all Visit 2 assessments are completed. In addition to pre-dose PK and safety laboratory samples, a sample for optional plasma/serum and DNA biobanking will be collected if Informed Consent is provided. A sample for optional DNA biobanking is preferentially collected at Visit 2 but can be collected at another time point thereafter.

Participants will be instructed to continue taking trial medication with the medication

adherence platform, daily in the morning.

Visit 3 – Videoconference visit
All visit procedures as specified in Flow Chart will be assessed through videoconference call.

Visit 4, Visit 6 – Home visits
Up to 7 days before the planned home Visits 4 and 6, IRT registrations must be completed for new assignments of trial medications to allow time for shipment and delivery of trial drugs to the participant's home. On the day of the home visit, the participant will take the morning dose of the trial drug after pre-dose PK samples are collected.

Visit 5, Visit 7 – Phone visits
Visits V5 (Week 3) and V7 (Week 5) are planned be conducted via phone, but may be conducted as a videoconferencing visit if there is a clinical need at the discretion of the investigator.

Visit 8 / End of Treatment (EOT) / early end of treatment (eEOT) – Home Visit
Visit 8 represents the regular end of the treatment period. Last trial drug administration should occur one day before the Visit 8. The overall duration of the anticipated treatment period (first dose to EOT) should be 42 days +4 days. The End of Treatment visit must be registered in the IRT system.

Premature discontinuation of trial drug
Participants who discontinue trial drug prematurely should ideally be observed until trial end as if they were still receiving blinded trial treatment (Option 1, see Flow Chart and section 3.3.4). If this is not possible, then participants should be encouraged to complete Week 6/ Visit 8 procedures, with the performance of the MADRS scale as a minimum requirement (Option 2). See Flow Chart and section 3.3.4 for prematurely discontinue options details. The early End of Treatment visit must be registered in the IRT system.

6.2.3 Withdrawal of consent

If a participant is not willing to continue in the trial, or early discontinued and not chose Option 1 or Option 2, then this is considered withdrawal from study. If the participant withdraws consent for any reason (without the need to justify the decision), the EoStudy/FUP visit (+28 days after drug discontinuation) is highly recommended to be performed to assess and monitor safety, and End of Treatment and Trial Completion pages of the eCRF have to be filled in. All unused trial medication will be collected and returned to site. It is important to distinguish between premature trial drug discontinuation, i.e. early discontinuation, and complete withdrawal of consent to participate in further trial procedures.

6.2.4 Follow-up period and trial completion

For all participants who had at least one dose of trial medication, the follow-up visits will be performed as described in section 3.3.4.

If the last day of trial drug intake is different from the day prior to the EOT visit, the date of the last day of trial drug intake will be used for calculation of the FUP visit dates.

Participants who finish the randomized treatment period according to the protocol will complete the end of study (EoStudy/FUP) visit. Trial completion is defined as participants having reached the FUP visit within the specified window per the Flow Chart.

For all randomized participants, termination of trial medication and trial completion must be recorded on the corresponding eCRFs.

Should it be not possible for the participant to complete the planned FUP visit, a visit out of time window should be performed as soon as possible; if this visit is not possible at all, at least a phone contact should occur at the scheduled follow-up visit time point.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This study will be conducted as a decentralized clinical trial (DCT). It will be a Phase II, 6-week parallel-group, randomized, double blinded, placebo-controlled, parallel-group trial in MDD participants with inadequate response to ongoing treatment with antidepressants (SSRI or SNRI). The main objectives of this trial are to evaluate the efficacy and safety of BI 1358894 compared to placebo utilizing a DCT model.

The primary endpoint is change from baseline in MADRS score at Week 6. The restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis (MMRM) will be used to obtain adjusted means for the treatment effects. This model will include categorical fixed effects of treatment, visit, treatment by visit interaction, and continuous fixed effects of baseline, and baseline by visit interaction. The primary treatment comparisons will be the contrast between treatments at Week 6 in MADRS total score.

