NASDAQ: BTAI

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Neuroscience R&D Day

December 12, 2023

1:00-2:30 pm ET

BioXcel Therapeutics | 555 Long Wharf Drive, 12th Floor | New Haven, CT 06511 | **bioxceltherapeutics.com**

Forward-Looking Statements

This presentation includes "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements in this presentation include but are not limited to: statements regarding BioXcel Therapeutics' expected timing of, and data results from, trials and clinical studies, and other milestones involving its product candidates and full clinical development pipeline including BXCL501, BXCL502, BXCL503, and BXCL504; its commercial plan, targets, and strategy for its developing product candidates; potential benefits of treatment with BXCL502 and BXCL503 for Alzheimer's-related symptoms, potential registrational paths and potential advocating activities relating to BXCL501, BXCL502 and BXCL503, the potential for BXCL501 to treat opioid withdrawal symptoms and potential benefits of such treatment, potential market size and opportunity for products and product candidates, and its future financial and operational results. When used herein, words including "anticipate," "being," "will," "plan," "may," "continue," and similar expressions are intended to identify forward-looking statements. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon BioXcel Therapeutics' current expectations and various assumptions. BioXcel Therapeutics believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain.

BioXcel Therapeutics may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various important factors, including, without limitation: its limited operating history; its incurrence of significant losses; its need for substantial additional funding and ability to raise capital when needed; its limited experience in drug discovery and drug development; its dependence on the success and commercialization of IGALMI™, BXCL501, BXCL502 and BXCL503 and other product candidates; the Company has no experience in marketing and selling drug products; IGALMI™ or the Company's product candidates may not be accepted by physicians or the medical community in general; the failure of preliminary data from its clinical studies to predict final study results; failure of its early clinical studies or preclinical studies to predict future clinical studies; its ability to receive regulatory approval for its product candidates; its ability to enroll patients in its clinical trials; undesirable side effects caused by the Company's product candidates; its novel approach to the discovery and development of product candidates based on EvolverAI; its exposure to patent infringement lawsuits; its ability to comply with the extensive regulations applicable to it; impacts from the COVID-19 pandemic; risks associated with the increased scrutiny related to environmental, social and governance (ESG) matters, its ability to commercialize its product candidates; and the other important factors discussed under the caption "Risk Factors" in its Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2023, as such factors may be further updated from time to time in its other filings with the SEC, which are accessible on the SEC's website at www.sec.gov and the Investors section of our website at www.bioxceltherapeutics.com.

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Presentation Focus on Advancing Innovation and Expanding Our Neuroscience Pipeline

Driven by company's unique AI-based approach

Advancing Innovative Pipeline in Alzheimer's-Related Symptoms

BXCL502

- Novel agent in development for treatment of neuropsychiatric symptoms and chronic agitation in dementia

BXCL503

- Potential to treat dementia-related symptoms outside of agitation
- Candidates targeting apathy in dementia

Seeking to Address Opioid Crisis

BXCL501

- Demonstrated positive results in treating patients diagnosed with opioid use disorder
- Over 110,000 deaths annually due to opioid use disorder (June 2023 - CDC)
- NIH/NIDA-sponsored (gov't funded) investigator-led program managed by Columbia University clinical operations team under CRADA

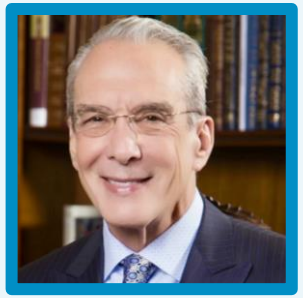
Agenda and Speakers

- Our Corporate Strategy: **Vimal Mehta**
- Our R&D Strategy: **Frank Yocca**
- BXCL502: A Novel Agent for Treatment of Chronic Agitation in Dementia: **Mike De Vivo**
- The Neuropsychiatric Inventory: Measuring Agitation Relief in Alzheimer's Disease: **Jeffrey Cummings**
- BXCL503 for Dementia-Related Apathy: **Friso Postma**
- BXCL501 (Sublingual Dexmedetomidine) for the Potential Treatment of Acute Opioid Withdrawal: **Sandra Comer**
- Q&A
- Closing Remarks**: Frank Yocca**

Vimal Mehta, Ph.D.
Founder & CEO

Frank Yocca, Ph.D.
Chief Scientific Officer

Mike De Vivo, Ph.D.
Vice President,
Neuroscience



Jeffrey Cummings, M.D.
Professor of Neurology

Friso Postma, Ph.D.
Vice President,
AI and Emerging Portfolio

Sandra Comer, Ph.D.
Principal Trial Investigator and
Professor of Neurobiology

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Our Corporate Strategy

Vimal Mehta
Founder and CEO

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Corporate Growth Drivers

Transformative drug re-innovation approach resulted in rapid approval of IGALMI™

Land

Agitation Associated With Bipolar Disorders or Schizophrenia

Medical Supervision

Igalmi™ (dexmedetomidine) sublingual film · 120 mcg, 180 mcg

16M

BPD/SCZ Institutional Episodes[1-3]

Expand

2024 Focus

BXCL501 Potential At-Home Expansion

Agitation Associated With:

- Alzheimer's Dementia
- Bipolar Disorders or Schizophrenia

Phase 3 TRANQUILITY and SERENITY Programs

100M

Alzheimer's* Agitation Episodes[1]

2024 & Beyond

Emerging Alzheimer's Symptoms-Based Pipeline

BXCL502
BXCL503

23M

BPD/SCZ Agitation Episodes[1-3]

The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

1. Data on file. BioXcel Therapeutics, Inc. New Haven, CT December 2020. 2. Wu EQ, Shi L, Birnbaum H, et al. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. Psychol Med. 2006;36(11):1535-1540. 3. National Institute of Mental Health. Prevalence of bipolar disorder in adults. November 2017. Accessed December 16, 2022. https://www.nimh.nih.gov/health/statistics/bipolar-disorder.

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Our R&D Strategy

Frank Yocca
Chief Scientific Officer

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R&D Strategy: Build Pipeline Depth with Innovation and Expansion

Pipeline as of December 12, 2023

Compound	Indication/Proposed Indication	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Marketed
Igalmi™ (dexmedetomidine) sublingual film • 120 mcg, 180 mcg	APPROVED APRIL 5, 2022 Acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults under provider supervision						
BXCL501	TRANQUILITY PROGRAM Acute treatment of agitation in Alzheimer's dementia						
	SERENITY III PROGRAM Acute treatment of agitation in bipolar disorders/schizophrenia						
	Opioid Use Disorder (OUD)						
	Post Traumatic Stress Disorder (PTSD)						
BXCL502	Neuropsychiatric symptoms Chronic agitation in Alzheimer's dementia						
Candidate BXCL503	Apathy in dementia						
Candidate BXCL504	Aggression in dementia						

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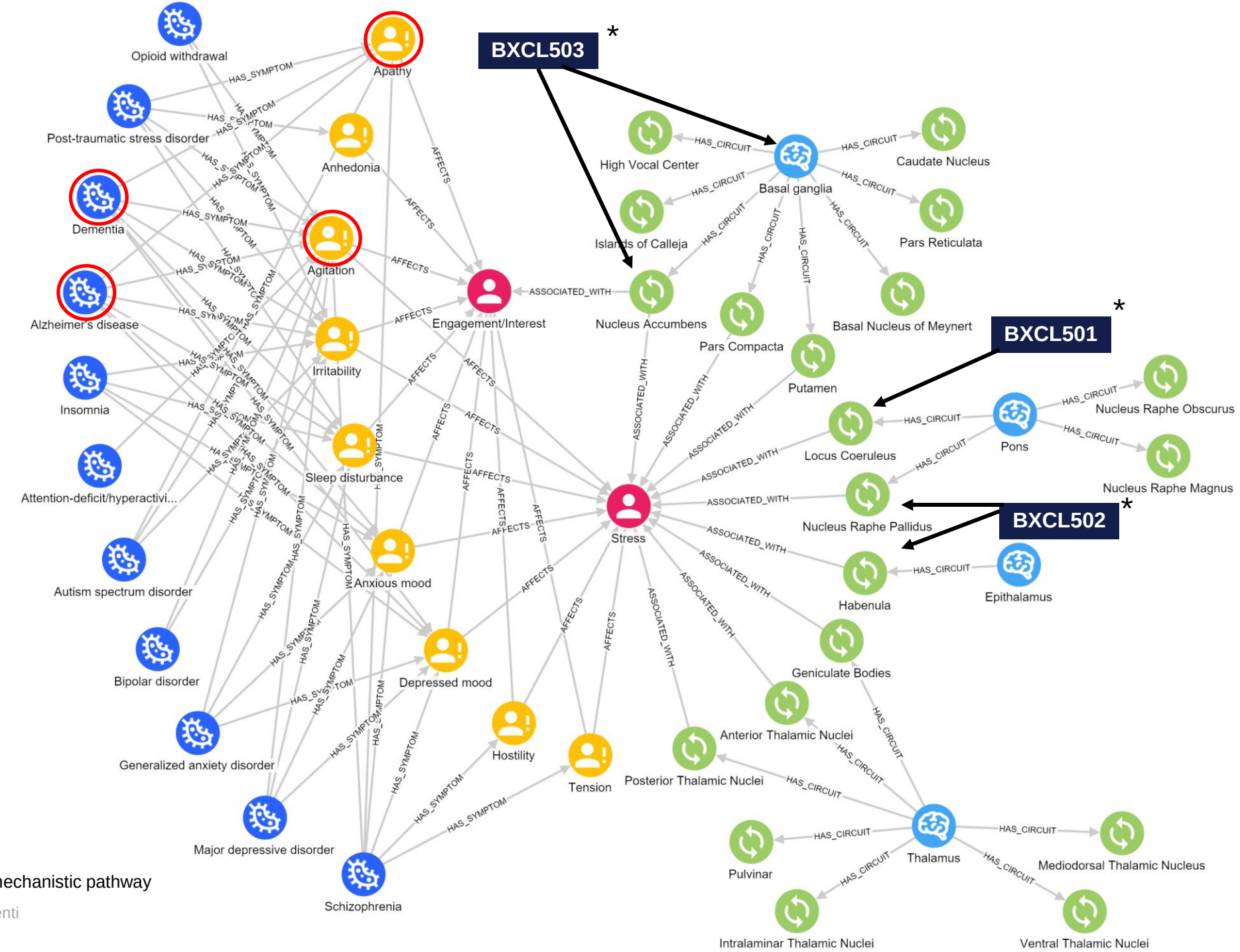
The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established



* Denotes potential mechanistic pathway

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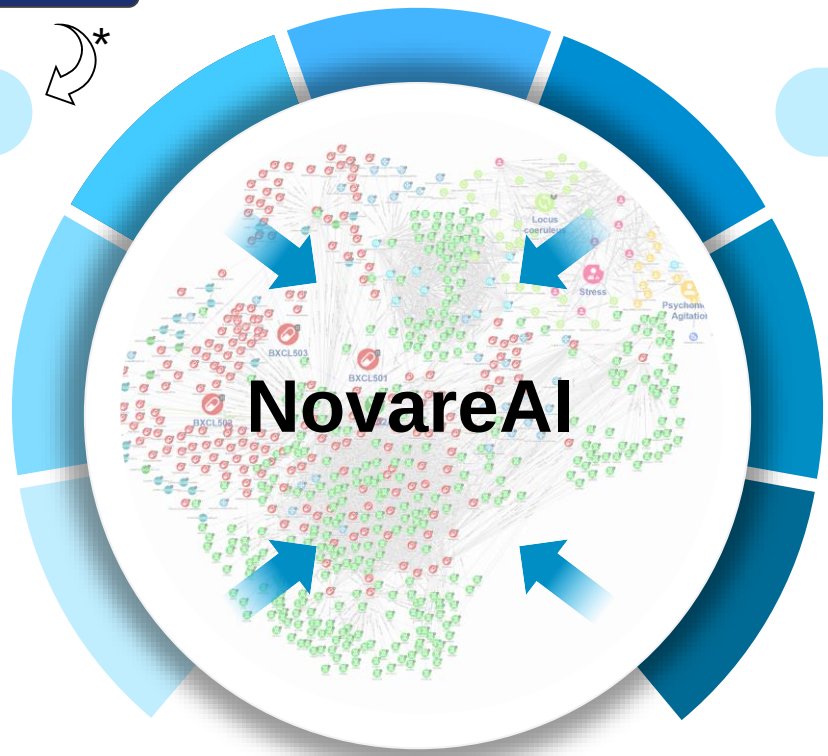
Behavioral and Psychological Symptoms in Alzheimer's Disease

Identifying targets and compounds designed to address unmet medical needs in dementia

BXCL501 - Norepinephrine
BXCL502 - Serotonin
BXCL503 - Dopamine



- 42.3% — Agitation/Aggression — BXCL501/502
- 35.6% — Sleep Disturbances — BXCL501/502 *
- 50.5% — Irritability — BXCL501/502 *
- 27.5% — Hallucinations
- 24.8% — Delusions
- BXCL501/502 * — Anxiety — 26.8%
- Depression — 38.8%
- BXCL503 * — Apathy — 57.4%
- Disinhibition — 26.3%

* Denotes a potential role for BXCL502 and BXCL503 in addressing these symptoms

The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

Prevalences derived from Laganà et al., 2022

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BXCL502:
A Novel Agent for Treatment of Chronic Agitation in Dementia

