Title Page

Protocol Title:

A Phase 3, Randomized, Double-blind, 2-arm, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy and Safety of BNC210 for the Acute, As-needed Treatment of Anxiety in Adults with Social Anxiety Disorder

Protocol Number: BNC210.014

Amendment Number: 1

Compound: BNC210

Brief Title: Efficacy of BNC210 in Acute, As-needed Treatment of Anxiety in Social Anxiety Disorder - 1

Study Phase: 3

Acronym: AFFIRM-1

Sponsor Name: Bionomics Limited

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

Regulatory Agency Identifier Number(s):

Registry	ID
IND	[redacted]

Approval Date: 12-NOV-2024

Confidentiality Statement

Sponsor Signatory:

[redacted]

Date

[redacted]

Bionomics Limited

[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Rationale for Amendment**
Protocol version 1.0	01-November-2023	Not applicable (original version)
Protocol version 1.1	12-November-2024	[redacted]

Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ADL	Activities of Daily Living
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ARCI	Addiction Research Center Inventory
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions – Severity
[redacted]	[redacted]
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatinine Phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	Follicle-Stimulating Hormone
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-treat
IUD	Intrauterine Device intrauterine hormone-releasing system
IUS	Intrauterine Hormone-Releasing System
IWRS	Interactive Web Response System
LSAS	Liebowitz Social Anxiety Scale
NCT	National Clinical Trial
[redacted]	[redacted]
MMRM	Mixed Model Repeated Measures
[redacted]	[redacted]
PK	Pharmacokinetic
P-gp	Permeability Glycoprotein
PGI-I	Patient Global Impressions - Improvement
PP	Per-Protocol
PRN	*pro re nata* or as needed
PTSD	Post-Traumatic Stress Disorder
QTcF	Fridericia-corrected QT Interval
QTL	Quality Tolerance Limit
RBC	Red Blood Cell
SAD	Social Anxiety Disorder
SAE	Serious Adverse Event
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SCID-5-CT	Structured Clinical Interview for DSM-5 Disorders - Clinical Trials version
SD	Standard Deviation

SIGH-D-17	Structured Interview Guide for the Hamilton Depression Rating Scale
SoA	Schedule of Activities
[redacted]	[redacted]
SUDS	Subjective Units of Distress Scale
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non-childbearing Potential

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, 2-arm, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy and Safety of BNC210 for the Acute, As-needed Treatment of Anxiety in Adults with Social Anxiety Disorder

Brief Title: Efficacy of BNC210 in Acute, As-needed Treatment of Anxiety in Social Anxiety Disorder - 1

Regulatory Agency Identifier Number(s):

Registry	ID
[redacted]	[redacted]

Rationale:

Social anxiety disorder (SAD) is a serious and chronic condition that is characterized by a persistent, intense fear of social and performance-related situations in which an individual is exposed to unfamiliar people and to potential for scrutiny by others. SAD carries a burden of functional disability, such as reduced workplace productivity, increased financial costs, and reduced health-related quality of life. If left untreated, SAD leads to an increased risk of depression, agoraphobia, alcohol abuse, and suicide attempts, which adversely impact self-esteem, socio-economic status, and survival.

There are no FDA-approved acute, taken as needed (PRN or *pro re nata*) treatments for SAD, although benzodiazepines, beta blockers, and other medications with anxiolytic properties (e.g., buspirone, pregabalin) are used off-label. There is an unmet medical need for safe and effective pharmacotherapies for the acute, as-needed treatment of anxiety in SAD to mitigate the chronicity and comorbidities of SAD and improve day-to-day functioning and quality of life.

BNC210 is a novel small molecule negative allosteric modulator of the α7 nicotinic acetylcholine receptor (nAChR), which is a novel mechanism of action with potential for treating neuropsychiatric disorders. BNC210 was identified in a program to develop non-sedating anxiolytic molecules and has been characterized in numerous nonclinical and clinical behavioral, pharmacological and safety studies. Based on the available data, BNC210 shows the potential to provide as-needed intermittent treatment of anxiety in SAD with similar efficacy to benzodiazepines, but with an improved safety profile.

[redacted]

[redacted]

This Phase 3, randomized, double-blind, 2-arm, parallel-group, placebo-controlled study will evaluate the efficacy and safety of a single 225 mg dose of BNC210 for the acute, as-needed treatment of anxiety in SAD.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 225 mg BNC210 for the acute, as-needed treatment of anxiety in social anxiety disorder (SAD)	• Change in Subjective Units of Distress Scale (SUDS) scores from baseline to the average of the performance phase of a public speaking challenge.
Key Secondary	
• To evaluate the efficacy of 225 mg BNC210 for the acute, as-needed treatment of anxiety in SAD	• Change in SUDS scores from baseline to the average of the anticipation phase of a public speaking challenge. • Change in Clinical Global Impressions-Severity (CGI-S) score from baseline to the end of the performance phase of a public speaking challenge. • Difference in Patient Global Impressions-Improvement (PGI-I) scores at the end of the performance phase of a public speaking challenge. • Change in State-Trait Anxiety Inventory-State component (STAI-State) scores from baseline to the end of the performance phase of a public speaking challenge.
Secondary	
• To evaluate the safety and tolerability of a single 225 mg dose of BNC210	• Incidence and severity of treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation and serious adverse events (SAEs), as well as changes from baseline in vital signs, electrocardiograms (ECGs), suicidality (Columbia Suicide Severity Rating Scale, C-SSRS), and laboratory (hematology, biochemistry, and urinalysis) parameters.

Exploratory	
• [redacted]	[redacted]
[redacted]	[redacted]

Overall Design:

This is a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study to compare the effects of a single 225 mg dose of BNC210 and placebo in approximately 332 participants with SAD during a public speaking challenge. Participants will attend a Screening Visit to conduct the assessments required to evaluate eligibility. Eligible participants will return to the clinic within 21 days after the Screening Visit and will be randomized in a 1:1 allocation ratio to either 225 mg BNC210 or matched placebo. Randomized participants will receive a single oral dose of their allocated study intervention and, approximately 1 hour later, will participate in a public speaking challenge. A follow-up assessment will be conducted by telephone or video conference approximately 7 days after administration of the study intervention to assess suicidal ideation and behavior, and record any adverse events (AEs) since the Treatment Day visit.

Brief Summary:

The purpose of this study is to evaluate the effects of a single, acute dose of BNC210 compared to placebo on reducing the severity of anxiety levels provoked by a public speaking challenge and measured using the SUDS in adult patients with SAD.

Number of Participants:

Approximately 500-550 participants will be screened to achieve a total enrollment of approximately 332 randomly assigned participants.

Study Arms and Duration:

The total duration for each participant enrolled in the study is expected to be approximately 4 weeks following the sequence below:

- Screening Period: 21 days (+3)
- Treatment Period with public speaking challenge: 1 day
- Follow-up Period: 7 (±3) days after treatment

Details of study assessments to be conducted at each visit are included in the Schedule of Activities (SoA) in Sections 1.3 and 1.4.