A detailed description of the model utilized is provided in section 7.2.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The trial is designed to assess the effect of BI 1358894 and placebo in participants with MDD with inadequate response to ongoing treatment of an SSRI or an SNRI.

The null hypothesis is that the mean change from baseline in MADRS total score at Week 6 for BI 1358894 is equal to the mean change from baseline in MADRS total score at Week 6 for the placebo group. The alternative hypothesis is mean change from baseline in MADRS total score at Week 6 for BI 1358894 is not equal to the mean change from baseline in MADRS total score at Week 6 for the placebo group.

A two-sided test using the MMRM model will be carried out to assess the primary endpoint, with an α level of 10%.

7.2 PLANNED ANALYSES

7.2.1 General considerations

All data will be listed and summarized by treatment group using appropriate methods. For continuous data, the number of observations, mean, standard deviation (SD), minimum, median and maximum will be provided. The frequency and proportion of participants in each category will be presented for categorical data.

Analysis sets defined for this trial include the full analysis set (FAS) and the treated set (TS).

The FAS comprises all randomized participants who received at least one dose of trial medication during the trial and had a baseline and a post-baseline observation recorded. Unless otherwise specified, efficacy analyses will be performed on FAS and will be based on

assigned treatment. Full specifications for the FAS will be provided in the Trial statistical analysis plan (TSAP).

Safety analyses will be conducted on the TS, which include all randomized participants who have received at least one dose of the trial medication. Safety analyses will be conducted using actual treatment received. Data from participants who were screened but not randomized will be listed but not included in any summaries or inferential statistics.

Any deviations from the TSAP will be carefully monitored and reported in the CTR. Important protocol deviation are those protocol deviations that have significant impact on patient safety or trial results. Important protocol deviations will be collected throughout the trial conduct and will be summarized in the CTR as defined in the TSAP.

7.2.2 Primary endpoint analyses

7.2.2.1 Primary analysis of the primary endpoint

As defined in section 2.1.2, the primary endpoint is the change from baseline to Week 6 in MADRS total score. Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication and is typically recorded at Visit 2. If data from Visit 2 are missing, the last value recorded prior to Visit 2 will be considered the baseline value. The investigator-reported MADRS total scores will be used for the primary analysis.

The primary estimand of interest is the treatment effect assuming all subjects remained adherent to the assigned trial medication and the trial protocol using a hypothetical approach, i.e. trial drug is taken as directed. The primary analysis of the primary endpoint will include all data collected while on treatment, which is defined as the time from the date of the first dose of trial medication until the last date of last dose of trial medication plus 7 days (3 times the estimated elimination half-life). Any data collected after a participant discontinues trial drug, regardless of reason, will not be included in the primary analysis.

The primary analysis will be the restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of MADRS score at week 6.

The analysis will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, as well as the continuous fixed covariates of baseline MADRS score and baseline by visit interaction.

Participant will be considered as random effect. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within patient measurements error. Additional covariates identified prior to database lock may be included in the MMRM model as applicable.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom

and adjust standard errors. Significance tests will be based on least-squares (LS) means using a two-sided $\alpha = 0.1$. Analyses will be implemented using SAS (version 9.4) PROC MIXED.

The primary treatment comparisons will be between BI 1358894 and placebo with respect to the mean change from baseline in the MADRS total score at week 6. Adjusted mean change from baseline as well as treatment contrasts will be presented together with the 90% confidence intervals. The primary treatment comparisons will be the contrast between BI 1358894 treatment arm and placebo at week 6.

If the analysis fails to converge, alternative covariance structures will be tested, details will be provided in the TSAP.

Sensitivity analyses for the primary analysis of the primary endpoint.

Sensitivity analyses to be conducted to assess the robustness of the primary analysis outcomes to the assumption of missing at random (MAR) will be described in the TSAP.