Michael De Vivo
Vice President, Neuroscience

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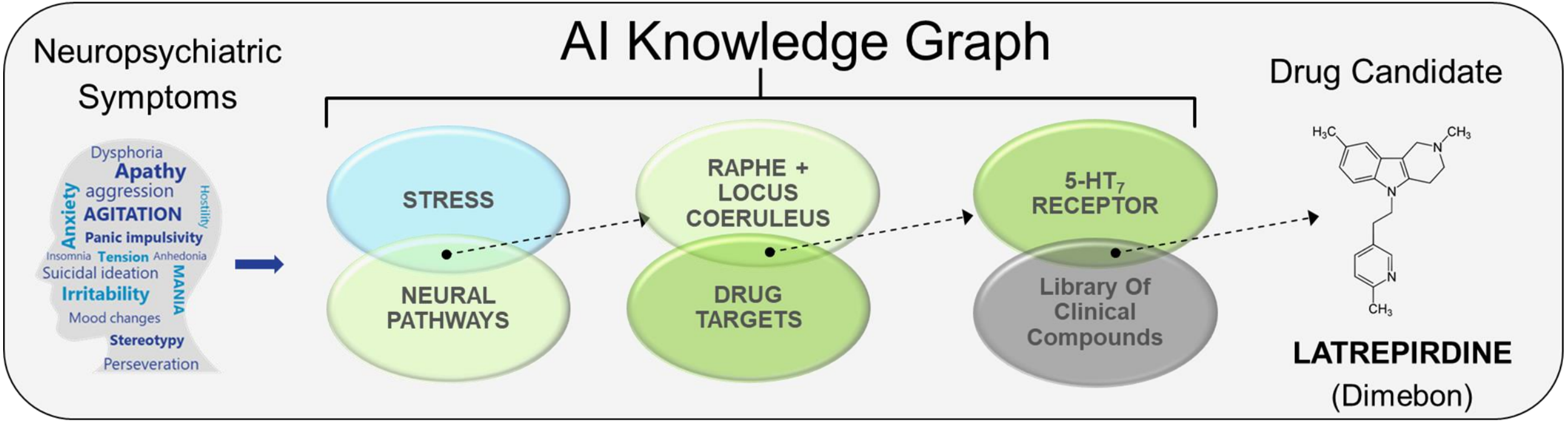
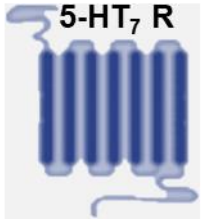
Drug-Sensitive Neural Pathways for Treatment of Neuropsychiatric Symptoms



Novel Pathway:

Raphe (5-HT) and Locus Coeruleus (NE)

Drug Target:



Compound:

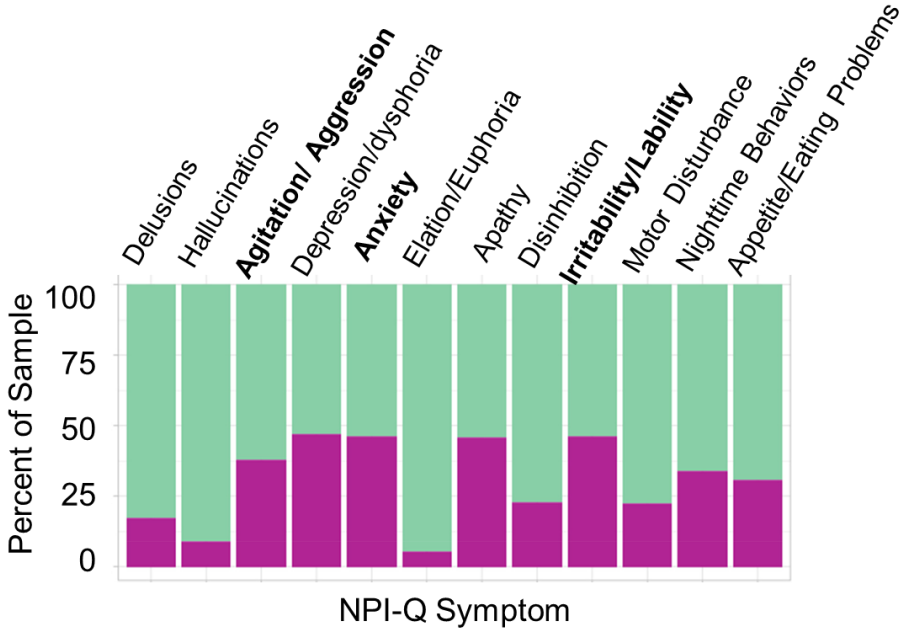
Latrepirdine:
Clinical Candidate
With Extensively Characterized Safety

Neuropsychiatric Symptoms are a Serious Unmet Medical Need

Latrepirdine is a promising candidate that potentially could address this need

- Neuropsychiatric symptoms occur early in patients with dementia
- These symptoms have serious adverse consequences for patients and caregivers, such as:
  - greater impairment in activities of daily living
  - more rapid cognitive decline
  - worse quality of life
  - earlier institutionalization
  - greater caregiver depression

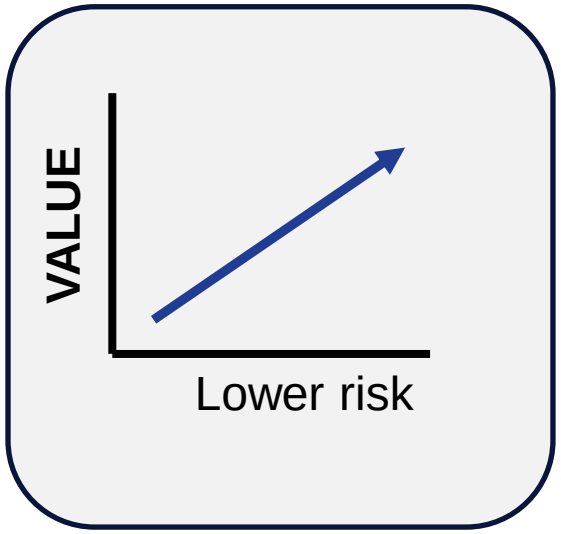
Prevalence of Neuropsychiatric Symptoms



National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) 12494 sample size

Goodwin GJ, Moeller S, Nguyen A, Cummings JL, John SE. Network analysis of neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Res Ther. 2023 Aug 11;15(1):135.

Latrepirdine: Clinical Safety Results, Preclinical Confidence in Rationale, and Early Sign of Potential Efficacy all Support Further Development



SAFETY RESULTS IN PATIENTS

- Over 1000 AD patients exposed for 26 weeks and 500 up to 52 weeks

(*Studies conducted by Pfizer and Medivation*)

PRECLINICAL Confidence in Rationale

- Showed activity in 5 preclinical models of neuropsychiatric symptoms

(*Studies conducted by BioXcel Therapeutics*)

CLINICAL Early Sign of Potential Efficacy

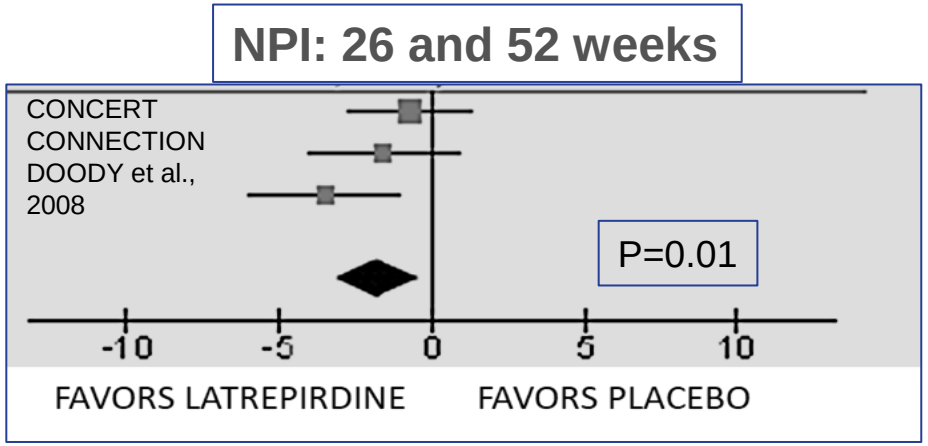
- Secondary efficacy endpoint, changes in NPI, showed statistical superiority over placebo in 3 studies

(*Studies conducted by Pfizer and Medivation*)

DATA SUPPORT DEVELOPMENT FOR TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH DEMENTIA

Clinical Safety Results and Early Sign of Potential Efficacy from Published Studies

Data support clinical development for chronic treatment of agitation in patients with Alzheimer's disease



	LATREPIRDINE (n = 518)	PLACEBO (n=516)
Adverse Events	313	301
Serious Adverse Events	33	38
Dropouts	57	63

- NPI is a measure of neuropsychiatric symptom frequency and severity in patients with dementia
- In 3 clinical studies latrepirdine dosed at 3 x 20 mg per day numerically reduced the NPI
- In 3 clinical studies in over 1000 Alzheimer's patients, latrepirdine was generally well tolerated when dosed in studies of duration of up to one year
- Favorable safety and tolerability results after 1 year of dosing in patients with Alzheimer's disease

References: Chau S, Herrmann N, Ruthirakuhan MT, Chen JJ, Lanctôt KL. Latrepirdine for Alzheimer's disease. Cochrane Database Syst Rev. 2015 Apr 21;2015(4)

Cano-Cuenca N, et al. J Alzheimers Dis. 2014;38:155-64. doi: 10.3233/JAD-130872

Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin SO, Seely L, Hung D; dimebon investigators. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet. 2008 Jul 19;372(9634):207-15

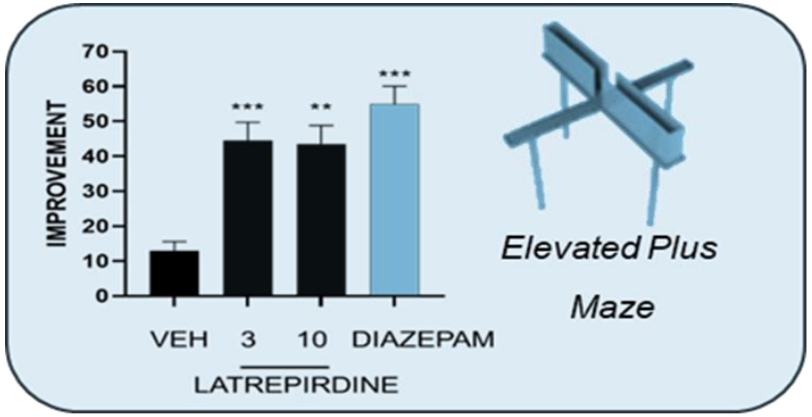
Pre-Clinical Confidence in Rationale

LC-mediated behaviors

LATREPIRDINE

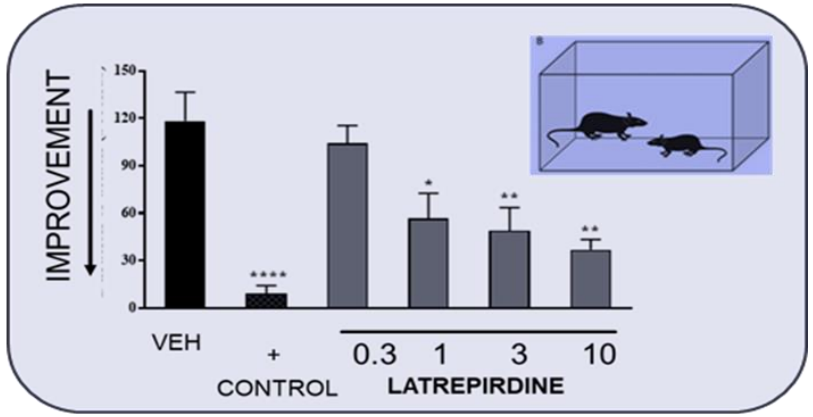
- Showed activity in 5 preclinical models of neuropsychiatric symptoms
- All models were chosen because they engage the LC and done at different CROs under blinded conditions
- Plasma levels matched IC_{50} for affinity for 5-HT_7 receptor and clinical exposures
- Results suggest that the clinical NPI signal may have been mediated, at least in part, by a reduction in agitation-related symptoms

BioXcel Therapeutics Data



ANXIETY/ AGITATION MODEL

- Mice are agitated by administering yohimbine
- Latrepirdine increases exploration of open arms (reduced agitated behaviors)



