Clinical Trial Protocol

	Document Number: **c34993667-05**
EudraCT No. **EU Trial No.**	2021-003154-23
BI Trial No.	1402-0030
BI Investigational Medicinal Product(s)	BI 1358894
Title	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Lay Title	A study to test whether taking BI 1358894 for 8 weeks helps adults with post-traumatic stress disorder
Clinical Phase	II
Clinical Trial Leader	[redacted] Phone: [redacted], Fax: [redacted] Email: [redacted]
Coordinating Investigator	[redacted] Phone: [redacted], Fax: [redacted]
Current Version and Date	Version 5.0, 09 JUN 2023

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	22 Jul 2021
Revision date	09 JUN 2023
BI trial number	1402-0030
Title of trial	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Coordinating Investigator	[redacted] Phone: [redacted], Fax: [redacted]
Trial site(s)	Multi-centre trial conducted in approximately 10 countries
Clinical phase	II
Trial rationale	Currently the only generally approved medication for treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. These medications produce reduction in symptom severity rather than symptom remission, do not treat all symptoms, and have a relatively low usage in patients with PTSD. Currently most national guidelines recommend psychotherapy as first line treatment for PTSD in adults and medications to be used as second line treatment. Thus there is a significant unmet medical need for more efficacious medications for first-line treatment of PTSD.
Trial objective(s)	The main objective of this trial is to provide proof of concept (PoC) of orally administered BI 1358894 125mg after eight weeks treatment in patients with PTSD compared to placebo.
Trial endpoints	Primary Endpoint: • Change from baseline in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at Week 8 Secondary Endpoints: • Response defined as ≥30% CAPS-5 reduction from baseline at Week 8 • Response defined as ≥50% CAPS-5 reduction from baseline at Week 8 • Change from baseline on the PTSD Checklist for DSM-5 total score at Week 8
Trial design	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in patients with Post-Traumatic Stress Disorder (PTSD)

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Total number of patients randomised	The planned maximum number of patients to be randomized is 286, which includes an expected drop-out rate of 30%
Number of patients per treatment group	Patients will be randomized in a 1:1 ratio
Diagnosis	Patients with an established diagnosis of Post-Traumatic Stress Disorder confirmed at the time of screening by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)
Main inclusion and exclusion criteria	Main Inclusion Criteria: • Established diagnosis of Post-Traumatic Stress Disorder (PTSD) corresponding to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. • Time since index event according to Life Events Checklist/ CAPS-5 Criterion A at least 3 months before screening visit. • PTSD must be the clinically pre-dominant disorder, as per investigator´s judgement. Other comorbid psychiatric disorders are allowed, unless specifically excluded in the exclusion criteria. • A total severity score of ≥ 33 on the PCL-5 at the screening visit. • Moderate to severe PTSD confirmed by CAPS-5 range ≥ 30 confirmed at screening visit. • Male or female patients, 18 to 65 years of age, both inclusively at the time of informed consent. • Women who are of child-bearing potential (WOCBP) must be able and willing to use two methods of contraception, as confirmed by the investigator. Main Exclusion Criteria: • Corresponding to DSM-5, had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder, brief psychotic disorder or any other psychotic disorder as well as MDD with psychotic features as assessed by the MINI at the time of screening. • Any psychiatric or non-psychiatric medical condition likely to negatively impact trial participation as per the judgement of the investigator. • Acute stress disorder or significant traumatic event within 3 months prior to the screening visit. • Use of stimulant medications within 3 months prior to the screening visit (Attention deficit hyperactivity disorder (ADHD) diagnosis alone is not exclusionary) • Severe traumatic brain injury (life-time) or moderate traumatic brain injury within the last 2 years prior to screening visit or 3 months for mild traumatic brain injury, based on the Ohio State University TBI Identification Method Short Form. Or history of traumatic brain injury that would impact ability to complete trial assessments or procedures according to investigator.

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	• Current treatment with trauma focused therapy (i.e. Cognitive Processing Therapy (CPT), Prolonged Exposure Therapy (PE), Eye Movement Desensitization and Reprocessing (EMDR)). A psychotherapy in type, intensity and/or frequency other than trauma focused therapy is allowed if stable within the last 8 weeks prior to screening and not anticipated to change during the entire course of the trial. Long-term psychotherapy is permitted as long as patients are not in an exposure phase during the trial. • Diagnosis of a current moderate or severe alcohol use disorder (AUD) according to MINI within 3 months prior to screening visit (mild AUD and patients in early remission = criterion not met for between 3 & 12 months are allowed). • Diagnosis of a substance use disorder (non-alcohol) according to MINI within 12 months prior to screening visit. Caffeine and nicotine are allowed. • Positive urine drug screen at the screening visit. Exception: stable opioid-treatment with medically prescribed opioids. Please refer to section 3.3 Retesting for retesting options within the screening period. • Any suicidal behavior in the past 12 months prior to screening (per investigator judgement including an actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior) and during the screening period. • Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months prior to screening or at screening or baseline visit (i.e. active suicidal thought with method and intent but without specific plan, or active suicidal thought with method, intent and plan). • Treatment with benzodiazepines is allowed if stable in dose and frequency of use for at least 2 months prior to randomization visit. Note: PRN- use is not permitted. • Antipsychotics, antidepressants and other psychiatric medication are allowed if stable in dose and frequency of use for at least 2 months prior to randomization visit • Any use of restricted medications within 7 days prior to randomization visit • Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. • Use of alternative medicine (e.g. Chinese traditional medicine, herbal medication, St. John's wort, etc.) during the entire course of the trial. • History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial.

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	• Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening. • Patients who are currently involved in any ongoing legal processes related to the index traumatic event (e.g. lawsuit or criminal prosecution). • In-patients are generally excluded, however in-patients who are admittedon a voluntary basis in an open-ward (i.e. "residential ward") and are non-suicidal are allowed.
Test product(s)	BI 1358894
dose	125 mg; once daily
mode of administration	Per os
Comparator product(s)	Placebo
dose	NA for placebo
mode of administration	Per os
Duration of treatment	8 weeks
Statistical methods	Restricted maximum likelihood (REML) based approach using a mixed effects model with repeated measures (MMRM) will be utilized as the main estimator of the primary estimand on the primary endpoint. Intercurrent events will be handled as specified in Section 7. The MMRM model will include the fixed categorical effects of treatment at each visit, fixed categorical effect of the stratification factor of presence of significant childhood trauma (yes vs. no) according to investigator´s judgement, assessed by CTQ at screening visit, and the fixed continuous covariates of time since index event (in years) and baseline CAPS-5 total score at each visit. Patient is treated as random effect. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-subject measurements. Sensitivity analyses for the primary estimand and analyses based on supplementary estimand(s) are planned to assess the robustness of the results from the primary estimand analysis, for details please see Section 7.2.3. An interim analysis is planned for internal planning of the PTSD indication with BI 1358894. PoC could be established and the trial may be stopped early if at the interim analysis an impressive standardized effect size is observed. For more details, please refer to Section 7.2.8.

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FLOW CHART 1

Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT)****	**11 Follow-up Visit (FUP) / End of Study (EOS)**
Week			0	1	2	3	4	5	6	7	8		12
Day	-28 days V1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discontinuation date) plus 28+2 days
Informed consent[4] (including informed consents for patient's duplicate check[5], optional biobanking and speech recording; counseling about the need of contraception)	x												
Demographics[6]	x												
Medical history (including headaches)	x												
Pandemic restrictions[7]			x				x				x	x	
Physical examination	x		x				x				x	x	x
Vital signs, including body weight (height only at SCR)	x		x		x		x		x		x	x	x

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT)****	**11 Follow-up Visit (FUP) / End of Study (EOS)**
Week			0	1	2	3	4	5	6	7	8		12
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discontinuation date) plus 28+2 days
12 lead-ECG	x		x				x				x	x	
Laboratory test (safety labs)	x		x		x		x		x		x	x	
Pregnancy tests[8]	x	x	x		x		x		x		x	x	x
Contraception counseling for WOCB[16]		x	x	x	x	x	x	x	x	x	x	x	
Infection testing[9]	x												
Urine drug screening	x		x				x		x		x	x	
Review of in-/exclusion criteria	x		x										
Randomisation			x										
Interactive Response Technology Use	x		x		x		x		x		x	x	
Patient Duplicate Check[5]	x		x								x	x	x

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**
Visit	**1**	**1A**[1]	**2**	**3** ☎ [2]	**4**	**5** ☎ [2]	**6**	**7** ☎ [2]	**8**	**9** ☎ [2]	**10/ EOT***	**Early EOT (eEOT)****	**11 Follow-up Visit (FUP) / End of Study (EOS)**
Week			0	1	2	3	4	5	6	7	8		12
Day	-28 days V 1A anytime up to 8 days before V2		1 [3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discontinuation date) plus 28+2 days
Administration of trial drugs at trial site[10]			x		x		x		x				
Dispense trial drugs[10]			x		x		x		x				
Drug Accountability[10]					x		x		x		x	x	
Termination of trial medication											x	x	
[redacted]													
PTSD specific assessments / procedures *(see Flow Chart 2)*	x	x	x	x	x	x	x	x	x	x	x	x	x

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT)****	**11 Follow-up Visit (FUP) / End of Study (EOS)**
Week			0	1	2	3	4	5	6	7	8		12
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discontinuation date) plus 28+2 days
All AEs/SAEs/AESIs[14]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x
Substance use [15]	x	x	x		x		x		x		x	x	x
Documentation of meal intake[11]			x		x		x		x		x	x	
Completion of patient's participation													x

At the screening visit, all clinical examinations and procedures as per Flow Chart 1 should be performed first, followed by PCL-5 (version comprising LEC, Extended Criterion A and PCL5),CAPS-5 and MINI, followed by the other clinical outcome assessments, listed in Flow Chart 2**.** Blood draws are preferably done after clinical outcome assessments . The order of assessments and procedures is described in detail in section 6.2.

For all further clinical visits, please refer to section 6.2.2 for details on order of assessments and procedures.

* End of treatment (EOT) for patients who complete the treatment period at Visit 10.

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** Patients who discontinue trial drug prematurely:

Ideally, the patients should attend all remaining visits and perform all study related procedures according to Flow Charts and section 6.2.2. An early EoT (eEOT) Visit shall be conducted within 7 days of the last dose of trial medication for patients who agree to conduct regularly scheduled visits after premature drug discontinuation (if consistent with the planned visit schedule, the eEOT can replace the next regularly scheduled clinic visit). After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits including Visit 10 and should be encouraged to complete the FUP Visit 28+2 days after the drug discontinuation date. All procedures should be completed, with the exception of trial drug procedures and [redacted]. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days), no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and FUP. If FUP visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

1 Eligibility of patients is to be confirmed before Visit 1A is scheduled. Visit 1A must be scheduled at minimum 8 days prior to V2 to allow for 7 days of EcMA assessments before randomization. The randomization visit V2 should be planned shortly (preferably within the same week) after completion of the 7 day EcMA baseline assessment period.

2 Visits 3, 5, 7 and 9 will be conducted via telephone or by video call, if in line with local regulation.

3 Day of Randomisation / Day of first intake of randomized medication – all activities, except [redacted], should be done before drug administration. For exceptions please refer to section 6.2.2.

4 Informed consent may also be done at an extra visit up to 2 weeks before V1., prior to any trial related procedure.The optional informed consent for speech recordings has to be signed prior to speech recording related study procedures at V1A at the latest.

5 Patients duplicate check is a mandatory process, local amendments will be prepared as applicable. Registration of patient in the [redacted] system by site staff is only required during the Screening Visit; no further action for the site staff during the course of the study.

6 Demographics in the eCRF will include questions on potential disability payments related to PTSD

7 The patient will be asked to evaluate the impact of COVID-19 pandemic restrictions. Please refer to section 6.2.2. for detailed information.

8 For WOCBP, a serum pregnancy test will be performed at screening and urine pregnancy tests at all clinic visits beginning with V1A. If a urine pregnancy test is positive, a serum test needs to be performed for confirmation.

9 Infection testing during V1 for hepatitis B and hepatitis C.

10 Patients will bring trial medication (used/unused blister and covering packages) to site visits for compliance check (V4,V6,V8, EOT/eEOT) and for resupply (V4,V6,V8). Patients have to take the IMP at the trial site at all treatment visits (except V10/EOT) to allow adequate sampling of pharmacokinetic samples. Last regular intake of the trial drug is the day before EOT

[redacted]

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

14 After the EoStudy visit (= individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form, please see section 5.4.6.2.2.

15 Substance in the eCRF is defined as: caffeine, nicotine and alcohol.

16 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.

For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to sections 4.1.4, 6.1, 8.1 and 10.3

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FLOW CHART 2

Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**	**Approx. performance duration per assessment**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT) ****	**11 Follow-up Visit (FUP)/ End of Study (EOS)**	
Week			0	1	2	3	4	5	6	7	8		12	
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discon-tinuation date) plus 28+2 days	
Clinician administered assessments														
MINI	x													20 min
CAPS-5[4]	x		x				x				x	x		45-60 min
CGI-S (total and domain)			x				x				x	x		5-10 min each
CGI-C											x	x		5-10 min
OSU TBI-ID-SF	x													5 min
C-SSRS[5]	x	x	x	X	x	x	x	x	x	x	x	x	x	5-10 min

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**	**Approx. performance duration per assessment**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT) ****	**11 Follow-up Visit (FUP)/ End of Study (EOS)**	
Week			0	1	2	3	4	5	6	7	8		12	
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discon-tinuation date) plus 28+2 days	
Speech recordings (optional)		x	x				x				x	x		10 min
Patient Reported Outcomes														
CTQ	x													10 min
PCL-5[6]	x		x				x				x	x		5-10 min
PGI-S			x				x				x	x		5 min
PGI-C											x	x		5 min
STAI			x				x				x	x		10 min
PHQ-9			x				x				x	x		5 min

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**	**Approx. performance duration per assessment**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT) ****	**11 Follow-up Visit (FUP)/ End of Study (EOS)**	
Week			0	1	2	3	4	5	6	7	8		12	
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discon-tinuation date) plus 28+2 days	
DERS-16			x				x				x	x		5-8 min
PSQI			x				x				x	x		5-10 min
SDS			x								x	x		3-5 min
EQ-5D-5L			x								x	x		5 min

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Trial Periods	**Screening**		**Randomized Treatment**									**Early D/C**	**Follow-up / End of Study**	**Approx. performance duration per assessment**
Visit	**1**	**1A**[1]	**2**	**3** ☎[2]	**4**	**5** ☎[2]	**6**	**7** ☎[2]	**8**	**9** ☎[2]	**10/ EOT***	**Early EOT (eEOT)***	**11 End of Study (EOS)**	
Week			0	1	2	3	4	5	6	7	8		12	
Day	-28 days V 1A anytime up to 8 days before V2		1[3]	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57+2		EOT / (Early drug discon-tinuation date) plus 28+2 days	
Additional Patient Assessments/Procedures														
Patient informational video placebo response mitigation[7]		x												5 min
Patient training video speech recording[7]		x												5 min
Training on Smartphone App[8]		x												10-15 min
Drug intake adherence monitoring[9]				← all IMP intake at clinical site and at home →										5 min
EcMA assessments[10]		←performed once daily/weekly for 7 days prior V2 and until the day before V10 →												5-10 min

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At the screening visit, all clinical examinations and procedures as per Flow Chart 1 should be performed first, followed by PCL-5 (version comprising LEC, Extended Criterion A and PCL5),CAPS-5 and MINI, followed by the other clinical outcome assessments, listed in Flow Chart 2. Blood draws are preferably done after clinical outcome assessments . The order of assessments and procedures is described in detail in section 6.2.

For all further clinical visits, please refer to section 6.2.2 for details on order of assessments and procedures.

1 Eligibility of patients is to be confirmed before Visit 1A is scheduled. Visit 1A must be scheduled at minimum 8 days prior to V2 to allow for 7 days of EcMA assessments before randomization. The randomization visit V2 should be planned shortly (preferably within the same week) after completion of the 7 day EcMA baseline assessment period.

2 Visits 3, 5, 7 and 9 will be conducted via telephone or by video call, if in line with local regulation.

3 Day of Randomisation / Day of first intake of randomized medication – all activities, except postdose PK sampling, should be done before drug administration. For exceptions please refer to section 6.2.2.

4 The CAPS-5 past month version will be used at the screening visit for PTSD diagnosis and eligibility assessment. At the randomization visit V2 and at all subsequent study visits, the CAPS-5 past week version will be used.

5 C-SSRS: Columbia Suicide Severity Rating Scale baseline/screening version used at Screening, Columbia Suicide Severity Rating Scale since-last-visit version used for all subsequent study visits

6 At the screening visit, the PCL-5 version including Life Events Checklist, DSM-5 version (LEC-5) and Criterion A assessment; on all subsequent assessments in the trial., the PCL-5 only, will be used. Please refer to section 6.2.

7 Short educational videos will be presented to patient to provide guidance on how to perform the optional speech recording sampling and about placebos (mandatory at V1A) - see further details in section 6.2.1

8 During visit 1A, the patient will receive the Smartphone App and will be trained on the EcMA and drug adherence monitoring procedures. Site staff will configure the App for the planned randomization visit date. Visit 1A must be scheduled at minimum 8 days prior to V2 to allow for 7 days of EcMA assessments before randomization and start of drug treatment.

9 Self-monitoring of IMP intake each treatment day by the patient via the Smartphone App. The drug-adherence assessments will start with the first administration of the trial drug at randomization. For site monitoring of patient adherence using the [redacted], please refer to section 5.8.3.

10 EcMA assessments will be performed by the patient using the Smartphone App. The baseline EcMA assessments will start the day after V1A and last for 7 days prior to the planned V2 (randomization visit date). Site staff will configure the App so that EcMAs will automatically start the day after V1A. EcMA assessments will then be performed daily/weekly in the evenings at each trial day until the end of treatment, the day before visit V10/EOT or eEOT. The exact timing of assessment can be defined by the patient and should be kept as consistent as possible throughout the study. For details, please refer to section 5.8.1.

