Evidence of target engagement in a multiple ascending dose study with BNC210, an α7 nAChR NAM in development for the treatment of anxiety disorders

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BACKGROUND BNC210 is a negative allosteric modulator (NAM) of the α7 nAChR in development for the treatment of anxiety disorders. Single ascending doses of BNC210 administered to 148 humans, have been safe, well tolerated and lacked the side effects seen with standard of care drugs for anxiety such as benzodiazepines and SSRIs.

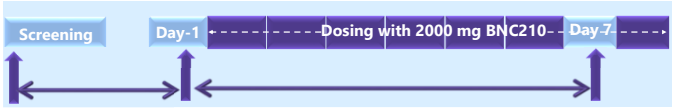
STUDY DESIGN Randomised, double-blind, placebo-controlled, single site, multiple ascending dose study with 4 cohorts. Cohorts 1-3 (300, 600 and 1200 mg/day) had 6 subjects on drug and 2 on placebo; Cohort 4 (2000 mg/day) was expanded to 24 drug/6 placebo for the nicotine shift assay. Doses were administered b.i.d for 8 days (D1 morning to D8 morning).

STUDY OBJECTIVES PRIMARY**:** Safety, tolerability of multiple ascending doses (MAD) of BNC210 in healthy male adult subjects SECONDARY**: (1)** Effects of MAD of BNC210 on cognitive functions **(2)** Effects of multiple doses of 2000 mg/day of BNC210 on nicotine shift assay (Figures 3 & 4) **(3)** PK of MAD oral doses of BNC210

TARGET ENGAGEMENT METHOD - NICOTINE SHIFT ASSAY

In EEG recordings, the alpha-2 band (10-12.5 Hz) responds to nicotine in a dose dependent manner when administered by inhalation, i.v. infusion or cigarette smoking (Lindgren et al; Psychopharmacology (1999)145:342–350). Cohort 4: 24 subjects were randomised to receive 2000 mg of BNC210 and 6 to receive placebo. Quantitative EEG (qEEG) recordings were performed on 3 occasions: (1) at screening (2) D-1 before dosing (3) D7, after 7 days dosing with 2000 mg BNC210 (Figure 1). Recordings were taken 6h after dosing during 2' eyes-closed intervals. Dose titrations of nicotine (from 0.5 to 2 mg) were administered by nasal spray (Nicorette®)10' prior to recordings. Each inhalation=0.5 mg nicotine.

FIGURE 1: Nicotine Shift Assay Schedule

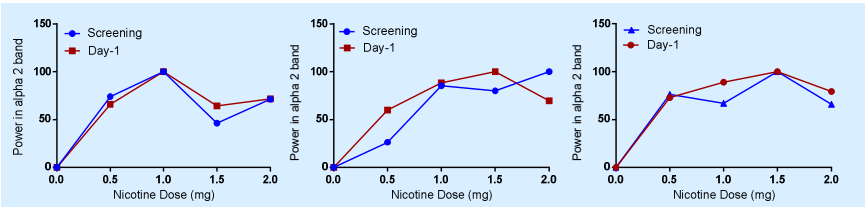


Subjects who produced a nicotine dose response at screening and Day-1 were used for analysis in the nicotine shift assay (RESPONDERS)

Analyses of the nicotine shift assay compared nicotine dose response data on Day-1 (before drug) with dose response data on Day 7 (after 2000 mg BNC210)

RESULTS: RESPONDERS Thirteen subjects showed dose responses to nicotine at screening and on Day-1 (Figure 2). Un-blinding showed that 12 were randomized to received BNC210 and 1 to receive placebo making a drug versus placebo comparison not possible. As a consequence, within-subject analyses were done on the 12 subjects who received drug. Statistics: Nicotine dose response data for D-1 and D7 was log transformed and normalised to the zero-nicotine response. Unpaired t-test, Mean±SEM

FIGURE 2: Examples of RESPONDER nicotine dose responses at Screening and on Day-1

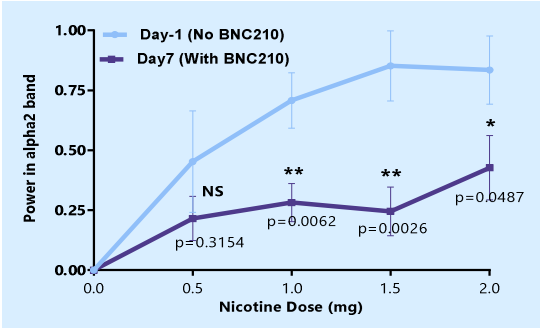


RESULTS: NICOTINE SHIFT The EEG response to nicotine at 10-12.5 Hz is predominantly achieved via activation of α4β2 and α7 nAChRs in the CNS. Their relative contributions are not known but α4β2 nAChRs (EC_{50} *in vitro*=0.35-5 µM) are more sensitive to nicotine than α7 (EC_{50} *in vitro*=49-113 µM; Wonnacott & Barik, 2007) and may therefore contribute more to the peak amplitude.

Figure 3 shows nicotine dose responses in subjects before and after dosing with BNC210, with significant inhibition occurring after BNC210 administration (Figure 4). This inhibition is partial because only the α7 component is suppressed by BNC210 through its α7-specific negative allosteric modulation.

In subjects dosed with BNC210 (2000 mg/day), the amplitude of responses to 0.5, 1 and 1.5 mg of nicotine is reduced to ~0.25 power, which suggests that full inhibition of the α7 contribution is occurring at this dose. Inhibition of the response to 2 mg nicotine is not as strong, perhaps because the contribution from the α4β2 receptors is higher in proportion to α7 when the level of nicotine in the brain increases.

FIGURE 3: Multiple doses of 2000 mg/day of BNC210 significantly reduced the peak height of nicotine responses on the α2 band measured using qEEG



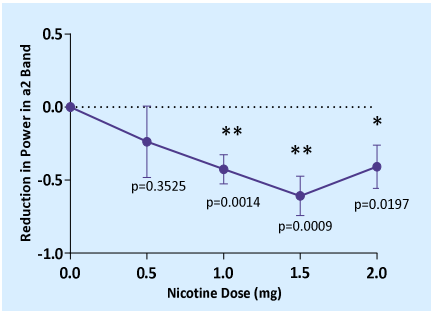
CONCLUSIONS

Nicotine shift assay indicated target engagement at the α7 nAChR by BNC210

Multiple ascending doses of BNC210, b.i.d for 8 days:

- Produced no detrimental effects on cognitive functions
- Were safe and well tolerated
- All doses reached steady state; 1200 mg/day gave highest exposure

FIGURE 4: After dosing with BNC210 for 7 days, subjects showed a significant reduction in α2 power amplitude on Day 7 compared to Day-1 (no BNC210)



POTENTIAL CONFLICT OF INTEREST: Dr. Philippe Danjou is on Bionomics' Scientific Advisory Board