Clinical Trial Protocol

Document Number:		c29983007-12
EudraCT No. **EU Trial No.**	2019-004264-21	
BI Trial No.	1402-0011	
BI Investigational Medicinal Product(s)	BI 1358894	
Title	A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.	
Lay Title	A study to test the effect of different doses of BI 1358894 and quetiapine in people with depression.	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: [redacted], Fax: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: Email:	
Version and Date	**Version: 11.0**	**Date: 07 Jun 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	16 Dec 2019
Revision date	07 June 2023
BI trial number	1402-0011
Title of trial	A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Coordinating Investigator	[redacted] Phone: [redacted] Fax: Email:
Trial site(s)	Multi-centre trial
Clinical phase	II
Trial rationale	Patients with Major Depressive Disorder (MDD), who inadequately respond to first line treatment, will receive augmentation treatment. However, there remains significant unmet medical need in those patients who either do not respond to or do not tolerate current augmentation approaches (e.g., atypical antipsychotics, lithium) and for whom last line therapies (ECT and ketamine) are either not available or unsuitable. A product that would show similar efficacy to the above mentioned augmentation treatments, but without the side effects and/or resource requirements would constitute a major medical advance. Only quetiapine has been approved in both the US and the EU in patients with inadeaquate response on first line treatment (SSRI; SNRI; bupropion), and has therefore been included as an additional treatment arm in this Phase II trial.

Trial objective(s)	The main objectives of this trial are to provide proof of concept (PoC) and dose-ranging data of BI 1358894 compared to placebo in patients with Major Depressive Disorder (MDD) to support dose selection for pivotal studies.
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 Week 6 • Change from baseline in STAI State and Trait version scores at Week 6 • Change from baseline in Clinical Global Impression Severity Scale (CGI-S) score at Week 6 • Change from baseline in SMDDS total score at Week 6
Trial design	A 6-week parallel-group multicenter, randomized, double blind, double-dummy, placebo controlled trial with different doses of BI 1358894 and with a quetipine arm in patients with Major Depressive Disorder (MDD) with inadequate response to ongoing treatment with an SSRI or an SNRI or bupropion.
Total number of participants randomized	Approximately 431 male and female participants with MDD meeting the entry criteria are planned to be randomized into this trial.
Number of participants on each treatment	• Placebo arm participants: Approx. 144 • BI 1358894 5 mg: participants: Approx. 41 • BI 1358894 25 mg: participants: Approx. 41 • BI 1358894 75 mg: participants: Approx. 41 • BI 1358894 125 mg: participants: Approx. 82 • quetiapine 150/300 mg: participants: Approx. 82
Diagnosis	Patients with an established diagnosis of Major Depressive Disorder (MDD) confirmed at the time of screening by Structured Clinical Interview for DSM-5 Clinical Trials (SCID-5)

Main in- and exclusion criteria	Main Inclusion Criteria: ➢ Established diagnosis of Major Depressive Disorder (MDD), 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 ≤ 24 months at the time of screening visit. ➢ Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 24 at screening, as confirmed by a trained site based rater AND interactive, computer administered MADRS. The difference in the rater and computer administered MADRS must not exceed more than 7 points. In addition, trial participants must have a score of ≥ 3 on the Reported Sadness Item on both MADRS scales (computer-administered and rater-administered MADRS). ➢ A documented ongoing monotherapy treatment of ≥ 4 weeks at the screening visit, with bupropion or 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). ➢ Male and female participants, 18 to 65 years of age, both inclusively at the time of consent. ➢ Women who are of childbearing potential (WOCBP) must be able and willing, to use two methods of contraception, confirmed by the investigator, Main Exclusion Criteria: ➢ Per DSM-5, has 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. ➢ Diagnosis of any other mental disorder (in addition to those as described in EX#1) that was primary focus of treatment within 6 months prior to screening or at baseline (as per clinical discretion of the investigator). ➢ 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. ➢ Diagnosis of a substance related disorder within 3 months prior to screening visit (with exception of caffeine and tobacco).

	➢ History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial. ➢ History of more than 2 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 bupropion or a protocol specified SSRI or SNRI as described in inclusion criteria #3. ➢ 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). ➢ 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). ➢ Has 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. ➢ Any use of restricted medications within 7 days prior to randomization and during the entire course of the trial 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 or bupropion until the end of the trial or end of treatment (eEOT/EOT), respectively ➢ Participants, who, in addition to their monotherapy with an SSRI/SNRI or bupropion, are taking additional low dose antidepressant medications for purposes other than treating depressive symptoms, are not excluded. The dose must be less than the lowest dose indicated for MDD (see ISF for details). ➢ Participants who are on stable treatment with ongoing benzodiazepines and/or non-benzodiazepine hypnotics 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. ➢ Participants who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. ➢ Use of alternative medicine (e.g. Chinese traditional medicine, herbal medication, St. John's wort, etc.) during the entire course of the trial. ➢ Have received electroconvulsive therapy and/or administration of Ketamine /S-Ketamine for the current ongoing depressive episode and/or transcranial magnetic stimulation (TMS) for the current ongoing depressive episode or within 12 months pior to screening. ➢ Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening.
Test product(s)	BI 1358894
dose	5 mg, 25 mg, 75 mg, 125 mg; once daily
mode of administration	Per os
Comparator product / Active reference	• Placebo • quetiapine extended release
dose	• NA for placebo, matching BI 1358894 and quetiapine • quetiapine, after uptitration, either 300 or 150 mg, once daily
mode of administration	Per os
Duration of treatment	6 weeks
Statistical methods	To demonstrate proof of concept and to evaluate the dose response relationship for BI 1358894, a multiple comparison procedure with modelling techniques (MCPMod) approach is planned for the primary analysis of the BI 1358894 and placebo treatment arms. As a basis for the MCPMod analysis and to assess quantitative treatment benefit, a mixed model for repeated measure (MMRM) analysis will be used to generate covariate adjusted estimates of mean change from baseline to Week 6 in MADRS total score and associated covariance matrices. No formal hypothesis testing will be performed to compare the quetiapine and BI 1358894 arms or the quetiapine and placebo arms.

FLOW CHART 1

Trial Periods	**Screening**		**Randomized Treatment**							**Early D/C**	**Follow-up / End of Study**
Visit	**1**	**1A[10]**	**2**	**3**	**4**	**5** ☎[8]	**6**	**7** ☎[8]	**8 / EOT***	**Early EOT****	**9 EoStudy**
Week			0	1	2	3	4	5	6		10
Day	-21 to -2		D1[9]	8±1	15±1	22±1	29±1	36±1	43+2		EOT / (Early drug discontinuation date) plus 28+2 days
Informed consent (including [redacted] counseling about the need of contraception)[1]	x										
Demographics	x										
Medical history (including headaches)	x										
Physical examination	x								x	x	x
Vital signs, including body weight (height only at SCR)	x		x		x		x		x	x	x
12 lead-ECG	x		x		x		x		x	x	x
Laboratory tests (including pregnancy tests [redacted])[2]	x		x	x	x		x		x	x	x
Contraception counseling for WOCBP[13]		x	x	x	x	x	x	x	x	x	
ESR test	x		x	x	x		x		x	x	x
Review of in-/exclusion criteria	x		x								
Randomisation			x								
Interactive Response Technology Use	x		x		x		x		x	x	

[redacted]	[redacted]		[redacted]						[redacted]	[redacted]	[redacted]
Dispense trial drugs			x		x		x				
Administration of trial drugs at trial site			x	x	x		x				
Drug Accountability [3]				x	x		x		x	x	
Termination of trial medication									x	x	
Sample for confirmation of urine or blood levels SSRI/SNRI/bupropion [12] *Please note: Duloxetine in serum only*	x								x	x	
[redacted]			x		x		x		x	x	x
Optional sampling for [redacted]			x[6]						x[5]	x[5]	
Trial specific examinations *(see Flow Chart 2)*	x		x	x	x	x	x	x	x	x	x
All AEs/SAEs/AESIs [7]	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
Completion of participant's participation											x
[redacted]											x

At the screening visit, all clinical assessments (Flow Chart 1) should be performed first, followed by the scale administrations, top to down, in the order as shown in Flow Chart 2. For all further clinical visits, scale administrations should be done first, top to down, in the order as shown in Flow Chart 2, followed by the clinical assessments, e.g., Flow Chart 1 (also refer to section 6.2 further details for the order of clinical assessments and scale performance).

* End of treatment (EOT) for participants who complete the treatment period at Visit 8.

** Participants who discontinue trial drug prematurely must perform an early EOT visit within 7 days and should ideally be observed until trial end as if they were still receiving blinded trial treatment, e.g., follow the regular visit schedule after the early EOT visit. In addition, all early D/C participants must also complete the FUP visit (early drug discontinuation date + 28+2 days) for a full trial safety follow-up. There are 2 options for observing participants after premature drug discontinuation (refer to section 3.3.4 for additional information).

Option 1: An early EoT 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 (if consistent with the planned visit schedule, the eEOT can replace the next regularly scheduled clinic visit). After this early EOT visit, participants should be followed up according to the regularly scheduled visit for both clinic and phone visits until Visit 8 and must complete the FUP Visit 28+2 days after the drug discontinuation date. All procedures should be completed, with the exception of trial drug procedures and [redacted]. If FUP visit (early drug discontinuation date + 28+2 days) can be completed prior to the date of the planned Visit 8, no additional FUP is needed. However, end of study participation must be completed.

Option 2: An early EoT Visit must be conducted within 7 days of the last dose of trial medication. If the participant is not willing to return for all regularly scheduled visits, at a minimum they must return for Visit 8 and FUP. If FUP visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 8, no additional FUP is needed. However, end of study participation must be completed.

1 Prior to any trial related procedure, may also be done at an extra visit up to 2 weeks before V1.

2 Urine drug screen at screening visit only. For WOCBP, a serum pregnancy will be performed at screening and a urine pregnancy tests at all clinic visits beginning with V2. If a urine pregnancy test is positive, a serum test needs to be performed for confirmation.

3 Participants will bring trial medication (used/unused blister and covering packages) to site visits for compliance check (V3/V4/V6/V8) and for resupply (V4 and V6). Participants have to take the morning dose of the IMP, at the trial site at all clinical visits, except EOT at Visit 8 also to allow [redacted]. Last regular intake of the trial drug is the day before EOT visit. Please refer to footnote 4.

[redacted]

7 After the EoStudy visit (= individual participant's end of the trial) the investigator should 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 SAE form, please see section 5.3.6.2.1.

8 Telephonic Visit

9 Day of Randomisation / Day of first intake of randomized medication – all activities, except [redacted] must be done before drug administration.

10 Visit 1A must be scheduled after confirmation of positive urine or blood levels of SSRI/SNRI/bupropion in the screening lab (please note: Duloxetine in blood only) and after completion of Visit 1 scale assessments, [redacted]

[redacted]

12 SSRI/SNRI/ bupropion assessment in urine at screening only, as applicable. See section 5.3.3 for details

13 This must include confirmation from the patient that she is using required contraception consistently and appropriately. Counseling and contraception confirmation must be recorded in CRFs. If contraceptive protection can not be confirmed, as deemed by the investigator, the patient must be discontinued from study drug and can only resume once contraception is used again and sufficient protection is reached

For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to sections 4.1.4, 6.1, 8.1 and 10.4.

