CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled Phase II Study of BNC210 in Adults with Post-Traumatic Stress Disorder (PTSD)

Protocol Number: BNC210.007

Investigational Product: BNC210

[redacted]

Sponsor: BIONOMICS LIMITED
31 Dalgleish Street
Thebarton SA 5031
AUSTRALIA

Date and version: Version 4.0, 30 May 2018

Confidentiality Statement

PROTOCOL SYNOPSIS

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Phase II Study of BNC210 in Adults with Post-Traumatic Stress Disorder (PTSD).
Rationale for the Study:	BNC210 acts through negative allosteric modulation (NAM) of the alpha 7 nicotinic acetylcholine receptor and is under development for the treatment of anxiety, and trauma and stressor-related disorders. [redacted]. This study will assess the safety and efficacy of BNC210 in subjects with a diagnosis of PTSD, a stress and trauma related disorder with limited pharmacotherapy treatment options.
Objectives:	**Primary Objectives** • To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (CAPS-5) scores. **Secondary Objectives** • To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by each of the four symptom clusters (Intrusion; Avoidance; Negative Alterations in Cognition and Mood; Arousal and Reactivity) of the CAPS-5. • To assess the effects of BNC210 on other psychiatric outcomes in subjects with PTSD including anxiety and depression. • To assess the effects of BNC210 on global functioning and Quality of Life in subjects with PTSD. • To assess the effects of BNC210 on patient-reported outcomes in subjects with PTSD. • To assess the safety and tolerability of BNC210 in subjects with PTSD. [redacted]
Endpoints	**Primary Efficacy Endpoint** The effect of BNC210 compared to placebo on baseline to endpoint change in CAPS-5 total symptom severity scores after 12 weeks of treatment. **Secondary Efficacy Endpoints** The effect of BNC210 on Investigator-rated and self-reported PTSD

	symptom severity, depression, anxiety, cognitive function, global function, quality of life, social functioning, and sleep quality after 12 weeks of treatment, when compared to placebo using the following instruments: • Symptom cluster severity score for CAPS-5 Criterion B: Intrusion. • Symptom cluster severity score for CAPS-5 Criterion C: Avoidance. • Symptom cluster severity score for CAPS-5 Criterion D: Negative Alterations in Cognition and Mood. • Symptom cluster severity score for CAPS-5 Criterion E: Arousal and Reactivity. • PTSD Checklist for DSM-5 (PCL-5). • Montgomery- Åsberg Depression Rating Scale (MADRS). • Hamilton Anxiety Rating Scale (HAM-A). • CANTAB Cognitive Assessment. • Clinical Global Impressions – Severity and Improvement Scale (CGI-S/CGI-I). • Patient Global Impression – Severity and Improvement Scale (PGI-S/PGI - I). • Assessment of Quality of Life (AQoL-8D). • Sheehan Disability Scale (SDS). • Pittsburgh Sleep Quality Index (PSQI). **Safety Analyses** Suicidal ideation, self-injurious non-suicidal and suicidal behavior will be monitored from Baseline to week 15 using the Columbia Suicide Severity Rating Scale (C-SSRS). Other safety parameters (e.g. vital sign measurements, electrocardiogram (ECG) readings, physical examination, and laboratory tests) will be monitored from Baseline to week 15 and described using descriptive statistics by treatment group when applicable, and by visit otherwise. All adverse events (AEs) will be listed and summarized by treatment group, organ class and preferred term with: • The number of subjects with at least one AE and number of AEs for each treatment group and overall. • Analyses taking into account intensity and drug relationship to treatment could also be carried out. Description of potentially clinically significant values will be performed for vital signs, ECG parameters, blood chemistry and hematology parameters. All these parameters will be listed by subject and measurement time. The data outside of normal ranges will be flagged.

	[redacted]
Criteria for evaluation:	**Efficacy:** Response to treatment will be assessed using the CAPS-5, PCL-5, CGI-I/CGI-S, HAM-A, MADRS, CANTAB Cognitive Assessment, SDS, PSQI, PGI-I/PGI-S and AQoL-8D. **Safety:** Vital signs, ECG, hematology and blood chemistry, urinalysis, physical examinations, C-SSRS and continuous AE reporting. **Adherence:** This will be assessed via blood sampling for determination of BNC210 plasma concentrations and counts of returned medication bottles. [redacted] **Nicotine intake:** The average daily number of tobacco products smoked and the use of nicotine replacement products will be recorded.
Overall Design:	This is a randomized, double-blind, parallel, placebo-controlled, multi-centre study with a 12-week, 4-arm treatment phase (placebo and 150mg bid, 300mg bid and 600mg bid BNC210). Subjects will attend a Screening visit within 3 weeks of randomization to confirm eligibility. Approximately 192 subjects who fulfill the inclusion criteria and none of the exclusion criteria will be randomized on Day 1 using a 1:1:1:1 ratio. Subjects will then complete 12 weeks of their allocated treatment. The Investigational Product or Placebo will be

	taken twice daily (bid) with food. Subjects will return to the clinical site at weekly or 2-weekly intervals to receive study medication, complete safety assessments and questionnaires. Subjects are then requested to attend a post-study visit at 15 weeks (i.e., 3 weeks after the last treatment). Subjects will undergo assessments for efficacy and safety during the study as per the schedule of assessments.
Study Duration:	Screening evaluation within 3 weeks of randomization Treatment phase: 12 weeks of treatment, bid (weekly or fortnightly visits to the clinic). Post-study visit: 3 weeks after the last treatment (i.e. 15 weeks after the first treatment). Recruitment timeframe estimate is 2 years.
Study Centers:	Approximately 20-30 centers located in Australia and the United States.
Number of Planned Subjects:	A total of 192 male and female patients with PTSD will be enrolled in the study at a 1:1:1:1 ratio (about 48 subjects per treatment arm). [redacted]
Investigational Product:	BNC210 (150 mg, 300 mg, and 600 mg) administered bid with food from a prefilled single-use bottle for 12 weeks (BNC210 will be suspended in a vehicle solution).
Reference Therapy:	Placebo administered bid from a prefilled single-use bottle for 12 weeks in a vehicle solution matching the Investigational Product.
Inclusion Criteria:	Subjects must satisfy all of the following inclusion criteria before being allowed to participate in the study: 1. Signed and dated informed consent 2. Male or female between 18 and 70 years of age, inclusive. 3. Diagnosed with current PTSD as defined by the CAPS-5 for DSM-5. 4. Currently not using any psychiatric medications except for: • No more than one selective serotonin reuptake inhibitor (SSRI) (fluvoxamine is excluded) or serotonin noradrenaline reuptake inhibitor (SNRI) within the licensed prescribing dose range. Subjects must have been on a stable dose for at least 3 months prior and through Screening, with the intent to remain on the same dose through to Week 15. • As needed (PRN) use of benzodiazepines (BZD) at a frequency not exceeding 2 days per week in the 3 months prior to Screening. The total dose must not exceed 30 mg/day in diazepam equivalents 5. Subjects not currently receiving psychotherapy except long term supportive counseling or subjects that have received intensive regular psychotherapy for a minimum of three months prior to Screening. 6. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine test at Day 1. Females not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least

	12 months prior to Screening and confirmed by follicle-stimulating hormone (FSH) levels in menopausal range at Screening). Sterilized male patients must be at least 1 year post-vasectomy to be considered of non-child bearing potential. Acceptable forms of sterilization include bilateral tubal ligation, bilateral oophorectomy, and hysterectomy for women or vasectomy for men. Females and males of childbearing potential must agree to use two effective methods of contraception (double barrier contraception or hormonal contraceptive along with a barrier contraceptive) during the study and for 16 weeks following last study treatment. Contraception that is deemed acceptable in this study includes the following: • Condoms. • Hormonal (includes oral, injected, intrauterine, transdermal, or implanted). Females must be using hormonal contraceptives for at least 3 months prior to randomization and not change the contraceptive during the trial. • Rhythm methods will not be considered as an effective method of birth control, however, abstinence may be allowed based on the opinion of the Investigator. o Requirement for contraception can be waived in certain circumstances (i.e. same sex relationships) if approved by the Sponsor. o Males must agree to not donate sperm for at least 16 weeks following last study treatment. 7. In the opinion of the Investigator the participant has a high probability for adherence with and completion of the study, and willing and able to withdraw and refrain from specific therapies. 8. Fluent in English and able to understand and comply with written and verbal protocol-related requirements.
Exclusion Criteria:	If any of the following exclusion criteria apply, the subject will not be allowed to participate in the study: 1. Current and ongoing exposure to the trauma that caused the PTSD. 2. 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. 3. The use of psychiatric medications within 2 weeks of Screening except for SSRIs, SNRIs or limited PRN BZD use as per inclusion criterion 4. Restricted psychiatric medications include (but are not limited to) antidepressants not allowed by inclusion criterion 4, antianxiety drugs (except limited BZD use per inclusion criterion 4), mood stabilizers, stimulants, antipsychotics, hypnotics and acetylcholinesterase inhibitors. 4. History of significant traumatic brain injury. 5. Depression as measured by Montgomery-Äsberg depression scale

	(MADRS) rating > 23. 6. Bipolar and psychotic disorders as identified at Screening using the MINI International Neuropsychiatric Interview (V7.0) (M.I.N.I). 7. A score ≥ 7 on the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) at Screening. 8. History of seizure disorders, uncontrolled sleep apnoea or severe neurologic disease. 9. Increased risk of suicide, defined as: • Any previous suicide attempt disclosed by the participant at Screening 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 year, as captured at Screening using the C-SSRS. • A score > 4 on item 10 of the MADRS at Screening. 10. The use of cytochrome P450 3A4 inducers within 30 days of Screening. 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, grapefruit or grapefruit-containing products. 11. The use of alprazolam or flunitrazepam within 3 months of Screening. 12. 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). 13. Liver disease or liver injury as indicated by abnormal liver function tests (LFTs), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or serum bilirubin (>2x upper limit of normal [ULN]) or history of hepatic cirrhosis. 14. Any clinically significant abnormalities in laboratory test results at Screening (biochemistry, hematology or urinalysis) as assessed by an Investigator. 15. Fridericia-corrected QT interval (QTcF) >460 msec for males and QTcF >480 msec for females as measure by ECG at Screening. 16. Any clinically significant ECG abnormality as determined by the Investigator at Screening. 17. A family history of congenital long QT syndrome, Brugada syndrome or unexplained sudden cardiac death. 18. Positive result for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) at Screening. 19. Any moderate to severe substance use disorder (any type) in the 12 months prior to Screening as identified by the DSM-5 using the M.I.N.I (V7.0).

