BNC210: A Negative Allosteric Modulator of Alpha7 Nicotinic Acetylcholine Receptor in Development for the Treatment of Anxiety, Depression & Post-Traumatic Stress Disorder

Neuropsychiatric Drug Development Summit, 12 November 2020
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BNC210: Agenda & Topics to be Addressed

- Relevance of α7 nAChR for treatment of anxiety, depression and stress-related disorders such as post-traumatic stress disorder (PTSD)
- BNC210 clinical data demonstrating target engagement and proof-of-biology in healthy subjects and generalized anxiety disorder (GAD) patients
- BNC210 for the treatment of PTSD: Initial Phase 2 study with liquid suspension formulation
  - Summary of safety and efficacy data
  - Pharmacokinetic modeling
  - Pharmacometric (exposure-response) analysis
- Development of solid dose spray dried tablet formulation
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  - Regulatory feedback
  - Next steps in development for the treatment of PTSD
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Increasing ACh signaling in hippocampus induces stress-related behaviors and anxiety.

Decreasing signaling through nAChRs containing the α7 subunit in hippocampus decreases stress-related behaviors.

Decreasing signaling through nAChRs containing the α7 subunit in the amygdala is anxiolytic.

Acetylcholine signaling modulates circuits regulating stress-related behaviors and may contribute to the etiology of anxiety.

Genetic variants in acetylcholine signaling could be risk factors for anxiety disorders.

The cholinergic system remains a potential therapeutic target for anxiolytic development.

The α7 nAChR is a novel target for anxiety- and stress-related disorders.
BNC210 is a novel, negative allosteric modulator of the α7 nicotinic acetylcholine receptor with anxiolytic and antidepressant properties.

Acetylcholine binds to orthosteric sites on the α7 receptor.

Calcium ions flow through the channel when α7 receptors are activated by acetylcholine.

BNC210 binds to allosteric sites on the α7 receptor.

Five alpha subunits make up the α7 receptor—Five potential binding sites.

Allosteric sites in the transmembrane domain.
Action of BNC210 Depends on Acetylcholine Neurotransmission and Allosteric Modulation of $\alpha_7$ nAChR

NAMs have self-limiting activity determined by the cooperative interaction between the compounds binding at the allosteric and orthosteric sites e.g. BNC210 and acetylcholine.
BNC210: Next Generation Drug Candidate with Potential to Treat Anxiety, Depression, PTSD and other Stress-Related Disorders

- **No sedation**
- **No withdrawal syndrome**
- **No memory impairment**
- **Fast acting**
- **No drug/drug interactions**

**Potential Competitive Advantages of BNC210**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No sedation</th>
<th>No withdrawal syndrome</th>
<th>No memory impairment</th>
<th>Fast acting</th>
<th>No drug/drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNC210</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Valium and other benzodiazepines</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Prozac and certain other SSRIs/SNRIs</td>
<td>✔</td>
<td>✗</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

*Based on data from preclinical studies, Phase 1 & 2 clinical trials
Market Opportunity: BNC210 has broad therapeutic potential

(Independent 3rd Party analysis done on behalf of Bionomics)

Clinical studies with BNC210 indicate efficacy in anxious humans and potential therapeutic benefit for other disorders

Anxiety Disorders
• Panic Disorder
• Generalized Anxiety
• Social Anxiety

Co-Morbid Anxiety
• Bipolar Disorder
• Major Depressive Disorder

Trauma and Stressor-Related Disorders
• PTSD

Neurodegenerative Disease
• Agitation
• Anxiety

<table>
<thead>
<tr>
<th></th>
<th>PTSD</th>
<th>MDD + Anxiety</th>
<th>Bipolar + Anxiety</th>
<th>Panic Disorder</th>
<th>Social Anxiety</th>
<th>Anxious Elderly</th>
<th>Generalized Anxiety</th>
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<tbody>
<tr>
<td>US Prevalence</td>
<td>9M</td>
<td>8.5M</td>
<td>3.5M</td>
<td>7M</td>
<td>17M</td>
<td>5M</td>
<td>7M</td>
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<tr>
<td># Eligible Patients</td>
<td>1.7M</td>
<td>1.0M</td>
<td>0.5M</td>
<td>1.5M</td>
<td>1.0M</td>
<td>0.5M</td>
<td>0.9M</td>
</tr>
<tr>
<td>*US$</td>
<td>4.7B</td>
<td>3.2B</td>
<td>1.5B</td>
<td>4.4B</td>
<td>2.5B</td>
<td>1.6B</td>
<td>2.7B</td>
</tr>
</tbody>
</table>