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ABBREVIATIONS AND DEFINITIONS

ACTH	Adrenocorticotropic hormone
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AUD	Alcohol use disorder
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BI	Boehringer Ingelheim
BOLD	Blood-oxygenation-level-dependent
BoPD	Borderline Personality Disorder
BUN	Blood Urea Nitrogen
CA	Competent Authority
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBT	Cognitive Behavioral Therapy
CCK	Cholecystokinin
CGI-C	Clinical Global Impression Change Scale
CGI-S	Clinical Global Impression Severity Scale
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
ClinRo	Clinician-rated Outcome
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CPT	Cognitive Processing Therapy
CRO	Contract Research Organisation
C-SSRS	Columbia Suicide Severity Rating Scale

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CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTgov	ClinicalTrials.gov
CTP	Clinical Trial Protocol
CTQ	Childhood Trauma Questionnaire
CYP	Cytochrome
DBL	Database Lock
D/C	Discontinuation
DDI	Drug-Drug Interaction
DERS-16	Difficulties in Emotion Regulation Scale – 16 item
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOB	Date of Birth
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethics Committee
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EcMAs	Ecological Momentary Assessments
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMDR	Eye Movement Desensitization and Reprocessing
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
eEOT	Early End of Treatment
EQ-5D-5L	The Euro Qol -5 Dimensions -5 Levels
ES	Effect Size
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration

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FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LC-MS/MS	Liquid Chromatography tandem Mass Spectrometry
LEC-5	Life Events Checklist (DSM-5 version)
LPLT	Last patient last treatment
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Activities
MDD	Major Depressive Disorder
MINI	MINI Neuropsychiatric Interview
MMRM	Mixed model repeated measures
MRD	Multiple Rising Dose
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
OSU TBI-ID-SF	Ohio State University TBI Identification Method Short Form
PANAS	Positive And Negative Affect Scales
PCL-5	PTSD Checklist for DSM-5
PCP	Phenylcyclohexyl piperidine
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PE	Prolonged Exposure Therapy
PGI-C	Patient Global Impression Change Scale

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PGI-S	Patient Global Impression Severity Scale
PHQ-9	Patient Health Questionnaire - 9 items
PK	Pharmacokinetics
PoC	Proof of Concept
PoCP	Proof of Clinical Principle
PRN	Pro re nata
PRO	Patient Reported Outcome
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
PXR	Pregnane X Receptor
q.d.	quaque die (once a day)
QTcF	Corrected QT Interval by Fridericia
RA	Regulatory Authority
REML	Restricted maximum likelihood
REP	Residual effect period
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SDS	The Sheehan Disability Scale
SES	Standardized Effect Size
SIB	Suicidal Ideation and Behavior
SNRI	Selective serotonin-noradrenalin-reuptake-inhibitor
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SSRI	Selective serotonin reuptake inhibitors
STAI	The State-Trait Anxiety Inventory for Adults
SUSAR	Suspected Unexpected Serious Adverse Reactions
TRPC	Transient receptor potential cation channel
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT	UDP-Glucuronosyltransferase
ULN	Upper limit of normal
WHO	World Health Organisation

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WOCBP	Woman of childbearing potential

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Post-Traumatic Stress Disorder (PTSD) is a serious debilitating disorder that may occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, rape or who have been threatened with death, sexual violence or serious injury. The lifetime prevalence is estimated at nearly 4% globally and over 8% in the USA[R21-1545, R21-0924]. Symptoms of PTSD include unwanted and intrusive thought and memories, avoidance of trauma-related thoughts, feelings, and reminders, negative thoughts or feelings following the trauma, and increased arousal and reactivity.

Most treatment guidelines generally recommend cognitive behavioral therapy (CBT) as 1st line treatment for PTSD in adults and pharmacotherapy as 2nd line treatment [R21-1276]. Despite the high prevalence, there are limited licensed pharmacological treatment options; only two medications are currently approved for the treatment of PTSD by the US FDA, EMA and PMDA, sertraline and paroxetine. However, pharmacotherapy is widely acknowledged to be ineffective for many people with PTSD [R21-1829]. There is currently an urgent need to find novel effective pharmacologic treatments for PTSD [R21-1828]

1.2 DRUG PROFILE

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

BI 1358894 is a TRPC4/5 inhibitor that is being developed for symptomatic treatment of Major Depressive Disorder and for the treatment of Borderline Personality Disorder (BoPD) and Post-Traumatic Stress Disorder (PTSD).

Therefore, it is expected that treatment with BI 1358894 has the potential to improve affective symptoms and impaired emotion regulation especially in patients with PTSD in order to develop a novel treatment option and in patients with MDD who inadequately respond to the current standard of care (SSRI; SNRI) and in patients with BoPD, where no approved treatment is currently available.

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

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[R16-5473].BI 1358894 is thought to decrease neuronal excitability leading to normalization of the activation state of limbic circuits which are known to be important for emotional control. Therefore, it is expected that augmentation treatment with BI 1358894 has the potential to improve symptoms of patients with PTSD addressing and improving core debilitating symptoms of the disease and helping patients to be less affected by triggers in daily life and develop healthier coping strategies.

Data from non-clinical studies
Pre-clinically, it has been demonstrated that lack of TRPC4 and TRPC5 or its pharmacological inhibition with BI 1358894 attenuated fear and anxiety without impairing other behaviours in mice.

BI 1358894 is a potent inhibitor of TRPC4 and TRPC5 containing channels. In vitro studies confirmed the high selectivity of the compound. In vivo the compound demonstrated efficacy in various rodent tests used to investigate circuits associated with depression and anxiety [c10354149].

BI 1358894-related effects on the central nervous system of rats were limited to an early and transient increase of motility at dose levels of 10, 30, and 100 mg/kg (nocturnal motility test). This is considered to reflect an increased arousal or decreased anxiety in a novel environment associated with the intended efficacy.

The toxicology profile of BI 1358894 has been evaluated so far in a comprehensive set of *in vitro* and *in vivo* studies. Doses and concentrations were adequately high to explore the full range of potential adverse effects following exposure to BI 1358894. The studies support clinical trials of up to 13 weeks duration in adults, including women of childbearing potential.

The single dose toxicity of BI 1358894 was low in mice and rats and moderate in dogs. Repeat dose toxicity studies up to 13 weeks in mice, rats and dogs revealed toxicologically relevant effects on the skin (mice), Harderian glands (mice), hepatic function (mice), the vascular system (rats) male genital track (rats), the Central Nervous System (CNS) function (dogs), and the digestive tract, renal function, and white blood cell parameters in all three species. Further details on specific toxicity are available in the Investigator's Brochure [IB, c10354149]. In addition, clinical pathology evaluation showed mild inflammatory response at high dose levels in rodents (for details including safety margins refer to section 4.1.2)

BI 1358894 did not show any genotoxic potential when tested in a battery of *in vitro* and *in vivo* studies. No relevant immunotoxicity was demonstrated in mice, rats, and dogs.
BI 1358894 was negative in the *in vitro* 3T3 Neutral Red Uptake phototoxicity test.

Dedicated studies on fertility and early embryonic development were not yet conducted. So far repeat-dose toxicity studies revealed no adverse effects on the male or female reproductive tract. However, the weight of male sex organs was slightly reduced in rats after dosing for 13 weeks.

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Testing for embryo-fetal development in rats revealed no findings related to BI 1358894. The highest dose tested, 1000 mg/kg/day, represented the NOAEL (No Observed Adverse Effect Level) for maternal and embryo-fetal toxicity. Safety margins derived thereof were 5.6 and 5.9 based on comparison of C_{max} and AUC_{0-24h}.

The well-known high sensitivity of rabbits to disturbances of intestinal physiology limited embryo-fetal toxicity testing in this species. Already sub-therapeutic doses of BI 1358894 induced a non-obstructive ileus. A NOAEL for maternal toxicity could not be established in the pivotal study. However, there were no effect on the offspring at any dose that was considered to be directly related to dosing with BI 1358894. The highest tested dose (10 mg/kg/day) was defined as the NOAEL for embryo-fetal toxicity in rabbits.

Oral administration of BI 1358894 to the pregnant Goettingen minipigs throughout organogenesis was associated with developmental effects including lower embryo-fetal survival (due to a reduced number of intrauterine implantations and an increased number of early resorptions) and decreased fetal weights, compared to control. In addition, there were higher incidences of skeletal malformations and/or variations. The NOAEL for embryo-fetal development (100 mg/kg/day) corresponded to a mean Cmax of 1,980 nmol/L and a mean AUC0-24h of 31,300 nmol·h/L of BI 1358894, therefore providing safety margins of 1.4 and 1.6, respectively (compared with the predicted exposure at the human dose of 125 mg).

Data from clinical studies
Overall, 211 healthy volunteers and 23 patients with MDD had been exposed to BI 1358894 in 8 Phase I clinical trials. There were no deaths or SAEs in any of these trials. Headache was the most frequently reported adverse event (AE) with a higher frequency in the BI 1358894 treated groups than in placebo. There was no evidence of a dose dependency based on the available data. Overall, BI 1358894 was well tolerated in healthy male patients, in male and female patients with MDD.

A comprehensive package of safety pharmacology and toxicology studies has been conducted and demonstrated that BI 1358894 can be safely administered to humans for up to 13 weeks.

Key pharmacokinetic characteristics
After administration of BI 1358894 tablets, maximum plasma concentration of BI 1358894 occurred around 1 to 5 hours after dosing.

A long BI 1358894 terminal half-life of 188 hours with low plasma concentrations was found when blood samples were taken up to 672 hours. The terminal half-life was 41 to 52 hours for blood sampling up to 200 hours. Steady state was reached after 11 to 14 days of BI 1358894 dosing, which is more in line with the half-life of 50 to 70 hours. Accumulation ratios for Cmax ranged from 1.6 to 1.8 and for AUC from 2.3 to 2.6.

Drug interactions
Based on *in vitro* Cytochrome (CYP) inhibition data and in perspective with clinical BI 1358894 exposure data, no restriction of concomitant therapy with sensitive substrates of CYP enzymes were defined. No restrictions of concomitant therapy were defined based on *in vitro* UGT inhibition data of BI 1358894.

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BI 1358894 is not inhibiting or inducing CYP3A as was shown with the CYP3A sensitive substrate midazolam. There was no clinically relevant effect on the midazolam exposure when co-administered after single or multiple BI 1358894 doses compared with midazolam administration alone. Comedications, which are sensitive substrates of CYP3A, are not restricted.

Furthermore, absence of a clinically relevant induction of CYP3A by BI 1358894 is considered surrogate of absence of relevant induction of CYP2C family due to the shared PXR dependent induction mechanism. Hence, sensitive drugs metabolised by the CYP2C family are also not restricted.

In vitro BI 1358894 induced CYP2B6, therefore a DDI study was performed with a CYP2B6 substrate. As no clinically relevant induction was seen, there are no restrictions on the use of comedications for sensitive substrates of CYP2B6.

A drug interaction effect of BI 1358894 was observed with a strong CYP3A4 inhibitor. Coadministration with the strong CYP3A4 inhibitor itraconazole increased BI 1358894 total exposure (<2-fold). As the increase is less than 2-fold, there are no restrictions for the use of concomitant CYP3A4 inhibitors.
In vitro data show that BI 1358894 is metabolised by UGTs and CYP3A4. *In vivo* data on metabolites was collected in the SRD and the MRD study. Human plasma was taken in both studies and analysed for human metabolites. The human plasma in both the SRD and the MRD study contained mainly the main metabolite, i.e. the carboxylic acid metabolite. Yet contained only minor amounts of other metabolites. Under steady state conditions, on day 14, for the 50 mg dose, only 1.6% glucuronide metabolite was found, which is formed via UGT enzymes. Since this is only a minor metabolic pathway, inhibitors of UGT enzymes can be included as concomitant therapy.

Strong CYP3A4 inducers are excluded from concomitant therapy due to potential lowering of BI 1358894 exposure.

Initial results from the DDI study 1402-0009 indicate that BI 1358894 has a weak drug interaction effect on drug transporter substrates. BI 1358894 may cause mild inhibition on P-gp (probe substrate dabigatran, 1.2-fold mean increase in AUC and Cmax). The mild inhibition was assessed as clinically not relevant. Hence, the use of substrates for the drug transporters P-gp is not restricted. However, results from 1402-0009 suggest a mild to moderate interaction with Breast Cancer Resistance Protein (BCRP)/OATP1B1/OATP1B3, which results in an increase of rosuvastatin levels (1.8-fold mean increase in AUC and Cmax) when concomitantly taken with BI 1358894. The interaction could affect BCRP and Organic Anion Transporting Polypeptide (OATP) channels and could impact all statins, since these transporters play a significant and general role in statin metabolism. If statins are concomitantly used during the trial, the highest dose of the statin should not be taken together with the investigational compound. Patients concomitantly taking statins in this trial should be monitored for statin related toxicity including myopathy.

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

For a more detailed description of the BI 1358894 profile, please refer to section 1.4 and the current Investigator's Brochure (IB). For the most frequently reported adverse events refer to table 1.4.2:1.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Currently the only generally approved medication for treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. These medications produce reduction in symptom severity rather than symptom remission, do not treat all symptoms, and have a relatively low usage in patients with PTSD. Currently most national guidelines recommend psychotherapy as first line treatment for PTSD in adults and medications to be used as second line treatment. Thus there is a significant unmet medical need for more efficacious medications for first-line treatment of PTSD.
TRPC4/5 channels modulate the excitability of the amygdala/cortico-limbic system. As a TRPC4/5 inhibitor, the therapeutic concept of BI 1358894 is to decrease amygdala hyperreactivity and thus decrease emotional reactivity, emotional dysregulation, and affective instability across a range of psychiatric disorders where these are prominent symptoms. Clinical evidence supporting the therapeutic concept was demonstrated in an fMRI study in patients with MDD, where BI 1358894 produced a significant and robust decrease in the Blood-oxygenation-level-dependent (BOLD) activation of the amygdala in an emotional face task. In an emotional scene task the BOLD signal was also significantly and robustly reduced in amygdala and additional brain areas. BI 1358894 is currently being tested in Phase II clinical trials in patients with MDD and BoPD. Thus the MoA of this compound in principle holds significant potential benefit for individuals with PTSD.

For the PTSD patient trial population, a cut-point on the CAPS-5 of ≥ 30 was selected with the following rationale: In literature, the cut-point on the CAPS-5 of ≥ 30 has been postulated to represent a reasonable lower score representing moderate PTSD, being roughly in the middle of the moderate severity range (23-34) [R21-0830]. The cutoff criteria for CAPS-5 were largely extrapolated from the empirically derived severity score ranges determined in the CAPS version based on DSM-IV (CAPS-IV), adjusting for the changes in the number of symptoms and the new metric for CAPS-5 item severities. The cutoff criterion of ≥ 30 is also acknowledged by PTSD experts to be clinically meaningful in terms of selecting for moderate severity of PTSD. It is further supported by evidence on the PCL-5 suggesting that our selected cut-off on CAPS-5 of ≥ 30 is a reasonable cut-off for inclusion of patients in a treatment intervention trial.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.7). 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 adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

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1.4 BENEFIT - RISK ASSESSMENT

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

1.4.1 Benefits

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

1.4.2 Risks

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

In one completed pivotal embryo-fetal development study in Goettingen minipigs, embryo-fetal development toxicity was identified (decreased number of implantations, increased number of early resorptions, decreased fetal weight, skeletal malformations) at relevant human exposure levels. Maternal toxicity was not seen at human relevant doses. The NOAEL shows that the findings are relevant for the maximum dose (125 mg once daily) tested in the ongoing clinical trials.

Therefore, a risk for teratogenicity in humans cannot be excluded. To mitigate this risk, women of childbearing potential (WOCBP) who are heterosexually active must agree and 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 trial. Pregnancy testing has to be performed at every site visit. 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 1 (including phone visits).

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

Because psychoactive drugs may impair thinking, judgment, and/or motor skills, 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 clinic visits and assessment of suicidal ideation during clinic visits) to ensure that

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worsening of pre-existing conditions or any newly occurring events are detected and any necessary actions taken according to stopping criteria.

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

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

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

- The mode of action does not appear to have a substantial effect on clinically relevant organs (e.g. respiratory or cardiovascular system) critically affected by COVID-19
- There is currently no evidence that intake of BI 1358894 leads to immunosuppression
- There is currently no evidence that their underlying disease (PTSD) makes the patients at higher risk to SARS-CoV-2 infection or to develop severe COVID-19
- The PTSD 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 or patients participating in these studies will not differ from the current general risk for humans of SARS-CoV 2 infection with all its potential consequences. A specific SARS-CoV 2 PCR (Polymerase Chain Reaction) serving as a tool for inclusion or exclusion of trial patients during the screening phase is not foreseen, since it is not believed that study substance or comparator imply an elevated risk for the patient to develop COVID-19. It is also not believed that a SARS-CoV2 infection or clinical apparent COVID-19 impacts the activity of the investigational or comparator compound.

There is no restriction for trial patients to receive vaccination against COVID-19 during or after the study treatment period.

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

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

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Table 1.4.2:1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product - BI 1358894		
Most commonly reported AEs in Phase I were: • Headache • Dizziness • Orthostatic intolerance • Fatigue • Disturbance in attention • Dyspepsia • Nasopharyngitis	All reported AEs were of mild or moderate intensity. None of the patients experienced any serious SAE or relevant alterations in laboratory parameters, vital signs, and ECG. Refer to IB for more details	Management of symptoms, evaluation, and follow-up as needed to ensure patient safety, per investigators clinical judgment.
Concomitant use of: • Strong inducers of CYP3A4 • Strong inhibitors of CYP3A4	Based on current non-clinical and BI 1358894 drug-drug interactions data, use of certain concomitant medications may increase or decrease such medications or BI 1358894. Refer to the investigator site file (ISF) for more information on restricted mediations.	Patients on these medications will be excluded from trial and use of these drugs will be restricted during the treatment period. If such medication is used during the trial for some reason, Investigator should stop either this medication or IMP per the clinical judgment.

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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product - BI 1358894		
Concomitant use of: Statins	Drug-drug interactions suggest a minor to moderate increase in rosuvastatin levels when concomitantly taken with BI 1358894. This interaction takes place on an OATP transporter level and is expected to affect all statins.	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 of the statin should not be taken together with the investigational compound. If patient in this trial is on the highest recommended statin dose, investigator should consider changing the statin dose to the next lower dose recommended for the respective statin if appropriate.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patient safety.

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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Embryo-fetal development toxicity	Decreased number of implantations, early resorptions, decreased fetal weight, skeletal malformations in minipigs at relevant human exposure levels. Thus, a risk for teratogenicity in humans cannot be excluded.	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 visits as per Flow Chart 1 (including phone visits). Refer to section 4.2.2.3 for more details regarding contraception counseling.

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

BI 1358894 – Placebo		
• Worsening of PTSD • Occurrence or increase of suicidality	Even though mitigation measures are applied, this cannot be completely ruled out	Patients will remain on their stable treatment with an SSRI and psychotherapy, where applicable. Placebo is adjunctive to this treatment. Frequency of clinic visits with suicidality assessments are optimized. Suicidal patients will be excluded form trial participation (refer to section 3.3.4.1)

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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
General risk of psychoactive drugs		
• Impair thinking, judgment, and/or motor skills	Psychoactive drugs are known to potentially cause unwanted side effect on brain function.	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.
Trial procedures		
• General discomfort • Blood draw	The potential risks of a blood draw include fainting and pain, bruising, swelling, or rarely infection where the needle is inserted. In rare cases a nerve may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain. The total volume of blood withdrawal per patient during the trial will be approximately up to 220 mL over 16 weeks. This amount may be exceeded if additional unscheduled (in case of necessary safety follow-up) monitoring of laboratory results is needed.	Management of discomfort, evaluation, and follow-up as needed to ensure patient safety. No health-related risk is expected from this blood withdrawal.

