Clinical Trial Protocol

	Document Number:	**c29157684-05**
EudraCT No. **EU Trial No.**	2020-000078-12	
BI Trial No.	1402-0012	
BI Investigational Medicinal Product(s)	BI 1358894	
Title	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder	
Lay Title	A study to test different doses of BI 1358894 and find out whether they reduce symptoms in people with borderline personality disorder	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Telephone: [redacted]	
Coordinating Investigator	[redacted] Telephone: [redacted]	
Version and Date	**Version: 5.0**	**Date: 23 Sep 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	26-Mar-2020
Revision date	23 Sep 2022
BI trial number	1402-0012
Title of trial	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with Borderline Personality Disorder
Coordinating Investigator	[redacted]
Trial site(s)	Multi-center
Clinical phase	II
Trial rationale	This study is designed to provide the proof of concept (PoC) for [redacted] BI 1358894 in patients with borderline personality disorder (BoPD) and provide data for further development of BI 1358894.
Trial objective(s)	The main objectives of this trial are to provide PoC and dose-ranging data of BI 1358894 compared to placebo in patients with BoPD to support dose selection for pivotal studies.
Trial endpoints	Primary endpoint: • Change from baseline in Zanarini rating scale for Borderline personality disorder (ZAN-BPD) total score at Week 10. Secondary endpoints: • Response defined as ≥30% ZAN-BPD reduction from baseline at Week 10 • Change from baseline in Difficulties in Emotion Regulation Scale (DERS-16) total score at Week 10 • Change from baseline in State-Trait Anxiety Inventory (STAI-State) total score at Week 10 • Change from baseline in Patient Health Questionnaire (PHQ-9) total score at Week 10 • Change from baseline in Clinical Global Impression Severity Scale (CGI-S) at Week 10 • Change from baseline in Patient Global Impression Severity Scale (PGI-S) at Week 10
Trial design	A 12-week multi-center, multi-national, randomized, double-blind, placebo-controlled parallel-group trial in patients with BoPD.
Total number of patients randomized	Approximately 355
Number of patients on each treatment	Placebo 119 BI 1358894 5 mg qd 47 BI 1358894 25 mg qd 47 BI 1358894 75 mg qd 47 BI 1358894 125 mg qd 95
Diagnosis	Patients meeting diagnostic criteria of BoPD per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and diagnosis confirmed at time of screening by Structured Interview for DSM-5 Personality Disorder (SCID-5-PD)
Main in- and exclusion criteria	Inclusion criteria: • Patients meeting diagnostic criteria of BoPD per DSM-5 at screening visit, confirmed by SCID-5-PD. • ZAN-BPD of ≥ 9 at screening (Visit 1) and randomization (Visit 2), with question #2 Affective Instability score of ≥2.

	• Male or female patients, 18-65 years of age at the time of consent • Women of childbearing potential (WOCBP) able and willing to use two methods of contraception, confirmed by the investigator Exclusion criteria: • Current diagnosis of paranoid, schizoid, schizotypal and antisocial personality disorders, as confirmed by SCID-5-PD at screening visit • Lifetime diagnosis for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, or delusional disorder as confirmed by the SCID-5 at the screening visit. • Any other mental disorder that is the primary focus of treatment in the last 6 months prior to randomization, as per the clinical judgement of the investigator. • Inpatient stay or hospitalization due to worsening of BoPD within 3 months prior to randomization. • Initiation or change in any type or frequency of psychotherapy for BoPD within the last 3 months prior to screening. • Any ongoing use of psychotropic medications within 7 days prior to randomization or during the course of study • Any suicidal behavior in the past 1 year • Any suicidal ideation of type 4 or 5 in the Columbia Suicidal Severity Rating Scale (C-SSRS) in the past 3 months
Test product(s)	BI 1358894
dose	5 mg qd, 25 mg qd, 75 mg qd, 125 mg qd
mode of administration	Per os
Comparator product(s)	Placebo
dose	Matching
mode of administration	Per os
Duration of treatment	12 weeks
Statistical methods	The primary analysis is performed using MCPMod, a methodology for dose finding employing both multiple comparison procedures and modelling techniques. 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%. 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 10 in ZAN-BPD total score and associated covariance matrices.

FLOW CHART

Trial Periods	Screening		Treatment													Early D/C	Follow-up		End of Trial
Visit	**1** [1]	**1A**	**2**	**3**	**4**	**4A** ☎	**5**	**5A** ☎	**6**	**6A** ☎	**7**	**7A** ☎	**8**	**8A** ☎	**9 EoT** [19]	**eEOT** [2]	**FUP1**	**FUP2** ☎	**EoTrial**
Week	-4 to -1			1	2	3	4	5	6	7	8	9	10	11	12		13	14	16
Day	-28 to -7	-5	1 [3]	8	15	22	29	36	43	50	57	64	71	78	85		EoT +7	EoT +14	EoT +28
Time window for visits (in days)	-28 to -7	-7 to -5	V1 + 7 to 28	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±2	±2	±2
Informed consent	X																		
Informed consent for biobanking [4]	X																		
[redacted]	[redacted]																		
Informed consent for participant's duplicate check (if applicable)	X																		
IRT registration	X																		
Demographics	X																		
Medical history	X																		
Substance use [20]	X		X	X	X		X		X		X		X		X	X	X		X
Headache history [20]	X																		
Meal intake [7, 20]			X		X				X				X		X	X			
SCID-5	X																		
SCID-5-PD	X																		
Physical examination	X		X	X			X				X				X	X			X

Trial Periods	**Screening**		**Treatment**													**Early D/C**	**Follow-up**		**End of Trial**
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Vital signs	X		X	X			X				X				X	X			X
Height	X																		
Body weight	X		X	X			X				X				X	X			X
Laboratory tests	X		X				X				X				X	X			X
Infection screening	X																		
Urine drug screening	X		X																
Pregnancy test [6]	X	X	X	X	X		X		X		X		X		X	X	X		X
Contraception counseling for WOCB [22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12 lead-ECG	X		X	X			X				X				X	X			
Review of inclusion/ exclusion criteria	X		X																
Randomization			X																
Dispense trial drugs [7]			X				X				X								
Administer trial drugs on site [8, 7]			X	X	X		X		X		X		X						
[redacted]			[redacted]		[redacted]				[redacted]				[redacted]		[redacted]	[redacted]	[redacted]		
Optional sampling for biobanking [9, 7]			X [10]										X						

Trial Periods	**Screening**		**Treatment**													**Early D/C**	**Follow-up**		**End of Trial**
Visit	**1** [1]	**1A**	**2**	**3**	**4**	**4A** ☎	**5**	**5A** ☎	**6**	**6A** ☎	**7**	**7A** ☎	**8**	**8A** ☎	**9 EoT** [19]	**eEOT** [2]	**FUP1**	**FUP2** ☎	**EoTrial**
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Time window for visits (in days)	-28 to -7	-7 to -5	V1 + 7 to 28	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±2	±2	±2
ZAN-BPD [11]	X		X [12]	X	X		X		X		X		X		X	X			
CGI-S [11]			X	X	X		X		X		X		X		X	X			
C-SSRS [11]	X	X	X [12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DERS-16 [13]	X		X	X	X		X		X		X		X		X	X			
STAI-S [13]	X		X	X	X		X		X		X		X		X	X			
PHQ-9 [13]	X		X	X	X		X		X		X		X		X	X			
[redacted]			[redacted]										[redacted]		[redacted]	[redacted]			
PGI-S [13]			X	X	X		X		X		X		X		X	X			
[redacted]			[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]			
[redacted]			[redacted]										[redacted]						
[redacted]			[redacted]										[redacted]						
[redacted]			[redacted]				[redacted]						[redacted]						
[redacted]	[redacted]												[redacted]			[redacted]			
[redacted]		[redacted]																	
All AEs/SAEs/ AESIs [18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check [7]				X	X		X		X		X		X		X	X			
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Periods	**Screening**		**Treatment**													**Early D/C**	**Follow-up**		**End of Trial**
Visit	**1** [1]	**1A**	**2**	**3**	**4**	**4A** ☎	**5**	**5A** ☎	**6**	**6A** ☎	**7**	**7A** ☎	**8**	**8A** ☎	**9 EoT** [19]	**eEOT** [2]	**FUP1**	**FUP2** ☎	**EoTrial**
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Time window for visits (in days)	-28 to -7	-7 to -5	V1 + 7 to 28	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±2	±2	±2
Termination of trial medication															X [7]	X			
Completion of patient participation																			X

☎ Phone visit

1 Visit 1 procedures are not required to be completed on the same day.
2 For patients who permanently discontinue trial drug prior to the scheduled Week 12 EoT visit, the Early EoT (eEoT) visit must be completed as soon as possible after trial drug discontinuation. See section 6.2.3 for further details regarding patient follow-up after premature treatment discontinuation.
3 Day of Randomization / Day of first intake of randomized medication
4 Serum/ plasma and DNA biobanking is optional. To allow the collection of additional blood samples for serum/plasma and DNA biobanking, a separate informed consent must be obtained.
[redacted]
6 Women of childbearing potential must perform urine (dipstick) pregnancy test. Urine pregnancy test can be performed more frequently if required by local regulations. Additionally, serum pregnancy test must be completed at Visit 1 and Visit 1A to rule out pregnancy before dosing. If urine (dipstick) pregnancy test is positive at any other visits, a serum test is required.
7 Not performed for visits conducted after early treatment discontinuation/eEOT visit. See section 6.2.3 for further details.
8 On the days of on-site visits, patients should not take their study drug at home, but bring their study drugs to site visit and take it there, especially at the visits when [redacted].
9 Collection of biobanking samples is optional. Samples will be collected at Visit 2 (serum, plasma and DNA samples) and Visit 8 (serum and plasma samples only). Patients are required to sign a separate informed consent for biobanking.
10 One sample for DNA biobanking will be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
11 Clinician-administered assessments, approximate total time: ZAN-BPD = 30 minutes, C-SSRS = 15 minutes, CGI-S = 5 minutes.
12 ZAN-BPD and C-SSRS must be completed before randomization (and IRT registration) take place.

13 Patient-reported assessments, approximate total time all assessments = 50 minutes

[redacted]

18 After the individual patient's end of the trial the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form. See section 5.2.6.2.1 for AE reporting requirements for patients who discontinue prematurely and continue with study visits.
19 For patients completing the 12-week treatment, this visit will be EOT visit. For patients who discontinue prematurely and continue with study visits, this visit will be Visit 9 when they reach week 12.
20 Refer to CRFs for details to be collected

[redacted]

22 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. Refer to section 4.2.2.3 for more details regarding contraception counseling.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine aminotransferase
[redacted]	[redacted]
AST	Aspartate aminotransferase
AUC	Area under the curve
BA	Bioavailability
BI	Boehringer Ingelheim
[redacted]	[redacted]
BoPD	Borderline personality disorder
BP	Blood pressure
BRCP	Breast cancer resistance protein
CA	Competent Authority
CBT	Cognitive behavior therapy
CCK-4	Cholecystokinin tetrapeptide
[redacted]	[redacted]
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CRA	Clinical research associate
COVID-19	Disease caused by SARS-CoV-2 virus
CRF	Case report form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract research organization
CRP	C-reactive protein
C-SSRS	Columbia Suicidal Severity Rating Scale
CT Leader	Clinical trial leader
CT Manager	Clinical trial manager

CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DERS-16	Difficulties in Emotion Regulation Scale
DBL	Database lock
DBT	Dialectical behavior therapy
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DIPD-4	Diagnostic Interview for DSM-4 Personality Disorder
DMC	Data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
[redacted]	[redacted]
ECG	Electrocardiogram
EcMA	Ecological Momentary Assessment
EDC	Electronic data capturing system
eGFR	Estimated glomerular filtration rate
(e)COA	(electronic) Clinical outcome assessment
eEoT	Early End of Treatment
EoT	End of Treatment
EoTrial	End of Trial
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
EVAS	Emotional visual analog scale
FAS	Full analysis set
[redacted]	[redacted]
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
IB	Investigator's Brochure
ICH	International Council on Harmonization
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator Site File
[redacted]	[redacted]
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LPLT	Last Patient Last Treatment
MAR	Missing at random
MCPMod	Multiple comparison procedure with modelling
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed model repeated measures model
MRD	Multiple rising dose
[redacted]	[redacted]
MRTpo	gMean of mean residence time after oral dosing
[redacted]	[redacted]
NOAEL	No Observed Adverse Effect Level
OATP	Organic-anion-transporting polypeptide
OPU	Operative Unit
P-gp	P-glycoprotein
PCR	Polymerase chain reaction
[redacted]	[redacted]
PGI-S	Patient Global Impression Severity scale
PHQ-9	Patient Health Questionnaire
PK	Pharmacokinetic
po	per os (oral)
PoC	Proof of concept
PR	Pulse rate
PRO	Patient reported outcome
[redacted]	[redacted]
qd	quaque die (once a day)
QTcF	Heart rate corrected QT interval using Fridericia's formula
RA	Regulatory Authority

REML	Residual maximum likelihood method
REP	Residual Effect Period
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCID-5-PD	Structured Interview for DSM-5 Personality Disorder
[redacted]	[redacted]
SIB	Suicidal Ideation and Behavior
SOP	Standard Operating Procedure
SRD	Single rising dose
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAI-S	State-Trait Anxiety Inventory
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half-life time
t_{max}	Time point of maximum plasma concentration
[redacted]	[redacted]
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper level of normal
VAS	Visual analogue scale
WBC	White blood cells
WHO	World Health Organization
[redacted]	[redacted]
WOCBP	Woman of childbearing potential
ZAN-BPD	Zanarini rating scale for Borderline personality disorder

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Borderline personality disorder (BoPD) is a chronic mental disorder with an estimated prevalence of around 2% in the general community and severe impairment on quality of life (R16-5474). Patients with BoPD often have psychiatric comorbidities; concomitant mood, anxiety, substance use, and eating disorders have been reported at high rates (R19-1118). The main symptom clusters of BoPD include impulsive-behavioral dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations, and affective instability. Affective symptoms and impulsivity have been considered core symptoms of BoPD. Patients typically experience intense fears of real or imagined abandonment, which may result in inappropriate anger even when faced with a realistic short-term separation or when there are unavoidable changes in plans (R19-1313). Even the presence of a single diagnostic feature of BoPD is predictive for poor functioning and psychiatric illness burden (R16-5483). Patients with BoPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times that in the general population (R16-5477).

Treatment guidelines recommend psychotherapy as the mainstay of treatment for BoPD (R17-0164). Particularly dialectical behavior therapy (DBT) has proven to be effective in BoPD. A disadvantage of DBT in clinical practice is that it is costly, time intensive, and requiring specialized clinical providers, making access for all patients in need of therapy difficult (R19-1550). While generalist models of care have shown potential, not all patients respond to them and patients with greater personality dysfunction still require intensive specialist treatment (R19-1092).

Pharmacotherapy is commonly used as an off-label adjunctive, symptom-targeted component of treatment. This includes treatment of affective dysregulation symptoms such as depressive symptoms (with selective serotonin reuptake inhibitors (SSRIs), mood stabilizers or related drugs), impulsive-behavioral dyscontrol symptoms such as impulsivity, aggression, self-destructive behavior (initially also with SSRI), and cognitive-perceptual symptoms such as paranoid thinking (with low-dose neuroleptics, (R17-0164). However, no drug is approved for the treatment of BoPD, and no standard-of-care pharmacological treatment of the disease exists.

The last large clinical studies exploring pharmacologic treatment for BoPD were conducted about a decade ago. The lamotrigine study assessing clinical effectiveness and cost effectiveness of lamotrigine vs. placebo in patients with BoPD (R19-1645) included 276 participants, of whom 195 were followed up 52 weeks later. Efficacy assessments using the Zanarini rating scale for Borderline personality disorder (ZAN-BPD) were performed at Weeks 12, 24 and 52. The primary efficacy outcome was the ZAN-BPD total score at Week 52. While the study failed to meet its primary efficacy outcome, the ZAN-BPD total score decreased from baseline to Week 12 and remained rather stable thereafter (R19-1645).

