Title Page

Protocol Title:

A Phase 2b, Randomized, Double Blind, Two Arm Study to Investigate the Effects of BNC210 Tablet Formulation Compared to Placebo in Adults with Post-Traumatic Stress Disorder (PTSD)

Protocol Number: BNC210.012

Amendment Number: 5

Compound: BNC210

Brief Title: A Phase 2b Study of BNC210 Tablet Formulation in Adults with Post-Traumatic Stress Disorder (PTSD)

Study Phase: 2b

Sponsor Name: Bionomics Limited

Legal Registered Address: 200 Greenhill Road, Eastwood, SA, 5063, AUSTRALIA

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Bionomics Limited

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Protocol Amendment Summary of Changes Table

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Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2b, Randomized, Double Blind, Two Arm Study to Investigate the Effects of BNC210 Tablet Formulation Compared to Placebo in Adults with Post-Traumatic Stress Disorder (PTSD)

Brief Title: A Phase 2b Study of BNC210 Tablet Formulation in Adults with Post-Traumatic Stress Disorder (PTSD)

Rationale:

This Phase 2b study will assess the potential effect of BNC210 in the treatment of Post-Traumatic Stress Disorder (PTSD), a condition which is classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a Trauma and Stressor-Related Disorder.

Previous human studies with BNC210 have established its safety and tolerability and demonstrated effects in a panic model in healthy volunteers. In a Phase 2a study in generalized anxiety disorder (GAD) patients (BNC210.006) using functional magnetic resonance imaging (fMRI), BNC210 reduced bilateral amygdala reactivity to fearful faces in an Emotional Faces Task and connectivity between the left amygdala and anterior cingulate cortex (ACC). In both anxiety and PTSD patients, significant arousal of the amygdala occurs in response to viewing fearful faces. Reduction of this response has been demonstrated by first line therapeutics for anxiety. In addition, anxious patients have a strong connection between the ACC and the amygdala. The reduction of connectivity in this circuit, and of amygdala hyperactivity, demonstrate BNC210 efficacy on two validated biomarkers of anxiety-induced brain changes. In the same study, BNC210 caused a significant reduction in defensive behavior (threat avoidance), demonstrating the positive effect of BNC210 on modulating hypothalamic pituitary adrenal axis behavior. These human data demonstrate proof-of-biology for BNC210 and potential for efficacy in the treatment of anxiety disorders and PTSD.

Furthermore, based on preclinical data demonstrating BNC210's positive effects on fear extinction, BNC210 is being studied in PTSD patients where deficits in fear extinction are thought to contribute to the pathology of this disorder.

BNC210 has previously been evaluated in patients with PTSD in a randomized, double-blind, placebo-controlled trial over 12 weeks (BNC210.007). BNC210 was administered orally as a suspension and was well tolerated with no pattern of drug-related adverse effects becoming apparent. However, improvements in the efficacy measurement of Clinician-Administered PTSD Scale for the DSM-5 (CAPS-5) Total Symptom Severity scores were not statistically different between BNC210 and placebo. Using population pharmacokinetics, exposure to BNC210 was modelled in the trial participants and was substantially less than that expected when compared to pharmacokinetic (PK) data from a healthy volunteer study with the same suspension formulation (BNC210.005). This may be attributed in part to the unsuitability of the suspension formulation for an out-patient study, in particular, its dependence on food for optimal absorption. A pharmacometric exposure-response relationship was modelled based on the population PK and

CAPS-5 scores from the study and suggests potential for BNC210 to have clinical efficacy in PTSD provided that adequate plasma exposures are achieved.

A spray-dried dispersion tablet formulation of BNC210 has since been developed and when evaluated in single and multiple dose PK studies in healthy adult volunteers has demonstrated that it can safely and reliably achieve the exposure predicted by the pharmacometric model for potential clinical efficacy in PTSD patients, without the dependence on food, and hence justifies further evaluation of BNC210 as a potential treatment for adults with PTSD.

Objectives and Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by CAPS-5 Total Symptom Severity Scores	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in CAPS-5 Total Symptom Severity Scores
Key Secondary	
• To assess the effects of BNC210 on Investigator-rated global functioning in participants with PTSD • To assess the effects of BNC210 on patient-reported social functioning in participants with PTSD	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Clinical Global Impression – Severity Scale (CGI-S) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Sheehan Disability Scale (SDS)
Secondary	
• To assess the effects of BNC210 on Investigator-rated symptom clusters of PTSD measured by Criterions B, C, D and E of the CAPS-5 symptom cluster scores • To evaluate the response rate and remission rate of BNC210 on Investigator-rated symptoms of PTSD measured by CAPS-5 Total Symptom Severity Scores • To assess the effects of BNC210 on Investigator-rated global functioning in participants with PTSD	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in symptom cluster severity scores for CAPS-5: ▪ Criterion B: Intrusion ▪ Criterion C: Avoidance ▪ Criterion D: Negative Alterations in Cognitions and Mood ▪ Criterion E: Arousal and Reactivity • Proportion of participants who achieve a) ≥30% improvement, or b) ≥50% improvement on CAPS-5 Total Symptom Severity Scores

• To assess the effects of BNC210 on Investigator-rated symptoms of anxiety and depression in participants with PTSD • To assess the effects of BNC210 on patient-reported symptoms of PTSD • To assess the effects of BNC210 on patient-reported global functioning and sleep quality in participants with PTSD • To assess the safety and tolerability of BNC210 in participants with PTSD	• Proportion of participants who achieve remission in PTSD symptoms with a score of ≤11 on CAPS-5 Total Symptom Severity Scores • The difference between BNC210 and placebo in endpoint scores (Week 12) in Clinical Global Impression – Improvement Scale (CGI-I) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Hamilton Anxiety Rating Scale (HAM-A) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Montgomery-Åsberg Depression Rating Scale (MADRS) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in PTSD Checklist for DSM-5 (PCL-5) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Patient Global Impression – Severity and Improvement Scales (PGI-S/I) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Insomnia Severity Index (ISI) • The following assessments will be used to monitor safety and tolerability from Baseline to Week 15: vital signs, electrocardiogram (ECG), hematology and blood chemistry, urinalysis, physical examination, and Columbia Suicide Severity Rating Scale (C-SSRS). Reporting of continuous Adverse Events (AE).

Overall Design:

This is a randomized, double-blind, placebo-controlled, parallel group, multi-center study with a 12 week, 2-arm treatment period. Participants will attend a Screening visit within 3 weeks before randomization to confirm eligibility. Approximately 200 participants who fulfill the inclusion criteria and none of the exclusion criteria will be randomized using a 1:1 ratio to receive either BNC210 900 mg twice daily (b.i.d.) or matched placebo. Participants will then complete 12 weeks of treatment with their allocated study intervention. Participants will complete study visits every 2 weeks during the treatment period and a Follow-up visit at Week 15 (i.e., 3 weeks after their last study intervention is administered). In the event that a participant cannot be physically present at the study site for a specified visit due to coronavirus disease 2019 (COVID-19) related restrictions, quarantine or positive test, or a natural disaster, a telehealth/remote visit may be completed instead if appropriate.

Brief Summary:

The purpose of this study is to assess the effects of BNC210 compared to placebo on PTSD s ymptom severity as measured by CAPS-5 Total Symptom Severity Scores.

Number of Participants:

Approximately 400 participants will be screened to achieve a total enrollment of approximately 200 randomly assigned participants.

Intervention Groups and Duration:

The total duration for each participant enrolled in the study is expected to be up to 18 weeks following the sequence below:

- Screening period: Up to 3 weeks
- Treatment period: 12 weeks
- Follow up visit: 3 weeks after the last study intervention is administered

The visit frequency during the treatment period will be every 2 weeks. Details of study assessments to be conducted at each visit are included in the Schedule of Activities (SoA).

Each participant will be randomized in a 1:1 ratio to receive b.i.d. doses of BNC210 900 mg OR placebo over the 12-week treatment period. Treatment assignments will be double-blinded.

Dose adjustments are not permitted during the study. Dose interruptions are only allowed for safety purposes in line with Section 7.1.4 of the study protocol. Discontinuation of study intervention for safety purposes is described in Section 7.1.

Data Monitoring/Other Committee:

An independent Safety Review Committee will be established to monitor participant safety throughout the study. The meetings will occur approximately every 3 months and will review all safety data including vital signs, ECG, pathology results, physical examinations, C-SSRS and continuous AE reporting.

1.2. Schema

Section not applicable.