FLOW CHART 2

Trial Periods	**Screening Period**		**Randomized Treatment**							**Early D/C**	**FU / EoStudy (EoS)**	**Performance Duration per assessment**
Visit	**1**	**1A** [6]	**2**	**3**	**4**	**5** ☎ [4]	**6**	**7** ☎ [4]	**8 / EOT***	**Early EOT ****	**9**	
Week			**0**	**1**	**2**	**3**	**4**	**5**	**6**		**10**	
Day	-21 to -2		D1 [7]	8±1	15±1	22±1	29±1	36± 1	43+2		(Early drug discontinuation date) / EoT plus 28+2 days	
SCID-5	x											90 min
ATRQ	x											10 min
MADRS rater administered [1]	**2 nd**		1 st	1st	1 st		1 st		1 st	1 st		
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]
SMDDS ***			x	x	x		x		x	x		10 min
STAI ***			x	x	x		x		x	x		10 min
[redacted]			x						x	x		10 min

[redacted]												
C-SSRS	x [2]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	10 min
CGI-S			x	x	x		x		x	x		10 min
[redacted]			x	x					x	x		15 – 20 min
[redacted]	[redacted]	[redacted]										[redacted]
[redacted]	x		x	x	x		x		x	x		10 min
Drug intake adherence [5]			<- ----------morning and evening dose of IMP at clinic site and at home ---------->									5 min
[redacted]		<-------	[redacted]					--------->				
Total Duration	150 min	35 min	125 min	100 min	85 min	15 min	85 min	15 min	120 min	120 min		

At the screening visit, all clinical assessments (Flow Chart 1) should be performed first, followed by the scale administrations, top to down, in the order as shown in Flow Chart 2. For all further clinical visits, scale administrations should be done first, top to down, in the order as shown in Flow Chart 2, followed by the clinical assessments, e.g., Flow Chart 1 (also refer to section 6.2 further details for the order of clinical assessments and scale performance).

* End of treatment for participants who complete the treatment period at Visit 8.

** Participants who discontinue trial drug prematurely must perform an early EOT visit within 7 days and should ideally be observed until trial end as if they were still receiving blinded trial treatment, e.g., follow the regular visit schedule after the early EOT visit. In addition, all early D/C participants must also completed the FUP visit (drug discontinuation date + 28+2 days) for a full trial safety follow-up. There are 2 options for observing participants after premature drug discontinuation (refer to section 3.3.4 for additional information).

Option 1: An early EoT 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 (if consistent with the planned visit schedule, the eEOT can replace the next regularly scheduled clinic visit). After this early EOT visit, participants should be followed up according to the regularly scheduled visit for both clinic and phone visits until Visit 8 and must complete the FUP Visit 28+2 days after the drug discontinuation date. All procedures [redacted] CGI-S, [redacted] are encouraged, but optional) should be completed, with the exception of trial drug procedures and [redacted] will be collected at Early EOT Visit and one at FU visit, e.g., 28+2 days after early drug discontinuation). If FUP visit (early drug discontinuation date + 28+2 days) can be completed prior to the date of the planned Visit 8 days, no additional FUP visit is needed. However, end of study participation must be completed.

Option 2: An EoT Visit must be conducted within 7 days of the last dose of trial medication. If the participant is not willing to return for all regularly scheduled visits, at a minimum they must return for Visit 8 and FUP. If FUP Visit (early drug discontinuation date + 28+2 days) can be completed prior to the date of the planned Visit 8 days, no additional FUP visit is needed. However, end of study participation must be completed. Please note: [redacted] CGI-S, [redacted] are encouraged, but optional for eEOT

*** Patient completed assessments

[redacted]

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

[3] C-SSRS: Columbia Suicide Severity Rating Scale since-last-visit scale

[4] ☎ = Telephonic Visits

[5] Self-monitoring of IMP intake each treatment day in the morning and evening by the participant via the smartphone app. (Training of the participant on the app at Visit 1A).

[6] Visit 1A must be scheduled after confirmation of positive urine or blood levels of SSRI/SNRI/bupropion (please note: Duloxetine in blood only) in the screening lab and after completion of Visit 1 scale assessments. [redacted] The drug-adherence assessments will start with the first administration of the trial drug at randomization. [redacted].

[7] All baseline assessments must be performed prior to the first intake of the trial medication

[8] Short informational videos to be shown to paricipants to educate [redacted] about placebos (mandatory at V1A) - see further details in section 6.2.

For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to sections 4.1.4, 6.1 and 10.4.

TABLE OF CONTENTS

ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criteria
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AST	Aspartate Aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Protein
BI	Boehringer Ingelheim
BoPD	Borderline Personality Disorder
CA	Competent Authority
CCK-4	Cholecystokinin Tetrapeptide
CGI-S	Clinical Global Impression Severity Scale
CI	Confidence Interval
ClinRO	Clinical 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
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CYP	Cytochrome P450
DASM	Data Analysis Methodology
DBL	Database Lock

DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
EC50	Half maximal effective concentration
ECG	Electrocardiogram
[redacted]	[redacted]
eCOA	electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
ED	Effectiove Dose
eDC	Electronic Data Capture
EoStudy / EoS	End of Study
EoT	End of Treatment
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
[redacted]	[redacted]
FST	Forced Swim Test
FU / FUP	Follow Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GMP	Good Manufacturing Practice
HA	Health Authority
HDL	High Densitiy Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator’s Brochure
IC	Informed Consent

ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine System
LDL	Low Density Lipoprotein
LPLT	Last Patient Last Treatment
LS	Least Square
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at random
MCPMod	Multiple comparisons procedure – modelling
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligramme
MGH	The Massachusetts General Hospital
MMRM	Mixed effects model for repeated measurements
MRTpo	gMean of mean residence time after oral dosing
MRD	Multiple Rising Dose
nM	Nanomole
NIMH	National Institute for Mental Health
NOAEL	No Observed Adverse Effect Level
OAD	Ongoing Antidepressants
OAT	Organic Anion Transporter
OPU	Operative Unit
[redacted]	[redacted]
PCR	Polymerase chain reaction
P-gp	P-Glykoprotein
PK	Pharmacokinetics
PoC	Proof of concept
PRO	Patient Reported Outcomes

PSS	panic symptoms
PV	Pharmacovigilance
QD	quaque die (once a day)
[redacted]	[redacted]
QM	Qualification Methodology
QTcF	Corrected QT interval by Fredericia
RA	Regulatory Authority
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAE	Serious Adverse Event
SC	Steering Committee
SCID-5	Structured Clinical Interview for DSM-5 Clinical Trials
SCR	Screening
SD	Standard deviation
[redacted]	[redacted]
SE	Standard Errors
SIB	Suicidal Ideation and Behavior
SMDDS	Symptoms of Major Depressive Disorder Scale
SmPC	Summary of Product Characteristics
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SNDRI	Selective Norepinephrine Dopamine 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
t.i.d.	ter in die (3 times a day)
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
[redacted]	[redacted]
TS	Treated Set
TSAP	Trial statistical analysis plan

UGT	UDP-Glucuronosyltransferase
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

MDD is a debilitating disease that is difficult to treat, even when using systematic antidepressant strategies. In the National Institue 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 residuals symptoms [R16-5475] which significantly impacted the patients' quality of life.

When monotherapy with a Selective Serotonin Reuptake Inhibitor (SSRI) / Serotonin Norepinephrine Reuptake Inhibitor (SNRI) / bupropion (Selective Norepinephrine Dopamine Reupdate Ingibitor (SNDRI) 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, convulsive therapies such as electroconvulsive therapy (ECT) can be used.

[redacted]

[redacted]

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

Despite the array of available treatment options, 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.

[redacted]

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.

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.

[redacted]

[redacted]

While there are no precedent clinical data implicating association between [redacted] 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 clinic visits and assessment of suicidal ideation during clinic 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.

The trial will be monitored by an external Data Monitoring Committee (DMC), independent from the sponsor; refer to section 8.7 for further DMC details.

[redacted]

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 or comparator imply 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 or comparator 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 patient'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 patient and the site environment.

For details on treatment related risks, refer to CTP section 1.2 and the IB.

Table 1.4.2:1 Overview over 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		
[redacted]	[redacted]	Management of symptoms, evaluation, and follow-up as needed to ensure participant safety, per investigators clinical judgment.
[redacted]	[redacted]	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 IMP per the clinical judgment.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product - BI 1358894		
[redacted]	[redacted]	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 of the statin 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.

[redacted]	[redacted]	WOCBP must adhere to contraceptive measures consisting of one highly effective method of birth control per ICH M3 (R2) during the treatment and follow-up period. Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active. Investigator must ensure that the patient understands the contraception requirements for the study and must confirm that the patient can reliably comply with contraception use during the study. Patients not expected to comply with contraception requirements should not be included in the study. Pregnancy testing must be performed at every site visit. Investigators must counsel WOCBP with regard to the need for contraception at all visits as per Flow chart (including phone visits). This must include confirmation from the patient that she is using required contraception consistently and

		appropriately. If contraceptive protection can not be confirmed, as deemed by the investigator, the patient must be discontinued from study drug and can only resume once contraception is used again and sufficient protection is reached
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/bupropion and psychotherapy, where applicable. Placebo is adjunctive to this treatment. Frequency of clinic visits with suicidality assessments are optimized. Suicidal participants will be excluded form trial participation (refer to section 3.3.4.1)
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Quetiapine		
[redacted]	[redacted]	Management of symptoms, evaluation, and follow-up as needed to ensure participant safety, per investigators clinical judgment.

[redacted]		
[redacted]	[redacted]	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 IMP per the clinical judgment.
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
quetiapine Placebo		
[redacted]	[redacted]	• Participants will remain on their stable anti-depressive treatment with an SSRI/SNRI/bupropion and psychotherapy, where applicable. Placebo is adjunctive to this treatment. • Frequency of clinic visits with suicidality assessments are optimized. • Suicidal participants will be excluded form trial participation (refer to section 3.3.4.1)

General risk of psychoactive drugs		
[redacted]	[redacted]	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.
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 285 mL over 13 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 and quetiapine is administered.	First dose of BI 1358894 administered on site, with safety clinic 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 patient population, and the need to adequately monitor suicidality, frequent clinic and phone visits, which include C-SSRS assessments, are planned in this trial to monitor participants.

Additionally, all participants will be on stable treatment of MDD with an SSRI/SNRI/bupropion at the time of trial entry and throughout the whole trial performance. 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.

[redacted] It is of high importance that WOCBP strictly adhere to contraceptive measures consisting of one highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% plus one additional barrier method during the treatment and follow-up period of the study. Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active. Pregnancy testing has to be performed at every site visit. Additionally, WOCBP will be repeatedly counselled with regard to the need for contraception at all vists as per Flow Chart (including phone visits).

Given the acceptable and manageable safety profile of BI 1358894 as demonstrated in nonclinical and toxicology studies, good tolerability in clinical studies performed to date, close monitoring (including the above mentioned activities to minimise the risk of pregnancy during the trial) planned during the trial visits and the involvement of an independent external DMC, the potential risks to the participants will be minimized and outweighed by a potential therapeutic benefit of the trial drug.

Quetiapine is approved in US and the European Union for augmentation of antidepressants therapy in patient with inadequate response to antidepressant monotherapy. Hence, a treatment arm with quetiapine at adequate dose according to SmPC in patients on stable treatment with an SSRI/SNRI/bupropion is regarded as ethically acceptable.

2. TRIAL OBJECTIVES AND ENDPOINTS

The main objectives of this trial are to provide proof of concept (PoC), assess dose-ranging data of BI 1358894 compared to placebo in participants with Major Depressive Disorder who show inadequate response to ongoing antidepressant treatment and to support the dose selection for pivotal studies.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

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

The trial will be performed to characterize the dose-response curve for BI 1358894 in participants with MDD by assessing 4 doses and placebo. The response is the change from baseline in MADRS total score at Week 6 summarized per arm by the adjusted mean. The multiple comparison procedure with modelling (MCPMod) approach will be used to characterize the dose-response curve.