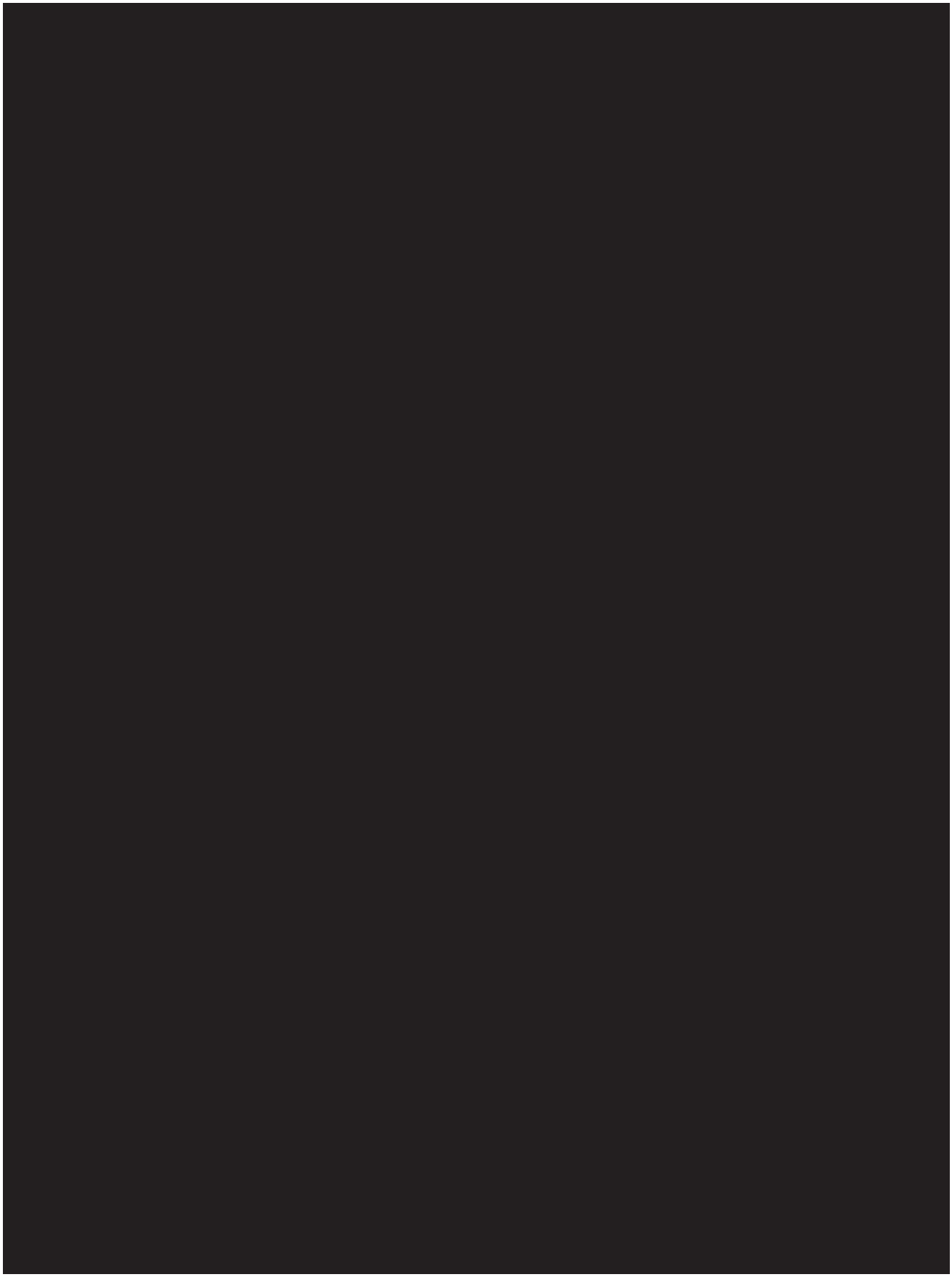
Similarly, the olanzapine vs. placebo study was a 12-week randomized, double-blind, placebo-controlled study in 451 patients with BoPD. In this study, statistically significant separation of olanzapine from placebo on ZAN-BPD was observed at Weeks 2, 4, 6, 8 and

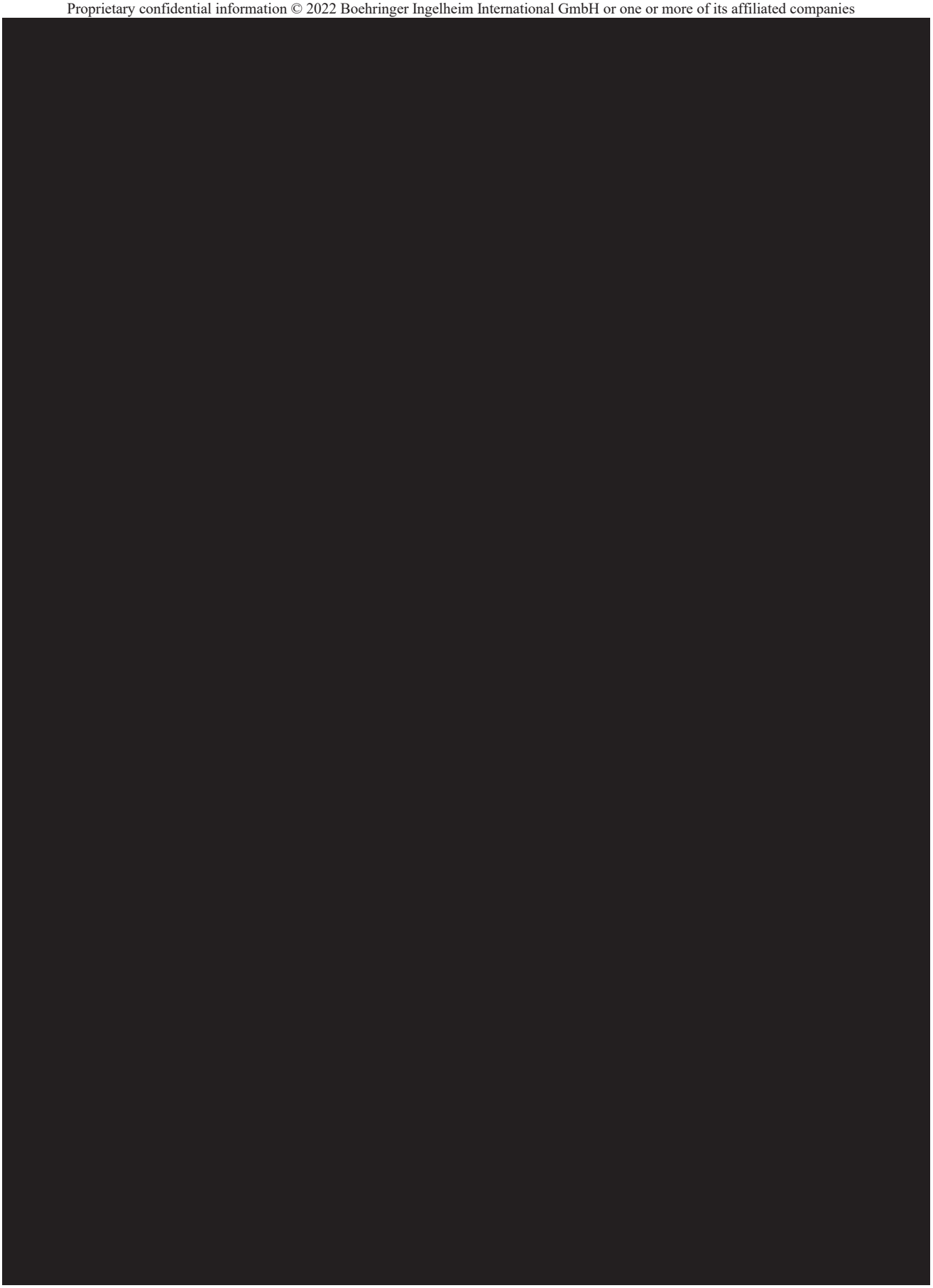
10, while the result at Week 12 was not statistically significant and thus the study failed to meet its primary efficacy outcome at 12 weeks (R19-1108).

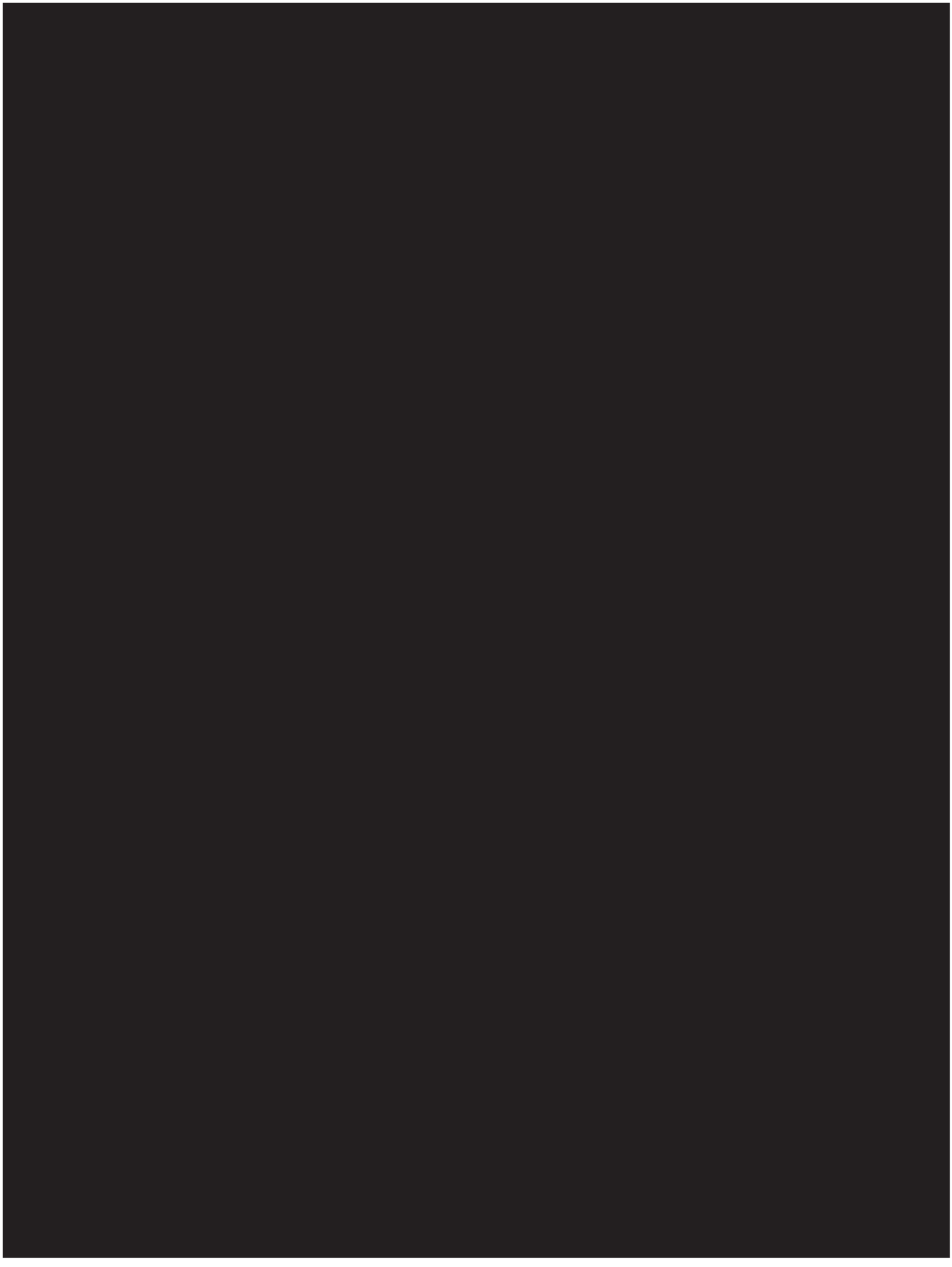
Despite the efforts in the therapy of BoPD, a sizeable portion of patients (about 40%) never achieve recovery from the disorder. In addition to their severely impacted quality of life, those patients have a poor prognosis for other important outcomes, such as vocational impairment, disability, physical morbidity, and mortality (R19-1119). As current pharmacological treatments are symptomatic and not supported by robust clinical evidence, a great unmet medical need remains for agents improving core characteristics of the disorder such as affective symptoms and emotion control.

In absence of any approved drug therapy and limitations related to availability and accessibility of psychotherapy for most BoPD patients, there is great unmet medical need to address and BI 1358894 would represent major therapeutic advance.

[redacted]







[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

This study is designed to provide the proof of concept (PoC) for [redacted] BI 1358894 in patients with BoPD and provide data for further development of BI 1358894. There are no qualified biomarkers for BoPD that could be taken as surrogate endpoints or that would be strongly indicative of therapeutic effect. Hence, the PoC can only be achieved in a large, sufficiently powered phase II study to address suitable dose(s), safety and efficacy of BI 1358894, which is the main rationale for this study.

[redacted]

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

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

1.4.1 Benefits

[redacted]

[redacted]

Therefore, it is expected that treatment with BI 1358894 has the potential to improve affective symptoms and emotion control in patients with BoPD.

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

1.4.2 Risks

Based on a comprehensive package of safety pharmacology, genetic toxicology and general toxicology, studies of BI 1358894 is expected 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 study procedures.

[redacted]

While there is no precedent clinical data implicating association between [redacted] and Suicidal Ideation and Behavior (SIB), in the interest of ensuring subject safety, trial patients will be proactively screened and monitored throughout the study for SIB in accordance with available regulatory guidance.

Because psychoactive drugs may impair thinking, judgment, and/or motor skills, patients 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 patients should exercise caution when driving or operating machinery.
Patients will be closely monitored during the trial participation (including AE monitoring beyond clinical visits and assessment of suicidal ideation during clinical 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 (see section 3.3.4).

The study 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 trial patients treated with BI 1358894 remains unchanged in relation to the COVID-19 pandemic given that:

- 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 BoPD increases the risk for SARS-CoV-2 infection or for developing severe COVID-19
- The BoPD 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 patients participating in the study will not differ from the current general risk for SARS-CoV-2 infection with all its potential consequences. The use of a specific SARS-CoV-2 polymerase chain reaction (PCR) as a tool for inclusion or exclusion of trial participants during the screening phase is not foreseen, since it is not believed that study drug raises the risk for the patient to develop COVID-19. It is also not believed that a SARS-CoV-2 infection or clinically apparent COVID-19 impacts the activity of the investigational or comparator compound.

Every patient will be assessed thoroughly, and individual benefit-risk assessments will be made prior to study entrance and during the study by the investigator in respect of SARS-CoV-2 infection. The investigators will take the totality of information related to each patient 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 protocol section 1.2 and the IB.

Table 1.4.2: 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal ProductBI 1358894		
[redacted]	[redacted]	Management of symptoms, evaluation, and follow-up as needed to ensure subject safety, per investigators clinical judgment.
[redacted]	[redacted]	Patients on these medications will be excluded from study and use of these drugs will be restricted during the treatment period. These medications can be started at the discretion of the investigator during the follow-up period considering the interaction data from IB.
[redacted]	[redacted]	Patients 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 patient in this trial is on the highest recommended statin dose,

Table 1.4.2: 1 Overview over trial related risks (continued)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
		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 subject 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, including confirmation of the use of contraception, at all

Table 1.4.2: 1 Overview over trial related risks (continued)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		visits as per Flow Chart (including phone visits). Refer to section 4.2.2.3 for more details regarding contraception counseling.
BI 1358894 Placebo		
• Worsening of BoPD • Occurrence or increase of suicidality	Even though mitigation measures are applied, this cannot be completely ruled out.	Frequency of visits with suicidality assessments are optimized. Suicidal patients will be excluded from trial participation (refer to section 3.3.4.1)
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 (paresthesia), impaired sensation of touch and persistent pain. The total volume of blood withdrawal per subject during the trial will be approximately 180 mL over 20 weeks. This amount may be exceeded if additional unscheduled monitoring of laboratory results is needed (in case of necessary safety follow-up).	Management of discomfort, evaluation, and follow-up as needed to ensure patient safety.

Table 1.4.2: 1 Overview over trial related risks (continued)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Other risks		
Hypersensitivity and allergic reactions	As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when BI 1358894 is administered.	First dose of BI 1358894 administered on site, with safety clinic visit at Week 1. Monitoring and management of symptoms and treatment as needed, per investigators clinical judgment.

1.4.3 Discussion

Considering this patient population, and to address any perceived abandonment issues, frequent visit and phone visits are planned in this study to monitor patients.

Additionally, all patients will be allowed to continue stable psychotherapy treatment of BoPD at the time of study entry. Considering the mechanism of action of BI 1358894 and the AEs reported in clinical trials to date, there is no undue risk related to stopping the study drug during the treatment period or at the end of the treatment period.

[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 results 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 visits as per Flow Chart (including phone visits).

Given the acceptable and manageable safety profile in nonclinical and toxicology studies, good tolerability in clinical studies performed until this date, close monitoring (including the above-mentioned risk mitigation activities to minimize the risk of pregnancy during the trial) planned during the study visits and the involvement of an external DMC, the potential risks to the participating patients will be minimized and outweighed by a potential therapeutic benefit of the study drug.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

The main objectives of this study are to provide PoC and dose-ranging data of BI 1358894 compared to placebo in patients with BoPD to support dose selection for pivotal studies.

2.1.1 Main objectives

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

The study will be performed to characterize the dose-response curve for BI 1358894 in patients with BoPD by assessing four BI 1358894 doses and placebo. The response is the change from baseline in ZAN-BPD at Week 10 summarized per arm by the adjusted mean. The multiple comparison procedure with modelling (MCPMod) approach will be used for the characterization of the dose-response curve.

The primary characterization will be on treatment which will assume all patients took randomized treatment for the duration of the study. See section 3.2 for justification of assessing endpoints at Week 10.

Assessments of secondary and further endpoints will also be performed to help support selection of a dose (range) and assess the treatment effect size.

2.1.2 Primary endpoint(s)

Change from baseline in ZAN-BPD total score at Week 10.

2.1.3 Secondary endpoint(s)

ZAN-BPD

- Response defined as ≥30% ZAN-BPD reduction from baseline at Week 10.

Difficulties in Emotion Regulation Scale (DERS-16)

- Change from baseline in (DERS-16) total score at Week 10.

State-Trait Anxiety Inventory (STAI-S)

- Change from baseline in STAI-S total score at Week 10.

Patient Health Questionnaire (PHQ-9)

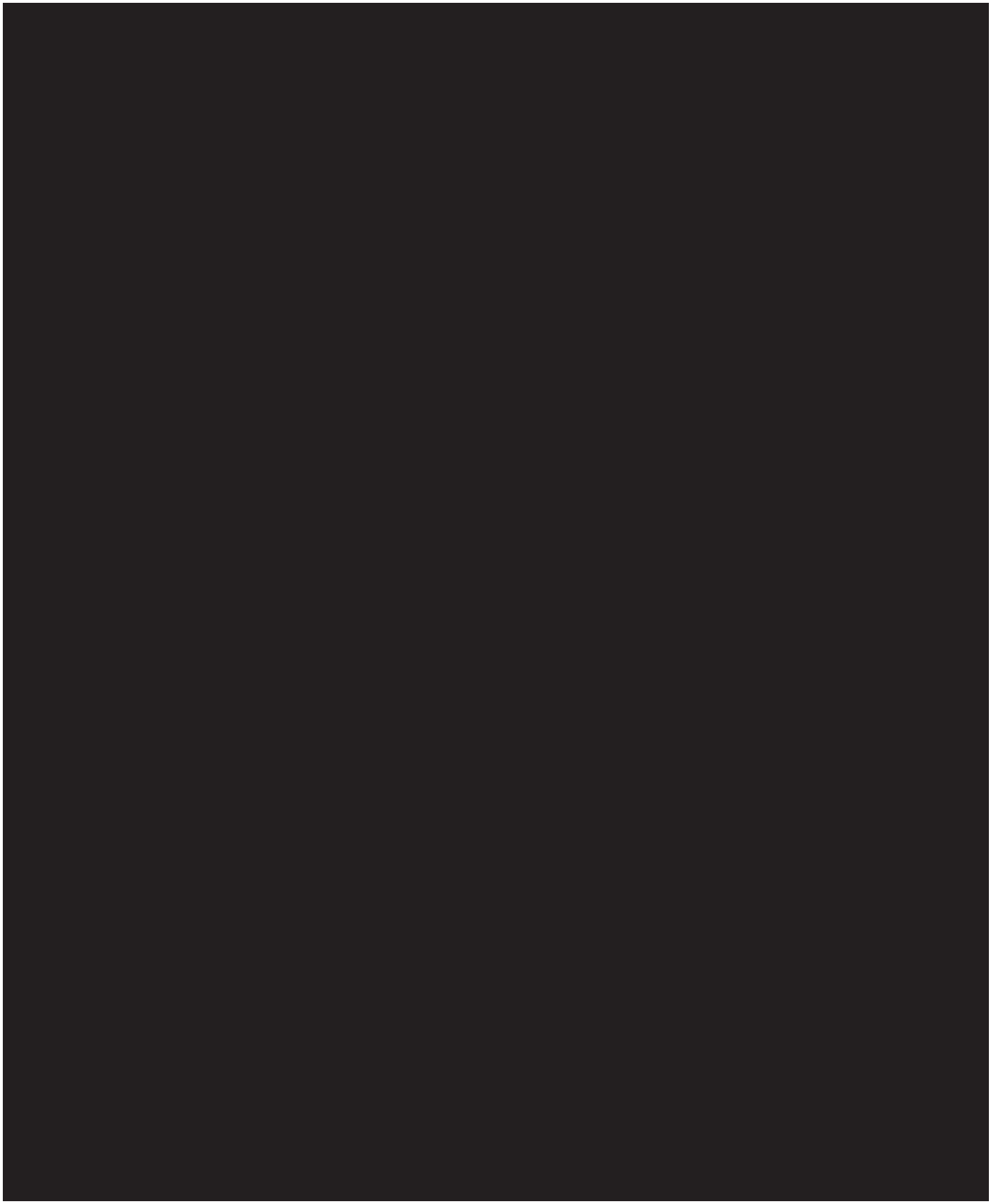
- Change from baseline in PHQ-9 total score at Week 10.