7.2.2.2 Supplemental analysis of the primary endpoint

[redacted]

[redacted]

7.2.3 Secondary endpoint analyses

7.2.3.1 MADRS response

Response over the 6-week treatment period will be assessed using the MADRS total score. Participants with ≥ 50% reduction in MADRS total score from baseline to Week 6 are considered responders. Participants experiencing < 50% reduction in MADRS total score values are considered non-responders. Percent reduction from baseline at a specific post-baseline visit (Visit X) is calculated as:

$$\%\, reduction = \frac{(MADRS\ total\ score\ at\ baseline - MADRS\ total\ score\ at\ Visit\ X)}{MADRS\ total\ score\ at\ baseline} * 100$$

The proportions of participants achieving response at Week 6 will be summarized as the frequency and percentage of participants in each treatment arm. In addition, if a sufficient number of responders are observed, a logistic regression model adjusted for treatment (BI 1358894 or placebo) will be used to calculate the odds ratio for response between the BI1358894 arm and placebo and corresponding confidence interval. Additional covariates

identified prior to database lock may be included in the MMRM model as applicable. The likelihood ratio test will be used to test for differences between the active treatment arm and placebo.

7.2.3.2 STAI

Change from baseline to Week 6 in STAI state and trait scores will be analyzed using an MMRM model similar to the model described for the primary endpoint analysis. Comparisons will be performed for the BI 1358894 arm versus placebo.

7.2.3.3 CGI-S

Change from baseline in CGI-S will be summarized by treatment arm as both a continuous and an ordinal variable. Mean change from baseline to Week 6 and standard deviation will be presented. In addition, the frequency and proportion of participants reporting each response category at baseline and at Week 6 will be displayed. To compare change in depression severity as assessed by the CGI-S between the BI 1358894 treatment arm and placebo, an MMRM model similar to the model described for the primary efficacy analysis will be used.

7.2.3.4 PGI-S

The secondary endpoint of change from baseline in PGI-S at Week 6 will be analyzed in a similar fashion as CGI-S (described above in 7.2.3.3).

7.2.3.5 PGI-C

The analysis of the secondary endpoint for PGI-C at Week 6 will be described in the TSAP.

7.2.3.6 SMDDS

Descriptive statistics will be presented for the responses to the SMDDS individual domains responses and total score. As described in section 7.2.2.1 for the primary efficacy analysis, an MMRM model will be used to compare change in SMDDS total score from baseline to Week 6 between the BI 1358894 treatment arm and placebo.

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated participants, i.e. all participants in the TS, will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Adverse event data will be summarized by treatment taken at the onset of the event.

Frequency, severity, and causal relationship of adverse events 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 the time specified in the database lock process.

Laboratory data will be analyzed 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 summarized.

Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of participants with abnormal values or clinically relevant abnormal values. Laboratory values of particular interest include:

- Low values of HDL, haemoglobin, and neutrophil count
- High values of triglyceride levels, total cholesterol, blood glucose, eosinophil count, ALT and GGT

Vital signs, physical examinations, or 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 to findings before start of treatment.

7.2.6 Other analyses

Additional analyses will be specified in the TSAP if deemed necessary.

7.2.7 Interim analyses

No interim analyses are planned for this trial.

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits.
The primary estimand of interest is the treatment effect assuming all participants remain adherent to the assigned trial medication and trial protocol using a hypothetical approach. For

the primary analysis of the primary endpoint, missing data will not be imputed. Data collected after discontinuation of trial medication will be considered missing for the primary analysis.

The mixed effects model will handle missing data based on a likelihood method under the assumption of missing at random.

[redacted]

Sensitivity analyses will be conducted and will be described in the TSAP, for the primary and supplemental analyses of the primary endpoint.

Similar methods for handling missing data will be used for secondary efficacy endpoints, as applicable.

With respect to safety evaluations, it is not planned to impute missing values.

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

7.4 RANDOMISATION

Participants will be randomly assigned to treatment or placebo in a 1:1 ratio as described in section 4.1.3.

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudorandom number generator so that the resulting treatment will be both reproducible and non-predictable.

The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented as described in section 4.1.5.

