

Evaluation of the pharmacokinetics and clinical tolerability of the novel anxiolytic compound BNC210 in healthy volunteers

P.4.a.010

Kremmidiotis G.¹, O'Connor S.¹, Doolin E.¹ and Rolan P.²1. *Bionomics Limited, 31 Dalglish Street, Thebarton SA 5031, Australia.*2. *Pain and Anaesthesia Research Clinic (PARC), Royal Adelaide Hospital, Adelaide SA 5000, Australia.*

BACKGROUND

BNC210 is a small molecule that exhibits potential utility for the treatment of anxiety and depression. Following a single oral administration, BNC210 elicits anxiolytic responses in several preclinical models that assess innate behavioural responses (the Light Dark box, the Elevated Plus Maze and the Marble Burying assay).

The anxiolytic activity of BNC210 is more pronounced in models of induced anxiety involving stress or chemical challenge (Forced Swim, CCK4 challenge - see poster P.1.d.021). In addition, BNC210 exhibits anti-depressant activity in the rat Forced Swim test. Preclinical GLP safety and toxicology studies in rats and dogs demonstrate that BNC210 is very well tolerated with no Dose Limiting Toxicities (DLT) seen at doses up to 2000 mg/kg. We have conducted a clinical evaluation of BNC210 in healthy volunteers to determine its safety and pharmacokinetics in man.

STUDY OBJECTIVES

Primary Objectives. Determine the clinical safety and tolerability of ascending single doses of BNC210. Determine the plasma pharmacokinetics following oral administration of BNC210 in the presence or absence of food.

Secondary Objectives. Evaluation of pharmacological effects on the Bond and Lader visual analogue scales. Measurement of plasma cortisol and prolactin.

STUDY DESIGN

Safety and pharmacokinetics were assessed in a double-blind, placebo controlled, ascending single dose design. Each dose level included four subjects. One subject was randomised to receive placebo and three received a single oral dose of BNC210 in a fasted state. Following establishment of safety and pharmacokinetics with administration in a fasted state, the effect of food at selected dose levels was determined.

RESULTS

Dose Escalation Scheme. A total of 27 healthy male volunteers were administered escalating single oral doses of BNC210 (Table 1). Twenty four subjects received BNC210 in a fasted state at doses ranging from 5 mg to 2000 mg. Three subjects received BNC210 with food at doses 300 mg to 2000 mg, with a 7 day washout between doses. A total of 9 subjects received placebo.

Table 1. BNC210 phase I trial - Dose escalation.

BNC210 Dose (mg)	Subjects Fasted	Placebo Fasted	Subjects Fed	Placebo Fed
5	3	1	-	-
15	3	1	-	-
50	3	1	-	-
150	3	1	-	-
300	3	1	3	1
600	3	1		
1200	3	1		
2000	3	1		

Plasma Pharmacokinetics. In a fasted state, the pharmacokinetics of BNC210 appeared approximately linear up to the 600 mg dose level. Exposure reached a plateau at a 600 mg dose, with small increases at the 1200 mg and 2000 mg doses. In a fed state, the pharmacokinetics of BNC210 appeared approximately linear up to the highest dose of 2000 mg (Figure 1). The fold-difference in exposure between the fed and fasted state increased with increasing dose from 4.1 - 8.4-fold.

Maximum plasma exposure was achieved following the 2000mg dose in a fed state ($AUC = 43,848 \text{ hr} \cdot \text{ng/mL}$; $C_{MAX} = 3680 \text{ ng/mL}$). These exposure levels exceed the plasma exposure required for efficacy in preclinical rat models (Table 2).

Figure 1. BNC210 plasma pharmacokinetics following a single oral administration in healthy volunteers in a fasted/fed state.

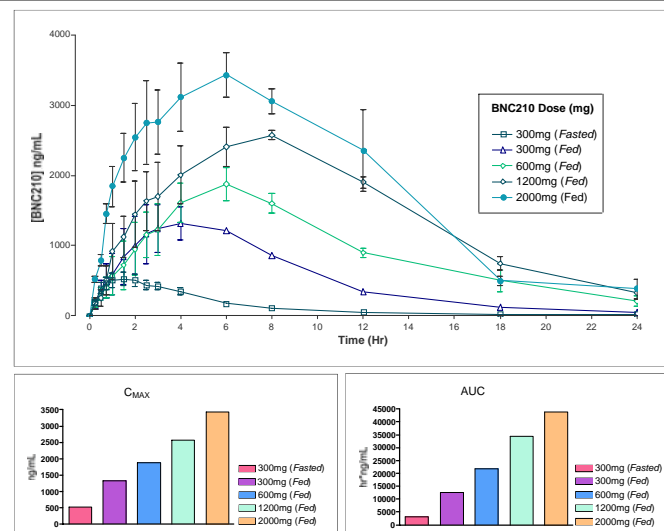


Table 2. BNC210 plasma exposure at doses producing efficacy in rat models following a single oral administration.

Rat Model	Effective Dose (mg/kg)	Drug Exposure AUC (hr*ng/mL)	Drug Exposure C _{MAX} (ng/mL)
Forced Swim test	30	<37,500 [#]	<3030 [#]
Elevated Plus Maze	1	688	222
CCK Challenge	10	6689	1502
EEG Signal	50	<37,500 [#]	<3030 [#]

[#] Exposure values obtained following a 100 mg/kg dose

Safety and Pharmacology. BNC210 was generally well tolerated. The most commonly occurring treatment-emergent adverse event was fatigue, reported as mild in all subjects, with no apparent dose-related trend (Table 3). There were no dose-related treatment-emergent adverse events or changes in laboratory safety data, vital signs, or 12-lead ECGs noted in those subjects who received BNC210, or in comparison with subjects who received placebo. The 16 item Bond and Lader Visual Analogue Scale scores recorded by subjects to assess CNS side effects of BNC210 showed no apparent dose-related trends in subjects who received a single oral dose of BNC210 and no differences in comparison with subjects who received placebo. Plasma cortisol and prolactin were evaluated in the 2000 mg fasted cohort. BNC210 treatment related decrease in plasma cortisol was seen. Further analysis of this potential biomarker in subsequent trials is warranted.

Table 3. Treatment emergent events observed in the BNC210 Phase I clinical trial.

Doses (mg)	Placebo	Fasted								Fed			
		5	15	50	150	300	600	1200	2000	300	600	1200	2000
Plasma Pharmacokinetics													
C _{MAX} (ng/mL)	0	45	116	248	294	334	800	821	852	1493	1876	2640	3680
AUC (h*ng/mL)	0	178	500	1397	1820	2270	5082	6133	5189	12500	21848	34499	43848
Treatment Emergent Adverse Events													
Nausea			1										
Fatigue	1		2		2		1	1	1				
Loss of Appetite	1												
Dizziness													
Light Headed													
Headache	1	1			2						1		1
Somnolence													
Skin Irritation											1	1	1
Sore Throat	1										1		
Sinus Congestion							1						

CONCLUSIONS

BNC210 is safe and well tolerated up to a dose of 2000 mg.

Highest plasma exposure occurs following oral dosing in a fed state.

Drug exposure attained in humans exceeds the drug levels required for efficacy in preclinical models.