

Pharmacodynamic effects of single oral doses of the novel anxiolytic compound BNC210 in healthy male volunteers

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BACKGROUND

BNC210 is a novel agent that exhibits potential utility for the treatment of anxiety and depression. In preclinical animal models it exhibits anxiolytic and antidepressant effects without inducing side effects associated with benzodiazepines (BZD) and SSRIs. A phase I clinical study was conducted at FORENAP Pharma (France) in healthy male subjects to investigate the potential side effect profile of BNC210 in comparison to Lorazepam, a BZD commonly used in the treatment of anxiety.

TRIAL DESIGN

Single centre, randomized, double-blind, double dummy, placebo-controlled and positive-controlled (Lorazepam).

In a four-way cross-over design, 21 healthy male subjects were randomised to receive single oral doses of BNC210 (300 and 2000 mg) and Lorazepam (2 mg) or corresponding vehicle placebos in four consecutive periods, each one week apart. A 300 mg dose of BNC210 was selected because the therapeutic range of BNC210 is expected to be ≤300 mg; a 2000 mg dose was selected in order to define a therapeutic window.

N=21; 4-Way Cross-Over			
PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
BNC210 Dose 300 mg & PLACEBO to Lorazepam	BNC210 Dose 2000 mg & PLACEBO to Lorazepam	PLACEBO to BNC210 & Lorazepam DOSE	PLACEBO to BNC210 & PLACEBO to Lorazepam

Lorazepam administration was performed 3.5 hours after administration of BNC210 to ensure that peak plasma concentrations of both agents occurred around the same (T0+6h) time point.