7.5 DETERMINATION OF SAMPLE SIZE

In this DCT home-based study, a nurse will be visiting the participant to execute the survey with a physician via computer and other study related activities. It is expected that the variability for a DCT will be less compared to a regular trial. Thus, the sample size is estimated assuming a standardized effect size of 0.375, which is based on a mean difference between placebo and BI 1358894 of 3.0 and standard deviation of 8.0. [P11-04859] A two-sided alpha of 0.10 will be used for the sample size calculation using a treatment allocation ratio of 1:1 for the placebo and BI 1358894 arms. Under these assumptions, a few different scenarios are summarized in Table 7.5:1.

Table 7.5:1 Sample size calculations based on two-sided alpha of 0.1

Treatment mean difference	3	3	**3**	3	3
Standard Deviation	8.5	8.0	**8.0**	7.5	7.0
Power	80	80	**77**	75	75
N for each treatment arm	100	89	**82**	68	60
Total	200	178	**164**	136	120

The sample size calculations in Table 7.5:1 include a fixed delta of 3 and a range of standard deviation values. Based on the sample size assumptions, 82 evaluable participants per arm are required to achieve a power of 77%. Evaluable participants are defined as those who have been randomized, received at least one dose of study medication, have a MADRS baseline measurement and at least one post-baseline MADRS measurement. The participants who dropout from the trial prematurely, but are evaluable will be included in the analysis set. For such participants, missing values will be handled by the MMRM model.

The missing data patterns and the proportion of non-evaluable subjects out of randomized subjects will be monitored during the conduct of the trial in a blinded fashion. The sample size may be re-evaluated if unexpected data patterns are observed. The details will be provided in the TSAP.

Calculations were performed using nQuery + nTerim 4.0 statistical package by [redacted]

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, 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 as will be treated as protocol deviation. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the participant.

The investigator will inform the Sponsor 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 finalization of the Clinical Trial Report. The certificate of insurance cover is made available to the investigator and the participants, and is stored in the ISF.

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

8.1 TRIAL APPROVAL, PARTICIPANT 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 to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional 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 or the participant’s legally accepted representative.

The investigator or delegate must give a full explanation to trial participants based on the participant information form.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

In order to achieve a high level of standardized processes, training and quality check of efficacy endpoints and C-SSRS is monitored centrally: [redacted] has been selected as service provider to support tasks related to the neuropsychological assessments. A detailed description of services can be found in the vendor contract. The services of [redacted] include:

- Necessary Rater prequalification
- Site Rater training for neuropsychological assessments used as primary and secondary endpoints (online and at investigator/rater's meeting)
- Provision of Rater materials
- Central Quality Review of Assessments; for that purpose, assessment procedures will be audio recorded (paper source may be used if audio is not available).

Details of rater prequalification, 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 ISF.

8.3 RECORDS

eCRFs for individual 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

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 should be traceable (audit trail).

Neuropsychological rating scales data entered into the [redacted] platform will be regarded as source data. For electronic participant reported outcomes the electronic record is the source document. These may be centrally reviewed and may be further analysed by the delegated third party vendor.

The electronic version of the ECG is regarded as source data. Electronic ECG will be uploaded to the participant's [redacted] profile and electronically signed and dated by the investigator.

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

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 three documented attempt to retrieve previous medical records. If this fails, a verbal history from the participant, documented in their medical records, would be acceptable. However, at a minimum, medical record confirming use of SSRI/SNRI for diagnosis of MDD should be available.

Copies of source documents necessary for SAE processing may be requested and provided to BI. 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 properly been removed or redacted from any copy of the participants' source documents.

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

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

- Participant identification: gender, 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 medication
- Medical history (including trial indication, current depressive episode, and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (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 for it).
- Prior to allocation of a participant to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the 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, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PARTICIPANT PRIVACY

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

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

8.6 TRIAL MILESTONES

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

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

A final report of the clinical trial data will be written only after all participants have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last participant (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

Relevant documentation on the participating Principal Investigator and sub-investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CT 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 (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

Vendors will be used in this trial for central laboratory services, IRT, central ECG services, ClinRO/PRO scales assessments including, medication intake monitoring, [redacted]

[redacted]. Details will be provided in the respective manuals available in the ISF.