AGGRESSION/ AGITATION MODEL

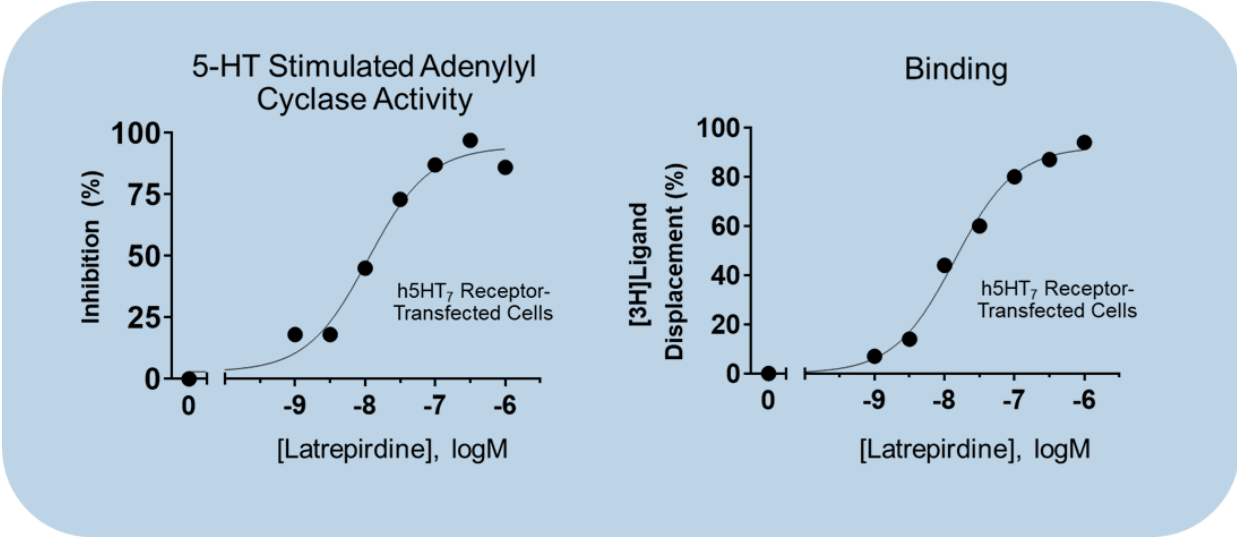
- Resident mouse acclimated to a cage
- Intruder mouse introduced
- Latrepirdine reduced aggressive behaviors (shown in graph) at doses that do not reduce motor activity (not shown)

Latrepirdine: Potential Mechanism of Action

5-HT_7 receptor antagonist with high potency

- Potential mechanism of action of latrepirdine previously not clear, many mechanisms were proposed (including 5-HT_7 receptor antagonism)
- BioXcel results suggest that latrepirdine may be potent 5-HT_7 receptor antagonist
- Observed potency was close to 10 nM, corresponding to approximately 4 ng/ml
  - Clinical studies (Pfizer) show that plasma exposure (C_{max} at 20 mg dose) was 3.2 ng/ml
  - Preclinical studies indicate that free brain concentrations at 1 hour post dosing (10 mg/kg in rats) was approx. 4 ng/ml
- 5-HT_7 antagonism important but BioXcel predicts also **need the LC component to potentially produce therapeutic activity**

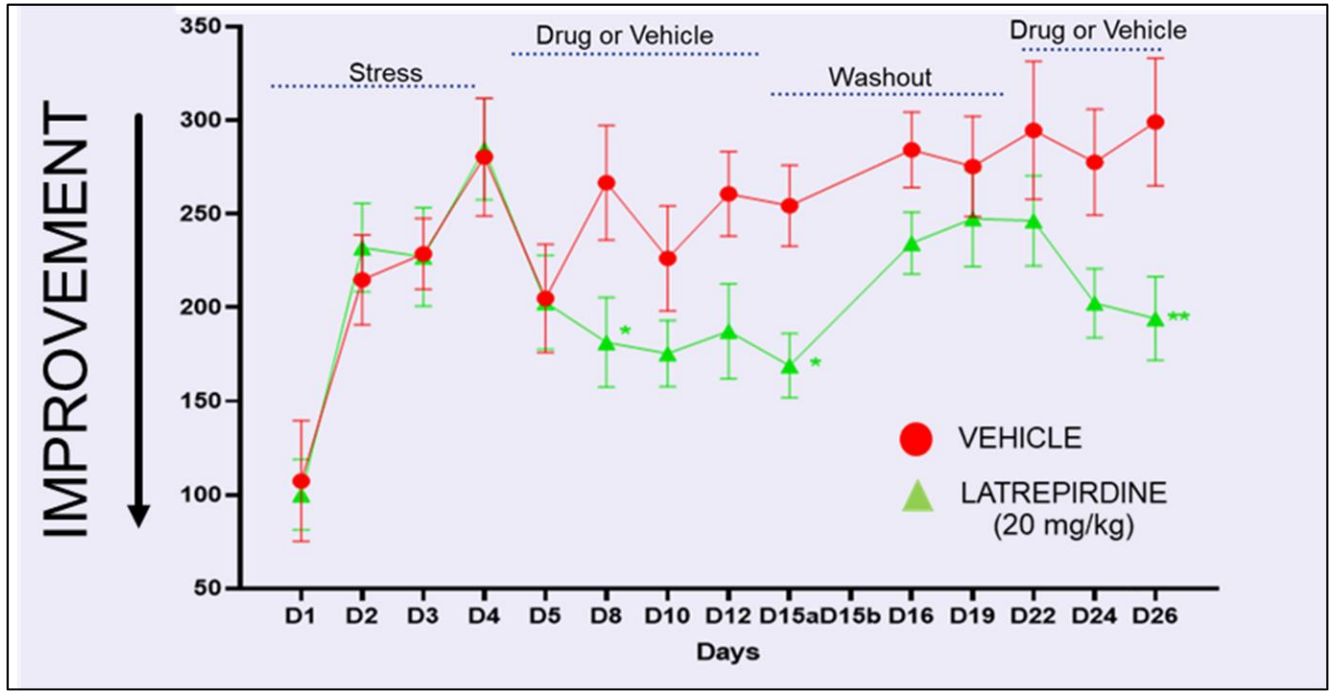
BioXcel Therapeutics Data



Preclinical Results Suggest Potential for Chronic Dosing

Repeat-dose studies in mice

- Chronic treatment requires:
  - Demonstration of persistent effect after repeat dosing
  - Able to washout quickly if needed (not irreversible)
- Mice treated for 5 days using stress paradigm no longer attempted to escape but remained immobile
- Performance improved by daily dosing from day 5 to 15
- Washout resulted in a return towards vehicle performance
- Reinstating latrepirdine on day 22 again improved performance



Stress paradigm is a swimming test

Recent Examples of Successful CNS Drug Re-Innovation

DRUG	CHALLENGE	SOLUTION	STATUS
Dextromethorphan (Axsome)	Metabolites cause unwanted side effects	Block metabolism with CYP2D6 inhibitor, bupropion	Successful clinical study/ depression
Xanomeline (Karuna)	Peripheral side effects	Block peripheral effects with trospium	Successful clinical study/ schizophrenia
Dexmedetomidine IGALMI (BioXcel Therapeutics)	Poor oral bioavailability (<20%)	Use sublingual film to administer directly to blood (oral bioavailability >80%)	Approved to treat agitation associated with schizophrenia and bipolar disorder
Latrepirdine (Dimebon) ***(BioXcel Therapeutics)***	**Variable plasma [3 times daily dosing]**	**Novel Formulation for PK stabilization [potential for once-a-day dosing]**	**Enabling POC study in humans**

Latrepirdine + "Metabolic Stabilizer" = BXCL502

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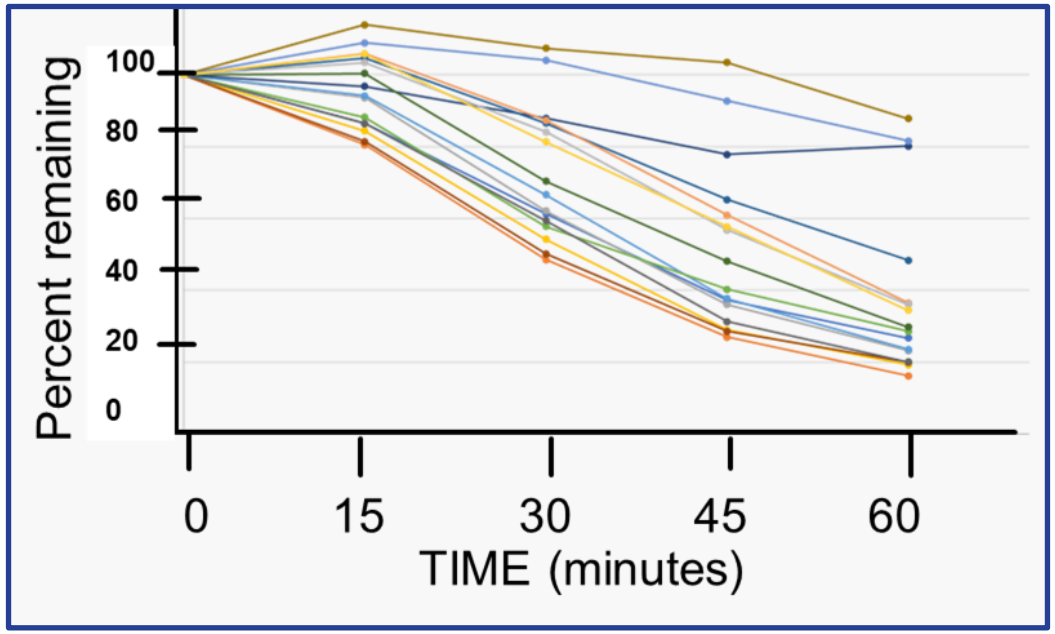
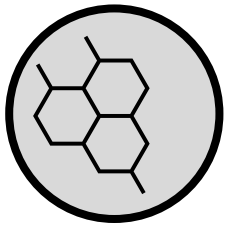
BXCL502: Potential Chronic Once a Day Dosing for Agitation

- Metabolic instability limited clinical development of latrepirdine
- BioXcel screened metabolic enzyme inhibitors to identify potential compounds that could enable latrepirdine to be used as a chronic drug
- 3 inhibitors were chosen as especially promising to be co-formulated with latrepirdine
- BioXcel has initiated a formulation strategy to combine latrepirdine with the metabolic stabilizer



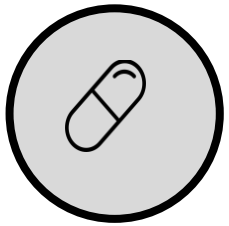
BXCL502 Presents a Compelling Value Proposition

Formulation studies are ongoing

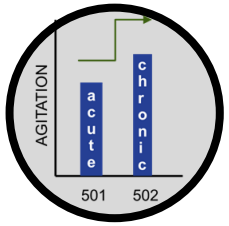


New Chemical Entity → **BXCL502 is a novel formulation of latrepirdine and a metabolic stabilizer**

Improved Understanding of Proposed Mechanism → **Potentially blocks excessive signaling mediated by 2 neurotransmitters: serotonin and norepinephrine (noradrenaline)**



Re-Innovation of Latrepirdine → **Improved PK results suggest potential for once daily dosing which could be suitable for chronic agitation**



Synergistic with Portfolio → **Expanding agitation development programs from episodic to chronic**

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The Neuropsychiatric Inventory:
Measuring Agitation Relief in Alzheimer's Disease

Jeffrey Cummings, M.D., Sc.D.(HC)
Chambers-Grundy Center for Transformative Neuroscience
Department of Brain Health, School of Integrated Health Sciences
University of Nevada Las Vegas (UNLV)

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The information contained in the following material is intended to provide background and educational information only and does not constitute medical advice. Individual results will vary among patients and depend on many factors. A patient's healthcare provider should consider the circumstances of each patient.

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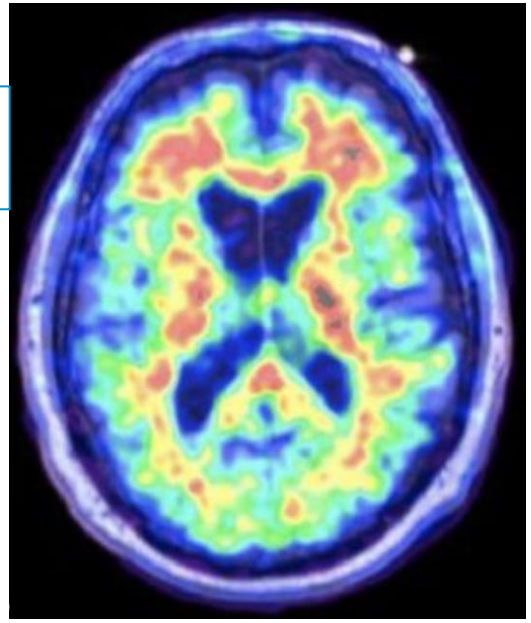
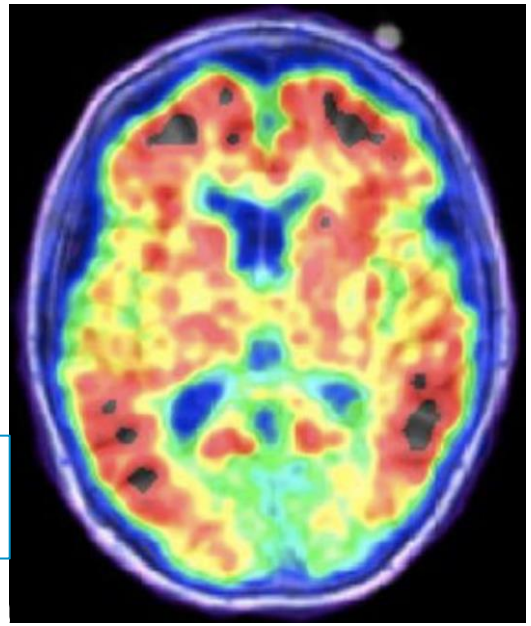
Prevalence of Alzheimer's Disease is Increasing