Each participant will be randomized in a 1:1 allocation ratio to receive a single dose of either 225 mg BNC210 or placebo. Treatment assignments will be double-blinded.

[redacted]

[redacted]

[redacted]

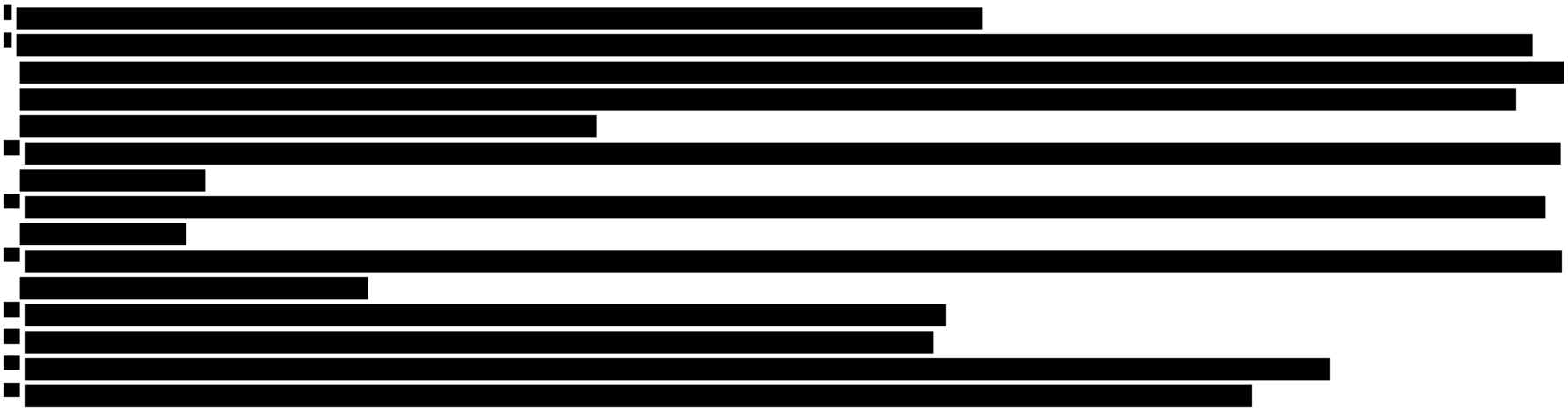
[redacted]

1.3. Schedule of Activities (SoA) – Overview

Assessment[1]	Screening (≤21 + 3 Days)[2]	Treatment (1 Day)[3]				Follow-up via Telephone or Video Conference (7 ± 3 Days Post-Treatment)[4]
		Baseline/ Predose	Dosing	Public Speaking Challenge	Post-Challenge	
Entrance and History						
Informed consent	X					
Inclusion/exclusion criteria	X	X[5]				
Demography	X					
Medical history, including prior/current medications	X					
Structured Clinical Interview for DSM-5 Disorders - Clinical Trials version (SCID-5-CT)	X					
Liebowitz Social Anxiety Scale (LSAS)	X	X				
Structured Interview Guide for the Hamilton Depression Rating scale (SIGH-D-17)	X					
Physical examination[6]	X	X				
Concomitant medications		X				
Randomization		X				
Efficacy Assessments[7]						
Subjective Units of Distress Scale (SUDS)		X		X		
State-Trait Anxiety Inventory-State Component (STAI-State)		X		X		
Clinical Global Impressions – Severity (CGI-S) Scale		X		X		
Patient Global Impressions – Improvement (PGI-I) Scale				X		

[redacted]

Assessment[1]	Screening (≤21 + 3 Days)[2]	Treatment (1 Day)[3]				Follow-up via Telephone or Video Conference (7 ± 3 Days Post-Treatment)[4]
		Baseline/ Predose	Dosing	Public Speaking Challenge	Post-Challenge	
Safety Assessments						
Vital signs[8]	X	X			X	
Triplicate 12-lead electrocardiograms (ECG)[9]	X				X	
Adverse event recording			X	X[10]	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[11]	X	X				X
Assessment of participant's readiness for discharge[12]					X	
Laboratory Assessments[13]						
Clinical laboratory tests (hematology, biochemistry, urinalysis)	X	X			X	
Serology (Human Immunodeficiency Virus [HIV]	X					
Serum pregnancy test (if applicable)	X					
Urine pregnancy test (if applicable)[14]		X				
Urine drug screen[15]	X	X				
Blood sample for BNC210 concentration[16]					X	
Study Intervention						



Assessment[1]	Screening (≤21 + 3 Days)[2]	Treatment (1 Day)[3]				Follow-up via Telephone or Video Conference (7 ± 3 Days Post-Treatment)[4]
		Baseline/ Predose	Dosing	Public Speaking Challenge	Post-Challenge	
Dosing with study intervention[17]			X			

1.4. Schedule of Activities (SoA) - Efficacy Assessments on Treatment Day

Assessment	Baseline/ Predose (~5 min)		Dosing (0 min)	Resting/ Post-dose (55 min)	Instructions on Challenge (60 min)	Public Speaking Challenge								
						Anticipation Phase			Performance Phase					
	Minutes					Minutes			Minutes					
	0	1				0	1	2	0	1	2	3	4	5
Subjective Units of Distress Scale (SUDS)	X	X		X		X	X	X	X	X	X	X	X	X
Clinical Global Impressions – Severity (CGI-S) Scale		X												X
Patient Global Impressions – Improvement (PGI-I) Scale														X
Anxiety Inventory – State component (STAI-State)		X		X										X

