BNC210: in Development For Anxiety, Panic, PTSD And Agitation

Creating Innovative Therapies For Serious Human Diseases.

Sue O’Connor PhD
VP Strategic Initiatives and Innovation
14th Bioshares Biotech Summit
27-28 July 2018
“It keeps me from looking at my phone every two seconds.”
Safe Harbor Statement

Factors Affecting Future Performance

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Subject to the requirements of any applicable legislation or the listing rules of any stock exchange on which our securities are quoted, we disclaim any intention or obligation to update any forward-looking statements as a result of developments occurring after the date of this presentation.
Lead candidate, BNC210 is a novel, orally-administered, first-in-class, negative allosteric modulator of the α7 nicotinic acetylcholine receptor, in development for anxiety, panic, agitation, and PTSD

BNC210 Highlights:
- Positive data from Phase 2 trial in Generalized Anxiety Disorder (GAD) patients; September 2016
- Phase 2 trial PTSD patients completed in Australia and US, data anticipated late 3Q, 2018
- Phase 2 trial in Agitated Elderly ongoing in Australia, data anticipated in 1Q, CY2019

Highlights of Strategic partnership with Merck & Co., (MSD)
- Cognition therapeutic candidate, entry into P1 triggered US$10M milestone payment in deal valued up to US$506M in upfront, research and milestone payments plus additional royalties on net sales of licensed drugs
- Merck & Co equity investment in October 2015, 4.5% ownership

Robust pipeline of first-in-class ion channel programs

Financials: Market Cap ~US$189.5M as at 11 July 2018; Cash at 30 June 2018 US$18.4M
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.

BNC210 binds to allosteric sites on the α7 receptor.

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

Five alpha subunits make up the α7 receptor = Five potential binding sites.
Extensive pre-clinical efficacy and safety profiling demonstrated anxiolytic, antidepressant and safety properties of BNC210

- Light Dark Box
- Marble Burying
- **Contextual Fear Conditioning**
- Elevated Plus Maze

- Elevated Plus Maze
- Pre-stress + Elevated Plus Maze
- CCK + Elevated Plus Maze
- Forced Swim Test

- Isolation-induced vocalizations in guinea pig pups

- Open Field – dark, light
- Rotarod
- Modified Irwin
- Novel Object Recognition
- T-maze

**MICE**

**RAT**

**GUINEA PIG**

**SAFETY**
BNC20 clinical data has demonstrated anxiolytic activity while maintaining a unique safety profile.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Description</th>
<th>Subjects</th>
<th>Location</th>
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<tbody>
<tr>
<td>P1</td>
<td>BNC210.001 &amp; 2 Safety &amp; Tolerability of Single Ascending Doses</td>
<td>24</td>
<td>Australia</td>
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<td>SAFETY &amp; TOLERABILITY, PK</td>
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<tr>
<td>P1</td>
<td>BNC210.003 Lorazepam &amp; BNC210 Comparison plus EEG</td>
<td>22</td>
<td>France</td>
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<tr>
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<td>SAFETY &amp; TOLERABILITY &amp; PD</td>
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<td>P1</td>
<td>BNC210.004 Panic Attack Model in Healthy Volunteers</td>
<td>59</td>
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<td>EFFICACY</td>
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<tr>
<td>P1</td>
<td>BNC210.005 Safety &amp; Tolerability of Multiple Ascending Doses, Target Engagement Study with Nicotine &amp; EEG</td>
<td>42</td>
<td>France</td>
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<tr>
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<td>SAFETY AND TOLERABILITY TARGET ENGAGEMENT</td>
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<td>P2a</td>
<td>BNC210.006 Imaging &amp; Behavioural Study In Generalised Anxiety Disorder Patients</td>
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<tr>
<td>P2</td>
<td>BNC210.007 Stress Disorder</td>
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<td>P2</td>
<td>BNC210.008 Agitation in the Elderly in a Hospital Setting</td>
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<td>EFFICACY</td>
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</table>

PTSD TRIAL 193 PATIENTS RECRUITED. DATA EXPECTED LATE Q3, 2018

AGITATION TRIAL: RECRUITING WELL DATA EXPECTED Q1, 2019
BNC210 enhanced fear extinction in mice - this translated to rapid improvement in healthy volunteers following a CCK-4-induced panic attack.