	2020/2023	2050
U.S.	6.5 million	19.5 million
Global	57.4 million	152 million

- Well-defined pathological entity (amyloid, tau, neurodegeneration [ATN])
- Advances in diagnosis: amyloid and tau PET, blood-based biomarkers
- Advances in treatment
  - Aducanumab, lecanemab – first disease-modifying therapies for Alzheimer's disease
  - Brexpiprazole – first approval for any neuropsychiatric syndrome in Alzheimer's disease (agitation)
- Heightened public awareness

Negative Amyloid PET





Positive Amyloid PET

GBD 2019 Dementia Forecasting Collaborators. Lancet Public Health 2022; 7: e105-25; Alzheimer's Association. 2023 Alzheimer's Disease Facts and Figures. Alz Dem 2023; 19(4).DOI10.1002/alz.13016; Chapleau M, et al. J Nucl Med 2022; 63: 13S-19S (images)

Agitation in Alzheimer's Disease

Demography[1,2]

- 70% of Alzheimer dementia patients are agitated sometime in disease course
- 40% in cross-sectional studies
- 60% of agitated patients will receive pharmacotherapy
  - Antipsychotics 13-24.2%; antidepressants 24.2-44.2%; benzodiazepines 11.1-13%

Etiology[3]

- Biological subtype
- Environmental influences

Consequences[2,3]

- Reduced patient and caregiver quality of life
- More rapid progression of cognitive decline
- Earlier nursing home placement

[1]Jones E, et al. J Alz Disease 2021; 83: 89-101; [2]Cloutier M, et al. Alz & Dem: TRCI 2019; 5: 851-861; [3]O'Gorman C, et al. J Prev Alz Dis 2020; 7: 274-282

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Defining Agitation in Alzheimer's Disease

- International Psychogeriatric Association (IPA) criteria for agitation in neurocognitive disorders:
  - Neurocognitive disorder present (e.g., Alzheimer's disease)
  - One of 3 agitated behaviors present for past 2 weeks
    - Verbal aggression
    - Physical aggression
    - Motor hyperactivity (pacing, etc.)
  - Not due exclusively to pain, delirium, environmental provocation
- Rating scales establish agitation severity at baseline

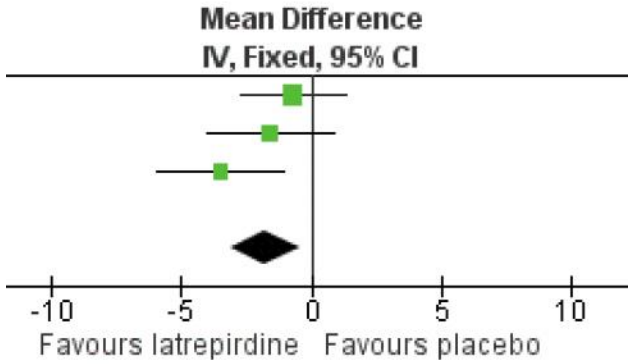
Sano M, et al. Internat Psychogeriatrics 2023; ahead of print; Cummings J, et al. Internat Psychogeriatrics 2023; ahead of print; Cummings J, et al. 2015; 27: 7-17

Neuropsychiatric Inventory (NPI)[1,2]

- Most commonly used instrument to measure behavior in clinical trials of Alzheimer's disease and other neurodegenerative disorders
- 12 neuropsychiatric syndromes
- Caregiver interview
- Past 1 month
- Frequency and severity
- Caregiver distress

Agitation/aggression	Apathy
Hallucinations	Depression
Delusions	Anxiety
Irritability	Appetite changes
Disinhibition	Aberrant motor behavior
Elation/euphoria	Sleep Changes

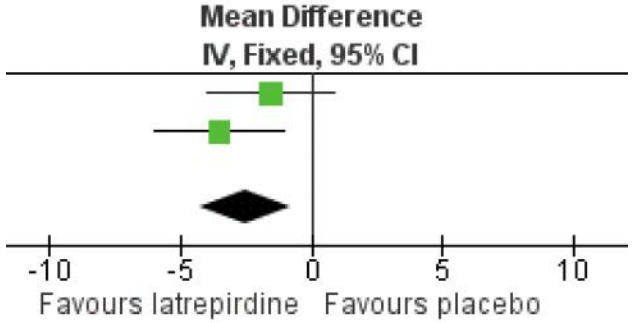
[1]Cummings J. J Geriatr Psychiatry and Neurol 2020; 33: 73-84; [2]Cummings j, et al. Neurol 1994; 44: 2308-2314



NCT00829374

- 611 patients on latrepirdine
- NPI d/p change from BL = 1.8 points
- Overall effect: p = 0.009

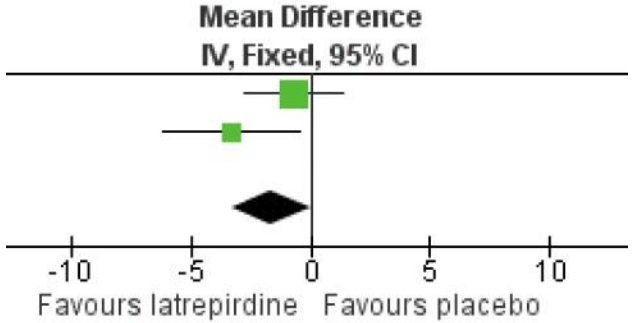
from baseline at 26 weeks).



NCT00675623

- 289 patients of latrepirdine
- NPI d/ change from BL at week 26 = 2.5 points
- Overall effect: p = 0.004

from baseline at 52 weeks).



NCT00377715

- 411 patients of latrepirdine
- NPI d/ change from BL at week 52 = 1.6 points
- Overall effect: p = 0.06

Latrepirdine Produced Generally Consistent Results on the NPI

Cochrane Reviews are very rigorous

- No meaningful effect observed on cognition or function
- Reproducible effect on total NPI score
- Similar effect observed across published studies
- Low baseline scores limit ability to show d/p difference

Chau S, et al. Cochrane Database of Systematic Reviews. 2015, Issue 4, No. CD009524

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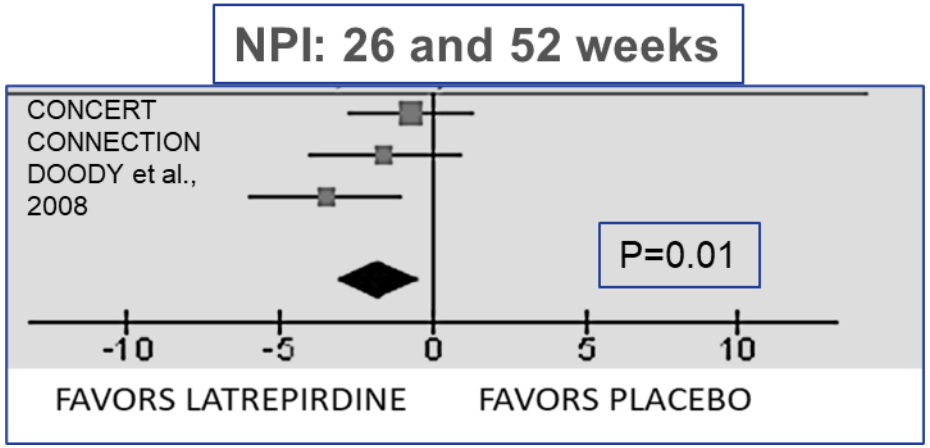
Meta-Analysis Supports Potential NPI Effect Across Latrepirdine Alzheimer's Disease Trials

Statistical approach differed from that of Cochrane Analysis

- 127 articles screened
- 5 with trials
- 3 with Alzheimer's disease
- No cognitive or functional benefit
- NPI showed significant benefit
  - P = 0.03

MEAN DIFFERENCE: NPI



Cano-Cuenca N, et al. J Alzheimers Dis. 2014;38:155-64. doi: 10.3233/JAD-130872

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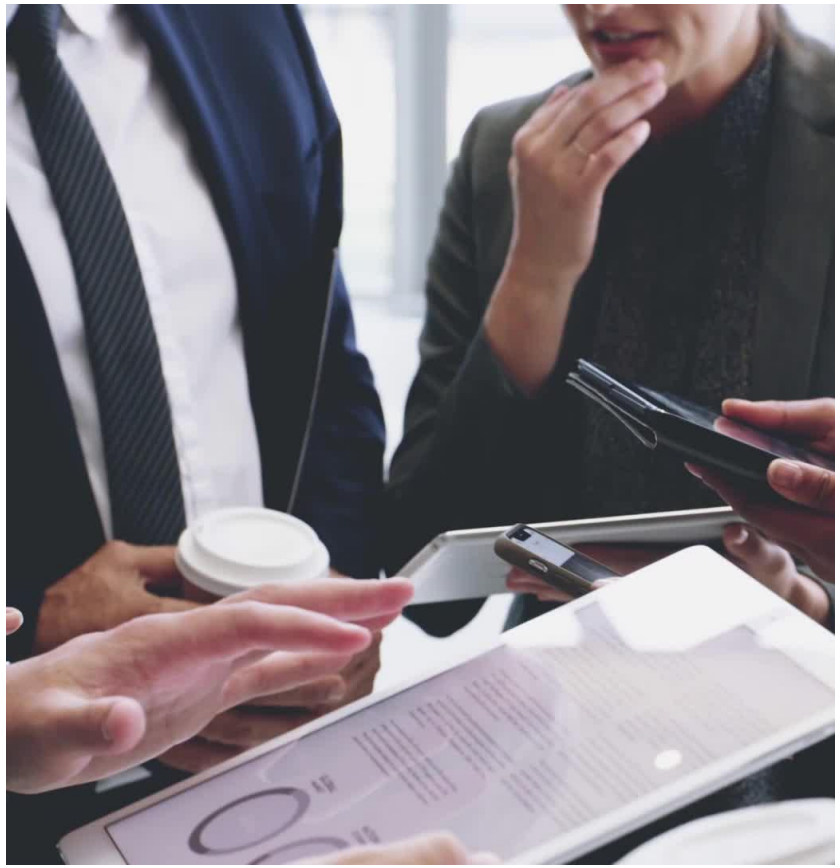
Measurement of Agitation in Clinical Trials of Alzheimer's Disease

- Two primary tools to measure agitation in Alzheimer's clinical trials
  - **Cohen-Mansfield Agitation Inventory (CMAI)**[1]
    - 29 agitated behaviors (kicking, shouting, hitting, etc)
  - **Neuropsychiatric Inventory (NPI)**[2]
    - 12 neuropsychiatric syndromes
- Clinical trials
  - CMAI – typically used as an outcome to assess treatment response
  - NPI – typically used to characterize syndromes and determine severity at baseline; primary outcome in some trials (NPI-C)
  - Global score for agitation (CGI-S) may be included

[1]Koss E, et al. Alz Dis Assoc Dis 1997; 11 (S2); S45-50; [2]Cummings j, et al. Neurol 1994; 44: 2308-2314

Agitation Trials: Risk Mitigation

- Planning can limit impact of challenges
  - Slow recruitment
  - Placebo response
- Latrepirdine
  - Which items responded on NPI
  - Explore if response in population with variable agitation predicts response in population constructed around agitation



Summary

- Alzheimer’s disease is common
- Alzheimer’s disease with agitation is common
- Treatment of agitation is a large unmet need (market)
- Trial foundations are established
  - Definition of agitation
  - Clinical outcome assessments
  - Regulatory pathway
- Preliminary latrepirdine NPI observations are encouraging

BXCL503 for Dementia-Related Apathy

Friso Postma, Ph.D.
VP, AI Drug Discovery

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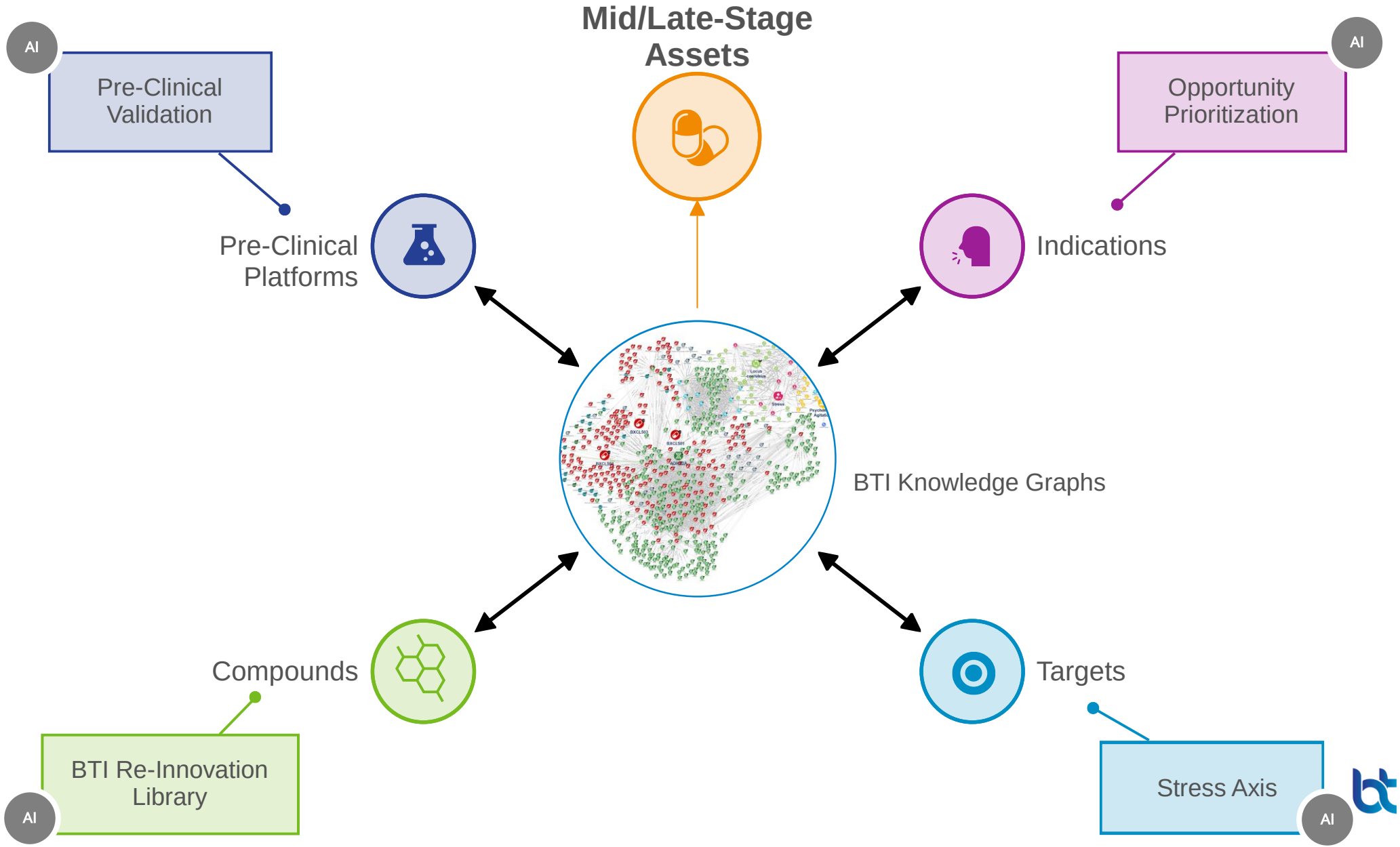
NovareAI: Ecosystem for Drug Discovery and Development