	20. Participation in an investigational study within 30 days of Screening. 21. Current Australian serving Defense personnel or any member of the US military currently serving on active duty. 22. Participants involved with ongoing insurance or workplace claims that in the opinion of the Investigator are likely to have an impact on the mental health, presentation or capacity of the patient to engage in the study. 23. Females who are pregnant, nursing, or intend to become pregnant during the study or within 16 weeks of last dose of Investigational Product, or any males who plan to father/conceive a child within 16 weeks of last dose of Investigational Product. 24. Blood or plasma donation or significant blood loss within 60 days of Day 1. 25. Known to have poor peripheral venous access. 26. Subjects 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 subject at risk or any other reason the investigator deems applicable. 27. History of allergies, allergic reactions or hypersensitivity to BNC210 or excipients. 28. Blood Pressure (BP) systolic >160 mmHg or diastolic >90 mmHg. Allow two repeat measures at the discretion of the Investigator.

Table 1: Schedule of Assessments

Visit	Screening	Baseline[1]	V1	V2	V3	V4	V5	V6	V7 / Early Term	Post-study
Study Days: Investigational Product to be administered pre-visit except at Baseline	≤-21	Day 1 *(+ 2 days)*	Week 1 Day 8 *(± 2 days)*	Week 2 Day15 *(± 2 days)*	Week 4 Day 29 *(± 2 days)*	Week 6 Day 43 *(± 2 days)*	Week 8 Day 57 *(± 2 days)*	Week 10 Day 71 *(± 2 days)*	Week 12 Day 85 *(± 2 days)*	Week 15 Day 106 *(± 5 days)*
Informed consent	X									
Register subject in Interactive Web Response System (IWRS)	X									
Medical history including current & prior medications	X									
[redacted]	X									
Physical examination[3]	X[4]			X		X			X	X
Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) antibody screen	X									
The M.I.N.I. International Neuropsychiatric Interview (V7.0)[5]	X									
McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD)	X									
Clinical labs (hem, biochem, C-reactive protein [CRP], urinalysis)	X			X		X			X	
Serum pregnancy test	X									
Urine pregnancy test		X							X	
Follicle stimulating hormone (FSH) for females of non-child bearing potential only	X									
[redacted]	X			X					X	
Blood sample collection for concentration of BNC210	X			X		X			X	
Vital signs [7]	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram (ECG) [8]	X[9]			X		X			X	

[1] All baseline assessments to be completed pre-dose. Subjects to administer one PM dose with food on Day 1.

[redacted]

[3] Full physical examination at Screening & V7 / Early Termination. Abbreviated physical examination at V2, V4, and Post Study.

[4] Include height and weight measurements.

[5] Modules C, I, J, K, and O are required for eligibility purposes. Other modules may be completed at the discretion of the Investigator. All diagnoses to be included in the subject's medical history.

[redacted]

[7] Blood pressure and heart rate will be measured in a sitting position after resting for 5 minutes.

[8] All ECGs are to be completed in triplicate with at least a 2-minute break between tests. Repeat ECGs must also be completed in triplicate. The subject 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 subject, where possible.

Visit	Screening	Baseline[1]	V1	V2	V3	V4	V5	V6	V7 / Early Term	Post-study
Study Days: Investigational Product to be administered pre-visit except at Baseline	≤-21	Day 1 *(+ 2 days)*	Week 1 Day 8 *(± 2 days)*	Week 2 Day15 *(± 2 days)*	Week 4 Day 29 *(± 2 days)*	Week 6 Day 43 *(± 2 days)*	Week 8 Day 57 *(± 2 days)*	Week 10 Day 71 *(± 2 days)*	Week 12 Day 85 *(± 2 days)*	Week 15 Day 106 *(± 5 days)*
Standard Life Events Checklist for DSM-5 (LEC-5)	X[10]									
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[11]	X	X	X		X		X		X	X
Columbia Suicide Severity Rating Scale (C-SSRS)[12]	X	X	X	X	X	X	X	X	X	X
Montgomery- Åsberg depression rating scale (MADRS)	X	X			X		X		X	X
Hamilton anxiety rating scale (HAM-A)		X			X		X		X	X
CANTAB Cognitive Assessment[13]	X[14]	X			X				X	
Clinical Global Impressions Improvement & Severity (CGI-I/CGI-S)		X[15]	X	X	X	X	X	X	X	X
Patient Global Impression – Improvement & Severity (PGI-I/PGI-S).		X[16]	X	X	X	X	X	X	X	X
Assessment of Quality of Life (AQoL-8D)		X			X		X		X	X
PTSD Checklist (PCL-5)[17]		X			X		X		X	X
Social functioning (Sheehan Disability Scale, SDS)		X			X		X		X	X
Sleep monitoring (Pittsburgh Sleep Quality Index, PSQI)		X	X		X		X		X	X
Randomization via Interactive Web Response System (IWRS)		X								
Investigational Product (IP) dispensing		X		X	X	X	X	X		
Subject dosing diary		X		X	X	X	X	X		
Adverse event (AE) recording			X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X
Nicotine use	X	X	X	X	X	X	X	X	X	X

[9] Single triplicate repeat allowed in the event of a clinically significant abnormality including prolonged QTcF.
[10] "Standard" LEC-5 to be completed prior to CAPS-5.
[11] "Past month" version used at Screening. "Past week" version used at all other visits.
[12] "Screening C-SSRS" to be used at Screening. "C-SSRS Since Last Visit" to be used at every other visit.
[13] All CANTAB cognitive assessments to be completed within ± 1hr of baseline assessment start time (excluding the test completed during the screening period).
[14] A single practice session on the CANTAB Cognitive Assessment to be completed ≥ 7 days prior to baseline visit
[15] Severity scale only.
[16] Severity scale only.
[17] "Standard" PCL-5 used at all visits.

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IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
[redacted]	[redacted]
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AQoL	Assessment of Quality of Life
AST	Aspartate Aminotransferase (SGOT)
[redacted]	[redacted]
BIC	Bayesian Information Criterion
bid	Twice Daily
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BZD	Benzodiazepines
C-SSRS	Columbia Suicide Severity Rating Scale
CAPS-5	Clinician-Administered PTSD Scale for the DSM-5
CBC	Complete Blood Count
CCK	Cholecystokinin
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity
CI	Confidence Interval
C_{max}	Maximal Observed Plasma Concentration
CRO	Clinical Research Organization
CRP	C-reactive Protein
CTN	Clinical Trial Notification
DBP	Diastolic Blood Pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
[redacted]	[redacted]
EMDR	Eye Movement Desensitization and Reprocessing
ET	Early Termination
[redacted]	[redacted]

Abbreviation	Definition
fMRI	Functional Magnetic Resonance Imaging
FSH	Follicle Stimulating Hormone
GAD	Generalized Anxiety Disorder
[redacted]	[redacted]
eGFR	Estimated Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAM-A	Hamilton Anxiety Rating Scale
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C virus
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
[redacted]	[redacted]
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LEC-5	Life Events Checklist for DSM-5.
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
[redacted]	[redacted]
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measurements
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
[redacted]	[redacted]
NAM	Negative Allosteric Modulation
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
PAL	Paired Associates Learning
PCL-5	Standard PTSD Checklist for DSM-5
PD	Pharmacodynamic
PGI-I	Patient Global Impressions – Improvement
PGI-S	Patient Global Impressions – Severity
PICF	Patient Informed Consent Form
PK	Pharmacokinetics
PRN	As Needed
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
QTcF	Fridericia-corrected QT Interval
RBC	Red Blood Cell
RVP	Rapid Visual Information Processing
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDS	Sheehan Disability Scale
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
SOP	Standard Operating Procedure
SSID	Study Subject Identification Number
SSRI	Selective Serotonin Reuptake Inhibitor
SWM	Spatial Working Memory
[redacted]	[redacted]
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODRUG	World Health Organization Drug Dictionary

PROTOCOL APPROVAL/SIGNATURES

I herewith approve the following protocol entitled "A Randomized, Double-blind, Placebo-controlled Phase II Study of BNC210 in Adults with Post-Traumatic Stress Disorder (PTSD)" Version 4.0 dated 30-May-2018

SPONSOR SIGNATURE

Signature:	_____
Name:	
Date:	____/____/2018

INVESTIGATOR SIGNATURE

A Randomized, Double-blind, Placebo-controlled Phase II Study of BNC210 in Adults with Post-Traumatic Stress Disorder (PTSD)

BNC210.007

Version: 4.0

Issue Date: 30-May-2018

Investigator Agreement

I have read the above-mentioned protocol and am aware of my responsibilities as Principal Investigator for this study. As such, I agree to:

- Personally supervise the conduct of this trial;
- Conduct the trial in accordance with International Conference on Harmonization (ICH) E6 Good Clinical Practice: Consolidated Guidance (GCP), applicable regulatory requirements, and the protocol;
- Comply with the procedures for data recording and reporting as required by the regulatory authorities and the Sponsor;
- Permit monitoring, auditing, and inspection of study records as required by ICH GCP;
- Retain the essential clinical study documents as required by ICH GCP and the Sponsor.

Principal Investigator Signature:	_____
Principal Investigator Name:	_____
Date:	____/____/2018

1 INTRODUCTION AND RATIONALE

1.1 Disease Background

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Post-Traumatic Stress Disorder (PTSD) results 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.

Treatment is based on early interventions, psychotherapies (cognitive behavioral therapy [Otis et al. 2009], exposure, eye movement desensitization and reprocessing [EMDR], etc.) and pharmacotherapy. For the latter, only two pharmacological agents, the antidepressants Paxil® (paroxetine) and Zoloft® (sertraline), belonging to the selective serotonin reuptake inhibitors class (SSRIs), are 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. Combat exposure, in particular, produces a virulent form of PTSD, which is highly resistant to current pharmacological interventions. Overall, antidepressants have (1) moderate efficacy (2) marginal efficacy on male military populations (3) rebound effect upon treatment discontinuation (worsening symptoms) (4) severe side effects upon initiation of treatment (depression, generalized anxiety, panic, substance abuse, suicidal ideation), (5) elevated risk of suicide in young adults (non-approved treatment for children) and (6) potential for sexual dysfunction.