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

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, including discontinuation of trial treatment as per investigators clinical judgment.

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1.4.3 Discussion

Considering this patient population, and the need to adequately monitor suicidality, frequent clinic and phone visits, which include C-SSRS assessments, are planned in this trial to monitor patients.

Additionally, all patients will be allowed to continue antidepressants and other psychiatric medications (i.e. non-benzodiazepine anxiolytics) if on stable treatment at the time of trial entry and throughout the whole trial performance. Considering the mechanism of action of BI 1358894 and the adverse events reported in clinical trials to date, there is no undue risk related to stopping the trial drug during the treatment period or at the end of the treatment period, nor any major risk related to potential aggravation of the side effect profile/s of the background medication/s.

After patients have completed trial participation, they should return to treatment as prescribed by their treating physicians.

Embryo-fetal development toxicity has been identified in a pre-clinical study in minipigs at relevant human exposure levels. Therefore, a risk for teratogenicity in humans cannot be excluded. 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 1 (including phone visits).

Considering the acceptable and manageable safety profile of BI 1358894 as demonstrated in nonclinical and toxicology studies, good tolerability in clinical studies performed to date, close monitoring (including the above-mentioned risk mitigation activities to minimize the risk of pregnancy during the trial) planned during the trial visits and the involvement of an independent external DMC, the potential risks to the patients will be minimized and outweighed by a potential therapeutic benefit of the trial drug and more effective treatment for patients with PTSD.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to provide proof of concept (PoC) of orally administered BI 1358894 125mg after eight weeks treatment in patients with PTSD compared to placebo.

2.1.2 Primary endpoint(s)

Change from baseline in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at Week 8

2.1.3 Secondary endpoint(s)

CAPS-5

- Response defined as ≥30% CAPS-5 reduction from baseline at Week 8
- Response defined as ≥50% CAPS-5 reduction from baseline at Week 8

PCL-5

- Change from baseline on the PTSD Checklist for DSM-5 total score at Week 8

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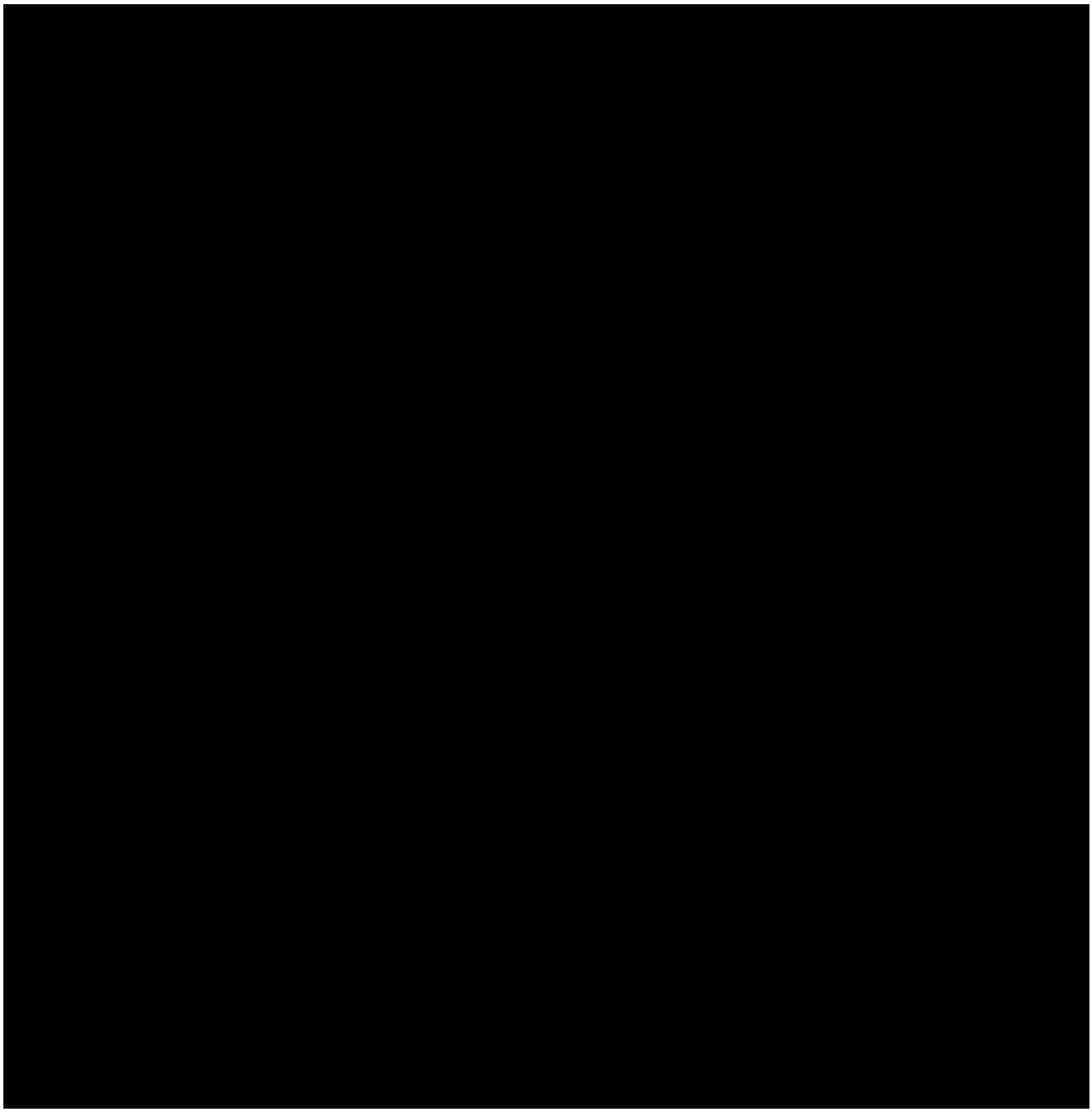

2.2.3 Safety

Safety will be assessed descriptively 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)

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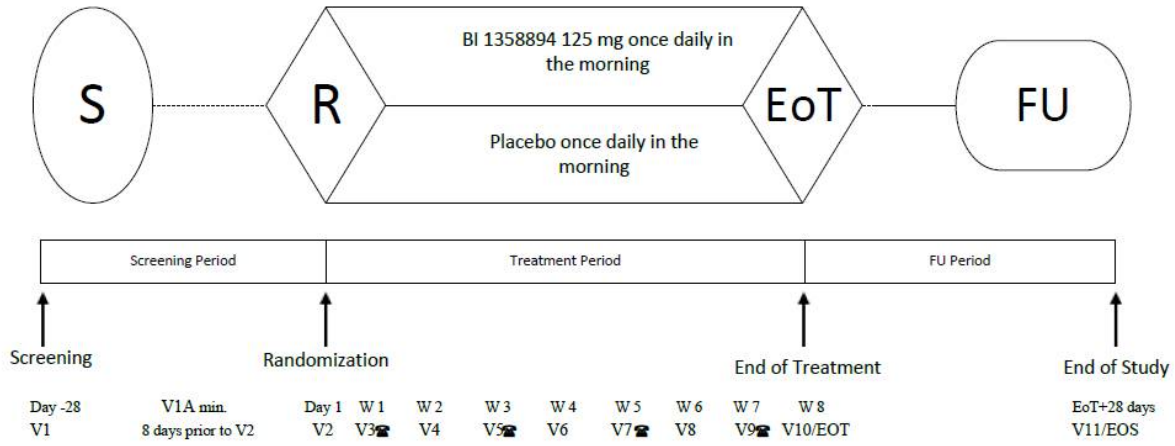
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a Phase II, 8-week-treatment, multicenter, randomized, double blind, placebo-controlled, parallel-group trial in patients with Post-Traumatic Stress Disorder (PTSD). In total, approximately 286 male and female patients with PTSD meeting the entry criteria are planned to be randomized into this trial.



V = Visit, W = Week, EOT = End of Treatment, EOS = End of study, ☎ = Telephonic Visit

Figure 3.1: 1 Trial design

Patients are enrolled into the trial after informed written consent has been obtained. Eligible patients will be randomized to double-blind treatment with either placebo (approx. n=143) or BI 1358894 at 125 mg QD (approx. n=143). Total treatment duration will be eight weeks, refer to Figure 3.1: 1.

After the completion of the 8-week double-blind treatment period or following early discontinuation of the trial at any timepoint, patients will complete the 4-week follow-up period with the end of study (EOS) visit. All (S)AEs, including those persisting after individual patient's end of study must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained. Individual patient participation is concluded when the patient has completed their last planned visit (end of study visit) (refer to sections 3.3.4.1 and 3.3.4.2).

An interim analysis is planned when the 120th evaluable patient completes the Week 8 visit. The purpose of this interim analysis is for internal planning of the PTSD indication with BI 1358894. Please refer to section 7.2.8

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

This is a randomized double-blind, placebo-controlled, parallel-design trial. This design is appropriate for providing proof-of-concept and assessing the safety and efficacy of BI 1358894 compared to placebo in patients with PTSD. It is important to have a placebo control to address potential confounding factors. This is acceptable as patients will remain on their stable background treatment and the duration of the placebo treatment will be limited to 8 weeks.

The design of the trial will provide efficacy and safety of BI 1358895 on PTSD patients to support proof of concept.

Data at Week 8 will provide evidence of efficacy and safety of BI 1358894 compared to placebo. In addition, safety data will also be obtained through the end of observation period (early drug discontinuation date / EOT+28+2 days). Exploratory outcomes from Ecological Momentary Assessments (EcMAs) are intended to assess the disease status in the patients' natural environments. Collectively, this information will help facilitate the design of the Phase III program.

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

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

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

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 286 patients is planned to be randomized into the trial. It is planned that about 70 trial centers in 10 countries will be participating in this trial to ensure a sufficient number of patients are randomized.

It is expected that approximately 4-10 patients will be randomized at each trial center. If enrolment is delayed, additional sites may be recruited. To avoid differential center influence on trial results, permission to randomize more than 15 patients per site must be obtained from the sponsor. This will only be allowed after a careful review of the enrolment status and the site.

Screening of 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

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notified when the appropriate number of patients has been screened and screening is complete, and will not be allowed to recruit additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomisation, if eligible.

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

Retesting
Retesting applies in situations when the issue can be resolved within the screening period of 28 days.For example patients that are testing positive on urine drug screen for cannabis or opioids at Visit 1 can be retested once (consider long half-life of cannabis) within the screening period of 28 days, if there is a reasonable explanation and expectation that the patient is not a regular user and will not test positive again on retest or has stable treatment with medically prescribed opioids, both at the discretion of the investigator.
In case of retesting, the patient will keep the same patient number. The results of all retests should be available within the 28 days of screening period. Once retests are available and negative for the retested parameter/eligibility confirmed, and in case all other eligibility criteria are met, the patient can be randomized on the planned Visit 2 date.

Rescreening of patients
Rescreening of a patient can be done once, if there is a reasonable explanation and expectation that the patient may have become eligible.
Potential reasons for rescreening could be:

- Active infection with SARS-CoV-2
- Suicidality once the required exclusion period is over
- Clinically significant findings per Investigators judgement
- Restricted medications like CYPs/ alternative or traditional medicine
- Positive urine drug test at screening visit, if longer wash-out period needed

Background therapy must be stable prior to re-screening.
For other potential reasons, please contact the clinical trial leader (CTL).
In case of re-screening, the patient will receive a new patient number. The patient must sign the current, approved version of the informed consent before any study specific procedures are performed.

- If rescreening is done within 12 weeks of screening, all procedures except CTQ, Life Events Checklist and extended Criterion A (as part of the Screening PCL-5) must be repeated. The exceptions above only apply if these assessments are not the reason for rescreening.
- If the rescreening is done more than 12 weeks after the screening, all procedures as shown in the Flow Chart 1 and Flow Chart 2 for Visit 1 must be repeated.

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For all re-screened patients, the screening period will be again 28 days as per protocol. In case all eligibility criteria are met during these repeated screening procedures, the patient can be randomized on the newly planned Visit 2 date.

3.3.1 Main diagnosis for trial entry

Patients with an established diagnosis of Post-Traumatic Stress Disorder confirmed at the time of screening by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) will be evaluated for eligibility for the study.

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

3.3.2 Inclusion criteria

1. Established diagnosis of Post-Traumatic Stress Disorder (PTSD) corresponding to DSM-5 criteria.
2. Time since index event according to Life Events Checklist / CAPS-5 Criterion A at least 3 months before screening visit.
3. PTSD must be the clinically pre-dominant disorder, as per investigator´s judgement. Other comorbid psychiatric disorders are allowed, unless specifically excluded in the exclusion criteria.
4. A total severity score of ≥ 33 on the PCL-5 at the screening visit.
5. Moderate to severe PTSD confirmed by CAPS-5 range ≥ 30 confirmed at screening visit.
6. Male or female patients, 18 to 65 years of age, both inclusively at the time of informed consent.
7. Women who are of child-bearing potential (WOCBP)[1] must be 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 result in a low failure rate of less than 1%, plus one additional barrier method.
   A list of contraception methods meeting these criteria and instructions on the duration of their use is provided in section 4.2.2.3.
8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

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

3.3.3 Exclusion criteria

1. Corresponding to DSM-5, had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder, brief psychotic disorder or any other psychotic disorder as well as MDD with psychotic features as assessed by the MINI at the time of screening.
2. Any psychiatric or non-psychiatric medical condition likely to negatively impact trial participation as per the judgement of the investigator.

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3. Acute stress disorder or significant traumatic event within 3 months prior to the screening visit.
4. Use of stimulant medications within 3 months prior to the screening visit (Attention Deficit Hyperactivity Disorder (ADHD) diagnosis alone is not exclusionary)
5. Severe traumatic brain injury (life-time) or moderate traumatic brain injury within the last 2 years prior to screening visit or 3 months for mild traumatic brain injury, based on the Ohio State University TBI Identification Method Short Form. Or history of traumatic brain injury that would impact ability to complete trial assessments or procedures according to investigator.
6. Current treatment with trauma focused therapy (i.e. CPT, PE, EMDR).
   A psychotherapy in type, intensity and/or frequency other than trauma focused therapy is allowed if stable within the last 8 weeks prior to screening and not anticipated to change during the entire course of the trial. Long-term psychotherapy is permitted as long as patients are not in an exposure phase during the trial.
7. Diagnosis of a current moderate or severe alcohol use disorder according to MINI within 3 months prior to screening visit (mild alcohol use disorder (AUD) and patients in early remission = criterion not met for between 3 & 12 months are allowed).
8. Diagnosis of a substance use disorder (non-alcohol) according to MINI within 12 months prior to screening visit. Caffeine and nicotine are allowed.
9. Positive urine drug screen at the screening visit. Exception: stable opioid-treatment with medically prescribed opioids. Please refer to section 3.3 Retesting for retesting options within the screening period.
10. Any suicidal behavior in the past 12 months prior to screening (per investigator judgement including an actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior) and during the screening period.
11. Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months prior to screening or at screening or baseline visit (i.e. active suicidal thought with method and intent but without specific plan, or active suicidal thought with method, intent and plan).
12. Treatment with benzodiazepines is allowed if stable in dose and frequency of use for at least 2 months prior to randomization visit (please refer to section 4.2.2). Note: PRN- use is not permitted.
13. Antipsychotics, antidepressants and other psychiatric medication are allowed if stable in dose and frequency of use for at least 2 months prior to randomization visit (please refer to section 4.2.2)
14. Any use of restricted medications within 7 days prior to randomization visit (refer to section 4.2.2).
15. Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial.
16. Use of alternative medicine (e.g. Chinese traditional medicine, herbal medication, St. John’s wort, etc.) during the entire course of the trial.
17. History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial.
18. 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.
19. Positive result for ongoing Hepatitis B or C infection.

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20. Known hypersensitivity to any of the excipients of BI 1358894 or the matching placebos.
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 5 half-lives of the investigational medicinal product).
22. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening.
23. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
24. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
25. Considered by the investigator, for any other reason, to be an unsuitable candidate for the trial.
26. Patients who are currently and during the course of the trial confined to an institution by court or administrative order.
27. Patients who are currently involved in any ongoing legal processes related to the index traumatic event (e.g. lawsuit or criminal prosecution).
28. Patients currently using Nightware™ Digital Therapeutic tool.
29. In-patients are generally excluded, however in-patients who are admittedon a voluntary basis in an open-ward (i.e. "residential ward") and are non-suicidal are allowed.
30. 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.
31. Symptomatic/unstable/uncontrolled or clinically relevant concomitant disease or condition (e.g. renal failure, hepatic dysfunction, cardiovascular disease, etc.) that would jeopardize the patient´s safety while participating in the trial or capability to participate in the trial, based on investigator´s discretion.

3.3.4 Discontinuation 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.

However, if the patient agrees, they should stay in the trial: even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.

After premature study drug discontinuation, patients will be asked to further attend scheduled trial visits unless they withdraw consent to participate in the study.

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 options for early discontinuation and explanation of the consequences in case of withdrawals.

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The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see section 5.4.6.2).

3.3.4.1 Discontinuation of trial treatment

Ideally, the patient should attend all remaining visits and perform all study related procedures according to Flow Chart 1, Flow Chart 2 and section 6.2.2 An early EoT (eEOT) Visit shall be conducted within 7 days of the last dose of trial medication for patients who agree to conduct regularly scheduled visits after premature drug discontinuation (if consistent with the planned visit schedule, the eEOT can replace the next regularly scheduled clinic visit). After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits including Visit 10 and should be encouraged to complete the EOS Visit 28+2 days after the drug discontinuation date. All procedures should be completed, with the exception of trial drug procedures and PK collections. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days), no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and EOS. If EOS visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

Should the patient not agree to any further clinic visits, at least phone contacts should occur at the scheduled visit time points, should that not be acceptable, a phone contact at the end of the planned observation period (i.e. 12 weeks after start of treatment or 4 weeks after last dose) should occur to collect the most relevant information: vital status (please see section 5.4.6.2.1) adverse events, or last contact date in case of lost to follow-up.

Patients who refuse all of the above are considered to have fully withdrawn consent to participate in the trial. In this case, the patient does not need to justify the decision and should be withdrawn from the trial and all follow-up assessments (please refer to section 3.3.4.2).

