Pharmacometrics Analysis and Drug Reformulation of BNC210 to Optimize its Evaluation in a Phase 2 Trial in PTSD Patients

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INTRODUCTION: POST-TRAUMATIC STRESS DISORDER (PTSD) is a serious psychiatric disorder that can occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, or violent personal assault. Patients with PTSD display multiple symptoms in the clusters of intrusion, avoidance, arousal and reactivity and negative alterations of cognition and mood. Currently approved therapeutics for PTSD, such as SSRIs, have adverse effects and limited efficacy that signify an unmet medical need for more effective and better-tolerated therapies.

BNC210 is a negative allosteric modulator of the alpha7 nicotinic acetylcholine receptor (α7 nAChR) in development for the treatment of anxiety and trauma- and stressor-related disorders which has been shown to attenuate symptoms of anxiety, panic, depression, threat avoidance and enhances fear extinction in clinical settings and in animal models indicating potential to treat PTSD symptoms.

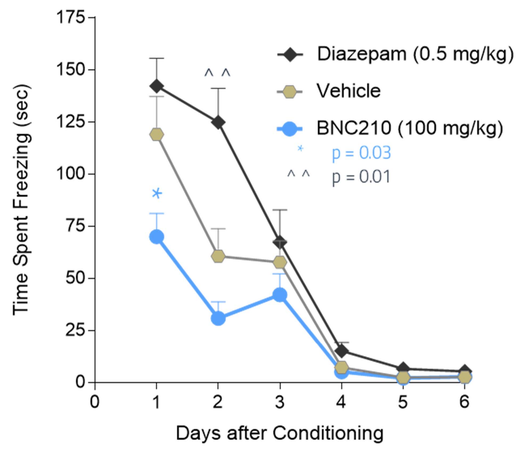
Acute doses of BNC210:

- ✓ **REDUCED ANXIETY:** Reduced anxious behavior in rodent models and reduced amygdala hyperactivity in GAD patients
- ✓ **ANTI-DEPRESSANT:** Antidepressant effects in a rat model and in prior PTSD clinical trial at early time points
- ✓ **ENHANCED FEAR EXTINCTION:** Enhanced fear extinction in mice and promoted more rapid recovery in healthy humans following a panic attack (CCK-4)
- ✓ **ANTI-PANIC ACTIVITY:** Reduced number and intensity of panic symptoms in healthy volunteer CCK-4 challenge
- ✓ **REDUCED THREAT AVOIDANCE:** Reduced threat avoidance behavior in animals and in GAD patients

ENHANCES FEAR EXTINCTION

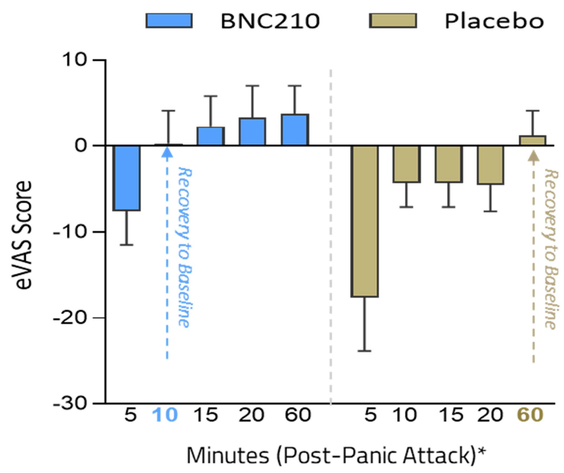
People with anxiety disorders and PTSD have amplified fear responses to trauma- or stress-related stimuli and impaired fear extinction. BNC210 promotes fear extinction in animal and human studies.

Figure 1: In a contextual fear-conditioning extinction paradigm in C56BL6 mice, BNC210 enhanced fear extinction



On Days 1 and 2 of extinction, mice treated with BNC210 (100 mg/kg) spent less time freezing in response to the conditioned stimulus (tone) compared to vehicle-treated mice. Conversely, diazepam treated mice (0.5 mg/kg) spent more time freezing on Days 1 and 2 compared to vehicle treated mice. *p0.03; ^^^p≤0.001 denotes significant differences to vehicle. (Mean ± SEM; n=12 mice).