1.3. Schedule of Activities (SoA)

Assessment[1]	**Screening** ≤-21 days	**Treatment Period**							**Week 15 / Follow-up** (±5 days)
		Baseline[2] (+3 days)	**Week 2**[3] (±3 days)	**Week 4** (±3 days)	**Week 6** (±3 days)	**Week 8** (±3 days)	**Week 10** (±3 days)	**Week 12 / Early Termination** (±3 days)	
Informed consent	X								
Inclusion and exclusion criteria[4]	X								
Demography	X								
Medical history including current & prior medications	X								
Structured Clinical Interview for DSM-5 disorders – Clinical Trials Version (SCID-5-CT) and Personality Disorders (SCID-5-PD) Borderline Personality Disorder section only	X								
Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) antibody screen	X								
Serum pregnancy test (if applicable)	X								
Urine pregnancy test (if applicable)		X						X	
Urine drug screen[5]	X	X		X		X		X	
12-lead electrocardiogram (ECG)[6]	X			X		X		X	
Vital signs[7]	X	X		X		X		X	X
Physical examination (including height only at Screening; weight only at Screening and Week 12 / Early Termination)[8]	X	X		X		X		X	X
Clinical labs (hematology, biochemistry, urinalysis)	X	X		X	X[9]	X	X[9]	X	X

[1] See Section 8 for guidance on the order of assessments to be completed at each visit
[2] All baseline assessments to be completed pre-dose
[3] Visit can be performed at the study site, or remotely via phone/video call
[4] Recheck eligibility and clinical status before randomization
[5] Screening assessment to be performed by the central laboratory. Subsequent assessments to be performed locally by study site using urine dip stick test
[6] ECGs to be completed in triplicate with an approximate 2-minute break between tests. Participants must be resting in a semi-supine or supine position for at least 5 minutes prior to performing the ECG. The same ECG machine should be used for all recordings from an individual participant, where possible. Single triplicate repeat during Screening allowed in the event of a clinically significant abnormality including prolonged Fridericia corrected QT interval (QTcF).
[7] Blood pressure and heart rate will be measured in a sitting position after resting for 5 minutes
[8] Full physical examination at Screening & W12 / Early Termination. Abbreviated physical examination at Baseline, Week 4, Week 8, and Follow-up
[9] Blood biochemistry testing only for Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Bilirubin (direct and total)

Assessment[1]	**Screening** ≤-21 days	**Treatment Period**							**Week 15 / Follow-up** (±5 days)
		Baseline[2] (+3 days)	**Week 2**[3] (±3 days)	**Week 4** (±3 days)	**Week 6** (±3 days)	**Week 8** (±3 days)	**Week 10** (±3 days)	**Week 12 / Early Termination** (±3 days)	
Columbia Suicide Severity Rating Scale (C-SSRS)[10]	X	X		X		X		X	X
Life Events Checklist for DSM-5 (LEC-5)[11]	X								
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[12]	X	X		X		X		X	
Montgomery-Åsberg Depression Rating Scale (MADRS)	X	X		X		X		X	
Randomization[13]		X							
Hamilton Anxiety Rating Scale (HAM-A)		X		X		X		X	
Clinical Global Impressions Severity and Improvement scales (CGI-S/I)[14]		X		X		X		X	
Patient Global Impression – Severity and Improvement scales (PGI-S/I)[14]		X		X		X		X	
PTSD Checklist (PCL-5)		X						X	
Sheehan Disability Scale (SDS)		X		X		X		X	
Insomnia Severity Index (ISI)		X		X		X		X	
Study Intervention dispensing		X[15]		X		X			
Concomitant medications recording		X	X	X		X		X	X
Adverse Event (AE) recording[16]			X	X		X		X	X
Blood sample collection for concentration of BNC210				X		X		X	

[10] "Screening C-SSRS" to be used at Screening. "C-SSRS Since Last Visit" to be used at every other visit
[11] To be completed prior to CAPS-5 assessment at Screening
[12] Past month version to be used at every visit and should be audio recorded at every visit using the provided iPhone.
[13] Once eligibility has been confirmed
[14] Improvement scale at Week 12 only
[15] Participants to administer one PM dose on day of completing Baseline assessments and randomization
[16] See Appendix 3 for definitions

2. Introduction

Bionomics Limited is developing BNC210 for the treatment of anxiety, and trauma- and stressor-related, disorders. BNC210 is a negative allosteric modulator of the alpha-7 nicotinic acetylcholine receptor (alpha-7 nAChR), which represents a novel target for the treatment of these disorders. BNC210 is a new chemical entity which has exhibited potent anxiolytic activity in a range of animal models at low doses with a wide therapeutic window. There is an absence of the adverse effects particularly associated with standard-of-care treatments for acute disorders, such as benzodiazepines, and the antidepressants used in first line therapy for chronic disorders.

2.1. Study Rationale

This Phase 2b study will assess the potential effect of BNC210 in the treatment of PTSD, a condition which is classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a Trauma and Stressor-Related Disorder.

Previous human studies with BNC210 have established its safety and tolerability and demonstrated effects in a panic model in healthy volunteers. In a Phase 2a study in generalized anxiety disorder (GAD) patients (BNC210.006) using functional magnetic resonance imaging (fMRI), BNC210 reduced bilateral amygdala reactivity to fearful faces in an Emotional Faces Task and connectivity between the left amygdala and anterior cingulate cortex (ACC). In both anxiety and PTSD patients, significant arousal of the amygdala occurs in response to viewing fearful faces. Reduction of this response has been demonstrated by first line therapeutics for anxiety. In addition, anxious patients have a strong connection between the ACC and the amygdala. The reduction of connectivity in this circuit, and of amygdala hyperactivity, demonstrate BNC210 efficacy on two validated biomarkers of anxiety-induced brain changes. In the same study, BNC210 caused a significant reduction in defensive behavior (threat avoidance), demonstrating the positive effect of BNC210 on modulating hypothalamic pituitary adrenal axis behavior. These human data demonstrate proof-of-biology for BNC210 and potential for efficacy in the treatment of anxiety disorders and PTSD.

Furthermore, based on preclinical data demonstrating BNC210's positive effects on fear extinction, BNC210 is being studied in PTSD patients where deficits in fear extinction are thought to contribute to the pathology of this disorder.

BNC210 has previously been evaluated in patients with PTSD in a randomized, double-blind, placebo-controlled trial over 12 weeks (BNC210.007). BNC210 was administered orally as a suspension and was well tolerated with no pattern of drug-related adverse effects becoming apparent. However, improvements in the efficacy measurement of Clinician-Administered PTSD Scale for the DSM-5 (CAPS-5) Total Symptom Severity scores were not statistically different between BNC210 and placebo. Using population pharmacokinetics, exposure to BNC210 was modelled in the trial participants and was substantially less than that expected when compared to pharmacokinetic (PK) data from a healthy volunteer study with the same suspension formulation (BNC210.005). This may be attributed in part to the unsuitability of the suspension formulation for an out-patient study, in particular, its dependence on food for optimal absorption. A pharmacometric exposure-response relationship was modelled based on the population PK and

CAPS-5 scores from the study and suggests potential for BNC210 to have clinical efficacy in PTSD provided that adequate plasma exposures are achieved.

A spray-dried dispersion tablet formulation of BNC210 has since been developed and when evaluated in single and multiple dose PK studies in healthy adult volunteers has demonstrated that it can safely and reliably achieve the exposure predicted by the pharmacometric model for potential clinical efficacy in PTSD patients, without the dependence on food, and hence justifies further evaluation of BNC210 as a potential treatment for adults with PTSD.

2.2. Background

2.2.1. Disease Background

PTSD may result from exposure to a traumatic event during which an individual experienced, witnessed, or was confronted with the actual threat of death or serious injury, or the threat to physical integrity to self or others. PTSD symptoms can be divided into four clusters: (1) persistent re-experiencing of the trauma, (2) avoidance behavior associated with feelings of detachment and emotional numbness, (3) negative alterations in cognitions and mood, and (4) symptoms of increased autonomic arousal.

The lifetime prevalence of PTSD in the general population is approximately 8% making PTSD the fifth most prevalent mental disorder in the United States (Krystal et al., 2017). People with PTSD continue to experience adverse effects of their exposure to trauma for years afterwards, when the trauma is no longer present, and this inability to return to the pre-trauma state differentiates PTSD from other stressor-related disorders.

Treatment is based on early interventions, psychotherapy and pharmacotherapy. Only two pharmacological agents, the antidepressants Paxil® (paroxetine) and Zoloft® (sertraline), belonging to the selective serotonin reuptake inhibitors class (SSRIs), are Food and Drug Administration (FDA)-approved for the treatment of PTSD, but they have not been shown to ameliorate the full range of PTSD symptoms, and complete remission of symptoms is rare. It has been estimated that no more than 20 to 30% of people with PTSD are effectively treated, and a high percentage of those who begin PTSD treatment eventually drop out (Alexander, 2012; VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, 2017). The use of benzodiazepines are contraindicated for PTSD based on their unproven efficacy and their risks for abuse and dependence in a population at risk of co-morbid substance use disorder.