Withdrawal from the trial of an individual patient may be considered also in case of administrative reasons, such as but not limited to multiple important protocol violations and persistent non-compliance. No patient should be withdrawn from the trial before discussion with the sponsor.
An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the

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patient cannot be guaranteed as he/she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment; refer to the ISF.
- The patient undergoes an ECT.
- Patient receives Ketamine /S-Ketamine treatment during the course of the trial.
- The patient can no longer receive trial treatment for serious medical reasons (such as surgery, adverse events, other diseases, or pregnancy), per investigator's clinical judgement. In case of a temporary reason, trial treatment should be restarted if medically justified.
- Pregnancy occurs during the trial. (Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy which occurred in a female trial patient to the Sponsor immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point).
- The patient must discontinue treatment with trial medication if the patient develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e., active suicidal thought with intent but without specific plan, active suicidal thought with plan and intent) or suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt or preparatory acts or behavior).

In addition to these criteria, the physician may discontinue treatment at any time based on his or her clinical judgment. For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported.

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

Even if the trial treatment is discontinued, the patients 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 1, Flow Chart 2 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:

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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.

Further treatment and follow up of patients affected will occur as described in section 3.3.4.1. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 1358894 film-coated tablets are manufactured by BI Pharma GmbH & Co. KG, Germany. Placebos, matching BI 1358894 film-coated tablets, are manufactured by BI Pharma GmbH & Co. KG, Germany and [redacted]

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 BI 1358894

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

Table 4.1.1:2 Placebo matching BI 1358894

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

4.1.2 Selection of doses in the trial and dose modifications

The dose of 125 mg BI 1358894, once daily, is selected for this trial based on the results of the PK and safety data obtained in the trials 1402-0001 (Single Rising Dose (SRD) and Food Effect), 1402-0002 (Multiple Rising Dose (MRD)), and 1402-0010 (rel Bioavailability (BA); formulation selection) combined with the preclinical efficacy data.

In the SRD trial, single dose levels up to 100 mg were well tolerated. In the MRD trial, multiple dose levels up to 200 mg were well tolerated. The 125 mg was selected to account for potential larger variability in PK in Phase II due to a more heterogeneous population that is expected compared to Phase I. This dose is expected to deliver a 5-fold concentration of the target $C_{16,ss}$ in 49.8 % to 96.6 % of patients depending on the food condition. Therefore it is concluded that the dose of 125 mg once daily has an acceptable safety margin

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and potential efficacious dose for BI 1358894.

BI 1358894 was tested in several Phase I studies:

- evaluation of safety, tolerability and PK after single and multiple dose
- evaluation of relative bioavailability under fasted and fed conditions of different solid oral formulations
- evaluation of drug-drug interaction with strong index CYP3A4 inhibitor
- evaluation of physiological response and circuit engagement in a Cholecystokinin Tetrapeptide (CCK-4) challenge in healthy volunteers
- evaluation of physiological response and circuit engagement in a functional MRI study in depressed patients after single dose

BI 1358894 was safe and well tolerated up to the highest dose tested (200 mg under fed conditions) after a single dose (after a high calorie/high fat breakfast) as well as after 14 day qd dosing (after continental breakfast). BI 1358894 (single dose of 100 mg administered under fed conditions) also demonstrated physiological response by attenuation of CCK-4 induced panic symptoms, attenuation of CCK-4 induced stress hormone elevation (Adrenocorticotropic hormone (ACTH) and Cortisol) and reduction in the score of the emotional Visual Analogue Scale (VAS).

Within preclinical research, the forced swim test in mice was evaluated to test potentially efficacious concentrations. This test resulted in an EC50 of 77 nM (and a corresponding EC90 of 165 nM). This target concentration of 77 nM BI 1358894 total plasma concentration was set as the minimal concentration to be reached at 16 h after dosing under steady state conditions for prediction of an estimated therapeutic dose in humans.

Pharmacokinetic data of BI 1358894 from the SRD, MRD and relative BA study for formulation finding and food effect assessment were integrated into a Population PK model in order to predict steady state exposure of the solid oral formulation selected for Phase II under fasted and high calorie high fat conditions. The predictions under different food conditions should indicate the range of exposures to be expected under different food conditions, with fasted and high calorie high fat conditions representing the extremes of potential exposures. It is expected that a standard breakfast would lead to exposures that lie somewhere in-between those predicted. Of note, exposure of BI 1358894 increases less than dose-proportionally. The current Pop PK model over predicts C_{max}, hence, predicted exposure may be higher than exposures to be observed in Phase II.

Repeat-dose toxicity testing with daily administration for 13 weeks revealed a NOAEL of 1000 mg/kg/day in rats. This NOAEL is considered to represent the most relevant NOAEL for repeat-dose toxicity testing in rats, as detailed in the IB [c10354149]. This dose resulted in maximum plasma levels and exposures that represented sufficient multiples of the same parameters as predicted for a 125 mg dose in humans and fed conditions. C_{max} and AUC_{0-24h} at the NOAEL in rats are also higher than the 95th percentile of the respective parameter at the maximum dose of BI 1358894 in Phase II under fed conditions (for details see IB).

Repeat dose toxicity testing for up to 13 weeks in dogs revealed an overall NOAEL of 30 mg/kg/day, as described in detail in the IB [c10354149]. This dose resulted in maximum

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plasma levels and exposures (AUC_{0-24h}) representing sufficient multiples of the same parameter at a 125 mg dose in humans and fed conditions. C_{max} and AUC_{0-24h} at the NOAEL in dogs were also higher than the 95^{th} percentile of the prediction of the respective parameter at the maximum dose of BI 1358894 in Phase II under fed conditions (for details see IB [c10354149].

In conclusion, results of repeat-dose toxicity testing support the conduct of Phase II clinical trials at the 125 mg dose once daily at fasted or fed conditions and for a maximum duration of treatment of 13 weeks.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomized to treatment groups according to a randomisation plan at Visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

Patients will be randomly assigned with an allocation ratio of 1:1 to the following treatment groups:
- 125 mg BI 1358894
- Placebo matching BI 1358894

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

Randomization into each treatment group will be stratified by:
- presence of significant childhood trauma (YES/NO, according to investigator´s judgement, assessed by CTQ at screening visit)

The kit(s) corresponding to the assigned medication number(s) should be given to the patient and entered in the eCRF. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.4 Drug assignment and administration of doses for each patient

The medication assignment will be provided through IRT. The assigned medication number(s) must be entered in the eCRF, and the corresponding medication kit(s) must be given to the patient. The duration of treatment is 8 weeks. The last dose of trial medication should be taken on the day before the EOT Visit. Dosing per treatment assignment is noted in Table 4.1.4:1.

At Visit 2, after randomization, patients will receive medication kits for the double-blind treatment period. The morning dose of trial medication will be taken at the trial site under supervision of the investigator or site staff. Patients will bring trial medication (used/unused blister and covering packages) to site visits for compliance check (V4/V6/V8/V10). At visits V4, V6 and V8, patients will return used/unused medication kits and receive new supplies.

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Each trial medication kit contains supplies for 14 days of treatment. For the first trial medication kit supplies, participants will receive two kits (one kit for the 14 treatment days plus a reserve kit), and all following re-supplies will be one kit of BI 1358894 or matching placebo.

Patients should be instructed not to take their trial medication in the morning of Visits 2, 4, 6, 8, as patients will be dosed at the site after pre-dose PK sampling. For patients who complete the treatment period, the last dose of trial medication should be taken on the day before the EOT Visit (V10). Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day.

Patients should be instructed to take the BI 1358894 tablets or matching placebos orally with water and in a consistent way, i.e., either with or without food every morning at approximately the same time. If a morning dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days prior to a visit, the morning dose should be taken approximately 24 hours before the planned morning dose at the clinic visit. A dose reduction of BI 1358894 is not possible.

Table 4.1.4:1 Dosage and treatment schedule

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

During the COVID-19 pandemic, there might be situations that would not allow a patient to come to the site for the study visit. If the investigator judges it as acceptable and safe to continue trial medication, trial medication might be shipped from the site to the patient (for more details see section 6.1 and 10.3).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regards to the randomized treatment assignments until the time specified in the database lock process, with the exceptions described in this section below and in section 7.2.8.

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

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

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Dedicated database snapshots (no partial DBL) will be generated prior to DBL to allow for development and refinement of population PK and exposure-response models ("Fast-track" PK and PK/PD analysis). 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 the first database snapshot for 'fast-track' PK/PD analyses.

No formal interim report will be generated. Final PK and PK/PD analyses will be reported once after availability of data from DBL.
The access to the randomisation code will be kept restricted until its release for analysis. The randomisation codes will be provided to bioanalytics before the last patient completed the trial to exclude placebo or comparator samples from the PK analysis. Bioanalytics will not disclose the randomisation code or the results of their measurements until the database lock.

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 patients. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

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

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate (as provided in the list of contacts) must be contacted immediately.

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4.1.8 Drug accountability

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

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

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Please refer to section 5.4.5.1 for handling patients with positive report of suicidal ideation and/or behavior.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following restrictions for comedications are defined for this trial:

- Strong inhibitors of CYP3A4
- Strong inducers of CYP3A4 (please refer to the ISF)

A list of restricted concomitant medications and drugs with potential pharmacokinetic interactions with the trial compound BI 1358894 can be found in the ISF. The list is not

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comprehensive. For example, drugs that are solely indicated for diseases that are excluded in this trial - like cancer drugs - may not be listed.

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

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 a patient in this trial is on the highest recommended statin dose, investigator should consider changing the statin dose to the next lower dose recommended for the respective statin if appropriate.

Please note:

- Investigators may use their clinical discretion to wash out (at least 3 half-lives of referenced medication) the restricted medications during the screening period. The patient must adhere to the screening visit dose of the allowed background medication for the entire duration of the trial.
- Patients who are on stable treatment with low-dose antipsychotics for treatment of insomnia or similar for at least 2 months prior to randomization should continue without change for the entire trial duration. Antipsychotic treatment for psychiatric symptoms is disallowed.
- Patients who are on stable treatment with ongoing antidepressants for at least 2 months prior to randomization should continue without change for the entire trial duration.
- Patients who are on stable treatment with ongoing benzodiazepine (including Z- drugs) or non-benzodiazepine hypnotics for at least 2 months prior to randomization should continue without change for the entire trial duration.

  For patients who are not on current treatment with benzodiazepine (including Z-drugs) or non-benzodiazepine hypnotics at the time of screening, the protocol will allow concomitant use of non-benzodiazepine-, non-Z-drug hypnotics at lowest dose of the compound as noted in the Summary of Product Characteristic (or SmPC) during the trial.

- Patients who are on stable treatment with medically prescribed opioids (except fentanyl) for at least 2 months prior to randomization should continue without change for the entire trial duration. Short-term opioid therapy up to 4 weeks per time, for example with cough syrup or pain killer, is allowed (except fentanyl).

- 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 are referred to the actual Investigator´s Brochure or may contact the sponsor.

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4.2.2.2 Restrictions on diet and life style

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

Note the following restrictions:

- Use of traditional medicine (e.g. Chinese traditional medicine, herbal medication, St. John's wort, etc.) during treatment period.
- Patients should not abuse alcohol or drugs during the trial. A urine drug screen will be performed at selected trial visits (see Flow Chart 1). For a list of drugs assessed by the urine drug screen please refer to table 5.4.3: 1.
- Patients should not enter or modify a smoking-cessation program during the conduct of the trial.
- It is recommended that patients should exercise caution when driving or operating machinery until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.

Patients do not have to come fasted to any trial visit.

4.2.2.3 Contraception requirements

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

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

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 1 (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.

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

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

- Placement of intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
- Bilateral tubal occlusion or ligation
- Vasectomy (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that male partner is the sole sexual partner of the WOCBP trial patient)
- Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the study patient. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception) - (in this specific case the barrier methods as mentioned below, are not applicable). Sexual abstinence as a contraceptive method will not be allowed for WOCBP who are heterosexually active.

plus one of the barrier methods:

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

4.3 TREATMENT COMPLIANCE

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

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

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

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The potential for trial drug abuse will be closely monitored. Events including overdose, misuse, lost and unaccounted for medication must be thoroughly documented in the patient's source and on the appropriate eCRFs. Furthermore, if the treatment compliance is less than 80% or greater than 100%, site staff should discuss and document the reasons on the eCRFs. Site staff will explain to the patient the importance of treatment compliance.

Additionally, as an exploratory approach, the intake of the trial drug at clinic visits and at home will be monitored by the patient with a smartphone app (see section 5.8.3). The identification of the tablet shapes and sizes, time and day, the patient face-ID, and the drug intake process will be captured in selfie mode of the smartphone camera, by the patient. The face of the patient will be anonymized by the managing software of the vendor before the data are submitted to the vendor for potential further analysis.

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5. ASSESSMENTS

5.1 CONFIRMATION OF DIAGNOSIS

Eligibility of patients for the trial will be evaluated using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) during screening for confirmation of the diagnosis of Post-Traumatic Stress Disorder (PTSD). To exclude patients with other psychiatric disorders as described in the exclusion criteria, the Mini International Neuropsychiatric Interview will be performed.

The CAPS-5 and MINI will be audio recorded at the screening visit 1 and the recordings will be reviewed by an independent external clinical reviewer from [redacted].

MINI - Mini International Neuropsychiatric Interview

The MINI is a structured diagnostic interview designed to provide a brief standardised evaluation of mental health disorders in line with DSM-5 criteria [R07-1303, R07-1261, R07-1263, R07-1262]. Each of the independent 17 diagnostic modules consists of screening and a series of secondary questions to be answered with "yes" or "no" responses. If the patient answers "no" to a screening question, the clinician starts asking questions from the next module. A clinician can use the MINI after a short training session. It takes approximately 20 minutes to administer the MINI.

In this study, the MINI for psychotic disorders studies (English verison 7.0.2 for DSM-5) customized for Boehringer Ingelheim International will be used. The customization comprises the following two modifications:

- Module Y "Borderline Personality Disorder" will be added to the MINI to assess comorbid BoPD.
- Module B "suicidality" will not be administered, all evaluations in relation to suicidality will be performed with the C-SSRS (please refer to section 5.4.5.1).

The Ohio State University TBI Identification Method Short Form will be used to assess any history of traumatic brain injury for patients.

OSU TBI-ID-SF – Ohio State University TBI Identification Method Short Form

The Ohio State University TBI Identification Method Short Form (OSU-TBI-ID-SF) is a structured clinical interview designed to detect lifetime history of exposure to TBI [R21-2334, R21-2333]. Multiple dimensions of history are available, including number of injuries without or with loss of consciousness; duration of loss of consciousness from none, < 30 minutes, 30 minutes to 24 hours to > 24 hours; age at (first) TBI, worst injury and repeated injuries.

A scoring system is used to quantify these dimensions and to categorize the likelihood of TBI exposure as: improbable - possible - mild - moderate - severe TBI.

It takes approximately 5 minutes to complete and score the OSU TBI-ID-SF.

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5.2 ASSESSMENT OF EFFICACY

5.2.1 Clinician administered assessments

In addition to confirmation of PTSD diagnosis, using the CAPS-5 past month version, the CAPS-5 past week version will be used to assess PTSD total symptom severity as well as cluster symptom severity at Baseline and during the course of the trial.

CAPS-5 - Clinician-Administered PTSD Scale for DSM-5

The Clinician-Administered PTSD Scale for DSM-5 **(**CAPS-5) is a 30-item structured interview designed to make a current and lifetime diagnosis of PTSD evaluating the past month period as well as to assess PTSD symptoms over the past month or past week, depending on the version used. [R21-2327, R21-0830, R21-2548].

In addition to assessing the 20 DSM-5 PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). Administration requires identification of an index traumatic event to serve as the basis for symptom inquiry.

Each of the 20 symptom items is rated on a 5-point severity rating scale ranging from 0 (absent) to 4 (extreme/incapacitating) with a single severity score combining information about frequency/amount and intensity according to detailed scoring rules. A CAPS-5 total symptom severity score is yield by summing individual item scores. The total severity score ranges from 0 to 80 with higher scores indicating higher symptom severity.

CAPS-5 symptom cluster severity scores are yield by summing individual item scores pertaining to the following clusters (sometimes also referred to as domain): Criterion B (re-experiencing), Criterion C (avoidance), Criterion D (negative alterations in cognitions and mood) and Criterion E (hyperarousal). A symptom cluster can also be calculated for dissociation by summing scores for items 29 and 30.

Two formats of the CAPS-5 measure will be used in this trial:

- CAPS-5 past month version for confirmation of PTSD diagnosis and evaluation of eligibility (for screening visit only) [R21-2327].
- CAPS-5 past week version for efficacy measurement (all subsequent trial visits) [R21-2548].

The CAPS was designed to be administered by trained clinicians. The full interview takes 45-60 minutes to administer.

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Categorization of index traumatic event

Investigators will be asked to categorize the index traumatic event as determined in CAPS-5 Criterion A at screeening visit according to the following categories:

Table 5.2.1:1 Index traumatic event categorization criteria

Category	Response options
Type of trauma	**Interpersonal** e.g. abuse, rape, hostage situation, assault, physical dispute, domestic violence
	General e.g. natural catastrophe, accident, (terrorist) attack, war
	Combat trauma (only for veterans/military-associated personnel) e.g. hand-to-hand combat
Frequency	**Isolated**
	Multiple (≥2) **unrelated**
	Recurrent/chronic (same or similar trauma experienced repeatedly) e.g. sexual abuse in the same context, domestic violence
Exposure level	**In-person "First-hand" including witnessed**
	Learned about it

A separate assessment with the patient is not requested. Investigators will review CAPS-5 Criterion A, Life Event Checklist and Extended Criterion A, as well as medical reocrds to decide on the categorization of the index traumatic event per their clinical judgement according to the criteria outlined above in Table 5.2.1: 1.
The index traumatic event, determined during the screening visit is to be referred to for all CAPS-5 and PCL-5 (incl. EcMA) assessments during the patient's treatment period.

The categorization will be documented in the patient records and the eCRF.

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CGI-S/C - Clinical Global Impression Severity/Change Scale

The Clinical Global Impression Severity Scale (CGI-S) is a single item rating scale designed to measure the clinician's impression of the severity of illness exhibited by a patient that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI-S evaluates the severity of psychopathology on a seven-point scale [R03-0520, R19-1932].

The CGI-S question states “Considering your total clinical experience with this particular population, how ill is the patient at this time (at the visit and over the course of the past 7 days) (Note that the subject’s illness is the disease under study; in this case, Post-Traumatic Stress Disorder – NOT other conditions/co-morbidities.)”, 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.
In the Flow Chart 2 this is referred to as CGI-S (total).

In addition, domain level CGI-S versions covering DSM-5/CAPS-5 domains (intrusion symptoms, persistent avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity) assessing clinicians’ impression on domain level severity at this time (at the visit and over the course of the past 7 days) will be performed.The domain level CGI-S are rated on the following five-point scale: 1=none; 2=mild; 3=moderate; 4=severe and 5=very severe.
In the Flow Chart 2 this is referred to as CGI-S (domain).

The Clinical Global Impression Change Scale (CGI-C) is a single item rating scale designed to measure the clinician's impression of change of the patient’s condition since start of medication intake [R03-0520].

