Development of an Improved Oral Tablet Formulation of BNC210, a Negative Allosteric Modulator of the α7 nAChR, Suitable for Evaluation as an Acute Treatment for Social Anxiety Disorder

Elizabeth Doolin, Dharam Paul, Julia Crossman, Michael Odontiadis, Susan O'Connor, Errol De Souza*

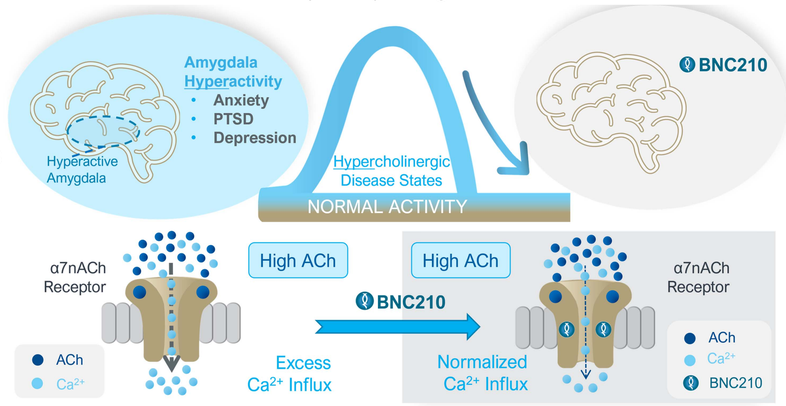
Bionomics Limited, Adelaide, Australia

SOCIAL ANXIETY DISORDER (SAD) is a serious disorder characterized by emotional symptoms of excessive fear of scrutiny by others in social or performance situations and can be accompanied by physical symptoms that often mimic a panic attack.

- SAD typically leads to significant distress or impairment in functioning in a persistent manner, interfering with work/education responsibilities and performance, as well as personal relationships.
- SAD is a chronic disorder which may also include severe episodes of acute anxiety such as those precipitated by performance-type events.
- The past year prevalence of SAD among US adults was estimated at ~7.1% based on a 2001-2003 study (higher for females than for males, with rates being 8.0% and 6.1%, respectively)
- FDA-approved medications for SAD are some SSRI antidepressants that are slow to act and are thus not suitable for acute treatment. Benzodiazepines are used off-label as a standalone treatment or to augment SSRIs, however, their use has declined due to undesired side effects and risks. β-blockers are also used off-label but mainly address only the physical symptoms of SAD.
- Thus, there is an unmet need for safe, more efficacious and better-tolerated medications for SAD.

BNC210 is a negative allosteric modulator of the alpha 7 nicotinic acetylcholine receptor (α7 nAChR) in development for the treatment of anxiety and stressor-related disorders which has demonstrated the potential for reducing anxiety in clinical studies without having the severe side effects associated with the current standard of care (SOC) drugs.

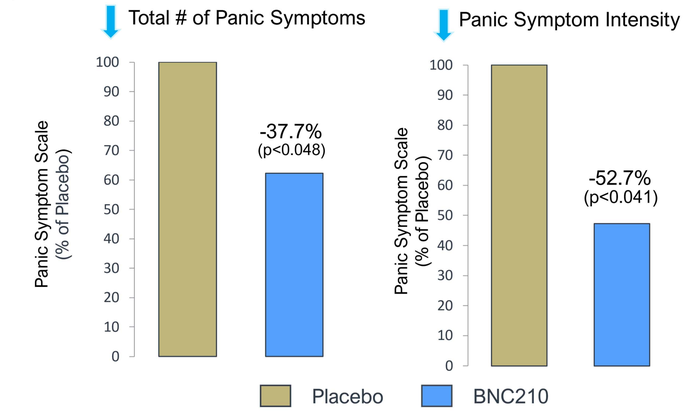
Figure 1. BNC210 allosterically binds to α7 nAChR and restores neurotransmitter balance - normalizing the amygdala hyperactivity that is associated with anxiety