*Market Potential of Eligible Patients in US$
Assume 5% premium to Trintellix 2016 AWP for 30-day supply of $380 – Compliance Adjusted
BNC210: Agenda & Topics to be Addressed

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• **BNC210 clinical data demonstrating target engagement and proof-of-biology in healthy subjects and generalized anxiety disorder (GAD) patients**

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## Summary of BNC210 Clinical Trials: Excellent Safety and Tolerability Profile in Healthy Subjects and Patients

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Phase</th>
<th>Description</th>
<th>Subjects Enrolled/Administered BNC210</th>
<th>Location</th>
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<tbody>
<tr>
<td>BNC210.001</td>
<td>1</td>
<td>Safety and Tolerability of Single Ascending Doses in Healthy Volunteers</td>
<td>83/67</td>
<td>Australia, US</td>
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<tr>
<td>BNC210.002</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ICP-2143-101</td>
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<tr>
<td>BNC210.003</td>
<td>1b</td>
<td>Lorazepam &amp; BNC210 Comparison in Healthy Volunteers</td>
<td>24/22</td>
<td>France</td>
</tr>
<tr>
<td>BNC210.004</td>
<td>1b</td>
<td>Panic Attack Model in Healthy Volunteers</td>
<td>60/59</td>
<td>France</td>
</tr>
<tr>
<td>BNC210.005</td>
<td>1b</td>
<td>Safety and Tolerability of Multiple Ascending Doses and EEG Target Engagement Study with Nicotine in Healthy Volunteers</td>
<td>56/44</td>
<td>France</td>
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<tr>
<td>BNC210.006</td>
<td>2a</td>
<td>Imaging and Behavioral Study In Generalized Anxiety Disorder Patients</td>
<td>27/25</td>
<td>UK</td>
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<td>BNC210.007</td>
<td>2</td>
<td>Post-Traumatic Stress Disorder</td>
<td>193/143</td>
<td>Australia, US</td>
</tr>
<tr>
<td>BNC210.008</td>
<td>2a</td>
<td>Agitation in the Elderly in Hospital Setting</td>
<td>38/18</td>
<td>Australia</td>
</tr>
<tr>
<td>BNC210.009</td>
<td>1</td>
<td>Pharmacokinetics of a Recently-Developed BNC210 Solid Dose Formulation in Healthy Volunteers</td>
<td>11/11</td>
<td>Australia</td>
</tr>
<tr>
<td>BNC210.010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BNC210 Treatment Reduced Nicotine-Induced EEG Responses: Demonstration of Target Engagement in Humans

- The EEG response to nicotine is achieved through activation of nicotinic receptors in the brain. The major populations targeted are α4β2 and α7 receptors.
- Oral dosing with 2000 mg BNC210 for 7 days reduced nicotine-induced EEG power in the α2 band.

Reduction in the EEG response is due to negative allosteric modulation of the α7 receptors by BNC210.
BNC210 Enhanced Fear Extinction in Mice - This Translated to Rapid Improvement Following a CCK-4-Induced Panic Attack in Healthy Subjects

Conditioned Fear Extinction Model

Emotional Visual Analog Scale (eVAS)

**MICE**
BNC210 enhanced fear extinction following conditioned stimulus training

**HUMANS**
BNC210 improved rate of return to emotional stability following CCK-4 challenge

People with PTSD and anxiety disorders have amplified fear responses to trauma- and stress-related stimuli and impaired fear extinction
BNC210 Significantly Reduced CCK4-Induced Panic Symptoms in Humans

Panic Symptom Scale:
BNC210 resulted in a significant reduction in the total number of panic symptoms and the panic symptom severity

37.7% Reduction in Total Symptoms (p<0.05)

Placebo: 5.3
BNC210 2000 mg: 3.3

52.7% Reduction in Symptom Intensity (p<0.05)

Placebo: 9.1
BNC210 2000 mg: 4.3

Evaluation conducted in 15 healthy volunteers who experienced a CCK-induced panic attack
Two single doses of BNC210 (300 and 2000 mg), lorazepam (1.5 mg) and placebo were administered to GAD patients.