Clinical Global Impression Severity scale (CGI-S)

- Change from baseline in CGI-S at Week 10.

Patient Global Impression Severity scale (PGI-S)

- Change from baseline in PGI-S at Week 10.



2.2.3 Safety

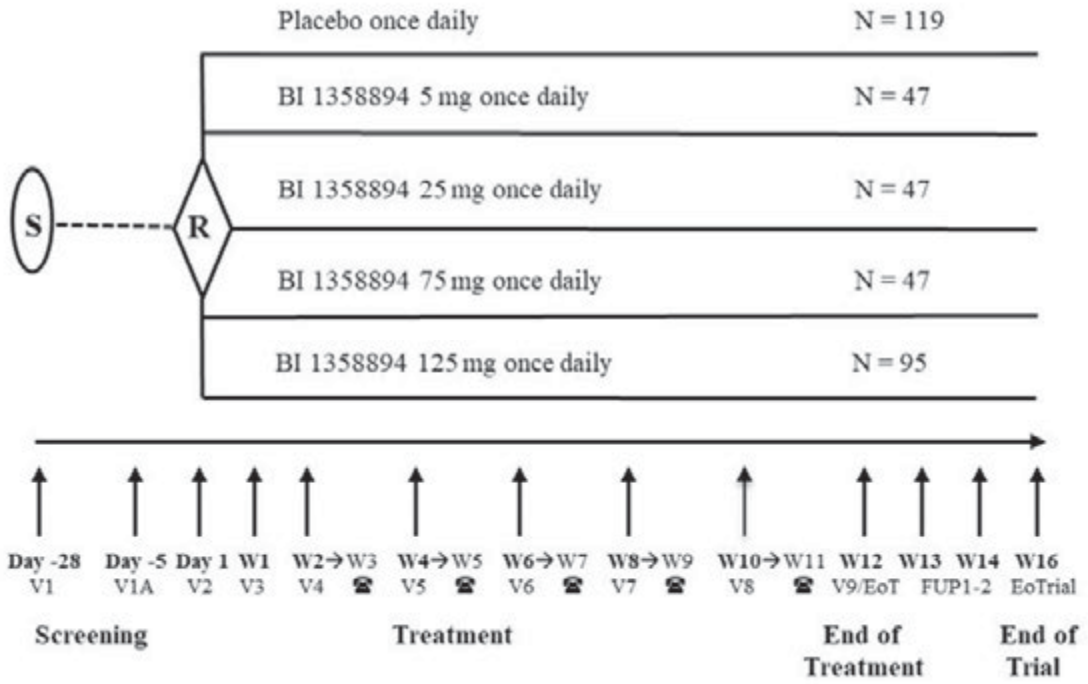
Safety will be assessed in patients who received at least one dose of study drug, including:

- Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)
- Suicidality as assessed by C-SSRS
- Occurrence of protocol-specified adverse events of special interest (AESI)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a Phase II, 12-week multi-center, multi-national, randomized, double-blind, placebo-controlled parallel-group trial in patients with BoPD. A targeted total of 355 patients with BoPD meeting the entry criteria are planned to be randomized into this trial.



V = Visit, W = Week, FUP = Follow-up, EoT = End of treatment, EoTrial = End of trial
☎ = Telephone visit

Figure 3.1: 1 Study design

Patients will be enrolled into the trial once consent has been signed. Patients suitable after screening will be randomized to the 12-week double-blind treatment period at Visit 2 and will be assigned to placebo or one of the four treatment groups in 2.5:1:1:1:2 ratio (Figure 3.1: 1).

After the completion of the 12-week double-blind treatment period or following early discontinuation of trial medication at any point, patients will complete the 4-week follow-up period. Individual patient participation is concluded when the patient has completed their last planned visit (End of Trial visit). Safety will be formally evaluated at each visit until the end of the observational period which is 28 days after the end of treatment or for a longer time in case of unresolved AEs.

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

This is a randomized double-blind, placebo-controlled, parallel-design study. This design is appropriate for providing proof-of-concept and dose-ranging and assessing the safety and efficacy of BI 1358894 compared to placebo in patients with BoPD. It is important to have a placebo control to address potential confounding factors.

The design of the study will provide efficacy, safety and dosing information to support PoC. 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 BI 1358894 doses were chosen 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 (2.5:1:1:1:2, PBO:5mg:25mg:75mg:125mg) has been selected for the treatment and placebo groups. An unequal allocation ratio will lead to better precision of the dose response modelling. In addition, increasing the proportion of patients 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.

Efforts to avoid real or imagined abandonment is one of the core and most prominent symptoms of BoPD. Patients with BoPD experience intense fears of abandonment, which may result in inappropriate anger even when faced with a realistic short-term separation or when there are unavoidable changes in plans (R19-1313). This phenomenon has not been understood adequately in context of a large controlled clinical trial setting; however, the observation of loss of effect towards the end of a large global clinical study can be hypothetically explained on the basis of fear of abandonment (R19-1108). Anecdotally, clinicians are sensitive to issue of perceived abandonment towards the end or change of a therapeutic relationship with a patient with BoPD.

Although this study is a 12-week treatment duration, we plan to evaluate the primary endpoint change in ZAN-BPD total score at Week 10, to avoid any potential issues related to perceived abandonment at the end of treatment period as explained above.

All efficacy will be collected and assessed until Week 12, i.e. until the end of treatment. In addition, safety measures will be collected until end of trial. Collectively, this information will help facilitate the design of the Phase III program.

3.3 SELECTION OF TRIAL POPULATION

The total of 355 patients are planned to be randomized into the study. It is planned that approximately 70 trial centers will be participating in this trial to ensure sufficient number of patients are randomized.

It is expected that approximately 5-10 patients will be randomized at each trial center. If enrollment is delayed, additional sites may be recruited. To avoid differential center influence on study results, permission to randomize more than 15 patients per site must be obtained from the sponsor. This will only be allowed after a careful review of the enrollment status and of the site.

Screening of patients for this trial is competitive, i.e., screening for the trial will stop at all centers when such a number of patients has been screened that it is anticipated that a sufficient number of patients will be randomized to trial treatment. Investigators will be notified when the screening is complete and will not be allowed to recruit additional patients for this trial. Patients who have completed Visit 1 procedures prior to notification of the termination of recruitment will be allowed to continue in the trial, if they meet all entry criteria and they are able to follow the visit schedule specified in the protocol.

A log of all patients 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 patient 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

Patients meeting diagnostic criteria of BoPD per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and diagnosis confirmed at time of screening by Structured Interview for DSM-5 Personality Disorder (SCID-5-PD) will be screened for suitability for the study.

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

3.3.2 Inclusion criteria

1. Patients meeting diagnostic criteria of BoPD per DSM-5 at screening visit, confirmed by SCID-5-PD.
2. ZAN-BPD of ≥ 9 at screening (Visit 1) and randomization (Visit 2), with question #2 Affective Instability score of ≥2.
3. Male or female patients, 18-65 years of age at the time of consent

4. Women of childbearing potential (WOCBP) [1] able and willing to use two methods of contraception, as confirmed by the investigator, which include one highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1%, plus one barrier method (refer to section 4.2.2.3).

5. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

[redacted]

3.3.3 Exclusion criteria

1. Current diagnosis of paranoid, schizoid, schizotypal and antisocial personality disorders, as confirmed by SCID-5-PD at screening visit

2. Lifetime diagnosis for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, or delusional disorder as confirmed by the SCID-5 at the screening visit.

3. Any other mental disorder (in addition to those described in Exclusion 1 and 2) that is the primary focus of treatment in the last 6 months prior to randomization, as per the clinical judgement of the investigator.

4. Inpatient stay or hospitalization due to worsening of BoPD within 3 months prior to randomization.

5. Initiation or change in any type or frequency of psychotherapy (e.g. DBT, cognitive behavior therapy (CBT), Interpersonal therapy) for BoPD within 3 months prior to screening. Patients with ongoing, stable psychotherapy >3 months prior to screening (and intend to maintain the same frequency during the study) may qualify as per clinical judgement of the investigator.

6. Any ongoing use of psychotropic medications within 7 days prior to randomization or during the course of study (unless allowed per protocol, see section 4.2.2.1). Investigators may use their clinical discretion to wash out (at least 3 half-lives of referenced medication) psychotropic medications during screening period. Such wash-out of ongoing psychotropic medication must complete at least 7 days prior to randomization.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile.
Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal occlusion/ ligation is NOT a method of permanent sterilization.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

7. Any suicidal behavior in the past 1 year (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior) prior to screening and during the screening period.
8. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent) prior to screening and during the screening period.
9. Any non-suicidal self-injury that leads to hospitalization within 3 months prior to randomization.
10. Diagnosis of moderate or severe substance use disorder within the last 3 months of screening visit (as defined in DSM-5-substance use disorder) or at randomization visit. In case of a positive drug screen, patient may be considered for inclusion in the study, at the discretion of the investigator, if patient does not have moderate or severe substance use disorder as per DSM-5.
11. Use of alternative or traditional medicine (e.g. Chinese traditional medicine, herbal medication, St. John's Wort, etc.) at the time of randomization and/or planned use during the course of the study.
12. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
13. Known history of HIV infection or positive result for active, ongoing Hepatitis B or C infection.
14. History of seizure disorders, stroke, brain tumor or any other major neurological or developmental illness
15. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to randomization or planned elective surgery requiring general anesthesia or hospitalization for more than 1 day during the study period, e.g. hip replacement.
16. 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.
17. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (that, in the investigator's opinion, makes the patient an unreliable trial participant).
18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
19. Clinically significant finding of the physical examination, vital signs [including blood pressure (BP) and pulse rate (PR)], ECG or laboratory value that would jeopardize the patient´s safety while participating in the trial or their capability to participate in the trial.
20. Symptomatic/unstable/uncontrolled or clinically relevant concomitant disease (e.g. renal failure, hepatic dysfunction, cardiovascular disease, etc.) or any other clinical condition

that would jeopardize the patient´s safety while participating in the trial or capability to participate in the trial.

21. 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 30 days or 5 half-lives of the investigational medicinal product, whatever is longer).

22. Patients with an allergy to BI 1358894 and/or any of the excipients. A list of BI 1358894 and placebo ingredients will be provided in the ISF.

[redacted]

3.3.4 Withdrawal of patients from treatment or assessments

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

After premature study drug discontinuation, patients will be asked to further attend scheduled trial visits unless they withdraw consent to participate in the study. If it is not possible to attend all visits, at least phone contacts will occur at the scheduled visit time points (section 6.2.3). It is vital to explain to patients the importance of continuing trial participation and the value of collecting data for all randomized patients. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal. See section 6.2.3 for procedures handling early discontinuation and patient follow-up.

The decision to discontinue trial treatment or withdraw consent to trial participation, together with the reason, must be documented in the patient files and case report form (CRF). If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with 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 patient can no longer receive trial treatment for medical reasons (such as surgery, AE, or other diseases), per investigator's clinical judgement.

- The patient shows disease progression/worsening that precludes further participation in the trial per investigator's clinical judgement.
- 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 behavior (i.e. actual attempt, interrupted attempt, aborted attempt or preparatory acts or behavior).
- Any Non-suicidal self-injury that impacts safety of the study participant and jeopardize continued participation in the trial as per the clinical judgement of investigator.
- Pregnancy occurs during the trial.

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 patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients should remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient 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. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.

Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

An unexpected and unusually high dropout rate.

Further follow up of patients affected will occur as described in section 3.3.4.1 and 6.2.2.

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 tablets (and placebos) have been manufactured by BI Pharma GmbH & Co. KG, Germany.

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
Method and route of administration:	Per os

Table 4.1.1: 2 Placebo matching BI 1358894

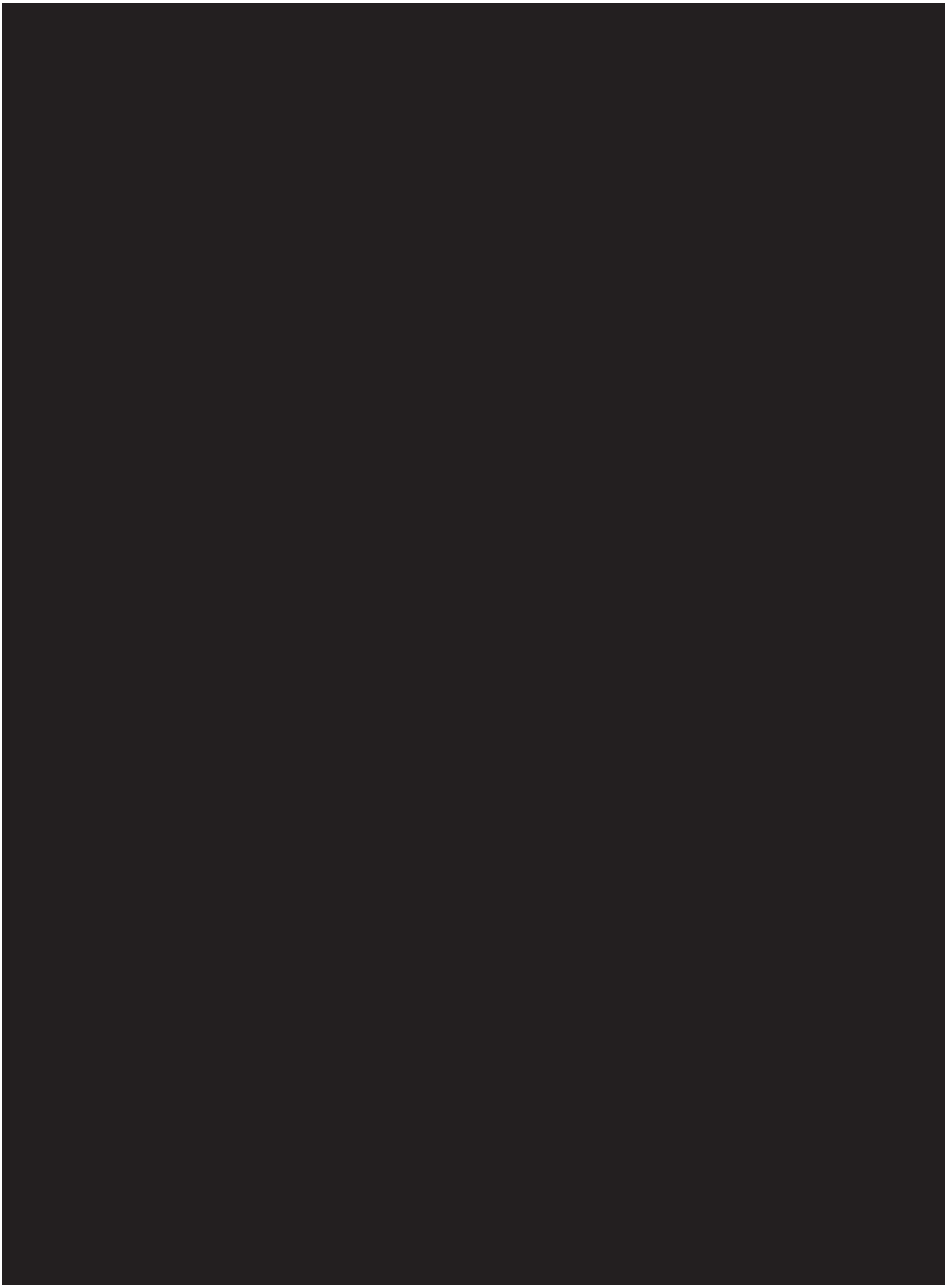
Substance:	Placebo matching BI 1358894
Pharmaceutical formulation:	Film-coated tablet
Source:	[redacted]
Unit strength:	n.a
Posology:	qd
Method and route of administration:	Per os

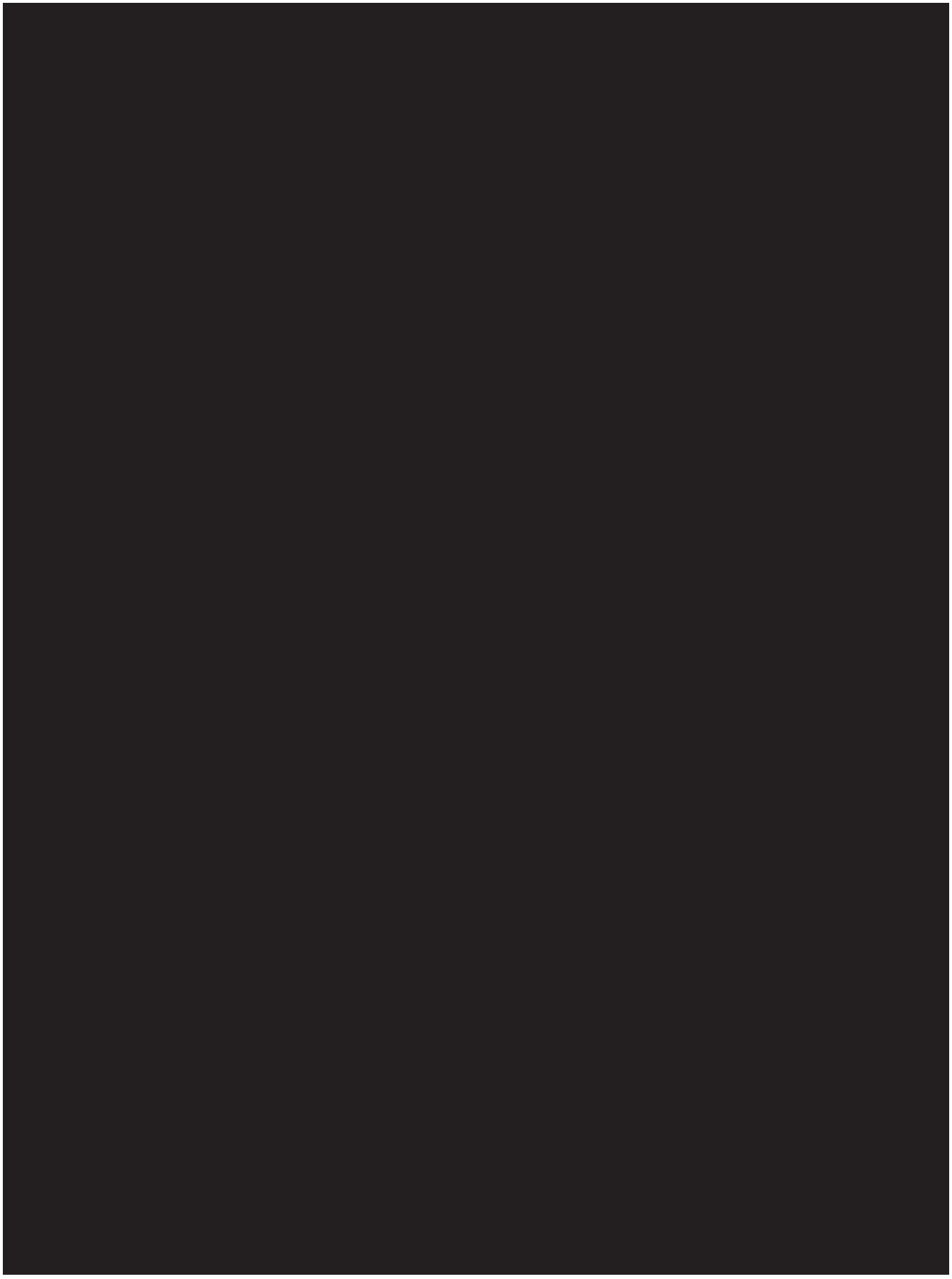
4.1.2 Selection of doses in the trial and dose modifications

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]





4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomized to treatment groups according to a randomization plan at Visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number. Instructions for the use of IRT are provided in the ISF.