There is a need for improved therapeutics for PTSD with greater clinical benefit, fewer side effects and a faster onset of action, something that might be achieved by targeting a different mechanism of action.

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2.3. Benefit/Risk Assessment

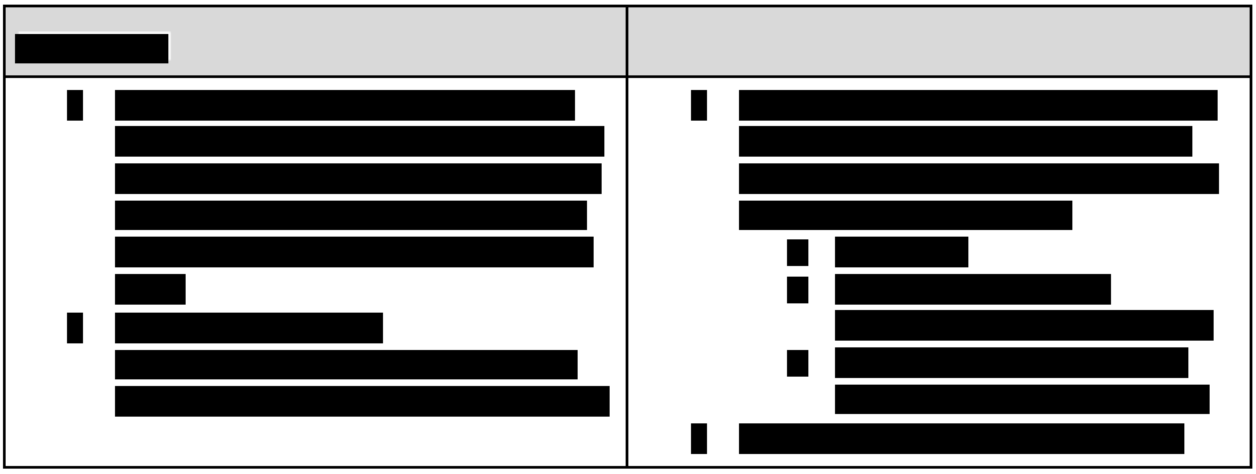
More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNC210 may be found in the Investigator's Brochure, and the participant Informed Consent Form (ICF).

No potential significant risks have been identified in the nonclinical or clinical studies of BNC210. At this stage in development, the benefit-risk profile of BNC210 appears favorable.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by CAPS-5 Total Symptom Severity Scores	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in CAPS-5 Total Symptom Severity Scores
Key Secondary	
• To assess the effects of BNC210 on Investigator-rated global functioning in participants with PTSD • To assess the effects of BNC210 on patient-reported social functioning in participants with PTSD	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Clinical Global Impression – Severity Scale (CGI-S) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Sheehan Disability Scale (SDS)
Secondary	
• To assess the effects of BNC210 on Investigator-rated symptom clusters of PTSD measured by Criterions B, C, D and E of the CAPS-5 symptom cluster scores • To evaluate the response rate and remission rate of BNC210 on Investigator-rated symptoms of PTSD measured by CAPS-5 Total Symptom Severity Scores • To assess the effects of BNC210 on Investigator-rated global functioning in participants with PTSD • To assess the effects of BNC210 on Investigator-rated symptoms of anxiety and depression in participants with PTSD	• The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in symptom cluster severity scores for CAPS-5: ▪ Criterion B: Intrusion ▪ Criterion C: Avoidance ▪ Criterion D: Negative Alterations in Cognitions and Mood ▪ Criterion E: Arousal and Reactivity • Proportion of participants who achieve a) ≥30% improvement, or b) ≥50% improvement on CAPS-5 Total Symptom Severity Scores • Proportion of participants who achieve remission in PTSD symptoms with a score of ≤11 on CAPS-5 Total Symptom Severity Scores

• To assess the effects of BNC210 on patient-reported symptoms of PTSD • To assess the effects of BNC210 on patient-reported global functioning and sleep quality in participants with PTSD • To assess the safety and tolerability of BNC210 in participants with PTSD	• The difference between BNC210 and placebo in endpoint scores (Week 12) in Clinical Global Impression – Improvement Scale (CGI-I) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Hamilton Anxiety Rating Scale (HAM-A) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Montgomery-Åsberg Depression Rating Scale (MADRS) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in PTSD Checklist for DSM-5 (PCL-5) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Patient Global Impression – Severity and Improvement Scales (PGI-S/I) • The difference between BNC210 and placebo in change from Baseline to endpoint (Week 12) in Insomnia Severity Index (ISI) • The following assessments will be used to monitor safety and tolerability from Baseline to Week 15: vital signs, electrocardiogram (ECG), hematology and blood chemistry, urinalysis, physical examination, and Columbia Suicide Severity Rating Scale (C-SSRS). Reporting of continuous Adverse Events (AE).



Primary estimand

The primary question of interest is: What is the difference between BNC210 and placebo in the mean change from Baseline to Week 12 in the CAPS-5 Total Symptom Severity Score among patients with PTSD when using randomized treatment.

In the course of the 12-week randomized treatment period, participants may be exposed to possible known or unknown inter-current events that could possibly impact the estimand, such as treatment discontinuation due to a specific adverse effect or perhaps a lack of effect. The "Treatment Policy Strategy" will be adopted for handling all known or unknown inter-current events in this study. To this end, the Intent-To-Treat (ITT) principle will serve as the analytical basis for interpreting the estimand. In other words, the difference in BNC210 and placebo in the mean change from Baseline to Week 12 in the CAPS-5 Total Symptom Severity Score will be evaluated regardless of the occurrence of any such inter-current event.

4. Study Design

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel group, multi-center study with a 1 2 week, 2-arm treatment period. Participants will attend a Screening visit within 3 weeks before randomization to confirm eligibility. Approximately 200 participants who fulfill the inclusion criteria and none of the exclusion criteria will be randomized using a 1:1 ratio to receive either BNC210 900 mg b.i.d. or matched placebo. Participants will then complete 12 weeks of treatment with their allocated study intervention. Participants will complete study visits every 2 weeks during the treatment period and a Follow-up visit at Week 15 (i.e., 3 weeks after their last study intervention is administered). In the event that a participant cannot be physically present at the study site for a specified visit due to coronavirus disease 2019 (COVID-19) related restrictions, quarantine or positive test, or a natural disaster, a telehealth/remote visit may be completed instead if appropriate (see Section 8).

Details are included in the Schedule of Activities (SoA).

4.2. Scientific Rationale for Study Design

This study evaluates as its primary endpoint, the effects of BNC210 compared to placebo on PTSD symptom severity using the CAPS-5. CAPS-5 is the universally accepted scale for diagnosis of PTSD as well as for assessment of PTSD symptom severity. It can monitor worsening or improvement in a participant's symptoms by applying a well-defined scoring system according to specific criteria. It is therefore an appropriate tool for measuring the primary endpoint of this study and clinically meaningful changes in PTSD symptom severity.

The primary and secondary endpoints in this study will utilize clinician-administered scales as well as patient-reported scales. A double blind, placebo-controlled study design has been chosen as a well-established and appropriate study design to minimize the potential for bias in study assessments or in reporting of AEs. Clinic staff and participants are blinded to treatment assignments to ensure objective reporting. In addition, participants will be randomized 1:1 to receive either BNC210 or placebo to ensure there are no order effects and to further minimize bias.

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4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Investigators will be responsible for evaluating potential participants against the study eligibility criteria during the Screening period. At the initial Screening visit, each participant will participate in the informed consent process and sign and date the ICF before any procedures specified in this protocol are performed.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 75 years of age inclusive, at the time of signing informed consent

Type of Participant and Disease Characteristics

2. Current diagnosis of PTSD as defined by the CAPS-5, with a CAPS-5 Total Symptom S everity Score of ≥30 at Screening and Baseline and no >25% decrease in Score from Screening to Baseline
3. The index trauma event must have occurred in adulthood, i.e., when the participant was ≥18 years of age
4. In the opinion of the Investigator the participant has a high probability for adherence with and completion of the study
5. Ability to swallow tablets
6. Fluent in English and able to understand and comply with written and verbal protocol-related requirements

Sex and Contraceptive/Barrier Requirements

7. Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 60 days after the last dose of study intervention:
        - Refrain from donating sperm PLUS, either:
            - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

              OR

            - Must agree to use a male condom with female partner using an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 4 Contraceptive and Barrier Requirements, when

having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b. Female participants are eligible to participate if they are not pregnant or breastfeeding and the following conditions applies:

- Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 Contraception and Barrier Guidance.

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 Contraception and Barrier Guidance during the study intervention period and for at least 60 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative serum pregnancy test at Screening and a negative urine test at Baseline (within 24 hours before the first dose of study intervention).