The CGI-C question states “Please choose the response that best describes the overall change in the patient’s condition since he/she started taking the study medication. (Note that the subject’s illness is the disease under study; in this case, Post-Traumatic Stress Disorder – NOT other conditions/co-morbidities.)” and is rated on the balanced five-point scale: much better, a little better, no change, a little worse, much worse.

The CGI-S/C is to be completed by a trained clinician and takes 5-10 minutes each to complete.

5.2.2 Patient Reported Outcomes

All Patient Reported Outcomes will be completed by the patient using the rater station/tablet provided by the vendor.

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PCL-5 - PTSD Checklist for DSM-5

The PTSD Checklist for DSM-5 (PCL-5) is a 20-item patient-reported assessment designed to measure the presence and severity of PTSD symptoms. Items on the PCL-5 correspond with DSM-5 criteria for PTSD. The PCL-5 is intended to assess patient symptoms in the past month [R21-1742, R21-1740, R21-2336, R21-2341, R21-2340]. Each item is rated on a five-point Likert scale, from 0 (not at all) to 4 (extremely). A total severity score can be yield by summing up individual item scores, and ranges from 0 to 80 with higher scores indicating higher severity.

In addition, cluster severity scores can be calculated for Criterion B (re-experiencing, Criterion C (avoidance), Criterion D (negative alterations in cognitions and mood), Criterion E (hyperarousal).

Two formats of the PCL-5 measure will be used in this trial:

- PCL-5 with Life Event Checklist (LEC-5) and extended Criterion A assessment (for screening visit only; as separate assessments) [R21-2326]
- PCL-5 without Criterion A component (for all subsequent trial visits)

It takes approximately 5-10 minutes to complete the PCL-5.

CTQ - Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ)[1] is a 28-item patient-reported assessment designed to measure five types of maltreatment: 1) emotional abuse, 2) physical abuse, 3) sexual abuse, 4) emotional neglect, and 5) physical neglect, and includes three items to screen for false-negative trauma reports [R21-2335, R21-2324, R21-2323].

Each item is rated on a five-point scale, from: never true to very often true. Scoring results in a classification of the level of maltreatment (None, Low, Moderate and Severe) for each of the five domains.

It takes approximately 10 minutes to complete the CTQ.

PGI-S/C - Patient Global Impression Severity/Change Scale

The Patient Global Impression Severity Scale **(**PGI-S) is a single item patient-reported assessment designed to measure the patient's impression of the severity of their illness on a five-point scale. The Patient Global Impression Change Scale (PGI-C) is a single item patient-reported assessment designed to measure the patient's impression of change of their illness since start of medication intake [R03-0520].

[1]Bernstein, D., & Fink, L. (1998). Childhood Trauma Questionnaire: A retrospective self-report. San Antonio, TX: The Psychological Corporation

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The PGI-S question states "Please choose the response below that best describes the overall severity of your Post-Traumatic Stress Disorder over the past week (Select one response)" 1=None, 2=Mild, 3=Moderate, 4=Severe, 5=Very severe.

The PGI-C states "Please choose the response below that best describes the overall change in your Post-Traumatic Stress Disorder (PTSD) since you started taking the study medication" and is rated on the balanced five-point scale: much better, a little better, no change, a little worse, much worse.

It takes approximately 5 minutes each to complete the PGI-S and PGI-C.

STAI - The State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) for adults has been used extensively in research and clinical practice. It comprises separate self-report scales for measuring state and trait anxiety. The S-Anxiety scale (STAI Form Y-1) consists of twenty statements that evaluate how respondents feel "right now, at this moment." The T-Anxiety scale (STAI Form Y-2) consists of twenty statements that assess how people generally feel [R98-0762].

Each STAI item is rated on a four-point scale, from 1 (not at all) to 4 (very much so). A rating of 4 indicates the presence of a high level of anxiety for ten S-Anxiety items and eleven T-Anxiety items (e.g., "I feel frightened," "I feel upset"). A high rating indicates the absence of anxiety for the remaining ten S-Anxiety items and nine T-Anxiety items (e.g., "I feel calm," "I feel relaxed").

A total score for the S-Anxiety and T-Anxiety scales is yield by summing the weighted 20 item scores per scale. Scores for the S-Anxiety and the T-Anxiety scale range each from 20 to 80 with higher scores indicating greater anxiety.

It takes approximately 10 minutes to complete the STAI-S and STAI-T.

PHQ-9 - Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item patient-reported assessment designed to be used for screening, diagnosing, monitoring and measuring the severity of depression [R12-3115].

Each of the nine items is rated on a four-point scale (0, 1, 2, 3) for the period of the last two weeks. A total score is yield by summing up individual item scores, and ranges from 0-27 with higher scores indicting higher symptom severity. Depression Severity is assessed as: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), or severe (20-27).

It takes approximately 5 minutes to complete the PHQ-9.

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DERS-16 - Difficulties in Emotion Regulation Scale – 16 item

The Difficulties in Emotion Regulation Scale (DERS) is a 16-item patient-reported assessment designed to measure emotion regulation difficulties [R19-1172, R19-1186, R19-1171] in the following five dimensions: 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).

Each of the 16 items is rated on a five-point Likert scale, from 1=almost never (0-10%); 2=sometimes (11-35%); 3=about half the time (36-65%); 4=most of the time (66-90%), to 5=almost always (91-100%).

A total score is yield by summing up individual item scores, and ranges from 16-80 with higher scores reflecting greater levels of emotion dysregulation.

It takes approximately 5-8 minutes to complete the DERS-16.

PSQI - Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)[2] is a 19-item patient-reported assessment designed to measure sleep quality over the past month grouped into seven components of sleep quality. The seven components comprise subjective sleep quality; sleep latency; sleep duration, habitual sleep efficiency; sleep disturbances; use of sleeping medication; daytime dysfunction [R00-0292].

Each of the seven components is rated on a four-point scale (0, 1, 2, 3) transforming patient responses to the 19 individual items into ratings based on a specific scoring algorithm.
In addition to the seven component scores, a global PSQI score is yield by summing up individual component scores, and ranges from 0-21 with higher scores indicting worse sleep quality

It takes approximately 5-10 minutes to complete and 5 min to score the PSQI.

SDS - The Sheehan Disability Scale

The Sheehan Disability Scale (SDS) is a patient-reported assessment of disability and functional impairment. The SDS is a composite of three self-rated items and two items on the days (lost and unproductive) due to the impairment. It is designed to assess functional impairment in three major life domains: work, social life/leisure activities, and family life/home responsibilities [P08-11546, R20-1844].

[2] The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research (Authors Daniel J. Buysse, Charles F. Reynolds III, Timothy H. Monk, Susan R. Berman, and David J Kupfer, © 1989 and 2010, University of Pittsburgh. All rights reserved.)

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Each item is rated on a 10-point visual analogue scale using spatiovisual, numeric and verbal descriptive anchors simultaneously to assess disability. A total score is yield by summing up individual item scores, and ranges from 0 (unimpaired) to 30 (highly impaired).

It takes approximately 3-5 minutes to complete the SDS.

EQ-5D-5L - The Euro Qol -5 Dimensions -5 Levels

The **E**uro **Q**uality **o**f **L**ife -**5 D**imensions -**5 L**evels is a standardized patient-reported instrument for use as a measure of health outcome. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS).

The EQ-5D-5L descriptive system comprises 5 dimensions of health (mobility, self care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health status on a vertical visual analogue scale graduated from 0 (worst) to 100 (best health the patient can imagine)[R12-1920].

It is a generic measure, rather than disease-specific, and is therefore applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status.

It takes approximately 5 minutes to complete the EQ-5D-5L.

5.3 RATER QUALIFICATION

Rater training and qualification on clinical outcome assessments for the purpose of this trial will be managed by the vendor as per vendor qualification methodology that has been agreed with the sponsor.

The vendor will manage rater training and qualification via evaluating the rater's experience and scoring performance, tracking required training, and collecting documentation of training and qualification. New raters joining the trial will be trained and qualified with the same defined Rater Training and Qualification Program using the vendor Learning Platform

The MINI, CAPS-5, CGI-S and CGI-C must be administered by a psychiatrist, psychologist or other clinician demonstrating adequate experience in patients with Post-Traumatic Stress Disorder and relevant Comorbidities. Exceptional situations will be reviewed on a case by case basis.
The C-SSRS must be administered by a trained staff member with a valid C-SSRS Training Certificate.

All raters for the trial will be trained on the handling of all Clinician administered assessments that they will be administering and Placebo Response Mitigation (except the C-SSRS). In addition, each rater will complete a scale specific training before considered qualified for rating a patient on the respective scale in the context of the trial.

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For raters, handling Patient Reported Outcomes throughout the trial (i.e. PCL-5 including Criterion A and Life Events Checklist, CTQ, PGI-S, PGI-C, STAI, PHQ-9, DERS-16, PSQI, SDS and EQ-5D-5L), the completion of a PRO scales training is obligatory.

The vendor will provide a Site Status Memo indicating the status for all raters who have completed the Rater Training and Qualification Program as well are Follow-up requirements (C-SSRS Certificate will be filed separately).

No patient is allowed to be rated before the Site Status Memo confirming the Qualified status for the rater is filed in the ISF.

For each individual patient, the same qualified rater should rate the patient throughout the trial, if at all possible. In case of unforeseen circumstances, a qualified back-up rater must be available throughout the trial.

5.4 ASSESSMENT OF SAFETY

5.4.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart 1. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart 1.
The results must be included in the source documents available at the site.

5.4.2 Vital signs

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

5.4.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.4.3:1. For the sampling time points please see Flow Chart 1. The total volume of blood withdrawal per patient during the trial will be approximately up to 200 mL over 16 weeks. This amount may be exceeded if additional unscheduled (in case of necessary safety follow-up) monitoring of laboratory results is needed.

Analyses will be performed by a central laboratory, the respective reference ranges will be provided in the lab manual, except in cases where the ESR will be done locally in which case the ESR results will be recorded in the CRF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

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Instructions regarding sample collection, sample handling / processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.4.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.4.6.1 and the DILI Checklist provided in the ISF and electronic data capturing (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.4.3:1 Safety laboratory tests

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

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Table 5.4.3:1 Safety laboratory tests (cont.)

Chemistry	Albumin AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Chemistry Amylase Calcium Sodium Urea (Blood Urea Nitrogen (BUN)) Potassium Glucose Creatinine Bilirubin Total, fractionated if increased Protein, Total C-Reactive Protein Cholesterol, total Triglycerides TSH (Reflex testing for fT3 and fT4 if TSH is > ULN) Testosteron[1] LH[1] FSH[1] Folate Estimated Glomerular Filtration Rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

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Table 5.4.3:1 Safety laboratory tests (cont.)

Urine (dipstick) Pregnancy test (only for female patients of childbearing potential - test done at all clinic visits beginning with Visit 1A)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential) at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick), with microscopic examination if urine analysis is abnormal	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Blood Leukocyte Esterase Urine pH
Urinalysis	Albumin (quantitative) Creatinine
Drug screening (urine)	Cannabis Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Methadone PCP
Infections screening[2]	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibody (qualitative) Hepatitis C Virus (HCV) RNA – only if Hepatitis C antibodies (qualitative) are positive

[1] Males only

[2] At screening only

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

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

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents a clinically relevant safety issue as an adverse event (please refer to section 10.3).

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Minimum required safety lab parameters include liver enzymes and Bilirubin, haematology including differential test, blood glucose, sodium, potassium, creatinine, urea (BUN) and eGFR. It is important that always the reference values of the local lab are also provided.

5.4.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart 1. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for at least 10-second duration after the patients have rested for at least 5 minutes in a supine position and prior to lab sampling. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all-time points indicated in the Flow Chart 1, 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 (in accordance with the central ECG report) noticed at screening (Visit 1) should be reported as baseline condition. Clinically relevant abnormal findings noticed at subsequent assessments will be reported as AEs and followed up and/or treated as medically appropriate until normal or stable condition.

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

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

5.4.5 Other safety parameters

5.4.5.1 Assessment of Suicidality

C-SSRS - Columbia-Suicide Severity Rating Scale

Suicidal risk 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.

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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 multinational clinical trials. The C-SSRS will be administered first at screening (Visit 1) (using the 'Baseline / Screening' version) with the aim to exclude patients with active moderate or severe symptomatology within a specified time prior to screening (i.e. 3 months for suicidal ideation and 1 year for suicidal behavior). The lifetime history of suicidal ideation and behavior will also be recorded.

After screening (Visit 1) the assessment 'since last visit' will be performed at each trial visit i.e. clinic and phone visits as per Flow Chart 2 ('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 patient's safety have to be initiated.

An experienced clinician can use the C-SSRS after a short training session. It takes approximately 5 minutes to administer and rate the C-SSRS. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Freetext entries are allowed; the investigator has to directly evaluate the scale and write a report.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior during the course of trial participation 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 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 5.4.6.1.3).

Any lifetime history of suicidal ideation, self-injurious behavior, no suicidal intent' or suicidal behavior at the screening visit that is not an exclusion criterion, should be considered as baseline condition/medical history.

5.4.6 Assessment of adverse events

5.4.6.1 Definitions of AEs

5.4.6.1.1 Adverse event

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

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

The following should also be recorded 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.

5.4.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.4.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency (EMA) 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 5.4.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.4.6.2, subsections “AE Collection” and “AE reporting to sponsor and timelines”.

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5.4.6.1.4 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 5.4.6.2.2.
The following are considered as AESIs:

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

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.
- These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

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

No other AESIs have been defined for this trial.

5.4.6.1.5 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.

5.4.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, 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 trial drug.
- The event is known to be caused by or attributed to the drug class.

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- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size (ES) 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 trial 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.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.4.6.2 Adverse event collection and reporting

5.4.6.2.1 AE Collection

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

- From signing the informed consent onwards until the individual patient's end of trial (= the End of Study (EoS) 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 drug related SAEs and trial drug 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 5.4.6.2.2), but not on the CRF.

Vital Status Data Collection
Patients who discontinue trial treatment 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 any occurrence of cancer, report all deaths / fatal AEs regardless of

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relationship, and trial drug related SAEs and trial drug related AESIs the investigator becomes aware of.

5.4.6.2.2 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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 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.

5.4.6.2.3 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 patient 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 patient 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.

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[redacted]

[redacted]

5.6 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.2 and 5.4.

5.7 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.

5.7.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart 1.
Approximately 45.5 mL blood will be drawn for DNA, Plasma and Serum banking purposes.

5.8 OTHER ASSESSMENTS

[redacted]

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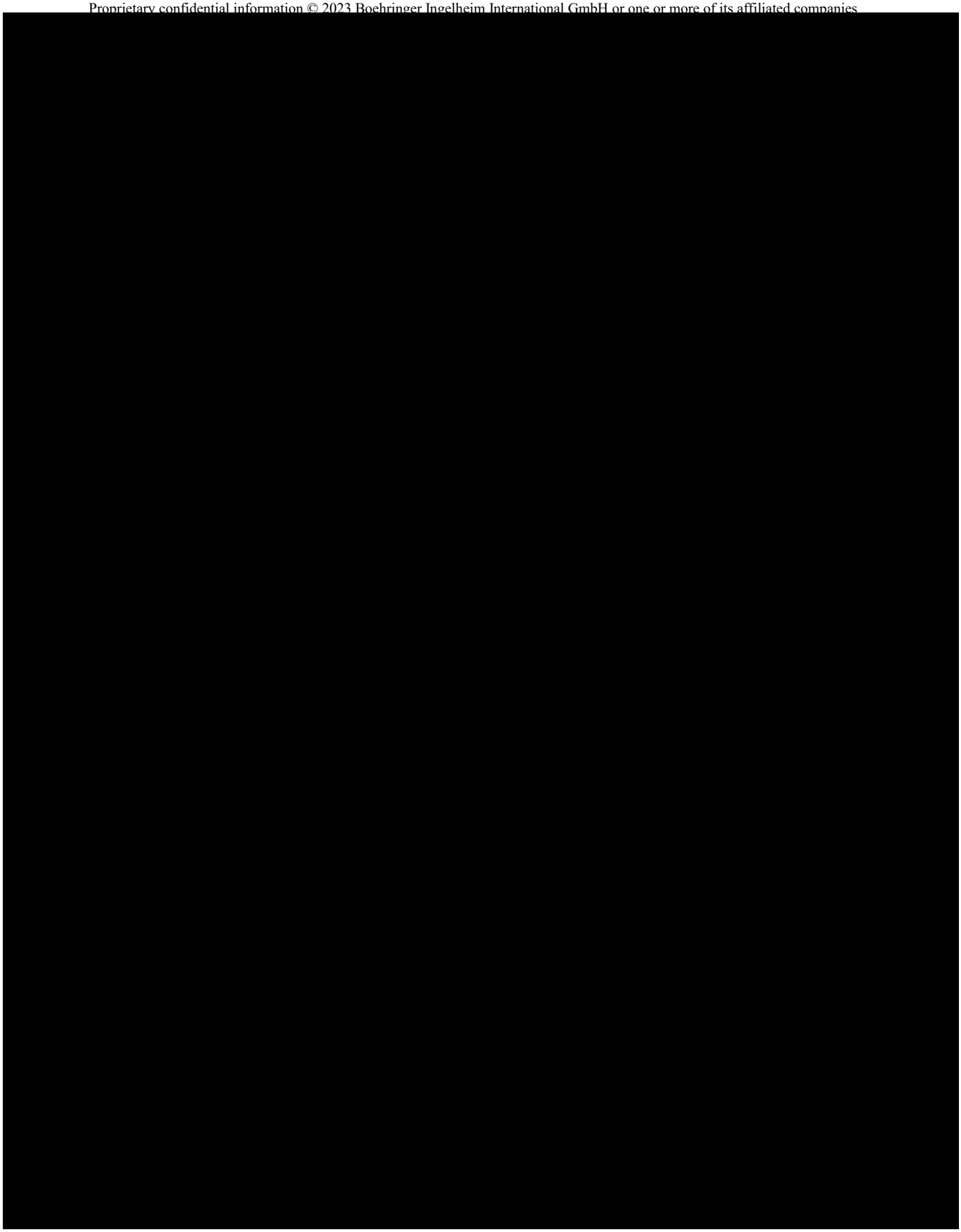

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[redacted]

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5.8.2 Speech recording

For use in future exploratory investigations, voluntary speech record samples will be collected after separate speech recording informed consent has been given in accordance with local ethical and regulatory requirements. Participation in the speech sampling is not a prerequisite for participation in the trial.

Speech records, along with related information on communication and mental state, will be collected with a tool on the tablet/rater station. The tablet/rater station will lead the patient through a set of speech elicitation tasks designed to assess motor and cognitive function as well as affect. Acoustic and language-level features will be extracted from the speech data and will be used to examine changes in speech and language features for each patient over time.