Targeting Selectivity Through Heteromeric Receptor Complexes

Selected compounds are believed to *modulate* dopamine signaling

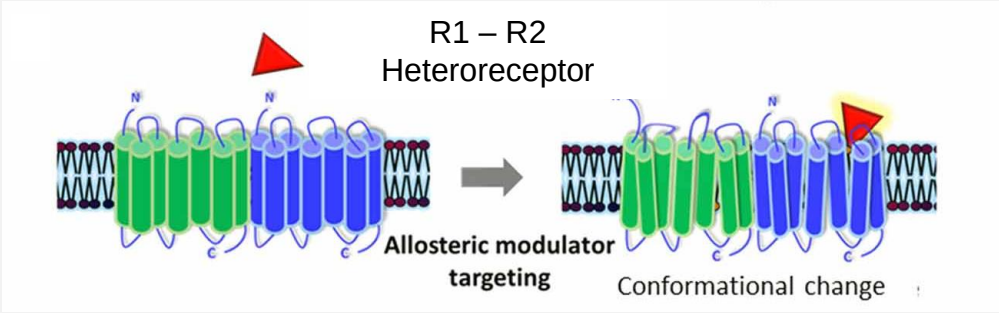
- Heteroreceptors through allosteric interactions may modify ligand affinity or stabilization of the receptor
- This may confer advantages over global receptor activation through re-uptake inhibitors or direct agonists
- Heteroreceptors can modify endogenous signaling in an anatomically restricted manner

Strategy:

- Find heteroreceptors that are expressed selectively in circuitry critical for goal directed behavior
- Select late-stage clinical compounds and run predictions with NovareAI on the potential for reducing Apathy
- Select and test compound-candidates pre-clinically

Heteromeric receptor examples include (but are not limited to):

- Dopamine D1R and NMDA receptors
- Serotonin 5HT2a and Glutamate mGluR2
- Adrenergic a1bAR-and Dopamine D4
- Dopamine D2R and Serotonin 5-HT2A
- Dopamine D2R and Neurotensin NTS1R
- Dopamine D2R and Sigma1R



From DelaCuesta-Barrutia et al., 2020

Apathy in Alzheimer's Disease is an Unmet Medical Need

Concept BXCL503 holds potential to address this need

- Defined as a loss of initiative, interest and emotional expression/responsiveness.
- Apathy is a deficit in voluntary, goal-directed behavior
- Prevalence is high with ~ 5 million patients within Alzheimer's Disease. No FDA approved drugs.
- Apathy has adverse consequences for patients and caregivers, such as:
  - Increased reliance on caregivers
  - High disease burden
  - Decreased quality of life
  - Cognitive and functional impairment
  - Increased mortality

BXCL503 Candidate:

- **Previously tested in two Phase2 studies but deprioritized for commercial reasons**
- **Safety results supporting development to treat Apathy symptoms**
- **May modify dopaminergic signaling in circuitry regulating goal directed behavior**

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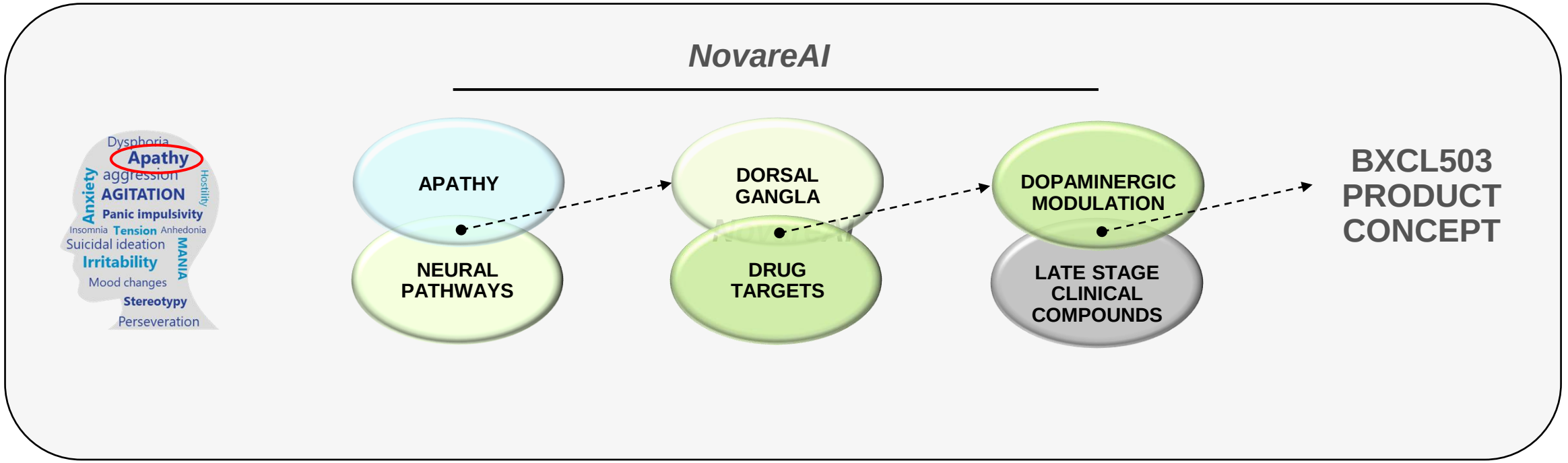
The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

Identifying Drug-Sensitive Neural Pathways for Treatment of Apathy

Dementia Related Neuropsychiatric Symptoms



NovareAI Predicted Efficacy:

Target engagement predicted to mitigate Apathy

Target:

Modulation of Dopaminergic Signaling

Compound:

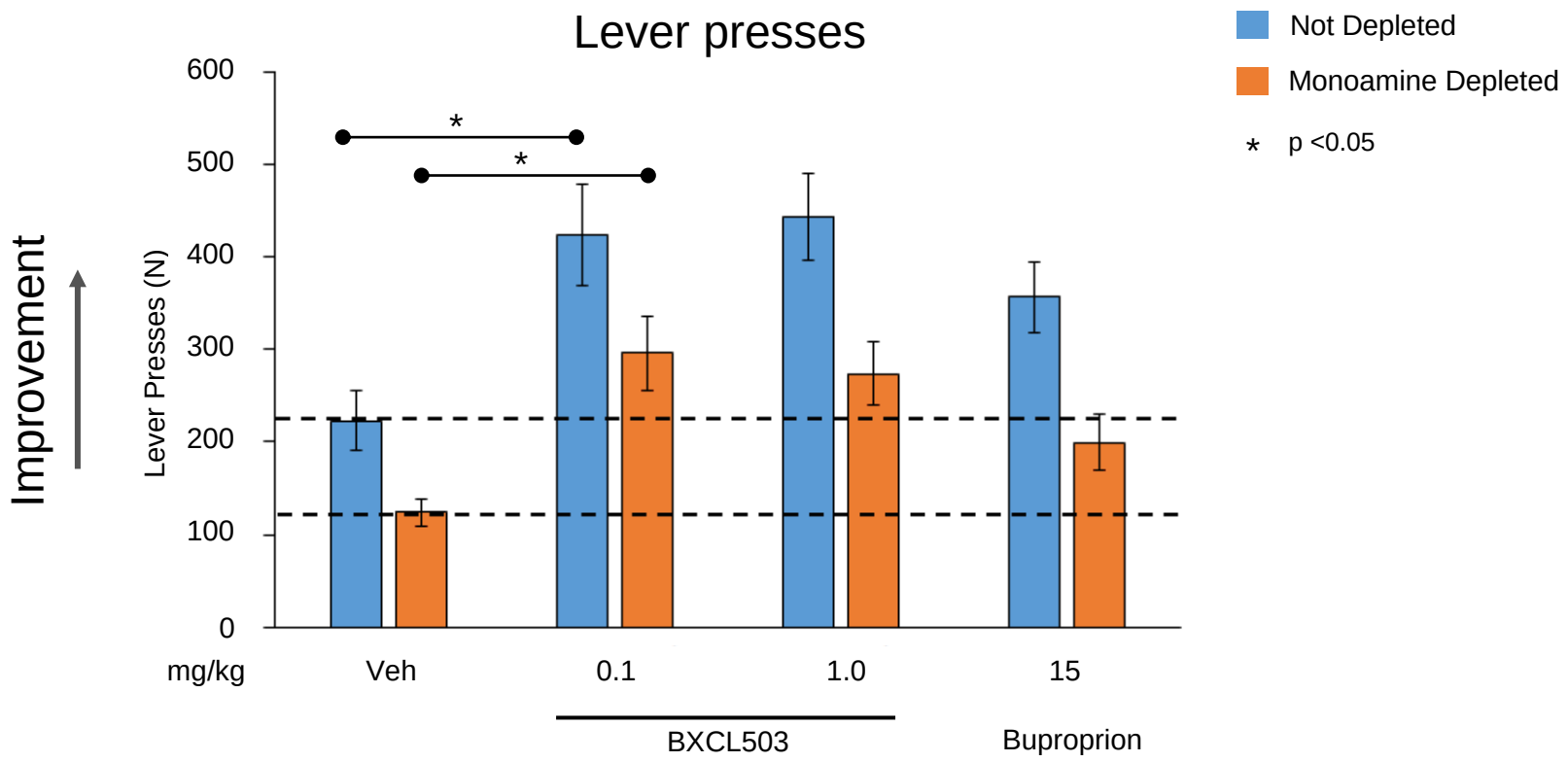
NovareAI discontinued Phase 2 compound identification: BXCL503

The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

Concept BXCL503 May Increase Goal Directed Behavior

Pre-clinical model of apathy: progressive ratio test

- Progressive Ratio Test measures goal directed behavior
- Animals repeatedly press a lever for a reward, the number of presses after which the animal gives up is recorded
- Potential BXCL503 candidate increased the effort animals are willing to make to receive the reward
- Monoamine depletion reduced the effort animals make, which is a model for Apathy
- Potential BXCL503 candidate improves the effort monoamine depleted animals make to obtain the reward

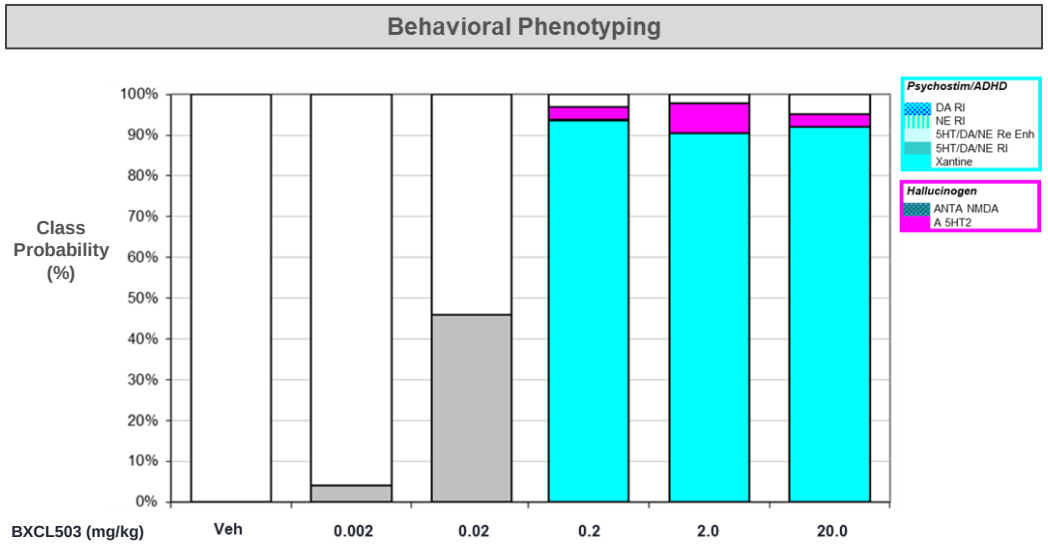


Pre-Clinical Confidence in Rationale

BioXcel Therapeutics Data

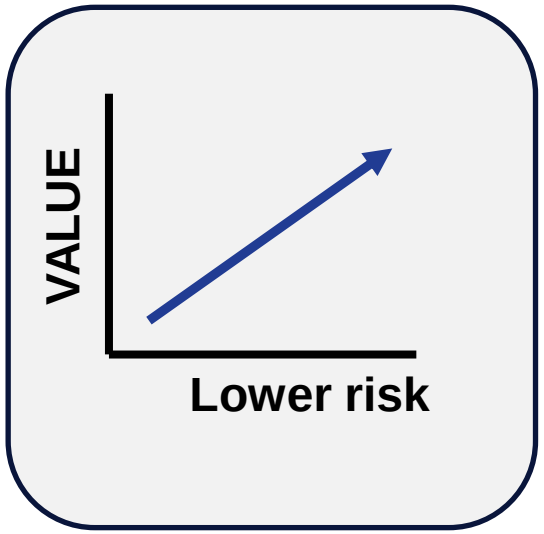
BXCL503

- Demonstrated in vivo activity in behavioral phenotyping (SmartCube*)
- Potential BXCL503 candidate is classified as a stimulant with activity in a dose-dependent manner