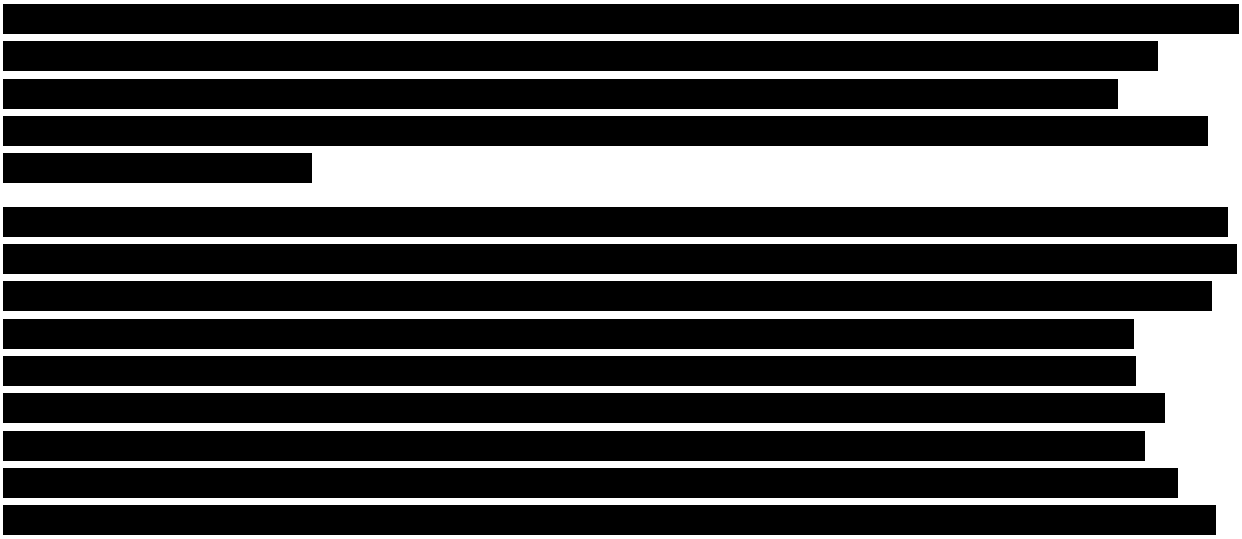
2. Introduction

Bionomics Limited is developing BNC210 for the acute, as-needed treatment of anxiety in SAD. BNC210 is a negative allosteric modulator of the α7 nAChR, which represents a novel target for the treatment of anxiety disorders. BNC210 is a new chemical entity that has exhibited potent anxiolytic activity in a range of animal models at low doses with a wide therapeutic window, and in Phase 2 clinical trials in patients with SAD and GAD. There is an absence of adverse effects, particularly those associated with acute, as-needed treatments for anxiety disorders, such as benzodiazepines.

2.1. Study Rationale

SAD is a serious and chronic condition that is characterized by a persistent, intense fear of social and performance-related situations in which an individual is exposed to unfamiliar people and to potential for scrutiny by others. SAD carries a burden of functional disability, such as reduced workplace productivity, increased financial costs, and reduced health-related quality of life. If left untreated, SAD leads to an increased risk of depression, agoraphobia, alcohol abuse, and suicide attempts, which adversely impact self-esteem, socio-economic status, and survival.

There are no FDA-approved acute, taken as needed (PRN or *pro re nata*) treatments for SAD, although benzodiazepines, beta blockers, and other medications with anxiolytic properties (e.g., buspirone, pregabalin) are used off-label. Benzodiazepines are potent, fast-acting anxiolytic drugs, but they are sedating and carry significant safety risks, including memory and motor impairment, serious risk of abuse, addiction, physical dependence, and withdrawal reactions. The updated (September 2020) boxed warning for benzodiazepines includes "*serious risk of abuse, addiction, physical dependence, and withdrawal reactions*" (U.S. FDA, 2020). Furthermore, currently approved antidepressant therapies for SAD are not useful in addressing the acute exacerbations of anxiety because of their slow onset of action and initial treatment can cause agitation and anxiety rather than alleviate those symptoms. Thus, there is an unmet medical need for safe and effective pharmacotherapies for the acute, as-needed treatment of anxiety in SAD to mitigate the chronicity and comorbidities of SAD and improve day-to-day functioning and quality of life.



[redacted]

This Phase 3, randomized, double-blind, 2-arm, parallel-group, placebo-controlled study will evaluate the efficacy and safety of a single 225 mg dose of BNC210 for the acute, as-needed treatment of anxiety in SAD.

[redacted]

[redacted]

[redacted]

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNC210 can be found in the IB and the participant Informed Consent Form (ICF).

No potential significant risks have been identified in the nonclinical and single dose clinical studies of BNC210 including the prior Phase 2 study in SAD (225 mg and 675 mg BNC210). At this stage in development, the benefit-risk profile of BNC210 appears favorable.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 225 mg BNC210 for the acute, as-needed treatment of anxiety in social anxiety disorder (SAD)	• Change in Subjective Units of Distress Scale (SUDS) scores from baseline to the average of the performance phase of a public speaking challenge.
Key Secondary	
• To evaluate the efficacy of 225 mg BNC210 for the acute, as-needed treatment of anxiety in SAD	• Change in SUDS scores from baseline to the average of the anticipation phase of a public speaking challenge. • Change in Clinical Global Impressions-Severity (CGI-S) score from baseline to the end of the performance phase of a public speaking challenge. • Difference in Patient Global Impressions-Improvement (PGI-I) scores at the end of the performance phase of a public speaking challenge. • Change in State-Trait Anxiety Inventory-State component (STAI-State) scores from baseline to the end of the performance phase of a public speaking challenge.
Secondary	
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Exploratory	
[redacted]	[redacted]

• [redacted]	[redacted]

Primary Estimand

The primary efficacy estimand is defined in Section 9.3.3.

4. Study Design

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study to compare the effects of a single 225 mg dose of BNC210 and placebo in approximately 332 participants with SAD during a public speaking challenge. Participants will attend a Screening Visit to conduct the assessments required to evaluate eligibility. Eligible participants will return to the clinic within 21 days after the Screening Visit and will be randomized in a 1:1 allocation ratio to either 225 mg BNC210 or matched placebo. Randomized participants will receive a single oral dose of their allocated study intervention and, approximately 1 hour later, will participate in a public speaking challenge. A follow-up assessment will be conducted by telephone or video conference approximately 7 days after administration of the study intervention to assess suicidal ideation and behavior, and record any adverse events (AEs)since the Treatment Day visit.

Details are included in the Schedule of Activities (SoA), Section 1.3 and 1.4).

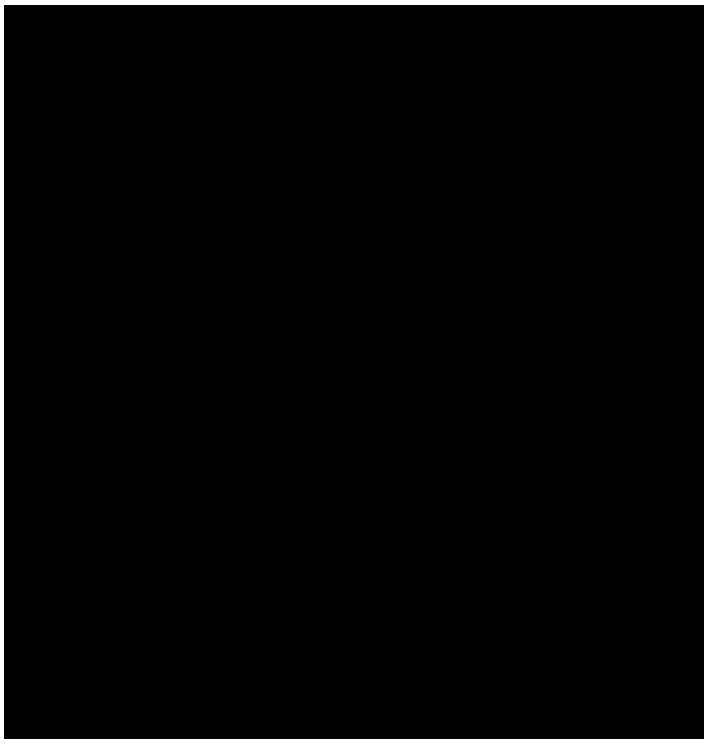
4.2. Scientific Rationale for Study Design

This, double-blind, placebo-controlled, parallel-group, multicenter study will compare the acute effects of administration of BNC210 or placebo in adult participants with SAD during an anxiety-provoking public speaking challenge. This challenge is a suitable model for examining the acute effects of BNC210 because it elicits anxiety in individuals with SAD who experience intense fear and anxiety in situations involving performance or evaluation by others. A performance of public speaking is the most commonly endorsed fear in individuals with SAD (Ruscio 2008). The public speaking challenge is a well-characterized model that has been used by others to investigate effects of pharmacological and nonpharmacological interventions on subjective measures of anxiety in SAD patients (Heimberg 1998; Helmus 2005; Bergamaschi 2011; Rodebaugh 2013; Leibowitz 2014; Morrison 2016), and was used in the Phase 3 clinical trials for evaluation of the investigational drug, fasedienol, for the acute treatment of anxiety in patients with SAD (NCT04754802 and NCT05011396).

