BNC210: A Novel Therapeutic in Development for PTSD

CREATING INNOVATIVE THERAPIES FOR SERIOUS HUMAN DISEASES.

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Vice President, Neuroscience Research

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Factors Affecting Future Performance

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What is Posttraumatic Stress Disorder?

PTSD is:
• a well defined and accurately diagnosed condition
• a set of reactions that can develop in some people who have experienced a traumatic event which threatened their life or safety, or that of others around them, like combat, a natural disaster, a car accident, or sexual assault.

People with PTSD continue to experience memories and feelings of intense fear, helplessness or horror long after the trauma was experienced.

Diagnosis of PTSD is performed using the Clinician Administered PTSD Scale based on symptom cluster criteria from DSM-5.

- B. Intrusion symptoms (1/5) (e.g., nightmares, flashbacks, intrusive thoughts, and physiological reactions to trauma reminders).
- C. Avoidance of stimuli associated with the trauma (1/2) (intentionally avoiding trauma-related people, places, or activities).
- D. Negative alterations in cognition and mood that are associated with the traumatic event (2/7) (e.g., dissociative amnesia, negative perception of self and world, anhedonia, social withdrawal).
- E. Alterations in arousal and reactivity (2/6) (e.g., irritability, aggression, problems concentrating, sleep disturbances, and hypervigilance).
What is BNC210?

- BNC210 is a truly novel anxiolytic compound, with antidepressant properties, developed by Bionomics;
- BNC210 selectively targets the alpha 7 nicotinic acetylcholine receptor (α7 nAChR);
- BNC210 is a negative allosteric modulator (NAM) of the α7 nAChR (electrophysiology; binding studies)
- The lack of side effects of BNC210 is unique and appealing to both patients and practitioners.
**α7 Nicotinic Acetylcholine Receptor: A perfect target for allosteric modulation**

- **Acetylcholine** binds to orthosteric sites on the α7 receptor.
- **BNC210** binds to allosteric sites on the α7 receptor.

Calcium ions flow through the channel when α7 receptors are activated by acetylcholine.

**Five alpha subunits make up the α7 receptor** = Five potential binding sites.

**Transmembrane Domain**
Negative allosteric modulators (NAMs) have many advantages over antagonists and channel blockers.

- Don’t bind to orthosteric site or compete with acetylcholine.
- Highly selective molecules.
- SAFE: no effect on receptor alone, only influence is when ligand is bound.
- Preserve signaling and kinetics of receptor - just tune up or down.
- A natural ceiling to magnitude of effect.
- Efficacy over a broad dose range, no u-shaped dose response.

NORMALISE RECEPTOR ACTIVITY
BNC210 Action Depends on Acetylcholine Neurotransmission
BNC210 has undergone extensive efficacy and safety profiling prior to entry into the clinic

- Light Dark Box
- Marble Burying
- Contextual Fear Conditioning
- Elevated Plus Maze

- Elevated Plus Maze
- Pre-stress + Elevated Plus Maze
- CCK + Elevated Plus Maze
- Forced Swim Test

- Isolation-induced vocalizations in guinea pig pups

- Open Field – dark, light
- Rotarod
- Modified Irwin
- Novel Object Recognition
- T-maze
BNC20 clinical data has demonstrated anxiolytic activity while maintaining a unique safety profile.

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Phase</th>
<th>Description</th>
<th>Subjects</th>
<th>Location</th>
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<tbody>
<tr>
<td>SAFETY AND TOLERABILITY</td>
<td></td>
<td>Safety and Tolerability of Single Ascending Doses</td>
<td>24</td>
<td>Australia</td>
</tr>
<tr>
<td>SAFETY AND TOLERABILITY</td>
<td></td>
<td>Lorazepam &amp; BNC210 Comparison plus EEG</td>
<td>22</td>
<td>France</td>
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<tr>
<td>EFFICACY</td>
<td>1b</td>
<td>Panic Attack Model in Healthy Volunteers</td>
<td>59</td>
<td>France</td>
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<tr>
<td>SAFETY AND TOLERABILITY</td>
<td></td>
<td>Safety and Tolerability of Multiple Ascending Doses</td>
<td>42</td>
<td>France</td>
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<tr>
<td>SAFETY AND TOLERABILITY</td>
<td></td>
<td>Target Engagement Study with Nicotine and EEG</td>
<td></td>
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<td>SAFETY AND TOLERABILITY</td>
<td></td>
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<tr>
<td>EFFICACY</td>
<td>2a</td>
<td>Imaging and Behavioural Study In Generalised Anxiety Disorder Patients</td>
<td>24</td>
<td>UK</td>
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<tr>
<td>EFFICACY</td>
<td>2</td>
<td>Post Traumatic Stress Disorder</td>
<td>Recruiting</td>
<td>Australia USA</td>
</tr>
</tbody>
</table>
Single and multiple doses of BNC210 show no impairment of cognition or mood, no sedation and no abuse potential in humans.

<table>
<thead>
<tr>
<th>Assessments</th>
<th>*SINGLE DOSES Lorazepam Comparison Study</th>
<th>^ REPEAT DOSING 8-DAYS Multiple Ascending Dose Study</th>
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</thead>
<tbody>
<tr>
<td>BNC210 300, 2000 MG</td>
<td>LORAZEPAM</td>
<td>BNC210 ALL DOSES</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Choice Reaction Time</td>
<td>No effect</td>
<td>Slowed</td>
</tr>
<tr>
<td>Psychomotor Speed /Sustained Attention /Working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital Substitution Test</td>
<td>No effect</td>
<td>Slowed</td>
</tr>
<tr>
<td>Visual/motor Co-ordination; Sleep Saccades</td>
<td>No effect</td>
<td>Slowed</td>
</tr>
<tr>
<td>Emotion eVAS</td>
<td>No effect</td>
<td>Lower scores</td>
</tr>
<tr>
<td>Sleep Karolinska Sleepiness Scale</td>
<td>No effect</td>
<td>Sedative</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>No effect</td>
<td>Impaired</td>
</tr>
<tr>
<td>Perceptual Priming Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numeric Working Memory</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td>Spatial working memory</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td>Addiction Potential ARCl49</td>
<td>No effect</td>
<td>Association with LSD and Phenobarbital/ Alcohol Group</td>
</tr>
</tbody>
</table>

* Lorazepam Comparison Study: Single doses of BNC210 (300 and 2000 mg), Lorazepam (2 mg) and placebo. N=24 healthy volunteers.

^ Multiple Ascending Dose Study: Assessed Day 1 and Day 8. N=6 for 300, 600 and 1200 mg/day; N=24 for 2000 mg/day, N=2 and 6 for placebo. All healthy volunteers.
qEEG study confirmed BNC210 brain penetration, lack of sedation and a unique EEG signature compared to Lorazepam

- Increase in δ power was not seen with BNC210 during the vigilance controlled session

<table>
<thead>
<tr>
<th>EEG Spectrum</th>
<th>δ</th>
<th>γ</th>
<th>α</th>
<th>α1</th>
<th>α2</th>
<th>β</th>
<th>β1</th>
<th>β2</th>
<th>β3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNC210</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

- Increase in δ spectral power during vigilance control session is sign of Lorazepam-induced sedation
- Increase in β spectral power is associated with the anxiolytic activity of Lorazepam

Arrows represent statistically significant changes in spectral power compared to placebo

qEEG showed:
- BNC210 effects detected in the brain
- BNC210 is not sedating
- BNC210 and Lorazepam share an EEG response associated with the anxiolytic effects of Lorazepam
The nicotine-shift assay: nicotine-induced EEG responses provide evidence of BNC210 target engagement

- Subjects treated with BNC210 will have reduced responses to nicotine if BNC210 binds to and inhibits the α7 receptor.

- BNC210 does not have an effect on α4β2 so the block of the EEG response will be partial, not full.

- The contribution to the spike amplitude may be greater from α4β2 receptors because nicotine is a more potent and efficacious agonist at α4β2 (EC50 0.35-5 μM) compared to α7 (49-113 μM).
BNC210 modulates the activity of the α7 receptor in the human brain.

As the doses of nicotine increase from 0.5 to 2 mg, the amplitude of the spike in the α2 band increases. This is caused by nicotine activation of α7 and α4β2 receptors.

- 2000 mg of BNC210 gives full block of the α7 receptor responses to 0.5, 1 and 1.5 mg of nicotine, leaving the residual response from α4β2 receptors (~0.25 power).

- The α4β2 response to 2 mg of nicotine is not fully inhibited by 2000 mg BNC210.
BNC210 significantly reduced CCK-4 induced panic symptoms in rodents and humans.

**RODENTS**

BNC210 Reversed the Anxiogenic Effect of CCK-4 in the Rat EPM

![Graphs showing entries into Open Arms and time spent in Open Arms for CCK-4, BNC210/CCK-4, and Diazepam/CCK-4 treatments.](image)

(Mean ± SEM; n=10-25 rats).

**HUMANS**

% Reduction in Total Number of Symptoms and Symptom Intensity

![Bar graphs showing score reduction 10' after CCK Injection for BNC210 treated subjects.](image)

When treated with BNC210, subjects experiencing panic symptoms showed a reduction in number and intensity of symptoms.
The effect of BNC210 on fear extinction in mice translated to improved emotional well-being following a CCK-4-induced panic attack in healthy volunteers.

**Conditioned Fear Extinction Model**

- **Time Spent Freezing (sec)**
- **Days after Conditioning**
- **Diazepam 0.5 mg/kg**
- **Vehicle**
- **BNC210 (100 mg/kg)**

**Emotional Visual Analog Scale (eVAS)**

- **Time in minutes after CCK-4 Injection**
- **BNC210**
- **Placebo**

**MICE**

BNC210 enhanced fear extinction following conditioned stimulus training.

**HUMANS**

BNC210 improved rate of return to emotional stability following CCK-4 challenge.
### Phase 2 study in Generalised Anxiety Disorder patients - using fMRI to examine effects of BNC210 on neural correlates of anxiety

<table>
<thead>
<tr>
<th>Title</th>
<th>A randomized, double-blinded, placebo &amp; lorazepam-controlled, four-way crossover, Phase II study to evaluate the effects of single oral administration of BNC210 on brain activity changes captured by functional magnetic resonance imaging in adults with Generalized Anxiety Disorder</th>
</tr>
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<tbody>
<tr>
<td>Protocol</td>
<td>BNC210.006</td>
</tr>
<tr>
<td>Study Centre</td>
<td>Institute of Psychiatry, Psychology and Neuroscience, King’s College London</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo and Lorazepam-controlled, 4-way crossover (BNC210 300 and 2000 mg, Lorazepam 1.5 mg, Placebo)</td>
</tr>
<tr>
<td>Population</td>
<td>Un-medicated male or female volunteers with Generalized Anxiety Disorder</td>
</tr>
<tr>
<td>Subjects</td>
<td>24</td>
</tr>
</tbody>
</table>
| Primary Objectives | (A) To determine whether BNC210 causes significant changes in cerebral perfusion using Arterial Spin Labelling (ASL) in the resting state.  
(B) To determine whether BNC210 causes significant changes in task-related brain activity using the emotional faces task during fMRI. |
| Secondary Objectives | To determine the effect on defensive behavior of two different oral doses of BNC210 using the Joystick Operated Runway Task and fMRI.  
To generate additional safety and tolerability information on BNC210. |
Arterial spin labelling showed that BNC210 caused significant local changes in cerebral blood flow.

**BNC210 low dose vs Placebo**
- FWE corrected, P = 0.05
- P = 0.047, cluster size = 356, peak located at -42/6/8
- P = 1.72e-08, cluster size = 1758, peak located at -40/-50/14

**BNC210 high dose vs Placebo**
- FWE corrected, P = 0.05
- P = 0.030, cluster size = 387, peak located at -34/-24/58
- P = 0.010, cluster size = 466, peak located at -40/-52/16

**Primary Endpoint**
BNC210 caused significant changes in anxiety-related brain activity while viewing emotional faces during fMRI.

**Emotional Faces Task**

*Thomas et al Arch Gen Psychiatry 2001 58, 1057-1063*

Neutral 20% 40% 60% 80% Fearful

**Primary Endpoint**

*MALE? FEMALE?*

Decide whether this face is male or female and press left/right button

BNC210 Treatment Reduced Connectivity Between the Left Amygdala and the Anterior Cingulate Cortex in GAD Patients

BNC210 (300 mg) reduced connectivity between the left amygdala and anterior cingulate cortex (ACC) while viewing fearful faces

- increased positive coupling between these regions is associated with elevated threat processing under stress.
- In pathological anxiety this circuit becomes permanently ‘switched-on’

This finding is highly supportive for the anxiolytic activity of BNC210
The Joystick Operated Runway Task (JORT) was used to model defensive behavior - threat avoidance.

Measure of defensive behaviour
- Flight intensity
- Average velocity/force used to escape in trials with threat
- Average velocity/force used to escape in trials with no threat

Joystick Operated Runway Task

Mean Intensity of Threat Avoidance Behavior
- Placebo
- Lorazepam 300 mg
- BNC210 2000 mg

Error Bars ± SEM
The potential advantages of BNC210, compared to standard anxiety treatments, have been demonstrated in preclinical and clinical studies.

Standard of care treatment for anxiety is acute use of Benzodiazepines like Valium and Lorazepam and long term treatment with SSRIs or SNRIs like Prozac, Effexor, and Cymbalta.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Fast acting</th>
<th>No sedation</th>
<th>No memory impairment</th>
<th>No motor impairment</th>
<th>No withdrawal</th>
<th>No drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNC210</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>BZD</td>
<td>✔</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✔</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>X</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Based on data from preclinical studies and Phase 1 and 2 clinical trials*
A next generation anxiolytic like BNC210 will have broad therapeutic potential.

Clinical data have provided sound evidence for the anxiolytic activity of BNC210.

- Anxiety Disorders
  - Panic Disorder
  - Generalized Anxiety
  - Social Anxiety
  - Animal and human behavioral data
  - Effects on neural correlates of anxiety

- Co-Morbid Anxiety
  - Bipolar Disorder
  - Major Depressive Disorder
  - Estimated Rates of Co-morbid Anxiety in:
    - Bipolar Disorder: 42-70%
    - Major Depression: ~50%
    - Dementia: ~20%
    - Schizophrenia (OCD): ~38%

- Trauma and Stressor-Related Disorders
  - PTSD
  - Anxiolytic activity data generated in animals and humans
  - Common underlying neural circuitry for anxiety and PTSD

- Neurodegenerative Disease
  - Agitation and Anxiety
  - Anxiolytic activity data generated in animals and humans
  - Side effect and safety profile suitable for elderly
The Phase II trial in PTSD: The mechanism and pharmacology of BNC210 indicate its therapeutic potential for PTSD symptoms.
Efficacy, safety and tolerability profiles of BNC210 provide an advantage over benzodiazepines for treatment of PTSD patients:

1. addiction liability
2. development of tolerance
3. cognitive impairment
4. motor impairment
5. sedation
6. lack of efficacy
7. overdosing
8. sudden unexplained deaths
9. car crashes
10. falls

VA/DoD recommend against the use of BZDs in the ‘Practice Guideline for PTSD’:

- Benzodiazepines have a negative effect on fear extinction in rodents and humans

VA has several initiatives in place to reduce prescriptions of BZDs to PTSD patients:

- 50% increase in overall mortality rates associated with long-term use.
Bionomics is currently recruiting for a Phase 2 Trial in Post Traumatic Stress Disorder (PTSD) in Australia and the USA

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>192 PTSD patients</th>
</tr>
</thead>
</table>
| PROTOCOL | • Double blind, placebo controlled, randomized, multi-centre  
• 4 arms: 1 placebo, 3 BNC210 dose levels  
• 12 weeks of dosing, twice daily oral treatment |
| PRIMARY OBJECTIVE | • To determine whether BNC210 causes a decrease in PTSD symptoms as measured by CAPS-5 |
| SECONDARY OBJECTIVES | • To determine the effects of BNC210 on Anxiety (HAM-A), Depression (MADRS) and Functioning and Quality of Life,  
• Safety and Tolerability |
| EXPLORATORY ENDPOINTS | Effects of smoking |

RESTORE STUDY OVERVIEW
The RESTORE Study is a clinical research study evaluating a new experimental medication to see if it helps reduce the symptoms of PTSD and other associated symptoms including anxiety, depression, and sleep disturbances.
High prevalence of PTSD worldwide

There is high off-label drug usage with unproven or contraindicated treatments.

Patients are not well served with current medications and

•
•
•
•

approach to managing PTSD. It is evaluating an experimental medication compared to placebo to see if it may help to reduce the symptoms of PTSD.

Don’t let PTSD have the last word. Speak with us today.

https://restoresresearchstudy.com/
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