BXCL503 Product Concept

Clinical safety results and preclinical confidence in rationale are favorable



SAFETY RESULTS IN PATIENTS

- Shelved asset. Well tolerated in over 500 subjects exposed up to 26 weeks in two phase 2 trials

PRECLINICAL CONFIDENCE IN RATIONALE

- Showed activity in 2 preclinical models

(*Studies conducted by BioXcel Therapeutics*)

NOVEL PROPOSED MECHANISM

- Dopaminergic modulation through heteromeric receptor complexes may confer an advantage in receptor specificity and circuit selectivity

DATA SUPPORT FURTHER DEVELOPMENT FOR TREATMENT OF APATHY ASSOCIATED WITH DEMENTIA

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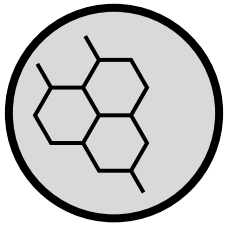
BXCL503 Product Concept Presents a Compelling Value Proposition

Confidence in the approach and further studies ongoing

Potential novel mechanism of action

BXCL503 may modulate dopaminergic signaling in an anatomically restricted manner to circuitry governing goal directed behavior

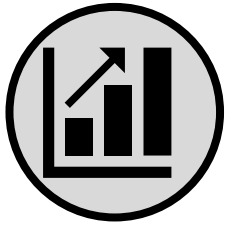


Prior safety data

Previously Tested in Phase 2 clinical trials

Clinical Path Forward

Trial foundations in Apathy have been established previously



Synergistic with Portfolio

Aligns with company's BXCL501 and BXCL502 development programs of Alzheimer's Disease related symptoms

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BXCL501 (Sublingual Dexmedetomidine) for the Potential Treatment of Acute Opioid Withdrawal

Sandra D Comer, Ph.D.
Professor of Neurobiology (in Psychiatry)
Columbia University Irving Medical Center
New York State Psychiatric Institute

Overview

Public Health Emergency

"Opioid Crisis" declared a Public Health Emergency in 2017

Emergent Threat

Fentanyl adulterated or associated with xylazine (FAAX) declared an "Emergent Threat" in 2023

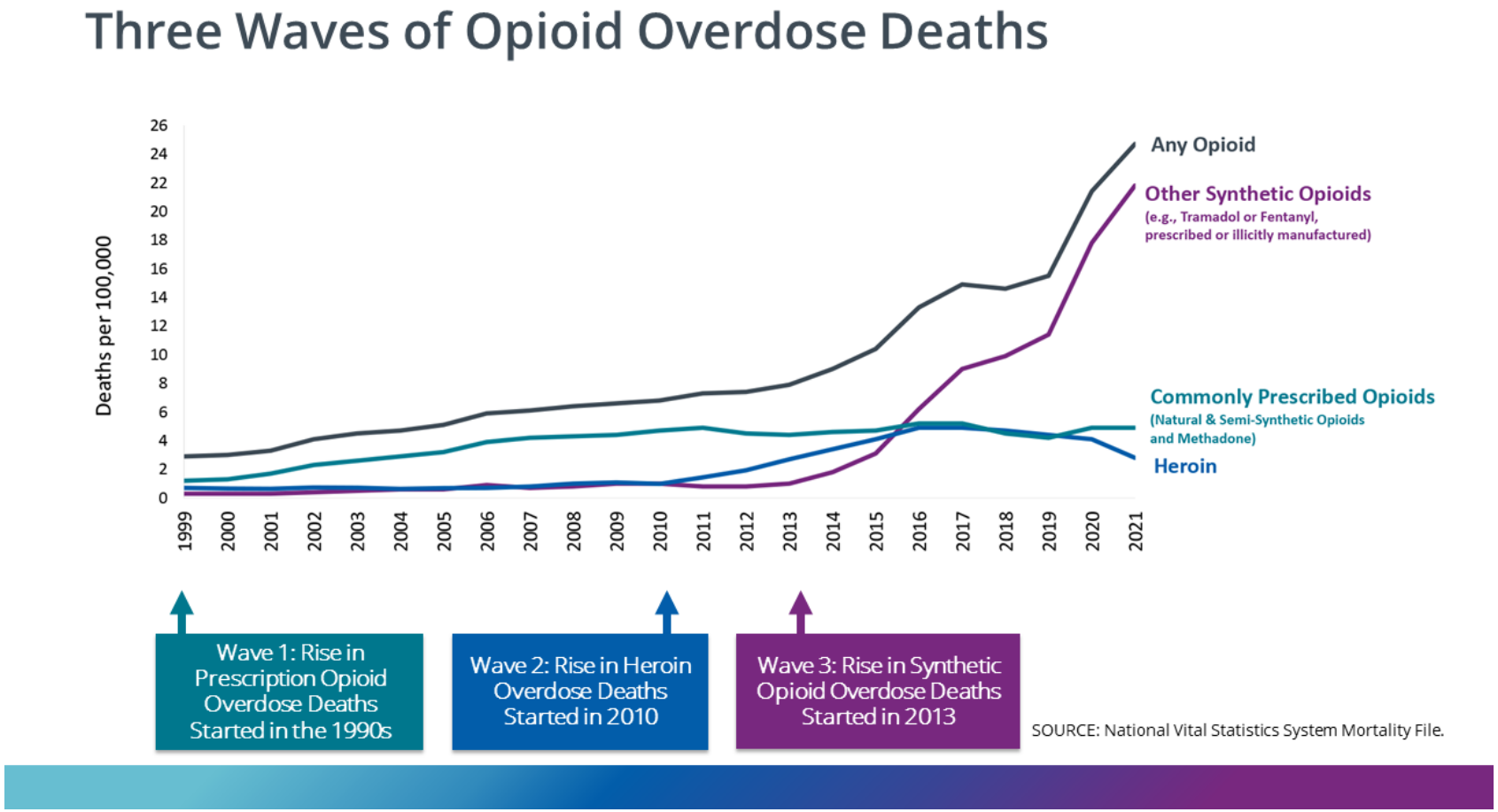
Treatment Gap

No treatments for opioid withdrawal have been tested against fentanyl or xylazine

Urgent Need

An estimated 1.22 million opioid-related deaths in the U.S. between 2020 to 2029 *(Rao et al., 2021)*

Majority of Opioid-related Overdose Deaths are due to Fentanyl



As of Jun 2023, 106,842 drug-related overdose deaths in the previous 12 months (NCHS).

Deaths involving synthetic opioids other than methadone (primarily fentanyl) continued to rise with 70,601 overdose deaths reported in 2021 (NCHS)

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Introduction of Xylazine to Fentanyl Makes Opioids Even More Dangerous and has now Been Identified as an “Emerging Threat”

Why are cartels producing fentanyl associated or adulterated with xylazine (FAAX)?

- Cartels are adding xylazine to fentanyl to prolong the effects of other opioids
- Sometimes called a “booster,” cartels have been adding CNS depressant drugs to fentanyl to “boost” the high users feel

”Opioid deaths could dramatically increase to about 165,000 by 2025” stated Dr. Rahul Gupta White House Office of National Drug Control Policy

In addition to making fentanyl more lethal, xylazine is also damaging users’ bodies

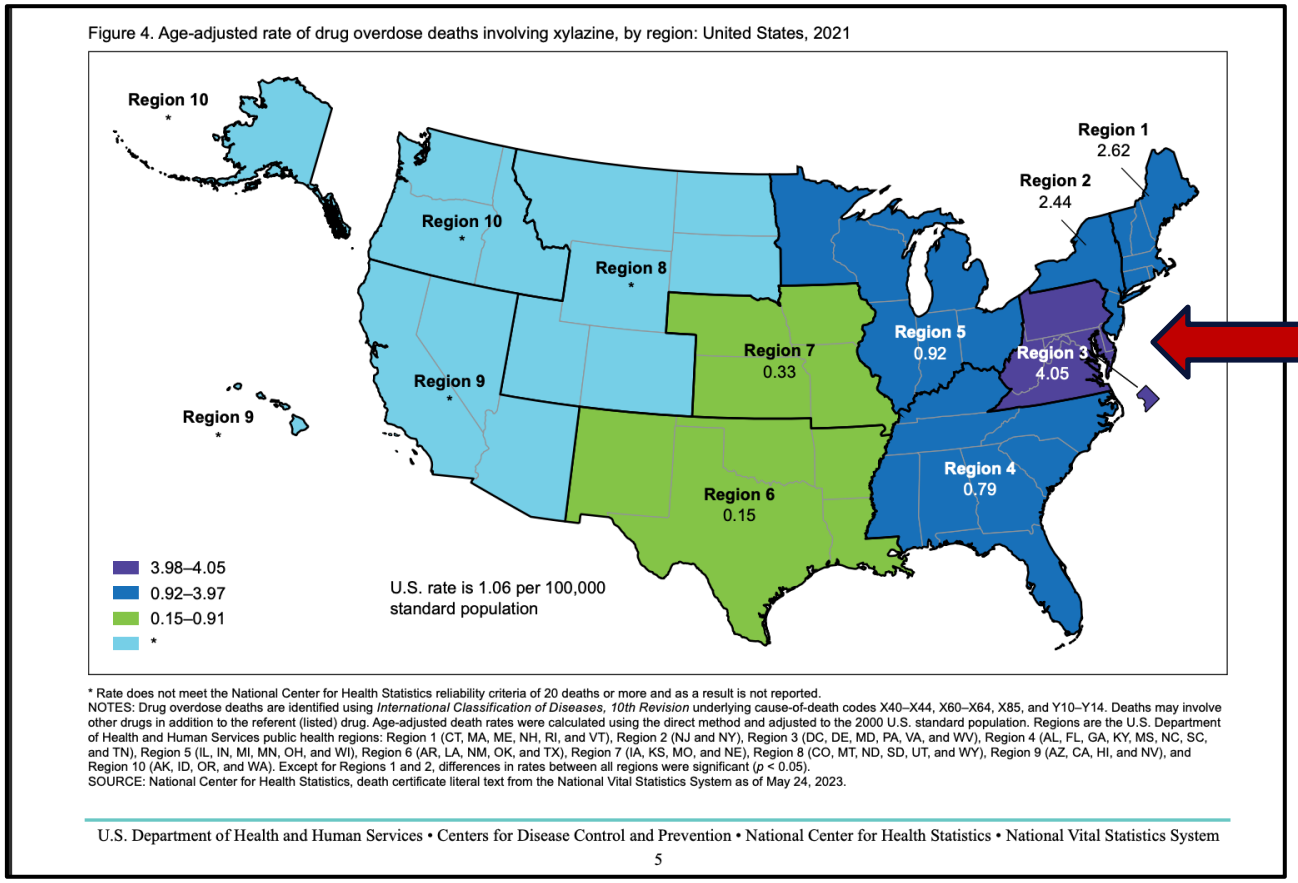
- Repeated xylazine use can be associated with skin ulcers, abscesses, and other related complications

APRIL 12, 2023

Biden-Harris Administration Designates Fentanyl Combined with Xylazine as an Emerging Threat to the United States

ONDCP › BRIEFING ROOM › PRESS RELEASES

And now the use of Xylazine is Rapidly Growing Across the U.S.



*The Drug Enforcement Administration (DEA) reports that between 2020 and 2021, forensic laboratory identifications of xylazine rose in all four U.S. census regions, most notably in the South (193%) and the West (112%).

- DEA Joint Intelligent Report

Epicenter of xylazine use is located in Mid-Atlantic States but distribution is rapidly moving West*

*Xylazine was found in over 90% of drug samples tested in Philadelphia in 2021

- Substance Use Prevention & Harm Reduction (SUPHR)

*Xylazine was involved in 19% of all drug overdoses in Maryland in 2021 and 10% of drug overdoses in Connecticut in 2020, the NIDA states.