Benzodiazepines (BZD) use is not indicated for PTSD. Data on alprazolam show that it has a deleterious effect on PTSD recovery during exposure therapy (Rothbaum et al. 2014, Rosen et al. 2013) and it is now contraindicated in the Veterans Administration Guideline (Kobayashi et al. 2015). The 2008 World Federation of Societies of Biological Psychiatry conference have also cautioned against the use of BZDs in PTSD (Bandelow et al. 2008). In an epidemiological study, the concomitant use of BZD with an antidepressant increased the risk of hospitalization, both in psychiatric and non-psychiatric wards (Hawkins et al 2013). However, despite a reduction in prescriptions, 30% of PTSD patients still received BZD in 2012 (Lund et al. 2012).

Community-based epidemiologic studies indicate a lifetime prevalence of PTSD ranging from 8% to 12% (Kessler et al. 1995, Breslau et al. 1991), with at-risk individuals (victims of criminal violence, survivors of civilian disasters, combat veterans) showing a prevalence rate from 4% to 30% (Berger et al. 2012, Burri et al. 2014, Thomas et al. 2010, Winfield et al. 1990, Shore et al. 1989, Jordan et al. 1991).

1.2 Investigational Product

The investigational product (IP), BNC210, is a new chemical entity being developed by Bionomics Limited for the treatment of anxiety, and trauma and stressor-related, disorders. BNC210 is a negative allosteric modulator (NAM) of the alpha 7 nicotinic acetylcholine receptor, which represents a novel target for the treatment of these disorders. *In vivo* pharmacology has confirmed BNC210 efficacy in animal models of anxiety at low doses with a wide therapeutic index. There is an absence of the adverse effects particularly those associated with standard-of-care treatments for acute disorders, such as BZD and the antidepressants used as first line therapy for chronic disorders. [redacted]

[redacted]

[redacted]

[redacted]

1.3 Rationale

[redacted]

This Phase II study is intended to assess the potential effect of BNC210 on the treatment of PTSD, a condition which is now classified in the DSM-5 as a Trauma and Stressor-Related Disorder rather than an Anxiety Disorder. Previous human studies have established safety, tolerability and demonstrated a reduction of CCK-induced anxiety in healthy subjects, as well as cognitive profiling. A Phase II imaging (fMRI) study [redacted] showed significant effects of BNC210 on anxiety-related brain activity and defensive behavior in drug-free GAD patients. In line with preclinical data demonstrating BNC210's positive effects on fear extinction, and in order to expand the usefulness of BNC210 to other disorders related to anxiety, this molecule will be studied in PTSD patients where deficits in fear extinction are thought to contribute to the pathology of this disorder. Thus, PTSD is a condition with unmet medical needs, for which BNC210 may be of benefit.

[redacted]

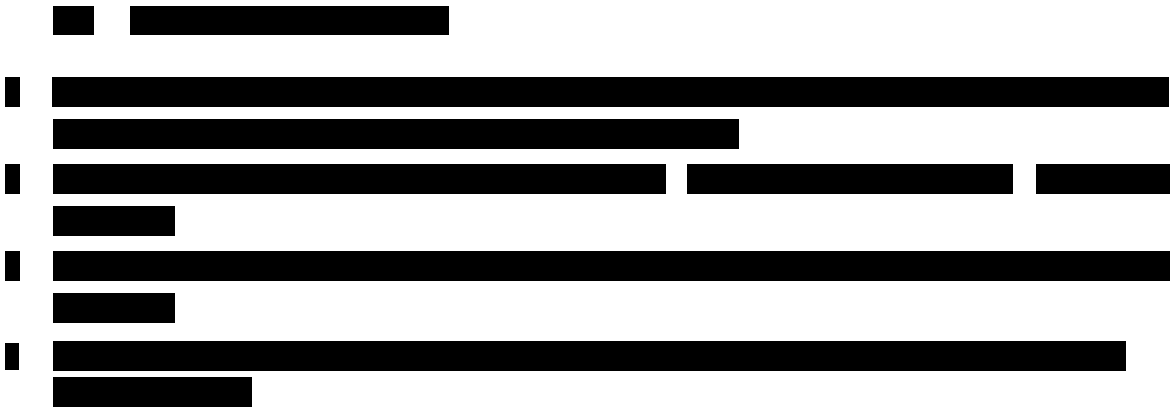
2 STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (CAPS-5) scores.

2.2 Secondary Objectives

- To assess the effects of BNC210 on Investigator-rated symptoms of PTSD measured by each of the four symptom clusters (Intrusion; Avoidance; Negative Alterations in Cognition and Mood; Arousal and Reactivity) of the CAPS-5.
- To assess the effects of BNC210 on other psychiatric outcomes in subjects with PTSD including anxiety and depression.
- To assess the effects of BNC210 on global functioning and Quality of Life in subjects with PTSD.
- To assess the effects of BNC210 on patient-reported outcomes in subjects with PTSD.
- To assess the safety and tolerability of BNC210 in subjects with PTSD.



3 INVESTIGATIONAL PLAN

3.1 Description of Overall Study Design and Plan

This is a randomized, double-blind, parallel, placebo-controlled, multi-center study with a 12-week, 4-arm treatment phase (placebo and BNC210). Subjects will attend a Screening visit within 3 weeks before randomization to confirm eligibility. Approximately 192 subjects who fulfill the inclusion criteria and none of the exclusion criteria will be randomized on Day 1 using a 1:1:1:1 ratio. Subjects will then complete 12 weeks of their allocated treatment. The IP (total daily dose 300 mg, 600 mg or 1200 mg) or Placebo will be taken bid with food. Subjects will return to the clinical site at weekly or 2-weekly intervals to receive study medication, complete safety assessments and questionnaires. Subjects are then requested to attend a post-study visit at 15 weeks (i.e., 3 weeks after the last treatment).

The details are included in the Schedule of Assessments (Table 1).

3.2 Discussion of Study Design Including Choice of Control Groups

This randomized, double-blind, placebo-controlled, Phase II study design was chosen to investigate whether BNC210 causes a decrease in symptoms of PTSD, as assessed by the CAPS-5 (National Centre for PTSD) compared to placebo. Subjects will be randomized to ensure that there are no order effects and to minimize bias. The study will be double-blind to ensure that the patients and clinic staff are unaware of the dosing assignment and to minimize the potential for bias in study assessments or in reporting of AEs.

Subjects will still receive standard of care, even if randomized to placebo as their wellbeing will be monitored through application of various questionnaires and safety assessments. Subjects who received psychotherapy on a regular basis in the previous 3 months before inclusion into the study may continue to receive this care. A stable as needed (PRN) dose of benzodiazepine use will still be allowed during the study.

3.3 Selection of Study Population

Each Investigator will identify potentially suitable patients from their active caseload. A recruitment campaign may also be implemented to facilitate recruitment. The campaign may consist of radio, print, and web based advertisements approved by the Human Research Ethics Committee (HREC) / Independent Review Board (IRB). The Principal or Co-Investigator will be responsible for enrolling patients who are referred by an external clinician or respond to an advertisement. All patients will be evaluated against the study eligibility criteria at Screening. Only eligible patients will proceed through to the treatment phase. Patients must complete all protocol defined visits at study centers listed on the Clinical Trial Notification (CTN) form (Australia) and the Investigational New Drug (IND) application (USA).

At the Screening visit, each patient will participate in the informed consent process and sign and date the patient informed consent form (PICF) before any procedures specified in this protocol are performed.

3.3.1 Inclusion Criteria

Subjects must satisfy all of the following inclusion criteria before being allowed to participate in the study:

1. Signed and dated informed consent.
2. Male or female between 18 and 70 years of age, inclusive.
3. Diagnosed with current PTSD as defined by the CAPS-5 for DSM-5.
4. Currently not using any psychiatric medications, except for:
   - No more than one selective serotonin reuptake inhibitor (SSRI) (fluvoxamine is excluded) or serotonin noradrenaline reuptake inhibitor (SNRI) within the licensed prescribing dose range. Subjects must have been on a stable dose for at least 3 months prior and through Screening, with the intent to remain on the same dose through to week 15.
   - As needed (PRN) use of benzodiazepines (BZD) at a frequency not exceeding 2 days per week in the 3 months prior to Screening. The total dose must not exceed 30 mg/day in diazepam equivalents
5. Subjects not currently receiving psychotherapy except long term supportive counseling or subjects that have received intensive regular psychotherapy for a minimum of three months prior to Screening.
6. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine test at Day 1. Females not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least 12 months prior to Screening and confirmed by follicle-stimulating hormone [FSH] levels in menopausal range at Screening). Sterilized male patients must be at least 1 year post-vasectomy to be considered of non-child bearing potential. Acceptable forms of sterilization include bilateral tubal ligation, bilateral oophorectomy, and hysterectomy for women or vasectomy for men.

   Females and males of childbearing potential must agree to use two effective methods of contraception (double barrier contraception or hormonal contraceptive along with a barrier contraceptive) during the study and for 16 weeks following last study treatment. Contraception that is deemed acceptable in this study includes the following:

   - Condoms
   - Hormonal (includes oral, injected, intrauterine, transdermal, or implanted). Females must be using hormonal contraceptives for at least 3 months prior to randomization and not change the contraceptive during the trial.

   Rhythm methods will not be considered as an effective method of birth control, however, abstinence may be allowed based on the opinion of the Investigator.

   Requirement for contraception can be waived in certain circumstances (i.e. same sex relationships) if approved by the Sponsor.

   Males must agree to not donate sperm for at least 16 weeks following last study treatment.

7. In the opinion of the Investigator the participant has a high probability for adherence with and completion of the study, and willing and able to withdraw and refrain from specific therapies.
8. Fluent in English and able to understand and comply with written and verbal protocol-related requirements.

3.3.2 Exclusion Criteria

If any of the following exclusion criteria apply, the subject will not be allowed to participate in the study:

1. Current and ongoing exposure to the trauma that caused the PTSD.
2. 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.
3. The use of psychiatric medications within 2 weeks of Screening except for SSRIs, SNRIs or limited PRN BZD use as per inclusion criterion 4. Restricted Psychiatric medications include (but are not limited to) antidepressants not allowed by inclusion criterion 4, antianxiety drugs (except limited BZD use per inclusion criterion 4), mood stabilizers, stimulants, antipsychotics, hypnotics and acetylcholinesterase inhibitors.
4. History of significant traumatic brain injury.
5. Depression as measured by Montgomery-Äsberg depression scale (MADRS) rating > 23.
6. Bipolar and psychotic disorders as identified at Screening using the MINI International Neuropsychiatry Interview (V7.0) (M.I.N.I).
7. A score $\geq$ 7 on the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) at Screening.
8. History of seizure disorders, uncontrolled sleep apnoea or severe neurologic disease
9. Increased risk of suicide, defined as:
   - Any previous suicide attempt disclosed by the participant at Screening 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 year, as captured at Screening using the C-SSRS.
   - A score > 4 on item 10 of the MADRS at Screening.
10. The use of cytochrome P450 3A4 inducers within 30 days of Screening. 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, grapefruit or grapefruit-containing products.
11. The use of alprazolam or flunitrazepam within 3 months of Screening.
12. 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 (glomerular filtration rate (GFR) <50 mL/min).