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

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

2.1.2 Primary endpoint(s)

- Change from baseline in MADRS total score at Week 6

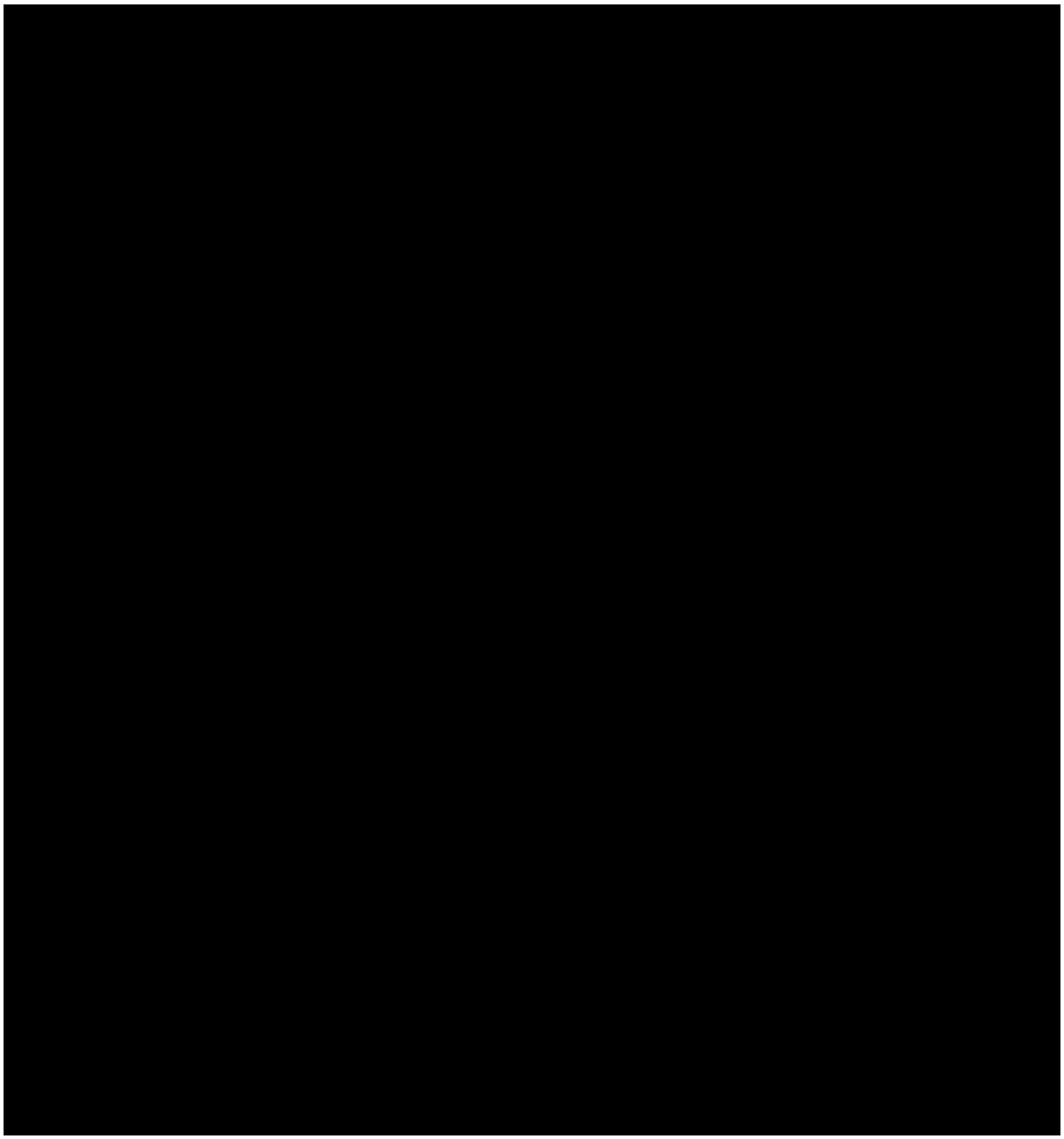
2.1.3 Secondary endpoint(s)

MADRS
- Response defined as ≥ 50% MADRS reduction from baseline at Week 6

STAI
- Change from baseline in STAI State and Trait version scores at Week 6

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

SMDDS
- Change from baseline in SMDDS total score at Week 6



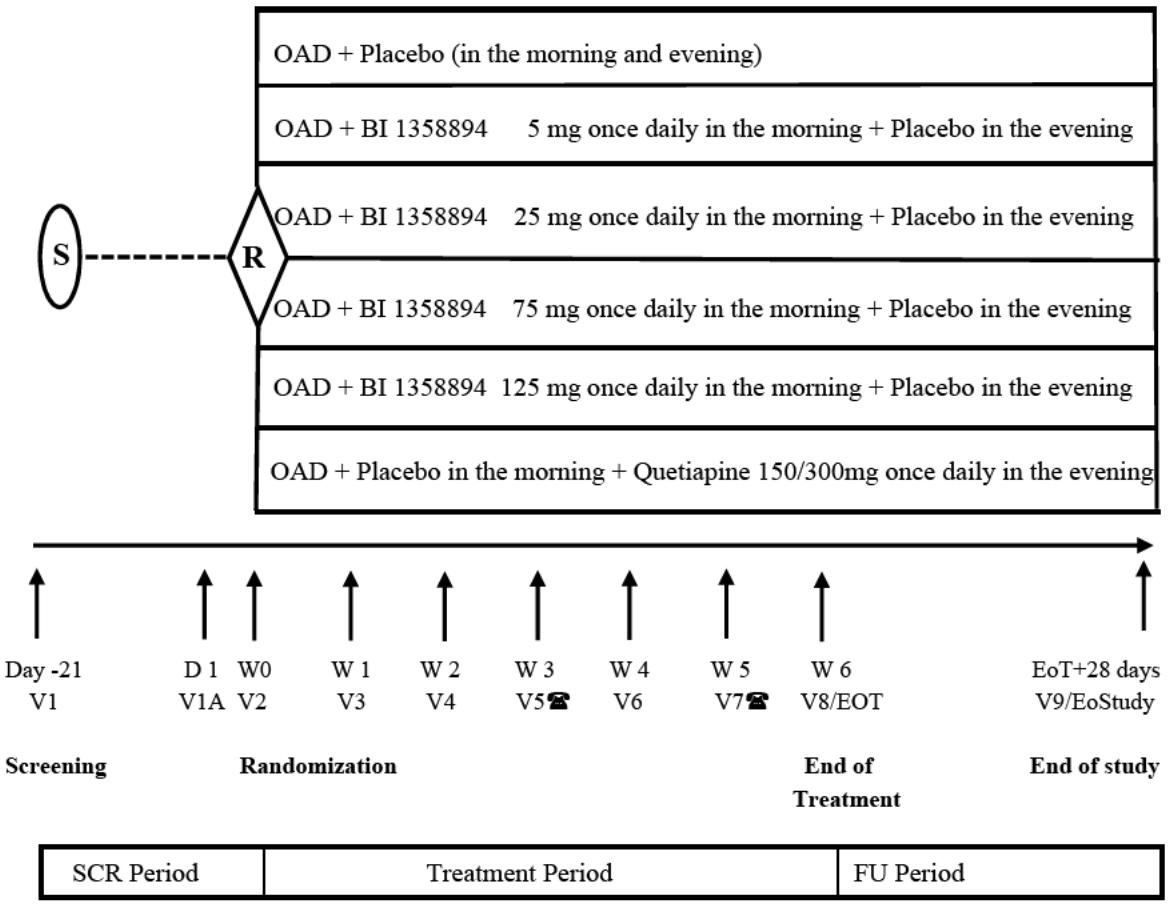
2.2.3 Safety

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a Phase II, 6-week parallel-group multicenter, randomized, double blind, double-dummy, placebo-controlled trial with a Quetipine arm in participants with Major Depressive Disorder with inadequate response to ongoing treatment with an SSRI or an SNRI or bupropion. In total, approximately 431 male and female participants with MDD meeting the entry criteria are planned to be randomized into this trial.



V = Visit, W = Week, EOT = End of Treatment, EoStudy = End of study,
OAD = Ongoing Antidepressants (SSRI/SNRI/bupropion),
☎ = Telephonic Visit

Figure 3.1: 1 Trial design

Participants are enrolled into the trial once informed written consent has been obtained. Eligible participants with background SSRI/SNRI or bupropion will be randomized to double-blind, add-on treatment, with either quetiapine at 150-300 mg QD (approx. n=82), placebo (approx. n=144), or BI 1358894 at 5 mg QD (approx. n=41), 25 mg QD (approx. n=41), 75 mg QD (approx. n=41), or 125 mg QD (approx. n=82). Total treatment duration will be six weeks, refer to Figure 3.1: 1.

After the completion of the 6-week double-blind treatment period, or following early discontinuation of trial 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 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 participant 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 randomized double-blind, placebo-controlled, parallel-design trial with an additional quetiapine arm as reference. This design is appropriate for providing proof-of- concept/dose range finding and assessing the safety and efficacy of BI 1358894 compared to placebo in participants with MDD. It is important to have a placebo control to address potential confounding factors. This is acceptable as participants will remain on their standard anti-depressive treatment (including ongoing stable psychotherapy, where applicable) and the duration of the placebo treatment will be limited to 6 weeks.

As BI 1358894 is a First-in-Class compound with a new therapeutic concept and mode of action, inclusion of an approved medication arm for the targeted population (i.e. quetiapine) is planned in this trial for reference. Descriptive comparisons between the quetiapine and placebo arms will be conducted to monitor the impact of placebo response in this trial. No formal hypothesis testing will be performed to compare BI 1358894 to quetiapine or to compare quetiapine to placebo.

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

A total of four active BI-doses will be administered to provide reasonable coverage for most monotonic shapes. A sufficiently broad set of candidate shapes for the dose-response relationship has also been chosen. In addition, an unequal allocation ratio (3.5:1:1:1:2) has been selected for the treatment and placebo groups. In general, an allocation of a higher proportion of participants to the placebo and active dose of interest versus other treatment arms will lead to better precision which then leads to a higher power. In addition, increasing the proportion of participants in the placebo group compared to other treatment arms may lead to the observation of a greater separation between the placebo and active treatment arms [P09-01434]. Details of the statistical approach including the set of candidate models as well as a sample size justification are given in section 7.5.

Data at Week 6 will provide evidence of efficacy and dosing information of BI 1358894 compared to placebo. In addition, we will also obtain safety data through the end of observation period (early drug discontinuation date / eEOT+28+2 days). [redacted]

[redacted] Collectively, this information will help facilitate the design of the Phase III program.

BI 1358894 is regarded as a first in class compound, hence, it was decided to include the review of data by an Independent Data Monitoring Committee (DMC), independent from the sponsor, to review the trial data as a general safety measure. The purpose of the DMC is to ensure that the safety of the participants participating in this trial is maintained by monitoring for possible untoward harmful effects or unexpected frequency of adverse safety events of trial drugs based on emerging data.

The DMC will evaluate and analyse accrued participant data in order to recommend whether the trial or program should continue, be modified or stopped for safety concerns.

The DMC will review pertinent trial data, including SAEs, AEs and laboratory data. DMC meeting frequency and logistics will be specified in a separate DMC Charter.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 431 participants is planned to be randomized into the trial. It is planned that about 86 trial centers in 14 countries will be participating in this trial to ensure a sufficient number of participants are randomized.

It is expected that approximately 6-10 participants will be randomized at each trial center. If enrolment is delayed, additional sites may be recruited. To avoid differential center influence on trial results, permission to randomize more than 15 participants per site must be obtained from the sponsor. This will only be allowed after a careful review of the enrolment status and the site.

Screening of participants for this trial is competitive, i.e., screening for the trial will stop at all centers when such a number of participants has been screened that it is anticipated that a sufficient number of participants will be randomized to trial treatment. Investigators will be notified when the appropriate number of participants has been screened and screening is complete, and will not be allowed to recruit additional participants for this trial.

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

If a participant is enrolled 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 Clinical Trials (SCID-5).

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 (MDD), 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 ≤ 24 months at the time of screening visit.
2. Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 24 at screening, as confirmed by a trained site based rater AND interactive, computer administered MADRS. The difference in the rater and computer administered MADRS must not exceed more than 7 points (for details refer to section 6.2). In addition, trial participants must have a score of ≥ 3 on the Reported Sadness Item on both MADRS scales (computer-administered and rater-administered MADRS).
3. A documented ongoing monotherapy treatment of ≥ 4 weeks at the screening visit, with bupropion or 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 who are of child-bearing potential (WOCBP) [1] must be able and willing, as confirmed by the investigator, to 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 additional barrier (refer to section 4.2.2.3).
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.