**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- or stress-related stimuli and impaired fear extinction.
PTSD is a prevalent, world-wide disorder arising from a variety of trauma – not just combat exposure

**Percentage of People who Develop PTSD after Trauma Exposure**

- Work Exposure
- Death of Family/Close Friend due to Violence, Accident, Disaster
- Threat or Injury to Family/Close Friend due to Violence, Accident, Disaster
- Witnessed Dead Bodies/Parts Unexpectedly
- Witnessed Physical or Sexual Assault
- Physical or Sexual Assault
- Combat/War Zone Exposure
- Exposure to Hazardous Chemicals
- Accident/Fire
- Disaster

National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria

**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

http://www.ptsduk.org/what-is-ptsd/who-is-affected-by-ptsd/

Bionomics has completed recruitment for a Phase 2 Trial in Post Traumatic Stress Disorder (PTSD) in Australia and the USA

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>192 PTSD patients</th>
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<tbody>
<tr>
<td>PROTOCOL</td>
<td>Double blind, placebo controlled, randomized, multi-centre</td>
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<tr>
<td></td>
<td>4 arms: 1 placebo, 3 BNC210 dose levels</td>
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<td>12 weeks of dosing, twice daily oral treatment</td>
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<tr>
<td>PRIMARY OBJECTIVE</td>
<td>To determine whether BNC210 causes a decrease in PTSD symptoms as measured by CAPS-5</td>
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<td>SECONDARY OBJECTIVES</td>
<td>To determine the effects of BNC210 on individual symptom clusters</td>
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<td>To determine the effects of BNC210 on Anxiety (HAM-A), Depression (MADRS) and</td>
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<td>Functioning and Quality of Life,</td>
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<td></td>
<td>Safety and Tolerability</td>
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<tr>
<td>EXPLORATORY ENDPOINTS</td>
<td>Effects of smoking</td>
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</tbody>
</table>

Trial enrolled 193 PTSD patients. Data expected late Q3.
Several rating scales included to capture efficacy of BNC210 for a range of symptoms and disorders

**PTSD Scales**

- CAPS-5 (Clinician-Administered PTSD Scale for DSM-5) Primary endpoint
- PTSD Checklist for DSM-5 (PCL-5) Self-reporting scale

**Affective Disorders**

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A)

**Scales to assess symptom severity, treatment response and efficacy**

- Clinical Global Impressions – severity and improvement scale (CGI-S/CGI-I)
- Patient Global Impression – Severity and improvement Scale (PGI-S/PGI - I)
- Assessment of Quality of Life (AQoL-8D)
- Social functioning: Sheehan Disability Scale (SDS)
- Sleep monitoring: Pittsburgh Sleep Quality Index (PSQI)
- Suicidal behavior (Columbia Suicide Severity Rating Scale, C-SSRS)
The mechanism and pharmacology of BNC210 indicate therapeutic potential for several PTSD symptom clusters

Four main PTSD symptom clusters (DSM-5 criteria)

- Avoidance
  - Anxiolytic in rodents and man
  - Acute effects on neural circuitry associated with anxiety and PTSD in man
  - Enhances fear extinction in mice and emotional recovery in man following panic attack
- Intrusive thoughts
  - Acute doses reduce defensive behavior in man
- Nightmares
  - Acute effects in rats, acute efficacy which is potentiated with repeat dosing
- Arousal and reactivity
  - Reduces amygdala hyperactivity – a feature shared by anxious patients and PTSD patients
  - Inhibition of α7 nAChRs modulate GABA and glutamate signaling in the amygdala and hippocampus
  - Clinical efficacy in model of panic in HVs, elevated levels of ACh stimulate the HPA axis, BNC210 treatment significantly reduced levels of ACTH in CCK study
- Negative alterations in cognition and mood.
  - α7 nAChRs modulate GABA and glutamate signaling in the amygdala and hippocampus

It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

Biological Psychiatry 2017; PMID: 28454621

- Reduced clinical efficacy in model of panic in HVs, elevated levels of ACh stimulate the HPA axis, BNC210 treatment significantly reduced levels of ACTH in CCK study
- 321x353
  - Enhanced fear extinction in mice and emotional recovery in man following panic attack
  - Acute doses reduce defensive behavior in man
  - Promotes neurite outgrowth in primary neurons
  - Reduces amygdala hyperactivity – a feature shared by anxious patients and PTSD patients
  - α7 nAChRs modulate GABA and glutamate signaling in the amygdala and hippocampus
  - It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