24 subjects received all treatments (4-way crossover study).

Patients were exposed to ‘fearful faces’ while in a Magnetic Resonance Imaging (MRI) machine and also performed a behavioral task called the Joystick Operated Runway Task (JORT).

Amygdala activation is an imaging surrogate for anxiety.

Connectivity between the amygdala and anterior cingulate cortex (ACC) is very strong in high anxiety.

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PTSD is a prevalent, world-wide disorder arising from a variety of trauma – not just combat exposure

U.S. Population Facts: 7-8% of the population will have PTSD at some point in their lives. ◆ About 8 million adults have PTSD during a given year. ◆ About 10% of women develop PTSD sometime in their lives compared with about 4% of men.

US Veterans with PTSD: ◆ Operations Iraqi Freedom and Enduring Freedom: between 11-20% have PTSD in a given year ◆ Gulf War (Desert Storm): 12% have PTSD in a given year. ◆ Vietnam War: about 30% of Vietnam Veterans have had PTSD in their lifetime.

UK Population Facts: 10% of people develop PTSD. ◆ 20% of firefighters ◆ 30% of teenagers who have survived a horrific car crash ◆ 70% of rape victims ◆ 66% of Prisoners of War ◆ 40% of people who experienced a sudden death of a loved one ◆ An estimated 10,000 women a year following a traumatic childbirth

Human Clinical Data Indicates BNC210 May Impact Multiple PTSD Symptom Clusters

**THE MECHANISM AND PHARMACOLOGY OF BNC210**

**INDICATE THERAPEUTIC POTENTIAL FOR SEVERAL PTSD SYMPTOM CLUSTERS**

**AVOIDANCE**
- GAD Phase 2 Trial

**AROUSAL & REACTIVITY**
- Phase 1 CCK-4 Induced Panic

**INTRUSION**
- Phase 1 CCK-4 Induced Panic

**NEGATIVE ALTERATIONS IN COGNITION & MOOD**
- GAD Phase 2 Trial
  - Phase 1 CCK-4 Induced Panic
## Phase 2 Trial of BNC210 in Adults with Post-Traumatic Stress Disorder (PTSD)

### Study Design
- Multi-center, randomized, double-blind, placebo-controlled
- BNC210 150 mg, 300 mg, 600 mg and placebo (1:1:1:1) (liquid suspension formulation taken twice daily, b.i.d. with food)
- 12-week treatment period
- 193 participants
- 20 US sites / 6 Australian sites

### Key Selection Criteria
- Current diagnosis of PTSD as defined by CAPS-5 (Clinician-Administered PTSD Scale for DSM-5)
- Concomitant use of one anti-depressant medication allowed

### Key Study Objectives
- Primary objective: To assess the effects of BNC210 on investigator-rated symptoms of PTSD measured by CAPS-5
- To assess the safety and tolerability of BNC210 in subjects with PTSD
- Secondary objectives: To assess individual symptom clusters in CAPS-5 such as intrusion, avoidance, arousal and reactivity and negative alterations in cognition and mood
BNC210 PTSD Trial Overall Conclusions:

- No overall effect on primary endpoint of CAPS-5 total severity score at 12 weeks

- **Australian patients had a greater improvement over placebo than US patients**
  - CAPS-5 statistically significant at Week 4 in Australians (p<0.05)

- **Evidence of antidepressant effect in high dose treatment group in the total population**
  - CAPS-5 Criterion D overall (negative changes in cognitions and mood) statistically significant at Week 1 (p<0.05)
  - CAPS-5 Criterion D, Qu. 2 (persistent and negative beliefs or expectations) statistically significant at Week 1 (p=0.001)
  - CAPS-5 Criterion D, Qu. 4 (persistent negative emotional state) statistically significant at Weeks 4 and 8 (p<0.05)