These data may be combined with data from other trials of psychiatric indications to explore possible association between speech parameters and clinical parameters.

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Speech record collection will occur at the time points indicated in the Flow Chart2. Instructions for recording are provided in a speech analysis procedures manual, filed in the ISF.

Note: All speech sampling tasks may not be available in all countries/languages and will therefore be implemented as available per country.

5.8.3 Medication Adherence and Reminder System

In addition to the regular calculation of treatment compliance as described in section 4.3, medication adherence will be monitored using a medication adherence monitoring platform. [redacted] time and day, the patient face-ID, and the drug intake process will be captured in selfie mode of the smartphone camera, by the patient. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

These measures will not supersede or replace the physician and/or prescribed medication protocol of the patients. The platform encourages adherence to the predefined protocol but does not change the medication protocol of the patients; thus, use of this platform presents minimal risk to the patients. Use of the platform will be required for all patients in the trial. Non-compliance with the system will not lead to patient discontinuation, however patients should be encouraged to be fully compliant.

Registration in the [redacted]

- In most countries, the platform may be downloaded as an application on the patient's personal smartphone. If a patient does not own a smartphone or prefers not to use his/ her personal smartphone, one of the backup provisioned devices should be provided. In some countries, all participants will use a provisioned device. Patients will receive the application along with a training during visit 1A (please refer to Flow Chart2 and section 6.2).
- At Visit 2 patients will begin using the platform to monitor study drug intake.

Ongoing use and monitoring of medication adherence

- Patients should use the application to record each intake of study medication throughout the trial. Patients will follow a series of prescribed steps in front of the front-facing webcam to confirm their ingestion of the medication by video and audio.

- When at home, patients will receive a medication reminder at a time within a predefined window. This notification reminds patients to take their medication dose while using the platform

- Site personnel are expected to check the [redacted] on an ongoing basis (minimum once per week) to ensure consistent medication adherence throughout the study. In cases of missed doses or pending data, site personnel should follow up with the patient as soon as possible to assess the reason for non-adherence and reinforce

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the importance of complying with the study drug dosing schedule. The aforementioned contact/intervention is expected to be logged in the dashboard.

- If the patient reports that a dose was taken but not logged in the application, site personnel should reclassify this dose to "site reported" using the dashboard.

5.8.4 Verification of current and past research study status of trial patient

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 patient, in this study, must have their current study status checked by utilizing the system of the vendor [redacted] This is a mandatory process, local amendments will be prepared as applicable.

Following proper informed consent and after issuing a study patient number, each patient will be checked in the [redacted] database, as indicated in the Flow Chart 1. Partial identifiers will be utilized. This will include checking a valid form of picture ID when available.
The first 3 letters of the first and last name will be entered along with the middle initial, Date of Birth (DOB), Sex, and last 5 digits of that ID. If the research patient is a Verification Success he/she may proceed in the study. Verification Failures status will not be permitted to screen without follow-up investigation and documentation of final decision . The duplicate patient check will be performed only after approval is received in accordance with local regulations.

5.9 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 on race will be collected because this demographic information is required for the calculation of eGFR (CKD-EPI formula) (please refer to section 6.2.1).

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6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology.
The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

All patients have to adhere to the visit schedule as specified in the Flow Chart 1 and Flow Chart 2. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

During the COVID-19 pandemic, there might be situations when patients might not be able to come to the site for the scheduled visit. This might be e.g. due to restrictions set by authorities or by the investigator site/institution, because the 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 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures to be performed at each visit are listed in the Flow Chart 1 and Flow Chart 2. Additional details regarding visit procedures are provided below.

The following requirements for the conduct of the PTSD assessments need to be followed:
- The site staff must be properly trained on all trial procedures and training documentation filed in the ISF.
- At all visits, following screening, it must be reiterated that WOCBP must use the appropriate methods of contraception.
- Qualification, training, remediation (if needed) and central reading of the scales will be provided by a specialized vendor. The training standards and standards for the conduct of the assessments will be defined for each assessment individually and can be found in the ISF; It is the responsibility of the Principal Investigator at the site to ensure that all members of the site staff involved in the PTSD assessments undergo qualification and training by the vendor (please also refer to section 5.3).
- The CAPS-5 and CGI-S/C assessments should preferentially be done by the same rater for a given patient throughout the study period.

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- For each individual patient, the same qualified rater should rate the patient throughout the trial, if at all possible. In case of unforeseen circumstances, a qualified back-up rater must be available throughout the trial.
- Results of the MINI, CAPS-5, PCL-5 (including Life Events Checklist), OSU TBI-ID-SF and C-SSRS assessments at screening are part of the eligibility evaluation.
- The CAPS-5 rater should review the LEC and Extended Criterion A upon completion by the patient before the patient completes the PCL-5 to identify the index traumatic event to be referred to during patient's PCL-5 completion and the CAPS-5 administration. It is essential that the referenced index traumatic event is consistent for PCL-5 and CAPS-5 assessments.
- All MINI and CAPS-5 administrations will be audio recorded for central review by the vendor for quality assurance.
- During the assessments, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator
- The Baseline/screening scale of the C-SSRS will be administered for eligibility confirmation and the follow-up scale at all visits for assessment of suicidality.

Order of Assessments and Procedures at Screening Visit
At the screening visit, all clinical examinations and procedures (Flow Chart 1) should be performed first, followed by the clinical outcome assessments (Flow Chart 2) in the below order. Blood draws are preferably done after clinical outcome assessments but may be done as part of the clinical examination and procedures (Flow Chart 1) as per investigator's discretion.

The following clinical outcome assessments 1. to 5. must be in the specific order:
1. Life Events Checklist (as part of PCL-5)
2. Extended Criterion A (as part of PCL-5)
3. PCL-5
4. CAPS-5 (in consideration of LEC and Extended Criterion A as part of PCL-5)
5. MINI

Assessments/procedures 6. to 8. should preferably be performed in the below order:
6. OSU TBI-ID-SF
7. C-SSRS
8. CTQ

6.2.1 Screening Visit and Screening Period

No trial procedures should be done unless the patient has consented to taking part in the trial. Prior to any trial related procedure, the patient information and informed consent may also be done at an extra visit but at a maximum up to 2 weeks before V1.

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.

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As duplicate enrolment imposes a risk for poor quality and safety, each patient in the trial following proper informed consent and after issuing a study patient number must have their study status checked by utilizing the system of the vendor "[redacted] The duplicate patient check will be performed only after approval is received in accordance with local regulations. Please refer to section 5.8.4 for details.

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.

Screening period
The Screening period, i.e. the phase before the first administration of the trial drug, starts at Visit 1 (screening visit). The Screening period may last up to a maximum of 28 days but should be kept as short as possible.
Within the screening period, screening procedures may be extended to more than one physical visit in exceptional situations to reduce patient burden (ahead and in addition to planned Visit 1A).

In such a case, the clinical assessments (Flow Chart 1) should be done on the first day and the clinical outcome assessments (Flow Chart 2) preferably on the following day but no longer than 3 days after completing the clinical assessments. Exceptional situations must be discussed and agreed upfront with the Clinical Trial Manager.

Splitting of required procedures for a visit over more than one day is only allowed for Visit 1. The screening visit date to be entered into the eCRF is the first day of visit 1, i.e. the day all clinical assessments are performed.

EcMA and medication adherence assessment
Eligibility of patients is to be confirmed (i.e. all results received from the screening Visit) before Visit 1A is scheduled. Visit 1A must be scheduled at minimum 8 days prior to Visit 2 to allow for 7 days of EcMA assessments (please refer to Flow Chart 1 and 2).

During the Visit 1A, patients must be trained on the EcMA and adherence assessment according to vendor's instructions. Patient may choose to download the app or will be provided with the loaner smartphone to use during the trial. The adherence assessments will start with the first administration of the trial drug at randomization.

In case Visit 2 is delayed after patient completes EcMA assessments, the EcMA assessment does not need to be repeated.

An informational video for placebo response risk mitigation will also be shown to the patient during Visit 1A. The video intends 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

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randomly assigned to placebo, and stresses the importance of reporting all symptoms, be they positive or negative or neutral

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.

Informed consent for speech recording. Participation in the sampling of speech recordings is voluntary and only allowed after the patient has given separate consent prior to the collection of the respective speech records.

Atraining video for speech recordings will be shown to the patient after having agreed to participate and having provided informed consent. The first speech recording should be performed at the Visit 1A already.

Infection screening
In case of positive hepatitis B surface antigen (qualitative), the patient will be excluded from the trial.
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
During the screening visit, demographics information will be collected.
This includes:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the patient`s sex at birth),
- Questions on potential disability payments related to PTSD
- For women: of childbearing potential yes / no in order to characterize the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.

Information on race will be collected because this demographic information is required for the calculation of eGFR (CKD-EPI formula). Blood pressure should always be measured before any blood samples are taken.

Any abnormal condition of clinical significance identified during physical examination, vital signs, 12 lead ECG and/or laboratory assessment should be recorded as a baseline condition.

Any diagnoses identified through MINI questionnaire must be recorded as baseline conditions.

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Any lifetime history of suicidal ideation, self-injurious behavior, no suicidal intent' or suicidal behavior at the screening visit that is not an exclusion criterion, should be considered as baseline condition/medical history.

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

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

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

Concomitant treatments which are restricted before and during trial participation, , are listed in the ISF. Patients will be instructed to continue allowed background medication without changes and to adhere to their administration algorithm.
Substance use, e.g., nicotine, alcohol, caffeine at screening and at subsequent clinic visits. Please refer to the current CRFs for details about substance use to be collected.

Eligibility Review
A central clinical review by an external clinical reviewer (i.e., [redacted] clinical reviewer) will be performed to ensure patient eligibility based on the audio recording of the MINI administration and CAPS-5 data and audio recording, at the screening visit.
Any uncertainty raised by the external clinical reviewer of these scales related to inclusion/exclusion criteria will be discussed with the investigator/rater in order to establish confidence in the diagnosis and level of symptom severity. Patients for whom diagnostic/severity agreement between the investigator/study center clinician and the vendor clinician(s) cannot be reached, may not be appropriate for study participation and should not be enrolled.

For eligibility documentation purpose, [redacted] will send a Subject Eligibility Notification to the site indicating one of the three following scenarios: a) the central reviewer had no comments to the assessment/rating, b) a discussion was held between the central reviewer and the site rater and a mutual agreement with respect to patient eligibility was reached or c), the discussion did not lead to an agreement and the patient should not be randomized.

Rescreening
For patients who fail screening, a rescreening may be done only once based on investigator judgement and prior permission from sponsor. Patient who are re-screened need to be re-

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consented and will be given a new patient number. All the study procedures for screening (Visit 1) must be repeated.

Please see Section 3.3 for further details regarding re-screening.

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 Assessments and Procedures during Treatment period

After the screening visit, is it up to investigator's discretion whether clinical outcome assessments (Flow Chart 2) or all clinical examinations and procedures (Flow Chart 1) are performed first, but for each individual patient, the entire order of all assesments and procedures (Flow Chart 1 & 2) should be kept consistent throughout the course of the trial, if at all possible.

ECG and vital signs should always be measured before any blood samples are taken. Other clinical examinations and procedures can be performed in any order.

All clinical outcome assessments should be completed in the order described below.

Order of clinical outcome assessments
All clinical outcome assessments to be performed per visit are listed in Flow Chart 2.

- PCL-5 must be performed first,
- followed by CAPS-5,
- CGI-S (total and domain),
- CGI-C
- and C-SSRS, as applicable per visit schedule.

Remaining patient reported outcome assessments as per Flow Chart 2 including optional speech recordings may be performed in the preferred order provided in the ISF (and as presented on the tablet) after IMP intake and before [redacted]

[redacted]

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Meal intake routine will be documented in the eCRF at visits with [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.

Pandemic restrictions
The patient will be presented with questions to evaluate the impact of COVID-19 pandemic restrictions. The assessment period will be aligned with the CAPS-5 recall period (i.e. past week).

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 will be performed by the central lab for confirmation.

Upon randomization via the IRT, medication kit will be dispensed. Trial medication is administered after [redacted]
The first dose should be taken at the clinic after all Visit 2 assessments and procedures are completed, except for remaining patient reported clinical outcome assessments including optional speech recordings as described above, and followed by [redacted]

. 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 4, Visit 6, 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 and [redacted] samples are taken if applicable (please refer to Appendix 10.2).

Pandemic restrictions
At Visit 6, the patient will be presented with questions to evaluate the impact of COVID-19 pandemic restrictions. The assessment period will be aligned with the CAPS-5 recall period (i.e. past week).

Phone visits
Visit 3, Visit 5, Visit 7 and Visit 9 will be conducted by phone or by video call, if in line with local regulation.

At Visit 9, patients will be instructed to take the last dose of study medication on **the day before** the EOT visit.

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Visit 10 / End of Treatment (EOT) Visit
For patients completing the 8-week treatment, this visit will be EOT visit. For patients who discontinue study treatment prematurely and continue with study visits, this visit at Week 8 will be their Visit 10.
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 56 days; therefore the EOT visit is scheduled at Day 57 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 8 visit, an Early End of treatment Visit (eEOT) visit will be completed instead of the planned treatment period visit within 7 days of the last dose of trail medication. See Flow Chart 1 and section 3.3.4 for further details regarding discontinuation of patients from treatment or assessments.

Pandemic restrictions
At Visit 10 or EOT repectively, the patient will be presented with questions to evaluate the impact of COVID-19 pandemic restrictions. The assessment period will be aligned with the CAPS-5 recall period (i.e. past week).

6.2.3 Follow-up period and trial completion

For all patients who had at least one dose of trial medication, the follow-up visit will be performed as described in section 3.3.4.1 and 3.3.4.2.

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

Patients who finish the randomized treatment period according to the protocol, will return to the clinic for the end of study (EOS) Visit 11. Trial completion is defined as patients having reached the EOS visit within the specified window per the Flow Chart 1. The trial completion page in the eCRF has to be entered.

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

Should it be not possible for the patient to attend a follow up visit at the trial site, a visit out of time window should be performed as soon as possible; if a visit at the site is not possible at all, at least a phone contact should occur at the scheduled follow-up visit time point (please refer to section 3.3.4.1 and 5.4.6.2.1).

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This trial is designed to assess the effects of BI 1358894 and placebo on patients with PTSD.

There will be no formal hypothesis testing performed. Inference concerning the efficacy of BI 1358894 will be assessed based on the estimated mean difference(s) between the treatment and placebo arm on the change from baseline to Week 8 in CAPS-5 total score, as well as other efficacy endpoints.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following patient analysis sets are defined for this trial:

- Full Analysis Set (FAS): includes all randomized patients who received at least one dose of trial medication during the trial and had a baseline and at least one post-baseline observation for the primary or secondary endpoints. The FAS is used for efficacy analyses and patients in FAS are analysed under the randomized trial medication.
- Treated Set (TS): includes all patients who signed informed consent and were treated with at least one dose of the trial medication. Patients in TS are analyzed under the actual trial medication received at randomization. The TS is used for safety analyses as well as demographics and baseline characteristics.

Data from patients who were screened but not randomized will be listed but not included in any summary or inferential statistics.

In general, baseline values are the last measurements taken prior to the first administration of trial medication at randomization (Visit 2), (see Flow Chart 1). Further details (e.g., the handling of randomized patients that receive the wrong treatment) will be provided in the TSAP.

7.2.2 Handling of Intercurrent Events

In the analyses of the primary endpoint, the following intercurrent events (ICEs) are of interest:

1. Change in background CNS active medication (e.g., non-SSRI antidepressant, anxiolytics)
2. Change in pharmacological therapy (SSRI)
3. Change in drug test result from negative to positive (Cannabis, Benzodiazepine, Barbiturates, Opiates, Cocaine, Amphetamines, Methadone, PCP)
4. Change in non-pharmacological therapy – trauma-focused psychotherapy

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5. Change in non-pharmacological therapy – all other cognitive/behavioral therapy (CBT) (e.g., any other kind of psychotherapy, nicotine withdrawal therapy, diet, etc.)
6. Withdrawal of study medication due to investigator assessed drug-related adverse events (e.g., headache)
7. Withdrawal of study medication due to perceived lack of efficacy or disease worsening
8. Withdrawal of study medication due to other adverse events
9. Withdrawal of study medication due to any other reasons

Table 7.2.2 :1 Handling rules for Intercurrent events

	ICE	Primary Estimand	Supplementary Estimand
Handling rules for ICEs	1-4	Treatment policy	Treatment policy
	5	Treatment policy	Treatment policy
	6-7	Hypothetical	Treatment policy
	8-9	Hypothetical	Hypothetical

The primary estimand estimates the treatment effect when changes to background CNS active medication, pharmacological SSRI therapies and non-pharmacological therapies (ICEs 1-5) are considered to be part of the treatment effect, but changes to randomized treatment (ICEs 6-9) are not considered to be part of the treatment effect of interest. ICEs are therefore handled by a hybrid estimand that combines the treatment policy and hypothetical approaches, where ICEs 1-5 are handled using the treatment policy approach, and measurements taken after the occurrences of these ICEs are included in the primary analysis; ICEs 6-9 are handled using the hypothetical approach, and measurements after their occurrences are therefore censored in the primary analysis.

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Regardless of the occurrence of ICEs, every attempt will be made to follow all patients until the end of the planned study period.

7.2.3 Primary objective analyses

The primary analysis of the primary efficacy endpoint uses the Full Analysis Set. Intercurrent events are handled as specified in Section 7.2.2 above and missing data as a result from the strategy (including both actual missing outcomes and excluded outcomes) will be handled using a mixed effects model with repeated measures (MMRM) under the assumption of missing at random (MAR). For change from baseline to Week 8 in CAPS-5 total score, a restricted maximum likelihood (REML) based approach using MMRM will be conducted to compare the adjusted mean between BI 1358894 125mg QD vs. placebo QD. The MMRM includes the fixed categorical effects of treatment at each visit, fixed categorical effects of the stratification factor of presence of significant childhood trauma (yes vs. no), and the fixed continuous covariates of time since index event (in years) and baseline CAPS-5 total score at each visit. Patient is treated as random effect. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The point estimates of the adjusted mean difference between treatment arms at each visit, together with the corresponding two-sided 95% confidence intervals and p-values will be presented. The p-values and 95% confidence intervals are considered descriptive statistics. The primary treatment comparison will be the contrast between treatment and placebo at Week 8.

Procedures to follow if the MMRM analysis fails to converge will be described in the Trial Statistical Analysis Plan.