[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 occlusion/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 more than 2 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 bupropion or 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/bupropion until the end of the trial or end of treatment (eEOT/EOT), respectively.
- Participants, who, in addition to their monotherapy with an SSRI/SNRI/bupropion, are taking additional low dose antidepressant medications for purposes other than treating depressive symptoms, are not excluded. The dose must be less than the lowest dose indicated for MDD (see ISF for details).
- 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 quetiapine or the matching placebos, respectively.
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).
19. Have received electroconvulsive therapy and/or administration of Ketamine /S-Ketamine for the current ongoing depressive episode and/or transcranial magnetic stimulation (TMS) for the current ongoing depressive episode or within 12 months prior to screening.
20. Have a lifetime history of vagal nerve stimulation or psychosurgery.
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening.
23. Participants not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
24. Considered by the investigator, for any other reason, to be an unsuitable candidate for the trial.

25. Participants who were confined to an institution by court or administrative order.
26. Participants who are dependent on the Sponsor, the investigator or the trial site.

3.3.4 Withdrawal of participants from treatment or assessments

Every effort should 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 participant 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, every effort should be made by the site staff to encourage participants to remain in the trial if medically safe. Participants who discontinue trial drug prematurely should ideally be observed until the end of the trial (week 10) as if they were still receiving blinded trial treatment. Participants should complete the early End of Treatment (eEOT) procedures as described in the Flow Charts and Section 6.2.2. If a participant refuses to return for all further visits after early treatment discontinuation, the participant should be encouraged to complete at least the week 6 visit as scheduled and a FUP visit 28+2 days after date of trial drug discontinuation. If FUP visit (early drug discontinuation + 28+2 days) can be completed prior to the date of the planned Visit 8, no additional FUP is needed. However, end of study participation must be completed.

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.

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 should be withdrawn from the trial before discussion with CTL.

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 or TMS.
- 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 should 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).
- 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 CRF. 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.

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 should 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 overall, or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. 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].

Quetiapine extended release tablets have been manufactured by [redacted]. Placebos, matching quetiapine, have been manufactured by [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:	5 mg, 25 mg, 50 mg
Posology:	QD
Mode of administration:	Per os

Table 4.1.1: 2 Quetiapine

Substance:	quetiapine extended release
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	50 mg, 150 mg
Posology:	QD
Method and route of administration:	Per os

Table 4.1.1: 3 Placebo matching BI 1358894

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

Table 4.1.1: 4 Placebo matching quetiapine

Substance:	Placebo matching quetiapine extended release
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany; [redacted]
Unit strength:	N.A.
Posology:	QD
Method and route of administration:	Per os

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 Treatment with BI 1358894

The following doses are selected for this trial:
5 mg, qd
25 mg, qd
75 mg, qd
125 mg, qd

The criteria for selection are based on preclinical and clinical data of BI 1358894 gathered during research and development.

In general, dose range finding studies intend to test a broad range of exposures for dose finding using the MCPMod approach.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.2.2 Treatment arm with quetiapine

After up-titration from Day 1 until Day 4 from 50 mg to 150 mg quetiapine, once daily, the targeted daily treatment dose until end of treatment will be 300 mg, which is the recommended daily dose according to the SmPC for the augmentation therapy as standard of care for the indication MDD.

If a participant, in the medical judgment of the investigator, and assuming that the participant is assigned to the treatment arm with quetiapine, is not able to tolerate the evening dose, then there is a one-time option of reducing dosage from two tablets (equals to 300 mg quetiapine /Placebo) to one tablet (equals to 150 mg quetiapine or placebo) in the evening, on Week 1 (V3) visit.

Thereafter, this finally chosen dose must be stable until end of treatment at Week 6. Further adjustments of the assumed daily quetiapine dose are not allowed and will lead to an early discontinuation.

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 plan at Visit 2 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 with an allocation ratio of 3.5:1:1:1:2:2 to the following treatment groups:

- Placebo matching BI 1358894 and placebo matching quetiapine
- 5 mg BI 1358894
- 25 mg BI 1358894
- 75 mg BI 1358894
- 125 mg BI 1358894
- 300/150 mg quetiapine

Participant assignment to 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.

Randomization into each treatment groups will be stratified by baseline MDD severity (baseline MADRS score ≤19 versus >19).

The kit(s) corresponding to the assigned medication number(s) should be given to the participant and 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. The duration of treatment is 6 weeks. The last dose of trial medication should be taken on the day before the EOT Visit.

At Visit 2, after randomization, participants will receive medication kits for the double-blind treatment period. The morning dose of trial medication will be taken at the trial site under supervision of the investigator or site staff. Participants will bring trial medication (used/unused blister and covering packages) to site visits for compliance check (V3/V4/V6/V8). At visits V2, V4 and V6, participants will return used/unused medication kits and receive new supplies for a total of 14 treatment days (14 treatment days plus 3 days reserve) for BI 1358894 and quetiapine.

Participants should be instructed not to take their trial medication in the morning of Visit 4 and Visit 6, as participants will be dosed at the site [redacted]. Participants should also be instructed not to take their trial medication in the morning of Visit 8/EOT/eEOT Visit, as a [redacted] at that visit. For participants who complete the treatment period, the last dose of trial medication should be taken on the day before the EOT Visit. Participants who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day.

Participants should 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 should be skipped and the next dose should be taken as scheduled. On days prior to a visit, the morning dose should be taken approximately 24 hours before the planned morning dose at the clinic visit. A dose reduction of BI 1358894 is not possible.

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

	5mg tablet	25mg tablet	50mg tablet	PBO matching 5mg tablet	PBO matching 25mg tablet	PBO matching 50mg tablet
Dose group	**Number of tablets to be taken daily – in the morning ☼**					
PBO	0	0	0	1	1	2
5 mg	1	0	0	0	1	2
25 mg	0	1	0	1	0	2
75 mg	0	1	1	1	0	1
125 mg	0	1	2	1	0	0

Quetiapine or matching placebo should be taken prior to bedtime. The daily active dose at the start of therapy is 50 mg on Day 1, 100 mg at Day 2 and 150 mg on Day 3 and 4. Beginning with Day 5, the recommended daily dose of 300 mg will be taken. If an evening dose is missed before midnight, that dose should be skipped and the next dose should be taken the next evening. On days prior to a visit, the evening dose should be taken at least 8 hours before the planned dose at the visit.

Table 4.1.4: 2 Dosage and Treatment Schedule for Quetiapine / Matching Placebo Titration and Maintenance Phase

	50 mg tablets or matching placebo	150 mg tablets or matching placebo
Trial Day	**Number of tablets to be taken daily – in the evening ☾**	
Day 1	1	0
Day 2	2	0
Day 3	0	1
Day 4	0	1
Day 5 - 43	0	2

The need to decrease the dose from 300 to 150 mg/day should be based on individual participant evaluation. In this case, the PI will instruct the participant to only take one tablet of the evening dose instead of two. This dose reduction is a one-time option at Visit 3 after the first week of treatment.

During the COVID-19 pandemic, there might be situations that would not allow a participant to come to the site for the study visit. If the investigator judges it as acceptable and safe to continue trial medication, trial medication might be shipped from the site to the participant (for more details see section 6.1 and 10.4).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

At each treatment day, all participants will take the trial medication in the morning and in the evening to ensure the blinding of their treatment arm. Participants, investigators, central reviewers, 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 randomisation code will be kept restricted until its release for analysis.

The randomisation codes will be provided to bioanalytics prior to last participant completed [redacted] Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

Dedicated database snapshots (no partial DBL) will be generated prior to DBL to allow for development and refinement of [redacted]

No formal interim report will be generated. Final [redacted] will be reported once after availability of data from DBL.

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 CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing

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

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

4.1.7 Storage conditions

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. They must not be forwarded to other investigators or clinics. Participants should be instructed to return used (empty blisters) 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

A list of restricted concomitant medications and drugs with potiential 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, TMS and Ketamine/S-Ketamine are restricted during the trial and 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:

- 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/bupropion until the end of the trial or end of treatment.
- Participants, who, in addition to their monotherapy with an SSRI/SNRI/bupropion, are taking additional low dose antidepressant medications for purposes other than treating depressive symptoms, are not excluded. The dose must be less than the lowest dose indicated for MDD (see ISF for details).
- 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 concomitant use of benzodiazepines or non benzodiazepine hypnotics during the trial for up to 7 days at dose equivalent to $\leq$ 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 the 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 actual Investigator´s Brochure 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. A urine drug screen will be performed at selected trial visits (see Flow Chart 1). 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 participants 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 come 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 additional barrier method. Contraception must be used during the treatment and follow-up period.

Women of childbearing 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.

Counseling about the importance of having birth control measures in place will be performed at study entry visit (during consenting process), informing woman about the risk of medication-induced births defects when exposed to potentially teratogenic medication. Investigator must ensure that the patient understands the contraception requirements for the study and must confirm that the patient can reliably comply with contraception use during the study. Patients not expected to comply with contraception requirements should not be included in the study.

The importance of continuing with their chosen forms of birth control during study conduct will be emphasized to mitigate this risk and it must be reiterated at all visits as per Flow Chart (including phone visits).This must include confirmation from the patient that she is using required contraception consistently and appropriately. Counseling and contraception confirmation must be recorded in CRFs. If contraceptive protection can not be confirmed, as deemed by the investigator, the patient must be discontinued from study drug and can only resume once contraception is used again and sufficient protection is reached.

Acceptable forms of contraception 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. Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active.

plus one of the barrier methods:

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

4.3 TREATMENT COMPLIANCE

Participants are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on non-missing tablet counts, treatment compliance for the morning and separately for the evening dose between following clinic visits will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

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

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 should discuss and document the reasons on the eCRFs.

5. ASSESSMENTS

5.1 CONFIRMATION OF DIAGNOSIS

The (SCID-5) Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th 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 semistructured 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.

Eligibility of potential participants will be confirmed by agreement with external clinical reviewer, in which screening data will be obtained to evaluate psychiatric status. The SCID and rater MADRS will be audio recorded at the Screening Visit 1. The SCID and MADRS recordings will be reviewed by an independent external clinical reviewer from [redacted].

5.2 ASSESSMENT OF EFFICACY

The current status of MDD will be assessed during course of the trial by using the MADRS, and SMDDS scores and, in a wider perspective, with the outcomes of the STAI, CGI-S, [redacted]

5.2.1 MADRS - Montgomery–Asberg 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).

5.2.2 ATRQ - Antidepressant Treatment Response Questionnaire

The Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) as the clinician-administered version will be used to determine treatment resistance in MDD. The MGH ATRQ customized for this study defines the minimal required duration of at least 4 weeks on an adequate dose of antidepressant medication. 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.

5.2.3 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 scale will be collected using the rater station eCOA tablet.

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 60 with a higher score indicating more severe depressive symptomatology.

5.2.4 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.

5.2.5 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.

[redacted]

[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 1. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

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

The results must be included in the source documents available at the site.

5.3.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart 1, 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.

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 1.

Analyses will be performed by a central laboratory, the respective reference ranges will be provided in the lab manual, except in cases where the ESR will be done locally in which case the ESR results must be recorded in the CRF.
Confirmation of detectable levels of background SSRI/SNRI/bupropion, either shown in urine or serum (as applicable), will be accepted for eligibility. The test in serum is mandatory and must be performed at screening and EOT. If a negative result in serum is received prior to randomization, then the patient will be a screen failure. Please also note, that Duloxetine cannot be measured in urine but in serum, only.

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

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 adverse events (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 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 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.