TRIAL ASSESSMENTS

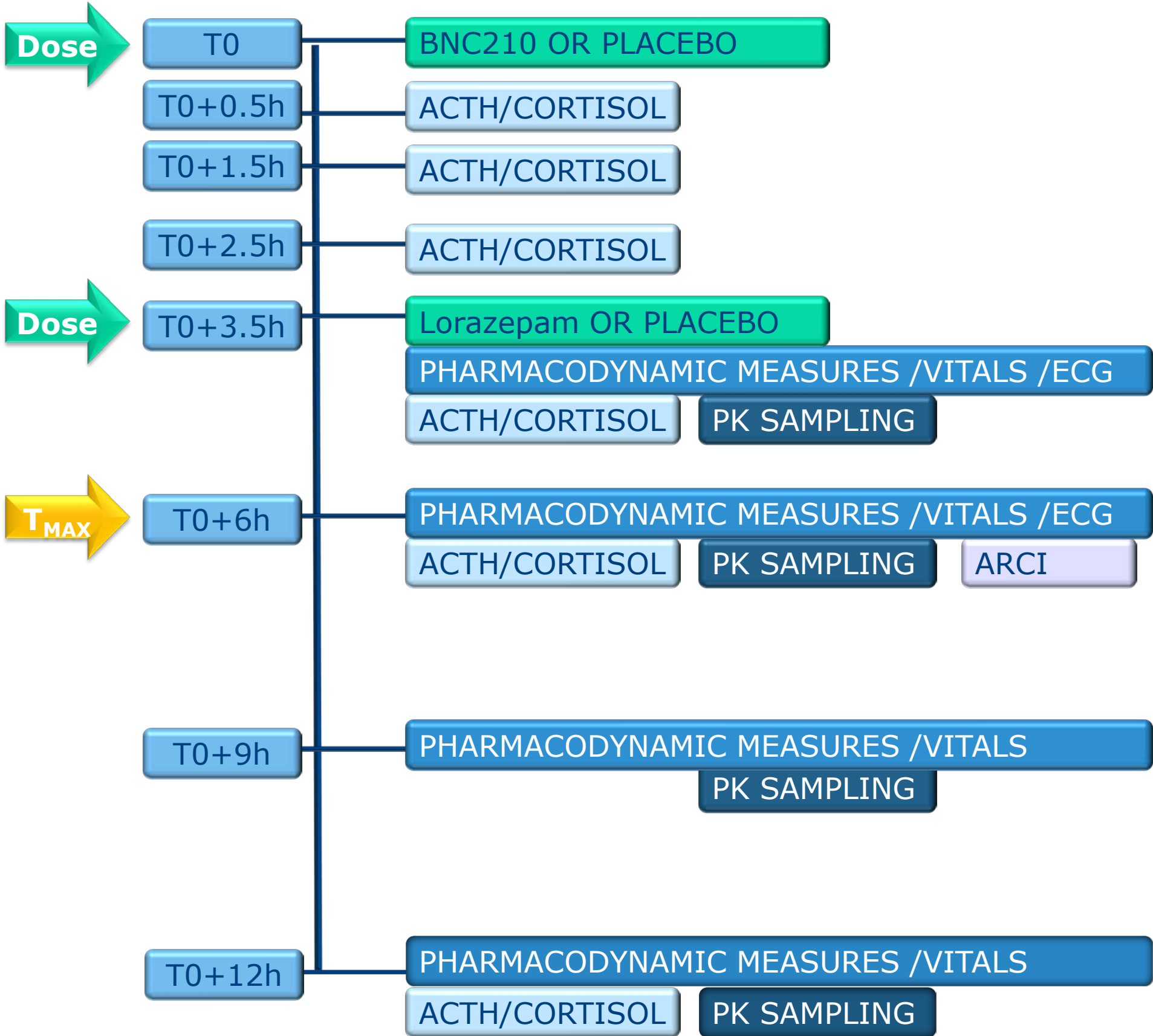
Primary Assessment

1. Attention - Multiple Choice Reaction Time

Secondary Assessments

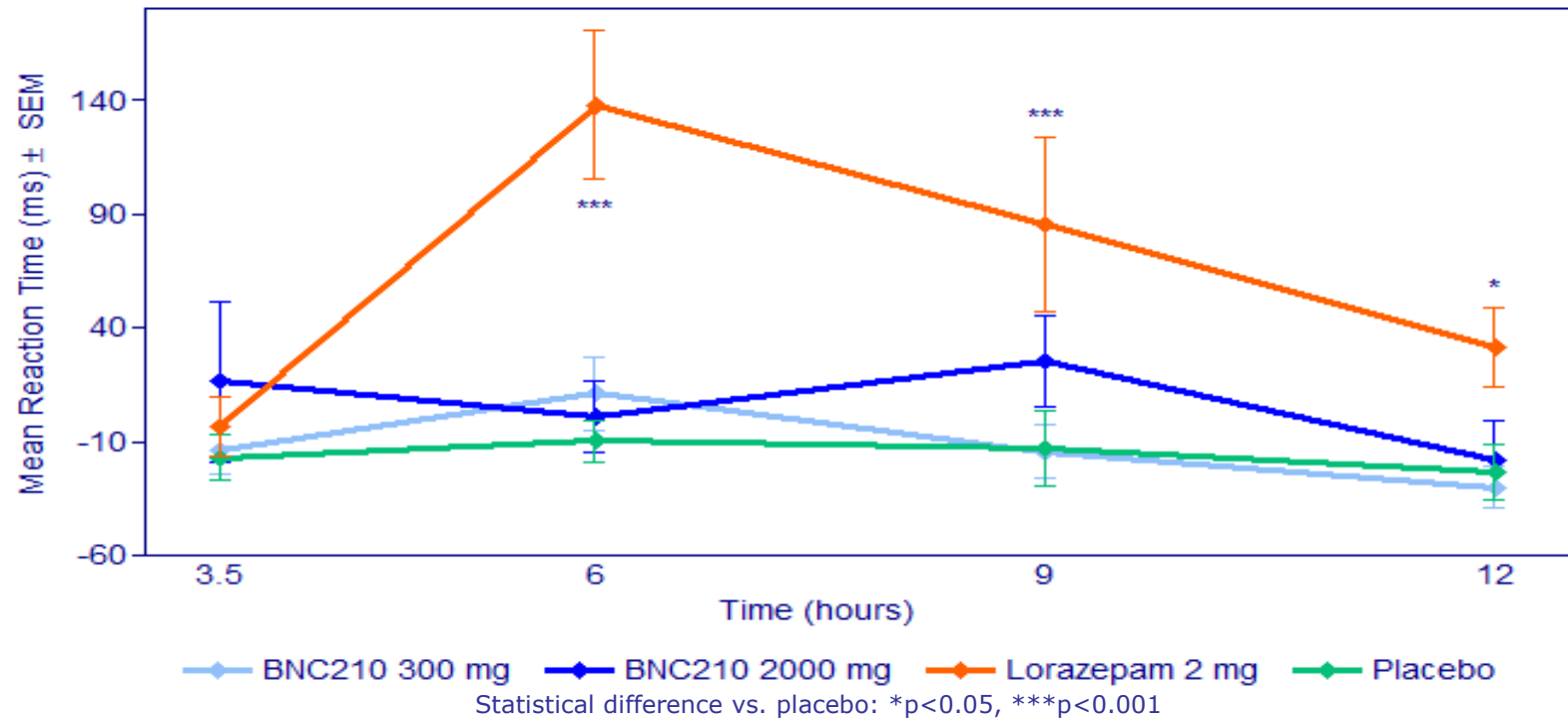
- Psychomotor Speed - Digit Symbol Substitution Test
- Visuo-motor Coordination - Peak Saccadic Velocity
- Sleepiness - Karolinska Sleepiness Scale
- Mood - emotional visual analog scale (eVAS)
- Stress hormones - Plasma Adrenocorticotrophic hormone (ACTH), Plasma Cortisol
- Addiction - Addiction Research Centre Inventory (ARCI)
- Quantitative Wake EEG (qEEG)
- Plasma BNC210 concentration
- Safety and Tolerability