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. A period of less than 6 months since the index trauma event occurred
2. Current and ongoing exposure to the trauma that caused the PTSD
3. Complex PTSD, defined as a condition that may develop following exposure to an event or series of events of an extreme and prolonged or repetitive nature, which the participant experienced as extremely threatening or horrific and from which escape was difficult or impossible (e.g., torture, slavery, genocide campaigns, prolonged domestic violence, repeated childhood sexual or physical abuse). If affect dysregulation and interpersonal dysfunction are primary over other core PTSD symptoms, in the Investigator's opinion, participants should be excluded.
4. Severe depression as measured by a score of ≥ 35 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at Screening

5. Bipolar, Borderline Personality and other psychotic disorders as identified at Screening using the Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version (SCID-5-CT) and Personality Disorders (SCID-5-PD).
6. History of moderate to severe traumatic brain injury
7. History of seizure disorders, uncontrolled sleep apnoea or severe neurologic disease
8. Any moderate or severe substance use disorder according to DSM-5 in the 12 months prior to Screening
9. Increased risk of suicide, defined as:
    - Any suicide attempt in the 12 months prior to Screening disclosed by the participant using the Columbia Suicide Severity Rating Scale (C-SSRS)
    - Any suicidal ideation with intent (yes to item 4 and/or 5) or suicidal behavior in the past 12 months, as captured at Screening using the C-SSRS
    - A score > 4 on item 10 of the MADRS at Screening.
10. History or presence of impaired renal function, as indicated by clinically significant abnormal creatinine, blood urea nitrogen (BUN) or plasma urea, or moderate to severe renal dysfunction as defined by the Cockcroft-Gault equation (estimated glomerular filtration rate (eGFR) <50 mL/min)
11. Alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase (ALP) > 2.0 x upper limit of normal (ULN)
12. Total bilirubin > 1.5 x ULN (isolated bilirubin > 1.5 x ULN is acceptable if total bilirubin is fractionated and direct bilirubin < 35%)
13. Current or chronic history of liver disease. This includes but is not limited to hepatitis virus infections, drug- or alcohol-related liver disease, nonalcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the Investigator
14. Any clinically significant abnormalities in laboratory test results (biochemistry, hematology or urinalysis) as assessed by the Investigator
15. Blood Pressure systolic >160 mmHg or diastolic >90 mmHg. Two repeat measures are allowed at the discretion of the Investigator
16. Fridericia-corrected QT interval (QTcF) >450 msec for males and QTcF >470 msec for females, or QTc >480 msec in participants with bundle branch block, as measured by ECG at Screening
17. Any clinically significant ECG abnormality as determined by the Investigator at Screening
18. A family history of congenital long QT syndrome, Brugada syndrome or unexplained sudden cardiac death

Prior/Concomitant Therapy

19. The use of antidepressant medications within 30 days (fluoxetine within 90 days) of Screening. The use of alprazolam, flunitrazepam and chronic daily use of other benzodiazepines within 90 days of Screening. The use of other psychotropic active medications within 5 days of Screening.
20. Failed more than three trials of antidepressant medication(s) prescribed for the treatment of PTSD. Each trial must have lasted at least 6 weeks to be considered a failed attempt. A trial that was terminated due to intolerability or side effects does not constitute a failed attempt.
21. Receiving concurrent trauma-based psychotherapy such as Cognitive Behavior Therapy, Prolonged Exposure Therapy, Eye Movement Desensitization and Reprocessing Therapy. Participants may continue to receive supportive counseling that has been in place for a minimum of three months prior to Screening.
22. The use of cytochrome P450 3A4 inducers within 30 days of Screening
23. The use of moderate-strong cytochrome P450 3A4 inhibitors within 2 weeks of Screening. This includes but is not limited to, grapefruit or grapefruit-containing products.

Prior/Concurrent Clinical Study Experience

24. Current enrolment OR past participation in another investigational study in which an investigational intervention (e.g., drug, vaccine, invasive device) was administered within 30 days before signing of consent in this clinical study.
25. Previously participated in Bionomics' Phase 2 PTSD study BNC210.007 (RESTORE study)

Diagnostic Assessments

26. Positive result for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) at Screening
27. Positive urine test for an illicit substance, excluding cannabis, at Screening or Baseline

Other Exclusions

28. History of allergies, allergic reactions or hypersensitivity to BNC210 or excipients
29. A member of the United States military currently serving on active duty
30. In the process of litigating for compensation for a psychiatric disorder. Participants who are in the process of applying for medical or Veterans Affairs benefits and/or those who have settled a disability claim prior to enrollment in the trial are eligible.
31. Participants that, in the opinion of the Investigator, are not suitable to participate in the study due to clinically significant findings from medical history that could interfere with the objectives of the study or put the participant at risk or any other reason the Investigator deems applicable

5.3. Lifestyle Considerations

There are no specific lifestyle considerations or restrictions applicable to this study outside of the criteria detailed in Sections 5.1, 5.2 and 6.8. However, over the course of the study, participants should be counseled on the importance of maintaining consistent behaviors. This includes limiting any change to alcohol, cannabis or tobacco use, dietary intake, and sleep patterns when compared to Baseline. Participants will also be encouraged to attend study visits at the same time of day to avoid possible diurnal variation in measurement responses.

5.4. Screen Failures

Participants who sign and date the ICF but who fail to meet the inclusion and exclusion criteria are considered screen failures. Reason(s) for screen failure must be documented by the Investigator and provided to the Sponsor in a timely fashion.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

In the event that a participant fails a clinical laboratory or ECG screening assessment, that assessment can be repeated once only during the screening period. The repeat assessment must be completed within the allowed screening period (21 days + 3 days of Baseline) for eligibility purposes. If the repeat assessment cannot be completed within the screening period, the participant must be re-screened in entirety. Participants who fail any other screening assessment must be screen-failed.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, if deemed appropriate by the Investigator and with prior approval from the Sponsor/Medical Monitor. However, individuals who do not meet the criterion for CAPS-5 Total Symptom Severity Score in line with inclusion criterion #2, will not be eligible for rescreening. Rescreened participants should be reconsented and assigned a new participant number (Subject ID) for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Randomization or Administration of Study Intervention

Section not applicable

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Detailed information related to the composition of the study interventions to be used in this study can be found in the study Investigational Product Manual and the Investigator's Brochure.

Participants will administer study intervention b.i.d. for 12 weeks. [redacted]

6.1. Study Intervention(s) Administered

Table 1. Study Intervention(s) Administered

Intervention Label	BNC210 900 mg	Placebo
Intervention Name	BNC210	Placebo
Intervention Description	BNC210 900 mg b.i.d. for 12 weeks	Placebo b.i.d. for 12 weeks
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength	225 mg	N/A
[redacted]	[redacted]	[redacted]
Route of Administration	Oral	Oral
Use	Experimental	Placebo Comparator
Investigational Medicinal Product (IMP)	IMP	IMP
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor

Packaging and Labeling	4[redacted]	[redacted]

Table 2. Study Arm(s)

Arm Title	BNC210	Placebo
Arm Type	Experimental	Placebo Comparator
Associated Intervention Labels	BNC210 900 mg	Placebo

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

4. Further guidance and information on the handling, storage, accountability, dispensing and for the final disposition of unused study interventions are provided in the Investigational Product Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

IWRS	After a participant signs the ICF at Screening, site personnel will register the participant in the interactive web response system (IWRS). Upon successful completion of the Screening module the system will assign the participant a unique participant number (Subject ID). Randomization will be performed as double blind, Central Randomization. Upon successful completion of randomization in the IWRS the system will determine the correct study intervention kit type to dispense. Once a participant is randomized to a treatment arm, the randomization will remain documented as such. The system will never reuse the same randomization number. The system will then determine which study intervention kit of that type is available for dispensing and inform the study site to dispense that kit. The kit assigned will correspond to the correct treatment for the participant. Study intervention will be dispensed at the study visits as summarized in the SoA.

Blind break (IWRS)	This is a double-blind study in which participants/Investigators/raters, etc. are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor and/or Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason that for the unblinding must be recorded.

[redacted]

6.5. Dose Modification

Dose reductions or increases will not be allowed in this study.

6.6. Continued Access to Study Intervention After the End of the Study

Participants will not have access to study interventions after completion of their participation in the study. Participants should be directed to receive standard of care treatments as directed by the Investigator or their primary care physician.

6.7. Treatment of Overdose

For this study, any dose of BNC210/placebo greater than 1,800 mg within a 24-hour time period will be considered an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until they have resolved or stabilized.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of Screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Use of any investigational drug, vaccine or invasive device within 30 days prior to Screening and at any point during the study is prohibited.