A double-blind, placebo-controlled study design has been chosen as a well-established and appropriate study design to minimize the potential for bias in study assessments or in reporting of AEs. Clinic staff and participants are blinded to treatment assignments to ensure objective reporting. In addition, participants will be randomized in a 1:1 allocation ratio to receive a single dose of 225 mg BNC210 or placebo to ensure there are no order effects and to further minimize bias. [redacted]

[redacted]

[redacted]



[redacted]

4.4. End of Study Definition

The end of the study is defined as the date of the follow-up assessment for the last participant in the study.

5. Study Population

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

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

5.1. Inclusion Criteria

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

Age

1. The participant is 18 to 65 years of age (inclusive) at the time of signing informed consent.

Type of Participant and Disease Characteristics

2. The participant has a current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and as confirmed by the Structured Clinical Interview for DSM-5 Disorders - Clinical Trials version (SCID-5-CT), and the maximum age of onset of clinical symptoms of SAD by history is 25 years old.
3. The participant has a total score of ≥60 on the Liebowitz Social Anxiety Scale (LSAS) at the Screening Visit and at Baseline with no >20% change in score from Screening to Baseline, and a sub-score of 2 or 3 on Question 6 (Fear or Anxiety subscale) at the Screening Visit and at Baseline.
4. In the opinion of the Investigator, the participant has a high probability for adherence with all study procedures.
5. The participant is fluent in English and is able to understand and comply with written and verbal protocol-related requirements.
6. Participant is able to swallow tablets.
7. The participant has received study inclusion approval through an adjudication process as to final suitability for the study

Sex and Contraceptive/Barrier Requirements

8. Participants are eligible for the study if they comply with the following requirements.
    a. Male participants are eligible to participate if they agree to:
        i. Refrain from donating sperm during the study intervention period and for at least 60 days after taking their dose of study intervention and
        ii. Be abstinent from heterosexual intercourse if this is their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent during the study intervention period and for at least 60 days after taking their dose of study intervention, or

iii. Agree to use a male condom with spermicide during the study intervention period and for at least 60 days after taking their dose of study intervention when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. The nonpregnant WOCBP partner must be using an additional highly effective contraceptive method (failure rate of <1% per year) as described in Appendix 4: Contraceptive and Barrier Guidance.

b. Female participants who are not pregnant or breastfeeding are eligible to participate if the following conditions apply:

i. The participant is of nonchildbearing potential (WONCBP) as defined in Appendix 4: Contraceptive and Barrier Guidance, or

ii. The participant is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) as described in Appendix 4: Contraceptive and Barrier Guidance including sexual abstinence, preferably with low user dependency (e.g., implantable progesterone only hormone contraceptive associated with inhibition, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], bilateral tubal occlusion, azoospermic partner) during the study intervention period and for at least 60 days after taking the dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the dose of study intervention and

iii. The participant is a WOCBP and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the study intervention period and for at least 60 days after taking the dose of study intervention and

iv. The participant has a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline (within 24 hours before the dose of study intervention).

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

Informed Consent

9. The participant is capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. The participant has a history of bipolar disorder, schizophrenia, schizoaffective disorder, psychotic disorders, anorexia or bulimia, body dysmorphic disorder, PTSD, autism-spectrum disorder or obsessive-compulsive disorder as identified at the Screening Visit, or has any other Axis I or II disorder which is currently the primary focus of treatment over SAD at the time of the Screening Visit.
2. The participant has a score of ≥18 on the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D-17) at the Screening Visit.
3. The participant has moderate or severe alcohol-use disorder, or any other substance-use disorder (any severity), according to DSM-5, in the 12 months before the Screening Visit.
4. The participant is at an increased risk of suicide, defined as:
    a. Any suicide attempt in the 12 months before the Screening Visit as disclosed by the participant using the Columbia-Suicide Severity Rating Scale (C-SSRS).
    b. Any suicidal ideation with intent (yes to item 4 and/or 5) or suicidal behavior in the past 12 months, as captured on the C-SSRS at the Screening Visit and Baseline Visit.
5. The participant has impaired renal function as indicated by clinically significant abnormal values for serum creatinine, serum blood urea nitrogen (BUN), or plasma urea.
6. The participant has a value for serum alanine transaminase (ALT), aspartate transaminase (AST) >2.0 × upper limit of normal (ULN) at the Screening Visit.
7. The participant has a serum total bilirubin value >1.5 × ULN (Participants with Gilbert's syndrome can be included with total bilirubin >1.5 x ULN as long as direct bilirubin is ≤ 1.5 x ULN) at the Screening Visit.
8. The participant has current or past history of cirrhosis, or unstable liver or biliary disease per investigator assessment. NOTE: Stable chronic liver disease or asymptomatic gallstones at Screening or within 3 months prior to starting study intervention is acceptable if the participant otherwise meets entry criteria.
9. The participant has any clinically significant abnormalities in laboratory test results (biochemistry, hematology, or urinalysis) as assessed by the Investigator.
10. The participant has a systolic blood pressure value >140 mmHg or diastolic blood pressure value >90 mmHg at the Screening Visit or Baseline. Two repeat measures are allowed at the discretion of the Investigator.
11. The participant has a QTcF (QT interval corrected for heart rate using Fridericia's method) value >450 msec if male or >470 msec if female or a QTc value >480 msec if the participant has bundle branch block, as measured by electrocardiogram (ECG) at the Screening Visit.

12. The participant has any clinically significant ECG abnormality as determined by the Investigator at the Screening Visit.
13. The participant has a family history of congenital long QT syndrome, Brugada syndrome, or unexplained sudden cardiac death.