13. Liver disease or liver injury as indicated by abnormal liver function tests (LFTs), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or serum bilirubin (>2x upper limit of normal [ULN]) or history of hepatic cirrhosis.
14. Any clinically significant abnormalities in laboratory test results at Screening (biochemistry, hematology or urinalysis) as assessed by an Investigator.
15. Fridericia-corrected QT interval (QTcF) >460 msec for males and QTcF >480 msec for females as measure by ECG at Screening.
16. Any clinically significant ECG abnormality as determined by the Investigator at Screening.
17. A family history of congenital long QT syndrome, Brugada syndrome or unexplained sudden cardiac death.
18. Positive result for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) at Screening.
19. Any moderate to severe substance use disorder (any type) in the 12 months prior to Screening as identified by the DSM-5 using the M.I.N.I (V7.0).
20. Participation in an investigational study within 30 days of Screening.
21. Current Australian serving Defense personnel or any member of the US military currently serving on active duty.
22. Participants involved with ongoing insurance or workplace claims that in the opinion of the Investigator are likely to have an impact on the mental health, presentation or capacity of the patient to engage in the study.
23. Females who are pregnant, nursing, or intend to become pregnant during the study or within 16 weeks of last dose of Investigational Product, or any males who plan to father/conceive a child within 16 weeks of last dose of Investigational Product.
24. Blood or plasma donation or significant blood loss within 60 days of Day 1.
25. Known to have poor peripheral venous access.
26. Subjects 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 subject at risk or any other reason, the investigator deems applicable.
27. History of allergies, allergic reactions or hypersensitivity to BNC210 or excipients.
28. BP systolic >160 mmHg or diastolic >90 mmHg. Allow two repeat measures at the discretion of the Investigator.

4 TREATMENTS

[redacted]

[redacted]

[redacted]

4.2 Identity of Investigational Product

BNC210 will be supplied in an amber single-use bottle as an 8 mL suspension in a vehicle. Placebo will be supplied in an amber single-use bottle as an 8 mL suspension of a suspension agent and yellow coloring agent in the same vehicle. These treatments will be very similar in appearance.

[redacted]

[redacted]

[redacted]

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

[redacted]

4.3 Methods of Assigning Subjects to Treatment

The IP in this study will only be administered to subjects included in the study following the procedures set out in the protocol. Treatment will be randomly assigned using an IWRS. [redacted] patients will be randomly assigned to the four treatment groups in a 1:1:1:1 ratio until the close of randomization.

4.4 Selection of Dose in the Study

The doses selected span the effective plasma exposure levels in the Phase II GAD patient study where significant results were obtained with single doses of 300 mg and 2000 mg BNC210. [redacted]

[redacted]

[redacted]

4.5 Selection and Timing of Dose for Each Subject

Subjects will take 150 mg or 300 mg or 600 mg BNC210 or placebo bid, with food, as oral suspensions from single-use bottles for 12 weeks. Doses should be administered approximately 12 hours apart (±2 hours), with breakfast, and with an evening meal. Subjects must document all missed and partially administered doses in their Dosing Diary.

4.6 Dose Interruptions and Reductions

Dose interruptions will be allowed following AEs. 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 treatment. Dose reductions will not be allowed.

4.7 Blinding

This study will be double-blind with the subject, Investigator, and rater being unaware of the treatment the subjects will receive.

4.8 Emergency Unblinding of Study Subjects

The Investigator should contact the Medical Monitor to discuss the need to break the blind. In the event that an emergency unblinding is required and the Medical Monitor is unavailable, the Investigator will be able to unblind via the Interactive Web Response System (IWRS). Refer to the IWRS User Guide for further instructions. The Sponsor and Medical Monitor must be notified within 24 hours of any emergency unblinding. Blinding codes should only be broken in emergency situations for reasons of subject safety and when knowledge of the treatment assignment will impact the clinical management of the subject. Every reasonable attempt should be made to complete the Early Termination Visit prior to unblinding, as knowledge of the treatment arm could influence subject assessment. In all cases, the reasons and rationale for unblinding will be documented in writing and maintained in the study file.

4.9 Supply, Packaging and Labeling of the Investigational Product

The IPs will be packaged in treatment kits according to Good Manufacturing Practice (GMP) and all local regulations. They will be labeled in accordance with Australian and USA requirements. Treatment kits will be supplied to each study site with an acknowledgement of receipt form. The manufacturer will provide a certificate of analysis and a batch release certificate for IPs used in the study.

The Investigator, or Designee, will only dispense treatment kits to subjects enrolled in this study. Kits will be allocated using the IWRS. All dispensing episodes, including the kit and batch number, will be captured in IWRS. Each subject will maintain a Dosing Diary where the time and date of each dose is recorded. These diaries will be returned at each visit after Baseline and a new diary issued. The data will then be captured in the eCRF.

[redacted]

[redacted]

4.10 Storage of the Investigational Product

Prior to dispensing, all IP must be stored in a secure and locked storage area with limited access, under monitored, temperature controlled conditions. The Pharmacist or Designee will be responsible for the correct storage and handling of the IP, the details of which are provided in the BNC210.007 Pharmacy Manual. Deviations from the storage requirements, including corrective action, must be documented.

Once the subjects have received their treatment kits, the clinical site will instruct them on the correct storage requirements.

4.11 Accountability, Reconciliation and Return of the Investigational Product

The Investigator must maintain complete and current IWRS dispensing and inventory records. The Investigator is accountable for all IP supplied by the Sponsor. The IWRS logs must be printed at the conclusion of the study and will contain the following information:

- Date of receipt.
- Number of kits received.
- Batch number(s).
- The identification of the subject to whom the kit was dispensed.
- The date(s) and quantity of kits dispensed to the subject.
- The cumulative total of kits at site.
- Kits damaged, destroyed, or returned.

Supplies will be shipped to the investigational site as needed. The Monitor will complete drug accountability during routine monitoring visits.

At the completion or termination of the study, final drug accountability and reconciliation will be completed and any discrepancies must be investigated and their resolution documented. All full, partially full, and empty bottles of IP must be returned to the Pharmacy, Manufacturer or Sponsor for destruction, and the appropriate form sent to the Sponsor.

Please refer to the Pharmacy Manual for further details and the storage, handling, and dispensing of IP.

4.12 Prior and Concomitant Therapy

Use of any investigational drug 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 one month 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.

Moderate – 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.

Subjects that are under consideration for the study and are being treated with a psychiatric medication that is not permitted under inclusion criterion 4, must have discontinued the medication for at least two weeks prior to Screening and be titrated off their treatment in accordance with current prescribing guidelines. The withdrawal of psychiatric medication is at the discretion of the subject in consultation with their primary physician and falls outside the scope of this study protocol.

Concurrent use of no more than one SSRI (fluvoxamine is excluded) or SNRI within the licensed prescribing dose range, is permitted from Screening through Week 15. Subjects must have been on a stable dose for at least 3 months prior and through Screening and no dose adjustments are allowed on study,

The use of any other psychiatric medication is prohibited during all stages of the study. This includes, but is not limited to, antidepressants / anxiolytics not otherwise listed under inclusion criterion 4, mood stabilizers, stimulants, antipsychotics, hypnotics, and acetylcholinesterase inhibitors.

Limited use of BZD is permitted on a PRN basis as rescue medication. The frequency of use must not exceed 2 times per week and the total dose in diazepam equivalents must not exceed 30 mg/day.

The use of antihistamines as a sleep medication is permitted. However, subjects must avoid the use of antihistamines for 12hrs prior to visits where cognitive function is assessed (Baseline, V3, and V7).

Subjects must not have been treated with alprazolam or flunitrazepam for 3 months prior to Screening and the use of these medications in prohibited during the study.

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. The use of all concomitant medication (including non-prescription medications) must be recorded for each subject over the duration of the study. The indication for use, generic name of the drug, dosage, and date of administration will be recorded.

Ongoing long-term supportive counseling or intensive regular psychotherapy is allowed only if the subject commenced therapy > 3 months prior to Screening and is willing to continue therapy at the same frequency through Week 15 or study withdrawal, whichever occurs last.

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

4.13 Treatment Compliance

Treatment compliance will be assessed by the following procedures:

- Blood sampling for the assessment of BNC210 concentrations at Screening and three times during treatment.
- Doses administered based on the number of IP bottles returned used and unused.

4.14 Measures to Minimize Bias

4.14.1 Randomization Procedures

At Screening, subjects will be allocated a sequential five-digit study subject identification number (SSID), the first two numbers of which denote the study center. This is followed by the sequential three-digit subject number. As an example, the first subject screened at site 10 will be allocated the SSID 10-001. Subjects will retain the same SSID for the duration of the study. An IWRS will allocate a randomization number at the baseline visit but the number will not be used for subject identification purposes.

Data associated with subjects that fail screening will not be entered into the eCRF.

[redacted] patients will be randomly assigned to the four treatment groups in a 1:1:1:1 ratio until the close of randomization.

The IWRS vendor will be supplied with a validated randomization list by an Independent Statistician.

4.14.2 Maintenance of Consistent Behaviors

Over the course of the study, subjects will be counseled on the importance of maintaining consistent behaviors. This includes limiting any change to alcohol or tobacco use, dietary intake, and sleep patterns when compared to baseline. Subjects will also be encouraged to attend study visits at the same time of day to avoid possible diurnal variation in measurement responses.

Cognitive function must be assessed at the same time during each visit ($\pm$ 1hr of baseline assessment start time). The use of rescue benzodiazepines, recreational drugs (e.g. cannabis, amphetamines), antihistamines, and excessive alcohol use within 12hrs prior to the assessment of cognitive function should also be avoided. Subjects who have used these medications / drugs within 12hrs should be invited to re-attend the following day where the visit can be completed. Should a subject refuse an invitation to re-attend, the Investigator should proceed with the assessment making a note within the CANTAB system indicating the results may be influenced by drug or medication use.