Biological Psychiatry 2017; PMID: 28454621
### Competitive Landscape for Industry Trials in PTSD

<table>
<thead>
<tr>
<th>Stage of Development</th>
<th>Company / Sponsor</th>
<th>MOA</th>
<th>Drug</th>
<th>Other Indications</th>
<th>Trial Overview</th>
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<tr>
<td>PI</td>
<td>SpringWorks</td>
<td>FAAH</td>
<td>PF-C</td>
<td>Ar*</td>
<td>Info other</td>
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<td>PII</td>
<td>Bionomics</td>
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<td>PIV</td>
<td>MSD</td>
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<td>Howard University</td>
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<td>Takeda University of Miami</td>
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<td>Serotonin modulator and stimulator</td>
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<td></td>
<td>University of Miami</td>
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<td></td>
<td>Depression</td>
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</tbody>
</table>

**Con** Of course you feel great. These things are loaded with antidepressants.
The potential advantages of BNC210 for PTSD, Anxiety & Agitation compared to standard of care treatments, have been demonstrated in preclinical and clinical studies.

### 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>
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<tbody>
<tr>
<td>BNC210</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Valium and other BZD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Prozac and certain other SSRI/SNRI</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Atypical Antipsychotics</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

### Anxiety Treatments
- Dominated by benzodiazepines (BZDs)
- Associated with sedation, abuse liability, tolerance and cognitive disturbances, falls, accidents
- Not recommended for long-term treatment

### Depression Treatments
- SSRIs and SNRIs used to treat depression and anxiety
- Modest efficacy, late onset of action, discontinuation syndrome, weight gain, sexual dysfunction and increased thoughts of suicide in adolescents
- Many have black box warnings

### Agitation Treatments
- In addition to BZD, anti-psychotics are used to treat agitation and anxiety. They cause dizziness, sedation, weight gain, constipation, movement disorders and have black box warnings for use in elderly (stroke, a 70–80% increased risk of pneumonia)

### PTSD Treatments
**ANTIDEPRESSANTS:**
- Sertraline (Zoloft) and paroxetine (Paxil) are only US FDA approved drugs for PTSD; VA also recommend Effexor and Prozac
- The 2017 VA/DoD Clinical Practice Guideline for PTSD further offers weak recommendation for other antidepressants if the four strongly recommended medications are ineffective, unavailable, or not tolerated. nefazodone (Serzone); imipramine (Tofranil); phenelzine (Nardil). Both nefazodone and phenelzine require careful management as they carry potentially serious toxicities.

**BENZODIAZEPINES:**
- VA/DoD 'Practice Guideline for PTSD' recommends against the use of BZDs such as Valium for PTSD.
- 50% increase in overall mortality rates associated with long-term benzodiazepine use in PTSD patients—overdosing, sudden unexplained deaths, car crashes, falls.
- Still over-prescribed despite lack of efficacy, addictive potential and other harms associated with chronic use. An estimated 2.8M scripts are written off-label for management of PTSD symptoms.

*Based on data from preclinical studies, Phase 1 & 2 clinical trials.
BNC210 has potential for the treatment of agitation.

BNC210 rapidly inhibits Amygdala activation in GAD patients during the performance of anxiety provoking tasks.

BNC210 works acutely for panic attack and in GAD patients. Has equivalent efficacy to benzodiazepines; safety profile greatly improved.

Higher prevalence of GAD in the elderly. Amygdala activation associated with agitation.

“I have a couple of other projects I’m excited about.”
Agitation in the elderly: prevalence, symptoms and treatments

Agitation in Alzheimer’s Disease

• >2 million AD patients in the US.¹,² Expected to nearly triple by 2050.³

• Agitation and aggression seen in approximately 45% of AD patients during 5-year period.⁴

• Characterized by emotional lability, restlessness, irritability, aggressive behaviors, disinhibition, and caregiver burden.⁵

• Agitation is associated with⁶,⁷:
  – Accelerated cognitive decline
  – Earlier nursing home placement³
  – Increased mortality

• 30% of caregivers rate stress associated with agitation / aggression as severely to extremely distressing.⁷

• Agitation is estimated to account for more than 12% of the healthcare and societal cost of Alzheimer’s disease; currently estimated to be $256 billion in US for 2017.³

Agitation Treatments

• No approved medication = unmet medical need

• Current treatments include benzodiazepines and antipsychotics, buspirone, β-blockers, serotonergic agents, carbamazepine, lithium, and divalproex sodium.³

Issues with Benzodiazepines:
• Sedating, cause disinhibition, cognitive and motor impairment, development of tolerance and addictive with long term use

• Decreased metabolism in the elderly leads to longer presence of drug in the body and increased risk of toxicity

Issues with Antipsychotics:
• Adverse effects: pseudo-parkinsonism, sedation, akathisia, a form of motor restlessness.