Bioanalysis of BI 1358894 is done by [redacted], [redacted].

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		17-Dec-2020
EudraCT number **EU number**		NA
BI Trial number		1402-0014
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants
Global Amendment due to urgent safety reasons		
Global Amendment		1
Sections to be changed		Protocol synopsis and Abbreviations
Description of change		Updated to align with new text in within this revised CPT.
Rationale for change		See below for specific sections and study procedures
Sections to be changed		Flow Chart
Description of change		Add new procedures and data collection to the study, including PGI-S, PGI-C, Substance Use, Meal intake and Participant Feedback Questionnaire. Update text to footnotes: • [d]PROs – to include PGI-S and PGI-C • Early discontinuation, Option 2 – to include text re. meal intake and PGI-C • #12 – to include collection of Meal intake at PK sampling timepoints • #19 – update to align within protocol re. collection of data from day -2 to until end

		of study (EoStudy) • #20 – to further clarify different apps used and addition of participant placebo video • #22 – new footnote to explain the End of Study Participant Feedback Questionnaire.
Rationale for change		See further below for specific sections and study procedures
Sections to be changed		Various sections where NORA was mention
Description of change		NORA was changed to [redacted] Platform
Rationale for change		[redacted] rebranded the NORA flatform to Platform
Sections to be changed		ABBREVIATIONS
Description of change		Added new relevant abbreviations and removed ones no longer applicable.
Rationale for change		Updates and edits of CTP contents.
Section to be changed		1.2. Drug Profile; Table 1.4.2:1; 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Updated Data from IB included: • Additional text re. data from clinical studies • Rationale added for restriction of CYP2B6 and CYP3A4 • Update on drug-drug interaction data Removed restriction for “combined CYP3A4 and UGT inhibitors” as co-meds • Precaution measure for operating machinery and driving automobiles added. • Revised text referring to drug administered on ‘site’ to mobile nurse oversight
Rationale for change		Consistency with updated IB
Sections to be changed		1.3 Rationale
Description of change		General wording changes regarding MDD
Rationale for change		Align with text in parent trial (1402-0011)
Sections to be changed		1.4.2 Risks
Description of change		Assessment of BI 1358894 safety in the scope of COVID-19
Rationale for change		Providing safety and consideration for patient

		participating in study
Sections to be changed		2.1.3 Secondary endpoints 2.2.2 Further endpoints 7.2.3 Secondary endpoint analysis
Description of change		Added endpoints to include PGI-S and PGI-C. Also add PK endpoints.
Rationale for change		Per FDA request to add PGI-S and PGI-C as anchors for the SMDDS. PK was not previously included.
Sections to be changed		3.3.2 Inclusion criteria
Description of change		Replaced MADRS item #2 with actual description of 'Reported Sadness'.
Rationale for change		For better clarity of item #2 on the MADRS
Sections to be changed		4.1 Investigational treatments; Table 4.1.1: 2 Placebo matching BI 1358894
Description of change		Added [redacted] as the manufacturer of placebo tablets.
Rationale for change		Correct the missed manufacturer of placebo tablets.
Section to be changed		5.2 Assessment of efficacy
Description of change		Added two sub-sections: • 5.2.5 PGI-S • 5.2.6 PGI-C Renumbered sequential sections as: [redacted]
Rationale for change		Per FDA request to add PGI-S and PGI-C as anchors for the SMDDS.
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		Texts added to further clarify scale and align with sister trial (1402-0012)
Section to be changed		5.5.3 Safety laboratory parameters
Description of change		Information and rational added that drug screen