5 STUDY ASSESSMENTS AND PROCEDURES

On days where study visits occur, subjects must take their scheduled morning dose of IP with food prior to attending clinic for the scheduled visit. Dispensing of IP should occur last, after all study tests and assessments have been completed. All visits should be scheduled to occur at approximately the same time of day.

5.1 Screening Evaluation

The Screening evaluation will take place up to 21 days prior to randomization. Subjects will sign and date the informed consent form before any study-related procedures are completed.

The following assessments will be performed during Screening:

- Register subject via IWRS.
- Medical and surgical history.
- Prior and concomitant medications.
- Record of nicotine use.
- Full physical examination including height and weight.
- HIV, HBsAg and HCV antibody testing.
- Vital signs.
- Triplicate 12-lead ECG.
- Serum pregnancy test (if applicable).
- Laboratory testing (hematology, clinical chemistry, C-reactive protein, urinalysis).
- FSH testing for postmenopausal female subjects only.
- Blood sample collection for BNC210 concentration.
- [redacted]
- Assessment of eligibility using the following instruments:
  - M.I.N.I. (V7.0).
  - 'Standard' Life Events Checklist for DSM-5 (LEC-5).
  - CAPS-5 (Past Month).
  - MSI-BPD.
  - C-SSRS.
  - MADRS.
- Check inclusion and exclusion criteria.
- A practice run on the CANTAB Cognitive Assessment occurring no later than 7 days prior to the Baseline visit.

5.2 Baseline Visit (Day 1 +2 days)

Subjects must report to the clinic on Day 1 where the following assessments will be completed:

- Vital signs.
- Urine pregnancy test (if applicable).
- Check eligibility.

- Baseline measures using the following instruments:
    - CAPS-5 (Past Week).
    - Assessment of Quality of Life (AQoL-8D).
    - C-SSRS (Since Last Visit).
    - MADRS.
    - Hamilton Anxiety Rating Scale (HAM-A).
    - CANTAB Cognitive Assessment.
    - Clinical Global Impression – Severity Scale (CGI-S).
    - Patient Global Impression – Severity Scale (PGI-S).
    - Standard PTSD checklist (PCL-5).
    - Sheehan Disability Scale (SDS).
    - Pittsburgh Sleep Quality Index (PSQI).
- Record concomitant medication use.
- Record of nicotine use.
- Randomization in IWRS.
- Dispensation of IP.
- Dispensation of Dosing Diary.
- Subjects will be provided with information on the storage and administration of the IP and instructed to administer their first dose in the evening with food.

5.3 Visit 1 (Week 1, Day 8 ±2 days)

Subjects must report to the clinic at the start of Week 1 where the following assessments will be completed:

- Vital signs.
- Assessment of efficacy using the following instruments:
    - CAPS-5 (Past Week).
    - Clinical Global Impression –Improvement Scale (CGI-I).
    - CGI-S
    - Patient Global Impression – Improvement Scale (PGI-I).
    - PGI-S
    - PSQI
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Review of IP for compliance purposes.

5.4 Visit 2 (Week 2, Day 15 ±2 days)

Subjects must report to the clinic at the start of Week 2 where the following assessments will be completed:

- Abbreviated physical examination.
- Vital signs.
- Triplicate 12-lead ECG.
- Laboratory testing (hematology, clinical chemistry, urinalysis, C-reactive protein (CRP)).
- Blood sample collection for BNC210 concentration.
- [redacted]
- Assessment of efficacy using the following instruments:
  - CGI-I/CGI-S.
  - PGI-I/PGI-S.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return and dispensation of IP.
- Return and dispensation of Dosing Diary.

5.5 Visit 3 (Week 4, Day 29 ±2 days)

Subjects must report to the clinic at the beginning of Week 4 where the following assessments will be completed:

- Vital signs.
- Assessment of efficacy using the following instruments:
  - CAPS-5 (Past Week).
  - MADRS.
  - HAM-A.
  - CANTAB Cognitive Assessment.
  - CGI-I/CGI-S.
  - PGI-I/PGI-S
  - AQoL-8D
  - PCL-5.
  - SDS.
  - PSQI.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return and dispensation of IP
- Return and dispensation of Dosing Diary.

5.6 Visit 4 (Week 6, Day 43 ±2 days)

Subjects must report to the clinic at the beginning of Week 6 where the following assessments will be completed:

- Abbreviated physical examination.
- Vital signs.
- Triplicate 12-lead ECG.
- Laboratory testing (hematology, clinical chemistry, urinalysis, CRP).
- Blood sample collection for BNC210 concentration.
- Assessment of efficacy using the following instruments:
    - CGI-I/CGI-S.
    - PGI-I/PGI-S.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return and dispensation of IP.
- Return and dispensation of Dosing Diary.

5.7 Visit 5 (Week 8, Day 57 ±2 days)

Subjects must report to the clinic at the beginning of Week 8 where the following assessments will be completed:

- Vital signs.
- Assessment of efficacy using the following instruments:
    - CAPS-5 (Past Week).
    - MADRS.
    - HAM-A.
    - CGI-I/CGI-S.
    - PGI-I/PGI-S.
    - AQoL-8D.
    - PCL-5.
    - SDS.
    - PSQI.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return and dispensation of IP.
- Return and dispensation of Dosing Diary.

5.8 Visit 6 (Week 10, Day 71 ±2 days)

Subjects must report to the clinic at the beginning of Week 10 where the following assessments will be completed:

- Vital signs.
- Assessment of efficacy using the following instruments:
  - CGI-I/CGI-S.
  - PGI-I/PGI-S.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return and dispensation of IP.
- Return and dispensation of Dosing Diary.

5.9 Visit 7 (Week 12, Day 85 ±2 days / Early Termination)

Subjects report to the clinic at the beginning of Week 12, or at Early Termination, where the following assessments will be completed:

- Full physical examination.
- Vital signs.
- Triplicate 12-lead ECG.
- Laboratory testing (hematology, clinical chemistry, urinalysis, CRP).
- Urine pregnancy test (if applicable).
- Blood sample collection for BNC210 concentration.
- [redacted]
- Assessment of efficacy using the following instruments:
  - CAPS-5 (Past Week).
  - MADRS.
  - HAM-A.
  - CANTAB Cognitive Assessment.
  - CGI-I/CGI-S.
  - PGI-I/PGI-S.
  - AQoL-8D.
  - PCL-5
  - SDS.
  - PSQI.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record concomitant medication use.
- Record of nicotine use.
- Return of IP[redacted]

- Return of Dosing Diary.

5.10 Post-study (Week 15, Day 106 ± 5 days)

Subjects must report to the clinic at the beginning of Week 15 where the following assessments will be completed:

- Abbreviated physical examination.
- Vital signs.
- Assessment efficacy using the following instruments:
    - CAPS-5 (Past Week).
    - MADRS.
    - HAM-A.
    - CGI-I/CGI-S.
    - PGI/PGI-S.
    - AQoL-8D.
    - PSQI.
    - PCL-5
    - SDS.
    - PSQI.
- C-SSRS (Since Last Visit).
- AE monitoring.
- Record of nicotine use.
- Record concomitant medication use.

5.11 Unscheduled Visits

Subjects may attend an unscheduled visit at any time. All assessments completed during an unscheduled visit must be captured in the electronic case report form (eCRF). This includes the results of all pathology tests scheduled by the Investigator.

Visits scheduled due to an increase in ALT or AST >3 x ULN (see Section 6) must be captured as an unscheduled visit.

A visit with a Subject'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.

5.12 Re-screening of Study Subjects.

In the event that a subject fails a clinical laboratory or ECG screening assessment, that assessment can be repeated once only. The repeat assessment must be completed within the allowed screening period (21 days $\pm$ 2 days of Baseline) for eligibility purposes. If the repeat assessment cannot be completed within the screening period, the subject must be re-screened in entirety. Subjects who fail any other screening assessment must be screen-failed. Subjects can be re-screened once only.

6 WITHDRAWAL OF SUBJECTS OR TERMINATION OF THE STUDY

Subjects should be encouraged to complete all study assessments. However, subjects may withdraw consent to participate in this study at any time and for any reason without penalty or loss of benefits to which they were otherwise entitled. The Sponsor or the Investigator may withdraw subjects at any time for safety or administrative reasons. If a subject is withdrawn from the study or treatment, the reason will be recorded on the eCRF and the Sponsor notified promptly.

Subjects who are withdrawn from treatment early due to SAEs must be followed-up and provided appropriate medical care until their signs and symptoms have remitted or stabilized, until the subject is lost to follow-up, or until the post study visit, whichever comes last. Subjects who experience an SAE that is deemed to be related to the IP will have treatment withdrawn.

A subject may be withdrawn from the study if any of the following occur during the study:

1. Subject withdraws consent;
2. AE makes the continuation of the subject impossible or inadvisable;
3. Pregnancy;
4. Subject is lost to follow-up;
5. Subject discovered after enrollment not to have met the protocol inclusion criteria;
6. Subject refuses to comply with required study procedures;
7. Use of any restricted medication (including experimental) or therapy;
8. The study Sponsor terminates the Investigator Site or the study.

Subjects are to have treatment withdrawn by the Investigator for any of the following:

- Any new suicidal behavior since Screening, as disclosed by the subject during administration of the C-SSRS.
- Any suicidal ideation with intent (yes to item 4 and / or 5) since Screening, as disclosed by the subject during administration of the C-SSRS.
- A score > 4 on item 10 of the MADRS.
- Prolonged QTcF interval: Subjects with prolonged QTcF interval of ≥500 msec (confirmed after triplicate repeated measurement at least 2 minutes apart) should be discontinued from treatment either temporarily or permanently and monitored for safety by the Investigator.
- Elevated serum transaminases (LFT abnormalities) confirmed to be:
    - ALT or AST >5 x ULN;
    - ALT or AST >3 x ULN for more than 2 weeks;
    - ALT or AST >3 x ULN and total bilirubin >2 x ULN (Hy's Law); or
    - ALT or AST >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.

Should a subject experience an elevation of ALT or AST >3 x ULN, the subject should return to the clinic for repeat LFT testing every 3 to 5 days while on study drug until the ALT or AST returns to baseline, becomes stable, or reaches any of the stopping rules for LFT abnormalities.

