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 attack, war/combat, rape or other violent personal assault. 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.

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, CGI-I/S, CGI-I/S, PCL-S, 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.

RESULTS: PK-PD MODELLING
- An inhibitory Emax model, including estimates of inter-individual variability on CL, V and MAT produced the best PD model fit and established an 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 used including the linear, Emax and power function models (Figure 1).

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).

RESULTS: PK/PD MODELLING
- 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).

RESULTS: PK MODELLING
- 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).

RESULTS: PTDS TRIAL DOSAGE-BASED ANALYSIS
- 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.

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.