- **Evidence of anxiolytic effect in high dose treatment group in the total population**
  - Trend towards improvement on CAPS-5 Criterion E (arousal and reactivity), Qu. 3 (hypervigilance)
  - Trend towards improvement on CAPS-5 Criterion E, Qu. 4 (exaggerated startle response)

- **BNC210 was safe and well tolerated in patients with PTSD**
  - No trend for increased adverse events with treatment
  - No evidence of cognitive impairment
  - No evidence of suicidal ideation or behavior worsening
# BNC210 Phase 2 Trial: Summary of Significant Clinical Trial Results & Trends

## CAPS-5 Severity Scores – LSMean Changes from Baseline*

| CAPS-5 Total | Australian cohort (n=31):  
| Week 4 (300 mg, p=0.052^; 600 mg, p=0.013)^  
| Week 12 (600 mg, p=0.088) |
|---|---|
| Criterion B | 
| Criterion C | 
| Week 1: Overall Criterion D (600 mg, p=0.037)  
| Week 1: Qu. D2 (300 mg, p=0.024; 600 mg, p=0.001)  
| Week 4: Qu. D4 (600 mg, p=0.013)  
| Week 8: Qu. D4 (600 mg, p=0.040) |
| Criterion D | 
| Week 8: Qu. E3 (600 mg, p=0.073)  
| Week 4: Qu. E4 (600 mg, p=0.063) |
| Criterion E | 

*MMRM with multiple imputation on ITT population; ^MMRM with observed data

## CAPS-5 Total Score Responder Analysis* – Proportion of Patients Achieving Response Thresholds

<table>
<thead>
<tr>
<th>Group (b.i.d. dose)</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold ≥30% improvement from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>55</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>BNC210 150 mg</td>
<td>51</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>BNC210 300 mg</td>
<td>51</td>
<td>55</td>
<td>66</td>
</tr>
<tr>
<td>BNC210 600 mg</td>
<td>71 (p=0.061)</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Threshold ≥50% improvement from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>35</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>BNC210 150 mg</td>
<td>26</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>BNC210 300 mg</td>
<td>38</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>BNC210 600 mg</td>
<td>52 (p=0.056)</td>
<td>58</td>
<td>56</td>
</tr>
</tbody>
</table>

*ITT Completers at each time point; One-sided proportion analysis with z-test

## CAPS-5 Total Score Remission Analysis* – Proportion of Patients With Loss of Diagnosis (CAPS-5<12)

<table>
<thead>
<tr>
<th>Group (b.i.d. dose)</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>BNC210 150 mg</td>
<td>23</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>BNC210 300 mg</td>
<td>24</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>BNC210 600 mg</td>
<td>38 (p=0.063)</td>
<td>50</td>
<td>44</td>
</tr>
</tbody>
</table>

*ITT Completers at each time point; One-sided proportion analysis with z-test

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**Potential reasons why clinically significant effects and trends seen at 4 Weeks did not translate into significant primary endpoint on CAPS-5 at 12 Weeks**

- Inadequate overall blood exposure of BNC210
- BNC210 blood levels declined over 12-week period
- Placebo effect continued to increase from 4W to 12W
Population pharmacokinetic (PK) modelling indicated that plasma levels of BNC210 were substantially lower than expected and declined over the 12-week period using the liquid suspension formulation in this out-patient trial setting.

b.i.d. = administered twice daily; MAD = multiple ascending dose
Pharmacometric Analysis: Exposure (PK) / CAPS-5 Response (PD) Modeling

- 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.

- Three different effects were evaluated using the linear, $E_{\text{max}}$ and power function models.

- An inhibitory $E_{\text{max}}$ model, including estimates of inter-individual variability produced the best PD model fit.