Inducers of cytochrome P450 3A4 should not be used within 30 days of Screening and their use is prohibited during the study. This includes, but is not limited to: carbamazepine, phenytoin, oxcarbazepine, barbiturates, phenobarbital, butalbital, St. John's wort, rifampicin, rifabutin, efavirenz, nevirapine, pioglitazone, troglitazone, corticosteroids by the systemic route (see Appendix 6 for a more extensive list).

Moderate to strong inhibitors of cytochrome P450 3A4 should not be used within two weeks of Screening and their use is prohibited during the study. These include grapefruit juice, verapamil, diltiazem, fluvoxamine, fluconazole and itraconazole and HIV antivirals (refer to the following website for a more extensive list https://drug-interactions.medicine.iu.edu/MainTable.aspx).

Participants that are under consideration for the study and are being treated with an antidepressant medication, must have discontinued the medication for at least 30 days prior to Screening (as per exclusion criterion #19) and be titrated off their medication in accordance with current prescribing guidelines. Participants must also have discontinued the use of alprazolam, flunitrazepam and chronic daily use of other benzodiazepines for at least 90 days prior to Screening. The use of other psychotropic medications must have been discontinued for at least 5 days prior to Screening. The withdrawal of these medications is at the discretion of the participant in consultation with their primary physician and falls outside the scope of this study protocol.

The use of antidepressants and psychotropic medications are also prohibited during all stages of the study. This includes, but is not limited to, mood stabilizers, stimulants, antipsychotics, anticonvulsant drugs (including gabapentinoids), hypnotics, benzodiazepines, methylphenidate, doxazosin, prazosin, clonidine, first generation sedating H1 antihistamines, quetiapine, eszopiclone, zolpidem extended-release and acetylcholinesterase inhibitors.

The use of non-prescription medications (including herbal medications) will be discouraged during the course of the study. Prescription medications should be limited and avoided if possible, but will be allowed where clinically indicated, e.g., for treatment of AEs or pre-existing medical conditions documented at Screening.

Ongoing long-term supportive counseling is allowed only if the participant commenced therapy > 3 months prior to Screening and is willing to continue therapy at the same frequency throughout the study.

If a medication or treatment is administered that is in breach of these restrictions, the Medical Monitor must be promptly notified in order to assess the participant's suitability for continued study participation.

6.8.1. Rescue Medications for Insomnia

Only the use of certain nonbenzodiazepine sleep inducers (e.g., zolpidem immediate-release [up to 10 mg at bedtime], zaleplon [up to 20 mg at bedtime]), melatonin, or ramelteon for sleep are allowed. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The process for discontinuation of specific sites or the study as a whole are detailed in Appendix 1.

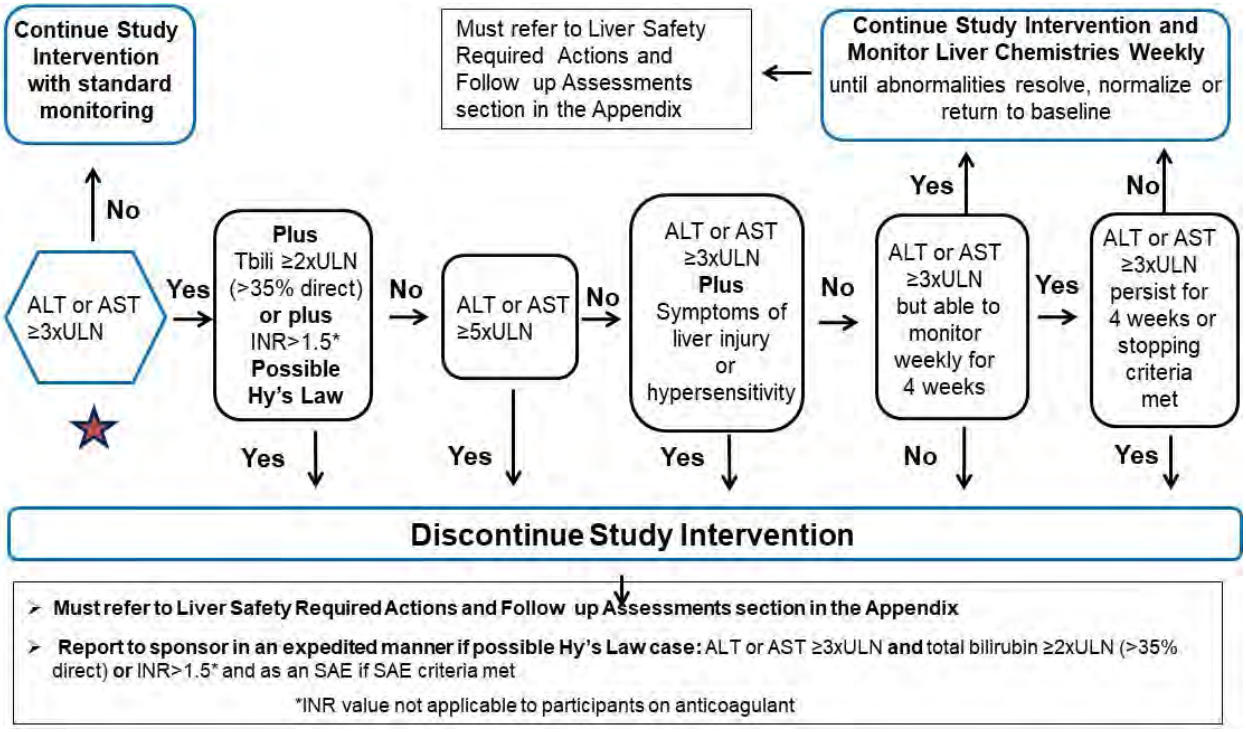
7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA for evaluations that need to be completed at the time of discontinuation of study intervention (Early Termination visit).

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant. Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin, ULN = upper limit of normal.

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 5.

7.1.2. QTc Stopping Criteria

A participant who meets the bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention.

- QTc > 500 msec OR change from Baseline of QTc > 60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Suicidal Behavior Stopping Criteria

A participant who meets any of the bulleted criteria below will be withdrawn from study intervention.

- Any new suicidal behavior since Screening, as disclosed by the participant during administration of the C-SSRS
- Any suicidal ideation with intent (yes to item 4 and/or 5) since Screening, as disclosed by the participant during administration of the C-SSRS
- A score > 4 on item 10 of the MADRS

7.1.4. Temporary Discontinuation

Dose interruptions will be allowed following the onset of AEs if deemed appropriate by the Investigator. However, should an interruption of 3 or more days occur, approval from the Medical Monitor and Sponsor must be obtained prior to re-commencing study intervention. Dose reductions will not be allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an Early Termination visit should be conducted, as shown in the SoA.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

[redacted]

- As a guide, diagnostic and efficacy assessment scales such as CAPS-5, PCL-5, SCID-5-CT and SCID-PD (Screening only) and LEC-5 (Screening only) should be administered first, followed by depression, anxiety and suicidality scales (i.e., MADRS, HAM-A, C-SSRS). Other efficacy scales such as CGI-S/I, PGI-S/I, SDS, and ISI should then be administered prior to remaining safety and diagnostic assessments such as clinical labs, physical examinations and ECGs. This order of procedures should be followed throughout the study where possible.
- At the Week 2 visit, assessment of AEs and recording of concomitant medications should be performed, as well as a general assessment of how the participant is managing their dosing with the study intervention. The Week 2 visit can be performed either at the study site or via phone/video call with the study participant.
- At the Week 6 and Week 10 visits, the only assessments required are routine safety blood laboratory testing for ALT, AST, ALP, and bilirubin (direct and total). Participants can have this testing performed at the study site for analysis at the central laboratory or testing can be performed at a local laboratory. There is no requirement for the participant to attend the study site to have this testing performed if a suitable alternative arrangement has been agreed with the study site (e.g., home health visit).
- All Investigator-rated assessments and Patient Recorded Outcomes (PROs) will be completed using paper assessment scales.
- Where possible, study assessments will be made available for remote administration in cases where restrictions, as a consequence of COVID-19 or other natural disasters, prevent participants from attending clinic visits. PROs will be provided to participants as paper versions to be completed at the appropriate time point and returned to the study site upon completion. Laboratory assessments, inclusive of samples for concentration of

BNC210 as well as physical examinations and vital signs assessments, may be collected per site COVID-19 protocols or as an unscheduled assessment upon lifting of any restrictions. Any procedures that are missed or cannot be performed within the allowed study visit window due these restrictions being in place will not be considered protocol deviations.