7.2.4 Secondary objective analyses

For the continuous efficacy endpoint of change from baseline on the PTSD Checklist for DSM-5 (PCL-5) total score at Week 8, the same strategy for handling the intercurrent events in the primary estimand analysis and a similar MMRM analysis used for the primary efficacy endpoint will be conducted to obtain the adjusted mean treatment effect between BI and placebo in terms of change from baseline to Week 8. This MMRM model includes the discrete fixed effects of treatment at each visit, fixed categorical covariate of the stratification factor of presence of significant childhood trauma (yes vs. no), and continuous fixed effects

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of time since index event (in years) and the corresponding baseline endpoint value at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure to model the within-subject measurements. Subjects will be considered as a random effect. The primary treatment comparison is the contrast between treatment and placebo at Week 8.

A logistic regression adjusted for treatment and stratification factor of presence of significant childhood trauma (yes vs. no) will be used for binary endpoints.

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

All treated patients will be included in the safety analysis and will be summarized under the actual trial medication received at randomization. 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. To this end, all adverse events occurring between the start of treatment and the end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as 28 days after the last dose of trial medication. 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 most updated version of the MedDRA at the time of reporting.

Frequency tables for all adverse events, protocol-specified adverse event of special interest (AESI), serious adverse event (SAE), adverse event leading to death, adverse event leading to discontinuation, investigator assessed drug-related adverse event and serious related adverse event will be generated for treatment-emergent adverse events. In addition, summary statistics and descriptive analyses will be conducted for other safety parameters that are assessed using dedicated scales, including suicidality as assessed by C-SSRS.

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Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. 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 trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

For more details, please refer to the TSAP.

7.2.7 Other Analyses

7.2.8 Interim Analyses

An interim analysis is planned when the 120th evaluable patient completes the preplanned treatment period. Here, an evaluable subject is one that has remained in the study, and has at least one change from baseline CAPS-5 severity score.

The purpose of this interim analysis is for internal planning of the PTSD indication with BI 1358894. PoC could be established and the trial may be stopped early if at the interim analysis an impressive standardized effect size is observed. The decision to stop or continue the trial will be made by BI based on the totality of evidence - to also include observations from secondary objectives and the safety profile. An independent team will be formed to perform this analysis. Details will be specified in an interim analysis logistic plan.

The same MMRM model and estimands used on the primary endpoint, will be used for this interim analysis. When the 120th evaluable patient has completed the preplanned treatment period, the analysis will be performed on the change from baseline to Week 8 in CAPS-5. Based on this observed standardized effect size of the change in CAPS-5 at Week 8 at interim, along with evidence from secondary objectives, as well as the observed safety profile, a team decision will be made to either stop the trial early for efficacy, and potentially claim the achievement of PoC in this indication, or continue enrolling patients until the maximum recruitment target of 200 evaluable patients is reached (assuming a drop-out rate of 30%, this is equivalent to a total sample size of 286 randomized patients, please refer to

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Section 7.5 for more details on the sample size justification). Detailed efficacy boundary at interim will be specified in a separate document.

During the conduct of the interim analysis, recruitment into the trial will continue. If the trial is stopped at interim, there will be a final analysis of the complete data set that will include all the patients that were enrolled during the conduct of the interim analysis period. In order to support the double-blinded conduct of the trial, the trial team will be kept blinded to the individual patients' treatment group assignment at interim. A separate team will perform the interim analysis. Details will be specified in a separate logistic plan.

More details about the interim analysis and final analysis will be specified in the TSAP and (or) in the interim logistic plan.

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the specific time points under patients' consent, even for subjects who terminated trial medication prematurely. For the primary analysis in the primary estimand, missing data will not be imputed. The MMRM analysis will handle missing data based on a likelihood method under the "missing at random" assumption. Please refer to section 3.3.4 for patient retention strategy to minimize missing data. For more details regarding missing data handling, please refer to the TSAP.

7.4 RANDOMISATION

Eligible patients will be randomised in equal ratio to BI 1358894 125mg arm and the placebo arm. The randomisation will be implemented in blocks to achieve balanced allocation to each treatment arm. In addition, randomisation will be stratified by presence of significant childhood trauma (yes vs. no), according to investigator´s judgement, assessed by CTQ at screening visit).
The randomization will be conducted via an interactive response technology (IRT). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudorandom number generator so that the resulting treatment will be both reproducible and nonpredictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to randomize a maximum of 286 patients in this trial, since this sample size is considered sufficient to provide a reasonable chance to achieve the aims of this trial (Please refer to Table 7.5: 1 for more details). Assuming an early study drop-out rate of 30%, this is equivalent to a total of 200 evaluable patients.

An interim analysis to potentially stop the trial due to efficacy will take place when the 120th evaluable patient (about 172 patients randomized, assuming an early drop-out rate of 30%) has completed the 8-week treatment duration. If the trial is not stopped at interim, then patient enrolment will continue to the pre-planned maximum of 286 patients (200 evaluable patients).

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The sample size calculation is based on a target SES of BI 1358894 vs. placebo of 0.35 for the primary endpoint. Recent research on drugs for the PTSD indication suggest that an estimated standardized ES around 0.38 – 0.53 could be expected (assuming equal variances of the treatment and the placebo groups) [R21-1623]. The assumed SES of 0.35 is based on the expectation that BI 1358894 has competitive efficacy with other drugs under development.

Based on these sample sizes, the probabilities of observing a (1) ES >= 0.5 at interim, and (2) ES <0.5 at interim, and ES < 0.25, between 0.25 and 0.32, or >= 0.32 at the final stage with 200 evaluable patients are presented in Table 7.5: 1. The estimated ES is between treatment and placebo on the change from baseline to Week 8 in CAPS-5 total score. In addition, the overall probability of observing an ES >=0.5 at interim or observing a standard ES of at least 0.32 at the final stage are presented in Table 7.5: 1.

Table 7.5: 1 Probabilities of observing a standardized ES at different stages of the study for treatment relative to placebo under different scenarios (60 and 100 evaluable patients per arm at interim, and at final analysis stage, respectively).

	True standardized ES					
Probabilities	**0.53**	**0.46**	**0.35**	**0.25**	**0.15**	**0.1**
P(observed SES >= 0.5 at interim)	0.579	0.422	0.204	0.081	0.028	0.015
P(obs SES < 0.5 at interim & final obs SES >= 0.32)	0.356	0.424	0.395	0.241	0.093	0.048
P(obs SES < 0.5 at interim & final obs ES < 0.25)	0.024	0.066	0.230	0.488	0.755	0.854
P(obs SES < 0.5 at interim & 0.25 <= final obs ES < 0.32)	0.041	0.088	0.171	0.190	0.124	0.084
P(observed SES >= 0.5 at interim or observed SES > 0.32 at final)	0.935	0.846	0.599	0.322	0.121	0.063

The calculation was performed using R studio version 3.5.1, based on 10000 simulations.

Hence, under the truly positive scenario of true standardized ES = 0.53, the probability of observing ES >= 0.5 at interim is 57.9%, and the probability of observing a standardized ES >= 0.5 at interim, or observing a standardized ES >= 0.32 at the final analysis stage is 93.5%. Assuming the true standardized effect size is 0.35, there is a 20.4% probability to observe a standardized ES between the treatment and placebo arm to be >= 0.5 at interim, and an overall 59.9% probability to observe a standardized ES >= 0.5 at interim, or to observe a standardized ES of at least 0.32 at the final analysis stage. And an overall 77% probability to observe a standardized ES >= 0.5 at interim, or to observe a standardized ES of at least 0.25

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at the final analysis stage. On the other hand, assuming the true standardized effect size is only 0.1, there is an 85.4% probability of observing an ES < 0.5 at interim and observing an ES < 0.25 at the final analysis stage. And the overall probability of observing a standardized ES >= 0.5 at interim or observing a standardized ES >= 0.32 at the final analysis stage is 6.3%.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC and/or EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate 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 finalisation of the Clinical Trial Report.

The certificate of insurance cover 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 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 [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial patient protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual 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 CRF must be consistent with the source data or the discrepancies must be explained.

Electronic records, i.e., clinician administered assessment data, related audio recordings (for central review) and patient reported outcome data entered into the tablet computer (Rater Station) will be regarded as source data.

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

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 one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

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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 (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of 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 patient 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 CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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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 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:
Personalised 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 patients 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 Informed Consent Form (ICF) is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and / or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first 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**

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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 DMC will evaluate safety data.

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

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.
Vendors will be used in this trial for central laboratory services, IRT, central ECG services, Clinician-rated Outcome (ClinRO)/PRO scales assessments including, medication intake monitoring, EcMAs, speech recordings and duplicate checks. Details will be provided in the respective manuals available in the ISF.

Bioanalysis of BI 1358894 is done by [redacted]

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.

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

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

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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

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

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

Refer to ISF.

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

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

Under these circumstances, the below modifications can be considered.

Safety lab, other laboratory tests

If taking blood samples for central lab is not possible, blood analysis for safety lab can be done in a local lab. The results of the lab tests are to be reported and transferred to the investigator, who has to ensure medical review and proper documentation.

Safety lab parameters should at least include liver enzymes and Bilirubin, haematology including differential test, blood glucose, sodium, potassium, creatinine, urea (BUN) and eGFR. It is important that always the reference values of the local lab are also provided.

Dispensation of Trial medication (IMP)

If a participant is not able to come to visit 4, visit 6 or visit 8 as planned and the investigator considers it acceptable and save for participant to continue with IMP, IMP can be shipped from site directly to the participant (if legally acceptable according to local regulations).

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

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment	03 May 2022
EudraCT number/EU number	2021-003154-23
BI Trial number	1402-0030
BI Investigational Medicinal Product(s)	BI 1358894
Title of protocol	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Global Amendment due to urgent safety reasons	X
Global Amendment	1
Sections to be changed	Flow Chart 1; Flow Chart 1 footnote 8; Table 5.4.3:1
Description of change	Added pregnancy test at EOS visit, corrected footnote text and table 5.4.3:1 to include pregnancy test at V1A as required by Flow Chart 1
Rationale for change	New safety information.
Sections to be changed	Flow Chart 1; Section 4.2.2.3; Section 6.2

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Description of change	Flow Chart 1 *The following text was added:* Informed consent [4] (including informed consents for patient's duplicate check[5], optional biobanking and speech recording; counseling about the need of contraception) Section 4.2.2.3 *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 1 (including phone visits). Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the study patient. When there is complete sexual abstinence, the patient refrains from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception). *Was changed to:* Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the study patient. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception) - (in this specific case the barrier methods as mentioned below, are not applicable). Sexual abstinence as a

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	contraceptive method will not be allowed for WOCBP who are heterosexually active. 6.2 *The following was added:* At all visits, following screening, it must be reiterated that WOCBP must use the appropriate methods of contraception.

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Rationale for change	New safety information.
Sections to be changed	Flow Chart 1, footnote 5; section 5.8.4
Description of change	Flow Chart 1, footnote 5 *The following was added:* Registration of patient by site staff in the [redacted] system is only required during the Screening Visit; no further action for the site staff during the course of the study. Section 5.8.4 If the research patient is a Verification Success he/she may proceed in the study. Verification Failures status will not be permitted to screen without sponsor approval. *Was changed to:* If the research patient is a Verification Success he/she may proceed in the study. Verification Failures status will not be permitted to screen without follow-up investigation and documentation of final decision.
Rationale for change	Clarification of process.
Sections to be changed	Flow Chart 1, footnote 12

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Description of change	Collection of biobanking samples is optional. Samples will be collected at Visit 2 (serum, plasma and deoxyribonucleic acid (DNA) samples) and EOT/Early EOT, respectively (serum, plasma only). Patients are required to sign a separate informed consent for biobanking. Samples will be stored at a biobanking facility for future research *Was changed to:* Collection of biobanking samples is optional. Samples must be collected at Visit 2 (serum, plasma samples) and EOT/Early EOT, respectively (serum, plasma only). Patients are required to sign a separate informed consent for biobanking. Samples will be stored at a biobanking facility for future research
Rationale for change	Clarification
Sections to be changed	Flow Chart 2, section 6.2.1
Description of change	Patient informational video speech recording *Was changed to:* Patient training video speech recording
Rationale for change	Clarify that purpose of the video is the training of patients on the assessment.
Sections to be changed	Section 1.2

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Description of change	*The following text was added:* Oral administration of BI 1358894 to the pregnant Goettingen minipigs throughout organogenesis was associated with developmental effects including lower embryo-fetal survival (due to a reduced number of intrauterine implantations and an increased number of early resorptions) and decreased fetal weights, compared to control. In addition, there were higher incidences of skeletal malformations and/or variations. The NOAEL for embryo-fetal development (100 mg/kg/day) corresponded to a mean Cmax of 1,980 nmol/L and a mean AUC0-24h of 31,300 nmol·h/L of BI 1358894, therefore providing safety margins of 1.4 and 1.6, respectively (compared with the predicted exposure at the human dose of 125 mg).
Rationale for change	New safety information
Sections to be changed	Section 1.2
Description of change	Overall, 217 healthy volunteers and 73 patients with MDD had been exposed to BI 1358894 in 7 Phase I clinical trials, which were completed at the time of CTP writing. *Was changed to:* Overall, 211 healthy volunteers and 23 patients with MDD had been exposed to BI 1358894 in 8 Phase I clinical trials.
Rationale for change	Update in numbers of participants in clincial studies for alignment with current Investigator's Brochure Version 7.
Sections to be changed	Section 1.4.2

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Description of change	*The following text was added:* In one completed pivotal embryo-fetal development study in Goettingen minipigs, embryo-fetal development toxicity was identified (decreased number of implantations, increased number of early resorptions, decreased fetal weight, skeletal malformations) at relevant human exposure levels. Maternal toxicity was not seen at human relevant doses. The NOAEL shows that the findings are relevant for the maximum dose (125 mg once daily) tested in the ongoing clinical trials. Therefore, a risk for teratogenicity in humans cannot be excluded. To mitigate this risk, women of childbearing potential (WOCBP) who are heterosexually active must agree and 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 trial. Pregnancy testing has to be performed at every site visit. Additionally, investigators must counsel WOCBP with regard to the importance of contraception at all visits as per Flow Chart 1 (including phone visits).
Rationale for change	New safety information
Sections to be changed	Table 1.4.2:1

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Description of change	*The following was added to the table:* Embryo-fetal development toxicity Decreased number of implantations, early resorptions, decreased fetal weight, skeletal malformations in minipigs at relevant human exposure levels. Thus, a risk for teratogenicity in humans cannot be excluded. 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. Pregnancy testing must be performed at every site visit. Investigators must counsel WOCBP with regard to the need for contraception at all visits as per Flow Chart 1 (including phone visits).
Rationale for change	New safety information
Sections to be changed	Section 1.4.3

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Description of change	*The following text was added:* Embryo-fetal development toxicity has been identified in a pre-clinical study in minipigs at relevant human exposure levels. Therefore, a risk for teratogenicity in humans cannot be excluded. 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 1 (including phone visits). Considering the acceptable and manageable safety profile of BI 1358894 as demonstrated in nonclinical and toxicology studies and the good tolerability in clinical studies performed to date together with the close monitoring… *Was changed to:* Considering the acceptable and manageable safety profile of BI 1358894 as demonstrated in nonclinical and toxicology studies, good tolerability in clinical studies performed to date, close monitoring (including the above-mentioned risk mitigation activities to minimize the risk of pregnancy during the trial) planned during the study visits …
Rationale for change	New safety information
Sections to be changed	Section 3.3

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Description of change	Retesting applies in situations when the issue can be resolved within the screening period of 28 days. For example patients are testing positive on urine drug screen for cannabis or opioids at Visit 1. These patients can be re-tested once (consider long half-life of cannabis) within the screening period of 28 days, if there is a reasonable explanation and expectation that the patient is not a regular user and will not test positive again on re-test or has stable treatment with medically prescribed opioids, both at the discretion of the investigator. In case of retesting, the patient will keep the same patient number. The results of all retests should be available within the 28 days of screening period. Once retests are available and negative for the retested parameter and in case all other eligibility criteria are met, the patient can be randomized on the planned Visit 2 date. *Was changed to:* Retesting applies in situations when the issue can be resolved within the screening period of 28 days, for example patients that are testing positive on urine drug screen for cannabis or opioids at Visit 1 can be retested once (consider long half-life of cannabis) within the screening period of 28 days, if there is a reasonable explanation and expectation that the patient is not a regular user and will not test positive again on retest or has stable treatment with medically prescribed opioids, both at the discretion of the investigator. In case of retesting, the patient will keep the same patient number. The results of all retests should be available within the 28 days of screening period. Once retests are available and negative for the retested parameter/eligibility confirmed, and in case all other eligibility criteria are met, the patient can be randomized on the planned Visit 2 date.

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	The following was added: The exceptions above only apply if these assessments are not the reason for rescreening.
Rationale for change	Clarification of procedures for retesting and rescreening.
Sections to be changed	Section 3.3.3
Description of change	Exclusion Criterion #26 Patients who were confined to an institution by court or administrative order. *Was changed to:* Patients who are currently and during the course of the trial confined to an institution by court or administrative order.
Rationale for change	Clarification
Sections to be changed	Section 3.3.3
Description of change	Exclusion Criterion #29 In-patients are generally excluded, however in-patients who are committed on a voluntary basis in an open-ward (i.e. "residental ward") and are non-suicidal are allowed. *Was changed to:* In-patients are generally excluded, however in-patients who are admitted on a voluntary basis in an open-ward (i.e. "residential ward") and are non-suicidal are allowed.
Rationale for change	Clarification
Sections to be changed	Section 3.3.4.1; 6.2.3; Flow Chart 1&2 visit description; Flow Chart 1 footnote **

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Description of change	Section 3.3.4.1 After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits until Visit 10 and should be encouraged to complete the EOS Visit 28+2 days after the drug discontinuation date. All procedures should be completed, with the exception of trial drug procedures and PK collections. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days), no additional FUP is needed. However, end of study participation must be completed. If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and EOS. If EOS visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP is needed. However, end of study participation must be completed. *Was changed to:* After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits including Visit 10 and should be encouraged to complete the FUP/EOS Visit 28+2 days after the drug discontinuation date. All procedures should be completed, with the exception of trial drug procedures and PK collections. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days), no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

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	If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and EOS. If EOS visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed. Section 6.2.3 If the last day of trial drug intake is different from the day prior to the EOT visit, the date of the last day of trial drug intake will be used for calculation of the EOS visit date. *Was changed to:* If the last day of trial drug intake is different from the day prior to the EOT visit, the date of the last day of trial drug intake will be used for calculation of the FUP/EOS visit date. Flow Chart 1&2 *The following was added to V11 visit description:* Follow-up Visit (FUP) / Flow Chart 1, Footnote** After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits until Visit 10 and should be encouraged to complete the FUP Visit 28+2 days after the drug discontinuation date All procedures should be completed, with the exception of trial drug procedures and PK collections. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days),

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	no additional FUP is needed. However, end of study participation must be completed. If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and FUP. If FUP visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP is needed. However, end of study participation must be completed. *Was changed to:* After this early EOT visit, patients should be followed up according to the regularly scheduled visit for both clinic and phone visits including Visit 10 and should be encouraged to complete the FUP Visit 28+2 days after the drug discontinuation date All procedures should be completed, with the exception of trial drug procedures and PK collections. If a regular planned visit is completed prior to the initially planned Visit10 (early drug discontinuation date + 28+2 days), no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed. If the patient does not agree to return for all remaining scheduled visits, the patient should be encouraged to return at least for an early EoT (eEOT) Visit within 7 days of the last dose of trial medication, for the regularly scheduled Visit 10 and FUP. If FUP visit (early drug discontinuation date + 28 +2 days) can be completed prior to the date of the planned Visit 10, no additional FUP Visit may be needed. However, end of study participation (EOS) must be completed.