All subjects that have treatment withdrawn prior to Visit 7 (week 12) for any reason should return to the study site within 10 calendar days of last dose and an Early Termination (ET) Visit completed. Should treatment be withdrawn during a visit, that visit becomes the ET Visit. After withdrawal from treatment, subjects will be asked to return to the study site at the regular protocol-defined visit schedule (calculated from Day 1) where only the following assessments will be completed as per the regular schedule of assessments:

- CAPS-5.
- HAM-A.
- MADRS.
- PCL-5.
- CANTAB Cognitive Assessment.
- SDS.
- AQoL-8D.
- PSQI.
- CGI-I/CGI-S.
- C-SSRS
- PGI-I/PGI-S.
- AE recording.
- Record concomitant medication use.
- Record of nicotine use.

The measurement of vital signs, the collection of pathology samples (including the BNC210 compliance, [redacted] samples), and the completion of ECGs during visits that occur after the treatment withdrawal are not required unless clinically indicated.

The timing of the post treatment withdrawal visits are calculated from Day 1 and should follow the study schedule of assessments through Visit 7 (week 12) as captured in Table 1. During this period, subjects must adhere to all concomitant medication and therapy restrictions as captured in protocol section 4.11. Those subjects unable to adhere to the medication and therapy restrictions post treatment withdrawal must be withdrawn from the study completely and attend an Early Termination Visit within 10 calendar days of their last dose. No further study visits are required. Subjects are also free to withdraw from the study at any time and without prejudice to further care according to standard clinical practice.

7 EFFICACY VARIABLES

7.1 Definitions of Variables

All the assessments/questionnaires below will be assessed at time-points as captured in the Schedule of Assessments (Table 1).

7.1.1 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 week. Information about the frequency and intensity of each item is combined into a severity rating, and the CAPS-5 total severity is calculated by adding the severity scores for the 20 PTSD symptoms in the DSM-5 (National Centre for PTSD). The severity of PTSD is rated from 0 (absent) to 4 (extreme/incapacitating).

7.1.2 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).

7.1.3 Clinical Global Impression scales – Improvement and Severity (CGI-I/CGI-S)

The CGI-S is a rating scale designed to assess the severity of the subject's symptoms, and the CGI-I is designed to assess the change in the subject'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 subjects). The changes in the subject's condition are rated on the CGI-I from 1 (very much improved) to 7 (very much worse).

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

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

7.1.5 Assessment of Quality of Life (AQoL-8D)

The AQoL-8D is a 35 question self-rating scale designed to assess a subject's quality of life on the following eight dimensions; Independent Living, Happiness, Mental Health, Coping, Relationships, Self-Worth, Pain and the Senses. The scale takes approximately 5 minutes to complete.

7.1.6 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). It takes approximately 15-20 minutes to complete and each parameter is rated on a scale of 0 (not present) to 4 (very severe).

7.1.7 Montgomery-Asberg 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).

7.1.8 CANTAB Cognitive Assessment

The CANTAB cognitive assessment is a battery of tests designed to detect both cognitive impairment and enhancement. The battery will measure cognitive function through assessing sustained attention, episodic memory, working memory and executive function. All tests will be completed electronically using iPads. The test battery will take approximately 20-25 minutes to complete. The CANTAB cognitive assessment must be completed at the same time during each visit (± 1hr of baseline assessment start time).

A Paired Associates Learning (PAL) task will be used to assess episodic memory. During the test, boxes are displayed on the screen and open in turn to reveal a number of patterns. Participants are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the participant touches the box in which the pattern was located. If an error is made, all the patterns are re-presented to remind the participant of their locations. As the test progresses so the stages become more difficult as the number of patterns to be remembered increases, up to a maximum of 8 patterns. For participants who fail to complete all levels, an adjusted total is calculated that allows for errors predicted in the stages that were not attempted. The key outcome measures for this task are total errors and first trial memory score.

A Spatial Working Memory (SWM) task will be used to assess the ability of the subject to retain spatial information and manipulate it in working memory. It is a self-ordered task that also gives a measure of strategy. A number of colored boxes are presented on the screen, and the computer hides a token in these boxes one at a time. The participant is instructed to touch the boxes in turn to search for the token that has been hidden. When a token is found it should be placed in a home area on the right side of the screen. The participant then searches for more tokens until the same number of tokens as the number of colored boxes has been found. The key task instruction is that the computer will never hide a token in the same colored box twice in the same problem. As the test progresses, so it becomes more difficult. The key outcome measures for this task are between errors and strategy.

A Rapid Visual Information Processing (RVP) task will be used to assess sustained attention, outputting measures of response accuracy, target sensitivity and reaction times. For the RVP task, single digits appear in a pseudo-random order at a rate of 100 digits per minute in box in the center of the screen. Subjects must detect a series of 3-digit target sequences (e.g. 3-5-7; 2-4-6; 4-6-8) and respond by touching the button at the bottom of the screen when they see the final number of the sequence. Nine target sequences appear every minute. Key outcome measures include target sensitivity and reaction times.

Factors that could influence the cognitive function assessments must be captured within the CANTAB system. This includes, but is not limited to, drug and medication use within 12hrs of assessment, lack of sleep, and failure to understand the test requirements. Please refer to the CANTAB User Manual for details on how to capture this information.

7.1.9 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.

7.1.10 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a questionnaire consisting of 19 questions designed to assess the following 7 components of sleep quality: subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the previous month. Each question is weighted on a scale from 0 to 3 and a global score is obtained, with lower scores correlating with better sleep quality.

8 COMPLIANCE, [redacted]

8.1 Blood Sampling for Plasma BNC210 Concentrations

Blood samples for the assessment of plasma BNC210 concentrations will be collected at Screening, Visit 2, Visit 4 and Visit 7/ET (Table 1). Samples will be collected to assess a subject's treatment compliance.

[redacted]

9 SAFETY VARIABLES

9.1 Safety Endpoint(s)

Safety will be assessed during the study through physical examination, urinalysis, vital signs, ECG, laboratory tests, C-SSRS and continuous AE reporting, as outlined in the Schedules of Assessment (Table 1).

9.2 Physical Examination

A complete physical examination will be performed at Screening, Visit 7 (Week 12), and Early Termination. A complete physical examination will include assessments of 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.

An abbreviated physical examination will be performed at Visit 2 (Week 2), Visit 4 (Week 6), and Post Study (Week 15). An abbreviated physical examination will include assessments of eyes, ears, nose, throat, cardiovascular system, respiratory system, and abdomen/gastrointestinal system. Other body systems may also be examined as required.

Clinically significant changes from first dose of Investigational Product will be recorded as AEs.

Height and weight will be recorded in centimeters (cm) and kilograms (kg), respectively and only at Screening. Weight is measured with subjects wearing light clothing without shoes.

9.3 Vital signs

Vital signs will be measured at every visit from Screening to Week 15 (Post Study Visit).

Vital signs include systolic and diastolic blood pressure, pulse rate, respiration rate and body temperature. Blood pressure and heart rate will be measured in a sitting position after resting for 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be measured in millimeters of mercury (mmHg), heart rate in beats per minute, respiration rate in breaths per minute and temperature (oral) in degrees Celsius (°C).

9.4 12-lead ECGs

ECGs will be taken at time-points as indicated in the Schedule of Assessments (Screening, Visit 2, Visit 4, Visit 7 / ET).

ECG recordings will be taken in triplicate, with at least a 2-minute break between each test. The QTcF value will be calculated as the mean of the 3 ECG readings. One repeat is allowed for screening purposes if abnormal findings are observed. The repeat must also be completed in triplicate.

The subject 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 subject, where possible. ECGs will be read by the Investigator or designated physician at the unit. Machine-read automated ECG intervals (PR, QRS, QT and HR), and calculated RR intervals will be captured in the eCRF and any other abnormalities noted. 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 subject's clinical file as part of the permanent record. The ECG intervals and interpretation will be recorded on the appropriate eCRF form.

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.

9.5 Clinical Laboratory Tests

Blood samples for laboratory assessments will be taken at Screening, Visit 2, Visit 4, Visit 7 / ET.

Laboratory data obtained at Screening will be used as baseline in the safety analyses. Safety Laboratory Data include:

- Complete blood count (CBC): hemoglobin, hematocrit, red blood cell (RBC) count, MCV, white blood cell (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.
- Chemistry panel: Albumin, ALP, ALT (SGPT), aspartate aminotransferase (AST, SGOT), gamma glutamyltransferase (GGT) bicarbonate, total and direct bilirubin, BUN or plasma urea, corrected calcium, chloride, sodium, creatinine, eGFR (Cockcroft Gault), glucose, potassium, uric acid and total protein.
- CRP.
- FSH on postmenopausal females.
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, blood, nitrite, and leukocyte esterase.
    - Specimens with abnormal Protein, WBC or RBC will be submitted for microscopy testing and reporting on WBCs, RBCs, epithelial cells, casts, crystals, yeast, and bacteria. Specimens with elevated WBC may be submitted for microbiological testing for infection.

Screening blood tests include:

Serology: hepatitis (HepB surface antigen, anti-HCV), HIV.

Pregnancy Tests

A serum pregnancy test will be performed on all females of childbearing potential at Screening and a urine pregnancy test on Day 1 before randomization and at Visit 7 / ET.

9.6 Columbia Suicide Severity Rating Scale (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.

9.7 Adverse Events (AEs)

The Principal Investigator and clinical facility staff are responsible for detection, recording, and reporting of events that meet the criteria and definition of various AEs as listed below. AEs will be recorded from first administration of IP through Week 15 (Post Study Visit). The Principal Investigator and clinical facility staff are responsible for detection, recording and reporting of pregnancy and appropriate follow up.

9.7.1 Definitions

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

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

AEs will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE).
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or social admissions)
- An overdose of either the IP or a concurrent medication without any resulting signs or symptoms.

9.7.2 Grading of Adverse Events

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded as indicated in the eCRF. If the intensity of an AE changes over a number of days, then separate entries should be made with distinct onset dates.

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment and does not interfere with the subject's daily activities. No limitation in daily activity.
- Grade 2 (Moderate): produces a low level of inconvenience to the subject and may interfere with daily activities. These events are usually ameliorated by simple therapeutic measures. Some limitation in daily activity.

- Grade 3 (Severe): interrupts daily activity and requires systemic drug therapy or other medical treatment. Unable to perform daily activity.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An AE is defined as 'serious' when it meets one of the pre-defined serious outcomes as described in Section 9.8.