- Friedman J et al., 2022

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BXCL501 Phase 1b/2 Study: Phase 1b Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Study

Jones et al., 2023

Am J Drug and Alcohol Abuse 49(1): 109-122

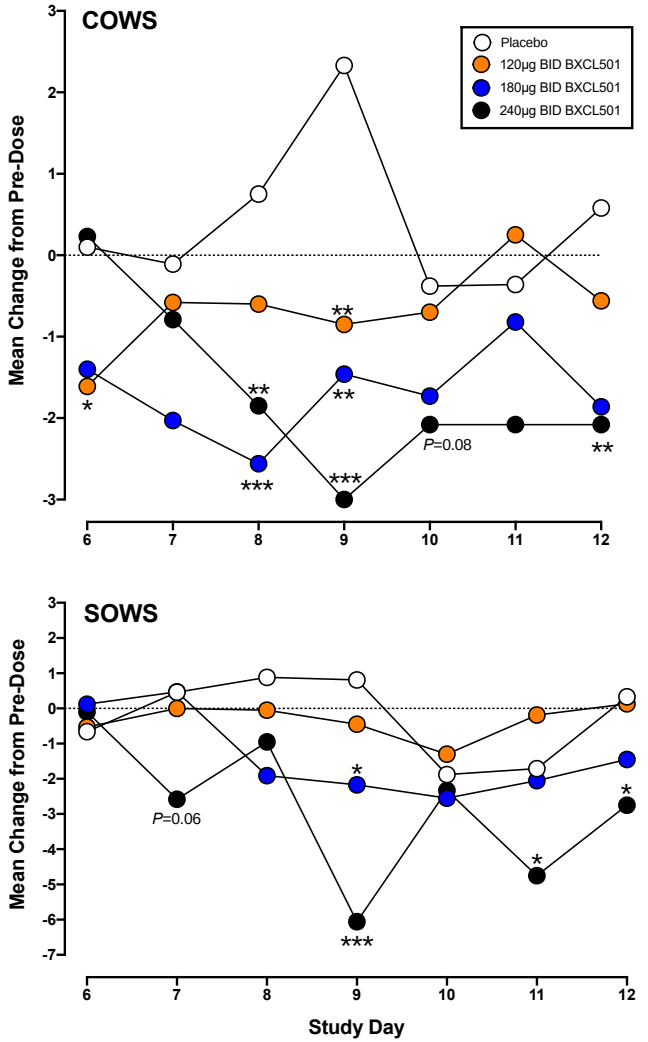
https://doi.org/10.1080/00952990.2022.2144743

BXCL501 Pilot Phase 1b/2 Study Design: Summary
(June 2020 – January 2021)

- Randomized, double-blind, placebo-controlled inpatient study
- Evaluate the safety and tolerability of ascending doses of BXCL501 relative to placebo in participants with opioid use disorder who are physically dependent on opioids and maintained on oral morphine
  - Days 1-5 (Stabilization Phase): Active morphine QID + Placebo BXCL501 BID
  - Days 6-12 (Treatment Phase): Placebo morphine QID + Placebo or active BXCL501 BID
- BXCL501 doses: Placebo, 30, 60, 90, 120, 180, and 240μg BID
- Randomization 4:1 active versus placebo in 6 different cohorts; N=15-25 per group
- Source: Jones et al., 2023

Phase 1b/2 Efficacy Results

- 120, 180, and 240mg BID BXCL501 reduced acute opioid withdrawal symptoms compared to placebo as measured by the **COWS with a 229% reduction in peak withdrawal** and **SOWS with a 853% reduction in peak withdrawal**. (Jones et al., 2023)
- These effects occurred at doses that produced no serious or severe adverse effects (orthostatic hypotension, bradycardia, dizziness, somnolence that are major liability issues for lofexidine)



* = $p < .05$
** = $p < .01$
*** = $p < .001$

The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

BXCL501 Pilot Phase 1b/2 Study Design

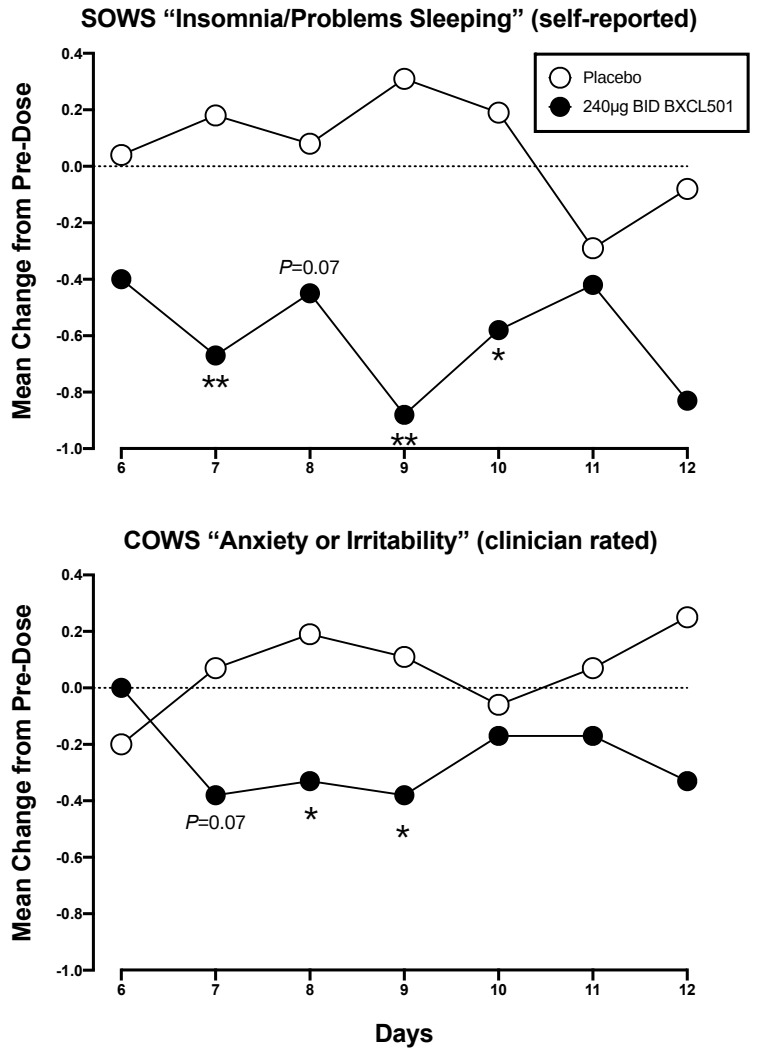
Note: Urine drug screens in 76-92% of patients in each dose cohort were fentanyl-positive at screening (Jones et al., 2023)

- In BioXcel's 2020 Ph1b study, 40% of patients dropped out during the morphine stabilization phase, whereas in the 2001-2002 lofexidine study 0% of patients dropped out in the morphine stabilization phase (Yu et al 2008)
  - Difference in dropout during morphine stabilization is likely due to the presence versus absence of fentanyl (Jones et al., 2023)

- **We currently do not know how to optimally manage withdrawal symptoms in fentanyl-dependent patients – the current study represented a unique opportunity to address this problem**

Phase 1b/2 Efficacy Results

- The 240mg BID BXCL501 dose significantly reduced both subjective ratings of insomnia and clinician ratings of anxiety or irritability (Jones et., 2023)
- These benefits were not reported in selected studies with lofexidine for opioid withdrawal *Gish et al 2010; Rehman et al 2019; sleep and anti-anxiety medications are commonly co-prescribed with lofexidine**



* = $p < .05$
** = $p < .01$
*** = $p < .001$

*FOR ILLUSTRATIVE PURPOSES ONLY: this discussion does not reflect a head-to-head analysis. Notable differences exist between the Company's trial design, conditions under study and subject characteristics as compared to those discussed above and caution should be exercised when comparing data across these studies.

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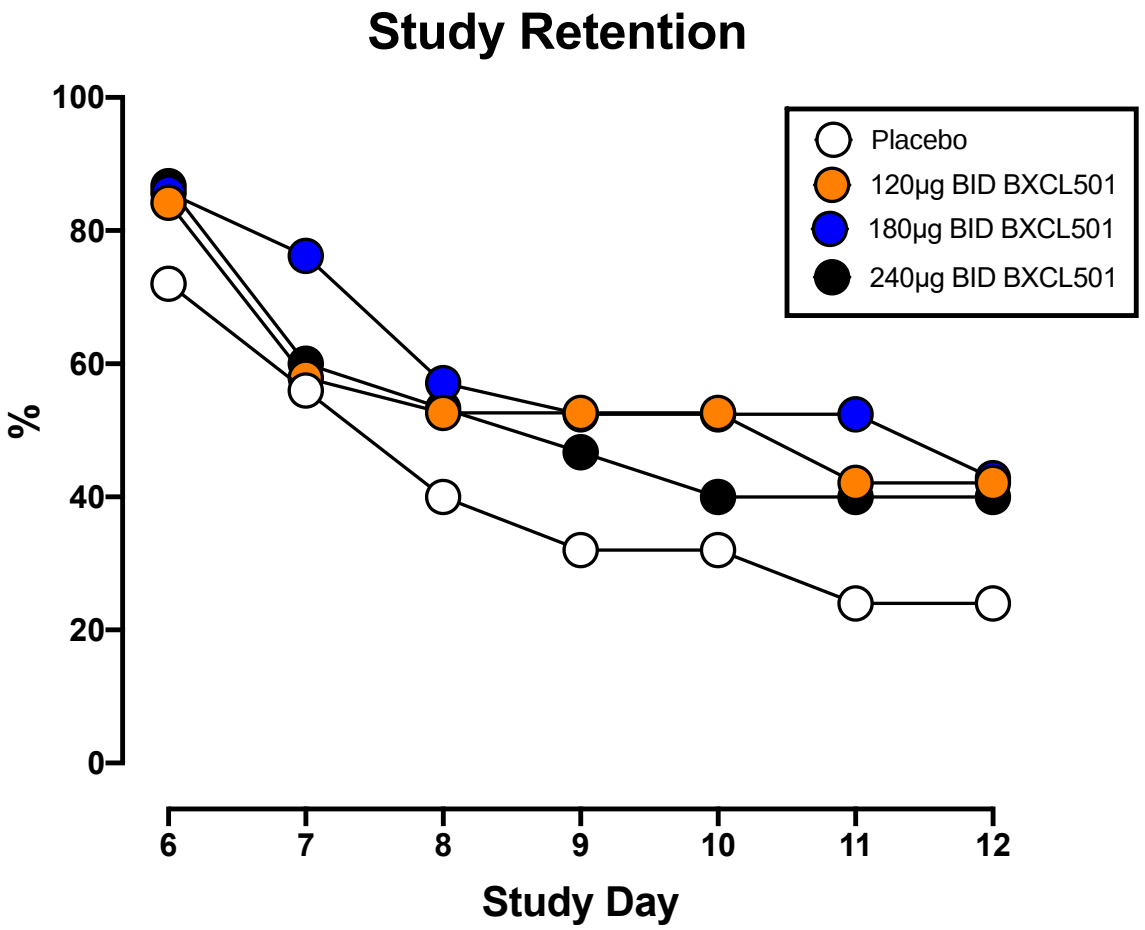
Phase 1b/2 Efficacy Results

- Higher study retention with all active doses of BXCL501 compared to placebo *(Jones et., 2023)*
- Results suggest potential to improve the successful transition of patients onto buprenorphine or SR naltrexone



Potential Safety Review of BXCL501 *(Jones et al., 2023)* vs. Lofexidine *(Fishman et al., 2019)*

	Placebo	BXCL501 (Jones et al 2023)			Lofexidine (Fishman et al 2019)*		
Adverse Event	**Placebo (N=25) n (%)**	**120µg BID BXCL501 (N=19) n (%)**	**180µg BID BXCL501 (N=21) n (%)**	**240µg BID BXCL501 (N=15) n (%)**	**Placebo (N=151) n (%)**	**2.16mg Lofexidine (N=229) n (%)**	**2.88mg Lofexidine (N=222) n (%)**
Orthostatic hypotension	0 (0)	**0 (0)**	**2 (9.5)**	**4 (26.7)**	7 (4.6)	**67 (29.3)**	**94 (42.3)**
Bradycardia	0 (0)	**0 (0)**	**0 (0)**	**1 (6.7)**	8 (5.3)	**54 (23.6)**	**70 (31.5)**
Dizziness	0 (0)	**0 (0)**	**1 (4.8)**	**0 (0)**	4 (2.6)	**44 (19.2)**	**51 (23.0)**
Somnolence	0 (0)	**0 (0)**	**2 (9.5)**	**7 (46.7)**	8 (5.3)	**25 (10.9)**	**29 (13.1)**

*Data were collected in Jun 2013 – Dec 2014 prior to the introduction of fentanyl to the illicit opioid supply

*FOR ILLUSTRATIVE PURPOSES ONLY: this discussion does not reflect a head-to-head analysis. Notable differences exist between the Company's trial design, conditions under study and subject characteristics as compared to those discussed above and caution should be exercised when comparing data across these studies.