PK-PD Modelling Equations

\[
Effect = \frac{\text{MAX} \cdot \frac{e^{(\text{Baseline} + f_{\text{Placebo}} + f_{\text{Drug}})}}{1 + e^{(\text{Baseline} + f_{\text{Placebo}} + f_{\text{Drug}})}}}{1 + \varepsilon}
\]

\[
f_{\text{Placebo}} = \text{Slope}_{\text{Placebo}} \cdot t
\]

\[
f_{\text{Drug}} = \frac{E_{\text{max}} \cdot \text{AUC}}{\text{AUC}_{50} + \text{AUC}}
\]

\[
f_{\text{Drug}} = a \cdot \text{AUC}^b
\]
Exposure-Response Analysis Showed the Potential for a Significant Response when Adequate Drug Exposure is Achieved

- Pharmacometric analysis of the Phase 2 data established an exposure-response relationship for CAPS-5 total severity scores where higher AUC values (plasma exposure) were related to a larger effect ($p<0.01$)

The figure shows the model-predicted exposure-response curve for a subject with a baseline CAPS-5 total severity score of 30 (this was the mean baseline score for the PTSD trial patients in the 600 mg b.i.d. BNC210 treatment group.)

~25 mg.hr/L is the model predicted $AUC_{90}$ being targeted in future BNC210 trials in PTSD patients.
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A Solid Dose Formulation of BNC210 is being Developed to Achieve Target Exposure in Clinical Trial Subjects

PTSD trial results indicated that the liquid suspension formulation of BNC210 did not achieve sufficient exposure in the out-patient setting.

Benefits of a solid dose formulation (tablets):

- Simple to administer with no need for thorough resuspension
- Formulated to overcome the need to take with food (the liquid suspension was administered with food to give best exposure)

Progress to Date:

- Spray dry dispersion technology used to manufacture BNC210 tablets
- Human single dose PK studies completed
BNC210 Tablet Formulation Overcomes Food Effect of the Liquid Suspension and has Dose Linear Exposure

Trial BNC210.009: single 300 mg dose of BNC210 liquid suspension versus solid dose formulation (fed and fasted conditions)

Trial BNC210.010: single 600, 900 and 1200 mg doses of solid dose formulation in fasted subjects

AUC >25 mg.hr/L achieved at BNC210 tablet doses of 900 mg and higher in fasted subjects
Bionomics has Achieved Key Milestones Towards Continuing Development of BNC210 for the Treatment of PTSD

2019

✓ Pharmacometric analysis of the Phase 2 PTSD trial data showed that there is potential for significant patient benefit in future trials provided adequate drug exposure is achieved.

✓ Successful development of a BNC210 solid dose formulation and evaluation in single dose PK studies achieved exposures adequate for future development.

✓ FDA Type C Meeting provided positive feedback on the BNC210 development program for the treatment of PTSD.

✓ FDA granted Fast Track designation to BNC210 for the treatment of PTSD.
BNC210 is Back on Track to Leverage Large Opportunity for Treatment of PTSD

2020: Preparations for Phase 2b PTSD Trial

• Optimized and selected the tablet formulation for a Phase 2b clinical trial
• Manufacturing underway of BNC210 tablets for a multiple dosing PK trial in healthy volunteers scheduled for late Dec 2020/Jan 2021
• Large scale manufacture of BNC210 drug substance and tablets for Phase 2b trial have been contracted

2021 – 2022: Implementation of Phase 2b PTSD Trial

• Conduct a Phase 2b clinical trial comparing one dose of BNC210 with placebo on the change in CAPS-5 total severity scores – commencing mid-2021
• CAPS-5 is the FDA-accepted primary endpoint for PTSD clinical trials
Clinical studies with BNC210 indicate efficacy in anxious humans and potential therapeutic benefit for other disorders

- Significantly changed anxiety-induced brain activity
- Significantly changed anxiety-induced behavior
- Acute anxiolytic efficacy, equivalent to lorazepam
- Reduced panic symptoms
- Safe and well tolerated

BNC210 also reduced connectivity between the ACC* and the amygdala which, combined with dampening down of amygdala activation, indicates potential for therapeutic intervention in other disorders e.g. PTSD which also feature hyperactive amygdala

*ACC=Anterior Cingulate Cortex (involved in decision making and emotional regulation)
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Neuropsychiatric Drug Development Summit, 12 November 2020