TRIAL SCHEDULE

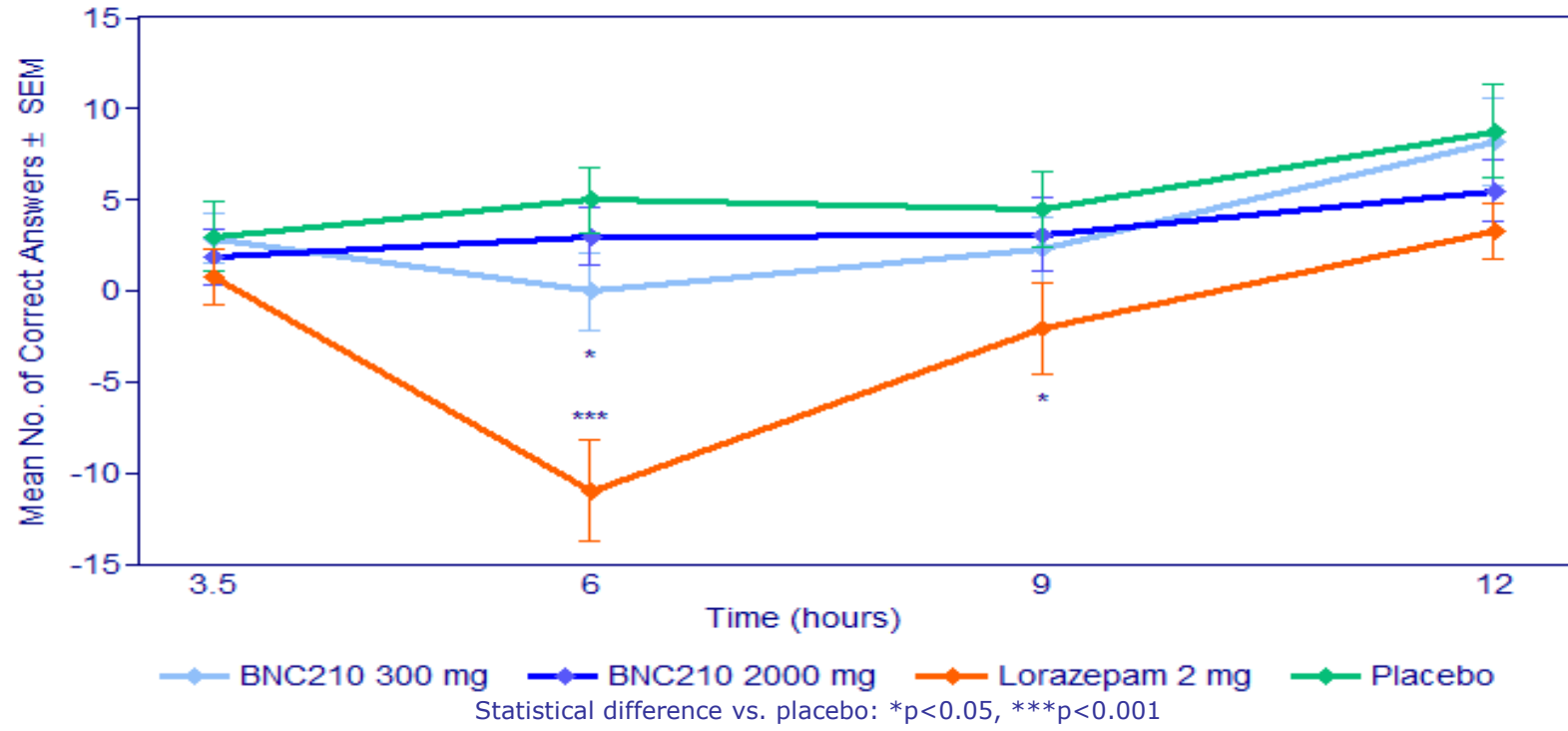


RESULTS

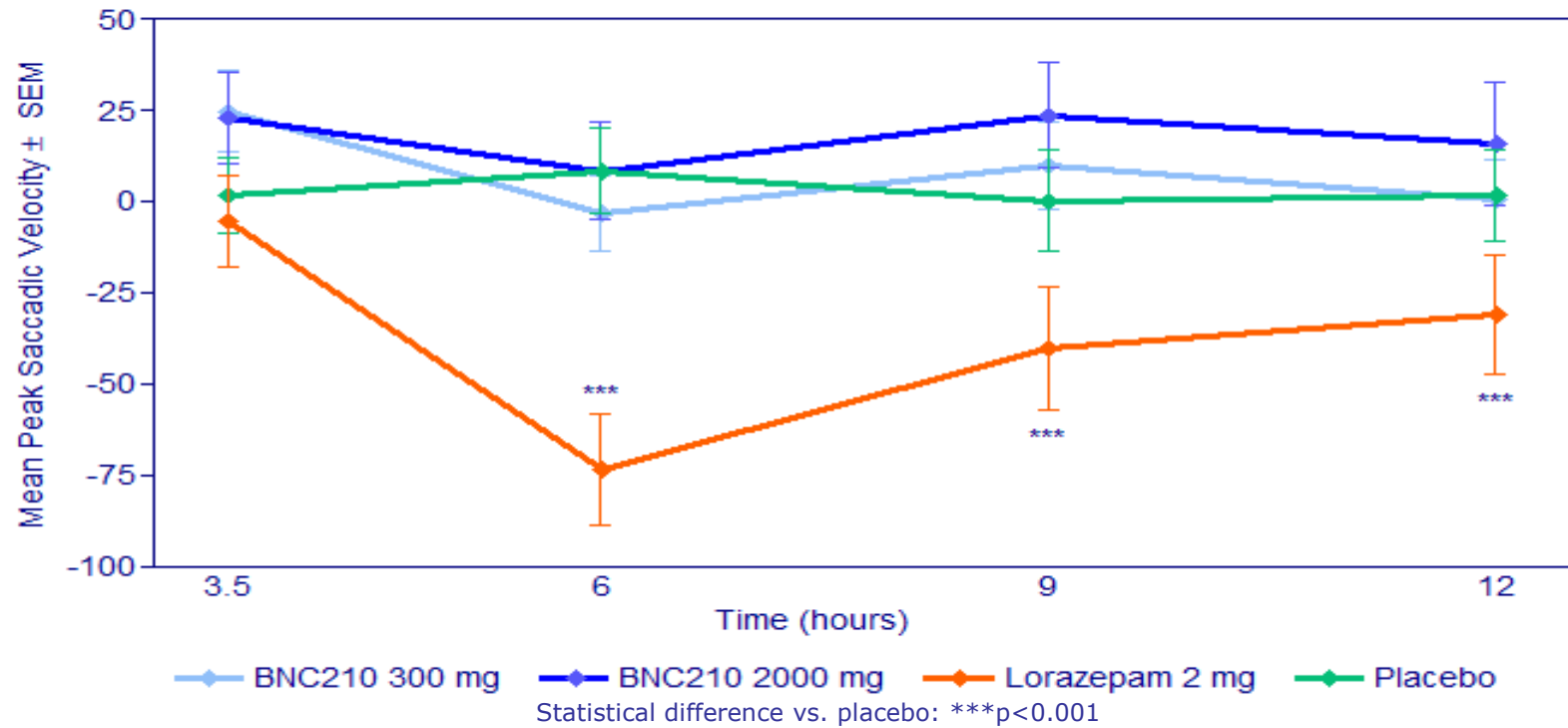
1. BNC210 did not alter attention in the Multiple Choice Reaction Time test as demonstrated by non significant increases in reaction time. Lorazepam significantly impaired performance at T0+6h, T0+9h and T0+12h.