Prior/Concomitant Therapy

14. The participant has used psychotropic medications, including antidepressants, mood stabilizers, stimulants, antipsychotics, anticonvulsant drugs (including gabapentinoids), hypnotics (zolpidem, zopiclone, eszopiclone, zaleplon), acetylcholinesterase inhibitors, or anxiolytics, such as benzodiazepines, within 30 days before the Screening Visit. Participants who have been taking benzodiazepines daily within 90 days before the Screening Visit are not eligible to participate in the study. No concurrent use of these medications is allowed during the study.
15. The participant has used beta blockers, doxazosin, prazosin, clonidine, first-generation sedating H1 antihistamines, any recreational drugs, over-the-counter medication, or herbal preparations to treat symptoms of anxiety or SAD within 7 days before the Screening Visit. No concurrent use of these medications is allowed on study.
16. The participant has used cytochrome P450 3A4 (CYP3A4) inducers within 30 days before the Screening Visit. No concurrent use of these medications is allowed during the study.
17. The participant has used moderate-strong CYP3A4 inhibitors within 2 weeks before the Screening Visit. This includes, but is not limited to, grapefruit or grapefruit-containing products. No concurrent use of these medications is allowed during the study.
18. The participant has used inhibitors of permeability glycoprotein (P-gp) that cause clinically significant drug interactions within 14 days (6 months for amiodarone) before the Screening visit. No concurrent use of these medications is allowed during the study.
19. The participant has received empirically supported psychotherapy (such as cognitive behavioral therapy) for the treatment of anxiety within the last 60 days prior to the Screening Visit. No new psychotherapy can start between the Screening Visit and the Follow-up Visit.
20. The participant has a history of treatment failure with 2 or more approved psychotropic medications prescribed for the treatment of SAD. Each trial must have lasted at least 6 weeks at an adequate dose to be considered a failed attempt. A trial that was terminated due to intolerability or side effects does not constitute a failed attempt.

Prior/Concurrent Clinical Study Experience

21. The participant is currently enrolled OR has previously participated in another investigational study in which an investigational intervention (e.g., drug, vaccine, invasive device) was administered within 30 days before the ICF for this study is signed.

22. The participant has previously participated in a study that involved a public speaking challenge.
23. The participant has previously participated in 5 or more clinical studies.
24. The participant has previously participated in a study in which BNC210 was administered.
25. The participant has family members, friends or colleagues who are employed by Bionomics, the Contract Research Organization managing the study, a clinical study site, or other organization providing services for the study.

Diagnostic Assessments

26. The participant has a positive result for human immunodeficiency virus (HIV), at the Screening Visit.
27. The participant has a positive urine test for an illicit substance, including cannabis, at the Screening Visit or Baseline Visit. No concurrent use of these substances is allowed on study.

Other Exclusions

28. The participant has a history of allergies, allergic reactions, or hypersensitivity to BNC210 or its excipients.
29. The participant is not suitable to participate in the study, in the opinion of the Investigator, because of clinically significant findings on medical history that could interfere with the objectives of the study or put the participant at risk or any other reason the Investigator deems applicable.

5.3. Lifestyle Considerations

There are no specific lifestyle considerations or restrictions applicable to this study outside of the criteria detailed in Sections 5.1, 5.2, and 6.9. [redacted]

5.4. Screen Failures

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

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

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, if deemed appropriate by the Investigator and with prior approval from the Sponsor/Medical Monitor. Rescreened participants should be reconsented and be assigned a new participant number (Subject ID) for every screening/rescreening event.

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

Section not applicable.

6. Study Intervention(s) and Concomitant Therapy

Detailed information related to the composition of the study interventions to be administered to participants in this study can be found in Table 1, the study Investigational Product Manual, and the IB.

[redacted]

6.1. Study Intervention(s) Administered

In this parallel-group, randomized study, participants who meet study entry criteria will be randomly assigned in a 1:1 allocation ratio to receive either 225 mg BNC210 or placebo.

[redacted]

Table 2. Study Arm(s)

Arm Title	225 mg BNC210	Placebo
Arm Type	Experimental	Placebo Comparator
Associated Intervention Labels	225 mg BNC210	Placebo

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Assignment to Study Intervention

IWRS	After a participant signs the ICF at Screening, site personnel will register the participant in the interactive web response system (IWRS). Upon successful completion of the Screening Module, the system will assign the participant a unique participant number (Subject ID). Randomization will be performed as double-blind, central randomization. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate study intervention to randomization numbers. The randomization numbers will be assigned sequentially through the IWRS as participants enter the study. Study center will not be a blocking factor in the randomization schedule. The randomization schedule will be prepared before the start of the study. No one involved in the study performance will have access to the

	randomization schedule before official unblinding of treatment assignment. No participant will be randomized into this study more than once. Upon successful completion of randomization in the IWRS, the system will determine the correct study intervention to dispense. Once a participant is randomized to a treatment arm, the randomization will remain documented as such. The system will never reuse the same randomization number. The system will then determine which specific carton (with assigned number) of the assigned study intervention type is available for dispensing and inform the study site to dispense that specific carton. The assigned carton will correspond to the correct treatment for the participant.

6.4. Blinding, Masking

Blinding and breaking of the blind via IWRS	This is a double-blind study in which all participants, investigators, raters, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment, with the exception of a specified unblinded statistician and IWRS manager, who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel. Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the participant's treatment assignment. Participant safety must always be the first consideration in making such a determination. Unblinding should be discussed in advance with the Medical Monitor, if possible. If the investigator is not able to discuss treatment unblinding in advance, then they must notify the Medical Monitor as soon as possible about the unblinding incident without revealing the participant's treatment assignment. For emergency unblinding, study personnel will use the IWRS. The IWRS will be programmed with blind-breaking instructions. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded. Overall unblinding will take place at the end of the study only after database lock.

6.5. Study Intervention Compliance

Study intervention will be administered at the study site under direct supervision of authorized site staff. A mouth check will be performed to ensure that the tablet dispensed for dosing was swallowed.

6.6. Dose Modification

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

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

Participants will not have access to study intervention immediately after completion of their participation in the study. Participants should be directed to receive standard of care treatments as directed by the Investigator or their primary care physician. Participants may be eligible to enroll at a later time in a future Phase 3 open label study designed to evaluate the long-term safety and tolerability of BNC210 when taken as-needed for the acute treatment of anxiety in SAD.

6.8. Treatment of Overdose

For this study, any dose of BNC210/placebo greater than 225 mg will be considered an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until they have resolved or stabilized.
- Document the quantity of the excess dose.

6.9. Prior and Concomitant Therapy

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

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

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

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

Inducers of cytochrome P450 3A4 should not be used within 30 days of Screening and their use is prohibited during the study. This includes, but is not limited to: carbamazepine, phenytoin, oxcarbazepine, barbiturates, phenobarbital, butalbital, St. John's wort, rifampicin, rifabutin, efavirenz, nevirapine, pioglitazone, troglitazone, corticosteroids by the systemic route (refer to the following website for a more extensive list https://drug-interactions.medicine.iu.edu/MainTable.aspx).

Moderate to strong inhibitors of cytochrome P450 3A4 should not be used within 14 days of Screening and their use is prohibited during the study. These include grapefruit juice, verapamil, diltiazem, fluvoxamine, fluconazole and itraconazole, and HIV antivirals (refer to the following website for a more extensive list https://drug-interactions.medicine.iu.edu/MainTable.aspx).

Inhibitors of P-gp that cause clinically significant drug interactions should not be used within 14 days (6 months for amiodarone) of Screening and their use is prohibited during the study. These include verapamil, amiodarone, clarithromycin, erythromycin, itraconazole, ketoconazole, ritonavir, cobicistat, cyclosporine, quinidine, diltiazem.

