THE THERAPEUTIC POTENTIAL OF BNC210 FOR THE TREATMENT OF PTSD IS INFORMED BY PHARMACOMETRIC ANALYSES

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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, rape or other violent personal assault[1]. Two antidepressants (paroxetine and sertraline) are currently approved for the treatment of PTSD but they have limited efficacy. There is an ongoing, concerted effort to discover new drugs and mechanisms to treat PTSD.

- **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 and panic in relevant human models indicating potential to relieve PTSD symptoms such as alterations in arousal and reactivity.
- BNC210 has been evaluated in a Randomized, Double-Blind, Placebo-Controlled Phase 2 Study (RESTORE) in Adults with PTSD.

1. https://www.psychiatry.org/patients-families/ptsd/what-is-ptsd.

METHODS: PTSD STUDY DESIGN

- 193 subjects; Randomized to 4 treatment arms (1:1:1:1); Placebo or BNC210 at 150, 300 and 600 mg b.i.d. (twice daily) in a liquid suspension taken with food. 3-week screening period; 12-week treatment period; 3-week follow up. Multi-center – 6 sites in Australia, 20 sites in the USA. Primary end-point was change in CAPS-5 (Clinician Administered PTSD Scale for DSM-5) total severity score at 12 weeks compared to placebo. Several secondary endpoints also investigated: MADRS, HAM-A, PGI-I/S, CGI-I/S, PCL-5, SDS, PSQI, AQoL-8D.
- The statistical analysis plan included population PK-PD modelling to explore an exposure-response relationship for BNC210 in the PTSD trial.
- Sparse pharmacokinetic (PK) sampling was performed during the trial with one blood sample taken per individual on three occasions. The available relevant information for PK modelling was: administered dose, measured BNC210 plasma concentration, time of PK sample and time since last dose.

METHODS: POPULATION PK MODELLING

- The estimated parameters in the base model were: clearance (CL), volume of distribution (V), mean absorption time (MAT), relative bio-availabilities for the 300 and 600 mg doses, a proportional error term and inter-individual variability on CL, V and MAT.
- When necessary, prior information was used for V from a previous healthy volunteer multiple ascending dose (MAD) PK study, and for MAT, set to 6 hours as a slow but not unreasonable absorption.
- A PK model was developed that allowed for time-varying bioavailability; it was evaluated using comparison of parameter estimates and visual predictive checks.

METHODS: PK/PD MODELLING

- A pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed to evaluate the exposure-response relationship for CAPS-5 Total Severity Score as a continuous direct effect.
- The effect was modelled on the logit scale which bound it not to be larger than the highest possible score or lower than the smallest possible score.
- Three different effects were evaluated using the linear, Emax and power function models (Figure 1).

Figure 1. PK-PD Modelling Equations

$$= MAX \cdot \frac{e^{(Baseline + f_{Placebo} + f_{Drug})}}{1 + e^{(Baseline + f_{Placebo} + f_{Drug})}} + \varepsilon$$

$$f_{Placebo} = Slope_{Placebo} \cdot t$$

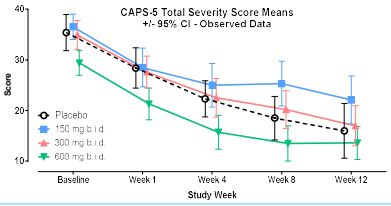
$$f_{Drug} = Slope_{Drug} \cdot AUC$$

$$f_{Drug} = \frac{E_{max} \cdot AUC}{AUC_{50} + AUC}$$

$$f_{Drug} = a \cdot AUC^{b}$$

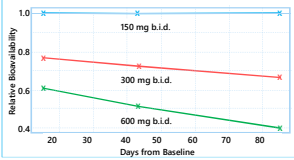
RESULTS: PTSD TRIAL DOSAGE-BASED ANALYSIS

Figure 2. The primary end-point of the trial, change in CAPS-5 total severity score at 12 weeks compared to placebo, was not met and a strong placebo response was observed



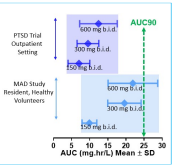
RESULTS: PK MODELLING

Figure 3 / Table 1. The PK model developed for BNC210 with time-varying bioavailability (FreI) indicated that higher doses were associated with a decreasing FreI over time such that, after ~3 months of treatment at 600 mg b.i.d., the achieved exposure was only 60% higher than at 150 mg b.i.d.