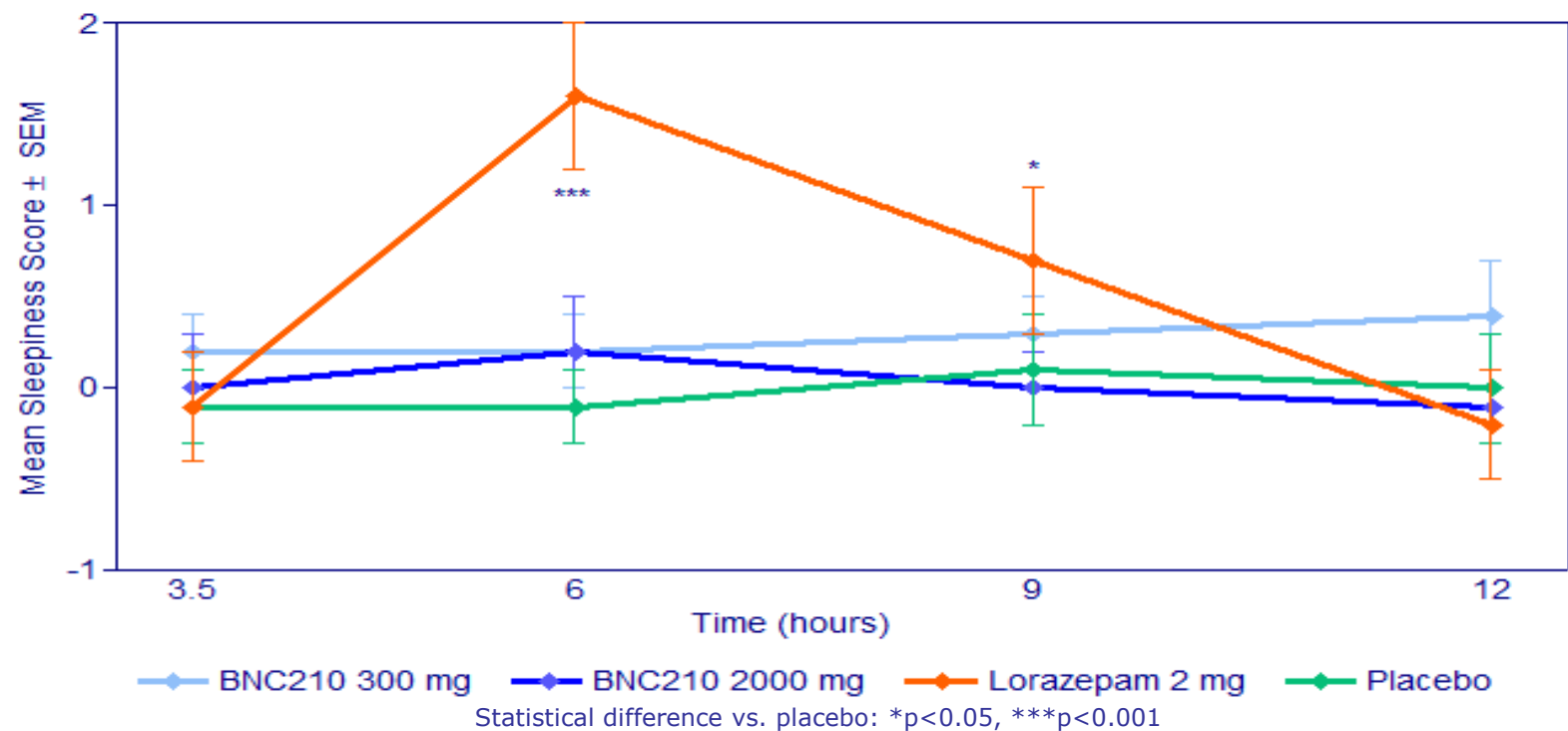
2. BNC210 did not affect psychomotor speed in the Digital Symbol Substitution Test. A slight effect seen with BNC210 (300 mg; T0+6h) was not dose-dependent and was interpreted as not clinically relevant. Lorazepam significantly impaired performance at T0+6h and T0+9h.