Participants who are being treated with an antidepressant medication must have discontinued the medication for at least 30 days prior to Screening (as per exclusion criterion #14) and be titrated off their medication in accordance with current prescribing guidelines. Participants must also have discontinued chronic daily use of benzodiazepines for at least 90 days prior to Screening. The withdrawal of these medications is at the discretion of the participant in consultation with their primary physician and falls outside the scope of this study protocol. Concurrent use of these medications is also prohibited during all stages of the study.

The use of any other CNS-acting medications, including intermittent use of benzodiazepines, beta blockers, recreational drugs, over-the-counter medications, or herbal preparations for the treatment of symptoms of anxiety or SAD, is also not allowed within 30 days of Screening and at no time during the study.

The CNS-acting medications prohibited during the study include, but are not limited to, antidepressants, mood stabilizers, methylphenidate and other stimulants, quetiapine and other antipsychotics, anticonvulsant drugs (including gabapentinoids), zaleplon and other hypnotics, benzodiazepines, doxazosin, prazosin, clonidine, first generation sedating H1 antihistamines, zopiclone, eszopiclone, zolpidem extended-release and acetylcholinesterase inhibitors.

The use of other nonprescription medications (including herbal medications not for the treatment of symptoms of anxiety or SAD) 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.

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The process for discontinuation of specific sites or the study as a whole are detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

7.1. Discontinuation of Study Intervention

Section not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- If the participant had received study intervention prior to discontinuing from the study, a Follow-up Visit should be conducted if possible, as shown in the SoA (Section 1.3).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Sections 1.3 and 1.4). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue on study.
- Adherence to the study design requirements, including those specified in the SoA (Sections 1.3 and 1.4), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

[redacted]

- Once all post-challenge assessments on the Treatment Day have been completed, the Investigator should assess the participant's suitability to be discharged from the study site based on their medical judgment.

[redacted]

- Visits scheduled due to increased safety monitoring, if applicable, must be captured as an unscheduled visit. 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.
- A visit with a participant's primary physician (i.e., not a study Investigator) is not considered an unscheduled visit. Similarly, hospital admissions due to SAEs are also not considered unscheduled visits. Assessments completed by external institutions should not be entered into the eCRF.

[redacted]

[redacted]

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3 and 1.4).

[redacted]

8.2.2. Subjective Units of Distress Scale (SUDS)

The SUDS measures the subjective intensity of disturbance or distress currently experienced by an individual and is a standard instrument for rating social and performance anxiety in patients with SAD during role-playing situations. The individual self-assesses where they are on the scale, between 0-100, with higher numbers indicating more anxiety/greater discomfort (Wolpe 1969).

8.2.3. Clinical Global Impressions – Severity (CGI-S) Scale

The CGI-S is a widely accepted tool, frequently employed in clinical trials for neuropsychiatric disorders that measures overall disease severity of the participant's symptoms as scored by a clinician (Guy 1976). Severity is rated on the CGI-S from 1 (normal, not at all ill) to 7 (among the most extremely ill of patients). [redacted]

8.2.4. Patient Global Impressions – Improvement (PGI-I) Scale

The PGI-I is a patient self-reported counterpart of the CGI designed to assess the patient's impression of their perceived change in overall symptoms. Improvement is rated on the PGI-I from 1 (very much improved) to 7 (very much worse). [redacted]

8.2.5. Spielberger State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger 1983) is a self-report measure of subjective anxiety. It comprises 2 scales of 20 items asking participants to report their feelings of anxiousness: the STAI-State scale requires reporting of feelings at the time of questionnaire completion and the STAI-Trait scale requires reporting of how the subject generally feels. Responses are marked on a 4-point scale from "not at all" to "very much so". The STAI-State component only will be used in this study.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, skin and lymphatics, eyes, ears, nose, throat, cardiovascular system, respiratory system, abdomen/gastrointestinal system, musculoskeletal, and neurological systems. Other body systems may also be examined as required. Height and weight will also be measured at Screening only.
- An abbreviated physical examination will include, at a minimum, assessments of the eyes, ears, nose, throat, cardiovascular system, respiratory system, and abdomen/gastrointestinal system. Other body systems may also be examined as required.

8.3.2. Vital Signs

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

8.3.3. Electrocardiograms

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

- QTcF values will be derived from the data available and the average QTcF will be used when assessing eligibility.

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

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

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2: Clinical Laboratory Tests for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor/Sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2: Clinical Laboratory Tests, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
    - All events of ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin >2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) which may indicate severe liver injury (possible Hy's Law), as well as all events of ALT or AST ≥ 3 x ULN, must be reported to the Medical Monitor in an expedited manner. Details of required actions and follow-up are given in Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments.

8.3.5. Suicidal Ideation and Behavior Risk Monitoring

BNC210 is considered to be a CNS-active intervention and patients with SAD can sometimes develop suicidal ideation or behavior as part of their mental condition (Olfson 2000).

Baseline assessment of suicidal ideation and behavior will be assessed using the C-SSRS.

The C-SSRS is a suicidal ideation rating scale designed to identify behaviors that may be indicative of a participant'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.

Prior to the participant being discharged from the study site on the Treatment Day, the Investigator will assess any intervention-emergent suicidal behavior as part of their overall assessment of the participant's suitability to be discharged.

The C-SSRS will be conducted by video/phone at the Follow-up visit.

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

The definitions of AEs and SAEs can be found in Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs/SAEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All AEs and SAEs will be collected from the start of intervention until the Follow-up Visit at the timepoints specified in the SoA (Section 1.3). Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

8.4.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants (after obtaining the necessary signed informed consent from the female partner) will be collected after the start of study intervention and until 1 week after the last dose of study intervention is administered. In addition, participants should be instructed to spontaneously report any pregnancy to the Investigator that occurs within 60 days of receiving study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy, signing and dating the Pregnancy Data Collection Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF. Pregnancy reporting contact information can be found in Appendix 3, Section 10.3.4.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner of the participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4.

While the Investigator is not obligated to actively seek this information in former study participants/pregnant partner, they may learn of an SAE through spontaneous reporting.

- Any participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

[redacted]

8.6. Pharmacodynamics

Section not applicable

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Section not applicable.

8.10. Medical Resource Utilization and Health Economics

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

[redacted]

9. Statistical Considerations

A SAP that describes the full details of the planned statistical analyses will be prepared. This section is a summary of the planned statistical analyses for the primary and secondary endpoints. Any planned exploratory analyses will be detailed in the study SAP.

9.1. Statistical Efficacy Hypotheses

The primary objective of this study is to assess the effects of a single dose of BNC210 compared to placebo on change in self-reported anxiety severity as measured by the SUDS from baseline to the performance phase in a public speaking challenge.

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

  H_{01}: Mean changes in SUDS scores between baseline and the average of the performance phase in a public speaking challenge between a single 225 mg dose of BNC210 and placebo are equal.