9.7.3 Causal Relationship to Investigational Product

The relationship of an AE to the IP is a clinical decision by the Investigator based on all available information at the time of reporting. The causal relationship must be graded as follows:

- **Not related:** a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is clearly related to other factors such as the 's clinical state, therapeutic intervention or concomitant therapy.
- **Possible:** a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals, information on drug withdrawals may be lacking or unclear.
- **Probable:** a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfill this definition.
- **Definite:** a reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

9.7.4 Documentation of Adverse Events by the Investigator

When an AE occurs, it is the responsibility of the Principal Investigator to review all documentation (e.g. progress notes, laboratory, and diagnostics reports) relative to the event. The Principal Investigator will then record the AE on the AE eCRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 9.8 below. The Principal Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the event and not the individual signs/symptoms.

9.7.5 Laboratory Test and other Test Abnormalities as Adverse Events

Abnormal assessments (e.g., ECGs and vital signs) that are judged by the Principal Investigator as clinically significant or if the abnormal assessment results in clinical sequelae will be recorded as AEs.

Laboratory abnormalities will be reported by the Investigator as AEs if the abnormality is considered clinically significant or if the abnormality results in clinical sequelae.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the first administration of IP will be reported as AEs.

The Principal Investigator and Co-Investigators will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.8 Serious Adverse Events (SAE)

An SAE is any AE that:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event/reaction in which the subject was at immediate risk of death at the time of the event/reaction; it does not refer to an event/reaction, which hypothetically might have caused death, if it were more severe.

Any planned procedures that require admission to hospital for compliance with this protocol as well as any planned elective procedures are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the subject’s condition). In addition pregnancy that occurs during the course of the study or absence of a treatment effect will also not be considered to be an SAE.

9.8.1 Reporting for Serious Adverse Events (24 Hours)

SAEs must be followed until their signs and symptoms have remitted or stabilized, until the subject is lost to follow-up, or until Week 15 (Post Study Visit), whichever comes last.

Investigators are not obligated to actively seek SAEs after Week 15 (Post Study Visit). However, if an Investigator learns of any SAEs that occur after study participation for a subject has concluded and the event is deemed relevant to the use of study drug, it should be promptly reported.

AEs meeting serious criteria MUST be reported promptly to the designated Clinical Research Organization (CRO) Safety Desk within 24 hours, and to the HREC/IRB in accordance with their safety reporting policy. The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the Principal Investigator (or Designee). If the Principal Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The Principal Investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.7.3.

Facsimile or email transmission of the SAE report form is the preferred methods to transmit this information to the designated CRO Safety Desk. In rare circumstances notification by telephone is acceptable, with a copy of the SAE report form sent by overnight mail.

Initial notification via the telephone does not replace the need for the Principal Investigator to complete and sign the SAE report form within the outlined time frames. The Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses

The Principal Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the HREC/IRB.

9.9 Safety Review Committee

An independent Safety Review Committee will be established to monitor subject safety throughout the study. The meetings will occur approximately every 6 months and will review all safety data including vitals signs, ECG, pathology results, physical examinations, C-SSRS and continuous AE reporting.

10 DATA MANAGEMENT AND STATISTICS

10.1 Data Collection

Designated investigator staff must enter all information required by the Protocol into the eCRF. Monitors will review the eCRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. All data will be collected in an eCRF with controlled access and audit trail.

10.2 Data Management and Quality Control

eCRF data will be validated by a series of programmed checks and listing reviews as defined in the Data Validation Plan and in accordance with the Data Management group's own internal standard operating systems (SOPs) that have been reviewed and approved by the study Sponsor. Queries will be either automatically generated or manually added to the eCRF for resolution by the site. Responses to queries will be entered directly into the eCRF by site staff. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the World Health Organization Drug Dictionary (WHODRUG) terminology.

Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The eCRFs will be reviewed and approved by the study Sponsor. The eCRFs and associated programmed validation checks and listings will undergo User Acceptance Testing prior to being released for use in the study. All access to the eCRF is controlled by user permissions and reviewed via audit trail.

Data Retention procedures will be conducted in accordance with the Data Management group's own internal SOPs that have been reviewed and approved by the study Sponsor. All eCRF and biometrics study related data to be archived will be maintained in the Biometrics Trial Master File.

Data will be retained in the electronic Biometrics Trial Master file for a period of 15 years after release of any related batch of finished product in accordance with the Data Management group's own internal SOPs. Bionomics Ltd, the study Sponsor will retain CDISC files and in addition the following documents will be provided by the Data Management group for inclusion in the Trial Master File, and other documents would most likely be provided from other sources:

- Blank copy of approved eCRF (including AE forms)
- Training records – eCRF system
- Relevant correspondence
- pdf of completed CRFs (including audit trail, discrepancies and AEs)

10.3 Statistical Considerations

The Biostatistical Department of [redacted] will be responsible for the analysis of demographic, safety, efficacy and compliance data. [redacted] using SAS® software version 9.3 (or higher) (SAS Institute Inc.,

Cary, NC, USA). A detailed statistical analysis plan (SAP) will be compiled before data base lock describing the methods used for the statistical analyses.

10.4 Sample Size

Sample size estimation is based on the following:

[redacted]. With the level of significance set to 0.05 and a 2-sided test, a sample size of 36 subjects per arm is required to achieve a power of 80%. For PTSD patients a relatively high withdrawal rate is anticipated, therefore the sample size was increased by 33% to 48 per arm (=1.33x36) (Hoskins et al. 2015, Marshall et al. 2001; Marshall et al. 2007; Tucker et al. 2001). Because this is a Phase II study the level of significance will be 0.05 with no adjustment for multiple comparisons.

10.4.1 Review of Sample Size calculation

[redacted]

10.5 Statistical Methods

Descriptive statistics will be supplied according to the nature of the criteria where Quantitative variables will be presented as follows: sample size, arithmetic mean, SD, median, minimum and maximum. Qualitative variables will be presented as follows: sample size, frequencies and percentages per category

10.6 Analysis Populations and/or Subsets

The Intent-to-treat (ITT) population will comprise all randomised subjects; analysed as per randomised treatment. The Modified ITT (mITT) population will be those subjects from the ITT population who received at least one dose of study medication. The mITT population will be used for all efficacy analyses, tabulations, and listings.

The safety population will comprise all randomised subjects who receive at least one dose of study medication and will be analyzed as per treatment received. The safety population will be used for all safety analyses and listings.

The analysis sets will be validated during a blind review meeting.

10.6.1 Description of the Populations

A summary table with the description of the number of subjects in each analysis set, the number of subjects who completed the study, and the number of subjects who discontinued classified by reason of withdrawal, will be prepared. Corresponding individual listings will be prepared.

Listings with end of study status and visit dates will also be prepared.

10.7 Demographics and Baseline Characteristics

The following analysis will be performed on the Randomized (mITT) set.

The subject's demographic characteristics and baseline characteristics (including the applicable questionnaires) will be summarized by treatment and overall. Details of drug dosing will be listed by subject.

10.8 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, Investigator, or site staff. All deviations will be tracked and should be reported to IRBs in accordance with their reporting policy. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria.
- Failure to comply with dispensing or dosing requirements.
- Use of medications, herbal remedies, supplements, or therapies that are specifically prohibited in the protocol.
- Missed or out-of-window visits.
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol.
- Procedural deviations such as incorrect storage of study drug, failure to update the PICF when new risks become known, failure to obtain HREC/IRB approvals for the protocol and PICF revisions.

10.9 Efficacy Analysis

10.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is CAPS-5 total symptom severity score at Week 12 and will be analyzed with a MMRM with sequential Multiple Imputation (MI) used to estimate the

missing observations. The repeated measurements will range from Baseline to Week 12 for the primary endpoint.

The primary efficacy model will include the CAPS-5 total symptom severity scores from Baseline to Week 12 as the dependent variable, the Baseline CAPS-5 value as a Baseline covariate, Week, and treatment group as factors, and treatment group by Week as an interaction term. Additional covariates in the model will include gender, age, country (Australia/USA), nicotine use at Baseline (Current/Former/Never), and concomitant antidepressant use at Baseline (Yes/No).

Further details of the MMRM and MI for missing values will be included in the SAP prior to database lock and subsequent unblinding.

Each dose group will be compared to placebo. Because this is a Phase II study, the level of significance will be 0.05 with no adjustment for multiple comparisons. Additional sensitivity analyses will include:

- MMRM with the 'as observed' (i.e. no imputation for missing values) dataset.
- MMRM with the last observation carried forward (LOCF) dataset.
- MMRM with the baseline observation carried forward (BOCF) dataset.

10.9.2 Secondary Efficacy Endpoints

The effect of each dose of BNC210 on Investigator-rated and self-reported PTSD symptom severity, depression, anxiety, cognitive function, global function, quality of life, social functioning, and sleep quality after 12 weeks of treatment, will be compared to placebo using the following instruments:

- Cluster score for CAPS-5 Criterion B: Intrusion.
- Cluster score for CAPS-5 Criterion C: Avoidance.
- Cluster score for CAPS-5 Criterion D: Negative Alterations in Cognition and Mood.
- Cluster score for CAPS-5 Criterion E: Arousal and Reactivity.
- PCL-5.
- MADRS.
- HAM-A.
- CANTAB Cognitive Assessment
- CGI-S/CGI-I.
- PGI-S/PGI-I.
- AQoL-8D.
- Social functioning: SDS.
- Sleep monitoring: PSQI.

The CAPS-5 symptom cluster severity scores, PCL-5, MADRS HAM-A, CANTAB Cognitive Assessment, SDS and PSQI, will be analysed as continuous variables using MMRM (and MI) as described for the CAPS-5 total symptom severity score. The covariate will be the respective baseline continuous variable. The MMRM analyses for the secondary efficacy variables will be repeated using the 'as observed' (i.e. no imputation) dataset. For all secondary efficacy variables the level of significance will be 0.05 with no adjustment for multiple comparisons.

For all variables the data will be graphed over time as adjusted means with 95% confidence intervals (CIs). As appropriate the means and 95% CI at Week 12 will be summarized as forest plots.

The CGI-I/CGI-S & PGI-I /PGI-S will be reported as tables of frequencies and percentages.

Treatment adherence will be summarized as frequencies and percentages.

[redacted]

10.11 Compliance Analysis

Plasma levels of BNC210 taken at Screening, Week 2, Week 6 and Week 12 will be used as a dichotomic compliance marker.

10.12 Safety Analysis

10.12.1 Safety Analysis Criteria

The safety criteria include the following:

- AEs
- Vital signs
- Standard 12-lead ECG
- Haematology, blood chemistry, urinalysis
- Physical examination, weight.
- C-SSRS

10.12.2 Statistical Methodology

Analysis of safety parameters will be performed on the Safety Population.