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	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count/ Erythrocytes Erythrocyte sedimentation rate (ESR) (either assessed centrally or locally)* 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
Chemistry	Albumin 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

Category	**Test name**
Chemistry (continued)	Protein, Total C-Reactive Protein Cholesterol, total Triglycerides TSH (Reflex testing for fT3 and fT4 if TSH > ULN) Testosteron[3] LH[3] FSH[3] Folate eGFR using the CKD-EPI equation
SSRI/SNRI/bupropion detectable drug levels in serum[1] or urine[4] (as applicable)	Bupropion Duloxetine[1] 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 clinic 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
Urinalysis (dipstick), with microscopic examination if urine analysis is abnormal	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Blood Leukocyte Esterase Urine pH
Urinalysis	Albumin (quantitative) Creatinine

Category	Test name
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 Vaccine (HCV) RNA – only if Hepatitis C antibodies (qualitative) are positive

[1] At screening and EOT only, duloxetine in serum only

[2] At screening only

[3] Males only

[4] At screening only (as applicable)

* In this protocol, ESR testing is used solely for the collection of data for analysis purpose at the end of the trial, per FDA's recommendation. The ESR Testing results are not intended to be used as Safety Parameter or for medical management decisions. For medical management decisions of Safety relevant inflammation parameter, the CRP test should be used.

For assessment of the kidney function, the formula of the estimated glomerular filtration rate (EGFR) CDK-EPI (Chronic Kidney Disease Epidemiology Collaboration) and EGFR CKD-EPI –JAPAN, respectively, will be used. This requires that ethnicity need to be captured. See details in the ISF.

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart 1. 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 baseline assessment (Visit 1) should 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. A centralized and independent re-evaluation will be done. 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 in the responsibility of the investigator.

5.3.5 Other safety parameters

5.3.5.1 Assessment of Suicidality

Suicidal risk assessed by the C-SSRS (clinician interview version equivalent to the paper-version, shall be administered electronically via a tablet/rater station):

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

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health 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 behaviour, and may be expanded to up to 17 items in case of positive responses. Freetext 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 lifetime history of suicidal ideation and behavior will also be recorded.

After screening (Visit 1) the assessment ‘since last visit’ will be performed at each clinic 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 clinic 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 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. Please note, that adverse event reports, that get coded to terms like suicidal depression, suicidal ideation, suicidal threat or similar, are on the "Always serious AE List" and therefore must be reported as SAEs (refer to section 5.3.6.1.3).

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

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 patient or clinical investigation patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

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

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):
- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should 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 fulfills at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,

- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the participant and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

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 should always be reported as SAEs as described in section 5.3.6.2.

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 5.3.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

Suicidal ideation terms are also part of the Always Serious AE list.

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 5.3.6.2.2.

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.

No other AESIs have been defined for this trial.

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 patient 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.

[redacted]

[redacted]

5.7 OTHER ASSESSMENTS

[redacted]

[redacted]

[redacted]

5.7.5 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 [redacted]. 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 [redacted], 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.

5.8 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 1 and Flow Chart 2. 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 come to the site for the scheduled visit. This might be e.g. due to restrictions set by authorities or by the investigator site/institution, because the participant is quarantined, or because of any participant-specific situation that the investigator judges as being not safe for the participant to come to the site.

For details on potential modifications of the trial conduct related to the COVID-19 pandemic, please refer to section 10.4.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures to be performed at each visit are listed in the Flow Charts. Additional details regarding visit procedures are provided below.

The following requirements for the conduct of the 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.
- At the screening visit, all clinical assessments (Flowchart 1) should be performed first, followed by the clinical outcome measurements (scale assessments - Flow Chart 2). After the screening visit, the scales should be performed first (Flow Chart 2), followed by the other clinical examinations (Flow Chart 1). All scales should be completed in the order as noted in the Flow Chart 2, top to down.

Each assessment of the site-rater administered scales (MADRS, CGI-S) should preferentially be done by the same members of the site staff for a given participant throughout the trial period. However, the rater who performs the C-SSRS and/or AEs should not also perform the MADRS and CGI-S for the same patient to prevent bias.

- Results of the MADRS assessments at screening are part of the eligibility evaluation (see below).

- All SCID and MADRS rater performed administrations will be audio recorded for central review by the vendor for quality assurance.
- During the neuropsychological testing, participants are allowed to take short breaks as needed, in the judgement of the rater/investigator.

The Baseline/screening scale of the C-SSRS will be administered for eligibility confirmation and the follow-up scale at all visits (if a visit is done over several days, only 1 C-SSRS follow up scale is needed per visit) for assessement of suicidality. If there is an unscheduled visit due to suicidal ideation or behavior, it is up to the investigator judgement as to what appropriate testing should be completed as part of that evaluation.

[redacted]

It must be reiterated, at all visits as per Flow Chart, that WOCBP are using the appropriate method of safe contraception pursuant to section 4.2.2.3.

Screening Period

No trial procedures should be done unless the participant has consented to taking part in the trial. Prior to any trial related procedure, the patient information and informed consent may also be done at an extra visit up to 2 weeks before V1. After given informed consent, the screening period will start with the first trial related procedure. The participant should be recorded on the enrolment log. The participant should be registered in IRT as a screened participant.

Visit 1: The screening visit must take place no more than 21 days before Visit 2. Within the screening period, screening procedures may be extended to more than one physical visit (in addition to Visit 1A), if needed. In such a case, the clinical assessments (Flow Chart 1) should be done on the first day and the scale assessments (Flow Chart 2) within 7 days of completing the clinical assessments. Completing required procedures for a visit over more than one day is only allowed for Visit 1. The screening period (i.e., period between Visit 1 and Visit 2) may be extended by additional 7 days (i.e., 28 days in total) for reasons including, but not limited to, the following: administrative reasons, receipt of lab SSRI/SNRI/bupropion results, adverse event, etc. If screening period needs to be extended any further, the clinical trial leader should be contacted to discuss further steps.

[redacted]

[redacted]

Demographics and Baseline Conditions
Information on race will be collected because this demographic information is required for the calculation of eGFR (CKD-EPI formula). Blood pressure should 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 should be recorded as a baseline condition.

Medical History
In order to collect previous medical reports to keep records of exact dates/diagnoses of relevant medical history or prior medication, up to three documented attempts at different days should be made and documented.

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 clinic 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 (refer to further samples in the ISF), will be collected throughout the trial from screening to FUP visit.
Clinical outcome assessments will also be performed as summarized in the trial Flow Chart 2.
Participants will be instructed to continue allowed/ required background medication without changes and to adhere to their administration algorithm.

[redacted] Subject Eligibility Review:

Eligibility of potential patients will be confirmed by external clinical review (i.e., [redacted] clinical reviewer). At the Screening visit, participant eligibility will be based on an external clinical review of the MADRS and SCID-5 data and audio recording of the administration of MADRS and SCID-5-CT. Any uncertainty raised by the external clinical reviewer of these scales related to inclusion/exclusion criteria will be discussed with the investigator/rater in order to establish confidence in the diagnosis and level of symptom severity. The external clinical reviewer will determine whether the participant is eligible to be randomized pending other screening procedures and issue a notification to the site regarding the participant eligibility. Patients for whom diagnostic/severity agreement between the investigator/study center clinician and the vendor clinician(s) cannot be reached may not be appropriate for study participation and should not be enrolled. Sites will be issued a notification from [redacted] regarding eligibility for a potential subject before randomization can occur.

[redacted]

[redacted]

[redacted] Data Correction Management:
[redacted] will manage the data correction process in this study. All data corrections requested by the sites will be processed and tracked by [redacted] Data corrections made to clinical assessments will be reviewed by a [redacted] ician. Access to the system is restricted to authorized users, each with a unique username and password. All data collected in, and access to, the system is captured in an audit trail, which includes an unalterable time and date stamp and the authorized user's identification for each data point and action.

Retesting:
Participants with unexpected lab values at Visit 1 may be re-tested once within the 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.

Rescreening 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 Clinical Trial Leader (CTL). All screening examination must be repeated, and new participant number assigned, in case of re-screening.

Potential reasons for rescreening could be:
- Positive urine drug screen
- Restricted medications like [redacted] alternative or traditional medicine
- Clinically significant findings per Investigator's judgement

All subsequent visits should be scheduled.

Visit 1A: This visit should be completed as soon as confirmation of positive urine or blood levels of SSRI/SNRI/bupropion (as applicable) has been received but at least 2 days prior to the planned randomization visit. [redacted]

In addition, participants will watch a short informational video intended to educate the participant about placebos, 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, be they positive or negative or neutral.

6.2.1 Treatment period(s)

General remarks
IRT should not be called in advance of Visit 2 until eligibility is fully confirmed, as randomization of a participant cannot be reversed.

Unscheduled visits 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.

Background medications (SSRI/SNRIs/bupropion)
The background antidepressive medications will be taken as usual (also at 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 national guidelines.

[redacted]

[redacted]

Visit 2 (Randomization)
At the start of Visit 2, it should be ensured that all Visit 1 procedures have been successfully completed and eligibility has been confirmed.

IRT should not be called in the event of a positive urine pregnancy test (to be completed locally on-site using kits provided by central lab). In this case, a serum pregnancy test can be performed by the central lab for confirmation at the discretion of the investigator, and a negative serum pregnancy test result must be received before the participant can be randomized.

Upon randomization via the IRT, sufficient trial drug for 14 days (14 treatment days plus 3 days reserve) will be dispensed. The first dose should be taken at the clinic after all Visit 2 assessments are completed (except post-dose PK samples and EcMAs at end of day).

Trial medication is administered after predose blood collection. In addition to [redacted] and safety laboratory samples, a sample for optional plasma/serum and [redacted] will be collected if Informed Consent is provided. [redacted]

Visit 3, Visit 4, Visit 6
On the day of a clinic visit, the participant will take the morning dose of the trial drug at the trial site and not at home.

Phone visits
Visits V5 (week 3) and V7 (week 5) will be conducted via phone.

Visit 8 / End of Treatment (EOT) Visit
Visit EOT (at treatment Week 6) represents the regular end of the treatment period. Last trial drug administration should occur one day before the Visit EOT. The overall duration of the anticipated treatment period (1st drug administration to the last drug administration (1 day prior to EOT Visit) should be 42 days. Visit 8 will be performed only for participants that had early treatment discontinuation.

Participants prematurely discontinuing trial drug
Participants who discontinue trial drug prematurely should ideally be observed until trial end as if they were still receiving blinded trial treatment. If this is not possible, then participants should be encouraged to come back to the site and complete week 6 visit procedures, with the performance of the MADRS scale as a minimum requirement. See section Flow Charts and 3.3.4. for further options.

Withdrawal of consent
If a participant is not willing to continue in the trial until to the end of the trial, Visit 8 should be scheduled and completed instead of the next scheduled visit as soon as possible. Also the EoStudy visit should be performed to assess and monitor safety. If the participant refuses to participate at an EOT Visit and withdraws consent for any reason (without the need to justify the decision), the trial completion page of the eCRF has to be filled in. All unused trial medication will be collected and trial drug diary will be checked by the site. If participant discontinues prematurely for safety reasons or withdraws consent, trial medication administration and [redacted] will not be performed at EOT Visit (please refer to section 3.3.4.1).

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.

6.2.2 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 return to the clinic for the end of study (EoStudy) Visit 9. Trial completion is defined as participants having reached the FUP visit within the specified window per the Flow Chart 1. The trial completion page in the eCRF has to be entered.

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 attend a follow up visit at the trial site, a visit out of time window should be performed as soon as possible; if a visit at the site is not possible at all, at least a phone contact should occur at the scheduled follow-up visit time point.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary trial objective of this Phase II trial includes demonstration of proof of concept of the clinical activity of BI 1358894 with respect to a non-flat dose response curve, characterization of the dose-response relationship within the therapeutic range, and selection of the dose range for phase III development. For this purpose, the primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod) to analyse 4 doses of BI 1358894 and placebo [R10-1424]. In addition, the benefit of BI 1358894 compared to placebo will be evaluated.