The secondary objectives of this study and their respective null hypotheses of the equality of a single 225 mg dose of BNC210 and placebo are:

- To assess the effects of BNC210 compared to placebo on change in self-reported anxiety severity as measured by the SUDS in a public speaking challenge:

  H_{02}: Mean changes in SUDS scores between baseline and the average of the anticipation phase in a public speaking challenge between a single 225 mg dose of BNC210 and placebo are equal.
- To assess the effects of BNC210 compared to placebo in reducing clinician assessed disease severity as measured by the CGI-S in a public speaking challenge:

  H_{03}: Mean changes in CGI-S scores between baseline and the end of the performance phase in a public speaking challenge between a single 225 mg dose of BNC210 and placebo are equal.
- To assess the effects of BNC210 compared to placebo in reducing participant assessed disease severity as measured by the PGI-I in a public speaking challenge:

  H_{04}: Mean differences in PGI-I scores at the end of the performance phase in a public speaking challenge between a single 225 mg dose of BNC210 and placebo are equal.
- To assess the effects of BNC210 compared to placebo in reducing self-reported symptoms of anxiety as measured by the STAI-State in a public speaking challenge:

  H_{05}: Mean changes in STAI-State scores between baseline and the end of the performance phase in a public speaking challenge between a single 225 mg dose of BNC210 and placebo are equal.

9.2. Analysis Sets

The following analysis populations are planned for this study:

- Safety Population (SAF): All participants who receive study intervention.
- Intent-to-Treat Population (ITT): All randomized participants. The ITT population will be the primary population used for all efficacy analyses.
- Modified Intent-to-Treat Population (mITT): All randomized participants who receive study intervention.
- Per Protocol Population (PP): All participants in the mITT who have no major protocol deviations [redacted]

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

9.3.2. Study Participants and Demographics

9.3.2.1. Disposition and Withdrawals

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

9.3.2.2. Protocol Deviations

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

9.3.2.3. Demographics and Other Baseline Characteristics

The following analyses will be conducted for all analysis populations:

- Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the study intervention in accordance with local regulatory requirements. Baseline participant characteristics will include medical history including smoking status, confirmation of SAD diagnosis, LSAS total score (Screening and Baseline), SIGH-D-17 score at

Screening, and baseline scores for SUDS (average of 2 baseline scores), CGI-S, and STAI-State.

- Prior and concomitant medications will be summarized by treatment group, by the number and percentage of participants taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

9.3.3. Primary Endpoint(s)/Estimand(s) Analysis

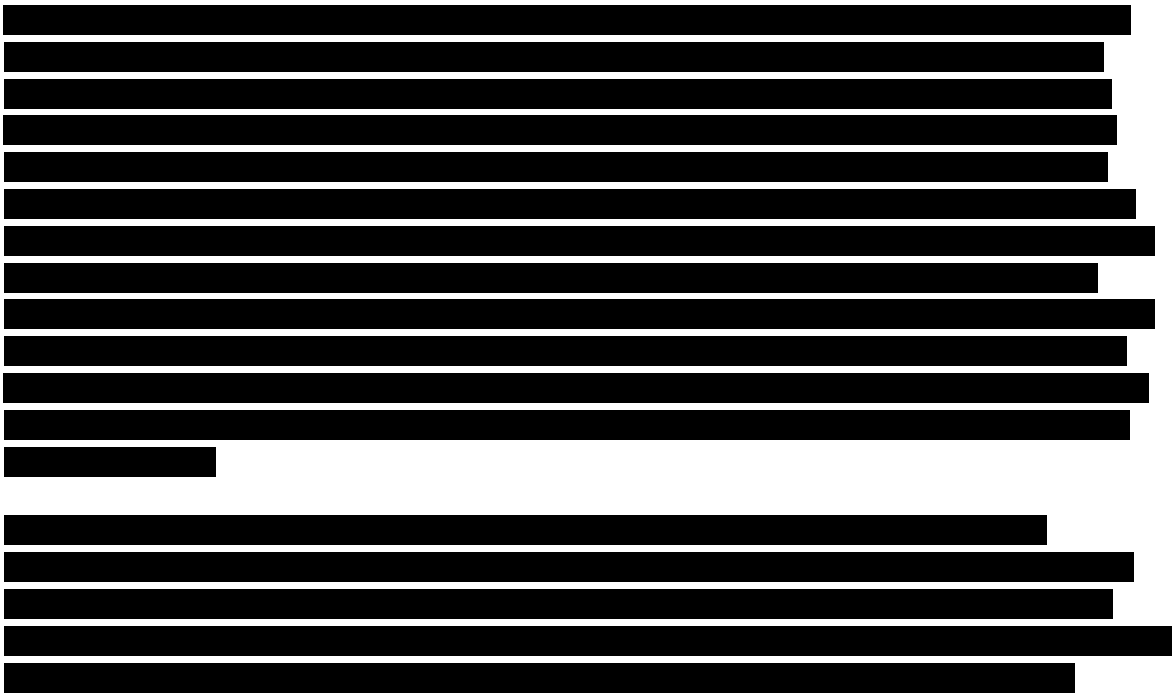
The primary efficacy estimand is defined by the following components:

1. The population is restricted to participants with SAD who meet all the inclusion/exclusion criteria.

2. The variable is change in SUDS score from baseline (average of 2 baseline SUDS scores) to the average of the performance phase of a public speaking challenge.

3. During the study, participants may be exposed to possible known or unknown intercurrent events that could perhaps impact the estimand. The treatment policy strategy will be adopted for handling participants who refuse to take study intervention, receive incorrect study intervention, and take prohibited medications during the study. In the unlikely event of a death of a participant, or a participant withdraws consent, a hypothetical strategy will be utilized.

4. The population-level summary is the treatment difference in least squares mean change in SUDS score from baseline to the average of the performance phase of a public speaking challenge, analyzed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with multiple imputation assuming missing data are missing not at random (MNAR).



[redacted]

[redacted] arm (placebo).

[redacted].

9.3.4. Key Secondary Endpoints Analysis

The first key secondary efficacy endpoint (change in SUDS score from baseline to the average of the anticipation phase) will be analyzed using the same model that is used for the primary efficacy endpoint. A linear contrast of the MMRM parameters will be used to compare treatments on the change from baseline to the average of the anticipation phase.

The second key secondary efficacy endpoint (change in CGI-S score from baseline to the end of the performance phase) will be analyzed using an analysis of covariance model [redacted] The model will include fixed effects for treatment, sex, and a covariate for baseline CGI-S.

The third key secondary efficacy endpoint (difference in PGI-I score at the end of the performance phase) will be analyzed using an analysis of covariance model with multiple imputation assuming missing data are MNAR. The model will include fixed effects for treatment and sex.

The fourth key secondary efficacy endpoint (change in STAI-State from baseline to the end of the performance phase) will be analyzed using similar methods to the second key second efficacy endpoint (CGI-S).