10.12.3 Columbia Suicide Severity Rating Scale Safety Analysis

The C-SSRS comprises several categorical questions, which are not summarized into a total score. The categorical responses will be summarized by tables of frequencies and percentages at Week 15, and over time.

10.12.4 Adverse Event Analysis

All AEs will be listed by and summarized by treatment group.

AEs will be considered as treatment-emergent according to the rule set out in Section 9.7.1.

Repetitions will only be counted once in summary tables. Repetitions are defined as follows:

If a given subject presents several AEs with the same verbatim text during the treatment period, only one event is defined; the others are considered repetitions or recurring episodes. The start time of the event will be the start time of the first occurrence, the end time will be the end time of the last episode. The intensity will be the highest recorded intensity for all episodes. The causality will be the highest likelihood recorded for all episodes.

AEs will be summarized by system organ class and preferred term in tables with:

- The number of subjects with at least one AE and number of AEs for each treatment group and overall,
- Analyses taking into account intensity and drug relationship to treatment could also be carried out.

Other Safety parameters (vital sign measurements, ECG readings, physical examination, and laboratory tests) will also be described using descriptive statistics by treatment group when applicable, by visit otherwise.

Description of potentially clinically significant values will be performed for vital signs, ECG parameters, blood chemistry and hematology parameters. All these parameters will be listed by subject and measurement time. The data outside of normal ranges will be flagged.

11 STUDY ADMINISTRATION

11.1 Ethical Considerations

11.1.1 Ethical Principles

This study will be conducted in accordance with the ICH Guideline for Good Clinical Practice E6(R1) as adopted within Australia and the United States of America and all relevant statements, guidelines, regulations and legislation. The Protocol will be submitted for approval to the appropriate HREC/IRB and written approval obtained before subjects are enrolled. If approval is suspended or terminated by the HREC/IRB, the Principal Investigator will notify the Sponsor immediately.

Bionomics Ltd and all clinical sites will abide by the agreed upon compensation guidelines within each country for injury resulting from participating in a company-sponsored study. A copy of these guidelines must be made available to all study subjects upon request.

11.1.2 Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. Study participation includes any and all screening procedures, as well as any washout of excluded medications.

It is the responsibility of the Principal Investigator (or medically qualified designee) to obtain a written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Principal Investigator (or medically qualified designee) must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time.

11.1.3 Human Research Ethics Committee / Institutional Review Board Approval

Prior to initiation of the study, written HREC/IRB approval of the Protocol and Consent Forms, based on the principles of ICH GCP procedures, will be provided to Bionomics Ltd. Any written information and/or advertisements to be used for subject recruitment will be approved by the HREC/IRB prior to use. A list of the HREC/IRB voting members, their titles or occupations, and their institutional affiliations will be requested before study initiation. Protocol modifications that may impact subject safety or the validity of the study will also be approved by the HREC/IRB.

11.2 Data Handling and Record Keeping

11.2.1 Data Collection and Reporting

The Investigator must maintain required documents for all study subjects. Data for this study will be recorded in the subject's source documents and on the eCRFs. The source documents are to be separate and distinct from the CRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate.

All data collected in the eCRFs should be recorded completely and promptly.

The Investigator or the appointed persons agree to complete the subject's eCRF forms after each study visit. Only the Investigator or the Investigator designee may enter and correct eCRF data.

Prior to database lock and when authorized by Data Management, the Investigator must sign and date the eCRF in order to attest respectively to:

- authenticity of the data collected in the eCRF,
- coherence between the data in the eCRF and those in the source documents.

At the end of the study, the Investigator will keep a .pdf copy of the correctly completed eCRFs for his/her own records. The Investigator will keep a log of study volunteers screened for study participation and as appropriate, will indicate the reason individual study volunteers did not enter the study. The Investigator must submit to the Sponsor or its representatives a completed eCRF for each subject who receives any IP.

The Investigator must guarantee the safety of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

11.2.2 Monitoring

All aspects of the study will be monitored carefully by the Sponsor's Designee with respect to current GCP and SOPs for compliance with applicable government regulations, the study protocol and Investigator's obligations. It is the responsibility of the Investigator to provide all study records, including eCRFs, source documents, among other records, for review and inspection by the Monitor.

All CRFs will be 100% verified against corresponding source documentation for each subject. Monitors will periodically evaluate the progress of the study, including the verification of the accuracy and completeness of the eCRFs. Prior to database lock, the completed eCRFs must be reviewed, signed and dated by a qualified physician who is delegated this responsibility by the Principal Investigator.

11.2.3 Audit

The study may be selected for an audit to inspect the facilities and review the study-related records in order to evaluate the trial conduct and compliance with the protocol, ICH, GCP and applicable regulatory requirements.

The Investigator will be informed that an audit will be carried out, at the request of the Sponsor, before, during or after the study.

The Investigator will be informed that the Regulatory Authorities may also carry out an inspection. In this case, the Investigator must inform the Sponsor as soon as he/she receives the notification of inspection.

The Investigator must allow the representatives of the Regulatory Authorities and persons responsible for the audit to inspect the site, facilities and material used for the study, meet all members of his team involved in the study, have direct access to study data and source documents and consult all the documents relevant to the study.

11.2.4 Study Records Retention

A file for each subject is maintained, and it includes the signed ICF and the copies of all source documents for that subject. Investigators are required to maintain all documentation, including documents in electronic format, for a minimum of 15 years following the end of the study. The Investigator must inform the Sponsor immediately if any documents are to be destroyed, transferred to a different facility or transferred to a different owner. The Sponsor will notify the site if the trial records are no longer needed.

11.3 Data Disclosure and Subject Confidentiality

All information provided by Bionomics Ltd and all data and information generated by the site as part of the study, (other than a subject's medical records), will be kept confidential by the Principal Investigator and other site staff. The Principal Investigator or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the Principal Investigator or site staff; (2) information which it is necessary to disclose in confidence to an HREC/IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

11.4 Publication Policy

No publication of the results shall take place without the express consent of the study Sponsor, Bionomics Ltd. Prior to submitting for any publication, presentation, use for instructional purposes or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the Principal Investigator shall provide Bionomics Ltd. with a copy of the proposed Publication and allow Bionomics Ltd. a period of at least forty (40) days [or for abstracts, at least five (5) working days] to review the proposed Publication. Proposed publications shall not include either Bionomics Ltd. or confidential information.

At the request of Bionomics Ltd, the submission or other disclosure of a proposed Publication will be delayed for a sufficient length of time to allow Bionomics Ltd. to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with the statement is executed, that contract's publication provisions shall apply rather than this statement.

12 REFERENCES

Berger W, Coutinho ES, Figueira I, Marques-Portella C, Luz MP, Neylan TC,Marmar CR, Mendlowicz MV. Rescuers at risk: a systematic review and meta-regression analysis of the worldwide current prevalence and correlates of PTSD in rescue workers. Soc Psychiatry Psychiatr Epidemiol. 2012 Jun;47(6):1001-11.

[redacted]

Bandelow B, Zohar J, Hollander E, et al; WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. World J Biol Psychiatry. 2008;9(4):248–312.

Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry. 1991 Mar;48(3):216-22.

Burri A, Maercker A. Differences in prevalence rates of PTSD in various European countries explained by war exposure, other trauma and cultural value orientation. BMC Res Notes. 2014 Jun 28;7:407.

Clinician Administered PTSD Scale for DSM-5. Accessed on 26 January 2016 at http://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp

George KC, Kebejian L, Ruth LJ, Miller CW, Himelhoch S. Meta-Analysis of the Efficacy and Safety of Prazosin versus Placebo for the Treatment of Nightmares and Sleep Disturbances in Adults with Post-Traumatic Stress Disorder. J Trauma Dissociation. 2016 Feb 2.

Hamilton M. "The assessment of anxiety states by rating." Br. J. Med. Psychol. 1959. 32:50–55.

Hawkins EJ, Malte CA, Grossbard J, Saxon AJ, Imel ZE, Kivlahan DR. Comparative safety of benzodiazepines and opioids among veterans affairs patients with posttraumatic stress disorder. J Addict Med. 2013 Sep-Oct;7(5):354-62.

Hoskins M, Pearce J, Bethell A, Dankova L, Barbui C, Tol WA, van Ommeren M, de Jong J, Seedat S, Chen H, Bisson JI. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. Br J Psychiatry. 2015Feb;206(2):93-100.

Jordan BK, Schlenger WE, Hough R, Kulka RA, Weiss D, Fairbank JA, Marmar CR. Lifetime and current prevalence of specific psychiatric disorders among Vietnam veterans and controls. Arch Gen Psychiatry. 1991 Mar;48(3):207-15.

Kobayashi TM, Patel M, Lotito M. Pharmacotherapy for posttraumatic stress disorder at a Veterans Affairs facility. Am J Health Syst Pharm. 2015 Jun 1;72(11 Suppl 1):S11-5.

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995 Dec;52(12):1048-60.

Lund BC, Bernardy NC, Alexander B, Friedman MJ. Declining benzodiazepine use in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2012 Mar;73(3):292-6.

Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. AmJ Psychiatry. 2001 Dec;158(12):1982-8.

Marshall RD, Lewis-Fernandez R, Blanco C, Simpson HB, Lin SH, Vermes D, Garcia W, Schneier F, Neria Y, Sanchez-Lacay A, Liebowitz MR. A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. Depress Anxiety. 2007;24(2):77-84.

Otis JD, Keane TM, Kerns RD, Monson C, Scioli E. The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic stress disorder. Pain Med. 2009 Oct;10(7):1300-11.

[redacted]

Rosen CS, Greenbaum MA, Schnurr PP, Holmes TH, Brennan PL, Friedman MJ. Do benzodiazepines reduce the effectiveness of exposure therapy for posttraumatic stress disorder? J Clin Psychiatry. 2013 Dec;74(12):1241-8.

Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B, Davis M,Bradley B, Duncan EJ, Rizzo A, Ressler KJ. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry. 2014 Jun;171(6):640-8.

Shore JH, Vollmer WM, Tatum EL. Community patterns of posttraumatic stress disorders. J Nerv Ment Dis. 1989 Nov;177(11):681-5.

Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch Gen Psychiatry. 2010 Jun;67(6):614-23.

Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry. 2001 Nov;62(11):860-8.

Williams, J. B. and K. A. Kobak. "Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA)." Br.J.Psychiatry. 2008. 192.1:52-58.

Winfield I, George LK, Swartz M, Blazer DG. Sexual assault and psychiatric disorders among a community sample of women. Am J Psychiatry. 1990 Mar;147(3):335-41.