Figure 2: In humans, BNC210 treatment reduced the emotional impact of a CCK-4 induced panic attack, showing enhanced recovery following an unpleasant physical and emotional experience

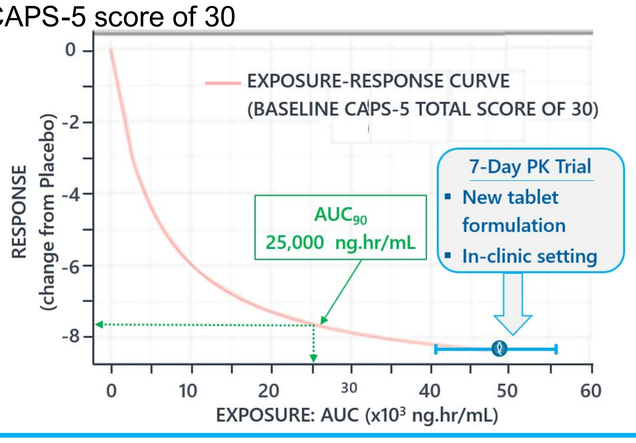


An emotional Visual Analogue Scale (eVAS) was used to subjectively assess emotional status at 5, 10, 20, 30 and 60 minutes following a CCK-4 induced panic attack. BNC210-treated subjects (2000 mg) were less distressed and recovered to baseline emotional status more rapidly than placebo-treated subjects (10' versus 60') (Mean ± SEM; n=15 healthy volunteers).

RESULTS: POPULATION PK MODELLING AND PK/PD MODELLING (RESTORE STUDY)

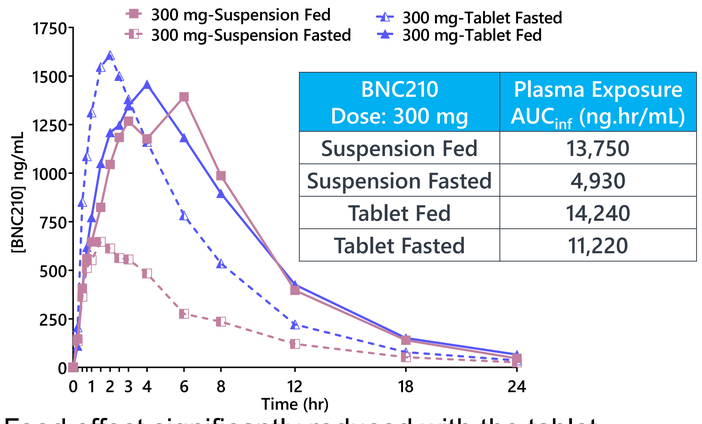
- RESTORE study: A 12-week Phase 2 study in PTSD patients (NCT04951076) where participants were asked to take BNC210 (150, 300 or 600 mg) or placebo bid, in a liquid suspension formulation with food. Trial did not meet the primary endpoint.
- The population PK model of sparse blood sampling estimated that AUC values in the out-patient setting were substantially lower than projected from in-clinic studies. Also, higher BNC210 dose levels were associated with decreasing bioavailability over time.
- An inhibitory Emax model produced the best PD model fit and established an exposure-response relationship for CAPS-5 Total Severity scores (p-value<0.01), where higher AUC values were related to a larger effect.
- The PK/PD model predicted AUC_{90} (90% of the maximum drug effect) is achieved at ~25,000 ng.hr/mL for a predicted change from placebo of ~7.5 points on the CAPS-5 scale (Figure 3).
- The PK/PD model informed the study design for a Phase 2b study in PTSD patients using a newly developed tablet with improved PK properties.