Patients will be randomly assigned by IRT, in a 2.5:1:1:1:2 ratio to one of these treatment groups:

1. Placebo
2. BI 1358894 5 mg qd
3. BI 1358894 25 mg qd
4. BI 1358894 75 mg qd
5. BI 1358894 125 mg qd

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

Randomization will be stratified by baseline ZAN-BPD total score (≤18 vs. ≥19).

4.1.4 Drug assignment and administration of doses for each patient

The medication assignment will be provided through IRT. The assigned medication numbers must be entered in the eCRF, and the corresponding medication kits must be given to the patient.

At Visit 2, after randomization, patients will receive their first medication kit. The first dose of trial medication will be taken at the study site under supervision of the investigator or site staff. At each dispensing visit (Visits 2, 5, and 7), patients will receive one medication kit containing supplies for a total of 35 treatment days (28 treatment days plus 7 days reserve). Return of the used/unused medication kits will occur at Visit 5, 7 and EoT/eEoT.

Patients should be instructed not to take their trial medication in the morning of Visits 3, 4, 5, 6, 7 and 8, as patients will be dosed at the site after pre-dose PK sampling. Patients should also be instructed not to take their trial medication in the morning of EoT visit, as a trough PK sample will be taken at that visit (approximately 24 hours after the last dose). For patients that complete the treatment period, the last dose of trial medication should be taken on the

day before the EoT visit. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day.

Each dose will consist of 4 tablets (Table 4.1.5.1: 1). Patients should be instructed to take the study medication orally with water and with or without food, every morning at approximately the same time. It is recommended that patients continue to take study medication in a consistent way, i.e. either with or without food. 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 dose at the visit.

During the COVID-19 pandemic, there may be instances that will prevent a patient from going to the site for a study visit. If the investigator concludes that it is acceptable and safe for the patient to continue trial medication, it is permissible for the trial medication to be shipped from the site to the patient (for more details see section 6.2 and 10.3).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Study medications will be administered double-blinded. In order to maintain blinding in regard to each treatment, each dose will contain 4 tablets in a double-dummy design, as shown in Table 4.1.5.1: 1. Double-dummy design is required since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes. Placebo tablets are identical in size and appearance to the corresponding active tablet and are combined with active tablets as needed in each dose group to maintain the blinding.

Table 4.1.5.1: 1 BI 1358894 and placebo tablets administration per dose group

Dose group	5mg tablet	25mg tablet	50mg tablet	Placebo matching 5mg tablet	Placebo matching 25mg tablet	Placebo matching 50mg tablet
Placebo	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

Patients, 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 after database lock, with the exceptions described in this section below.

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

The randomization codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of PK samples taken from placebo patients.

Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

Dedicated database snapshots (no partial database lock (DBL)) will be generated prior to DBL to allow for development and refinement of population PK and exposure-response models ("Fast-track" PK/PD analysis). The exact time points for the data cut-offs will be aligned with general project planning. Details of this analysis will be defined in the PK/PD analysis plan. Only personnel involved in the population PK and exposure-response analyses will be granted access to the unblinded data before DBL, whereas the trial team and all other functions not involved in the population PK and exposure-response analyses will remain blinded. The analysis plan for the population PK and exposure-response analyses will be finalized and signed prior to this database snapshot for 'fast-track' PK/PD analyses.

No formal interim report will be generated. Final PK and PK/PD analyses will be reported separately from the clinical trial report (CTR) 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 randomization code for individual patients during trial conduct. The access to the code will only be given to authorized 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. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

Initial study drug supplies will be sent to the site after the first patient is screened at the site. 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 must 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 process outlined in the ISF should be followed.

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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- 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 (for USA).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records in the ISF that adequately document the investigational medicinal product's (IMP) delivery to the trial site, inventory at the site, and distribution to and return from each patient. On-site destruction or return of IMP to the sponsor/vendor must also be documented in the ISF. If applicable, the sponsor/vendor will maintain records of destruction for any returned IMP.

These records must include the dates, quantities, batch/serial numbers, expiry ('use- by') dates, IMP kit numbers and patient numbers, as applicable. The investigator or designee must maintain records that adequately document the dose and amount of IMP distributed to each patients as specified in the protocol and must reconcile all investigational medicinal products received from the sponsor. Drug accountability at the site level will also be documented in the IRT. At the time of the final IMP return to the sponsor/ vendor, or the final destruction at the site, the investigator or designee must verify that all unused or partially used drug supplies distributed to patients have been returned by all patients and that no IMP supplies remain in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Following medications are prohibited during the treatment period:

- All psychotropic medications except short term usage of protocol stipulated benzodiazepines and non-benzodiazepine hypnotics (described below)
- [redacted]
- Use of alternative or traditional medicines (e.g. Chinese traditional medicine, herbal medication, St. John's Wort, Ayurveda medications, etc.).

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 study drug. If participant in this trial is on the highest recommended statin dose, the investigator should consider changing the statin dose to the next lower dose recommended for the respective statin, if appropriate.

Concomitant use of benzodiazepines and non-benzodiazepine hypnotics are allowed during study for up to 7 days at a dose equivalent to $\leq$ 1.0 mg of lorazepam per day, for the 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 a longer duration of treatment is needed, re-evaluation of the need for treatment by the investigator is required every 7 days per treatment cycle. Refer to ISF for dose equivalency information.

In case of AEs, any treatment deemed necessary per the clinical judgment of investigator for the management of AEs considering patient safety is allowed.

For further guidance, investigators should refer to the current IB or contact the sponsor.

4.2.2.2 Restrictions on diet and lifestyle

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

It is recommended that patients 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.

Patients do not have to fast prior to trial visits.

4.2.2.3 Contraception requirements

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

Counseling about the importance of having birth control measures in place will be performed at study entry visit (during consenting process), informing women 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. If contraceptive protection cannot be confirmed, as judged by the investigator, the patient must be discontinued from the study drug. Study drug can be restarted only when contraception is used again, and sufficient protection is reached. Counseling and contraception confirmation must be recorded in CRFs.

Acceptable forms of contraception are:
One of the following 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 these barrier methods:

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

4.3 TREATMENT COMPLIANCE

Patients are required to bring all trial medication, including empty package materials, with them to each visit.

Treatment compliance will be calculated based on tablet count, as shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) by using the returned-tablet count that is recorded in the source documents.

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

The potential for abuse of trial medication should be closely monitored. Site staff should discuss and thoroughly document the reasons for compliance that is less than 80% or greater than 100% and events of overdose, misuse, lost and unaccounted medication in the participant's source, and on the appropriate eCRFs.

[redacted]

5. ASSESSMENTS

The current status of BoPD will be assessed during the course of the trial by using the ZAN-BPD (Zanarini rating scale for Borderline personality disorder) as the primary scores and, for a wider perspective, with the outcomes of the DERS-16, STAI-S, PHQ-9, S-UPPS-P, CGI-S, PGI-S, EQ-5D-5L, and SDS scores. EcMA outcomes will be utilized as an additional source of information in an exploratory manner to examine its potential use in future trials.

5.1 ASSESSMENT OF EFFICACY

Zanarini rating scale for Borderline personality disorder (ZAN-BPD)
The ZAN-BPD scale has been widely used in borderline personality research in both academic and clinical research settings. The psychometric properties of the ZAN-BPD have been evaluated, and the results indicate that it is a sensitive scale for assessing changes in BoPD over time (R15-1332). The ZAN-BPD scale is based on the borderline module of the Diagnostic Interview for DSM-4 Personality Disorder (DIPD-4). Considering that there has been no change in the core diagnostic criteria for BoPD from DSM-4 to DSM-5, the ZAN-BPD scale remains relevant as a clinical outcome measure for BoPD.

The ZAN-BPD scale reflects the nine DSM-5 disease criteria and intrinsically aims to cover the entire symptomology of BoPD. The ZAN-BPD scale includes a 5-point rating scale (i.e., 0 = No Symptoms to 4 = Severe Symptoms) for each criterion and measures frequency and severity of BoPD over time with a 1-week recall period. In addition, the scale has 4 sector scores that reveal reflect core areas of BoPD (i.e., affective, cognitive, impulsive and interpersonal symptoms). The total ZAN-BPD score is the sum of these 4 sector scores and ranges from 0 to 36.

The ZAN-BPD scale will be administered as an interview in this study. This assessment should take approximately 25-30 minutes. The ZAN-BPD will be captured using the rater station/tablet provided by the vendor.

Difficulties in Emotion Regulation Scale – 16 item (DERS-16)
The DERS is a widely-used, theoretically driven, and psychometrically sound self-report measure of emotion regulation difficulties (R19-1172, R19-1186). While the DERS was originally developed as a 36-item self-report measure, the brief, 16-item version (DERS-16), was developed to reduce patient burden (e.g. in larger studies and clinical trials that required repeated assessments) (R19-1171).

The DERS-16 is to be completed by the patient using the rater station/tablet provided by the vendor and should take about 5-8 minutes to complete. It consists of 16 items that assess the following dimensions of emotion regulation difficulties: non-acceptance of negative emotions (three items), inability to engage in goal-directed behaviors when distressed (three items), difficulties controlling impulsive behaviors when distressed (three items), limited access to emotion regulation strategies perceived as effective (five items), and lack of emotional clarity (two items). Respondents rate the extent to which each item applies to them on a 5-point Likert-type scale, where 1 is “almost never (0-10%),” 2 is “sometimes (11-35%),” 3 is “about half the time (36-65%),” 4 is “most of the time (66-90%),” and 5 is “almost always (91-

100%).” Total scores on the DERS-16 can range from 16 to 80, with higher scores reflecting greater levels of emotion dysregulation.

The DERS-16 is completed by the patient, and should take approximately 5-8 minutes to complete. The DERS-16 will be captured using the rater station/tablet provided by the vendor.

State-Trait Anxiety Inventory (STAI)
The STAI has been used extensively in research and clinical practice (R98-0762). It is comprised of separate self-report scales for measuring state and trait anxiety. For this study, only the state anxiety questions (STAI-S) will be used.

The STAI-S (STAI Form Y-1) consists of 20 item statements that evaluate how respondents feel “right now, at this moment.” All items are rated on a weighted score of 1 to 4 scale (e.g. from ‘Almost Never to ‘Almost Always’); with higher scores indicating greater anxiety.

The STAI-S is to be completed by the patient and should take approximately 10-12 minutes to complete. The STAI-S will be captured using the rater station/tablet provided by the vendor.

Patient Health Questionnaire-9 (PHQ-9)
The PHQ-9 is a 9-item brief self-reported tool used for screening, diagnosing, monitoring and measuring the severity of depression (R12-3115). The PHQ-9 asks patient ‘Over the last two weeks, how often have you been bothered by any of the following problems?’ in nine questions, with a maximum total score of 27. Depression Severity is assessed as: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), or severe (20-27).

The PHQ-9 is to be completed by the patient and should take approximately 5 minutes to complete. The PHQ-9 will be captured using the rater station/tablet provided by the vendor.

[redacted]

Clinical Global Impression Severity Scale (CGI-S)

The CGI-S rating scale measures the clinician's impression of the severity of illness exhibited by a participant and takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function (R03-0520, R19-1932). The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Higher scores indicate worsening of the patient's illness. This rating is based upon observed and reported symptoms, behavior, and function over the past seven days (R19-1932).

The CGI-S question states "Considering your total clinical experience with this particular population, please choose the response below that best describes how mentally ill the patient was over the past week?", and is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

The CGI-S is to be completed by the interviewer and should take a few minutes to complete. The CGI-S will be captured using the rater station/tablet provided by the vendor.

Patient Global Impression-Severity (PGI-S)

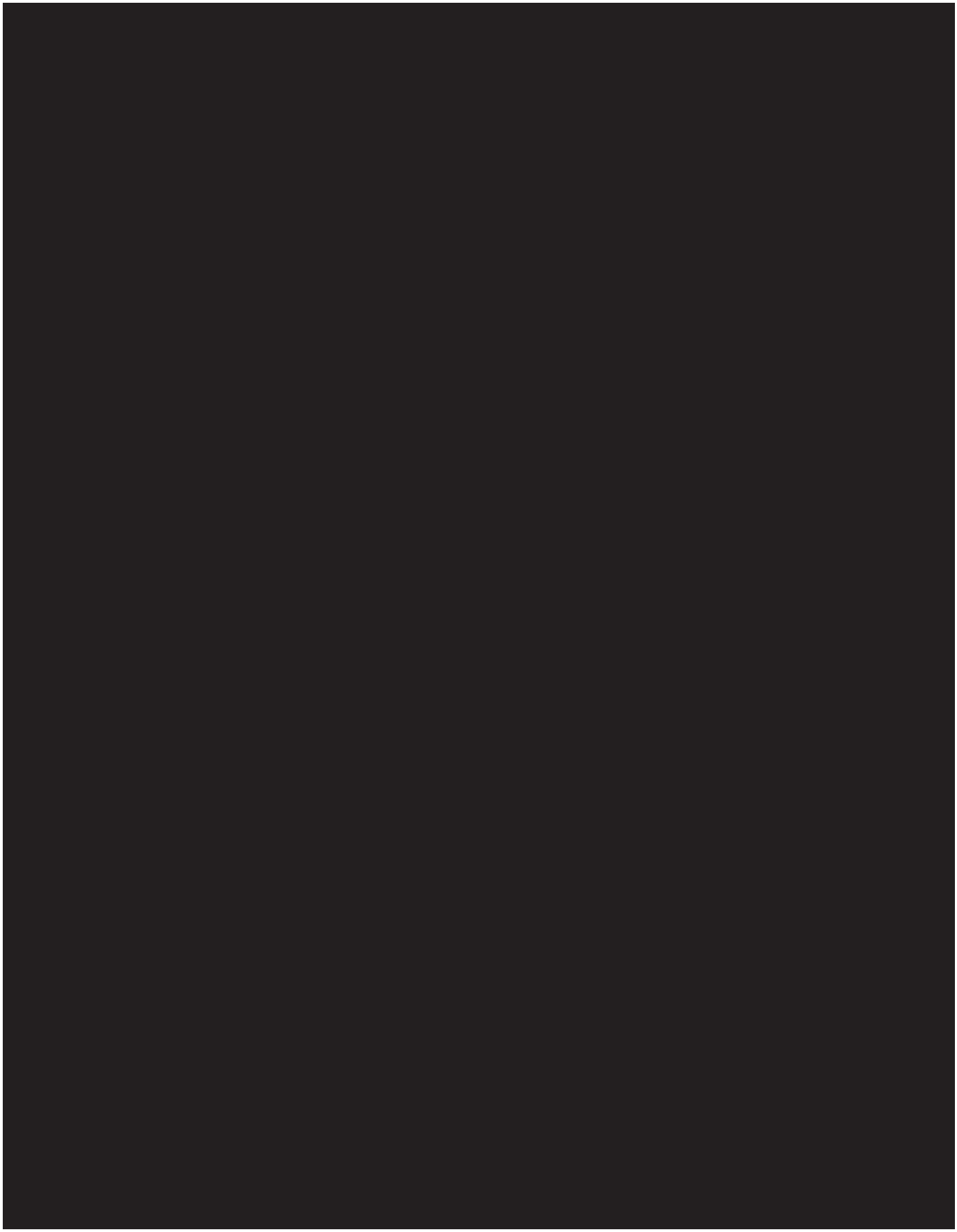
The PGI-S, similar to the CGI-S, will be used to measure the patient's impression of the severity of their illness (R03-0520, R19-1931). It is a single item 5-point scale that ask patients to rate the severity of their illness.

The PGI-S question states "Please choose the response below that best describes the overall severity of your symptoms of Borderline Personality Disorder at this time. (Select one response)"

1. No symptoms
2. Mild
3. Moderate
4. Severe
5. Very severe

The PGI-S is completed by the patient and should take a few minutes to complete. The PGI-S will be captured using the rater station/tablet provided by the vendor.

[redacted]



[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. 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 flowchart. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, 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.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart.

Analyses will be performed by a central laboratory, except the ESR will be done locally at sites with an ongoing inability to obtain ESR result from the central lab. In case of the ESR done locally, results and normal ranges must be recorded in the CRFs. In case of COVID-19 related kit shortage, analyses can be performed at the local lab. Please refer to section 10.3 for further details.