As a basis for the MCPMod analysis, a mixed model for repeated measure (MMRM) analysis will be used to generate covariate adjusted estimates of mean change from baseline to Week 6 in MADRS total score and associated covariance matrices. These estimates will be used as the basis for the PoC analysis using MCPMod. If PoC is established, dose response models will be evaluated to select suitable doses for confirmatory testing in future studies.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response curve comparing placebo and the BI 1358894 dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 1358894 over placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10%. The pre-specified models and their parameters used for this test are outlined in section 7.2.2.

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 observation recorded. Unless otherwise specified, efficacy analyses will be performed on the FAS and will be based on assigned treatment. Full specifications for the FAS will be provided in the TSAP.

Safety analyses will be conducted on the TS, which includes 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.

Important protocol deviations (iPDs) will be collected throughout the trial conduct and will be summarized in the CTR as defined in the iPD specification document.

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 value recorded at Visit 1 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 participants 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 date of the 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 be censored and will not be included in the primary analysis. Data from participants assigned to the quetiapine arm will not be included in the primary analysis.

MCPMod is used to evaluate several possible dose response models (patterns) and to identify the best-fitting model or subset of models based on the BI 1358894 and placebo treatment groups. To account for the longitudinal nature of the data and covariates of interest, a restricted maximum likelihood (REML) based MMRM analysis will be carried out to obtain covariate adjusted estimates of the mean change from baseline to Week 6 in MADRS total score for each treatment group with an associated covariance matrix. The analysis model will

include discrete fixed effects for treatment at each visit, baseline MADRS severity level, concomitant psychotherapy use and the continuous effects of baseline MADRS total score at each visit. Additional covariates identified prior to database lock may be included in the MMRM model as applicable. Visit will be treated as a repeated measure with an unstructured covariance matrix used to model within-participant error.

The primary treatment comparisons will be the contrasts between each BI 1358894 treatment arm and placebo at Week 6. Procedures to be followed if the planned analysis fails to converge will be described in the TSAP. Resulting adjusted estimates from the MMRM will then be extracted for use in the MCPMod analysis.

For the PoC testing and for the sample size calculations, the basic shape of each of the models to be tested must be predefined. The following candidate models were selected based on healthy volunteer data to cover a plausible and diverse range of dose response patterns for the trial medication. Associated graphs of each model are shown in Figure 7.2.2.1: 1.

- Emax1: 50% of the maximum effect is achieved at 25 mg; corresponding to the assumed true ED50 = 25 mg.
- Emax2: 70% of the maximum effect is achieved at 5 mg; corresponding to a drug effect achieved mainly with low doses, ED50 = 2.14 mg.
- Sigmax: 50% of the maximum effect is achieved at 25 mg, and
- 90% of the maximum effect is achieved at 75 mg; corresponding to a more flexible model of the assumed true ED50 = 25 mg.
- Exponential: 5% of the maximum effect is achieved at 25 mg; corresponding to a drug effect achieved mainly at higher doses.
- Linear: No parameter assumptions required. Corresponding dose response is linear.

These models are based on the following assumptions:

a. BI 1358894 dose groups: Dose 5 mg, Dose 25 mg, Dose 75 mg, Dose 125 mg
b. ED50 = 25 mg*

* ED50 assumes dose corresponding to EC50, FST = 77nM plasma concentration in trough at 16h.

EC50: Half maximal effective concentration

The EC50 of a graded dose response curve represents the concentration of a compound where 50% of its maximal effect is observed.

FST: forced swimtest (in mice)

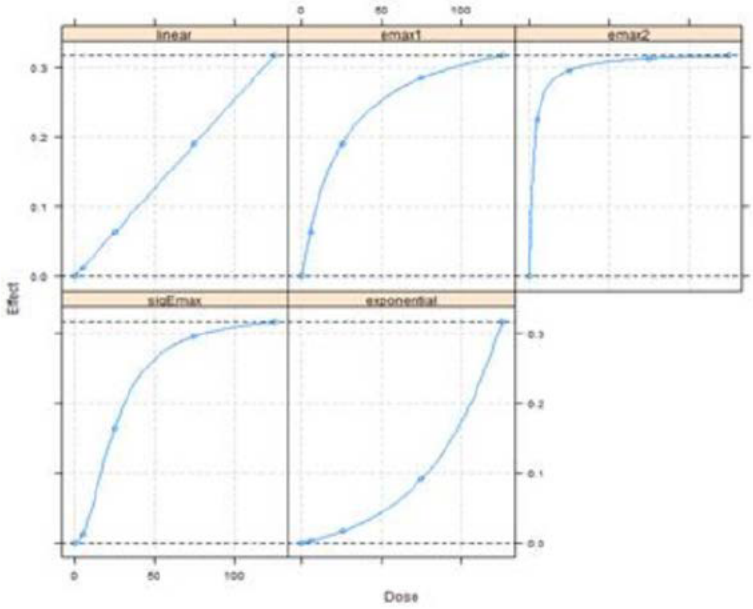


Figure 7.2.2.1: 1 Shape of the considered dose response patterns for the MCPMod analysis.

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

If a non-flat response is established, the statistically significant (i.e., best fitting) model(s) are refitted to the data to generate new estimates for all model parameters. The final model will be obtained via model averaging across the significant models based on Akaike Information Criteria (AIC). The target dose(s) can be estimated from each significant model by incorporating information on the minimum clinically relevant effect. Safety will be taken into account in the selection of a target dose(s).

No formal hypothesis tests will be performed to compare BI 1358894 and quetiapine or to compare quetiapine and placebo. Descriptive summaries of quetiapine and placebo responses will be generated to help assess the impact of placebo response in this trial. LS mean change in MADRS total score, standard errors (SE) and confidence intervals will be calculated to assess the magnitude of response, variability and precision of the estimated values.

[redacted]

[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 or missing all post-baseline 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 is observed, a logistic regression model adjusted for treatment (BI 1358894 or placebo) and baseline MADRS severity will be used to calculate the odds ratio for response between each of the BI treatment arms and placebo and corresponding 95 % confidence intervals. The likelihood ratio test will be used to test for differences between each active treatment arm and placebo.

7.2.3.2 STAI

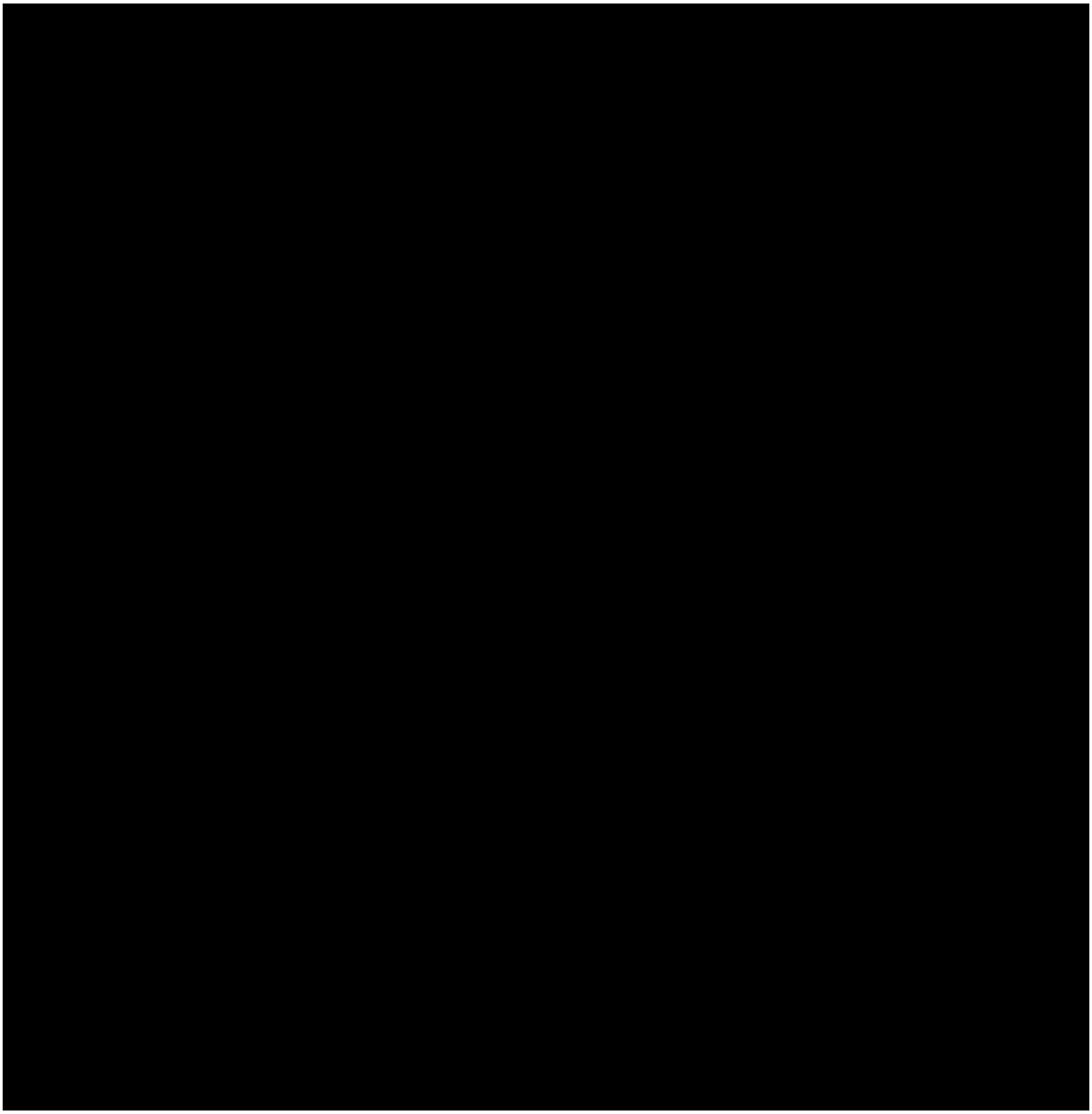
Change from baseline to Week 6 in STAI state and trait scores will be analysed using an MMRM model similar to the model described for the primary endpoint analysis. Comparisons will be performed for each of the BI 1358894 treatment arms versus placebo.

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 arms and placebo, an MMRM model similar to the model described for the primary efficacy analysis will be used.

7.2.3.4 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 each of the BI 1358894 treatment arms 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 analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of participants with abnormal values or clinically relevant abnormal values. Laboratory values of particular interest include:

c. Low values of HDL, haemoglobin, and neutrophil count
d. 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

[redacted]

[redacted]

[redacted] and [redacted] will be provided in the TSAP.

[redacted]

7.2.7 Interim Analyses

In general, no interim analysis is planned for this non-pivotal trial.
However, in case of unforeseen, blinded trial results or external results, that put into question critical trial design assumptions, administrative interim analyses (IA) may need to be performed.
The decision and independent team to conduct such an administrative IA will be documented in an IA Logistics Plan and an IA Results Access Plan, together with details how to protect the scientific credibility of the trial. It will also be stated, whether & how results of such an administrative IA will be used for a subsequent trial adaptation, which is to be planned in a protocol amendment.

A DMC will review safety data during the trial as described in section 8.7.

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

For the supplemental analysis of the primary endpoint based on a treatment policy estimand, i.e. intention to treat, all available data including data collected after treatment discontinuation or other intercurrent event will be analysed.

[redacted]

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 in a 3.5:1:1:1:2:2 ratio as described in section 4.1.3. Randomization will be stratified by baseline MDD severity, defined as baseline MADRS total score ≤19 versus >19.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented as described in section 4.1.4.

7.5 DETERMINATION OF SAMPLE SIZE

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

This trial is not powered for statistical comparisons between BI 1358894 and quetiapine or between quetiapine and placebo.

The calculations for the PoC step have been performed using the DoseFinding R-package. The R codes for the power calculations and the analyses using the MCPMod approach will be provided in the TSAP. The family-wise type I error rate at a one-sided $\alpha = 10\%$ is controlled in the power calculations and the analyses.

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, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations 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 finalisation 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, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to participant 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 patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each participant.