[redacted]

9.3.5. Multiplicity Adjustment

To control for multiplicity, a sequential testing procedure will be used on the key secondary efficacy endpoints. Thus, if the primary efficacy endpoint is statistically significant, then the first key secondary efficacy endpoint can be tested. Then if the first key secondary efficacy endpoint is statistically significant, the next key secondary efficacy endpoint can be tested. This will continue until all key secondary efficacy endpoints have been tested, or until non-significance is observed for an endpoint. The ordering of the tests will be SUDS (performance phase – primary endpoint), SUDS (anticipation phase), CGI-S, PGI-I, and then STAI-State. Following this procedure will not result in any need for α-adjustments to conclude statistical significance.

[redacted]

[redacted]

[redacted]

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10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier as part of their study participation. Any participant records or datasets that are transferred to the Sponsor will contain the identifier and information collected as part of the study only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the ICF.
- The study data entry and study management systems used by clinical sites and by the Sponsor/designee will be secured and password protected.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Data Quality Assurance

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

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, recorded data from automated instruments, memoranda, and pharmacy dispensing records.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7. Study and Site Closure

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 3 will be performed by the central laboratory at the timepoints described in the SoA (Section 1.3).

Local laboratory results may only be required in the event that the central laboratory results are not available in time to support urgent safety or study intervention administration decisions, following consultation with the Medical Monitor. If a local sample is required, it is important that the sample for central analysis is also obtained, where possible. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 3. Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count		RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Transaminase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Transaminase (ALT)	Total protein
	Glucose	Calcium	Alkaline phosphatase (ALP)[2]	
Routine Urinalysis	Specific gravity, urobilinogen, pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase, color, appearance Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]			

Laboratory Tests	Parameters
Other Screening Tests	Urine drug test at Screening Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Serology (Human Immunodeficiency Virus [HIV] antibody) All study-required laboratory tests will be performed by a central laboratory, with the exception of: ○ Urine drug test at Baseline / Pre-dose ○ Urine pregnancy test at Baseline / Pre-dose[3]

NOTES:

1. All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin >2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value), which may indicate severe liver injury (possible Hy's Law), as well as all events of ALT or AST ≥ 3 × ULN, must be reported to the Medical Monitor in an expedited manner. Details of required actions and follow-up are given in Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments.

2. If ALP is elevated, consider fractionating.

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

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

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

Definition of Unsolicited and Solicited AE

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

Events Meeting the AE Definition

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

AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

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

10.3.2. Definition of SAE

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

a. Results in death

b. Is life threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and

accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other important medical event situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

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

AE and SAE Recording

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

- At each specified time point, the participant will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as
    - "How are you feeling?"
    - "Have you experienced any issues since your last visit?"
    - "Have you taken any new medications since your last visit?"
- Any clinically relevant observations made during the visit will also be considered AEs.
- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number (Subject ID), will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories, following the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (published 27 November 2017).

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

- Grade 1 Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 Life Threatening: Life-threatening consequences; urgent intervention indicated
- Grade 5 Death: Death related to AE.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The Investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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

with the onset of the event and the administration of study intervention and/or a causal relationship is considered biologically implausible.

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

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

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

[redacted]

If the email was not successfully transmitted and a second attempt is unsuccessful, contact the site's CRA.

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

- Protocol number
- Reporter (study site and Investigator)
- Participant number (Subject ID)
- Participant's year of birth
- Participant's sex
- Date of study intervention dose
- Date of last dose of study intervention prior to SAE onset, if applicable
- SAE term
- Date the event met a seriousness criteria
- Severity of the SAE term
- A brief description of the event, treatment, outcome to date, and any actions taken with study intervention
- The seriousness criteria(on) that were met
- Investigator causality assessment
- Concomitant medications taken within 30 days of onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Whether and when the Investigator was unblinded as to the participant's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the [redacted] via the same contact details above as soon as possible on a new blank the SAE Report Form noting a follow-up report, together with the following minimal information: initial report, SAE, date of occurrence, study participant

identifier, treatment period of study intervention, and site number. This will allow the follow-up information to be linked to the initial SAE report.

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

The Investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of their health authorities, IRB, principal and coordinating investigators, study investigators, and institutions. Each Investigator is obligated to learn about the reporting requirements for investigators in their country. The study monitor may be able to assist with this.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

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

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

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

10.4.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

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

The table below describes suggested actions and follow-up assessments should a participant's post-challenge clinical safety laboratory results meet the following criteria.

<table>
<tr><th colspan="2">Liver Chemistry Criteria Requiring Increased Follow-up[1]</th></tr>
<tr><td>ALT or AST-absolute</td><td>ALT or AST ≥ 3 × ULN</td></tr>
<tr><td>Bilirubin[2]</td><td>ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN
(for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin >2xULN and at least doubled from baseline value)</td></tr>
<tr><td>Symptomatic</td><td>ALT or AST ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)</td></tr>
<tr><th colspan="2">Suggested Actions, Monitoring, and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments
(if not already performed)</th></tr>
<tr><td>• Report the event to the Medical Monitor within 24 hours.
• Complete a Serious Adverse Event Report Form <u>if the event</u> also met the criteria for an SAE.[2]
• Perform follow-up assessments as described in the Follow-up Assessment column.
• Repeat blood work within 24 hours
• Assess for symptoms
MONITORING:
<u>If ALT or AST >5 x ULN and no change in total bilirubin or symptoms</u>
• Repeat liver chemistry tests (include ALT, AST, , ALP, and total & direct bilirubin) and perform follow-up assessments within 72 hours.</td><td>• Viral hepatitis serology[3]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), International Normalized Ratio (INR) and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥ 2 × ULN (if not already done).
• Obtain complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity.
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications).
• Record alcohol use</td></tr>
</table>

• Monitor participants **weekly** until liver chemistry abnormalities return to normal or ≤1.5× baseline values. **<u>If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN with or without symptoms OR ALT or AST ≥ 3 x ULN and symptomatic</u>** • Repeat liver chemistry tests (include ALT, AST, ALP, and total & direct bilirubin) and perform follow-up assessments within **24 hours**. • Monitor participant **twice weekly** until liver chemistry test abnormalities return to normal or ≤1.5× baseline values. • A specialist or hepatology consultation is recommended. **<u>If ALT or AST ≥ 3 x ULN AND total bilirubin ≤ 2 x ULN</u>** <u>and asymptomatic</u> • Repeat liver chemistry tests (include ALT, AST, ALP, and total & direct bilirubin) and perform follow-up assessments within **5-7 days**. • Monitor participants **weekly** until liver chemistry abnormalities return to normal, or ≤1.5× baseline values.	**If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or ALT or AST ≥ 3 × ULN associated with symptoms** Obtain the following in addition to the assessments listed above: • Antinuclear antibody, anti-smooth muscle antibody and quantitative total immunoglobulin G (IgG), or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease. • Liver biopsy may be considered and discussed with local specialist if available. **Report all assessments conducted to the Medical Monitor as they become available.**

1. If a participant's liver chemistry results for ALT, AST and/or total bilirubin are >ULN at baseline, instead of applying fold-increase >ULN in each case described in the table, replace this with fold-increase >baseline value.
2. All events of ALT or AST >3 × ULN **and** total bilirubin > 2 × ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin >2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to Sponsor in an expedited manner and as an SAE if SAE criteria met**.
3. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

11. References

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