RATIONALE FOR BNC210 IN ACUTE TREATMENT OF SOCIAL ANXIETY DISORDER

ANTI-PANIC: In a single dose, placebo-controlled study, BNC210 reduced panic symptoms in healthy volunteers experiencing a CCK-4 induced panic attack

Figure 2: BNC210 2000 mg significantly reduced the number and intensity of panic symptoms as measured with the Panic Symptom Scale



ANTI-ANXIETY: In a single dose, placebo- and lorazepam-controlled study, BNC210 reduced acute anxiety-related biomarkers in patients with generalized anxiety disorder

Figure 3: BNC210 300 mg significantly reduced activation of L & R amygdala caused by viewing fearful faces (L: p=0.011; R: p=0.006)

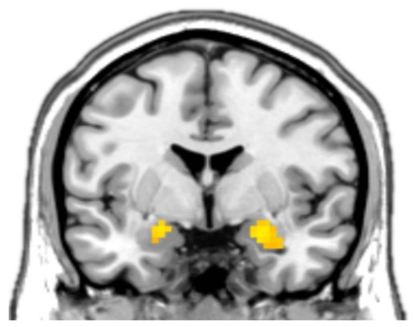


Figure 4: BNC210 300 mg significantly reduced connectivity between the amygdala and anterior cingulate cortex while viewing fearful faces (p=0.012)

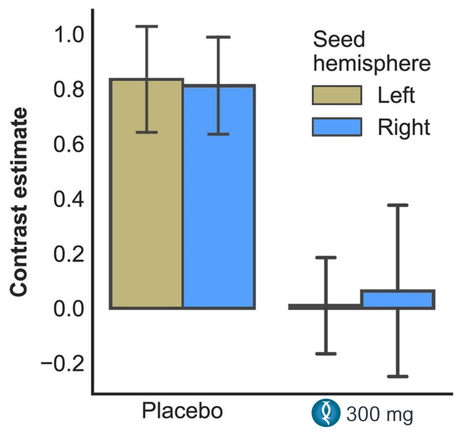
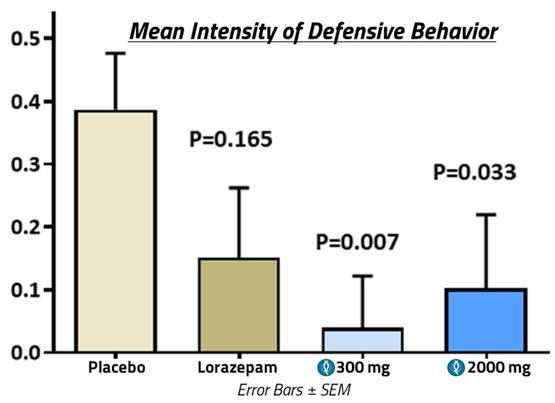


Figure 5: BNC210 300 mg and 2000 mg significantly reduced threat avoidance behavior in a behavioral task

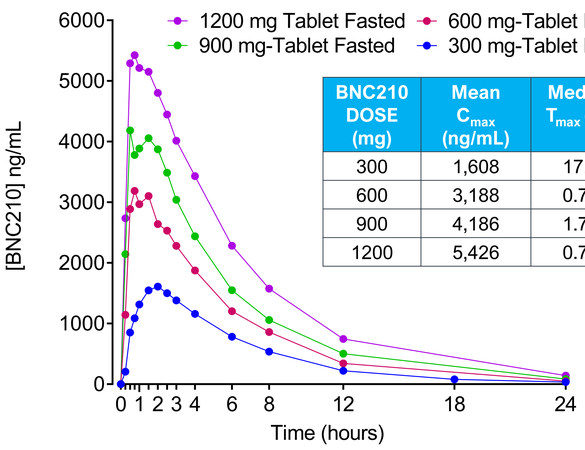


Wise T. et al., Biological Psychiatry 2020 (https://doi.org/10.1016/j.biopsych.2019.12.013); Perkins A. et al., Translational Psychiatry 2021 (https://doi.org/10.1038/s41398-020-01141-5)

FAST-ACTING: Rapid onset of action with novel oral BNC210 tablet formulation

Spray-dried dispersion (SDD) technology was applied to develop an oral, solid dose tablet formulation of BNC210 with improved solubility that could overcome the limitations of the liquid suspension used in prior in-clinic trials, specifically, a strong food effect and non-linear absorption.