Figure 3. The model predicted exposure-response relationship curve for a typical patient with a baseline CAPS-5 score of 30



REFORMULATION AND HUMAN PK STUDIES

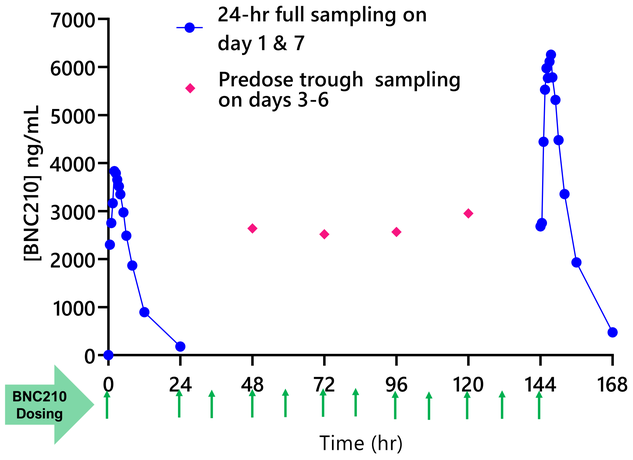
Figure 4: Plasma concentration vs time profile of BNC210 administered with food and fasted, as the suspension and tablet formulation



BNC210 Dose: 300 mg	Plasma Exposure AUC_{inf} (ng.hr/mL)
Suspension Fed	13,750
Suspension Fasted	4,930
Tablet Fed	14,240
Tablet Fasted	11,220

- Food effect significantly reduced with the tablet

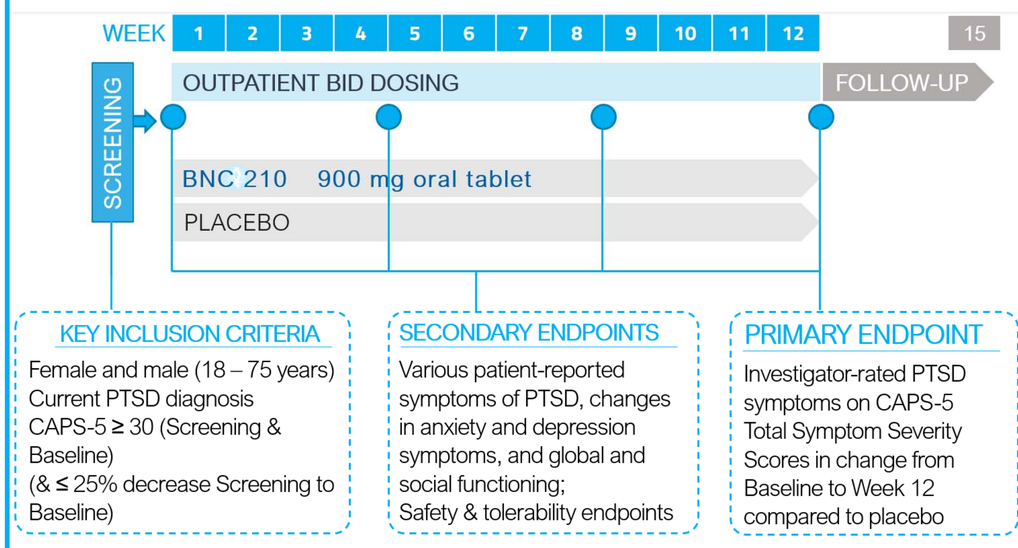
Figure 5: Plasma concentration vs time profile of BNC210 tablet administered bid for 7-days in healthy volunteers



- Steady state was achieved from day 3 (48 hours)
- Steady state PK parameters were similar for both genders
- Mean $AUC_{0-\tau}$ was 49,409 ng*hr/mL, exceeding the target exposure of AUC_{0-12} = ~25,000 ng*hr/mL

ATTUNE Study

Figure 6: Phase 2b, 2-arm, placebo-controlled, BNC210 monotherapy in PTSD patients (~200 subjects)



- Fast Track designation from FDA for treatment of PTSD

SUMMARY:

- Studies in animals and humans indicate that the mechanism and pharmacology of BNC210 have therapeutic potential for the treatment of PTSD
- PK-PD analysis of the Phase 2 PTSD trial data (RESTORE) showed potential for significant patient benefit in future trials provided adequate drug exposure is achieved (target AUC of ~25,000 ng.hr/mL)
- Successfully developed a novel oral BNC210 tablet formulation, exhibiting dose linear PK and significantly reduced food effect, and achieved the target exposure in a 7-day PK study
- These results justified further evaluation of BNC210 in PTSD and provided a basis for optimal design of the ongoing 200-patient Phase 2b trial (ATTUNE. NCT04951076)
- Top line data are expected in mid-2023

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