• Lack therapeutic efficacy on wandering, apathy, withdrawal, hypersexuality, and symptoms of executive dysfunction or other cognitive aspects of dementia.

• FDA “Black Box Warning” for elderly patients- increased risk of death (pneumonia, stroke)

7. Raskin, MA, Disruptive Agitation in Alzheimer’s Disease: Medication Treatment
### Phase 2 clinical trial to assess the efficacy and safety of BNC210 in hospitalised elderly patients with agitation

**Objectives**
- Primary: to compare the effects of BNC210 and placebo on the time to resolution of agitation as measured by the Pittsburgh Agitation Scale (PAS)
- Secondary: to compare the effects of BNC210 and placebo on the change in global function as assessed by the Clinical Global Impression Scale (CGI-S/I)
- Exploratory: to assess safety and tolerability of BNC210 in elderly patients with agitation

**Design**
- Randomized, double-blind, placebo controlled parallel dosing, 1:1 ratio
- BNC210 300 mg and placebo (twice daily)
- 5 days treatment; 2 days follow up
- Approximately 40 participants

**Key Selection Criteria**
- Hospitalised elderly patients under the care of a specialist Geriatrician
- Presenting with agitation requiring intervention in addition to standard-of-care behavioural management
## Current Industry Sponsored Trials for Agitation and Aggression in Dementia July 2018

<table>
<thead>
<tr>
<th>Stage of Development</th>
<th>P2</th>
<th>P3</th>
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<td>MOA</td>
<td>a7 nAChR NAM</td>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt; receptor antagonist</td>
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<td>Drug</td>
<td>BNC210</td>
<td>MP-101 (LY2979165)</td>
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<td>Indication</td>
<td>Agitation in the Elderly</td>
<td>Dementia-Related Psychosis and/or Agitation and Aggression</td>
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<td>Pharmacology</td>
<td>Anxiolytic Anti-depressant, Enhances fear extinction</td>
<td>Atypical Anti-psychotic</td>
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<tr>
<td>Trial Overview</td>
<td>40 pts, End 2018</td>
<td>80 pts, July 2019</td>
</tr>
</tbody>
</table>

**“I don’t know about you, but I say it’s time we started experimenting with drugs.”**
Depression, PTSD and Agitation are dominating psychiatric drug discovery and development efforts.

“*These medicines all taste pretty good—let’s approve them.*”

* = Recruiting, Not yet Recruiting, Active, not Recruiting, Recruiting by Invitation
The FDA has initiated five approaches to make potentially important new drugs available as rapidly as possible:

**PRIORITY REVIEW** 1992: A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions.

**FAST TRACK DESIGNATION** 1997: The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.

**ACCELERATED APPROVAL:** In 2012, Allows the FDA to base accelerated approval on whether the drug has an effect on a surrogate or an intermediate clinical endpoint for drugs for serious conditions that fill an unmet medical need.

**BREAKTHROUGH THERAPY DESIGNATION:** July 9, 2012 - Breakthrough Therapy Designation - If a drug is designated as breakthrough therapy, it will demonstrate substantial treatment effects early in clinical development (P2). FDA will expedite the development and review of such a drug.