Figure 6: Plasma concentration vs time profile of BNC210 tablet formulation administered to fasted participants



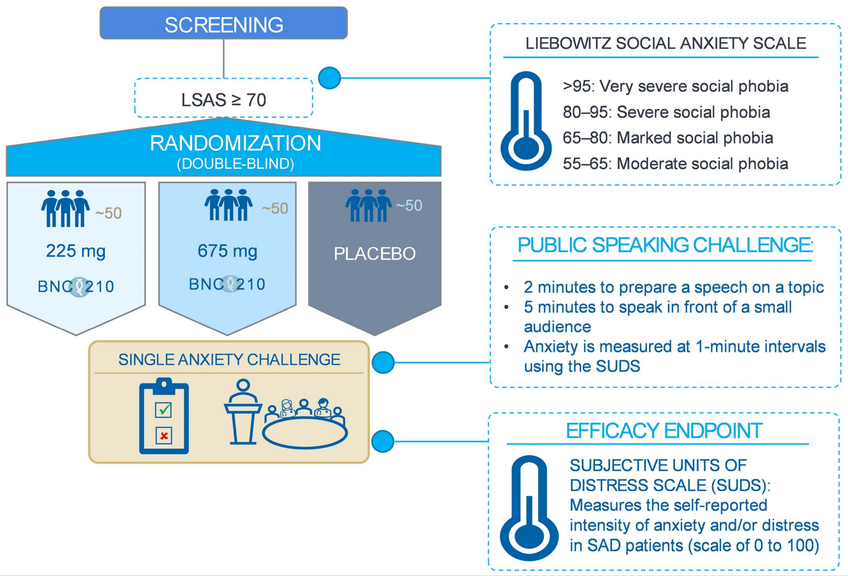
BNC210 DOSE (mg)	Mean C_{max} (ng/mL)	Median T_{max} (hr)	Time conc. remains at 75% of mean C_{max} (hr)
300	1,608	17.5	0.8 – 3.8
600	3,188	0.75	0.4 – 2.8
900	4,186	1.75	0.4 – 2.9
1200	5,426	0.75	0.3 – 2.9

The newly developed tablet achieves:

- Dose-linear increases in C_{max} and AUC
- Maximum plasma concentrations at 0.75 – 1.75 hr across the dose range under fasted conditions, with concentrations close to C_{max} values maintained for several hours

PREVAIL STUDY

Figure 7: Phase 2 single dose, 3-arm, placebo-controlled study of BNC210 tablet formulation in acute treatment of SAD



- The public speaking challenge activates the core fear in SAD patients (negative evaluation) and is very sensitive to detecting acute treatment effects
- The public speaking challenge is an FDA-endorsed registration trial endpoint for acute treatment of SAD
- This provides a cost-effective trial design with an efficacy endpoint conducive to rapid data generation
- Fast Track designation from FDA for acute treatment of SAD and other anxiety disorders

SUMMARY:

- BNC210 has demonstrated the potential for reducing anxiety in clinical studies without having the severe side effects associated with the current SOC drugs used in the treatment of SAD.
- The novel tablet formulation of BNC210 has significantly improved PK properties making it ideal to evaluate as an acute treatment - with a relatively short time to maximal concentrations and sustained plasma levels for several hours, BNC210 could be taken just prior to an anticipated anxiety-provoking event such as a performance or social event.
- Topline data from the BNC210 Phase 2 study for the acute treatment of SAD (PREVAIL Study, NCT05193409) are expected in late 2022.

Disclosures: Elizabeth Doolin, Dharam Paul, Julia Crossman, Michael Odontiadis, Susan O'Connor, Errol De Souza are employees of Bionomics Limited