- Where restrictions due to COVID-19 or other natural disasters, prevent participants from performing study visits in person, a participant or verified representative of the participant, may attend the study site to return/obtain study intervention. If Sponsor approved procedures are in place at a study site, study intervention may also be delivered to a participant's home.
- Analyte results that could unblind the study will not be reported to study sites or other blinded personnel.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, should not exceed 110 mL.
- On days where study visits occur, participants should continue to take their morning dose of study intervention at their scheduled time, even if prior to attending the study site for the scheduled visit. If the scheduled time of dosing coincides with a study visit, participants can take their dose of study intervention during the study visit.
- Dispensing of study intervention should occur last, after all study tests and assessments have been completed for a specified study visit. All visits should be scheduled to occur at approximately the same time of day.
- Participants may attend an unscheduled visit at any time. All assessments completed during an unscheduled visit must be captured in the eCRF. This includes the results of all pathology tests scheduled by the Investigator.
- Visits scheduled due to increased safety monitoring in line with Section 7.1 must be captured as an unscheduled visit.
- A visit with a participant's primary physician (i.e., not a study Investigator) is not considered an unscheduled visit. Similarly, hospital admissions due to SAEs are also not considered unscheduled visits. Assessments completed by external institutions should not be entered into the eCRF.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.1.1. Clinician-Administered PTSD Scale for the DSM-5 (CAPS-5)

The CAPS-5 is a 30-item structured interview used to diagnose PTSD and assess PTSD symptoms over the past month. Information about the frequency and intensity of each item is combined into a severity rating, and the CAPS-5 total symptom severity score is calculated by adding the severity scores for the 20 PTSD symptoms in the DSM-5 (National Centre for PTSD). The CAPS-5 interview should be audio recorded using the provided iPhone at every study visit.

8.1.2. PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is a 20-item self-report assessment of the 20 DSM-5 symptoms of PTSD (National Centre for PTSD). Each symptom is rated on a scale from 0 (not at all) to 4 (extremely).

8.1.3. Clinical Global Impression Scales – Severity and Improvement (CGI-S/I)

The CGI-S is a rating scale designed to assess the severity of the participant's symptoms, and the CGI-I is designed to assess the change in the participant's condition since the initial assessment. Severity is rated on the CGI-S from 1 (normal, not at all ill) to 7 (among the most extremely ill of participants). The changes in the participant's condition are rated on the CGI-I from 1 (very much improved) to 7 (very much worse).

8.1.4. Patient Global Impression Scales – Severity and Improvement (PGI-S/I)

The PGI-S is a self-rating scale designed to assess the severity of the participant's symptoms, and the PGI-I is designed to assess the change in the participant's condition since the initial assessment. Severity is rated on the CGI-S from 1 (normal) to 4 (severe). The changes in the participant's condition are rated on the CGI-I from 1 (very much better) to 7 (very much worse).

8.1.5. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is an interview questionnaire that measures severity of anxiety symptoms based on 14 parameters, including anxious mood, tension, fears, insomnia, somatic complaints and behavior during the interview (Hamilton, 1959). Each parameter is rated on a scale of 0 (not present) to 4 (very severe).

8.1.6. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item self-diagnostic and clinician-rated questionnaire to measure the presence and severity of depressive episodes and includes the following symptoms: 1) apparent sadness; 2) reported sadness; 3) inner tension; 4) reduced sleep; 5) reduced appetite; 6) concentration difficulties; 7) lassitude; 8) inability to feel; 9) pessimistic thoughts; and 10) suicidal thoughts (Williams and Kobak, 2008). The rater must decide whether the rating lies on defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

8.1.7. Sheehan Disability Scale (SDS)

The SDS is a rating scale designed to measure impairment in three domains: work/school, social life, and family life/home responsibilities. Each item is rated on a scale of 0 (not at all) to 10 (extremely), for a total score of 0 to 30.

8.1.8. Insomnia Severity Index (ISI)

The ISI is a brief self-report instrument measuring both nocturnal and diurnal symptoms of insomnia (Morin 1993). The ISI comprises seven items, each scored from 0 to 4, assessing the perceived severity of difficulties initiating sleep, staying asleep, and early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. The scores from each of the 7 questions are added up to get a total score of 0 to 28.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, skin and lymphatics, eyes, ears, nose, throat, cardiovascular system, respiratory system, abdomen/gastrointestinal system, musculoskeletal and neurological systems. Other body systems may also be examined as required. Height and weight will also be measured and recorded at the time points specific in the SoA.
- An abbreviated physical examination will include, at a minimum, assessments of the eyes, ears, nose, throat, cardiovascular system, respiratory system, and abdomen/gastrointestinal system. Other body systems may also be examined as required.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Clinically significant changes from first dose of study intervention will be recorded as AEs.

8.2.2. Vital Signs

- Body temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a seated position for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3. Electrocardiograms

- Triplicate 12-lead ECGs will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At each time point, 3 individual ECG tracings should be obtained in succession, approximately 2 minutes apart.
- One repeat is allowed for screening purposes if abnormal findings are observed. The repeat must also be completed in triplicate.
- Participants must be resting in a semi-supine or supine position for at least 5 minutes prior to obtaining ECG.
- The same ECG machine should be used for all recordings from an individual participant, where possible.

- ECGs will be read by the Investigator or designated physician at the unit.
- QTcF values will be derived from the data available and the average QTcF will be used when assessing eligibility and treatment withdrawal.

For safety monitoring purposes, the Investigator or designee must review, sign and date all ECG tracings. Paper copies will be kept at the study center with the participant's clinical file as part of the permanent record. The ECG intervals and interpretation will be recorded on the appropriate eCRF.

Paper ECG recordings should be photocopied and maintained as a permanent source document. The Sponsor reserves the right to request copies of paper ECG recordings for independent cardiology review.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor/Sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
    - If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose interruption), then the results must be recorded.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

BNC210 is considered to be a Central Nervous System (CNS) active intervention. Patients with PTSD may occasionally develop suicidal ideation or behavior.

Participants being treated with study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Participants who experience

signs of suicidal ideation or behavior, should undergo a risk assessment. All factors contributing to suicidal ideation or behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with study intervention should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study Investigator.

Baseline assessment of suicidal ideation and behavior/ intervention emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS.

The C-SSRS is a suicidal ideation rating scale designed to identify behaviors that may be indicative of a patient's intent to commit suicide. The scale is administered via a semi-structured interview and measures both passive and active suicidal ideation and the intensity and duration of the ideation. Both suicidal and non-suicidal self-injurious behavior is also assessed.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

The definitions of unsolicited and solicited AEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs/SAEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the Follow-up visit at the time points specified in the SoA.

All AEs will be collected from the start of intervention until the Follow-up visit at the time points specified in the SoA. Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB) and Investigators.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants w ill be collected after the start of study intervention and until 3 weeks after the last dose of study intervention is administered.
- If a pregnancy is reported in a female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner), the Investigator will record pregnancy information on the appropriate form and submit it promptly, within 24 hours of learning of the pregnancy, signing and dating the Pregnancy Data Collection Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF. Pregnancy reporting contact information can be found in Appendix 3, Section 10.3.4.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

8.4. Pharmacokinetics

- Whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of BNC210 as specified in the SoA. Samples will be used to evaluate the pharmacokinetics of BNC210.
- As the study is double-blind, samples will be collected from all participants but only those allocated to the BNC210 treatment arm will have their samples analyzed at the appropriate time.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in the study specific Laboratory Manual.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Efficacy Hypotheses

The primary objective of the current study is to evaluate the efficacy of BNC210 on Investigator-rated total symptom severity of PTSD in adult participants with PTSD.

- The null hypothesis for the primary efficacy endpoint of equality of BNC210 and placebo is:

  H_{01}: Mean change in CAPS-5 Total Symptom Severity Scores between Baseline and Week 12 in the two treatment groups are equal.

The key secondary objectives of the current study and their respective null hypotheses of the equality of BNC210 and placebo are:

- To evaluate the efficacy of BNC210 on Investigator-rated global functioning in adult participants with PTSD.

  H_{02}: Mean change in CGI-S between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on patient-reported social functioning in adult participants with PTSD.
  - H_{03}: Mean change in SDS between Baseline and Week 12 in the two treatment groups are equal.

Other secondary objectives of the current study and their respective null hypotheses of the equality of BNC210 and placebo are:

- To evaluate the efficacy of BNC210 on Investigator-rated symptom clusters of PTSD in adult participants with PTSD.

  H_{04}: Mean change in CAPS-5 Intrusion Severity Scores (Cluster B) between Baseline and Week 12 in the two treatment groups are equal.

  H_{05}: Mean change in CAPS-5 Avoidance Severity Scores (Cluster C) between Baseline and Week 12 in the two treatment groups are equal.

  H_{06}: Mean change in CAPS-5 Negative Alterations in Cognitions and Mood Severity Scores (Cluster D) between Baseline and Week 12 in the two treatment groups are equal.

  H_{07}: Mean change in CAPS-5 Arousal and Reactivity Severity Scores (Cluster E) between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the response rate and remission rate of BNC210 on Investigator-rated total symptom severity of PTSD in adult participants with PTSD.