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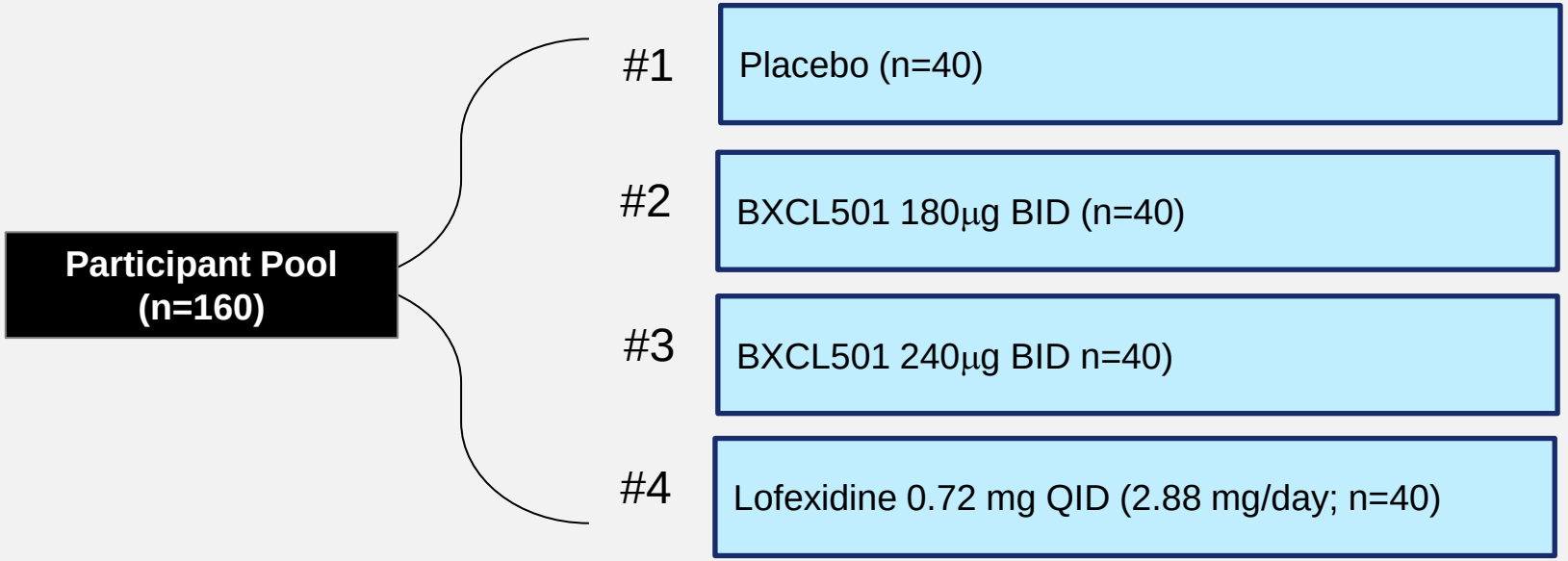
Current Ongoing Study Design

Just Added 4th site to Accelerate Enrollment



Methadone: QID at 9am, 2pm, 7pm, 11pm
Total daily dose* (mg): 30, 25, 20, 15, 10, 5, 0

Participants are stratified into each group as a function of xylazine +/- UDS at admission

Triple-dummy dosing:	Sublingual strips/oral tablets/oral solution (all will be identical in appearance at each dosing time within and across study days) at 9am, 2pm, 7pm, and 11pm
COWS and SOWS assessments:	Approximately 9am*, 11am, 2pm*, 4pm, 7pm*, 9pm, 11pm* *Assessments are made just prior to dosing
Retention:	After randomization

Ongoing Trial Offers Opportunity to Evaluate Possible Opioid Withdrawal Treatment

- **BXCL501 reduced COWS and SOWS scores relative to placebo** at doses that produced no serious or severe adverse events
- **BXCL501 improved patient-reported ratings of insomnia and clinician-reported ratings of anxiety and irritability**
- Phase 1b/2 study further demonstrated that **more subject were retained in the BXCL501 arm than the placebo arm**
- Fentanyl-related withdrawal differs from heroin-related withdrawal and is not well characterized – and even less is known about xylazine

BXCL501, if Approved for Treatment of Opioid Withdrawal, Could Potentially Address Several Clinical Scenarios

Many patients could benefit if BXCL501 was approved for treatment of opioid withdrawal

Setting	Possible Treatment
 Emergency Department	• People who receive ED services after an overdose on opioids often experience severe opioid withdrawal • ED staff increasingly are directly transitioning patients to MOUD (e.g., buprenorphine)
 Treatment Facility	• People who enter an inpatient treatment facility for detoxification or transition to MOUD frequently require treatment for withdrawal symptoms
 Home	• People who are maintained on opioids for pain frequently need treatment for withdrawal symptoms • Addiction specialists are increasingly transitioning patients to MOUD (e.g. buprenorphine) on an outpatient basis

The safety and efficacy of investigational agents and/or investigational uses of approved products have not been established.

References

1. **DEA Joint Intelligent Report.** DEA-DCI-DIR-001-23. The Growing Threat of Xylazine and its Mixture with Illicit Drugs OCTOBER 2022. https://www.dea.gov/sites/default/files/2022-12/The%20Growing%20Threat%20of%20Xylazine%20and%20its%20Mixture%20with%20Illicit%20Drugs.pdf
2. **FDA EUAs**. Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products. https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products
3. **Fishman et al., 2019**. Fishman M, Tirado C, Alam D, Gullo K, Clinch T, Gorodetzky CW. CLEEN-SLATE Team. Safety and Efficacy of Lofexidine for Medically Managed Opioid Withdrawal: A Randomized Controlled Clinical Trial. J Addict Med. 2019 May/Jun;13(3):169-176. doi: 10.1097/ADM.0000000000000474. PMID: 30531234; PMCID: PMC6541556.
4. **Friedman J et al., 2022.** Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. Drug Alcohol Depend. 2022;233:109380. doi:10.1016/j.drugalcdep.2022.109380.
5. **Gish et al., 2010.** Gish EC, Miller JL, Honey BL, Johnson PN. Lofexidine, an {alpha}2-receptor agonist for opioid detoxification. Ann Pharmacother. 2010 Feb;44(2):343-51. doi: 10.1345/aph.1M347. Epub 2009 Dec 29. PMID: 20040696.
6. **Jones et al., 2023.** Jones JD, Rajachandran L, Yocca F, Risinger R, De Vivo M, Sabados J, Levin FR, Comer SD. Sublingual dexmedetomidine (BXCL501) reduces opioid withdrawal symptoms: Findings from a multi-site, Phase 1b/2, randomized, double-blind, placebo-controlled trial. Am J Drug and Alcohol Ab. 2023 49(1): 109-122. https://doi.org/10.1080.00952990.2022.2144743.
7. **Kharti et al., 2021.** Khatri UG, Samuels EA, Xiong R, Marshall BDL, Perrone J, Delgado MK. Variation in emergency department visit rates for opioid use disorder: Implications for quality improvement initiatives. Am J Emerg Med. 2022 Jan;51:331-337. doi: 10.1016/j.ajem.2021.10.04. Epub 2021 Nov 9. PMID: 34800906.
8. **NCHS.** National Center for Health Statistics. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates#:~:text=Nearly%2075%25%20of%20overdose%20deaths,than%20methadone%20(primarily%20fentanyl).
9. **NIDA Research Report.** https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/overview
10. **NIDA 2021.** National Institutes of Health, U.S. Department of Health and Human Services. https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/overview
11. **NIDA 2023.** Only 1 in 5 U.S. adults with opioid use disorder received medications to treat it in 2021. https://nida.nih.gov/news-events/news-releases/2023/08/only-1-in-5-us-adults-with-opioid-use-disorder-received-medications-to-treat-it-in-2021
12. **Non-Fatal Opioid Overdose Tracker.** Office of National Drug Control Policy (ONDCP). https://nemsis.org/opioid-overdose-tracker/
13. **Rao et al., 2021.** Rao IJ, Humphreys K, Brandeau ML. Effectiveness of Policies for Addressing the US Opioid Epidemic: A Model-Based Analysis from the Stanford-Lancet Commission on the North American Opioid Crisis. Lancet Reg Health Am. 2021 Nov;3:100031. doi: 10.1016/j.lana.2021.100031. Epub 2021 Jul 31. PMID: 34790907; PMCID: PMC8592267.
14. **Rehman et al., 2019**. Rehman S, Maqsood M, Bajwa H, et al. (June 04, 2019) Clinical Efficacy and Safety Profile of Lofexidine Hydrochloride in Treating Opioid Withdrawal Symptoms: A Review of Literature. Cureus 11(6): e4827. DOI 10.7759/cureus.4827
15. **SAMHSA.** Substance Abuse Center for Behavioral Health Statistics and Quality. Results from the 2020 National Survey on Drug Use and Health: Detailed Tables. SAMHSA. Published October 25, 2021. Accessed November 29, 2021.
16. **Substance Use Prevention & Harm Reduction (SUPHR).** Department of Public Health City of Philadelphia. https://www.substanceusephilly.com/tran

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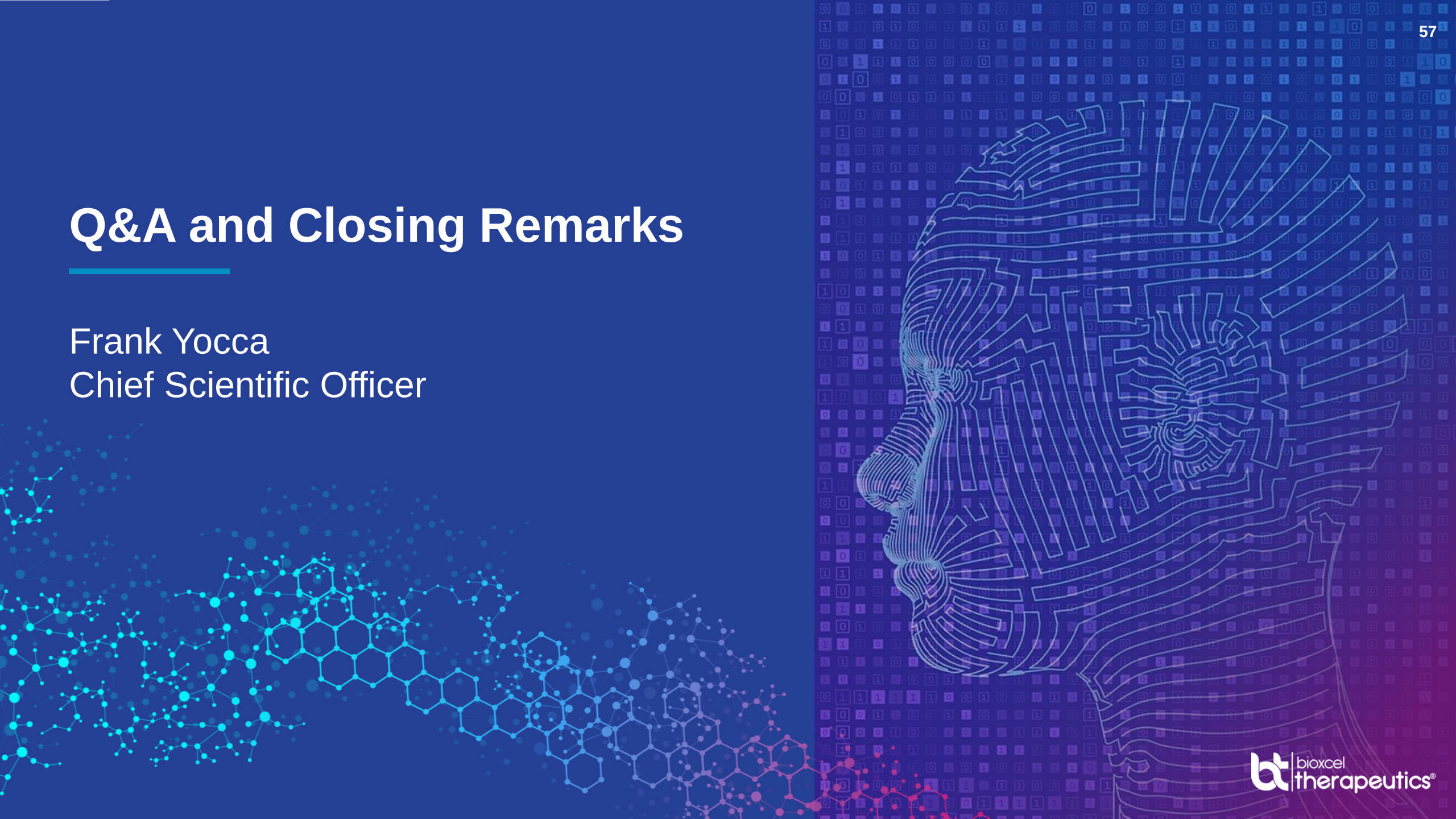
Q&A and Closing Remarks

Frank Yocca
Chief Scientific Officer



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R&D Strategy: Build Pipeline Depth with Innovation and Expansion

Pipeline as of December 12, 2023

Compound	Indication/Proposed Indication	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Marketed
Igalmi™ (dexmedetomidine) sublingual film - 120 mcg, 180 mcg	APPROVED APRIL 5, 2022 Acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults under provider supervision						
BXCL501	TRANQUILITY PROGRAM Acute treatment of agitation in Alzheimer's dementia						
	SERENITY III PROGRAM Acute treatment of agitation in bipolar disorders/schizophrenia						
	Opioid Use Disorder (OUD)						
	Post Traumatic Stress Disorder (PTSD)						
BXCL502	Neuropsychiatric symptoms Chronic agitation in Alzheimer's dementia						
Candidate BXCL503	Apathy in dementia						
Candidate BXCL504	Aggression in dementia						

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Thank you!