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

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

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

If study conduct needs to be adjusted (see sections 4.1.4, 6.1 and 10.4) during the COVID-19 pandemic, participants must be made aware of any modifications and their consent needs to be obtained prior to implementation.

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, data collection of efficacy endpoints is coordinated 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 meeting)
- Provision of Rater materials
- Central Quality Review of SCID-5 and the MADRS; for that purpose, the SCID-5 and the rater administered MADRS will be audio recorded

Details of rater prequalifications, Rater Training, Rater Materials (including assessments) and of the Central review procedures will be available in separate documents Qualification Methodology document and Data Analysis Methodology filed in the ISF.

8.3 RECORDS

CRFs 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).

Electronic records, i.e. clinician administered assessment data, related audio recordings (for central review) and patient reported outcome data entered into the tablet computer (Rater Station) will be regarded as source data. These may be further analysed by the delegated third party vendor.

[redacted]

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the participant's medical file.

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 should make up to 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.

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 CRF, 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 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)
- Patient reported outcome forms and investigator assessment forms, if done on paper
- 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(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

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

Relevant documentation on the participating (Principal) Investigators 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 [redacted] 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 delegated to 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.

If applicable, in addition to the Protocol, approved and effective local protocol amendment(s) should be followed by investigators.

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.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The main focus of the DMC will be the evaluation of safety data. Efficacy data may be reviewed if requested by the DMC to support the risk/benefit assessment. The DMC will receive urgent significant safety concerns including severe infections, suicidality reports and DILI, for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial conduct. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.
Vendors will be used in this trial for central laboratory services, IRT, central ECG services, ClinRO/PRO scales assessments including, medication intake monitoring [redacted] Details will be provided in the respective manuals available in the ISF.

[redacted] is done by a suitable CRO.

9. REFERENCES

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[redacted]

[redacted]

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Can J Psychiatry 62 (1), 11 - 23 (2017)

[R19-1647] Request for qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty (applicant: Janssen Pharmaceuticals and Novartis Pharmaceuticals, application date: 22 April, 2015).
https://www.fda.gov/media/99313/download (access date: 13 May 2019) ; U.S. Food and Drug Administration (FDA), Office of Clinical Pharmacology (OCP), Division of Pharmacometrics (2015)

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9.2 UNPUBLISHED REFERENCES

[c10354149] Investigator's Brochure BI13558894; 1402.P1-P2; ,

10. APPENDICES

[redacted] [redacted]

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10.4 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

As mentioned in section 6.1, in case of any restrictions during the COVID-19 pandemic, study conduct may need to be adjusted. The following contingency measures have been introduced to ensure participant safety and appropriate trial continuation based on a thorough benefit-risk assessment (see section 1.4.2).

In exceptional cases, when it is impossible to conduct the visits at the trial site, visits may be performed at the participant's home (e.g., by a study nurse) or remotely (via telephone and/or internet-based means of communication). The visits may also be performed as a combination of home and remote visits. For such cases, the visit procedures may be adjusted, after evaluation of operational feasibility and minimal required data (i.e. primary /secondary /exploratory endpoints. etc.), whereby critical safety measures will remain in place. All home/remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country need to be respected for all modifications.

Under these circumstances and after approval by the sponsor, the below modifications can be considered. Patients need to be informed about the modifications and give their consent before implementation:

Remote visit
If a participant is not able to come to the site for an outpatient visit, a remote visit should be performed instead and all assessments that can be done by telemedicine. Raters will receive training on conducting remote assessments and verifying the identity of patients. Documentation of the remote visit will be collected in the eCRF.

Assessments that can be performed during a remote visit are using the eCOA tablet and telemedicine are the following:

Rater performed MADRS, C-SSRS, CGI-S.

The SMDDS, STAI, [redacted] are questionnaire(s) that should be answered by the participant alone. Participants can be supplied with the questionnaire(s) to be filled out at home. The questionnaire(s) should be answered on the day of the remote visit and sent back to the site. The participant needs to be instructed to go alone to a quiet area where she/he can record her/his response in the questionnaire(s) without interaction with others. In instances where a participant cannot give or decide upon a response, no response should be recorded.

[redacted]

Safety lab, other laboratory tests

If taking blood samples for central lab 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 always the reference values of the local lab are also provided.

Dispensation of Trial medication (IMP)

If a participant is not able to come to visit 4 as planned and the investigator considers it acceptable and save for participant to continue with IMP, IMP can be shipped from site directly to the participant (if legally acceptable according to local regulations).

If home visits by trial staff members or e.g. “Home Healthcare Nurse” are possible, further assessments can be done like e.g. vital sings, blood draw for safety lab and biomarkers as well as collection of urine samples to be sent to central lab, or compliance check.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 Mar 2020
EudraCT number **EU number**		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No

Global Amendment		1
Sections to be changed		Synopsis; Flow charts; 1.3; 1.4.2; Table 1.4.2:1; 3.1; + 3.2; 3.3.2 - 3.3.4; 4.1.2.1; 4.1.4.; 4.1.5.1; 4.2.2.3; 4.3; 5.1; 5.2.2; + 5.2.3; 5.3.3; Table 5.3.3:1; 5.4.2.; 5.7.1.2; 5.7.2; 6.2; 6.2.1; + 6.2.2; 7.5; 8.1; + 8.2; 8.3.1; 8.7; 9.2;
Description of change		See below
Rationale for change		Typos removed; Clarifications; Specifying details; Alignment with sister trials
Section to be changed		1.2. Drug Profile; 1.4.2 Risks; Table 1.4.2:1; 4.2.2.1 Restrictions reg. concomitant treatment 4.2.2.2 Restrictions on diet and life style

Description of change		Updated Data from IB included; Rationale for precautions for concomitant use of statins added. Precaution measure for operating machinery and driving automobiles added. Update on drug-drug interaction data
Rationale for change		Consistancy with IB update
Section to be changed		4.1.4 Drug assignment and administr. of doses
Description of change		Advice added to take IMP with or without food in a consistent way
Rationale for change		Following advice from PMDA
Section to be changed		Flowchart 2; 6.2 Details on Trial Procedures
Description of change		Participant Placebo Response Mitigation Video added
Rationale for change		To teach participants about the placebo effect in order to mitigate this effect during the trial performance

11.2 GLOBAL AMENDMENT 2

Date of amendment		07 Jul 2020
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		2
Sections to be changed		• Synopsis • Flow Chart 1 • Flow Chart 2 • 3.1 Overall Trial Design • 1.3 Rationale for performing the trial • 3.3.2 Inclusion criteria • 3.3.3 Exclusion criteria • 5.2.1 MADRS • 5.2.2 ATRQ • 5.3.3 Safety laboratory parameters • 6.2 Details of trial procedures
Description of change		• Removal of typos, clarifications, re-wording
Rationale for change		• Clarifications
Sections to be changed		• Flow Charts 1 • Flow Charts 2 • 1.4.2 Risks • 4.1.4 Drug assignment and administration of doses for each participant • 6.1 Visit Schedule • 8.1Trial Approval, Pateint Information, Inforemd Consent • Appendix 10.4

Description of change		• Backup procedures added to cover for potential impact of COVID-19 during trial conduct
Rationale for change		• To maintain trial data continuity in case of restrictions due to COVID-19
Sections to be changed		• 1.2 Drug profile • Table 1.4.2.:1 Overview of trial related risks • 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		• Flow Chart 2 • [redacted] • 6.2 Details of trial procedures • 7.6.2 Other Analyses

Description of change		[redacted]
Rationale for change		[redacted]
Sections to be changed		• Synopis • 3.3.2 Inclusion criteria • 6.2 Details of Trial Procedures
Description of change		• Change of inclusionary MADRS entry score from ≥22 to ≥26.
Rationale for change		• Inclusion of more severely impacted patients will help to mitigate a potential placebo effect
Section to be changed		• 3.3.3. Exclusion criteria
Description of change		• Ex #24 and #25 added
Rationale for change		• Clarification, following request from IRBs
Section to be changed		• 5.1 Confirmation of Diagnosis • 6.2 Details of Trial Procedures at selected visits
Description of change		• Decription added of the role of the external external vendor responsible for confirmation of eligibility
Rationale for change		• Clarification of who is responsibilities to assess eligibility based on psychiatric status of the participants
Section to be changed		• 5.5.3 Safety laboratory parameters
Description of change		• ESR test added to Haematology • Information and rational added that drug screen results will be included in the clinical database
Rationale for change		• Following FDA request • To better understand reasons of screening failures and potential impact of drug use on the efficacy

11.3 GLOBAL AMENDMENT 3

Date of amendment		07 Sep 2020
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability 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		3
Sections to be changed		• Synopsis • Flow chart 1 • Section 1.2 Drug Profile • Section 2.1.3 Secondary endpoint(s) • Section 5.2.2. ATRQ - Antidepressant Treatment Response Questionnaire • Section 10.4 Potential Modification of trial conduct n case of restrictions due to COVID-19
Description of change		• Removal of typos
Rationale for change		• Clarification
Sections to be changed		• Flowcharts - Footnotes • Section 6.2 Details of trial procedures
Description of change		• Specification added how to split the screening visit on separate days, if needed
Rationale for change		• Clarifications

Sections to be changed		• Section 1.2 Drug Profile • Table 1.4.2:1 Overview over trial related risks • Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]
Rationale for change		• Spelling out of the label for Quetiapine
Sections to be changed		• 4.1 Investigational treatments • Table 4.1.1:1 BI 1358894
Description of change		• Adding an additional manufacturer of the Placebos
Rationale for change		• Clarification
Sections to be changed		• Section 8.3.1 Source documents
Description of change		• Definition of PROs data as source documents
Rationale for change		• Clarification
Sections to be changed		• Section 8.7 Administrative Structure of the trial
Description of change		• Investigator must adhere to the globale CTP and referring local amendments, where applicable
Rationale for change		• Clarification
Sections to be changed		• Section 10.4 Potential Modification of trial conduct n case of restrictions due to COVID-19
Description of change		• Definition of minimum required lab parameteres in case a local lab is needed
Rationale for change		• Clarification

11.4 GLOBAL AMENDMENT 4

Date of amendment		03 Mar 2021
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability 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		4
Sections to be changed		• Flow chart 1 and 2, including footnotes • Abbreviations • Section 1.4.2 Risks • Section 2.2.2 Further endpoints [redacted] • Section 6.2 Details of Trial Procedures • Section 6.2.1 Treatment Period(s) • Section 7.2.1 General Considerations • Section 7.2.2.1 Primary Analysis of …. • Table 7.5:1 Power for each candidate… • Section 8.7 Adminstrative Structure
Description of change		• Removal of typos, improved descriptions
Rationale for change		• Clarification
Sections to be changed		• Flowcharts 1 • Section 5.7.5 Verification of current and past rsearch study status of trial participant
Description of change		[redacted]
Rationale for change		• Prevention of simultaneous trial participation by study participants

Sections to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Sections to be changed		• Table 5.3.3:1 Safety Laboratory Tests
Description of change		• Revision of Urinalysis test to align with Central lab testing standards • Added Norfluoxetine to Fluoxetine
Rationale for change		• Alignement with standards of Central Laboratory

11.5 GLOBAL AMENDMENT 5

Date of amendment		28 Jun 2021
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		5
Sections to be changed		4.2.2.3 Contraception requirements
Description of change		WOCBP, who are sexually abstinent, fulfill the requirement of safe contraception
Rationale for change		Clarification. Sexual abstinence, as defined in the protocol, meets the criterion of an highly effective method of contraception
Sections to be changed		6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change		Optional extention of the screening period by additional 7 days added (i.e. 28 days in total)
Rationale for change		For administrative reason like delayed reporting of SSRI/SNRI blood levels
Sections to be changed		Section 8.3.1 Source documents
Description of change		Audio recordings for central review are also regarded as source data
Rationale for change		Clarification
Sections to be changed		8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

Description of change		“[redacted] changed to [redacted]”
Rationale for change		Change of the brand name by the provider of the central laboratory

11.6 GLOBAL AMENDMENT 6

Date of amendment		28 Sep 2021
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		6
Sections to be changed		Synopsis and Section 3.3.2 Inclusion criteria
Description of change		Duration of the current depressive episode extended from 12 months to 18 months
Rationale for change		COVID-19 pandemic impacts the timely access to medical treatment and consequently to the diagnosis. Therefore, it is considered justified to extend the duration of the current episode from 12 to 18 months.
Sections to be changed		Synopsis and Section 3.3.2 Inclusion criteria; Section 6.2
Description of change		Change of MADRS entry score from total score “≥ 26” to “≥ 24”
Rationale for change		A MADRS score of 24 is still high enough for signal detection in frame of potentially present placebo effect.