  H_{08}: Proportion of participants who achieve a ≥30% improvement in CAPS-5 Total Symptom Severity Scores between Baseline and Week 12 in the two treatment groups are equal.

  H_{09}: Proportion of participants who achieve a ≥50% improvement in CAPS-5 Total Symptom Severity Scores between Baseline and Week 12 in the two treatment groups are equal.

H_{10}: Proportion of participants who achieve a score ≤11 on the CAPS-5 Total Symptom Severity Score between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on Investigator-rated global functioning in adult participants with PTSD.

  H_{11}: Mean scores of the CGI-I at Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on Investigator-rated symptoms of anxiety in adult participants with PTSD.

  H_{12}: Mean change in HAM-A Total Scores between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on Investigator-rated symptoms of depression in adult participants with PTSD.

  H_{13}: Mean change in MADRS Total Scores between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on patient-reported symptoms of PTSD in adult participants with PTSD.

  H_{14}: Mean change in PCL-5 Total Scores between Baseline and Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on patient-reported global functioning in adult participants with PTSD.

  H_{15}: Mean change in PGI-S between Baseline and Week 12 in the two treatment groups are equal.

  H_{16}: Mean scores of the PGI-I at Week 12 in the two treatment groups are equal.

- To evaluate the efficacy of BNC210 on patient-reported sleep quality in adult participants with PTSD.

  H_{17}: Mean change in ISI between Baseline and Week 12 in the two treatment groups are equal.

9.1.1. Multiplicity Adjustment

Because this is a Phase 2 study, the level of significance will be set at 0.05 for primary and secondary endpoints with no adjustment for multiple comparisons.

9.2. Analysis Sets

The following analysis populations are planned for this study:

- Safety Population (SAF): The safety population includes all participants who receive any amount of the study intervention. The safety population will be used for the analysis of the safety endpoints. Participants will be analyzed by actual treatment received.
- Intent-to-Treat Population (ITT): The ITT population includes all randomized participants. Participants will be analyzed by randomized treatments.
- Modified Intent-to-Treat Population (mITT): The mITT population includes all participants in the ITT population who receive any amount of the study intervention and have at least one post-baseline efficacy assessment. Participants will be analyzed by randomized treatment.
- Per-Protocol Population (PP): The per-protocol population will include participants from the mITT population who have no major protocol deviations. Before data are released for statistical analysis, a blinded review of all data will be performed in conjunction with the Sponsor to identify protocol deviations that may potentially affect the results. At this time, it will be determined if participants and/or data should be excluded from the PP population. The list of participants or observations to be excluded from the PP population will be provided in the Clinical Study Report. Participants will be analyzed by randomized treatments.
- PK Population (PK): The PK population will include all participants from the safety population who have a valid concentration measurement.

9.3. Statistical Analyses

9.3.1. General Considerations

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be written prior to the study database being locked.

Unless otherwise indicated, all testing of statistical significance will be two-sided and a difference resulting in a p value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of participants in each category.

9.3.2. Study Participant and Demographics

9.3.2.1. Disposition and Withdrawals

The number of participants randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of participants in each analysis population will be reported.

Completers will be recorded as Week 12 completers and Week 15 completers. Week 12 completers will be defined as all participants who complete the randomized treatment period, while Week 15 completers will be defined as those who complete the randomized treatment period as well as the Follow-up visit.

9.3.2.2. Protocol Deviations

Protocol deviations will be identified and classified as important or non-important for statistical analysis purposes before unblinding and will be summarized or listed as appropriate. Important protocol deviations that might affect efficacy data will be used to exclude participants from the per protocol analysis.

9.3.2.3. Demographics and Other Baseline Characteristics

The following analyses will be conducted for all analysis populations:

- Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the study intervention in accordance with local regulatory requirements.
- Baseline participant characteristics will include medical history including confirmation of PTSD diagnosis, index trauma event and time since index trauma event. Baseline evaluation of the CAPS-5 Total Severity Score, PCL-5 total score, CGI-S score, PGI-S score, MADRS total score, HAM-A total score, SDS total score, and ISI total score will also be reported.
- Prior and concomitant medications will be summarized by treatment group, by the number and percentage of participants taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

9.3.3. Primary and Key Secondary Endpoint/Estimand Analyses

The primary efficacy endpoint for the current study will be the change in CAPS-5 Total Sy mptom Severity Scores from Baseline to Week 12 for participants receiving BNC210 compared to participants receiving placebo. The analysis of the primary efficacy endpoint will be evaluated for the mITT population according to the planned treatment.

Taking into consideration the potential for missing data, the primary and key secondary endpoints will be assessed for the mITT population according to the planned treatment with a Mixed Model for Repeated Measures (MMRM) with multiple imputation (MI). Each model will include fixed effects for treatment, interaction between treatment and visit, center, and covariate for Baseline score. MMRM with no MI will be used as a supportive analysis for the primary and key secondary endpoints for the mITT and PP populations according to the planned treatment.

Additionally, a figure with the Least Squares (LS) means ± Standard Error (SE) of change from Baseline in the CAPS-5 Total Symptom Severity Score in the mITT population will be presented by treatment group and visit.

9.3.4. Supportive Analyses for Primary and Key Secondary Efficacy Endpoints

Supportive analyses will be performed on the primary and key secondary efficacy endpoints to demonstrate the robustness of the conclusions. Supportive analyses will be conducted using MMRM with no MI on the mITT and PP populations.

Summary statistics on the endpoints by treatment group and visit, including the end of treatment visit (Week 12), will also be presented.

9.3.5. Multiple Imputation Methods

Although the assumption of missing at random (MAR) is often reasonable in clinical trials, the possibility of missing not at random (MNAR) data cannot be ruled out. Therefore, analysis valid under MNAR will be performed as the primary analysis. Both MNAR- and MAR-based analyses using MI methods will be the basis upon which sensitivity of the analysis to missing data are assessed.

Any participants who withdraws or is discontinued from the study or who misses a scheduled visit or assessments up through Week 12 will have their primary and key secondary efficacy missing data analyzed as imputed using MI techniques. This analysis will be presented as the primary analysis.

Multiple imputation is a simulation-based approach where missing values are replaced using an appropriate stochastic model given the observed data and covariates, creating multiple completed data sets. These completed datasets are then analyzed using standard analysis methods (MMRM for this study), and the different parameter estimates across the datasets are then combined to produce unique point estimates, standard errors, and confidence intervals taking into account the uncertainty of the imputation process.

In most randomized clinical trials that collect data over time, the great majority of missing data follow a monotone pattern. That is, once a participant has a missing data for some visit, data will be missing for all subsequent visits. Typically, there is also a small amount of non-monotone missing data (i.e., some participants have missing values for intermediate visits, but have non-missing data at subsequent visits).

The following MI analysis model, based on the MNAR approach, will be used as the primary analysis.

<u>MI with Placebo-Based Imputation</u>

A placebo-based (jump to control) multiple imputation for missing primary and key secondary endpoints will be carried out for participants who withdraw from the study or have missing data at a scheduled visit through Week 12, as indicated previously. The imputation has three broad components; i) the multiple imputation process for the placebo data; ii) the multiple imputation process for the BNC210 data; and iii) the analysis model that will be used to draw inference regarding the primary causal estimands along with the method for combining the results across the multiply-imputed datasets. Specific steps for this imputation will be outlined in the SAP.

9.3.6. Other Secondary Endpoints Analyses

All other secondary efficacy endpoints will be conducted with MMRM with no MI on the mITT population only. Summary statistics on the endpoints by treatment group and visit, including the end of treatment visit (Week 12), will also be presented.

For the binary outcomes of the proportion of participants who achieve a) ≥30% improvement; b) ≥50% improvement; c) remission of PTSD symptoms, the number and proportion will be summarized by treatment group and visit. A Pearson's Chi-squared test or Fisher's exact test will be used to calculate the p-value for the difference between treatment groups.

9.3.7. Safety Analyses

Safety analyses will be conducted using data from the safety population. Safety variables include C-SSRS, AEs, physical examination findings, ECGs, vital signs, and clinical laboratory test results (hematology, biochemistry, urinalysis). No formal inferential analyses will be conducted for safety variables unless otherwise noted.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1 or higher.

TEAEs are defined as AEs that are newly occurring or worsening after the first dose of study intervention. The incidence of TEAEs will be summarized by treatment group, by system organ class (SOC) and preferred term (PT), by severity, and by relationship to study intervention. Serious TEAEs and TEAEs leading to study termination will also be summarized by SOC, PT, and treatment group.

[redacted]

9.4. Population Pharmacokinetic (PK) Analysis

Systemic concentrations of BNC210 will be determined at Weeks 4, 8, and 12. Plasma concentration data will be presented nominally. A data dependent population PK analysis will be outlined under a separate analytical plan.