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

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (please refer to section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.6.1.4 and the DILI Checklist provided in the ISF and the

electronic data capturing (EDC) system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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

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

Table 5.2.3: 1 Safety laboratory tests

Category	Test name
Hematology	Hematocrit Hemoglobin Red blood cell count/ erythrocytes Reticulocyte count White blood cells / leucocytes Platelet count/ thrombocytes MCV, MCH, RDW, MCHC Erythrocyte sedimentation rate
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	AST ALT Alkaline phosphatase (AP) Creatine kinase (CK) CK-MB, only if CK is elevated Gamma-glutamyl transferase (GGT/γ-GT) Lactic dehydrogenase (LDH) Lipase Amylase Calcium
Chemistry (continued)	Sodium Urea (BUN) Potassium Glucose Creatinine eGFR Bilirubin total, fractionated if increased Protein, total C-reactive protein Cholesterol, total Triglycerides Free fatty acids Insulin TSH [1] (Reflex testing for T3 and T4 if TSH is positive)

Table 5.2.3: 1 Safety laboratory tests (continued)

Category	Test name
Hormones (male patients only)	LH FSH Testosterone
Urine (dipstick) pregnancy test (WOCB only) [2]	Human chorionic gonadotropin
Serum pregnancy test (WOCB only) at screening or if urine pregnancy test is positive	Human chorionic gonadotropin
Urinalysis (dipstick), with microscopic examination if urine analysis is abnormal	Color and clarity Specific gravity Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Blood Leukocyte esterase Urine pH
Urinalysis	Albumin (quantitative) Creatinine
Drug screening (urine)	Cannabis Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Methadone PCP
Infections screening [1]	Hepatitis B surface antigen (qualitative) Hepatitis C antibody (qualitative) Hepatitis C RNA – only if Hepatitis C antibody (qualitative) is positive

[1] Screening only

[2] Completed locally on-site using kits provided by central lab.

Estimated glomerular filtration rate (eGFR) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009).

5.2.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for at least 10-second duration after the subjects 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 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 patient'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 Visit 1 should be reported as baseline conditions. Clinically relevant, abnormal findings noticed after Visit 1 should be reported as AEs and followed up and/or treated locally until the condition returns to normal or becomes 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.

Central evaluation on an 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.

5.2.5 Other safety parameters

5.2.5.1 Assessment of suicidality

Suicidal risk will be assessed by the C-SSRS. The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal 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 is completed by the interviewer and is captured using the rater station/tablet provided by the vendor.

The C-SSRS has been widely used in large multi-national clinical trials. The C-SSRS will be administered first at screening (Visit 1) (using the 'Baseline / Screening' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to screening.

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. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

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

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

For each C-SSRS 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 AEs, 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 5.2.6.1.3).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

An AE can therefore be any unfavorable 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 5.2.5.1 should be adhered.

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization 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.

5.2.6.1.3 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 5.2.6.2.
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 section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

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

- An elevation of AST (Aspartate aminotransferase) and/or ALT (Alanine aminotransferase) ≥3 fold upper level of normal (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 patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the EDC system. 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 analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

No other AESIs have been defined for this trial.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study 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 etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

For patients who complete the treatment period, the following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (the EoTrial visit):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient 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 5.2.6.2.2), but not on the CRF.

For patients who discontnue treatment prematurely and continue follow-up in the study (see section 6.2.3), the following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the 28 days after the last study drug administration:
  all AEs (non-serious and serious) and all AESIs.
- After 28 days follow-up until the individual patient's end of trial:
  cancers of new histology and exacerbations of existing cancer, all trial treatment related SAEs and all trial treatment related AESIs.
- After the individual patient's end of the trial:
  the investigator does not need to actively monitor the patient for new AEs but should 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 5.2.6.2.2), but not on the CRF.

Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 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 patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient 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]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

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

5.5.1 Methods and timing of sample collection

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

5.6 OTHER ASSESSMENTS

5.6.1 Confirmation of diagnosis

The Structured Clinical Interview for DSM-5 (SCID-5) will be used during screening for confirmation of the diagnosis of BoPD (SCID-5-PD) and to exclude patients with other psychiatric disorders (SCID-5-CT) as described in the exclusion criteria. The SCID-5 is a semi-structured interview guide for making the major DSM-5 diagnoses.

SCID-5 is administered as an interview and is captured on the paper form provided by the vendor.

[redacted]

5.6.4 Verification of current and past research study status of trial participant

Duplicate enrolment and protocol violations are risk factors for poor quality data and safety concerns. These issues may result in increased placebo rates and failed clinical trials. Each participant, in this study, must have their current study status checked by utilizing the system

of the vendor Verified Clinical Trials. This is a mandatory process where approval is received in accordance with local regulations.

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

The first 3 letters of the participant's first and last name will be entered along with the middle initial, date of birth, sex, and last 5 digits of that ID. If the status of the research subject is a 'Verification Success' he/she may proceed in the study. If, however, the status is a 'Verification Failure' he/she will not be permitted to screen without sponsor approval. The duplicate patient check will be performed only after approval is received in accordance with local regulations.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements 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.

Information about race should be obtained from all study participants as allowed by local regulations. It is necessary to collect these data to assess consistency of treatment effects across different patient populations.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

The following requirements for the conduct of the rating scales assessments need to be followed:

- The ZAN-BPD and CGI-S assessments should preferentially be done by the same rater for a given patient throughout the study period.
- During the assessments, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator
- The site staff must be properly trained and certified by the trial vendor and training documentation has to be filed in the ISF; 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 proper training of all members of the site staff involved in the neuropsychological assessments

It must be reiterated at all visits per Flow Chart, that WOCBP must use the appropriate method of safe contraception according to section 4.2.2.3.

During the COVID-19 pandemic, there may be instances that will prevent a patient from going to the site for a study visit. This may be, for example, due to restrictions set by authorities or by the investigator site/institution, because the patient is quarantined, or because of any patient-specific situation that the investigator judges as being not safe for the patient to come to the site.

For details on potential modifications of the trial conduct related to the COVID-19 pandemic, please refer to section 10.3.

6.2.1 Screening and run-in period(s)

Informed Consent for trial participation
All patients must sign an Informed Consent consistent with ICH-GCP guidelines prior to any study specific procedures. Please refer to section 8.1 for details.

Screening period
The Screening period, i.e. the phase before the first administration of the trial drug, starts at Visit 1. The Screening period may be as long as 28 days but should be kept as short as possible.
Visit 1 procedures may be extended to more than one physical visit, if needed.

[redacted]

Optional
- Informed Consent for sample biobanking of plasma and serum for biochemical markers and DNA; this separate consent must be obtained prior to the collection of the respective blood samples.
- [redacted]

Infection screening
In case of positive hepatitis C antibody (qualitative), a hepatitis C RNA will be performed. If hepatitis C infection is confirmed by hepatitis C RNA, the patient will be excluded from the trial.

Demographics and Baseline Conditions
Information on race will be collected because it is required for eGFR calculation (CKD-EPI formula).

Any diagnoses identified through SCID-5 questionnaire must be recorded as baseline conditions.

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 need to be recorded in CRFs for 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.

Substance use, e.g., nicotine, alcohol, caffeine, cannabis, etc., will be collected at screening and at subsequent clinic visits. Please refer to the current CRFs for details about substance use to be collected.

IRT
All patients who are screened must be registered with IRT. If the screening results in a screen failure, patient must be recorded as screen failure in IRT as soon as possible and within the 28-day screening period. Details of IRT procedures can be found in the IRT Manual filed in the ISF.

Eligibility Review
Eligibility assessment will be performed by an external vendor based on clinical review of the SCID-5-CT, SCID-5-PD and ZAN-BPD data and audio recordings from the screening visit, in regard to certain inclusion and exclusion criteria. Uncertainties identified by the external clinical reviewer related to inclusion/exclusion criteria will be discussed with the rater. In cases where an agreement on a patient's assessments cannot be reached between the site and the external reviewer, the patient should not be randomized. At the conclusion of the eligibility review, the vendor will send a Subject Eligibility Notification to the site. The Subject Eligibility Notification will indicate whether the patient is "eligible" or "ineligible" to proceed to the next steps toward randomization (pending results of other screening procedures).

Retesting
Screening evaluations may be repeated once during the screening period.

Rescreening
Rescreening of patients may be done only once based on investigator judgement and prior permission from CTL. Patient who are re-screened need to be re-consented and will be given a new patient number. All the study procedures for screening (Visit 1) must be repeated.

Potential reasons for rescreening could be:

- Suicidality (once the required EX period is over) (EX 7, 8)
- Substance abuse (EX 10)
- Restricted meds like CYPs/ alternative or traditional medicine (EX 11, 12)
- Clinically significant findings per Investigators judgement (EX 19, 20)

6.2.2 Treatment period

General remarks
After all the screening procedures have been completed and eligibility of screened patients is confirmed, Visit 2 can be conducted including randomization via IRT. IRT should not be called in advance of Visit 2 until eligibility is fully confirmed, as randomization of a patient cannot be reserved.

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

Order of rating scales assessments
ZAN-BPD should be performed first followed by C-SSRS. The remaining scales can be performed in any order.

[redacted]

Visit 2 (Randomization)
At the start of Visit 2, it should be ensured that all Visit 1 and Visit 1A procedures have been successfully completed within the past 28 days and eligibility has been confirmed.

Randomization should not be performed in case of a positive urine pregnancy test (to be completed locally on-site using kits provided by central lab). In this case, a serum pregnancy test can be performed by the central lab for confirmation at the discretion of the investigator.

Upon randomization via the IRT, medication kit will be dispensed. The first dose should be taken at the clinic after all Visit 2 assessments are completed.

Trial medication is administered after pre-dose blood collection. Samples for optional plasma/serum and DNA biobanking will be collected if Informed Consent is provided. A sample for DNA biobanking is preferentially collected at Visit 2 but can be collected at another time point thereafter.

Trial drug kits will be dispensed for home administration.

Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8
Patients should not take trial medication before coming to the clinic. This is because patients will be dosed at the clinic. When applicable, dosing should occur after safety lab samples [redacted]

Patients should be instructed to bring all trial medication (used and unused kits/packaging including blisters) with them to these clinic visits.

Phone visits
Visits 4A, 5A, 6A, 7A and 8A will be conducted by phone.

At Visit 8A, patients will be instructed to take the last dose of study medication on the **day before** the EoT visit.

Visit 9 / End of Treatment (EoT) Visit
For patients completing the 12-week treatment, this visit will be EoT visit. For patients who discontinue study treatment prematurely and continue with study visits, this visit will be Visit 9 when they reach Week 12.

EoT visit represents the end of the treatment period. Last study drug administration will be on the day before EoT visit. The overall duration of the anticipated treatment period

(Randomization to EoT) should not be less than 83 days; therefore, the EoT visit is scheduled at Day 85 with a visit window of up to ±2 days.

Patients prematurely discontinuing study drug
If the trial drug intake needs to be permanently stopped for any reason prior to the scheduled Week 12 visit, the eEoT visit will be completed instead of the planned treatment period visit as soon as possible after trial drug discontinuation. See section 6.2.3 below for further details regarding patient follow-up after premature treatment discontinuation.

6.2.3 Follow-up period and trial completion

Patients who complete the treatment period should have FUP1, FUP2 and EoTrial visits completed as described in the Flow Chart. FUP2 visit is performed as phone visit.

EoTrial visit is the final scheduled visit and the End of Study eCRF must be entered. If it is not possible for the patient to attend a follow up visit at the study site as scheduled, a visit outside of the visit window should be performed as soon as possible. If a visit at the site is not possible at all, at least a phone contact should occur at the scheduled follow-up visit time point.

In case of early treatment discontinuation, the patient should be asked to continue with study visits without study treatment. If the patient agrees, the patient will continue with the regular study visit schedule. Alternatively, if the patient does not agree to continue with regular study visits, then the patient should be asked to return to clinic for Visit 8 (preferably) or Visit 9, and the remaining visits can be performed by phone.

See the phone visits in the Flow Chart for a list of procedures that must be completed. [redacted] Once the patient reaches Week 12 (Visit 9), the investigator must assess whether the patient had at least four weeks of observation after end of treatment. If the patient did not have at least four weeks of observation after end of treatment, the patient should continue with follow-up visits per the Flow Chart until the patient reaches the four weeks of visits. Once the patient reaches four weeks of observation, the patient is considered as completed the trial at that time and the End of Study eCRF must be completed. If the patient already had at least four weeks of observation at the time of Week 12 (Visit 9), no further visits are required. The patient is considered as completed the trial and the End of Study eCRF must be completed.

If the patient does not want to continue with study visits after early discontinuation of study medication, the patient must complete FUP1, FUP2 and EoTrial visits for safety reasons.

If the patient refuses any further follow-up after treatment discontinuation, this will be considered as "withdrawal of consent" by the patient and must be recorded as such in the CRFs.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary trial objective of this Phase II trial includes demonstration of PoC of the clinical activity of BI 1358894 with respect to a non-flat dose response curve, characterization of the dose-response relationship by assessing 4 doses and placebo, 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 analyze 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 10 in ZAN-BPD 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 the 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 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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. The category “missing” will be displayed where applicable (i.e., if and only if there are actually missing values in the data). 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.

For in-text tables, the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD) or median, Q1, Q3, depending on the data. For end-of-text tables, the set of summary statistics is: N/Mean/SD/Q1 (lower quartile)/Median/Q3 (upper quartile). For appendix tables, the set of summary statistics is: N/Mean/SD/Min/Q1/Median/Q3/Max.

Analysis sets defined for this trial include the full analysis set (FAS) and the treated set (TS). The FAS comprises all randomized patients 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 Trial statistical analysis plan (TSAP).

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

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

7.2.2 Primary endpoint analyses

7.2.2.1 Primary analyses

As defined in section 2.1.2, the primary endpoint is the change from baseline to Week 10 in ZAN-BPD total score. Baseline refers to the measurement recorded at randomization (Visit 2), if data at Visit 2 is missing, then data from Visit 1 will be considered baseline.

The primary estimand of interest is the treatment effect assuming all subjects remained adherent to the assigned trial medication and the study protocol using a hypothetical approach, i.e. study 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 patient discontinues trial drug, regardless of reason, will be censored and will not be included in the primary analysis.

The analyses for PoC and dose-finding will be performed using multiple comparison and modelling techniques (MCPMod). 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 while keeping full control of the type I error at 10%, one-sided. The primary endpoint will be analyzed using a mixed model repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. Under the MMRM model, there’s no explicit imputation of missing data, rather, the future statistical behavior of those participants who drop out given their past measurements is assumed to be the same as those who remain with the same history.

In particular, between-treatment differences in the change in ZAN-BPD total score at Week 10 (from baseline) will be evaluated using a MMRM adjusted for treatment arm, clinical visit and baseline ZAN-BPD total score. In addition, participants will be included in the model as a random effect. Additional covariates (such as stable concomitant psychotherapy use (yes/no) and sex) or factors identified prior to database lock may be included in the MMRM model as applicable.

The primary treatment comparisons will be the contrasts between each BI 1358894 treatment arm and placebo at Week 10. 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. Parameter estimation of the MMRM will be based on the residual maximum likelihood method (REML).

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 candidate models in Table 7.2.2.1: 1 were selected 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.

Table 7.2.2.1: 1 Models for the MCPMod analysis

Model	Estimate	Rationale
Emax1	50% of the maximum effect is achieved at 25 mg	Emax curve corresponds the assumed true estimate of ED50=25 mg.
Emax2	70% of the maximum effect is achieved at 5 mg	To cover the possibility for which 70% of the maximum effect is achieved at 5 mg. This is a scenario in which much of the effect is achieved early on with relatively low doses. The rationale behind the two Emax models is to construct one (emax1) where the dose response is achieved as expected, while the other (emax2) accounts for the setting of which the assumed dose response is not as expected.
Sigmax	50% of the maximum effect is achieved at 25 mg, and 90% of the maximum effect is achieved at 75 mg	Another more flexible model to cover the new estimate ED50=25 mg
Exponential	5% of the maximum effect is achieved at 25 mg	To cover the case where the effect of drug is mainly achieved at the higher doses.
Linear	No parameter assumptions required	In the event, dose response is linear.

The models were based on the following assumptions:

- BI 1358894 dose groups 5mg, 25mg, 75mg, 125mg and
- ED50 = 25 mg *

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

EC50: Half maximal effective concentration

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

FST: forced swim test (in mice)

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 10 in ZAN-BD 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. 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).