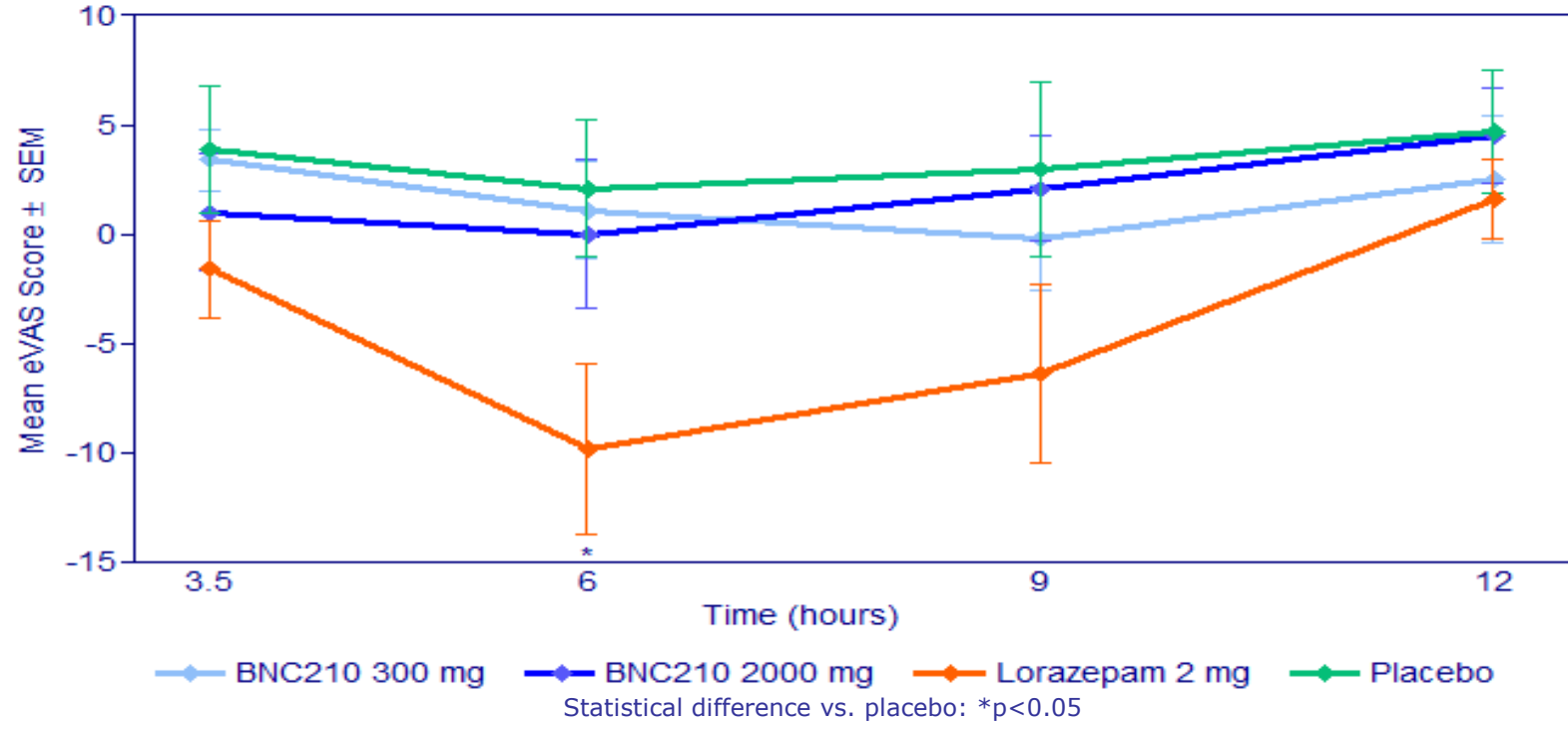
3. BNC210 did not affect visuo-motor coordination. Lorazepam significantly reduced peak saccadic velocity at T0+6h, T0+9h and T0+12h.