Run 130 (with time varying bioavailability)	
CL (L/h)	22.51
V (L)	243.41 FIX
MAT (h)	6 FIX
F 300 mg	0.79
F 600 mg	0.67
$\Theta_{\text{Time-varying F}}$	1.3×10^{-5}
Error (SD)	0.46
IIV CL (SD)	0.46

Figure 4. Modelled exposure (AUC) values in the PTSD patients were ~60% of those achieved with BNC210 in a previous healthy volunteer Multiple Ascending Dose study using the same doses and formulation



RESULTS: PK-PD MODELLING

An inhibitory Emax model, including estimates of inter-individual variability 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 model showed that the AUC90 (90% of the maximum drug effect) is achieved at ~25 mg.hr/L with a predicted change from placebo of ~7.5 points on the CAPS-5 scale (Figure 5).
- A visual predictive check was used to support the appropriateness of the model (Figure 6).

Figure 5. The model predicted curve for a typical patient with a baseline CAPS-5 score of 30 (mean baseline score for patients on the RESTORE trial in the 600 mg, b.i.d. treatment group).

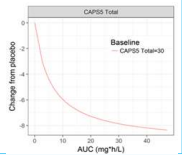
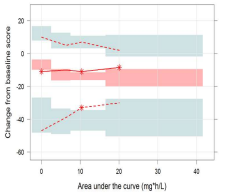


Figure 6. Visual Predictive Check of change from baseline score versus AUC. Solid line represents the observed median, dashed lines represent the 2.5th and 97.5th percentiles. Shaded areas are the corresponding 95% confidence intervals based on model simulations (n=500). Red stars indicate areas where the observed data are outside, and on the upper side of, the confidence intervals indicating a slight tendency for the model to overestimate the drug effects.



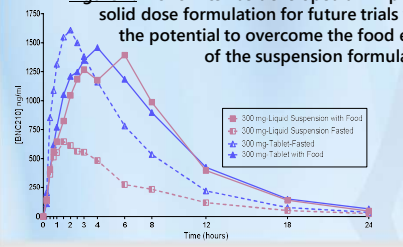
CONCLUSIONS:

1. Exposure-response modelling indicated the potential for BNC210 to have benefit in PTSD provided that adequate blood levels are achieved (~25 mg.hr/L).
2. Pharmacometric (PK) modelling showed that exposure from the BNC210 liquid suspension formulation was insufficient to achieve efficacy in the PTSD study [600 mg b.i.d, mean AUC at steady state was 14.3 mg.hr/L (SD 5.4)].
3. These analyses justify further evaluation of BNC210 in PTSD patients and provide a basis for optimal design of future trials to demonstrate efficacy.

DISCUSSION:

The unanticipated reduction in drug exposure in the PTSD outpatient population on the RESTORE trial may be attributed in part to the liquid suspension of BNC210 being highly dependent on administration with food for maximum absorption (Figure 7).

Figure 7. Bionomics has developed an improved solid dose formulation for future trials with the potential to overcome the food effect of the suspension formulation.



NEXT STEPS

- ❖ Human PK evaluation of the tablet formulation in multiple dosing studies
- ❖ The goal is to achieve steady state concentrations of ~25 mg.hr/L based on the outcome of the PK-PD analysis, to increase the likelihood of a statistically significant reduction in CAPS-5 scores with BNC210 compared to placebo.

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