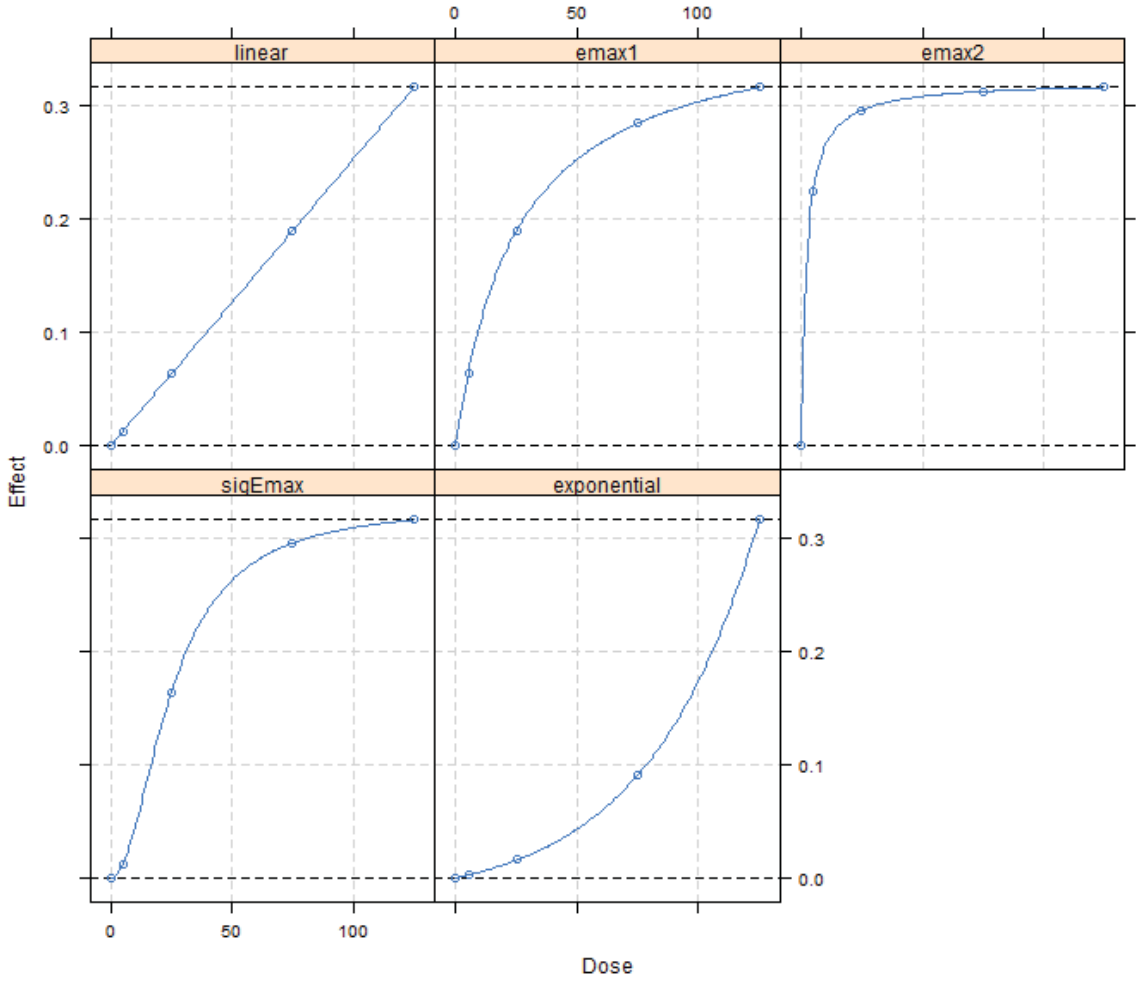
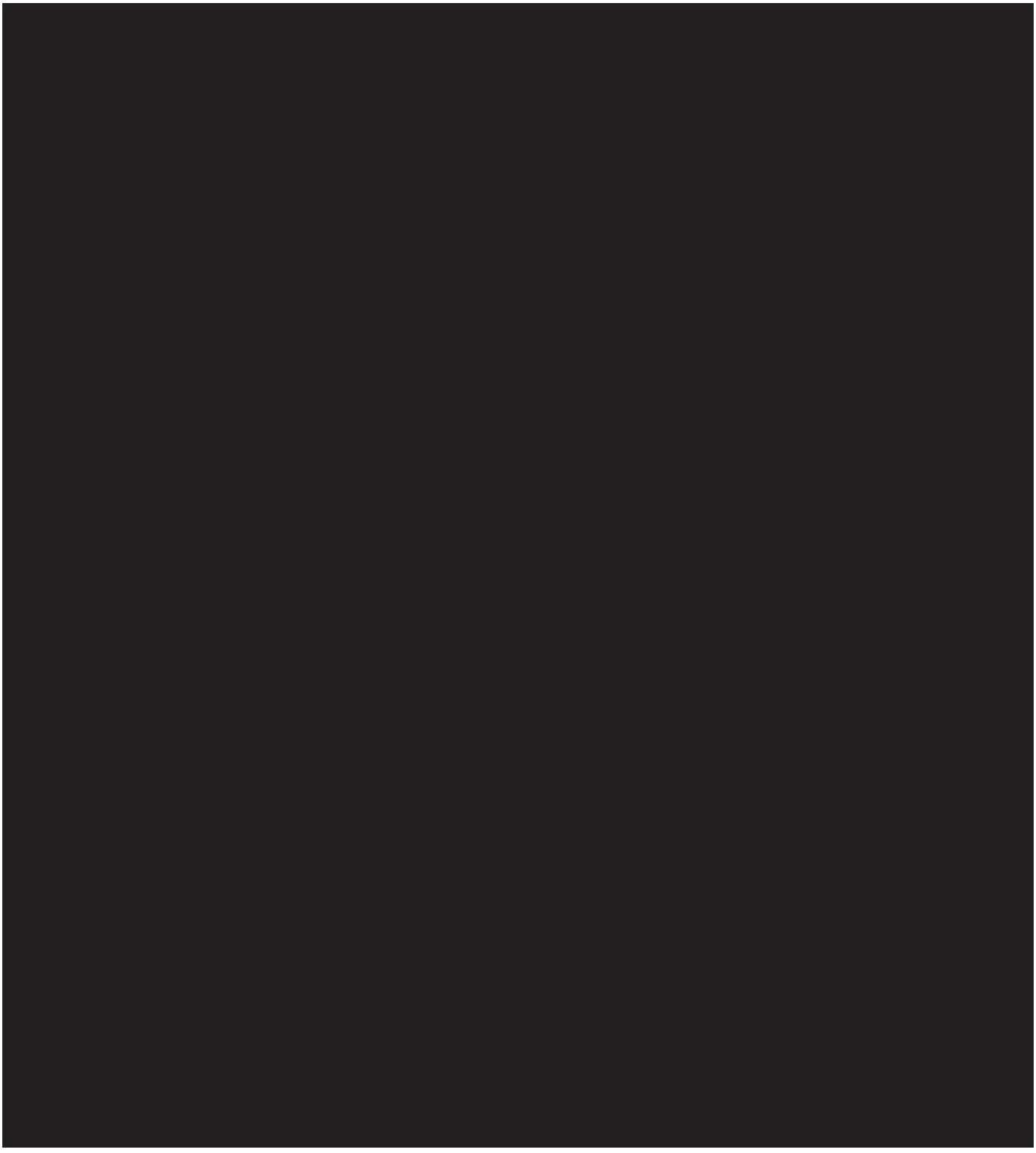


Figure 7.2.2.1: 1 Shape of the considered dose response patterns for the MCPMod analysis

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates.

Sensitivity analyses to assess the robustness of the primary analysis outcomes to the assumption of MAR will be described in the TSAP.



7.2.3 Secondary endpoint analyses

ZAN-BPD response

The secondary endpoint of ZAN-BPD response (defined as ≥30% ZAN-BPD reduction from baseline at Week 10) is a binary endpoint. This endpoint will be analyzed through a logistic regression model to obtain an estimate of the population odds ratio and associated CIs

between BI 1358894 and placebo. This statistical model may be adjusted for factors that may influence response to treatment for BoPD, such as baseline ZAN-BPD total score (≤18 vs ≥19), stable concomitant psychotherapy (yes/no), and sex (male/female).

DERS-16
The secondary endpoint of change from baseline in DERS-16 total score at Week 10, will be analyzed by a MMRM model similar to that of the primary efficacy endpoint.

STAI-S
The secondary endpoint of change from baseline in STAI-S total score at Week 10, will be analyzed by a MMRM model similar to that of the primary efficacy endpoint.

PHQ-9
The secondary endpoint of change from baseline in PHQ-9 total score at Week 10, will be analyzed by a MMRM model similar to that of the primary efficacy endpoint.

PGI-S
The secondary endpoint of change from baseline in PGI-S will be summarized by treatment arm as follows. Mean change from baseline to Week 10 and standard deviation will be presented. In addition, the frequency and proportion of patients reporting each response category at baseline and at Week 10 will be displayed. To compare change in severity as assessed by the PGI-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.

CGI-S
The secondary endpoint of change from baseline in CGI-S at Week 10 will be analyzed in a similar fashion as PGI-S (described above).

[redacted]

[redacted]

[redacted]

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 period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients 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’.

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 MedDRA at database lock.

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

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.

[redacted]

7.2.7 Interim Analyses

No interim analysis is planned. A Data Monitoring Committee (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 analyzed.

Sensitivity analyses may be conducted utilizing multiple imputation techniques for the primary and supplemental analyses of the primary endpoint. Similar methods for handling missing data will be used for secondary efficacy endpoints, as applicable. With respect to

safety evaluations, it is not planned to impute missing values. More details for missing data handling will be included in the TSAP, if needed.

7.4 RANDOMISATION

Participants will be randomly assigned to treatment in a 2.5:1:1:1:2 ratio as described in section 4.1.3. Randomization will be stratified by baseline ZAN-BPD total score (≤18 vs. ≥19).

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a 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 (CTR). Access to the codes will be controlled and documented as described in section 4.1.5.1.

7.5 DETERMINATION OF SAMPLE SIZE

Sample size is estimated assuming a maximum standardized effect size of 0.32, which is based on a mean difference between placebo and BI 1358894 of 3.0 and standard deviation of 9.5 for the primary endpoint, a one-sided alpha of 0.10, a treatment allocation ratio of 2.5:1:1:1:2 (placebo, BI 5mg, BI 25mg, BI 75mg, BI 125mg, respectively) and the pre-specified models listed in section 7.2.2.1. Information on the change from baseline and its standard deviation is limited since there is no BoPD approved drug. BoPD is a symptomatic and clinically heterogeneous condition and in clinical studies a high discontinuation rate has been observed. Consequently, sample size assumptions are based on expert opinion, previous BoPD research and a quetiapine pivotal trial (R19-1108, R19-1645, P11-04859).

For the PoC analysis of the BI 1358894 dose groups and placebo using MCPMod approach with the parameters as listed in section 7.2.2, a sample size of 285 (95:38:38:38:76) evaluable patients are needed to establish PoC with about 81% average power (one-sided 10% alpha level). The powers for each model shape under different assumptions are summarized in the table below.

Assuming a 20% dropout rate is considered reasonable based on unique characteristics of this population. Therefore, a total sample size of approximately 355 randomized patients are needed for this phase II trial:

- 119 patients in placebo arm
- 47 patients in each of the three lowest BI 1358894 arms
- 95 patients in the highest BI 1358894 arm

The calculations for the PoC step have been performed using DoseFinding R-package (R15-2001).The R codes for the sample size calculations as well as the analyses using the MCPMod approach will be provided in the TSAP. The family–wise type I error rate at one sided $\alpha = 10\%$ is controlled in the sample size calculations and the analyses.

Table 7.5: 1 Power of MCPMod for each candidate set model and average power for change from baseline in ZAN-BPD at Week 10

Model	**Assumption A**	Assumption B	Assumption C
Maximum effect size	**0.32 (Mean=3, SD=9.5)**	0.35 (Mean=3.3, SD=9.5)	0.38 (Mean=3.6, SD=9.5)
Linear	**81.9%**	86.7%	91.6%
Emax 1	**81.7%**	87.7%	91.6%
Emax 2	**75.2%**	82.7%	86.6%
Sigmax	**85.4%**	89.1%	93.7%
Exponential	**81.0%**	85.8%	90.5%
Average	**81.1%**	86.4%	90.8%

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, 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 patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover, if required locally, is made available to the investigator and the patients, 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 patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional 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 patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the

informed consent form after confirming that the patient understands the contents. The investigator or his 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, 6.2 and 10.3) during the COVID-19 pandemic, patients 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 subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

In order to achieve a high level of process standardization, data collection of neuropsychological assessments will be coordinated centrally by a third party vendor. Services to be provided include:

- Rater pre-qualification
- Rater training (face-to-face and online)
- Provision of rater materials
- Central quality review of the SCID-5-CT, SCID-5-PD and ZAN-BPD assessments. For this purpose, SCID-5-CT, SCID-5-PD and ZAN-BPD interviews will be recorded (audio only).

Details of raters' pre-qualifications, raters' training, raters' materials (including assessments) and the central review procedures will be described in the vendor documentation available in TMF.
All data corrections to rating assessments requested by the sites will be processed and tracked by the vendor. Data corrections made to rating assessments will be reviewed by a vendor

clinician. 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.

In addition, patients will be offered to watch a short informational video intended to educate the patient about placebos, and why they are used in clinical trials. The video advises the patient 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 placebo, and stresses the importance of reporting all symptoms, be they positive or negative or neutral.

8.3 RECORDS

eCRFs for individual patients 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 patient. 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). Data reported on the eCRFs must be consistent with the source data or the discrepancies must be explained.

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

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

In case local laboratory is used for ESR or due to COVID-19 related variations, local laboratory results report will be considered as source document. The investigator must maintain in the ISF both local laboratory results and corresponding reference ranges.

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

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

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

- Patient identification: gender, year of birth (in accordance with local laws and regulations)

- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient'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 (indication, start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documentation of medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient 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 patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria, does not make the patient 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 eCRF 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 the 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 PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organization (WHO) GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalized treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient'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-purpose documentation (biomarker proposal, analysis plan and report) to 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 patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient 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 patients 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 patient (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.

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 risk/benefit assessment. The DMC will receive urgent, significant, safety concerns 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. 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.

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

The investigators will have access to the BI web portal, Clinergize, to access documents provided by the sponsor. If applicable, in addition to the protocol, approved and effective local protocol amendment(s) should be followed by investigators.

BI has appointed a Clinical Trial Leader (CTL), 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), CRAs, and investigators of participating countries.

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

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

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

Vendors will be used in this trial for central laboratory services, IRT, central ECG services, scales administration management, [redacted]. Details will be provided in the respective manuals available in the ISF. Bioanalysis of BI 1358894 will be done by a vendor.

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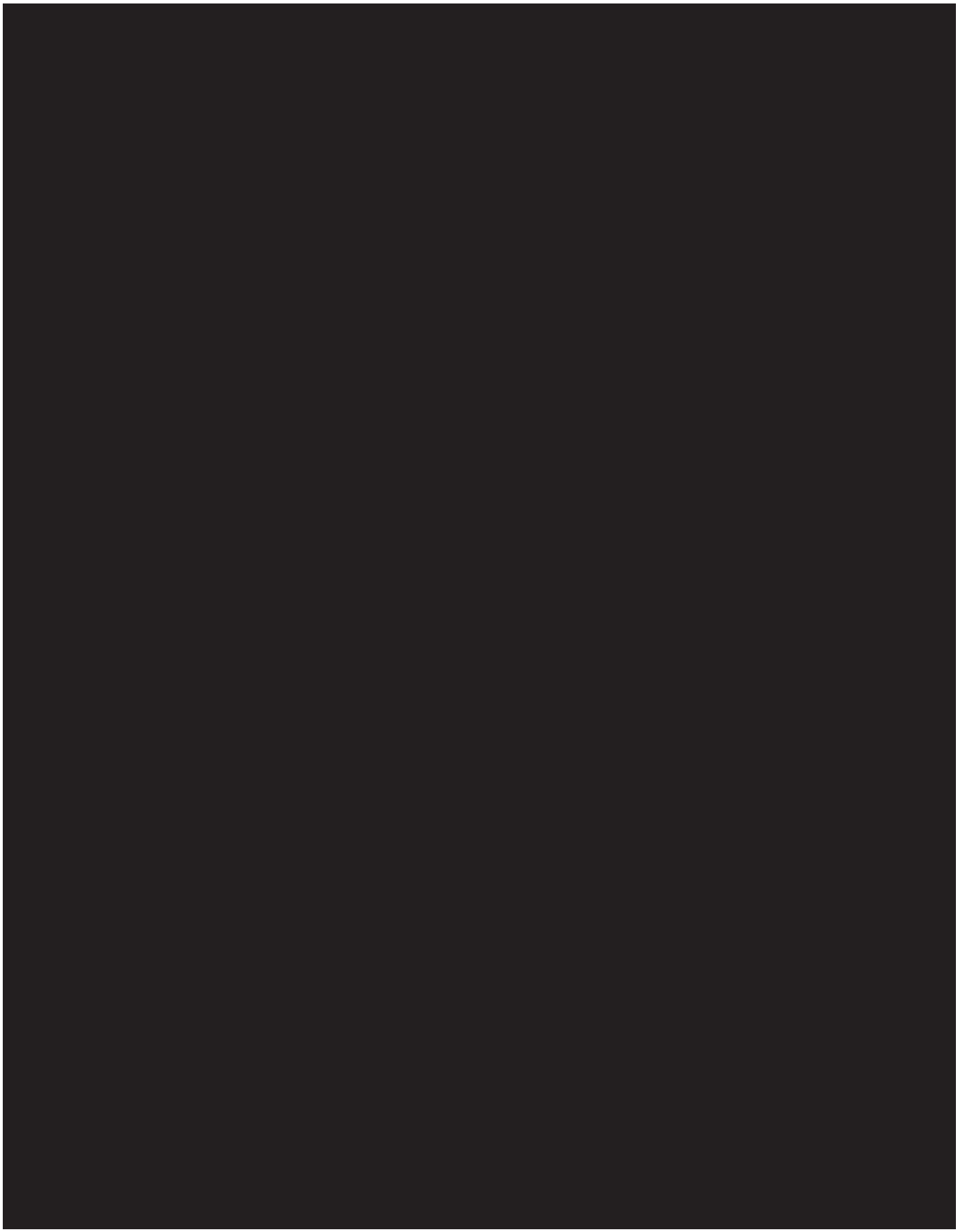
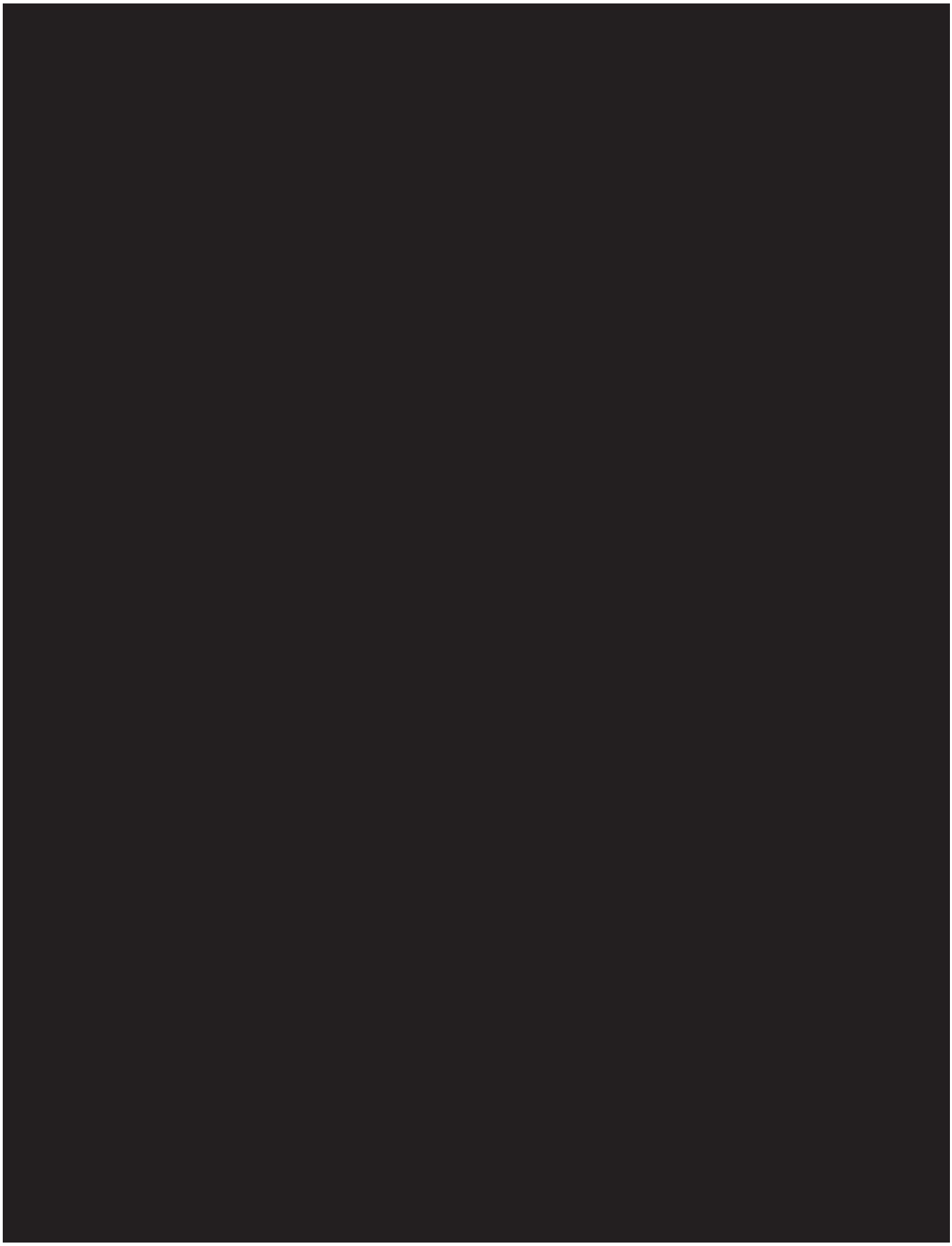
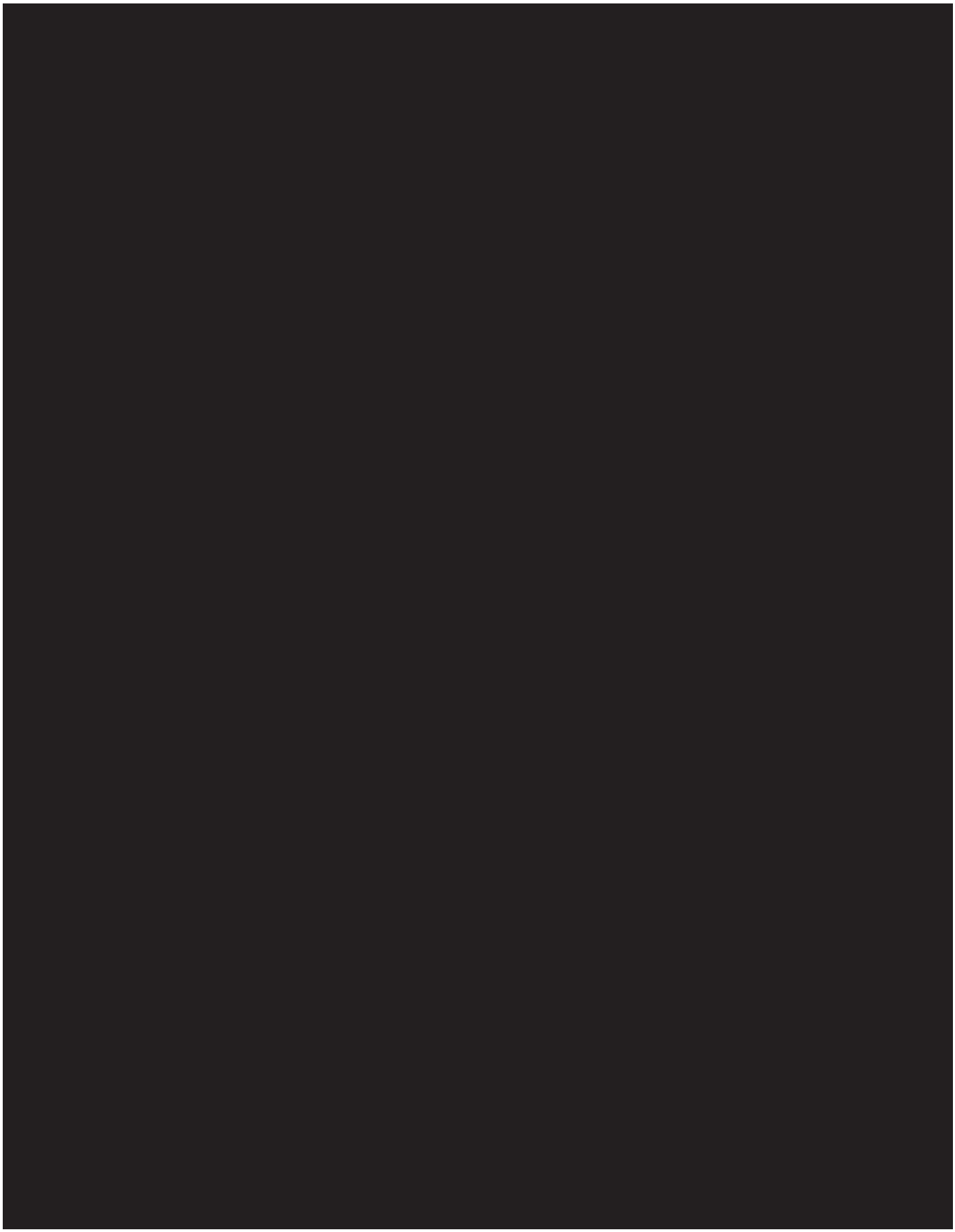
10. APPENDICES