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Rationale for change	Clarification
Sections to be changed	Section 4.2.2.1
Description of change	For patients who are not on current treatment with benzodiazepine (including Z-drugs) or non-benzodiazepine hypnotics at the time of screening, the protocol will allow concomitant use of non-benzodiazepine-, non-Z-drug hypnotics during the trial at dose equivalent to ≤ 1.0 mg lorazepam per day. *Was changed to:* For patients who are not on current treatment with benzodiazepine (including Z-drugs) or non-benzodiazepine hypnotics at the time of screening, the protocol will allow concomitant use of non-benzodiazepine-, non-Z-drug hypnotics at lowest dose of the compound as noted in the Summary of Product Characteristic (or SmPC) during the trial.
Rationale for change	Removal of lorazepam dose equivalent as this is not applicable in this trial for concomitant use started during the trial.
Sections to be changed	Table 5.4.3:1
Description of change	Hepatitis C Vaccine *Was changed to:* Hepatitis C Virus
Rationale for change	Correction of term.
Sections to be changed	Section 5.4.5.1

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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 5.4.6.1.3).
Rationale for change	Reference to "Always serious adverse event list" added for clarification.
Sections to be changed	Section 6.2
Description of change	*The following text was added:* The CAPS-5 rater should review the LEC and Extended Criterion A upon completion by the patient before the patient completes the PCL-5 to identify the index traumatic event to be referred to during patient's PCL-5 completion and the CAPS-5 administration. It is essential that the referenced index traumatic event is consistent for PCL-5 and CAPS-5 assessments. CTQ was added to listed assessments.
Rationale for change	Clarification of process.
Sections to be changed	Section 6.2.1

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Description of change	Concomitant treatments which are allowed or restricted before and during trial participation, including required washout durations, are listed in the ISF. Patients will be instructed to continue allowed/required background medication without changes and to adhere to their administration algorithm. *Was changed to:* Concomitant treatments which are restricted before and during trial participation, are listed in the ISF. Patients will be instructed to continue allowed background medication without changes and to adhere to their administration algorithm.
Rationale for change	Correction to remove not applicable text.
Sections to be changed	Section 8.1
Description of change	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. *Was changed to:* Prior to patient participation in the trial, written informed consent must be obtained from each patient according to ICH-GCP and to the regulatory and legal requirements of the participating country.
Rationale for change	Legal accepted representatives are not applicable for this trial.
Sections to be changed	Throughout the document
Description of change	Typos, formatting and duplicate wording corrected and paragraph moved within section
Rationale for change	Administrative changes to increase clarity, quality and readability.

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11.2 GLOBAL AMENDMENT 2

Date of amendment	26 Sep 2022
EudraCT number/EU number	2021-003154-23
BI Trial number	1402-0030
BI Investigational Medicinal Product(s)	BI 1358894
Title of protocol	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Global Amendment due to urgent safety reasons	N/A
Global Amendment	2
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	To follow an FDA request and to ensure that the investigator confirms the contraception requirement with the patient.
Section to be changed	**Flow Chart 1 footnote 16**
Description of change	Contraception counseling for WOCB *Was changed to:* Contraception counseling for WOCB[16] 16 This must include confirmation from the patient that she is using required contraception consistently and appropriately. Counseling and contraception confirmation

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	must be recorded in CRFs Refer to section 4.2.2.3 for more details regarding contraception counseling.
Rationale for change	To follow an FDA request and to reinforce that contraception counseling is done at every visit and documented.
Section to be changed	Section 1.4.2
Description of change	Additionally, investigators must counsel WOCBP with regard to the importance of contraception at all visits as per Flow Chart (including phone visits). *Was changed to:* Additionally, investigators must counsel WOCBP with regard to the importance of contraception and confirmation of appropriate contraception use at all visits as per Flow Chart (including phone visits).
Rationale for change	To follow an FDA request and to reinforce that contraception counseling is done at every visit and documented.
Section to be changed	Table 1.4.2: 1
Description of change	Embryo-fetal development toxicity *Section was updated:* 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 visits as per Flow Chart 1 (including phone visits). Refer to section 4.2.2.3 for more details regarding contraception counseling.

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Rationale for change	To follow an FDA request and to reinforce that contraception counseling is done at every visit and documented.
Section to be changed	Section 3.3.2
Description of change	7. Women who are of child-bearing potential (WOCBP)[1] must be able and willing to use two methods of contraception which include one highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1%, plus one additional barrier method. *Was changed to:* 7. Women who are of child-bearing potential (WOCBP)[1] must be 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 result in a low failure rate of less than 1%, plus one additional barrier method.
Rationale for change	To follow an FDA request and to ensure that the investigator confirms the contraception requirement with the patient.
Section to be changed	4.2.2.3
Description of change	*Section was updated:* 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.

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	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 1 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.
Rationale for change	To follow an FDA request and to reinforce that contraception counseling is done at every visit and documented. Also to provide guidance for investigators on contraception rules.

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Sections to be changed	Flow Chart 1 & 2
Description of change	*Description* -28 days to 0 V1A anytime up to day -7 *Was changed to:* -28 days V1A anytime up to 8 days before V2
Rationale for change	Clarifcation of screening period definition.
Sections to be changed	Section 5.8.1, Figure 5.8.1.1:1

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Description of change	Section 5.8.1 A daily/weekly diary design beginning 7 days prior to the randomization visit and then over the 8-week treatment period will be used. *Was changed to:* A daily/weekly diary design for 7 days prior to the randomization visit and then over the 8-week treatment period will be used. Figure 5.8.1.1:1 Visit 1A up to day -7 *Was changed to:* Visit 1A min. 8 days prior V2 56 days Day 2 (the day after V2) to Day 56 (day before V10) *Was changed to:* 55 days (+2) Day 2 (the day after V2) to Day 56 (+2) (day before V10)
Rationale for change	Clarification of assessment period definition. Figure 5.8.1.1.:1 was updated to be aligned screening period clarification and EcMA PANAS daily was corrected.
Sections to be changed	Footnotes Flow Chart 1 & 2, section 6.2, section 6.2.2

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Description of change	Footnote to Flow Chart 1 & 2: At the screening visit, all clinical examinations and assessments as per Flow Chart 1 will be performed first, except for the blood draws, followed by PCL-5,CAPS-5 and MINI, followed by the other scale administrations, listed in Flow Chart 2.The order of assessments is described in detail in section 6.2. For all further clinical visits, scale administrations should be done first, followed by the clinical examinations and assessments (Flow Chart 1) Please refer to section 6.2 for further details. *Was changed to:* At the screening visit, all clinical examinations and procedures as per Flow Chart 1 should be performed first, followed by PCL-5 (version comprising LEC, Extended Criterion A and PCL5),CAPS-5 and MINI, followed by the other clinical outcome assessments, listed in Flow Chart 2. Blood draws are preferably done after clinical outcome assessments. The order of assessments and procedures is described in detail in section 6.2. For all further clinical visits, please refer to section 6.2.2 for details on order of assessments and procedures. *The following text was removed:* All baseline assessments must be performed prior to the first intake of the trial medication. Section 6.2: Order of Assessments at Screening Visit At the screening visit, all clinical examinations and assessment (Flow Chart 1) should be performed first except for the blood draws, followed by the clinical outcome measurements (Flow Chart 2) in the following order.

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	The following assessments 1. to 5. must be in the specific order: 1. Life Events Checklist (as part of PCL-5) 2. Extended Criterion A (as part of PCL-5) 3. PCL-5 4. CAPS-5 (in consideration of LEC and Extended Criterion A as part of PCL-5) 5. MINI Assessments/procedures 6. to 8. should preferably be performed in the below order: 6. OSU TBI-ID-SF 7. C-SSRS 8. CTQ *Was changed to:*

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	Order of Assessments and Procedures at Screening Visit At the screening visit, all clinical examinations and procedures (Flow Chart 1) should be performed first, followed by the clinical outcome assessments (Flow Chart 2) in the below order. Blood draws are preferably done after clinical outcome assessments but may be done as part of the clinical examination and procedures (Flow Chart 1) as per investigator's discretion. The following clinical outcome assessments 1. to 5. must be in the specific order: 1. Life Events Checklist (as part of PCL-5) 2. Extended Criterion A (as part of PCL-5) 3. PCL-5 4. CAPS-5 (in consideration of LEC and Extended Criterion A as part of PCL-5) 5. MINI Assessments/procedures 6. to 8. should preferably be performed in the below order: 6. OSU TBI-ID-SF 7. C-SSRS 8. CTQ *The following text was removed:* After the screening visit, the scales should be performed first (Flow Chart 2), followed by the other clinical examinations (Flow Chart 1). All scales should be completed in the order described in section 6.2.2 below. Section 6.2.2 Order of assessments All clinical outcome assessments to be performed per visit are listed in Flow Chart 2. PCL-5 should be performed first, followed by CAPS-5, CGI-S (total and domain) and CGI-C as applicable per visit schedule. For the remaining clinical outcome assessments, a

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	preferred order will be provided in the ISF. Clinical examinations (Flow Chart 1) should be performed after clinical outcome assessments (Flow Chart 2). ECG and blood pressure should always be measured before any blood samples are taken. Other assessments can be performed in any order. *Was changed to:* Order of Assessments and Procedures during Treatment period After the screening visit, is it up to investigator's discretion whether clinical outcome assessments (Flow Chart 2) or all clinical examinations and procedures (Flow Chart 1) are performed first, but for each individual patient, the entire order of all assesments and procedures (Flow Chart 1 & 2) should be kept consistent throughout the course of the trial, if at all possible. ECG and vital signs should always be measured before any blood samples are taken. Other clinical examinations and procedures can be performed in any order. All clinical outcome assessments should be completed in the order described below. Order of clinical outcome assessments All clinical outcome assessments to be performed per visit are listed in Flow Chart 2. • PCL-5 must be performed first, • followed by CAPS-5, • CGI-S (total and domain), • CGI-C • and C-SSRS, as applicable per visit schedule. Remaining patient reported outcome assessments as per Flow Chart 2 including optional speech recordings may be performed in the preferred order provided in the ISF (and as presented on the tablet) after IMP intake and before PK post-dose blood sampling.

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	The following text was removed: For the remaining clinical outcome assessments, a preferred order will be provided in the ISF. Clinical examinations (Flow Chart 1) should be performed after clinical outcome assessments (Flow Chart 2). ECG and blood pressure should always be measured before any blood samples are taken. Other assessments can be performed in any order.
Rationale for change	Operational relief and reduction of patient and site burden.
Sections to be changed	Section 1.2
Description of change	In vitro BI 1358894 induced CYP2B6, therefore comedications which are sensitive substrates of CYP2B6 are excluded. *Was changed to:* In vitro BI 1358894 induced CYP2B6, therefore a DDI study was performed with a CYP2B6 substrate. As no clinically relevant induction was seen, there are no restrictions on the use of comedications for sensitive substrates of CYP2B6.
Rationale for change	New information available from a clinical DDI study with bupropion (see IB v9)

Sections to be changed	Table 1.4.2: 1 section 4.2.2.1
Description of change	*The following text was removed:* Sensitive substrates of CYP2B6
Rationale for change	New information available from a clinical DDI study with bupropion (see IB v9)

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11.3 GLOBAL AMENDMENT 3

Date of amendment	18 JAN 2023
EudraCT number/EU number	2021-003154-23
BI Trial number	1402-0030
BI Investigational Medicinal Product(s)	BI 1358894
Title of protocol	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Global Amendment due to urgent safety reasons	N/A
Global Amendment	3
Section to be changed	Flow Chart 1 & 2 Footnote 1
Description of change	Eligibility of patients should be confirmed before Visit 1A is scheduled. Visit 1A must be scheduled at minimum 8 days (day -7) prior to V2 to allow for 7 days of EcMA assessments before randomization. The randomization visit V2 should be planned shortly (preferably within the same week) after completion of the 7 day EcMA baseline assessment period. *Was changed to:* Eligibility of patients is to be confirmed before Visit 1A is scheduled. Visit 1A must be scheduled at minimum 8 days prior to V2 to allow for 7 days of EcMA assessments before randomization. The randomization visit V2 should be planned shortly (preferably within the same week) after completion of the 7 day EcMA baseline assessment period.
Rationale for change	Clarification of process
Section to be changed	3.3.3
Description of change	Exclusion Criterion 9: Positive urine drug screen at the screening visit. Exception: stable

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<table>
<tr><td></td><td>opioid-treatment with medically prescribed opioids. Please refer to section 3.3 Retesting for retesting options within the screening period.

Was amended with:

Please refer to section 3.3 Retesting for retesting options within the screening period.</td></tr>
<tr><td>Rationale for change</td><td>Reference section added for clarification</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Section to be changed</td><td>5.2.1</td></tr>
<tr><td>Description of change</td><td>The following text has been added:
Categorization of index traumatic event

Investigators will be asked to categorize the index traumatic event as determined in CAPS-5 Criterion A at screeening visit according to the following categories:

A separate assessment with the patient is not requested. Investigators will review CAPS-5 Criterion A, Life Event Checklist and Extended Criterion A, as well as medical reocrds to decide on the categorization of the index traumatic event per their clinical judgement according to the criteria outlined above in Table 5.2.1: 1.
The index traumatic event, determined during the screening visit is to be referred to for all CAPS-5 and PCL-5 (incl. EcMA) assessments during the patient’s treatment period.

The categorization will be documented in the patient records and the eCRF.

Table 5.2.1:1 was added:

Table 5.2.1:1 Index traumatic event categorization criteria
<table>
<tr><th>Category</th><th>Response options</th></tr>
<tr><td>Type of trauma</td><td>Interpersonal
e.g. abuse, rape, hostage situation, assault, physical dispute, domestic violence</td></tr>
</table>
</td></tr>
</table>

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<table>
<tr><td></td><td>
<table>
<tr><td></td><td>General
e.g. natural catastrophe, accident, (terrorist) attack, war</td></tr>
<tr><td></td><td>Combat trauma (only for veterans/military-associated personnel) e.g. hand-to-hand combat</td></tr>
<tr><td>Frequency</td><td>Isolated</td></tr>
<tr><td></td><td>Multiple (≥2) unrelated</td></tr>
<tr><td></td><td>Recurrent/chronic (same or similar trauma experienced repeatedly)
e.g. sexual abuse in the same context, domestic violence</td></tr>
<tr><td>Exposure level</td><td>In-person “First-hand” including witnessed</td></tr>
<tr><td></td><td>Learned about it</td></tr>
</table>
</td></tr>
<tr><td>Rationale for change</td><td>Trauma type categorization was added</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Section to be changed</td><td>5.4.5.1 Assessment of Suicidality
6.2.1 Screening Visit and Screening Period</td></tr>
<tr><td>Description of change</td><td>Any lifetime history of suicidal ideation, self-injurious behavior, no suicidal intent’ or suicidal behavior at the screening visit that is not an exclusion criterion, should be recorded as baseline condition/medical history in the eCRF.

Was changed to:

Any lifetime history of suicidal ideation, self-injurious behavior, no suicidal intent’ or suicidal behavior at the screening visit that is not an exclusion criterion, should be considered as baseline condition/medical history.</td></tr>
<tr><td>Rationale for change</td><td>Administrative change to reduce site burden</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Section to be changed</td><td>6.2.1 Screening period and Eligibility Review</td></tr>
<tr><td>Description of change</td><td>Screening period
Eligibility of patients should be confirmed (i.e. all results received from the screening Visit) before Visit 1A is scheduled.</td></tr>
</table>

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	Was changed to: Eligibility of patients is to be confirmed (i.e. all results received from the screening Visit) before Visit 1A is scheduled. Eligibility Review For documentation purpose, [redacted] will send a Subject Eligibility Notification to the site (...) *Was changed to:* For eligibility documentation purpose, [redacted] will send a Subject Eligibility Notification to the site (...)
Rationale for change	Clarification and alignment with updated Flow Chart 1& 2 Footnote 1
Section to be changed	Throughout the document
Description of change	Typos and formatting corrected
Rationale for change	Administrative changes to increase consistency and quality.

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11.4 GLOBAL AMENDMENT 4

Date of amendment	09 JUN 2023
EudraCT number/EU number	2021-003154-23
BI Trial number	1402-0030
BI Investigational Medicinal Product(s)	BI 1358894
Title of protocol	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)
Global Amendment due to urgent safety reasons	N/A
Global Amendment	4
Section to be changed	3.3.3 Exclusion criteria
Description of change	18. 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. Was changed to: 18. 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.
Rationale for change	Clarification.
Section to be changed	5.4.3 Safety laboratory parameters
Description of change	All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the lab manual. *Was changed to:*

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	Analyses will be performed by a central laboratory, the respective reference ranges will be provided in the lab manual, except in cases where the ESR will be done locally in which case the ESR results will be recorded in the CRF.
Rationale for change	Process updated to implement local ESR assessment.
Section to be changed	Table 5.4.3:1 Safety laboratory tests
Description of change	Cross reference (*) added for Erythrocyte sedimentation rate (ESR) that ESR will be assessed either centrally or locally and the ESR Testing results are not intended to be used as Safety Parameter or for medical management decisions. For medical management decisions of Safety relevant inflammation parameter, the CRP test should be used.
Rationale for change	In this protocol, ESR testing is used solely for the collection of data for analysis purpose at the end of the trial, per FDA's recommendation. The ESR Testing results are not intended to be used as Safety Parameter or for medical management decisions. For medical management decisions of Safety relevant inflammation parameter, the CRP test should be used.
Section to be changed	Table 5.4.3:1 Safety laboratory tests
Description of change	Added Reflex testing (once technically implemented) for fT3 and fT4 if TSH > ULN
Rationale for change	Alignment with sister trial
Section to be changed	6.2.1 Screening Visit and Screening Period Demographics and Baseline Conditions
Description of change	Gender identity removed from the demographics information collection
Rationale for change	Gender identity information not collected in this trial.

APPROVAL / SIGNATURE PAGE

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Title: A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	09 Jun 2023 16:01 CEST
Author-Clinical Trial Leader		12 Jun 2023 13:03 CEST
Approval-Biostatistics		12 Jun 2023 14:57 CEST
Verification-Paper Signature Completion		12 Jun 2023 15:04 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed