BNC210: A Novel Therapeutic for the Treatment of Anxiety, Conditions with Co-morbid Anxiety and Stress and Trauma Related Disorders.
α7 Nicotinic Acetylcholine Receptor: Rich Area of Biology with Increasingly Recognised Role in Anxiety & Depression

- Ligand gated ion channel highly expressed in the brain
- Key driver of emotional and memory responses
- Allosteric modulators have no effect on the receptor alone and do not desensitize the receptor
- This approach provides a mechanism for selectively and specifically modulating the receptor to achieve desired outcomes
  - Aim to normalise receptor activity
- Allosteric inhibition of the α7 receptor may reduce anxiety and depression
BNC210 Engages with the \( \alpha_7 \) Nicotinic Acetylcholine Receptor in the Human Brain

Spectral EEG power in the \( \alpha_2 \) bandwidth (10-12.5 Hz) is reduced in subjects dosed with 2000 mg BNC210.

The EEG response to nicotine is achieved through activation of nicotinic receptors in the brain. The major populations targeted are \( \alpha_4\beta_2 \) and \( \alpha_7 \) receptors. Reduction in the response in the presence of BNC210 is due to antagonism of the \( \alpha_7 \) receptors.
**BNC210 Overview: Novel, Best-in-Class Modulator of α7 Nicotinic Acetylcholine Receptor**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>• Negative allosteric modulator of α7 nicotinic acetylcholine receptor</th>
</tr>
</thead>
</table>
| Target Indications | • Anxiety (Generalized Anxiety Disorder or GAD & Post Traumatic Stress Disorder or PTSD)  
|                     | • Potential for other CNS indications |
| Ongoing Clinical Trials | • Phase 2 trial in GAD patients, reported positive topline data Sept 2016  
|                     | • Phase 2 trial in PTSD initiated Q2 2016 calendar year |
| Completed Clinical Trials | • 6 completed Phase 1 trials in > 200 healthy subjects  
|                     | • Demonstrated safety and tolerability, no sedation, cognitive impairment or impaired motor co-ordination; suppressed symptoms of CCK4 induced panic; target engagement in human brain demonstrated  
|                     | • Phase 2 in GAD patients met co-primary endpoints; low dose BNC210 outperformed Lorazepam, measured by cerebral perfusion and degree of amygdala activation  
|                     | • Secondary endpoint met; high and low dose BNC210 outperformed Lorazepam in an anxiety provoked behavioural task (JORT) |
**BNC210: Next Generation Drug Candidate to Treat Anxiety & Depression**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No sedation</th>
<th>No withdrawal syndrome</th>
<th>No memory impairment</th>
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<th>Once-a-day dosing</th>
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<tr>
<td>BNC210</td>
<td>✅</td>
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<tr>
<td>Valium and other BZD</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>✅</td>
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</tr>
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<td>Prozac and certain other SSRI/SNRI</td>
<td>✅</td>
<td>✗</td>
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<td>✅</td>
</tr>
</tbody>
</table>

**Potential Competitive Advantages of BNC210**

- Drug
  - BNC210
  - Valium and other BZD
  - Prozac and certain other SSRI/SNRI

**Anxiety Treatments**

- Dominated by benzodiazepines
- Associated with sedation, addiction and tolerance and cognitive disturbances
- Not recommended for long-term treatment

**Depression Treatments**

- SSRIs and SNRIs used to treat depression and anxiety
- Modest efficacy, late onset of action, discontinuation, changes in weight, sexual dysfunction and increased thoughts of suicide in adolescents
- Many have black box warnings

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*Based on data from preclinical studies and Phase 1 & 2 clinical trials.*
Posttraumatic Stress Disorder was formerly classified as an Anxiety Disorder – now a Trauma and Stressor-Related Disorder

- The American Psychiatric Association (APA) publishes the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) a classification and diagnostic tool. [https://www.psychiatry.org/psychiatrists/practice/dsm](https://www.psychiatry.org/psychiatrists/practice/dsm)

In the United States the DSM is the universal authority for psychiatric diagnoses. DSM classifications guide: treatment recommendations : payment by health care providers

- Changes made in 2013 from DSM-4 to DSM-5
  - A new chapter and class created: Trauma and Stressor-Related Disorders
  - Because there are variety of clinical phenotypes in the PTSD diagnostic criteria it can no longer be considered an Anxiety Disorder
- Other Trauma and Stressor-Related Disorders described in DSM-5 are:

  Reactive Attachment Disorder | Disinhibited Social Engagement Disorder | Posttraumatic Stress Disorder | Acute Stress Disorder | Adjustment Disorders | Other Specified Trauma- and Stressor-Related Disorders | Unspecified Trauma- and Stressor-Related Disorder
PTSD is a set of reactions that can develop in some people who have been through 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 who have 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 CAPS-5 based on criteria from DSM-5:

Expression for over 1 month of debilitating symptoms from four clusters (A) following exposure to traumatic events such as threat of death, or actual or threatened serious injury or violence:

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).

PTSD is a Prevalent, World-Wide Disorder Arising from a Variety of Trauma – Not just Combat Exposure

U.S. population Facts: 7-8% of the population will have PTSD at some point in their lives. ♦ About 8 million adults have PTSD during a given year. ♦ About 10% of women develop PTSD sometime in their lives compared with about 4% of men.

US Veterans with PTSD: ♦ Operations Iraqi Freedom and Enduring Freedom: between 11-20% have PTSD in a given year ♦ Gulf War (Desert Storm): 12% have PTSD in a given year. ♦ Vietnam War: about 30% of Vietnam Veterans have had PTSD in their lifetime.

UK Population Facts: 10% of people develop PTSD. ♦ 20% of firefighters ♦ 30% of teenagers who have survived a horrific car crash ♦ 70% of rape victims ♦ 66% of Prisoners of War ♦ 40% of people who experienced a sudden death of a loved one ♦ An estimated 10,000 women a year following a traumatic childbirth

http://www.ptsduk.org/what-is-ptsd/who-is-affected-by-ptsd/

Who gets PTSD?

Not everyone exposed to trauma develops PTSD

Women are 2x more susceptible to developing PTSD

75% of Bosnian refugee women
37% of Cambodian refugees
3% of Cambodian civilians
86% of women refugees in Kabul and Pakistan

30-50% of a tsunami-affected population
50%+ of Armenian earthquake, mudslides in Mexico, Hurricane Andrew in the US
32-60% of adult survivors and 26-95% of children survivors of earthquakes

7%–8% of people in the United States
30% of US Vietnam veterans
10% of US Desert Storm veterans
6–11% of US Afghanistan veterans
12–20% of US Iraq veterans
60%+ of US rape victims

90 percent of sexually abused children exposed to a school shooting
77 percent of children exposed to a school shooting
35 percent of urban abused children

29% of US high school students
28% of women
50% of UK sexually abused children, 45% of UK battered women, 35% of UK adult rape victims, 30% of UK veterans, 18% of UK professional fire-fighters, 13% of suburban police officers (Higher rates in urban and armed situations)

16% of children and adolescents who lived approximately 100 miles from Oklahoma City reported significant PTSD symptoms related to the bombing two years after the bombing, 44% of Americans reported at least one symptom of PTSD after 9/11.
30% of those actually in the building or injured during the 9/11 New York City attacks.

Psychotherapy:
- Cognitive Processing Therapy – Understanding how the trauma changed your thoughts and feelings so that you can change how you think and feel about the trauma.
- Prolonged Exposure Therapy – Talking about the trauma repeatedly until the memories of the trauma are no longer upsetting.
- Virtual Reality Exposure Therapy for PTSD in the military – emerging early evidence

Pharmacotherapy:
- Currently sertraline (Zoloft) and paroxetine (Paxil) are approved by the FDA for PTSD, only 30% patients achieve remission
- The VA/DoD Clinical Practice Guideline for PTSD also recommends the SSRI fluoxetine (Prozac) and the SNRI venlafaxine (Effexor) as first-line treatments.
- Prazosin is used off label for nightmares, atypical antipsychotics for psychosis, depression, cognition and anxiety (~40% patients on atypicals)
- Benzodiazepines are not recommended

https://www.ptsd.va.gov/professional/treatment/overview/clinicians-guide-to-medications-for-ptsd.asp
In Spite of their Anxiolytic Activity, Benzodiazepines are Contraindicated for Treatment of PTSD

Benzodiazepines are medications to improve anxiety and sleep. They do not help with PTSD symptoms and can have serious side effects over time

- **Accidental overdose.** Taking benzodiazepines and alcohol, street drugs, strong pain medication (opioids) or other sedatives at the same time can be fatal.
- **Mood problems.** Benzodiazepine use can create problems with depression, irritability, and anger.
- **Trouble with thinking and memory.** Benzodiazepines can lead to poor attention, confusion, and fogginess and actually delay fear extinction and promote PTSD. Use of benzodiazepines is linked to dementia and Alzheimer's disease.
- **Slow reaction time.** People taking benzodiazepines have more car accidents and falls, which can result in fractures and other injuries.
- **Breathing problems.** Benzodiazepines make chronic obstructive pulmonary disease (COPD) and sleep apnea worse.
- **Pregnancy risks.** Women who are pregnant or planning to become pregnant should be aware of possible risks of benzodiazepine use on their newborn. These children may be born early, have a low birth weight, or experience symptoms of withdrawal.

BNC210 has demonstrated acute anxiolytic efficacy in humans, equivalent to benzodiazepines, but **without** their serious side effects, including abuse potential.
New Treatment Options for PTSD are Limited

PTSD Patients Need:

- More Effective Drugs
- Drugs without side-effects (causing non compliance)
- Drugs that lack the potential to become drugs of abuse
- Drugs that are safe to give with other drugs – polypharmacy is the norm for PTSD patients

Potential Competitive Advantages of BNC210*

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<tr>
<td>BZD</td>
<td>X</td>
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<td>✔</td>
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<tr>
<td>Antidepressants</td>
<td>✔</td>
<td>X</td>
<td>✔</td>
<td>X</td>
<td>X</td>
<td>✔</td>
</tr>
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*Based on data from preclinical studies and Phase 1 & 2 clinical trials.
What Methods are Being Used to Develop New Treatments for PTSD?

• Imaging - identify a PTSD signature that responds to pharmacotherapy
• Animal Models – develop and use to identify new drugs/validate old ones
• Consider use of Controlled Drugs: “reset the brain” ketamine, psilocybin, MDMA
• Genetics – susceptibility markers?
• Work on fear extinction deficits: Psychotherapy / Exposure Therapy/Memory Reconsolidation/ Drugs to facilitate
• Promote neurogenesis and recover the stress related neurotrophy – e.g., hippocampal volume changes
• Drugs to promote sleep /reduce hyperarousal
• Efforts to promote drug discovery and development

State of Science Summit: Pathophysiology of PTSD – rethinking drug targets

HPA AXIS, excitatory/inhibitory neurotransmitter systems, chronobiology, circadian rhythms, sleep, fear extinction
Currently there are just four *industry-run* trials in PTSD evaluating two novel drugs and two repurposed drugs.

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Bionomics</strong></td>
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<td><strong>Tonix Pharmaceuticals</strong></td>
<td><strong>Otsuka</strong></td>
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<td>a7 nAChR NAM</td>
<td>Vasopressin V1a antagonist</td>
<td>Multiple mono-amines</td>
<td>Dopamine</td>
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<tr>
<td>BNC210</td>
<td>SRX246</td>
<td>TNX102</td>
<td>Brexpiprazole</td>
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<td>Anxiolytic,</td>
<td>Anti-fear, Aggression,</td>
<td>Sleep, Nightmares</td>
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<td>Antidepressant,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enhances fear</td>
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<td></td>
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<tr>
<td>extinction</td>
<td>Depression, and Anxiety</td>
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<td>Antipsychotic, Antidepressant</td>
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<tr>
<td>mid 2018</td>
<td>June 2018</td>
<td>October 2018</td>
<td>December 2018</td>
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</table>
The Mechanism and Pharmacology of BNC210 indicate its Therapeutic Potential for Several PTSD Symptom Clusters

PTSD presents in a highly individualized manner with a complex and challenging set of symptoms that varies from patient to patient.
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

Entries into the Open Arms

Time Spent in the Open Arms

(Human: ± SEM; n=10-25 rats)

HUMANS

% Reduction in Total Number of Symptoms and Symptom Intensity

When treated with BNC210, subjects experiencing panic symptoms showed:
- Reduction in number and intensity of Symptoms
- More rapid return to baseline emotional stability compared to placebo
The effect of BNC210 on fear extinction in a mouse assay translated to the eVAS results from a CCK-4 challenge in humans

**Conditioned Fear Extinction Model**

- **MICE**
  - BNC210 enhanced fear extinction following conditioned stimulus training

- **HUMANS**
  - BNC210 improved rate of return to emotional stability following CCK-4 challenge

**Emotional Visual Analog Scale (eVAS)**
BNC210 Caused Significant Changes in Anxiety-related Brain Activity while Viewing Emotional Faces during fMRI.

**Emotional Faces Task**

- There was significant activation to fearful faces in both left $p < .001$ and right $p < .001$ amygdala.
- This was significantly reduced by BNC210 (300 mg)

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


- Decide whether the face is male or female and press left/right button
- This involves implicit processing of emotional faces and robust amygdala activation

Note: N = 21 (19 Female, 2 Male). Three subjects excluded for excessive head movement.*
BNC210 Reduced Anxiety-induced Behaviour in the Joystick Operated Runway Task (JORT)

**Measure of defensive behaviour**
- **Flight intensity**

**Average velocity/force used to escape in trials with no threat**

**Average velocity/force used to escape in trials with threat**

- Significant separation from placebo occurred in the case of both the low and high dose of BNC210 (simple contrasts showed $p = 0.007$ and $= 0.033$ respectively).

- Lorazepam showed a similar direction of effect but failed to separate significantly from placebo ($F = 2.072$, $p = .165$).

- Note: $n = 21$ (females).
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 while viewing fearful faces ($p = 0.04$)

✓ This finding is highly supportive for the anxiolytic activity of BNC210:
  - Interactions between the dmPFC/ACC and amygdala constitute an ‘aversive-amplification’ circuit - increased positive coupling between these regions is associated with elevated threat processing under stress.
  - In pathological anxiety this circuit becomes permanently ‘switched-on’ (Robinson et al. 2011).
Pharmacology of BNC210 and Clinical Trial Results Supports Broad Commercial Opportunity

RESULTS FROM CLINICAL STUDY IN GAD PATIENTS PROVIDES PROOF OF BIOLOGY FOR SEVERAL INDICATIONS

- Anxiety Disorders
  - Panic Disorder
  - Generalized Anxiety
  - Social Anxiety
- Co-Morbid Anxiety
  - Bipolar Disorder
  - Major Depressive Disorder
- Trauma Related Disorders
  - PTSD
- Neurodegenerative Disease
  - Agitation and Anxiety
The Potential Market Value of BNC210

US Prevalence and Revenue Potential

Assume 5% premium to Trintellix 2016 AWP for 30-day supply of $380 – Compliance Adjusted

- Innovative, first-in-class
- Unmet need in large patient population
- Advancement in care
- Limited branded competition
- Ability to achieve large market share

1. PTSD prevalence >18yrs., ~25% of patients diagnosed and treated
2. MDD+Anxiety prevalence, ~50% co-morbid anxiety, ~50% diagnosed and treated
3. BP+Anxiety prevalence, 50% co-morbid anxiety (range in literature 25 to 75%), ~50% diagnosed and treated
4. Panic prevalence, ~50% diagnosed and treated
5. SAD prevalence, 15-20% diagnosed and treated
6. GAD prevalence, ~9% agitation patients diagnosed and treated
7. PTSD MDD+Anxiety BP+Anxiety Panic SAD Agitation GAD

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Phase 2 Trial in Post Traumatic Stress Disorder (PTSD) Initiated in Q2 2016 - Ongoing

**SUBJECTS**
192 PTSD patients

**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, genotype, evaluate soluble biomarkers

PTSD is a risk factor for depression, alcohol and substance abuse, absenteeism, unemployment, homelessness, violent acts, suicidal thoughts and suicide
POST-TRAUMATIC STRESS DISORDER

IT BEGINS WITH A STORY...

A story that is unique to you. One that has shaped your world in ways that people may not understand. It’s a story full of twists and turns, especially if current treatments don’t provide the relief you need. But every story has chapters – each building on the last. We may be able to help you write those next chapters.

Ask your doctor about the RESTORE Study, a potential new 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.
# PTSD has Potential to Provide a Rapid Path-to-Market for BNC210

<table>
<thead>
<tr>
<th>Phase III</th>
<th>Anticipated PTSD</th>
<th>Anticipated GAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>1 x Phase III (500-600 pts)</td>
<td>Anticipate 3 x Phase III, 1 x Phase IV (each 500 – 1,000 pts)</td>
</tr>
<tr>
<td>Comparators included in trial design</td>
<td>Placebo</td>
<td>Compare with placebo and marketed drugs (several marketed drugs may be compared eg GABA modulator or SNRI, unless a treatment resistant population)</td>
</tr>
<tr>
<td>Length of Trial</td>
<td>~20 months to recruit</td>
<td>Up to 3 years to recruit</td>
</tr>
<tr>
<td>Primary End Point</td>
<td>CAPS-5</td>
<td>HAM-A (and may be other anxiety measures)</td>
</tr>
<tr>
<td>Clinical Sites</td>
<td>30-35 sites in USA</td>
<td>Phase III – 20–70 trial sites across 7-8 countries Phase IV - 57 sites, 16 countries (based on Lyrica not approved in US)</td>
</tr>
<tr>
<td>Advantages</td>
<td>Breakthrough designation, Potential for Fast track</td>
<td>Not clear</td>
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<tr>
<td>Projected Time to Approval</td>
<td>2021</td>
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