		results will be included in the clinical database Updates to Table 5.3.3: 1 include: • ESR test added to Haematology • Revision of Urinalysis test to align with [redacted] lab testing • Added details regarding urine sediment microscopic analysis • Added Norfluoxetine to Fluoxetine
Rationale for change		Added ESR per FDA request (in sister trial 1402-0012). Adding inclusion of drug screen results to better understand reasons of screening failures and potential impact of drug use on the efficacy Norfluoxetine is active component of Fluoxetine also being tested by central laboratory.
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		New section 5.6.5 End of study participant feedback questionnaire
Description of change		New section added
Rationale for change		To allow of collection of patient experience feedback at the end of study.
Section to be changed		6.1 Visit schedule
Description of change		Updates to this section include: • Revised and aligned collection of Beiwe data to End of Study. • Added language for consideration of potential study visit impact due to COVID
Rationale for change		Align Beiwe collection period within CTP, and to acknowledge for COVID circumstances
Sections to be changed		6.2 Details on Trial Procedures

Description of change		Addition of texts related to: • PGI-S and PGI-C • Clarification of only MADRS and SCID-5 are to be reviewed by central reviewer, not PROs • Participant Placebo Response Mitigation Video added
Rationale for change		Provide details of when PGI-S and PGI-C are to be completed. Administrative edit for clarification re. central reviewer. To teach participants about the placebo effect in order to mitigate this effect during the trial performance
Sections to be changed		7.2.3 Secondary endpoint analysis
Description of change		Updates to this section include: • Added endpoints to include PGI-S and PGI-C • Clarify Beiwe data analysis will provided in a separate plan
Rationale for change		Per FDA request to add PGI-S and PGI-C as anchors for the SMDDS. Beiwe data is not to be part of the CTR.
Sections to be changed		[redacted]
Description of change		
Rationale for change		
Sections to be changed		7.2.6 Other analyses
Description of change		Add within patient change analyses for SMDDS score using PGI-S and PGI-C
Rationale for change		Per FDA request to add PGI-S, PGI-C and CGI-S as anchors for the SMDDS.
Sections to be changed		9.1 Published references
Description of change		Added two new references
Rationale for change		New references related to PGI-S.
Sections to be changed		9.2 Unpublished references
Description of change		Remove IB version number and date
Rationale for change		Reference to the IB should the latest and current,

		not the version noted in the CTP.

11.2 GLOBAL AMENDMENT 2

Date of amendment		20-Jul-2021
EudraCT number **EU number**		NA
BI Trial number		1402-0014
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants
Global Amendment due to urgent safety reasons		
Global Amendment		2
Sections to be changed		Title Page and Protocol Synopsis
Description of change		Site and investigator address
Rationale for change		Change of addresss
Sections to be changed		Protocol Synopsis and Abbreviations
Description of change		Updated to align with new updates within this revised CPT.
Rationale for change		As noted per respective sections.
Sections to be changed		Flowchart
Description of change		• Informed consents, added texts '(include consents for participant's duplicate check)'. • Sample for confirmation of blood/urine levels SSRI/SNRI, added 'urine'.
Rationale for change		• Specify new VCT consent needed for participant's duplicate check.

		• Added urine sample collection for testing of SSRI/SNRI
Sections to be changed		Flowchart, Footnote
Description of change		Changes made to the following Footnotes: • Footnote 'a' – added texts '(repeat of MADRS is allowed once to maintain within this 21-day window)' • #6, correct typo 'Adverse' Event • #8, delete extra wording 'at screening' • #11, added text for Visits 1 and 8 for collection of SSRI/SNRI samples; urine sample only collected at Visit 1 (except for Duloxetine which is serum only). • #18, changed Visit 8 to EOT
Rationale for change		• Footnote a, allow for flexibility of repeating MADRS, reducing patient burden of rescreening procedures. • #6, correct typo • #8, remove duplicated texts • #11, added clarification to specify visits when SSRI/SNRI serum and urine samples are to be collected. • #18, correct Visit 8, should be EOT
Sections to be changed		Section 1.4.3 Discussion
Description of change		Added 'or till end of treatment if a change is clinically needed per investigator discretion' for duration of continued use of background SSRI/SNRI
Rationale for change		Allow flexibility for when and if clinically needed or participants want to change their dosing of background SSRI/SNRI after ending study treatment
Sections to be changed		Section 3.3.2 Inclusion criteria
Description of change		Changes made to the following Inclusion criteria: • #1, changed duration of current major depressive episode to ≤ 18 months • #3, added urine to screening SSRI/SNRI samplings
Rationale for change		• Increase of MDD episode duration to more reflect real-world patient population