Sections to be changed		Synopsis and Section 3.3.2 Inclusion criteria
Description of change		The minimal needed duration of ongoing monotherapy with an SSRI/SNRI at screening will be reduced from 8 to 6 weeks.
Rationale for change		To be aligned with the "APA Guideline for Treatment of Depression" [R21-3130] which recommends a change of pharmacotherapy for patients where no sufficient response could be demonstrated after 4 to 6 weeks of treatment.
Sections to be changed		Synopsis; Flow Chart 1; Section 3.3.2; Section 5.3.3; Table 5.3.3:1: Section 6.2
Description of change		Confirmation of SSRI/SNRI levels in urine at screening added in addition to analysis in serum
Rationale for change		For operational reasons
Sections to be changed		Synopsis, Section 3.3.3 and 4.2.2.1
Description of change		Background SSRI/SNRI could alternatively already be stopped after (e)EOT instead at the end of the trial
Rationale for change		This allows investigators to change the treatment already at (e)EOT and not only 4 weeks later at EOS. It supports adequate handling of patients who do not show any improvement of their depression during the treatment phase.
Sections to be changed		Synopsis, Section 3.3.3 and 4.2.2.1
Description of change		Allow for use of other antidepressants (excluding bupropion) if less than lowest dose indicated for MDD e.g., for treatment of anxiety or sleep disorder
Rationale for change		This follows usual clinical practice as long as the given low doses are not listed in the table for treatment of depression.
Sections to be changed		Flow Chart 1; Table 5.3.3:1 Safety Lab Tests
Description of change		ESR testing will be changed from central to on-site assessment
Rationale for change		For operational reasons
Sections to be changed		Section 5.2.2

Description of change		MH-ATRQ: Minimal required duration on adequate dose of an antidepressant medication was lowered from 8 weeks to 6 weeks
Rationale for change		To be aligned with the referring adjustment of the inclusion criteria.
Sections to be changed		Section 5.3.5.1;
Description of change		Note added that reporting of AE terms like suicidal depression, suicidal ideation or similar, are on the “Always serious AE List” and therefore must be reported as SAEs
Rationale for change		Clarification
Sections to be changed		Section 5.3.5.1; Section 5.1.6.1.3; Section 6.2; Section 6.2.1; Section 10.4
Description of change		Removal of typos; rewording
Rationale for change		Clarification

11.7 GLOBAL AMENDMENT 7

Date of amendment		27 Apr 2022
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		Yes
Global Amendment		7
Sections to be changed		Flowchart 1; Section 1.4.3; Section 4.2.2.3; Section 6.2
Description of change		Counseling about the need of contraception at V1 during IC. Additionally, reiteration of adherence to contraception at all visits.
Rationale for change		New safety information
Sections to be changed		Flowchart 1; section 5.3.3; Table 5.3.3:1
Description of change		Onsite ESR removed again (central ESR analysis will remain as is)
Rationale for change		Central laboratory cannot provide onsite ESR test kits. Therefore, the existing central ESR analysis will remain as the only measurement.
Sections to be changed		Flowchart 1 (footnotes); Section 5.3.3; Table 5.3.3:1; section 6.2
Description of change		Confirmation of SSRI/SNRI exposure can be done either in urine or serum under conditions as described in section
Rationale for change		Clarification

Sections to be changed		Section 1.2; Section 1.4.2; Table 1.4.2:1; Section 1.4.3
Description of change		[redacted]
Rationale for change		[redacted]
Sections to be changed		Section 6.2.1
Description of change		Renaming of Visits
Rationale for change		Clarification about difference between Visit 8 and EOT
Sections to be changed		Table 1.4.2:1; Section 9.1
Description of change		Update of the Seroquel Summary of Product Characteritics reference
Rationale for change		SmPC version did not refer to the most recent version

11.8 GLOBAL AMENDMENT 8

Date of amendment		26 Sep 2022
EudraCT number/EU number		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		8
Sections to be changed		Synopsis; 3.3.2
Description of change		"*Women who are of childbearing potential (WOCBP) must be able and willing to use two methods of contraception".* Was changed to: *"Women who are of childbearing potential (WOCBP) must be able and willing to use two methods of contraception**, confirmed by the investigator**"*
Rationale for change		To follow an FDA request and to ensure that the investigator confirms the contraception requirement with the patient.

Sections to be changed	Flowchart 1; Table 1.4.2:1
Description of change	A footer on contraception counseling was added: *"This must include confirmation from the patient that she is using required contraception consistently and appropriately. Counseling and contraception confirmation must be recorded in CRFs. If contraceptive protection can not be confirmed, as deemed by the investigator, the patient must be discontinued from study drug and can only resume once contraception is used again and sufficient protection is reached".*
Rationale for change	To follow an FDA request and to reinforce that contraception counselling is done at every visit and documented. Also to provide guidance for investigators who to handle non-compliaces to contraception rules.
Sections to be changed	1.4.2. Risks
Description of change	"*Additionally, investigators must counsel WOCBP with regard to the importance of contraception at all visits as per Flow Chart (including phone visits)."* Was changed to "*Additionally, investigators must counsel WOCBP with regard to the importance of contraception* ***and confirmation of appropriate contraception use*** *at all visits as per Flow Chart (including phone visits)."*
Rationale for change	To follow an FDA request and to reinforce that contraception counselling is done at every visit and documented.
Sections to be changed	Table 1.4.2:1: 4.2.2.3.

Description of change	Investigator must ensure that the patient understands the contraception requirements for the study and must confirm that the patient can reliably comply with contraception use during the study. Patients not expected to comply with contraception requirements should not be included in the study.
Rationale for change	To follow an FDA request and to reinforce that contraception counselling is done at every visit and documented. Also to provide guidance for investigators not to include patients in the trial who are not expected to be able to comply with contraception requirements.

11.9 GLOBAL AMENDMENT 9

Date of amendment		26 Oct 2022
EudraCT number **EU number**		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		9
Section to be changed		Flowchart1 + 2, footnote #10 and #6, respectively; Sections 5.3.3; 6.2; 6.2.1
Description of change		Rewording
Rationale for change		Clarification
Section to be changed		Synopsis; Flowchart 1+2; 1.1; 1.2; Table 1.4.2.1,1.4.3; 3.1; 3.3.2; 3.3.3; 4.2.2.1; 5.3.3; Table 5.3.3:1; 6.2; 6.2.1
Description of change		Bupropion (SNDRI) was added as one of the acceptable antidepressant background treatments
Rationale for change		[redacted]

Section to be changed		1.2. Drug profile; Table 1.4.2:1 4.2.2.1 Restrictions regarding concomitant medication
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		Section 3.3
Description of change		Number of planned countries was adapted
Rationale for change		Formal change in order to be more accurate with the country contribution
Section to be changed		Synopsis; 3.3.2. Inclusion criteria
Description of change		Maximum duration of the current depressive episode isextended from 18 to 24 months
Rationale for change		This extension to 24 months still separates from chronic forms of depression, in line with DSM-5 criteria, and would open recruitment for patients with a longer current MDD episode
Section to be changed		Synopsis; 3.3.2. Inclusion criteria
Description of change		The minimal needed duration of ongoing monotherapy with an SSRI/SNRI/bupropion at screening is reduced from 6 to 4 weeks.
Rationale for change		Following advice from the majority of participating investigators and clinical experts who underlined that after a maximum of 4 weeks of insufficient response to an antidepressant at adequate dose an adjustment of the treatment is common practise. This is in line with the “APA Guideline for Treatment of Depression” [R21-3130]. In order to account for the clinical practice as per medical advice from the investigators in the majority of countries.

Section to be changed		Synopsis; 3.3.3; 3.3.4.1; 4.2.2.1
Description of change		Changing lifetime exclusion of transcranial magnetic stimulation to now only exclude TMS if used during the current depressive episode or within 12 months prior to screening.
Rationale for change		In order to account for the changes in clinical practice in some countries where TMS is now used more often and not only in proven treatment resistant depression.
Section of change		4.1.1: 4
Description of change		Manufacturer of placebo matching quetiapine was added
Rationale for change		To clarify that placebo matching quetiapine is also packaged at BI
Section to be changed		Section 5.2.2
Description of change		Customized ATRQ, defining the minimal required duration for stable antidepressant therapy at Screening, changed from 6 to 4 weeks
Rationale for change		To be aligned with the adjusted inclusion criterion #3 in section 3.3.2.
Section to be changed		Section 6.2
Description of change		Adding the recommendation for rater of C-SSRS scale and rating of adverse events to be different
Rationale for change		To ensure that the rating of C-SSRS is not biased by the knowledge of adverse events from the patient.
Section to be changed		Section 8.3.1.
Description of change		Investigators should make three attempts to retrieve information on a patients' medical history; was changed from only one attempt
Rationale for change		To be consistent with section 6.2.

Section to be changed		Section 8.3.1.
Description of change		To define paper versions of PRO forms or investigators assessment forms as being source documentation
Rationale for change		To include additional options of source documents
Section to be changed		Flowchart 1 and 2; 5.3.3.
Description of change		Duloxetine added that only is measured in serum
Rationale for change		To be consistent with table 5.3.3.1.
Section to be changed		7.2.7.
Description of change		[redacted]
Rationale for change		[redacted]

11.10 GLOBAL AMENDMENT 10

Date of amendment		07 Jun 2023
EudraCT number **EU number**		2019-004264-21
BI Trial number		1402-0011
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Global Amendment due to urgent safety reasons		No
Global Amendment		10
Section to be changed		5.3.3 Safety laboratory parameters; Table 5.3.3:1 Safety laboratory tests
Description of change		Analysis of ESR can be either performed centrally or locally
Rationale for change		Process updated to local ESR assessment.
Section to be changed		Table 5.3.3:1 Safety laboratory tests
Description of change		Cross reference (*) added for Erythrocyte sedimentation rate (ESR) that the ESR Testing results are not intended to be used as Safety Parameter or for medical management decisions. For medical management decisions of Safety relevant inflammation parameter, the CRP test should be used.
Rationale for change		In this protocol, ESR testing is used solely for the collection of data for analysis purpose at the end of the trial, per FDA's recommendation. The ESR Testing results are not intended to be used as Safety Parameter or for medical management decisions. For medical management decisions of Safety relevant inflammation parameter, the CRP test should be used.

Section to be changed		Table 5.3.3:1 Safety laboratory tests
Description of change		Added Reflex testing (once technically implemented) for fT3 and fT4 if TSH > ULN
Rationale for change		Alignment with sister trials
Section to be changed		Section 11 - Global Amendment 7
Description of change		Correction of amendment date
Rationale for change		Typo

12. REFERENCES FOR CTP AUTHORS

Not applicable

APPROVAL / SIGNATURE PAGE

Document Number: c29983007 **Technical Version Number:12.0**

Document Name: clinical-trial-protocol-version-11

Title: A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	09 Jun 2023 16:12 CEST
Approval-Clinical Trial Leader		12 Jun 2023 08:09 CEST
Approval-Clinical Program Leaders		12 Jun 2023 08:47 CEST
Verification-Paper Signature Completion		12 Jun 2023 09:13 CEST

(Continued) Signatures (obtained electronically)

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