4. BNC210 did not induce sleepiness on the Karolinska Sleepiness Scale. Lorazepam significantly induced subjective sleepiness at T0+6h and T0+9h.



5. BNC210 did not affect mood on the emotional visual analog scale. Lorazepam significantly lowered subjects' mood at T0+6h.



6. Neither BNC210 or Lorazepam induced changes in circadian variations of the two stress hormones, cortisol and ACTH. The plasma dynamic range of the two hormones was low in this no-stress paradigm trial.

7. BNC210 did not affect any of the ARCI subgroups. Subjects treated with Lorazepam reported significant feelings of sedation, dysphoria and psychotomimetic changes.

ARCI Results : Pairwise Comparison to Placebo			
ARCI Subscale	BNC210 300 mg	BNC210 2000 mg	Lorazepam 2 mg
Amphetamine	ns	ns	ns
Benzedrine	ns	ns	p=0.056
Lysergic Acid Diethylamine (LSD)	ns	ns	p<0.01
Morphine/ Benzedrine	ns	ns	ns
Pentobarbital/ Chlorpromazine/Alcohol	ns	ns	p<0.001

ns, non significant

8. qEEG profile summary – BNC210 and Lorazepam

- 300 mg or 2000 mg of BNC210:
 - qEEG modifications seen - little overlap with Lorazepam profile except increases in beta 3 activity;
 - No reduction in the Alpha Slow Index for the vigilance-controlled recording condition; low likelihood of sedation;
- 2 mg of Lorazepam:
 - Typical BZD profile - increases in delta and beta activity and decreases in alpha and theta activity;
 - qEEG changes fit with hypovigilance and sedation even in the vigilance-controlled recording condition – significant reductions in the Alpha Slow Index.

9. Plasma exposure to BNC210 was obtained over the time period when pharmacological evaluations were performed.

Mean Plasma BNC210 Concentration (ng/mL±SEM)		
Time (h)	300 mg BNC210	2000 mg BNC210
3.5	1025±46	2228±110
6	878±49	1897±126
9	513±37	1206±114
12	269±24	708±85

10. Treatment with a single oral dose of 300 mg or 2000 mg BNC210 was safe and generally well tolerated.

Treatment-related Adverse Events				
AE	BNC210 300 mg	BNC210 2000 mg	Lorazepam 2 mg	Placebo
Nausea			1	
Asthenia		1		
Hot flush	1			
Sluggishness			1	
Dizziness			1	
Dysgeusia			1	
Head discomfort		1		
Headache		3	1	
Sleep disorder				1
Somnolence	3	1	5	
TOTAL	4	6	10	1

- In total, 15 subjects reported 37 adverse events.
- 21 adverse events were reported as related to treatment: 3 severe (2 somnolence with 300 mg BNC210; 1 headache with 2000 mg BNC210); 7 moderate and 11 mild.
- No serious adverse events were reported.
- No clinically significant changes in electrocardiogram, vital signs or laboratory parameters were recorded.

SUMMARY AND CONCLUSIONS

Key Findings from the Trial		
Assessment	BNC210	Lorazepam
Attention	No effect	Reduced at T0+6, 9, 12h
Psychomotor speed	Slightly reduced at T0+6h (300 mg)	Reduced at T0+6, 9h
Visuo-motor coordination	No effect	Reduced at T0+6, 9, 12h
Sleepiness	No effect	Increased at T0+6, 9h
Mood	No effect	Reduced at T0+6h
Addiction	No effect	Sedation, dysphoric and psychoto-mimetic changes
qEEG	Slight hypo-vigilance in the resting condition only	Hypo-vigilance in resting and vigilance-controlled conditions
Stress hormones	No effect	No effect
Adverse Events	Somnolence/Headache	Somnolence

This study was sponsored by Neurofit SAS.

- Psychomotor, qEEG and cognitive assessments were sensitive to the positive control, Lorazepam, and the results were consistent with data reported in the literature.
- BNC210 has none of the key side effects of Lorazepam; BNC210 does not induce deleterious effects on attention, speed of processing, peak saccadic velocity or subjective mood feelings.
- qEEG data showed BNC210-related changes in brain activity clearly differentiated from those observed with Lorazepam and not indicative of sedation.
- A single oral dose of BNC210 at 300 mg and 2000 mg is safe and well tolerated in healthy male subjects.