		• Inclusion of urine sampling to allow flexible testing and turnaround time for results
Sections to be changed		Section 3.3.3 Exclusion criteria
Description of change		Changes made to the following Exclusion criteria: • #6, changed to history 4 or more unsuccessful monotherapy treatments • #12 a) changed duration of background SSRI/SNRI use to end of treatment period (EOT), and b) allow for use of other anti-depressants not indicated for MDD to be used. • #18, added texts 'this also applies to prescribed medications'
Rationale for change		• #6, with increase of major depressive episode duration to 18 months, this allow for possible unsuccessful treatments • #12, allow flexibility for a) if clinical need and participants want to change their dosing of background SSRI/SNRI and b) flexible for other common use of medications. • #18, allow for patients who are currently taking prescribed medications (e.g. opioids) testing positive that are not drugs of abuse
Sections to be changed		Section 4.1.1 Identity of the IMP
Description of change		Update to change from [redacted] to [redacted]'s 'designated vendor' as the responsible party for IMP management.
Rationale for change		[redacted] outsourced IMP management to Vendor.
Sections to be changed		Section 4.1.4 Drug assignment and administration of doses for each participant
Description of change		Added text regarding home visits to occur in afternoon or evening visits
Rationale for change		Allow for some flexibility of afternoon or evening visits due to participant's scheduling conflicts.
Sections to be changed		Section 4.2.2.3 Contraception requirements
Description of change		WOCBP, who are sexually abstinent, fulfil the requirement of safe contraception
Rationale for change		Clarification. Sexual abstinence, as defined in the protocol, meets the criterion of a highly effective method of contraception

Sections to be changed		Section 5.3.3 Safety laboratory parameters
Description of change		Added text to allow use of local labs without study provided lab kits.
Rationale for change		Ensuring flexibility to allow for changes due to disruption, such as central lab stock out (shortage)
Sections to be changed		Table 5.3.3:1
Description of change		Added texts below to footnote 1: (at screening, urine samples will also be collected, except for Duloxetine)
Rationale for change		Provided clarification for collection of urine and serum SSRI/SNRI samples
Sections to be changed		Section 5.4.1
Description of change		Added text: If collection of PK samples is scheduled at the visit when local lab is used, PK samples will not be taken.
Rationale for change		Provided clarification that PK samples are not taken when using local lab.
Sections to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Sections to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Sections to be changed		[redacted]
Description of change		[redacted]

		[redacted]
Rationale for change		[redacted]
Sections to be changed		Added. Section 5.6.6 Verification of current and past research study status of trial participant
Description of change		Verification of duplicate participants (VCT) added
Rationale for change		Prevention of simultaneous trial participation by study participants
Sections to be changed		Section 6.2.1 Screening period(s)
Description of change		• Added text 'completed the first study activity or assessment after' • Changed 72 hours to '3 business days' for countersigning of consent
Rationale for change		• Additional text to clarify the start of screening window • Aligning with [redacted] SOP.
Sections to be changed		Section 7.2.1
Description of change		Added texts: Any deviations from the TSAP will be carefully monitored and reported in the CTR.
Rationale for change		Provided further clarification re. monitoring of deviations.
Sections to be changed		Section 8.2 Data Quality Assurance
Description of change		Add text in parentheses: Central Quality Review of Assessments; for that purpose, assessment procedures will be audio recorded (paper source may be used if audio is not available).
Rationale for change		Allow vendor to quality review paper source if there are (technical/computer/programmatic) issues that make audio not available.
Sections to be changed		Section 8.7
Description of change		Changed [redacted] lab name to [redacted]
Rationale for change		Vendor name change