**REGENERATIVE MEDICINE ADVANCED THERAPY** 2016: Preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition.

“What’s the next best medicine?”
Drugs in development for Depression and PTSD are leading the indications receiving Breakthrough Therapy Designation

<table>
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<tr>
<th>Year</th>
<th>Drugs</th>
<th>Companies</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>2018</td>
<td>Sage217</td>
<td>Sage Therapeutics</td>
<td>MDD</td>
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<tr>
<td></td>
<td>Balovaptan</td>
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<td>Posttraumatic Stress Disorder</td>
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<tr>
<td>2017</td>
<td>Valbenazine</td>
<td>Neurocrine Biosciences</td>
<td>Tardive Dyskinesia</td>
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<td></td>
<td>Midomafetamine</td>
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<td>2016</td>
<td>Pimavanserin</td>
<td>Acadia Pharmaceuticals</td>
<td>Parkinson's Disease - related Psychosis</td>
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<td>Oliceridine</td>
<td>Trevena</td>
<td>Analgesia And Pain Management</td>
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<td>Sage 547</td>
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<td>Post Partum Depression (IV)</td>
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<td>Esketamine</td>
<td>Janssen</td>
<td>Treatment Resistant Depression</td>
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<td>Rapastinel (Glyx-13)</td>
<td>Allergan</td>
<td>MDD Rapid Onset</td>
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<td>Tonmya</td>
<td>Tonix Pharmaceuticals</td>
<td>Posttraumatic Stress Disorder</td>
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<td>2014 &amp; 2015</td>
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<td>2013</td>
<td>Esketamine</td>
<td>Janssen</td>
<td>Treatment Resistant Depression</td>
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Drugs with dissociative properties are being investigated for therapeutic benefit in many difficult-to-treat disorders.

Ketamine*
- Suicide Prevention (5)
- Autism Spectrum Disorder (2)
- Agitation Control in Emergency Depts (2)
- Treatment Resistant Depression (5)
- Major Depression (3)
- Bipolar Depression (1)
- PTSD (1)
- Major Depression in Veterans (1)
- Pediatric OCD (1)

* = Clinical Trials.gov: Recruiting, Not Yet Recruiting, Active, Not Recruiting, Recruiting by Invitation

MDMA*
- PTSD (1)
- Startle Response (1)
- Fear Extinction (1)
- Psychotherapy–assisted treatment for PTSD (2)
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 efficacy, equivalent to Lorazepam
- Reduced Panic Symptoms
- 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 and Agitated Elderly which also feature hyperactive amygdala.

Anxiety Disorders
- Panic Disorder
- Generalized Anxiety
- Social Anxiety

Confidential Presentation

*ACC = Anterior Cingulate Cortex (involved in decision making and emotional regulation)

It's fine to discover cures, but remember, chronic conditions are our bread and butter
BNC210 targets multi-billion dollar markets with unmet need: US market potential

- Innovative, first-in-class
- Unmet need in large patient population
- Advancement in care
- Limited branded competition
- Ability to achieve large market share

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Eligible Patient Population</th>
<th>Eligible Patient US$ Market Potential</th>
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<tbody>
<tr>
<td>PTSD</td>
<td>8.7-9M</td>
<td>US$4.7b</td>
</tr>
<tr>
<td>MDD + Anx</td>
<td>8-8.5M</td>
<td>US$3.2b</td>
</tr>
<tr>
<td>BP+Anx</td>
<td>3-3.5M</td>
<td>US$1.5b</td>
</tr>
<tr>
<td>Panic</td>
<td>6.5-7M</td>
<td>US$4.4b</td>
</tr>
<tr>
<td>SAD</td>
<td>17M</td>
<td>US$2.5b</td>
</tr>
<tr>
<td>Agitation</td>
<td>5M</td>
<td>US$1.6b</td>
</tr>
<tr>
<td>GAD</td>
<td>7M</td>
<td>US$2.7b</td>
</tr>
</tbody>
</table>

Eligible Patient US$ Market Potential
Assume 5% premium to Trintellix 2016 AWP for 30-day supply of $380 – Compliance Adjusted

1 3.4-4% prevalence >18yrs., ~25% of patients diagnosed and treated
2 6.7% prevalence, ~50% co-morbid anxiety, ~50% diagnosed and treated
3 ~2.9% prevalence, 50% co-morbid anxiety (range in literature 25 to 75%), ~50% diagnosed and treated
4 ~2.7% prevalence, ~50% diagnosed and treated
5 ~6.8% prevalence, 15-20% diagnosed and treated
6 ~3.1% dementia prevalence >40yrs., ~9% agitation patients diagnosed and treated
7 3.1% GAD prevalence, assumes ~25% diagnosed and treated, ~50% of SSRI patients treated are partial responders or relapsers

Major Depressive Disorder (MDD). Bipolar Disorder (BP). Social Anxiety Disorder (SAD). Generalized Anxiety Disorder (GAD).