9.5. Interim Analysis

No interim analysis is planned for this study.

9.6. Sample Size Determination

A sample size of approximately 200 participants (100 participants per treatment arm) is calculated to provide ≥80% power to detect a 6-point difference between BNC210 and placebo groups in change from Baseline to Week 12 for the CAPS-5 Total Symptom Severity Scores,

with an expected SD of 12.5. These assumptions are based on data from the previous BNC210 Phase 2 PTSD study and pharmacometric analysis. In a two-sample t-test using a two-sided significance level of 0.05 and power of 80%, 70 participants per treatment group would be needed to demonstrate a 6-point difference between treatment groups, and assuming 30% drop-out over the 12-week treatment period leads to a planned sample size of 100 per group.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- The protocol cannot be altered or changed except through a formal protocol amendment, which requires written approval from the Sponsor. Any amendments to the protocol will require IRB approval and health authority approval where applicable and must be signed by the Investigator before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study center.
- The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Informed consent will be obtained before the participant can participate in the study.
- The Investigator or his/her representative must also explain to the participant that they are completely free to refuse to enter the study or to withdraw from it at any time.
- Participants who are rescreened are required to sign a new ICF.
- Participants who are rescreened will not need to repeat routine clinical laboratory assessments or ECGs if an eligible result from the prior screening period has been obtained within 21 (+3 days) of randomization into the study.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research.

10.1.4. Data Protection

- Participants will be assigned a unique identifier as part of their study participation. Any participant records or datasets that are transferred to the Sponsor will contain the identifier and information collected as part of the study only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.
- The study data entry and study management systems used by clinical sites and by the Sponsor/designee will be secured and password protected.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Independent Safety Review

An independent Safety Review Committee will be established to monitor participant safety throughout the study. The meetings will occur approximately every 3 months and will review all safety data including vital signs, ECG, pathology results, physical examinations, C-SSRS and continuous AE reporting.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the study specific eCRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the study specific Risk Log to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

The publication policy is outlined in the study site specific Clinical Trial Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory at the timepoints described in the SoA.
- Local laboratory results may only be required in the event that the central laboratory results are not available in time to support urgent safety or study intervention administration decisions, following consultation with the Medical Monitor. If a local sample is required, it is important that the sample for central analysis is also obtained where possible. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 3. Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count		RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Transaminase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Transaminase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein
	Glucose	Calcium	Alkaline phosphatase[2]	
Routine Urinalysis	• Specific gravity, urobilinogen, pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase, color, appearance, occult blood • Microscopic examination (if blood or protein is abnormal)			

Pregnancy testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • All study-required laboratory tests will be performed by a central laboratory, with the exception of: o Urine drug test and pregnancy test at Baseline, Week 4, Week 8 and Week 12 o ALT, AST, ALP, and bilirubin (direct and total) at Week 6 and Week 10

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Chemistry Stopping Criteria and Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments. All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) which may indicate severe liver injury (possible Hy's Law), must be reported to the Medical Monitor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

2. If alkaline phosphatase is elevated, consider fractionating.

3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by a participant will be collected during interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other Important Medical Event:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously.

- At each visit, the participant will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as
    - "How are you feeling?"
    - "Have you experienced any issues since your last visit?"
    - "Have you taken any new medications since your last visit?"
- Any clinically relevant observations made during the visit will also be considered AEs.

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number (Subject ID), will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Specifically related to AEs associated with clinical laboratory abnormalities (i.e., chemistry, hematology, urinalysis), the Investigator will assign severity following the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (published 27 November 2017).

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- The Investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will use clinical judgment to determine the relationship following the below definitions:

- ***Not Related:*** This category applies to an AE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of study intervention and/or a causal relationship is considered biologically implausible.

- ***Unlikely Related:*** This category applies to an AE that could reasonably be considered caused by something else, and where there is no known or expected response pattern to the suspected study intervention.

- ***Possibly Related:*** This category applies to an AE that follows a reasonable temporal sequence from administration of the study intervention and that follows a known or expected response pattern to the suspected study intervention, but that could readily have been produced by a number of other factors

- ***Probably Related:*** This category applies to an AE that follows a reasonable temporal sequence from administration of the study intervention; that follows a known response pattern to the suspected study intervention; that is confirmed by an improvement on stopping the study intervention; and that cannot be reasonably explained by the participant's clinical state.
- ***Definitely Related:*** This category applies to an AE that is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology, if available and appropriate.
- New or updated information will be recorded using a new copy of the SAE Report Form and contain the site and Investigator information, participant information, SAE and SAE onset date as minimum reporting information, as well as all new information and all data changed. It should be made clear whether the new information is in addition to or meant to replace the previously reported information.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting

The Investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE Report Form to [redacted] by one of the following methods:

[redacted]

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the Investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and Investigator)
- Participant number (Subject ID)
- Participant's year of birth
- Participant's gender
- Date of first dose of study intervention
- Date of last dose of study intervention prior to SAE onset, if applicable
- SAE term

- Date of occurrence of the event
- Severity of the SAE term
- A brief description of the event, treatment, outcome to date, and any actions taken with study intervention
- The seriousness criteria(on) that were met
- Investigator causality assessment
- Concomitant medications being taken within 30 days of onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Whether and when the Investigator was unblinded as to the participant's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the [redacted] via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information; initial report, adverse event, date of occurrence, study participant identifier, and site number. This will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the [redacted] using a follow-up request form or via email communication.

The Investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, IRB, Principal and Coordinating Investigators, Study Investigators, and institutions. Each Investigator is obligated to learn about the reporting requirements for Investigators in his/her country. The study monitor may be able to assist with this.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement and FSH levels within the institutional postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT or AST-absolute</td><td>ALT or AST ≥ 5 x ULN</td></tr>
<tr><td>ALT or AST Increase</td><td>ALT or AST ≥ 3 x ULN persists for ≥ 4 weeks</td></tr>
<tr><td>Bilirubin[1,2]</td><td>ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN (> 35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT or AST ≥ 3 x ULN and international normalized ratio (INR) > 1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT or AST ≥ 3 x ULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT or AST ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Suggested Actions, Monitoring, and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention.
• Report the event to the Medical Monitor within 24 hours.
• Complete a Serious Adverse Event Report Form <u>if the event</u> also met the criteria for an SAE.[2]
• Perform follow-up assessments as described in the Follow Up Assessment column.
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline.
MONITORING:
<u>If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5:</u></td><td>• Viral hepatitis serology[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥ 2 x ULN.
• Obtain complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity.
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter</td></tr>
</table>

• Repeat liver chemistry tests (include ALT, AST, ALP, total bilirubin, and INR) and perform liver event follow up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A hepatology consultation is recommended. **If ALT or AST ≥ 3 x ULN AND total bilirubin < 2 x ULN and INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline. • **Do not restart/rechallenge** participant with study intervention.	medications) on the concomitant medications eCRF. • Record alcohol use If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5 obtain the following in addition to the assessments listed above: • Antinuclear antibody, antismooth muscle antibody, Type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG), or gamma globulins • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected drug induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • Report all assessments conducted to the Medical Monitor as they become available

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN (> 35% direct bilirubin) or ALT or AST > 3 x ULN and INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis).** The INR stated threshold value will not apply to participants receiving anticoagulants.

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

10.6. Appendix 6: Abbreviations

Abbreviation	Definition
AE	Adverse Event
ACC	Anterior Cingulate Cortex
ADL	Activities of Daily Living
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC_{90}	Exposure at 90% of maximal effect
b.i.d.	Twice Daily
BUN	Blood Urea Nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CAPS-5	Clinician-Administered PTSD Scale for the DSM-5
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
fMRI	Functional Magnetic Resonance Imaging
FSH	Follicle Stimulating Hormone
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAM-A	Hamilton Anxiety Rating Scale
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy

ICH	International Conference on Harmonization
ICF	Informed Consent Form
INR	International Normalization Ratio
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intent-To-treat
IWRS	Interactive Web Response System
LEC-5	Life Events Checklist for DSM-5.
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	Missing at Random
MI	Multiple Imputation
mITT	Modified Intent-To-Treat
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
NOAEL	No Observed Adverse Effect Level
PCL-5	Standard PTSD Checklist for DSM-5
PEER	Pre-Enrollment Eligibility Review
PGI-I	Patient Global Impressions – Improvement
PGI-S	Patient Global Impressions – Severity
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient Reported Outcome
PT	Preferred Term
PTSD	Post-Traumatic Stress Disorder
QTcF	Fridericia-corrected QT Interval
QTL	Quality Tolerance Limit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID-5-CT	Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version
SCID-5-PD	Structured Clinical Interview for DSM-5 Disorders – Personality Disorders
SD	Standard Deviation

SDS	Sheehan Disability Scale
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential

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