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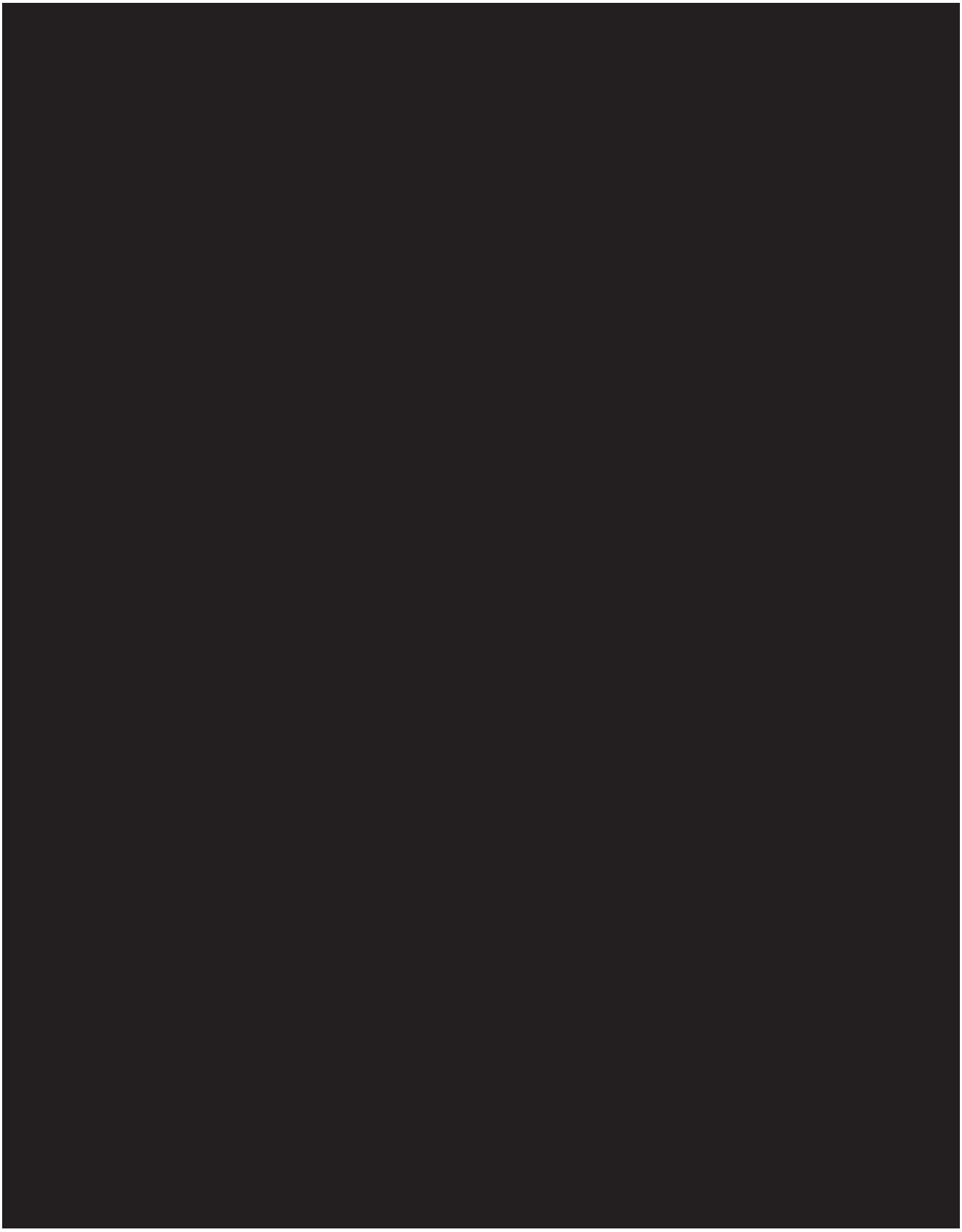


10.3 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

As mentioned in section 6.2, 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 addition, collection of efficacy COAs remotely would support evaluation of study endpoints, with the focus on the primary and secondary endpoints, by reducing missing data.

Accordingly, when it is impossible to conduct the visits at the trial site, visits may be performed via telemedicine (video-enabled internet-based means of communication or audio only) or at the patient's home (e.g., by a study nurse). Visits may also be performed as a combination of home visit and telemedicine. 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 telemedicine/home visits must be discussed with and approved by the sponsor`s trial team.

Local regulatory and legal requirements of the participating country must be respected for all modifications. Under these circumstances, the below modifications can be considered. Patients must be informed about the modifications and give their consent before implementation.

Telemedicine visit
For telemedicine visits, video is the preferred mode. Every effort should be made to conduct the telemedicine visit via video. If for a visit, video communication is not possible, then assessments can be performed via audio. The mode of administration (i.e., in person, video, or audio only) will be recorded in the eCRFs.

Prior to implementing telemedicine visits, sites/raters will receive additional training on the administration of assessments remotely. The objectives of the training will be to standardize the administration of the assessments and ensure consistent monitoring of patient safety in a remote setting. Instructions on the logistics, recommended interview environment, and the identity verification plan will also be addressed in the training. The training will also include patient safety measures for telemedicine visit. At the beginning of each telemedicine visit, Telemedicine Checklist (available in the ISF) must be completed.

Prior to the first telemedicine visit, sites should conduct a brief session with the patient to evaluate the technology and connectivity requirements for the remote visit.

The following should be ensured for remote visits:
- Raters must conduct telemedicine visit from a suitable location to protect patient privacy and confidentiality
- Identification of the reviewer and the patient must be confirmed
- Confirm patient's location in case of emergency identified during the remote visit

- Patient should be in a quiet, comfortable location to ensure patient privacy and uninterrupted interview. Patients should be alone to avoid others influencing patient's answers.

Visit 1, Visit 1A and Visit 2 must always be completed as a clinic visit.

eCOA assessments
During the telemedicine visit, the following eCOA assessments must be completed: ZAN-BPD, C-SSRS, CGI-S, PGI-S, [redacted].

Administration of ZAN-BPD, C-SSRS, ZAN-BPD, and CGI-S by telemedicine will follow the administration rules, existing procedures and requirements for raters training and certification that are already in place for in-clinic assessments. Interview conduct and scoring during a telemedicine visit will be performed by using the same eCOA tablet that is currently used during in-clinic visits.

During the telemedicine visit, the site will present the PGI-S and [redacted] from the eCOA tablet to the patient on the video. The patient will review the response options, and verbally communicate the response that best describes their condition to the site. The site staff that is logged into the eCOA tablet will record and attest to the patient's response. If only audio is possible during a telemedicine visit, the PGI-S and [redacted] question and response options will be read to the patient.

Telemedicine administration of PGI-S and [redacted] scales must follow guidances given in the PRO administration training in order to minimize any potential bias.

Laboratory tests
If taking blood samples for central laboratory is not possible, analysis can be done in a local laboratory. The results of the laboratory tests are to be reported and transferred to the investigator, who must ensure medical review and proper documentation. The use of local laboratory must be recorded in the corresponding CRF page.

Local laboratory tests should at least include tests listed in the Table 10.3: 1. Abnormal local laboratory results should be assessed and reported according to the AE/SAE reporting rules (section 5.2.6). If laboratory results are reported, for example within the SAE report, it is important that the reference ranges of the local laboratory are also provided. If collection on PK samples is scheduled at the visit when local lab is used, PK samples should be collected if feasible (considering time of PK samples collection, logistics for sample processing and shipment, etc.)

Dispensation of study medication (IMP)
If a patient is not able to come to the planned clinic visit and the investigator considers it acceptable and safe for patient to continue with IMP, IMP can be shipped from the site directly to the patient (if legally acceptable according to local regulations).

If home visits by site staff members or, for example 'Home Healthcare Nurse', are possible, further assessments can be done, as appropriate.

Table 10.3: 1 Local laboratory tests

Visit 1	**Visit 1A**	**Other visits with scheduled laboratory tests**
All laboratory tests as defined in the Table 5.2.3: 1	N/A	Hematology including differential test, erythrocyte sedimentation rate, C-reactive protein, liver enzymes and bilirubin, blood glucose, sodium, potassium, creatinine, urea (BUN), eGFR
N/A	N/A	Testosterone, LH, and FSH[1]
Serum pregnancy test[2]	Serum pregnancy test[2]	Serum pregnancy test if urine test is positive[2]
[redacted]	[redacted]	[redacted]

1 Male patients only, if the local laboratory is able to perform it
2 WOCB only

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		08-Dec-2020
EudraCT number **EU number**		2020-000078-12
BI Trial number		1402-0012
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flow chart 3.1 OVERALL TRIAL 6.2.2 Treatment period
Description of change		Flow chart: Rename EoT visit to Visit 9/EoT Added footnote #19 Figure 3.1:1 was modified to rename EoT visit to Visit 9/EoT <u>End of Treatment (EoT) Visit</u> *Was changed to:* <u>Visit 9 / End of Treatment (EoT) Visit</u> For patients completing the 12-week treatment, this visit will be EoT visit. For patients who discontinue study treatment prematurely and continue with study visits, this visit will be Visit 9 when they reach Week 12. … Week 12 (EoT visit) … *Was changed to:* … Week 12 (Visit 9) …
Rationale for change		For patient who continue with study visits after discontinuing study drug, this visit will be Visit 9 when the reach week 12. This was included in the Administrative letter #1 07-May-2020.

Section to be changed		Flow chart
Description of change		Adding Headache history and Meal intake items, including corresponding footnote #20 to the Flow chart
Rationale for change		Clarification
Section to be changed		Flow chart
Description of change		Footnote #2: "Patients who permanently discontinue …" *Was changed to* "For patients who permanently discontinue …"
Rationale for change		Clarification
Section to be changed		1.2 DRUG PROFILE 1.4.2 Risks 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]

		[redacted]
Rationale for change		New information available.
Section to be changed		1.4.2 Risks
Description of change		Added risk/benefit evaluation for patients with COVID-19 related to their participation in the trial.
Rationale for change		Due to ongoing COVID-19 pandemic, patients may present with COVID-19 or acquire COVID-19 during their participation in the trial.
Section to be changed		3.3.4 Withdrawal of patients from treatment or assessments
Description of change		Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data. *Was changed to:* After premature study drug discontinuation, patients will be asked to further attend scheduled trial visits unless they withdraw consent to participate in the study. If it is not possible to attend all visits, at least phone contacts will occur at the scheduled visit time points (section 6.2.3). It is vital to explain to patients the importance of continuing trial participation and the value of collecting data for all randomized patients.
Rationale for change		Request from Health Authority
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		*The following text was added:* • The patient shows disease progression/ worsening that precludes further participation in the trial per investigator's clinical judgement.
Rationale for change		Request from Health Authority
Section to be changed		3.3.4.3 Discontinuation of the trial by the sponsor
Description of change		*The following text was added:* 4. An unexpected and unusually high dropout rate.
Rationale for change		Request from Health Authority

Section to be changed		Table 4.1.1: 2 Placebo matching BI 1358894
Description of change		Source of placebo was changed to [redacted]
Rationale for change		Correction
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		[redacted]
Rationale for change		Correction
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Last paragraph was added.
Rationale for change		Description of alternate study procedures in case of COVID-19 restrictions.
Section to be changed		4.1.8 Drug accountability
Description of change		Last two paragraphs were revised.
Rationale for change		Clarification request from Health Authority.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		7th paragraph was added.
Rationale for change		Rationale for substance use screening.
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		"Erythrocyte sedimentation rate" was added in hematology tests
Rationale for change		Request from Health Authority
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		Urinalysis (dipstick)[2] *Was changed to:* Urinalysis (dipstick), with microscopic examination if urine analysis abnormal *The following has been added:* Color and clarity Specific gravity

		Urine RBC/ erythrocytes Urine WBC/ leukocytes *Was changed to:* Blood Leukocyte esterase "Urine-Sediment" section was deleted.
Rationale for change		Urinalysis section was revised to align with central laboratory reporting.
Section to be changed		6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change		• Each assessment of the rating scales should preferentially be done by the same rater … *Was changed to:* • The ZAN-BPD and CGI-S assessment should preferentially be done by the same rater …
Rationale for change		Clarification
Section to be changed		6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change		Last two paragraphs were added.
Rationale for change		Description of alternate study procedures in case of COVID-19 restrictions.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Subject Eligibility Review section was added.
Rationale for change		Addition of eligibility verification by the vendor.
Section to be changed		6.2.2 Treatment period Pharmacokinetic blood sampling
Description of change		The PK blood sampling times are given in Appendix 10.1. The actual time of drug administration and blood samplings must be recorded in the eCRF. Time of the last drug administration on the day before PK sampling must be recorded in the eCRF. *Was changed to:* The PK blood sampling times are given in Appendix 10.1. The actual date/times of drug administration and blood samplings must be recorded in the eCRF.
Rationale for change		Clarification
Section to be changed		6.2.2 Treatment period

		Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8
Description of change		This is because patients will be dosed at the clinic after safety lab samples and pre-dose PK blood samples are taken. Please refer to section 5.3 for further information regarding PK sampling at these visits. *Was changed to:* 
Rationale for change		Clarification
Section to be changed		6.2.3 Follow-up period and trial completion
Description of change		Clinic visits, with the exception of Visit 8, can be performed via phone if the patient cannot attend the clinic. *Was changed to:* Clinic visits, with the exception of Visit 8 and Visit 9, can be performed via phone if the patient cannot attend the clinic.
Rationale for change		This was implemented in order to be able to complete eCOA assessments.
Section to be changed		6.2.3 Follow-up period and trial completion
Description of change		… at least four weeks of visits … *Was changed to:* … at least four weeks of observation …
Rationale for change		Clarification
Section to be changed		ABBREVIATIONS 7.2.1 General considerations
Description of change		*The following abbreviation was deleted:* IQRMP Important protocol deviations will be identified in the TSAP and Integrated quality and risk management plan (IQRMP). *Was changed to:* Any deviations from the TSAP will be carefully monitored and reported in the CTR. Important protocol deviation are those protocol deviations that have significant impact on patient safety or trial results. Important protocol deviations will be collected throughout the trial

		conduct and will be summarized in the CTR as defined in the TSAP.
Rationale for change		Clarification request from Health Authority.
Section to be changed		7.2.2.1 Primary analyses
Description of change		*The following sentence was deleted:* The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjusted standard errors. Significance tests will be based on least-square (LS) means using a two-sided $\alpha = 0.10$ (two-sided 90% confidence intervals).
Rationale for change		Clarification request from Health Authority.
Section to be changed		ABBREVIATIONS 7.2.6 Other Analyses
Description of change		*The following abbreviation was deleted:* MCID MCID *Was changed to:* Within-patient change
Rationale for change		Correction
Section to be changed		8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT
Description of change		*The following sentence was added:* If study conduct needs to be adjusted (see sections 4.1.4, 6.1 and 10.3) during the COVID-19 pandemic, participants must be made aware of any modifications and their consent needs to be obtained prior to implementation.
Rationale for change		Description of alternate study procedures in case of COVID-19 restrictions.
Section to be changed		8.2 DATA QUALITY ASSURANCE
Description of change		Last three paragraphs were added.
Rationale for change		To provide additional information regarding raters' qualification and raters' system access. Information regarding placebo video.
Section to be changed		8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change		The DMC will evaluate safety and efficacy data. *Was changed to:*

		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 risk/benefit assessment.
Rationale for change		Clarification regarding DMC review of study data.
Section to be changed		8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change		*The following sentence was added:* If applicable, in addition to the protocol, approved and effective local protocol amendment(s) should be followed by investigators.
Rationale for change		Request from Health Authority.
Section to be changed		10.2.5 Endpoints
Description of change		List of sub-study endpoint was revised.
Rationale for change		Correction
Section to be changed		ABBREVIATIONS 10.3 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19
Description of change		*The following abbreviation was added:* PCR Section 10.3 was added.
Rationale for change		Description of alternate study procedures in case of COVID-19 restrictions.

11.2 GLOBAL AMENDMENT 2

Date of amendment		28-Jun-2021
EudraCT number **EU number**		2020-000078-12
BI Trial number		1402-0012
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder
Global Amendment due to urgent safety reasons		

Global Amendment		X
Section to be changed		10.3 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19
Description of change		*Multiple changes and additions throughout the section* *Table 10.3: 1 was added*
Rationale for change		Addition of telemedicine visits To allow the use of local laboratory in case of COVID-19 related kit shortage
Section to be changed		7.2.2.2 Sensitivity analyses for the primary analysis of the primary endpoint
Description of change		*The section header was deleted.* *The following text was added:* Implementation of telemedicine due to COVID-19 – primary analysis In this study, telemedicine refers to the administration of assessments via video or audio, please see Section 10.3 for further details. If telemedicine assessments need to be implemented due to COVID-19 related factors, it will be assumed that there is no discernible difference between the in-person and telemedicine (video) administration of the ZAN-BPD. All data while patients are on treatment, whether in-person or telemedicine (video) will be included in the evaluation of the primary endpoint. However, any ZAN-BPD assessment conducted by audio administration will be excluded from the primary analysis. Any data collected after a patient discontinues trial drug, regardless of reason, will be censored and will not be included in the primary analysis. Sensitivity analyses for the primary analysis of the primary endpoint - telemedicine If telemedicine assessments need to be implemented, sensitivity analyses of the primary endpoint will be performed to assess the robustness of the primary analysis results. The sensitivity analyses will assess the integration of the different modes (i.e., in-person, video, and audio) for administrating the ZAN-BPD. The details related to these sensitivity analyses will be provided within the TSAP.

		The planned analyses will be reviewed and, if necessary, will be updated within the TSAP in order to adopt appropriate strategies. Additional analyses may be performed if deemed necessary (e.g., sub-group analyses, analyses to assess the impact of missing data and safety analyses).
Rationale for change		Addition of telemedicine visits
Section to be changed		7.2.2.3 Supplemental analyses of the primary endpoint
Description of change		*Section number was changed from* 7.2.2.3 *to* 7.2.2.2 Every attempt will be made to follow patients who discontinue treatment till the end of planned study participation. *Was changed to:* Attempts will be made to follow patients who discontinue treatment until the end of planned study participation. *The following paragraph was added:* If telemedicine assessments need to be implemented due to COVID-19 related factors, the treatment policy estimand will use all available data regardless of administration method (i.e. in-person, video and audio).
Rationale for change		Addition of telemedicine visits
Section to be changed		7.2.3 Secondary endpoint analyses
Description of change		*The following paragraph was added:* If telemedicine assessments need to be implemented due to COVID-19 related factors, the details related to the PGI-S and CGI-S analyses will be provided in the TSAP.
Rationale for change		Addition of telemedicine visits
Section to be changed		7.2.6 Other Analyses
Description of change		The primary anchors for ZAN-BPD scale will be the Patient Global Impression of Severity (PGI-S) and Clinical Global Impression Severity Scale (CGI-S). In addition, the distribution-based methods will be utilized to assess the variability of the ZAN-BPD scale. *Was changed to:* The primary anchors for ZAN-BPD scale will be the Patient Global Impression of Severity (PGI-S)

		and Clinical Global Impression Severity Scale (CGI-S) and Patient Global Impression of Impact (PGI-Impact). In addition, the distribution-based methods will be utilized to assess the variability of the ZAN-BPD scale. The details related to the within-patient change analyses will be described in a separate TSAP.
Rationale for change		Addition of telemedicine visits
Section to be changed		8.3.1 Source documents
Description of change		*The following text was added:* In case local laboratory is used due to COVID-19 related variations, local laboratory results report will be considered as source document. The investigator must maintain in the ISF both local lab results and corresponding reference ranges.
Rationale for change		Addition of telemedicine visits To allow the use of local laboratory in case of COVID-19 related kit shortage
Section to be changed		FLOW CHART
Description of change		*The following row was added to the Flow chart:* PGI-Impact 13 Patient-reported assessments, approximate total time all assessments = 45 minutes *Was changed to:* 13 Patient-reported assessments, approximate total time all assessments = 50 minutes
Rationale for change		Request from the FDA to add PGI-Impact scale
Section to be changed		ABBREVIATIONS
Description of change		*The following abbreviation was added:* [redacted]
Rationale for change		[redacted]
Section to be changed		5.1 ASSESSMENT OF EFFICACY
Description of change		*The following section was added:* [redacted]
Rationale for change		[redacted]
Section to be changed		[redacted]
Description of change		[redacted]

Rationale for change		[redacted]
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		7.2.6 Other Analyses
Description of change		The primary anchors for ZAN-BPD scale will be the Patient Global Impression of Severity (PGI-S) and Clinical Global Impression Severity Scale (CGI-S). In addition, the distribution-based methods will be utilized to assess the variability of the ZAN-BPD scale. *Was changed to:* The primary anchors for ZAN-BPD scale will be the Patient Global Impression of Severity (PGI-S) and Clinical Global Impression Severity Scale (CGI-S) [redacted] In addition, the distribution-based methods will be utilized to assess the variability of the ZAN-BPD scale. The details related to the within-patient change analyses will be described in a separate TSAP.
Rationale for change		[redacted]
Section to be changed		5.1 ASSESSMENT OF EFFICACY Clinical Global Impression Severity Scale (CGI-S)
Description of change		*The following sentence was added:* This rating is based upon observed and reported symptoms, behavior, and function over the past seven days (R19-1932). The CGI-S question states "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?", and is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill;

		5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. *Was changed to:* The CGI-S question states "Considering your total clinical experience with this particular population, please choose the response below that best describes how mentally ill the patient was over the past week?", and is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.
Rationale for change		Seven-day observation period is standard for CGI-S and this has been addressed during raters training. Changes in the protocol are just to reinforce the 7-day observation period.
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Main in- and exclusion criteria • Initiation or change in any type or frequency of psychotherapy for BoPD within the last 3 months prior to randomization *Was changed to:* • Initiation or change in any type or frequency of psychotherapy for BoPD within the last 3 months prior to screening.
Rationale for change		Correction
Section to be changed		FLOW CHART
Description of change		*The following row was added to the Flow chart:* IRT registration
Rationale for change		Correction for consistency with section 6.2.1
Section 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 a highly effective method of contraception
Section to be changed		FLOW CHART 5.6 OTHER ASSESSMENTS
Description of change		*The following row was added to the Flow chart:* Informed consent for participant's duplicate check *The following section was added:*

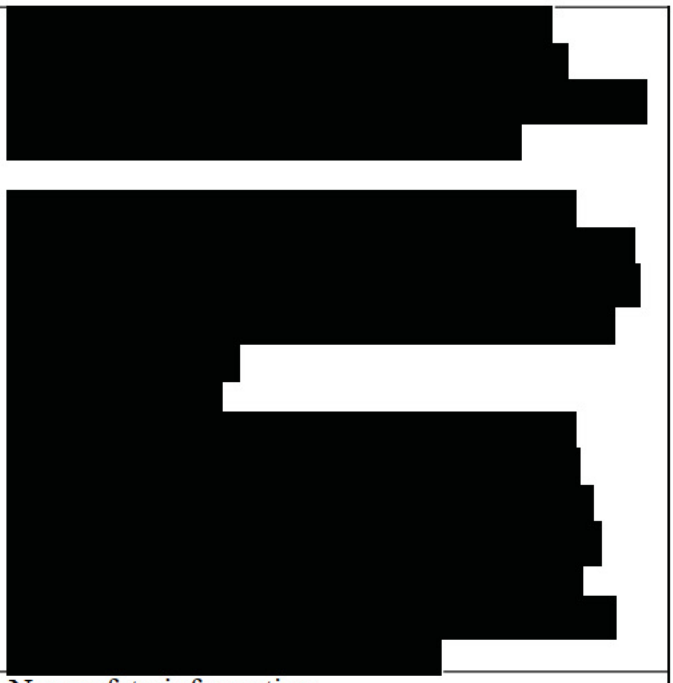
		5.6.5 Verification of current and past research study status of trial participant
Rationale for change		Addition of the procedure to check for patients enrolled in multiple trials
Section to be changed		Table 4.1.1: 2 Placebo matching BI 1358894
Description of change		*The following was added as a source:* Boehringer Ingelheim Pharma GmbH & Co KG, Germany
Rationale for change		Correction
Section to be changed		6.2.3 Follow-up period and trial completion
Description of change		EoTrial visit is the final scheduled visit and the End of Study eCRF has to be entered. Should it be not possible for the patient to attend a follow up visit at the study 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. *Was changed to:* EoTrial visit is the final scheduled visit and the End of Study eCRF must be entered. If it is not possible for the patient to attend a follow up visit at the study site as scheduled, a visit outside of the visit window should be performed as soon as possible. If a visit at the site is not possible at all, at least a phone contact should occur at the scheduled follow-up visit time point.
Rationale for change		Clarification
Section to be changed		6.2.3 Follow-up period and trial completion
Description of change		In case of early discontinuation, the patient should be asked to continue with study visits without study treatment. If the patient agrees, the patient will continue with the regular study visit schedule. Clinic visits, with the exception of Visit 8 and Visit 9, can be performed via phone if the patient cannot attend the clinic. *Was changed to:* In case of early treatment discontinuation, the patient should be asked to continue with study visits without study treatment. If the patient agrees, the patient will continue with the regular study visit schedule. Alternatively, if patient does not agree to continue with regular study visits, patient should be asked to return to clinic for

		Visit 8 (preferably) or Visit 9, and the remaining visits can be performed by phone.
Rationale for change		Requirement for follow-up was changed to one of the two visits, instead of both, to make it easier for patients.
Section to be changed		Table 7.2.2.1:1 Models for the MCPMod analysis Table 7.5:1 Power of MCPMod for each candidate set model and average power for change from baseline in ZAN-BPD at Week 10
Description of change		Linearlog *Was changed to:* Linear
Rationale for change		Correction
Section to be changed		3.3.3 Exclusion criteria
Description of change		*The following text was deleted from Exclusion criteria 19:* (as measured by the central laboratory)
Rationale for change		To allow the use of local laboratory in case of COVID-19 related kit shortage
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		*The following text was added:* In case of COVID-19 related kit shortage, analyses can be performed at the local lab. Please refer to section 10.3 for further details.
Rationale for change		To allow the use of local laboratory in case of COVID-19 related kit shortage
Section to be changed		8.3.1 Source documents
Description of change		Neuropsychological rating scales data entered into the rater station will be regarded as source documentation. These may be centrally reviewed and further analyzed by the third-party vendor. For electronic patient reported outcomes, the electronic record is the source document. *Was changed to:* 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 analyzed by the third-party vendor.
Rationale for change		Clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		27-Apr-2022
EudraCT number **EU number**		2020-000078-12
BI Trial number		1402-0012
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder
Global Amendment due to urgent safety reasons		X
Global Amendment		
Section to be changed		**FLOW CHART**
Description of change		*Pregnancy test was added at the following visits:* Visit 3, Visit 4, Visit 6, Visit 8, Follow-up 1 *The following row was added:* Contraception counseling for WOCB
Rationale for change		New safety information
Section to be changed		1.2 DRUG PROFILE
Description of change		[redacted]
Rationale for change		New safety information
Section to be changed		1.4.2 Risks
Description of change		*The following text was added:*

		[redacted]
Rationale for change		New safety information
Section to be changed		Table 1.4.2: 1 Overview of trial related risks
Description of change		*The following row was added to the table:* Embryo-fetal development toxicity
Rationale for change		New safety information
Section to be changed		1.4.3 Discussion
Description of change		*The following text was added:* [redacted]

		
Rationale for change		New safety information
Section to be changed		3.3.2 Inclusion criteria
Description of change		*The following text was added at the end of the inclusion criterion #4:* (refer to section 4.2.2.3)
Rationale for change		New safety information
Section to be changed		4.2.2.3 Contraception requirements
Description of change		*The following text was added:* Counseling about the importance of having birth control measures in place will be performed at study entry visit (during consenting process), informing women about the risk of medication-induced births defects when exposed to potentially teratogenic medication. 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). *The following text was added:* Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active.
Rationale for change		New safety information

Section to be changed		6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change		*The following text was added:* It must be reiterated at all visits per Flow Chart, that WOCBP must use the appropriate method of contraception according to section 4.2.2.3.
Rationale for change		New safety information
Section to be changed		5.2.5.1 Assessment of suicidality
Description of change		For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied. *Was changed to:* For 'Self-injurious behavior, no suicidal intent' standard AE / SAE reporting rules are to be applied. *The following text was added to the last paragraph:* 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 5.2.6.1.3).
Rationale for change		Clarification
Section to be changed		5.6.4 Verification of current and past research study status of trial participant
Description of change		This is a mandatory process where local regulatory approval has been obtained. *Was changed to:* This is a mandatory process where approval is received in accordance with local regulations.
Rationale for change		Change per Protocol Administrative/Clarification Letter #2

11.4 GLOBAL AMENDMENT 4

Date of amendment		23 Sep 2022
EudraCT number **EU number**		2020-000078-12
BI Trial number		1402-0012
BI Investigational Medicinal Product(s)		BI 1358894

Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		• Women of childbearing potential (WOCBP) able and willing to use two methods of contraception, … *Was changed to:* • Women of childbearing potential (WOCBP) able and willing to use two methods of contraception, confirmed by the investigator, …
Rationale for change		Request from the FDA
Section to be changed		**FLOW CHART**
Description of change		Contraception counseling for WOCB *Was changed to:* Contraception counseling for WOCB [22] 22 This must include confirmation from the patient that she is using the contraception consistently and appropriately. Counseling and contraception confirmation must be recorded in CRFs. Refer to section 4.2.2.3 for more details regarding contraception counseling.
Rationale for change		Request from the FDA
Section 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		Request from the FDA
Section to be changed		Table 1.4.2: 1 Overview of trial related risks
Description of change		Embryo-fetal development toxicity

		The following text was added: 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. Investigators must counsel WOCBP with regard to the need for contraception, at all visits as per Flow Chart (including phone visits). *Was changed to:* Investigators must counsel WOCBP with regard to the need for contraception, including confirmation of the use of contraception, at all visits as per Flow Chart (including phone visits). Refer to section 4.2.2.3 for more details regarding contraception counseling.
Rationale for change		Request from the FDA
Section to be changed		3.3.2 Inclusion criteria
Description of change		4. Women of childbearing potential (WOCBP) [1] able and willing to use two methods of contraception, which include … *Was changed to:* 4. Women of childbearing potential (WOCBP) [1] able and willing to use two methods of contraception, as confirmed by the investigator, which include …
Rationale for change		Request from the FDA
Section to be changed		4.2.2.3 Contraception requirements
Description of change		*The following text was added:* 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. This must include confirmation from the patient that she is using the contraception consistently and appropriately. If contraceptive protection cannot be confirmed, as judged by the

		investigator, the patient must be discontinued from the study drug. Study drug can be restarted only when contraception is used again, and sufficient protection is reached. Counseling and contraception confirmation must be recorded in CRFs.
Rationale for change		Request from the FDA
Section to be changed		1.2 DRUG PROFILE
Description of change		[redacted]
[redacted]		
Section to be changed		Table 1.4.2: 1 Overview of trial related risks
Description of change		[redacted]
[redacted]		
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]
[redacted]		
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF. *Was changed to:* Analyses will be performed by a central laboratory, except the ESR will be done locally at sites with an ongoing inability to obtain ESR result from the central lab. In case of the ESR

		done locally, results and normal ranges must be recorded in the CRFs.
Rationale for change		Incorporated by the Protocol Notification Letter #3
Section to be changed		8.3.1 Source documents
Description of change		In case local laboratory is used due to COVID-19 related variations, local laboratory results report will be considered as source document. *Was changed to:* In case local laboratory is used for ESR or due to COVID-19 related variations, local laboratory results report will be considered as a source document.
Rationale for change		Incorporated by the Protocol Notification Letter #3

APPROVAL / SIGNATURE PAGE

Document Number: c29157684 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12 week treatment period in patients with borderline personality disorder

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	26 Sep 2022 17:40 CEST
Approval-Biostatistics		27 Sep 2022 19:07 CEST
Approval-Clinical Program [redacted]		28 Sep 2022 18:33 CEST
Verification-Paper Signature Completion		30 Sep 2022 13:56 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed