Alkermes Orexin Portfolio Strategy Review

October 9, 2024

Forward-Looking Statements

Note Regarding Forward-Looking Statements

Certain statements set forth in this presentation constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the company's expectations regarding development plans, activities and timelines for, and the potential therapeutic and commercial value of, ALKS 2680 for the treatment of narcolepsy and idiopathic hypersomnia and the company's orexin portfolio and strategy; and the company's expectations regarding the effectiveness and potential of its orexin portfolio strategy. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether ALKS 2680 or any other compounds from the company's orexin portfolio could be shown to be ineffective or unsafe; potential changes in the cost, scope and duration of development programs for ALKS 2680 and the company's orexin portfolio; whether the company's preclinical development strategy for its orexin portfolio will prove effective or yield the anticipated results; whether preclinical and initial clinical results will be predictive of results of future clinical studies or real-world results; whether future clinical trials or future stages of ongoing clinical trials for ALKS 2680 will be initiated or completed on time or at all; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2023 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this presentation. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation.

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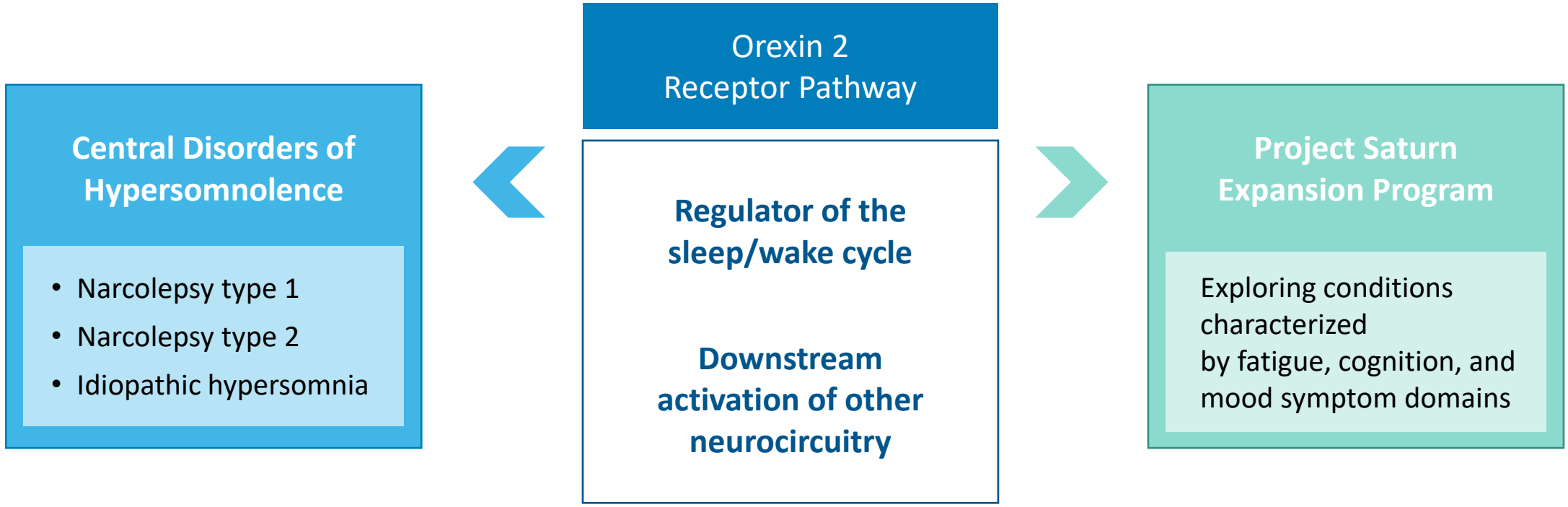
Note Regarding Development Candidates: ALKS 2680 and the company's other orexin compounds are investigational and have not been approved by the FDA or any other health authority, and their safety and efficacy have not been established.

Alkermes Orexin Portfolio Strategy Session

Craig Hopkinson, M.D.
Executive Vice President & Chief Medical Officer

Alkermes Orexin Portfolio Strategy: Data-driven Progression



Today's Agenda

- **Advanced Molecular Design Principles to Harness Orexin Mechanism**
  Brian Raymer, Ph.D.
  Exec. Director, Project Leadership & Strategy
- **ALKS 2680: Differentiated Orexin 2 Receptor Agonist Advancing in Phase 2**
  Julie Himes, M.D.
  SVP, Clinical Development
- **Narcolepsy and Idiopathic Hypersomnia: Insights into Prevalence & Unmet Patient Need**
  Charlie Pak
  VP, New Product Planning
- **Thought Leader Roundtable Discussion**
  Kiran Maski, M.D., Boston Children's Hospital
  David Plante, M.D., University of Wisconsin-Madison
  Monica Gow, Wake Up Narcolepsy
- **ALKS 2680 Dose Selection and Orexin Portfolio Expansion Strategy**
  Bhaskar Rege, Ph.D.
  SVP, Pharmaceutical and Early Stage Development
- **Preclinical Research to Identify New Clinical Opportunities for Orexin 2 Receptor Agonists**
  Julie Brooks, Ph.D.
  Director, CNS Biology
- **Closing Remarks**
  Richard Pops
  CEO
- **Q&A**

Advanced Molecular Design Principles to Harness the Potential of the Orexin Mechanism

Brian Raymer, Ph.D.
Executive Director, Project Leadership and Strategy

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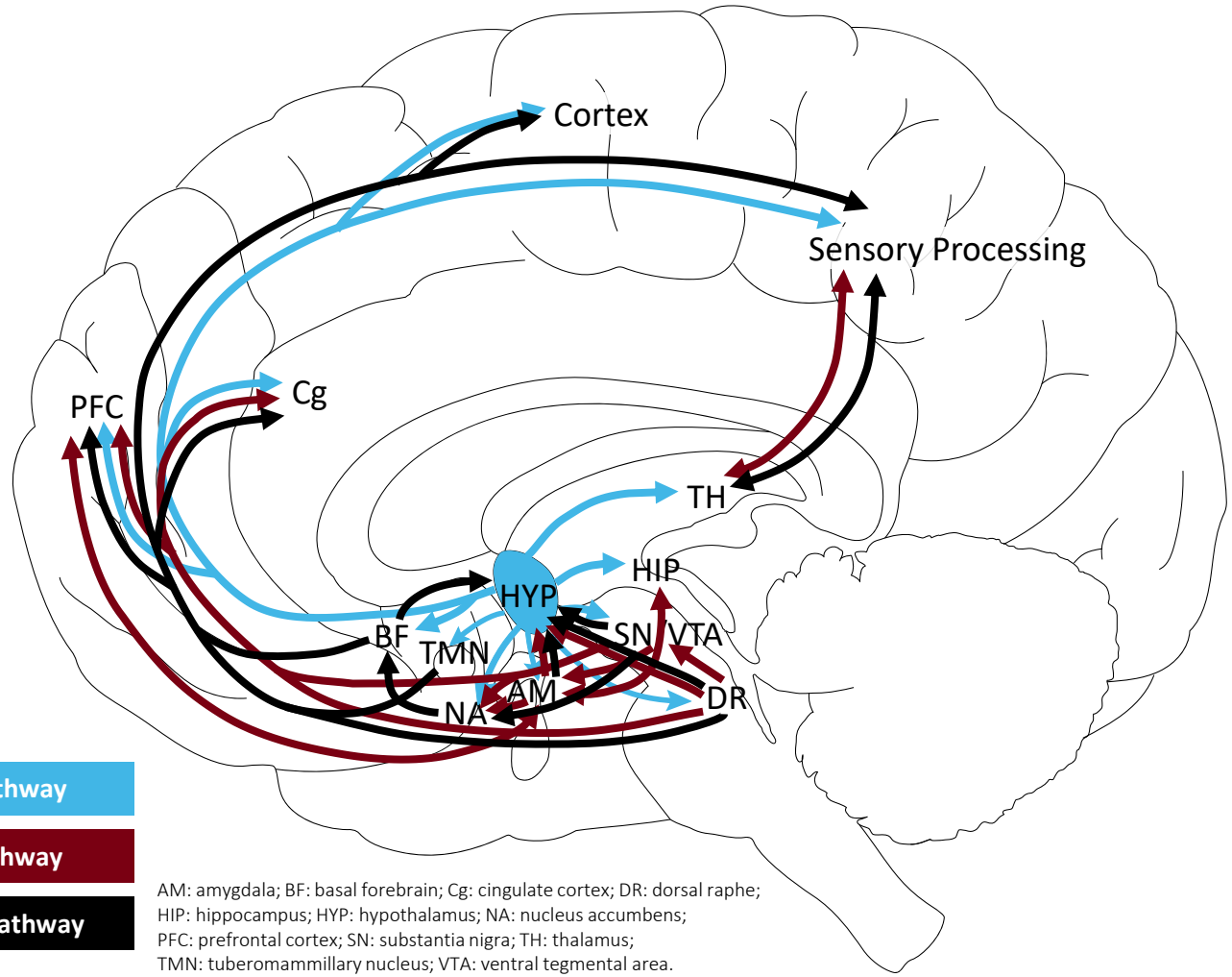
Utilizing Advanced Molecular Design Principles to Harness the Broad Potential of the Orexin Mechanism

- Orexins, also known as hypocretins, are neuropeptides produced in the hypothalamus
- Based on orexin's role in regulating the sleep-wake cycle, initial drug development for the orexin 2 receptor mechanism has been focused on sleep disorders
- Orexin neurons are "multi-tasking" neurons that regulate a set of vital functions, including sleep/wake states, feeding behavior, energy homeostasis, reward systems, cognition and mood[1]
- Understanding interactions between molecular properties is key to designing differentiated small molecule orexin 2 receptor agonists

[1]Front Neuroscience; 2020 Jul 10:14:691. doi: 10.3389/fnins.2020.00691

Orexin 2 Receptor Pathways and Neurotransmission

- Orexin neurons project from the hypothalamus into multiple brain regions and modulate an array of downstream neurotransmitters
- These neurons exert central control of **wakefulness**
- Pathways modulated by orexin may also be involved in control of **mood**
- Pathways modulated by orexin may also be involved in control of **attention**

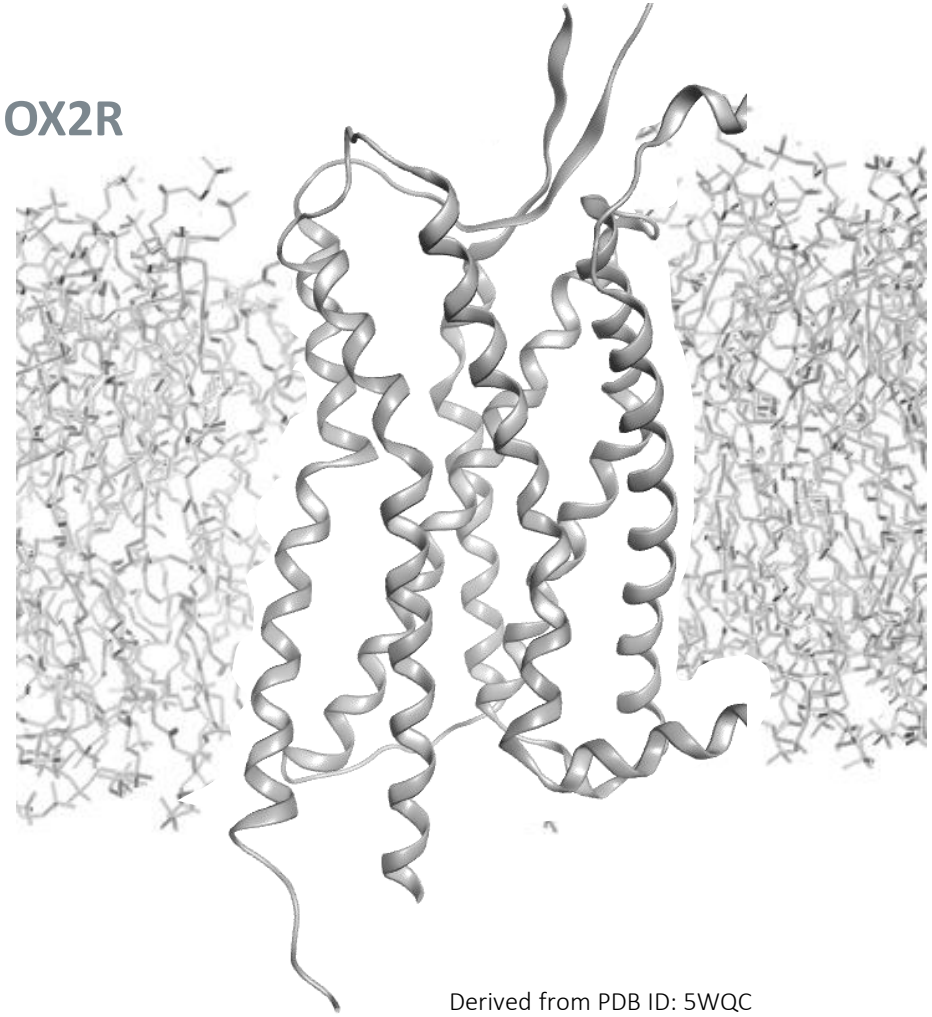


AM: amygdala; BF: basal forebrain; Cg: cingulate cortex; DR: dorsal raphe; HIP: hippocampus; HYP: hypothalamus; NA: nucleus accumbens; PFC: prefrontal cortex; SN: substantia nigra; TH: thalamus; TMN: tuberomammillary nucleus; VTA: ventral tegmental area.

Marcus, et al. *J. Comp. Neurology* 2001.
Alexandre, et al. *Curr. Op. Neurobiology* 2013.
Sarter, et al. *Brain Res. Rev.* 2006.
Katzman & Katzman, *Brain Sci.* 2022.

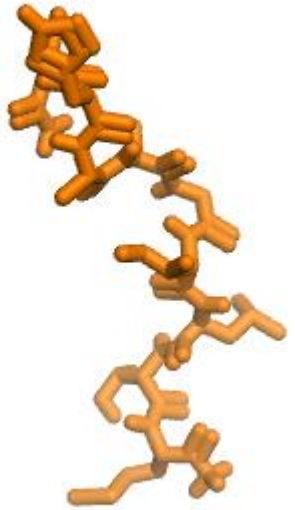
Orexin 2 Receptor (OX2R) is a Transmembrane G-Protein Coupled Receptor Stimulated by Orexin Peptides

Inactive OX2R



Derived from PDB ID: 5WQC

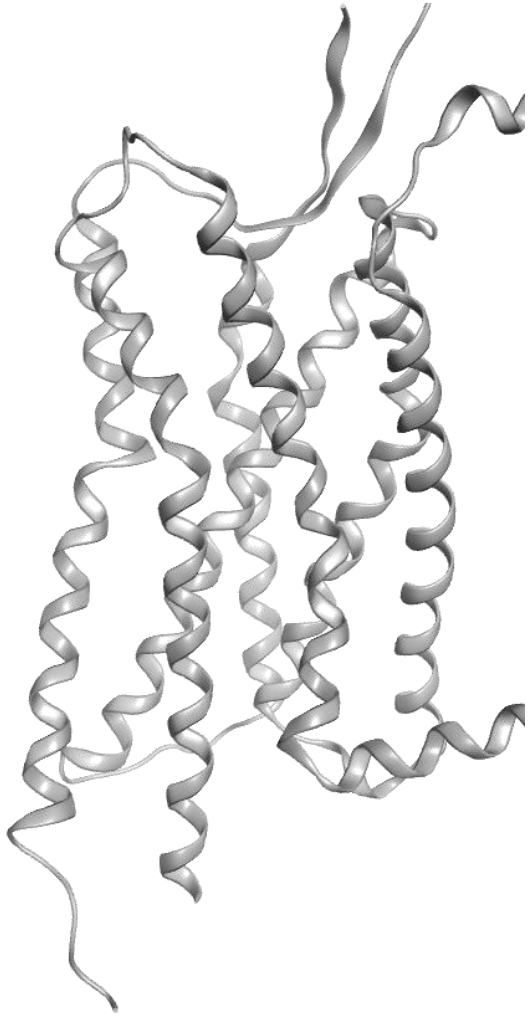
Orexin-B (Fragment)



Crystal structure of 9aa orexin B fragment bound to OX2R

Orexin 2 Receptor Does Not Signal Downstream in the Inactive State

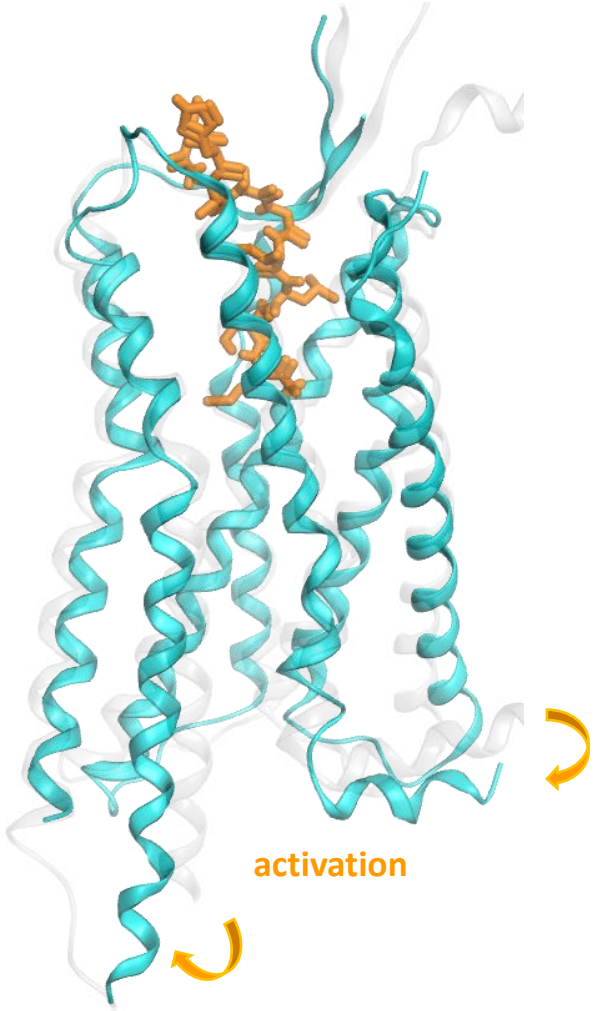
Inactive OX2R



Derived from PDB ID: 5WQC

Orexin Peptides Activate the Receptor and Initiate a Broad Signaling Cascade

Active OX2R

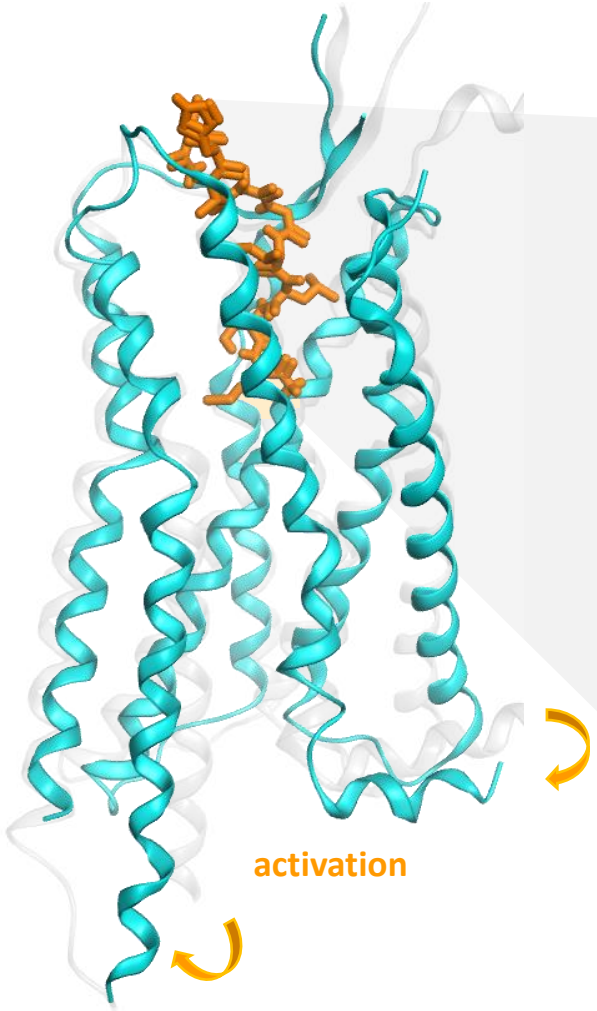


- In the **active state**, receptor signaling is “**on**"
  - Downstream cellular (neuron) signaling and neurotransmitter release facilitated by movement of transmembrane regions and release of G proteins

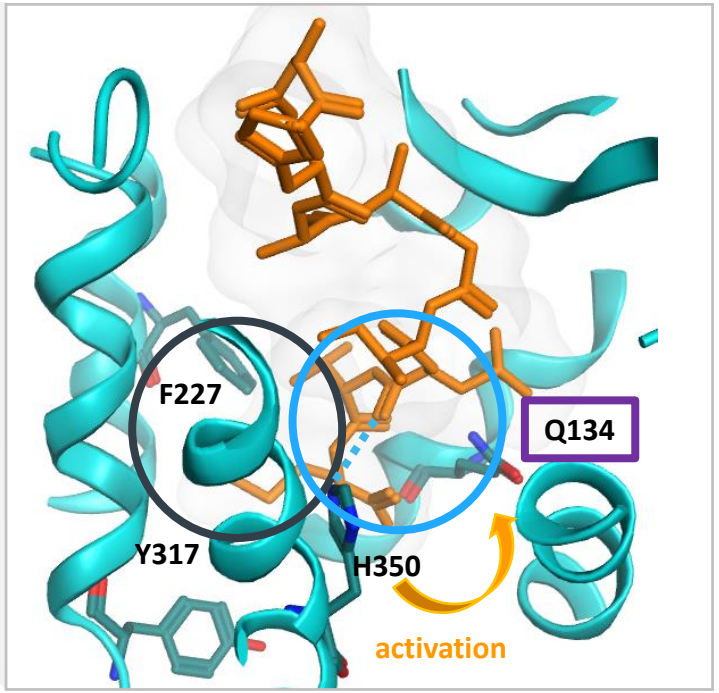
Crystal structure of 9aa orexin B fragment bound to OX2R

Understanding the Peptide Interaction is Key to Replicating Activation With a Small Molecule

Active OX2R



Key Activator Interactions



Hydrophobic interactions

Hydrogen bond

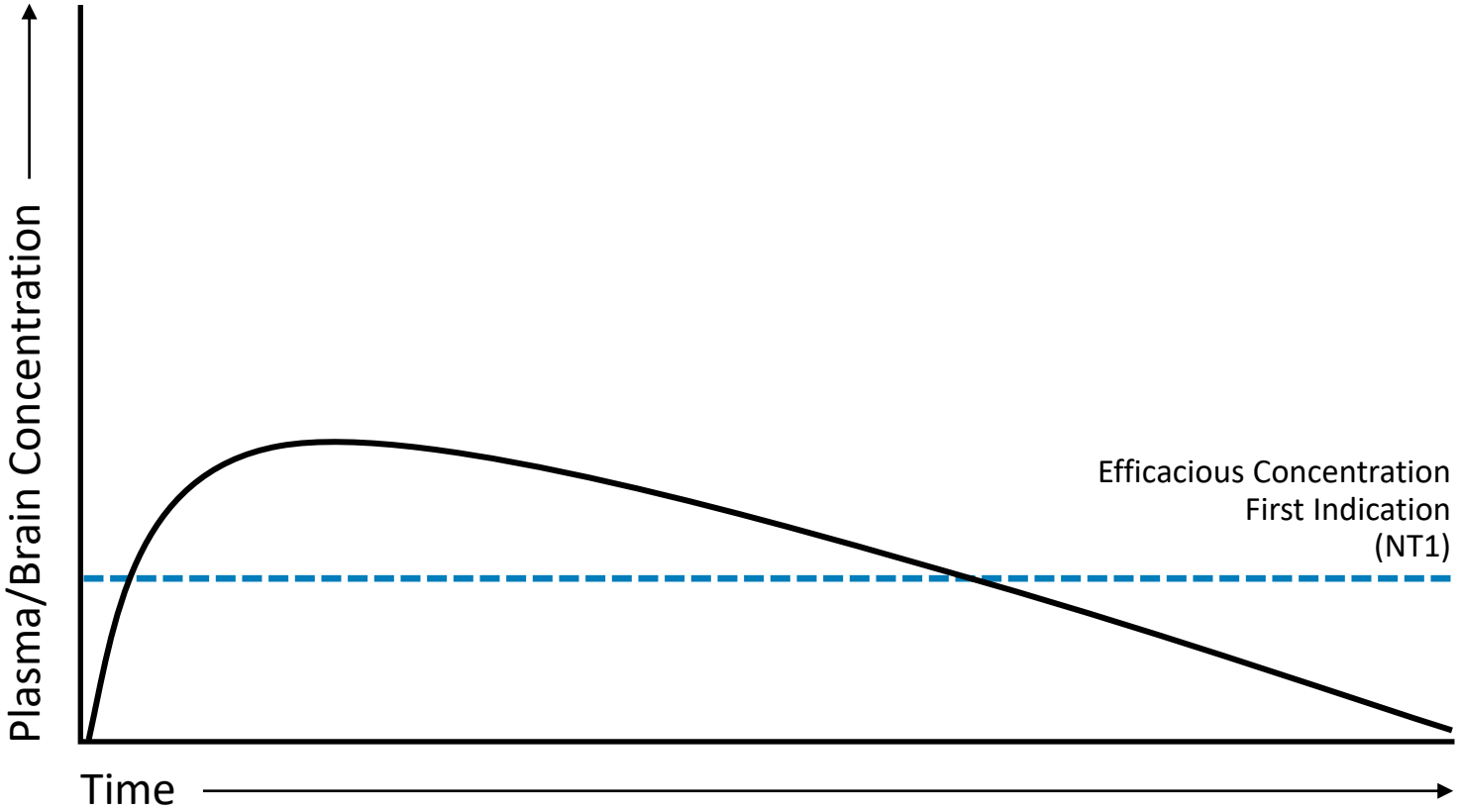
Q134 movement

Numerous Challenges in Replicating the Orexin Peptide in a Small Molecule

Balancing complex and often competing critical variables is key to designing small molecule orexin 2 receptor agonists

- **Potency**
- **Selectivity**
- **Metabolic profile**
- **Oral bioavailability**
- **Brain penetration**
- **Pharmacokinetic profile**

Pharmacokinetic (PK) Profile Impacts Key Safety and Efficacy Features



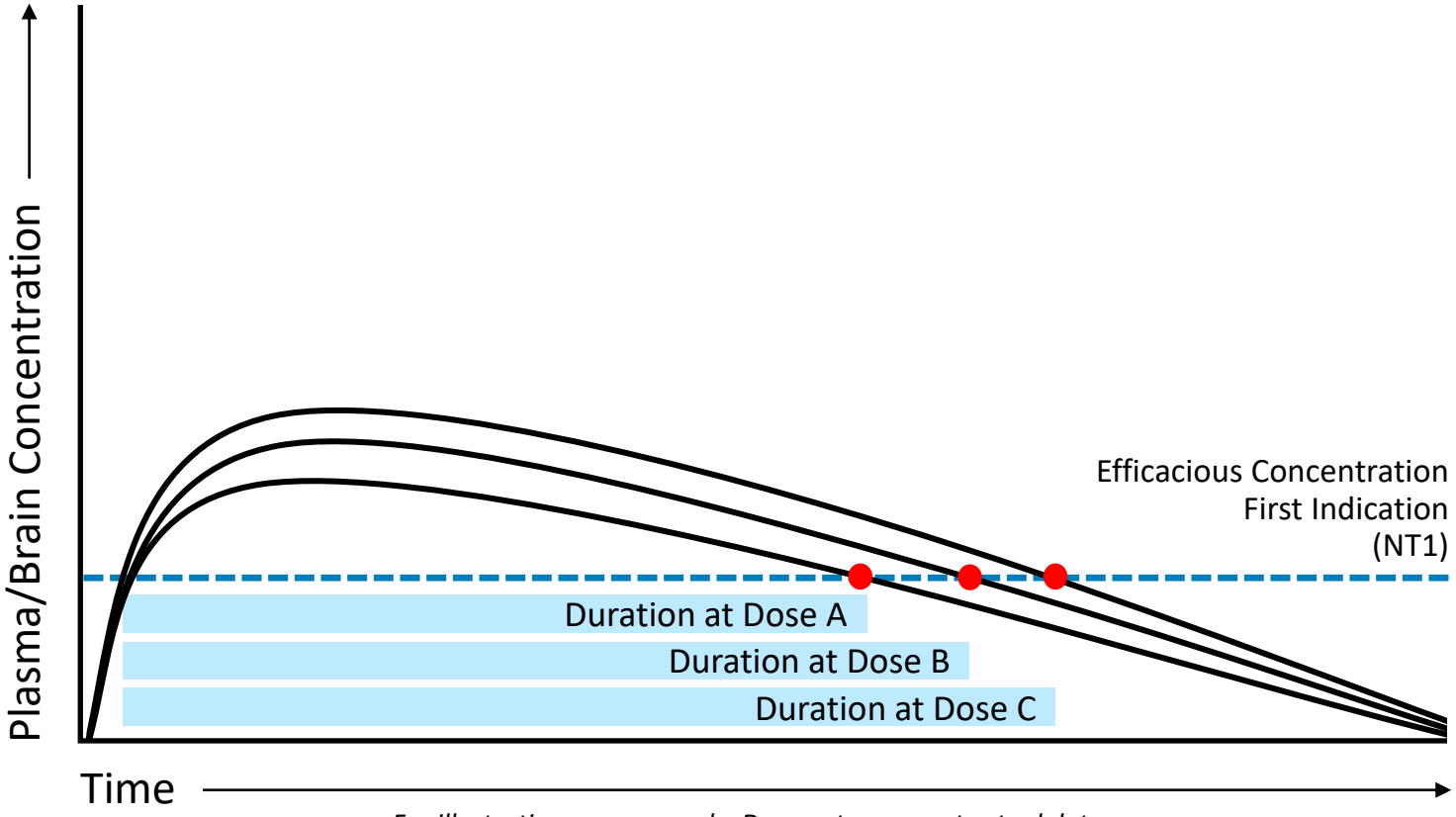
For illustrative purposes only. Does not represent actual data.

PK objective:

- Mimic natural sleep/wake cycle with once-daily, oral dosing
- High potency to allow for low overall doses and exposures

NT1: Narcolepsy type 1

Magnitude and Duration of Pharmacodynamic Effect Determined by Pharmacokinetic Profile



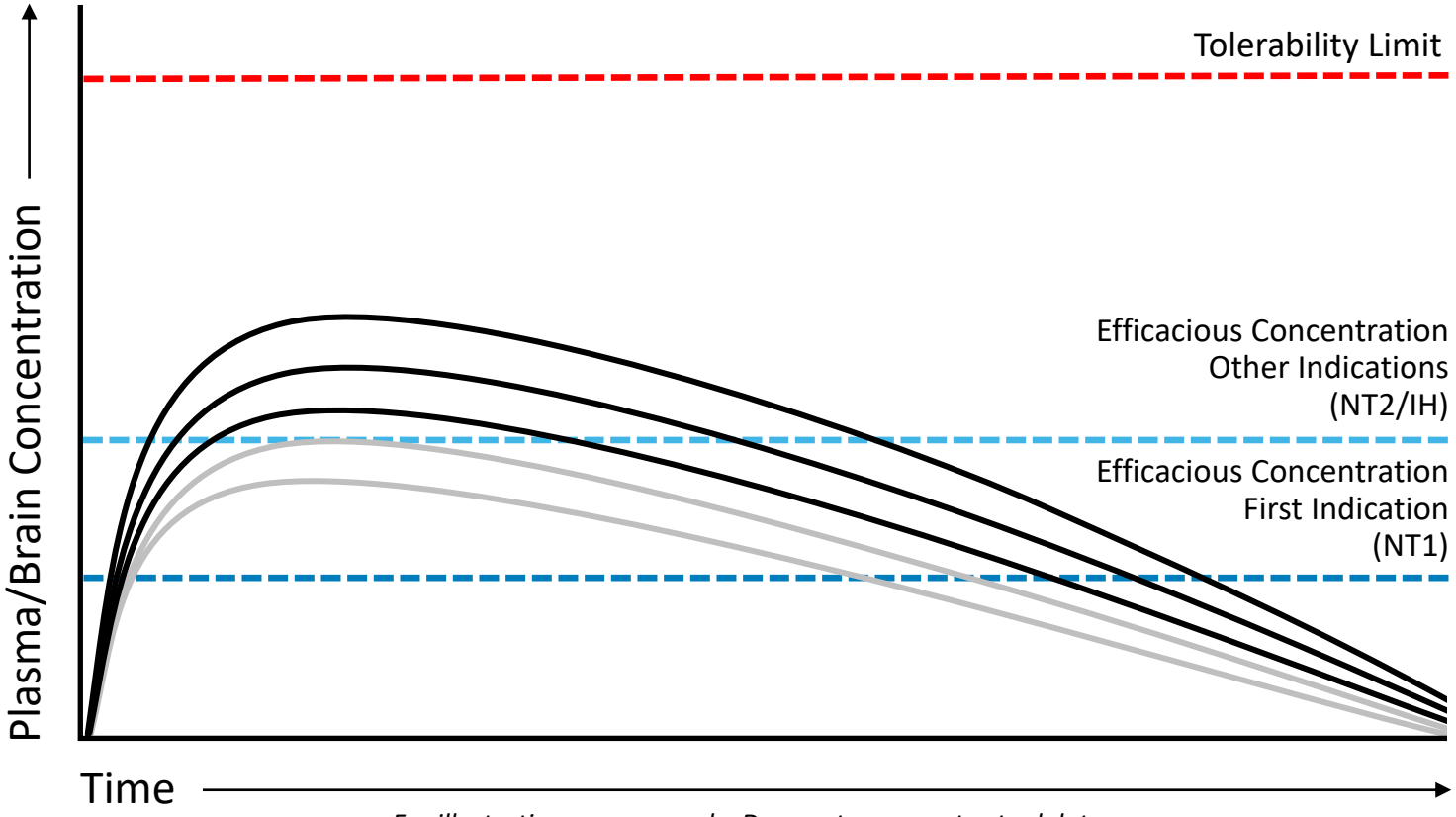
For illustrative purposes only. Does not represent actual data.

PK objective:

- Dose-dependent, proportional increase in AUC with lower-than-proportional increase in C_{max}

NT1: Narcolepsy type 1; AUC: Area under the curve; C_{max}: Maximum concentration

Efficacious Concentrations and Required Doses May Differ by Indication



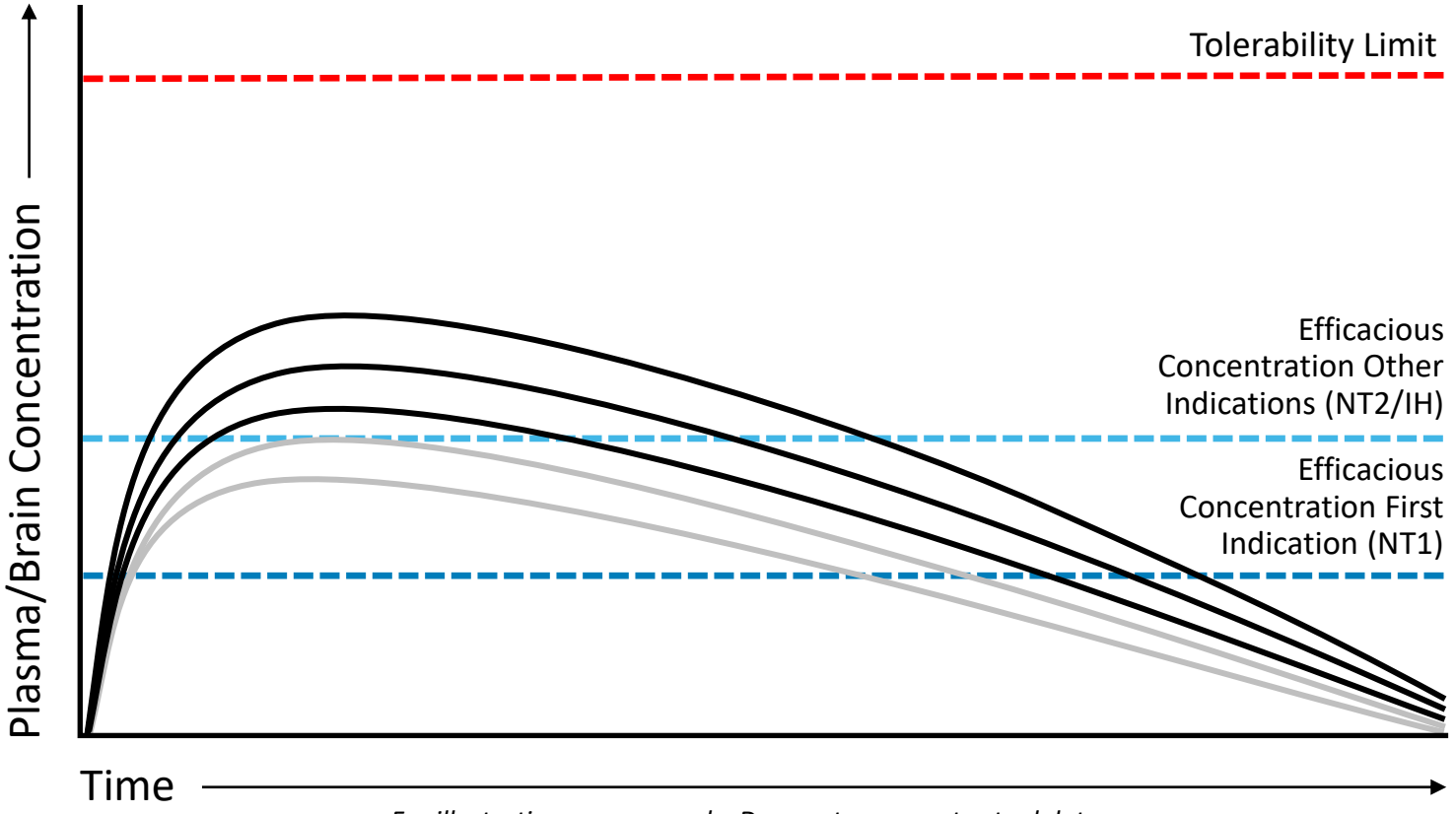
For illustrative purposes only. Does not represent actual data.

PK objective:

- Dosing flexibility to accommodate NT1, NT2 and IH as well as variability in patient profiles
- Wide therapeutic window well below tolerability limit

NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

ALKS 2680 Design Reflects Key Pharmacokinetic Features



For illustrative purposes only. Does not represent actual data.

ALKS 2680 design objective

- Mimic natural sleep/wake cycle with once-daily, oral dosing
- High potency to allow for low overall doses and exposures
- Non-proportional increase in C_{max} to increase tolerability
- Dosing flexibility to accommodate NT1, NT2 and IH as well as variability in patient profiles

NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia; C_{max}: Maximum concentration

Utilizing Advanced Molecular Design Principles to Harness the Broad Potential of the Orexin Mechanism

- Orexin neuropeptides are key regulators of wakefulness and work in a diurnal manner
- In addition to wakefulness, the orexin pathway may benefit additional symptomatic domains such as fatigue, mood, cognition and attention
- Understanding how the orexin peptide activates the receptor and cascades signaling across the brain is key to designing targeted small molecules that harness this potential
- Alkermes' chemistry design approach is focused on key parameters such as potency and targeted PK profile to address the needs of patients across a range of potential indications

ALKS 2680: Differentiated Orexin 2 Receptor Agonist Advancing in Phase 2 in NT1, NT2 and IH

Julie Himes, M.D.
Senior Vice President, Clinical Development

NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

Symptom Commonality Across Sleep Disorders Results in Diagnostic Challenges

Common Symptoms in Narcolepsy Type 1, Narcolepsy Type 2 and Idiopathic Hypersomnia

Symptoms	NT1	NT2	IH
Excessive daytime sleepiness (EDS)			
Sleep-onset REM periods (SOREMP)			
Cataplexy			
Disrupted nighttime sleep			
Needed naps: short, refreshing			
Sleep-related hallucinations			
Sleep paralysis			
Brain fog			
Long sleep			
Severe sleep inertia			
Needed naps: long, unrefreshing			

Almost always (90 to 100% of people with this disorder have this symptom)
More common (41 to 89% of people with this disorder have this symptom)
Less common (11 to 40% of people with this disorder have this symptom)
Rare (0 to 10% of people with this disorder have this symptom)

www.hypersomniafoundation.org/classification/; Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146:1387–94.; Rassu, Evangelista, Barateau, et al. *J Clin Sleep Medicine*. 2022, 617-629.
NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia; REM: rapid eye movement

ALKS 2680: Investigational Oral Orexin 2 Receptor Agonist for the Treatment of Narcolepsy and Idiopathic Hypersomnia

ALKS 2680 is a highly potent, selective OX2R agonist

- ≥10-fold more potent than orexin A[a]
- >5,000-fold selectivity relative to OX1R[a]

ALKS 2680 phase 1 data demonstrated desired pharmaceutical properties:

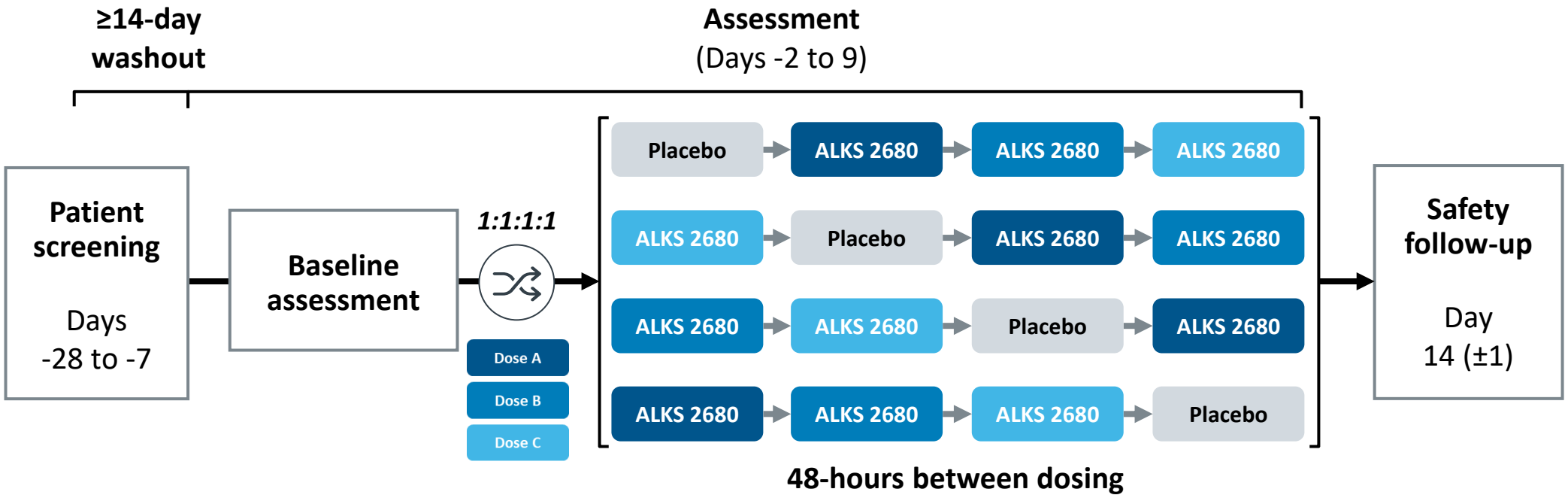
- Orally bioavailable
- PK profile supportive of once-daily dosing
- Mimics natural sleep/wake cycle

2024 Clinical Program Status

- Phase 1 single ascending dose and multiple ascending dose study complete
- Phase 1b proof-of-concept study complete
- Vibrance-1 phase 2 NT1 study enrolling
- Vibrance-2 phase 2 NT2 study enrolling
- Vibrance-3 phase 2 IH study planning underway
- Open-label, long-term safety study expected to initiate in Q4 2024

[a]Data from preclinical studies using CHO (Chinese hamster ovary) cells.; OX1R: orexin 1 receptor; OX2R: orexin 2 receptor; PK: pharmacokinetic; NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

Phase 1b: Randomized, Double-Blind, PBO-Controlled Study of ALKS 2680 in Patients With NT1, NT2 and IH Provides Proof-of-Concept



- Patients had a confirmed diagnosis with no baseline criteria for MWT
- Key objectives:
  - Safety and tolerability
  - Mean sleep latency on Maintenance of Wakefulness Test (MWT) at baseline and each day of dosing

Patient Population	n	ALKS 2680 Doses
NT1	10	1, 3 & 8 mg
NT2	9	5, 12 & 25 mg
IH	8	5, 12 & 25 mg

PBO: Placebo; NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

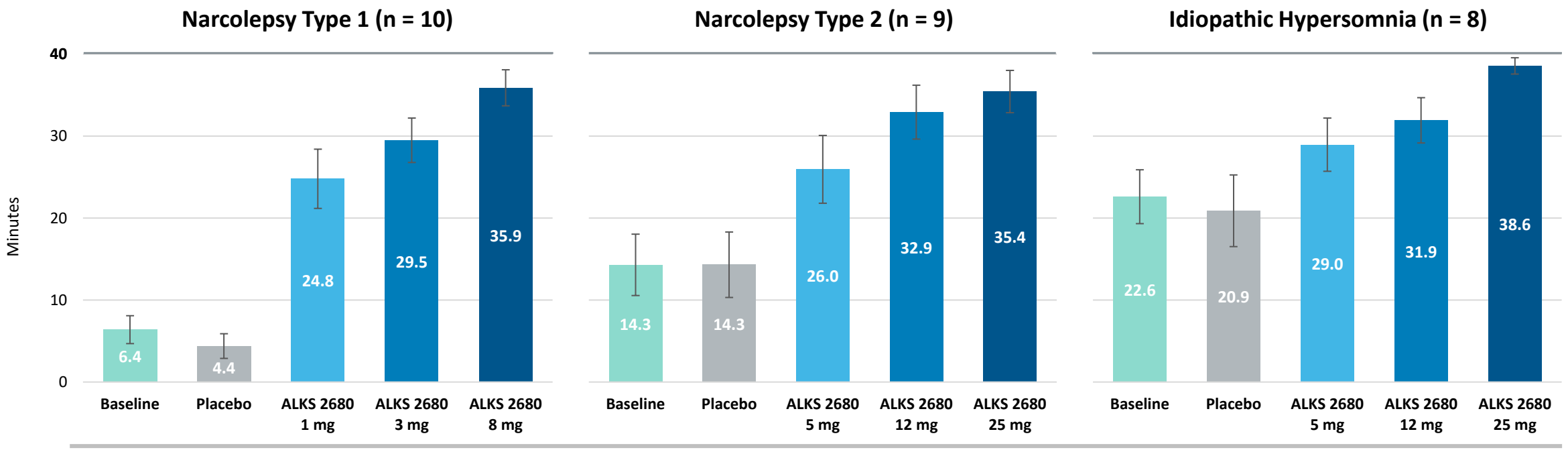
Phase 1b: ALKS 2680 Generally Well-Tolerated at all Doses Tested in NT1, NT2 and IH

- Most TEAEs were mild in severity and transient
- No deaths, serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation
- Treatment-related TEAEs* reported in >1 subject in each population listed below:
  - NT1: insomnia, pollakiuria, salivary hypersecretion, decreased appetite, dizziness, and nausea
  - NT2: pollakiuria, insomnia, and dizziness
  - IH: pollakiuria, insomnia, and dizziness
- No clinically meaningful changes in laboratory parameters
- No cardiovascular safety signals in vital signs or ECGs

*Relationship per investigator determination.
Insomnia includes TEAE terms of insomnia, middle insomnia, and initial insomnia. Dizziness includes TEAE terms of dizziness and dizziness postural.
NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia; TEAE: Treatment-Emergent Adverse Event; ECG: Electrocardiogram

Phase 1b: Results Demonstrated Meaningful, Consistent and Dose-Dependent Effect on Wakefulness in NT1, NT2 & IH Patients

Absolute Mean Sleep Latency on Maintenance of Wakefulness Test (MWT) - Mean ± SE



Primary Analysis	**LS mean (95% CI) difference vs placebo[1]**	18.38 (10.95, 28.80)	22.57 (15.56,29.58)	33.97 (26.72,41.21)		11.60 (2.22, 20.98)	18.55 (9.17, 27.93)	20.96 (11.58, 30.34)		8.07 (0.06, 16.07)	11.05 (3.04, 19.05)	17.67 (9.67, 25.68)
	p-value	**0.0002**	**0.0001**	**<0.0001**		**0.0178**	**0.0005**	**0.0001**		**0.0484**	**0.0096**	**0.0002**

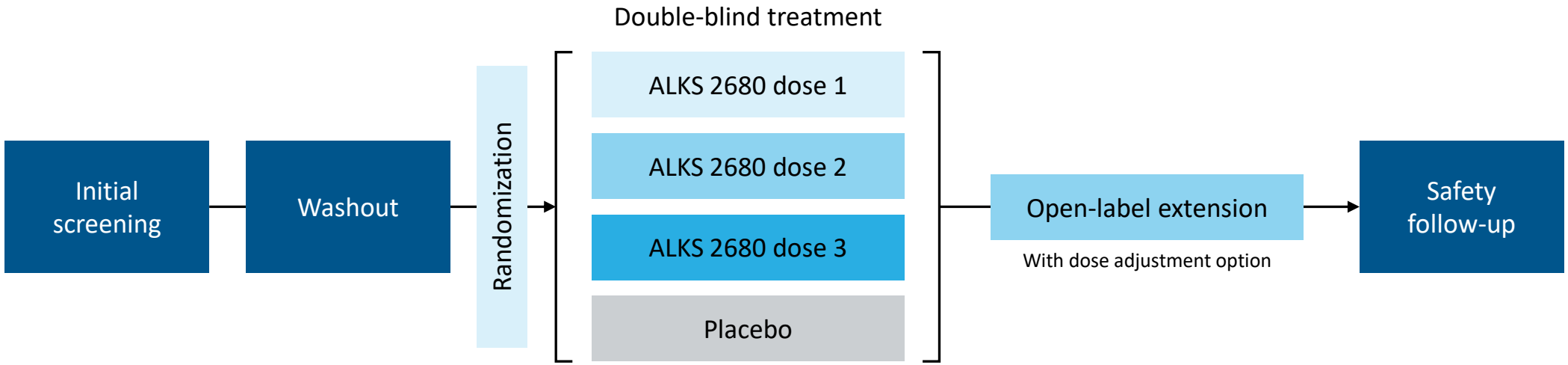
1: Primary analysis based on a mixed effect model of repeated measurement with the dose level and the period as fixed factors, and the average sleep latency on Day -1 is included as the baseline covariate
SE: standard error; LS: least squares

Phase 1b: ALKS 2680 Patient Data Support Advancement and Dose Selection in Phase 2 in NT1, NT2 and IH

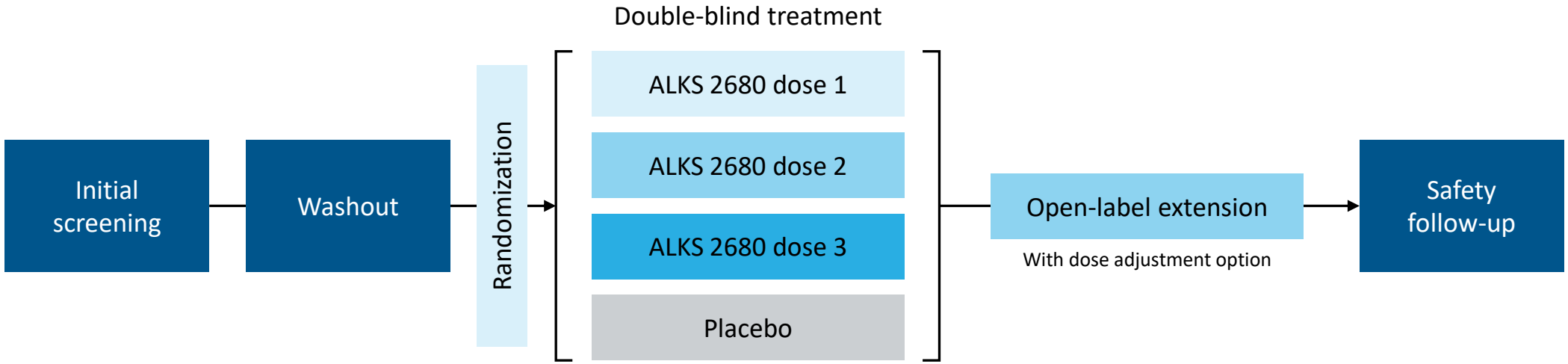
- Tested a range of doses to explore dose response for each patient population
- Generally safe and well tolerated with no treatment related discontinuations
- Statistically significant and clinically meaningful increases in mean sleep latency observed at all doses
- Patients achieved MWT results within the normal sleep range for healthy individuals[1]
- PK profile mimicked natural sleep/wake cycle in patients with NT1, NT2 and IH, with once-daily dosing
- Phase 1b design and results enabled data-driven phase 2 dose selection

1. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498; Mean sleep latencies for healthy individuals (30.4 ± 11.2 minutes)
NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia; MWT: Maintenance of Wakefulness Test; PK: Pharmacokinetic

Phase 2 Clinical Program Evaluating Once-Daily Administration of ALKS 2680 Across a Range of Patient Populations



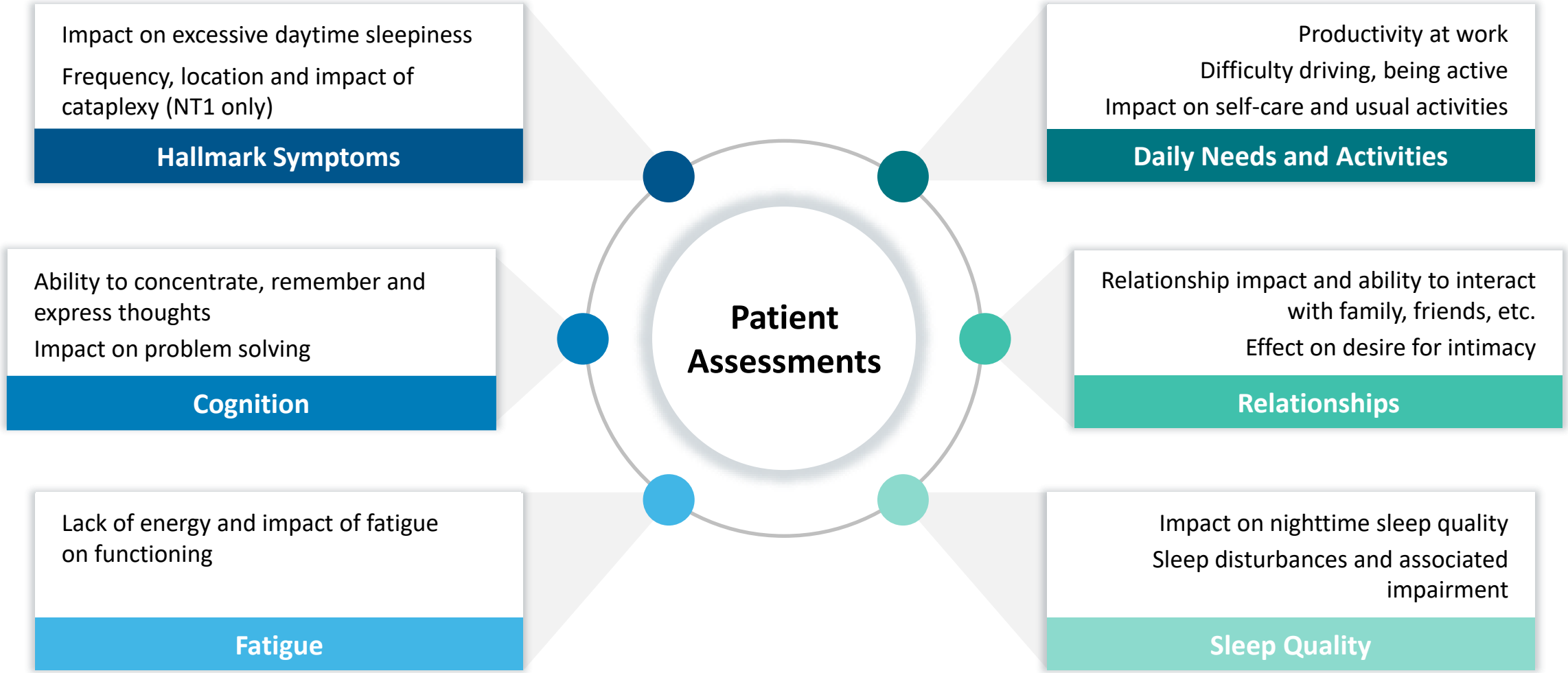
Phase 2 Clinical Program Evaluating Once-Daily Administration of ALKS 2680 Across a Range of Patient Populations



Study	n	ALKS 2680 Doses	Screening Period		Double-blind Treatment Period	Open-label Extension Period	Follow-up Period	Primary Endpoint
			Initial	Washout				
Narcolepsy Type 1 VIBRANCE-1	80	4, 6 & 8 mg	≤ 4-weeks	2-weeks	6-weeks	7-weeks	2-weeks	Δ MWT at week 6
Narcolepsy Type 2 VIBRANCE-2	80	10, 14 & 18 mg	≤ 4-weeks	2-weeks	8-weeks	5-weeks	2-weeks	Δ MWT at week 8
Idiopathic Hypersomnia VIBRANCE-3	Study design in progress							

MWT: Maintenance of Wakefulness Test; Δ: change from baseline

Evaluating the Impact of ALKS 2680 on Symptoms and Outcomes Important to Patients in Phase 2



NT1: Narcolepsy type 1

Phase 1 Data Support Rapid Advancement of ALKS 2680 Into Phase 2 in Multiple Indications

Patient data underscore unique profile of ALKS 2680

- Clinically meaningful, statistically significant and dose-dependent effect on wakefulness observed across all indications and doses evaluated
- Generally well tolerated across all doses evaluated
- Patients achieved maintenance of wakefulness results within the normal sleep range for healthy individuals[1]
- Profile supports once-daily dosing

Executing comprehensive clinical program

- Advancing phase 2 program:
  - Vibrance-1 (NT1): 4, 6 and 8 mg
  - Vibrance-2 (NT2): 10, 14 and 18 mg
  - Vibrance-3 (IH): Study design underway
- Phase 2 designed to evaluate efficacy, safety and outcomes important to patients
- Planned initiation of long-term safety study by year-end
- Phase 2 topline results in NT1 and NT2 expected H2 2025

1: Krahn LE, et al. *J ClinSleepMed.* 2021;17(12):2489-2498.

NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

Narcolepsy and Idiopathic Hypersomnia: Insights into Prevalence and Patient Experiences

Charlie Pak, Ph.D.
Vice President, New Product Planning

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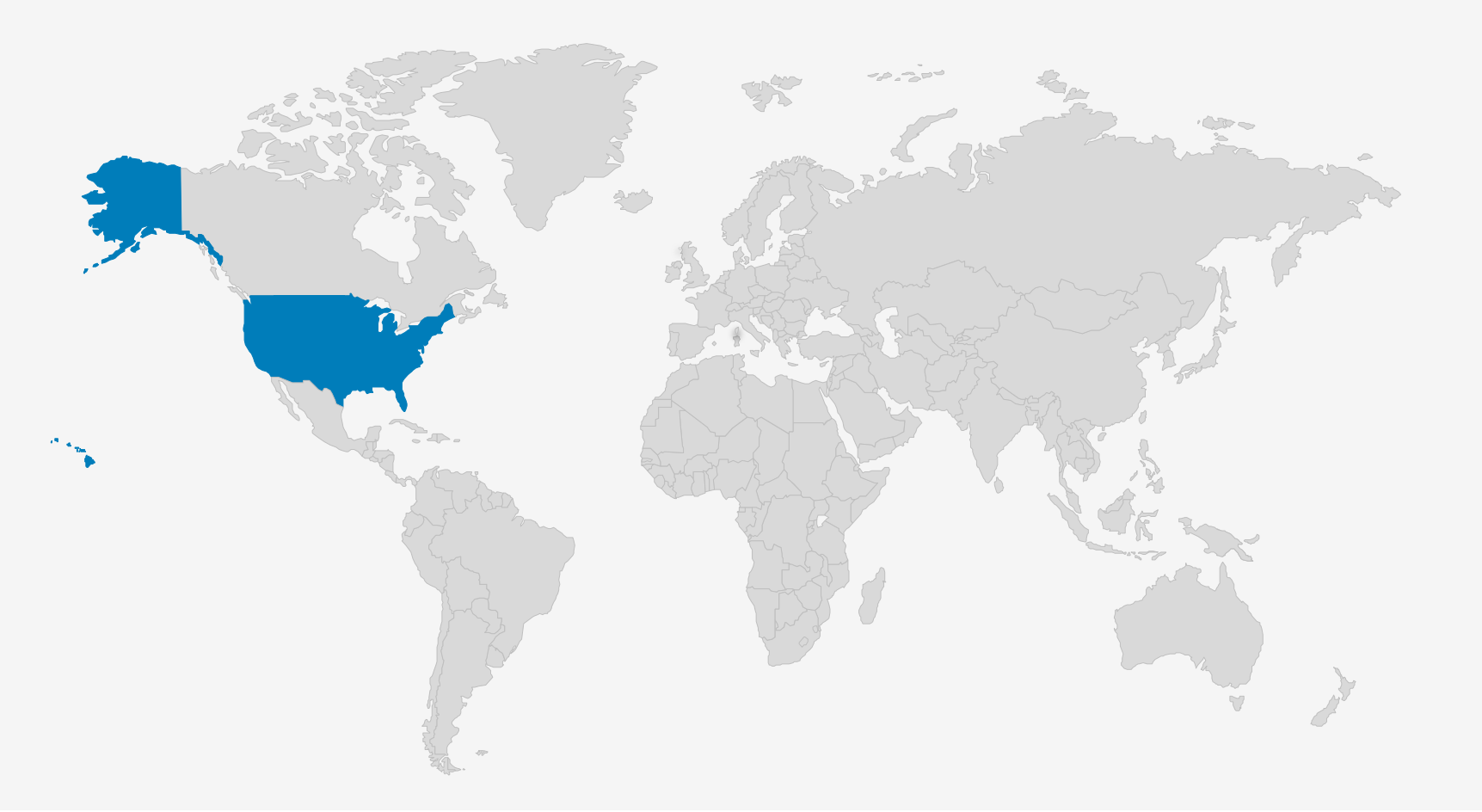
Narcolepsy and IH Prevalence

Narcolepsy and IH Affect People Around the World

Narcolepsy (Types 1 & 2) and **Idiopathic Hypersomnia** (IH) affect people around the world



Narcolepsy and Idiopathic Hypersomnia in the U.S.

Narcolepsy prevalence **200,000**[a]

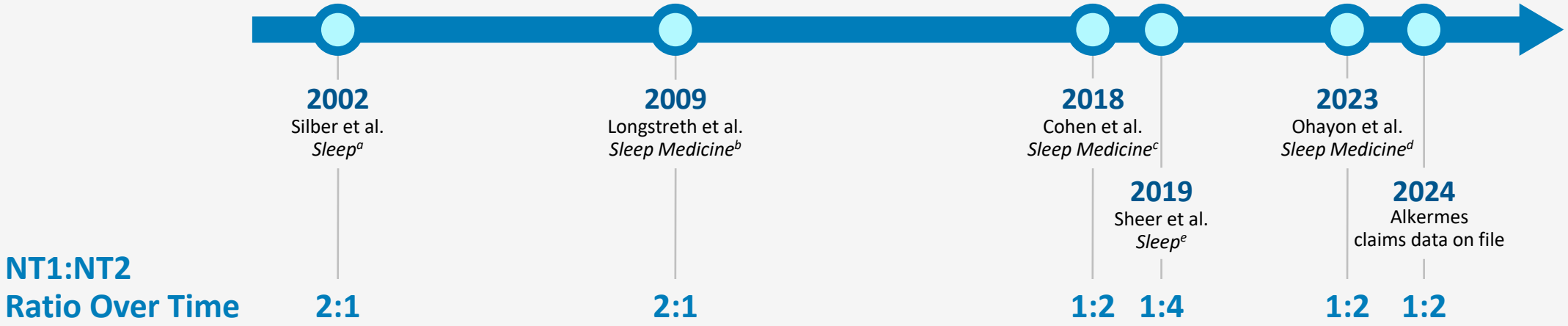
100,000
diagnosed[b]

Idiopathic Hypersomnia

40,000
diagnosed[c]

[a]Narcolepsy Network Fast Facts
[b]Cohen et al., *Sleep Med* 43:14 (2018) and Longstreth et al., *Sleep Med* 10:422 (2009) prevalence rates applied to U.S. population
[c]Acquavella et al., *J Clin Sleep Med* 16:1255 (2020)

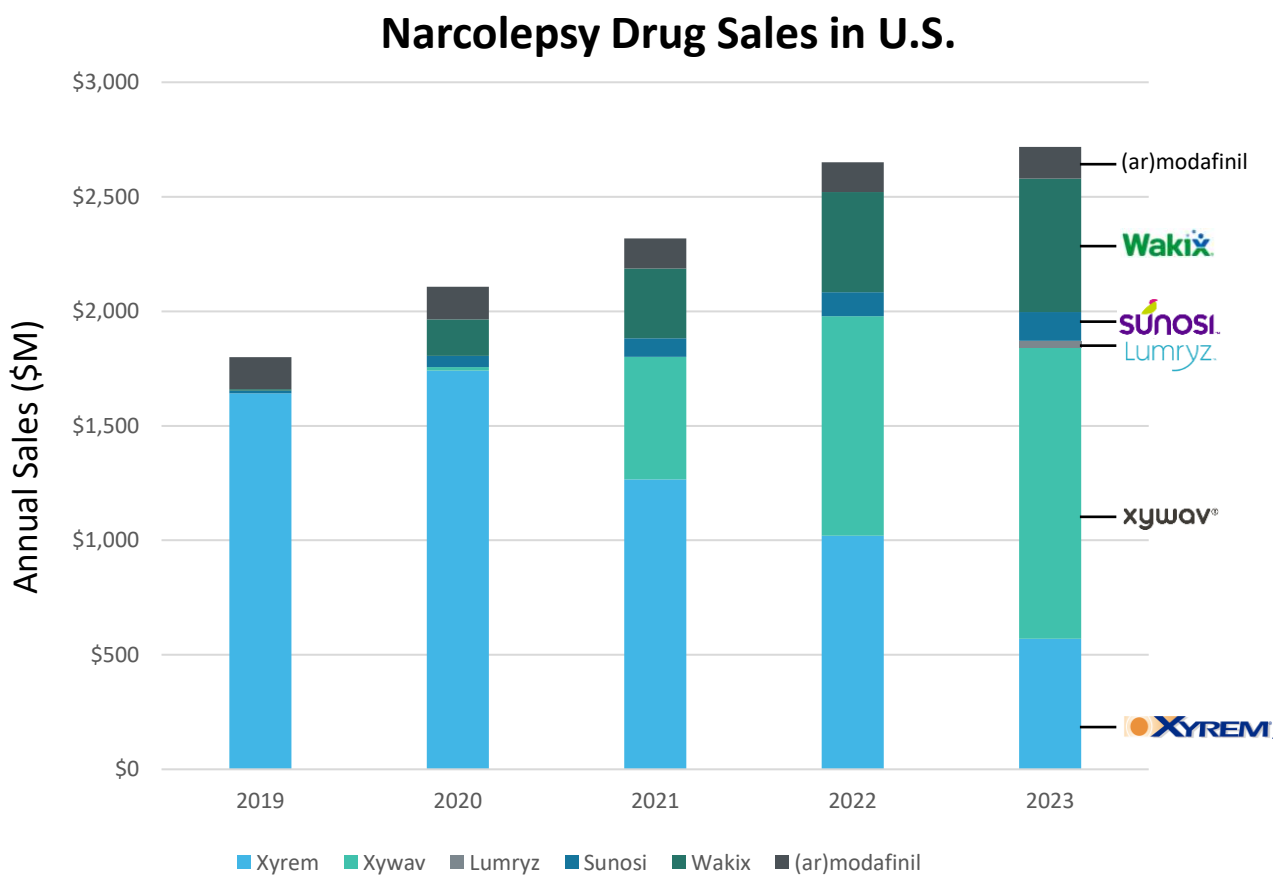
Recent Literature and Data Demonstrate Shift Toward Higher Prevalence of Narcolepsy Type 2 vs. Type 1



Recent data suggest higher prevalence of NT2

[a]Silber et al., Sleep 25:197 (2002)
[b]Longstreth et al., Sleep Med 10:422 (2009)
[c]Cohen et al., Sleep Med 43:14 (2018)
[d]Ohayon et al., Sleep Med, https://doi.org/10.1016/j.sleepx.2023.100095 (2023)
[e]Scheer et al., Sleep, 42:1 (2019)
NT1: Narcolepsy type 1; NT2: Narcolepsy type 2

Approved Narcolepsy Treatments Generate Net Sales > $2.5B in the U.S.

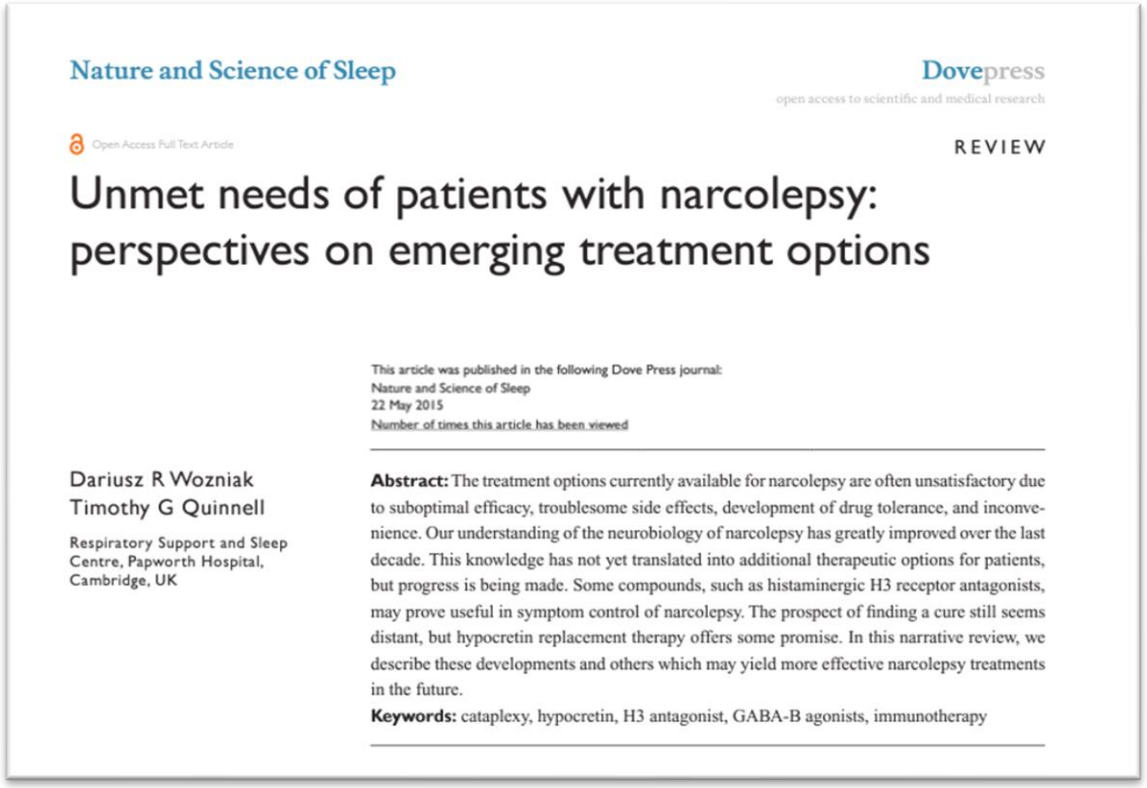


FDA-Approved Medicines
(ar)modafinil
WAKIX® (pitolisant)
SUNOSI® (solriamfetol)
LUMRYZ™ (sodium oxybate) ER
XYWAV® (Ca, Mg, Na, K oxybates)
XYREM® (sodium oxybate)

Source: IQVIA, company 10-K reports

Patient Experiences

High Unmet Patient Need Remains Despite Available Treatments



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REVIEW

Unmet needs of patients with narcolepsy: perspectives on emerging treatment options

This article was published in the following Dove Press journal:
Nature and Science of Sleep
22 May 2015
Number of times this article has been viewed

Dariusz R Wozniak
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Abstract: The treatment options currently available for narcolepsy are often unsatisfactory due to suboptimal efficacy, troublesome side effects, development of drug tolerance, and inconvenience. Our understanding of the neurobiology of narcolepsy has greatly improved over the last decade. This knowledge has not yet translated into additional therapeutic options for patients, but progress is being made. Some compounds, such as histaminergic H3 receptor antagonists, may prove useful in symptom control of narcolepsy. The prospect of finding a cure still seems distant, but hypocretin replacement therapy offers some promise. In this narrative review, we describe these developments and others which may yield more effective narcolepsy treatments in the future.

Keywords: cataplexy, hypocretin, H3 antagonist, GABA-B agonists, immunotherapy

A recent survey was conducted in the United States with the aim of sharing patients' perspectives on the treatment of narcolepsy with the US Food and Drug Administration (FDA). It included over 1,000 people with narcolepsy…95% of responders reported having been prescribed at least one of the FDA-approved medications. Nonetheless, ***74% complained of daily narcolepsy symptoms. Eighty-four percent described impaired work or school performance and judged their condition as moderate or severe.***

Patients Adapt Lifestyle By Prioritizing Where and When Energy is Exerted

Maslow's Hierarchy of Needs[a]

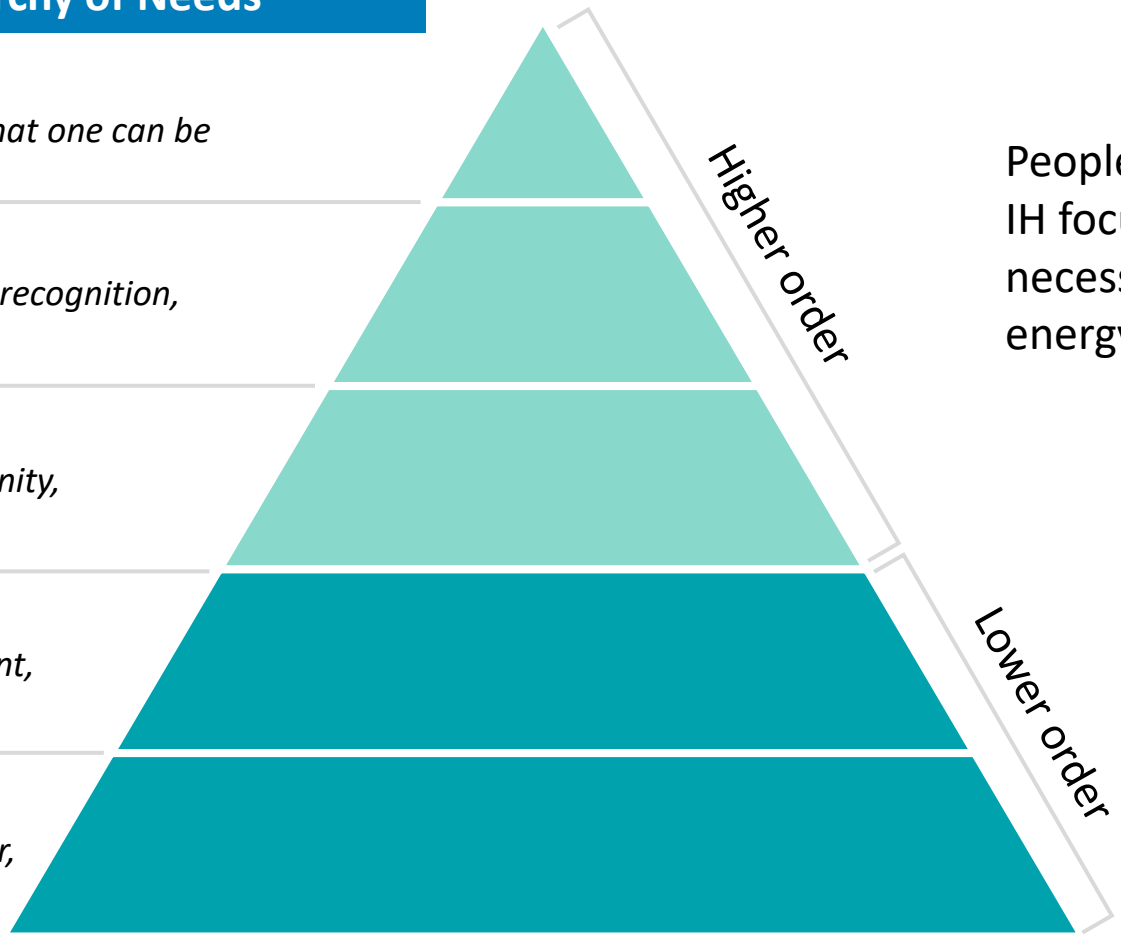
Self-Actualization:
Desire to become the most that one can be

Esteem:
Respect, self-esteem, status, recognition, strength, freedom

Love & Belonging:
Friendship, intimacy, community, sense of connection

Safety Needs:
Personal security, employment, resources, health, prosperity

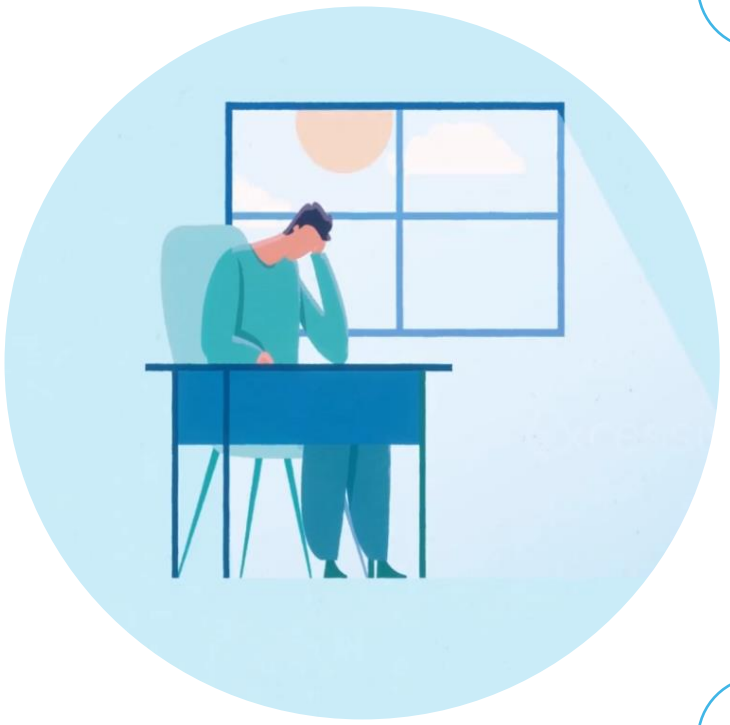
Physiological Needs:
Sleep, air, water, food, shelter, clothing, reproduction



People living with narcolepsy and IH focus energy toward basic life necessities and avoid "wasting" energy on higher-order needs[b]

[a]Maslow, AH (1954). Motivation and personality. Harper & Row. [b]Qualitative primary market research study with narcolepsy and IH patients (n=30 [Feb 2024])

Narcolepsy and IH Symptoms May Impact Many Facets of Life



- Career/job choices
- Academic pursuits
- Living situations
- Social engagements, friendships, romantic relationships
- Ability to be a caregiver
- Daily accommodations: Naps, coffee, etc.

Source: Qualitative primary market research studies with narcolepsy and idiopathic hypersomnia patients (n=24 [Aug 2022], n=30 [Feb 2024])

Narcolepsy and IH Symptoms Can Severely Impact Daily Activities

Safety	• Car accident • Mishandling / dropping heavy items • Losing focus while watching children	*"I was at work one day, and* ***I fell asleep holding a piece of industrial glass and I dropped it and it almost cut my artery*** *in my neck." – NT1 patient*
Productivity	• Falling asleep during an important test • Falling asleep at desk • Loss of job or place in school	***"I used to fall asleep in class all the time and everyone would get upset. I would end up in detention for sleeping in class…****I would try so hard to stay awake…everyone just thought I didn't care enough to stay awake." – NT1 patient*
Mental Health	• Question sanity • Severe episode of depression • Suicidal thoughts	*"****I felt inadequate, had low self esteem due to not having the energy to do basic things my peers did, and lonely*** *because I would spend* ***so much time on my own sleeping****." – NT2 patient*
Relationships	• Lashing out or snapping at loved ones • Forgetting or missing a milestone • Not being reliable to watch children	*"We're at the beach right now on vacation.* ***I don't feel comfortable taking my son or my foster son on vacation alone because sometimes I have to sleep****. I can't not sleep. So we're at the beach and I have to bring somebody with me so that I can make sure the children are safe." – NT1 patient*

Source: Qualitative primary market research studies with narcolepsy and IH patients (n=24 [Aug 2022], n=30 [Feb 2024]) NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

Patients Identify Multiple Areas of Unmet Needs Despite Current Therapies

Symptom control

"I would be ***alert*** *and… I wouldn't constantly feel like I need to take a nap, despite all of the treatments I'm taking." – NT2 patient*

Disease modifying

"I wish there was an option for my sleep disorder that could ***treat the cause****, and not just the symptoms. It would allow my body to do what it should be able to do on its own…" – NT2 patient*

Non-stimulant

*"****On stimulants, I'm fearful that I am hurting my body or that I'll lash out at people****. It's scary being on something that's so strictly controlled.* ***I can't really trust stimulants*** *to help me." – IH patient*

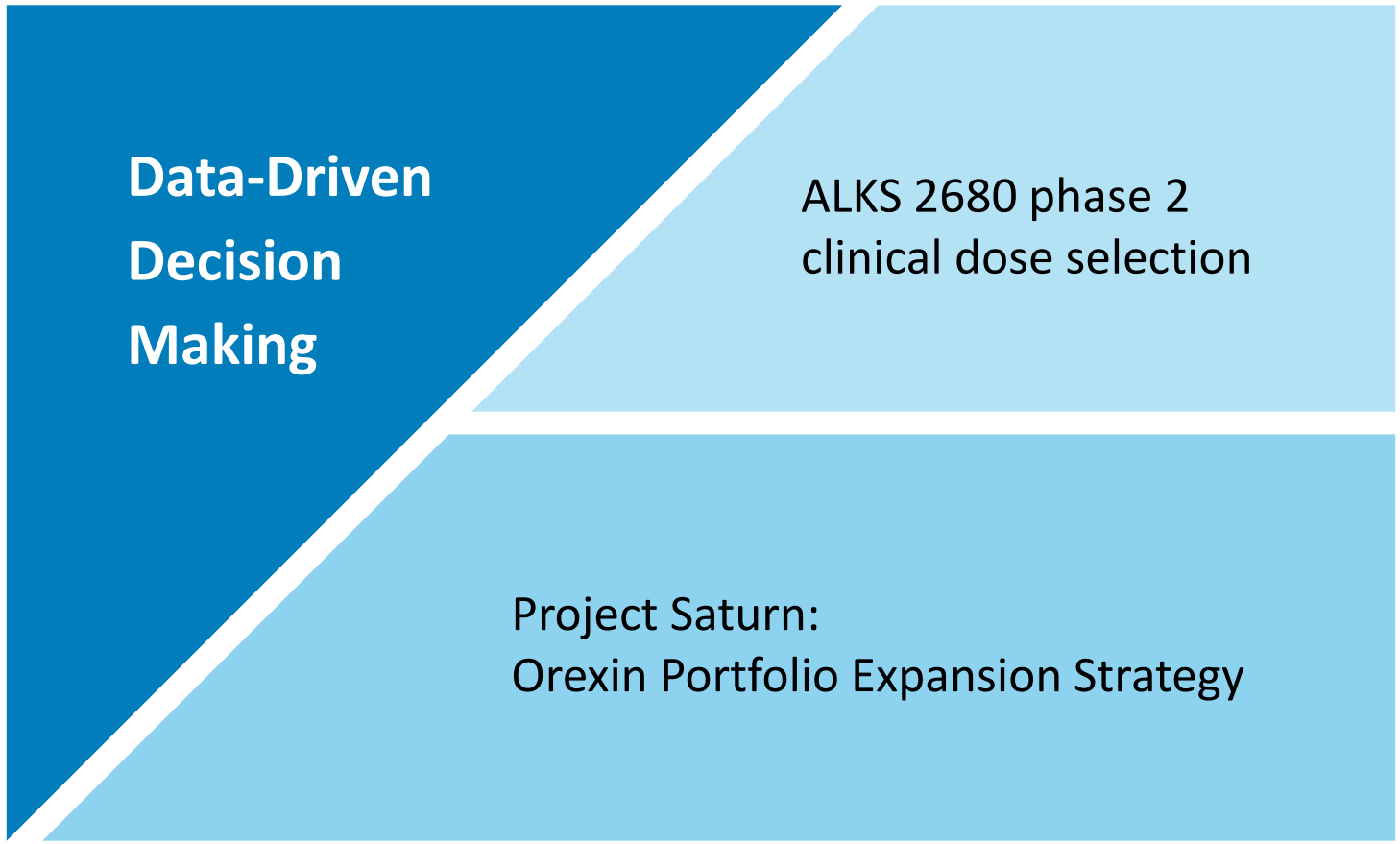
Source: Qualitative primary market research studies with narcolepsy and IH patients (n=24 [Aug 2022], n=30 [Feb 2024]) NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

Patient Needs Integrated into Development Strategy

Data-Driven Decision Making: ALKS 2680 Dose Selection and Orexin Portfolio Expansion Strategy

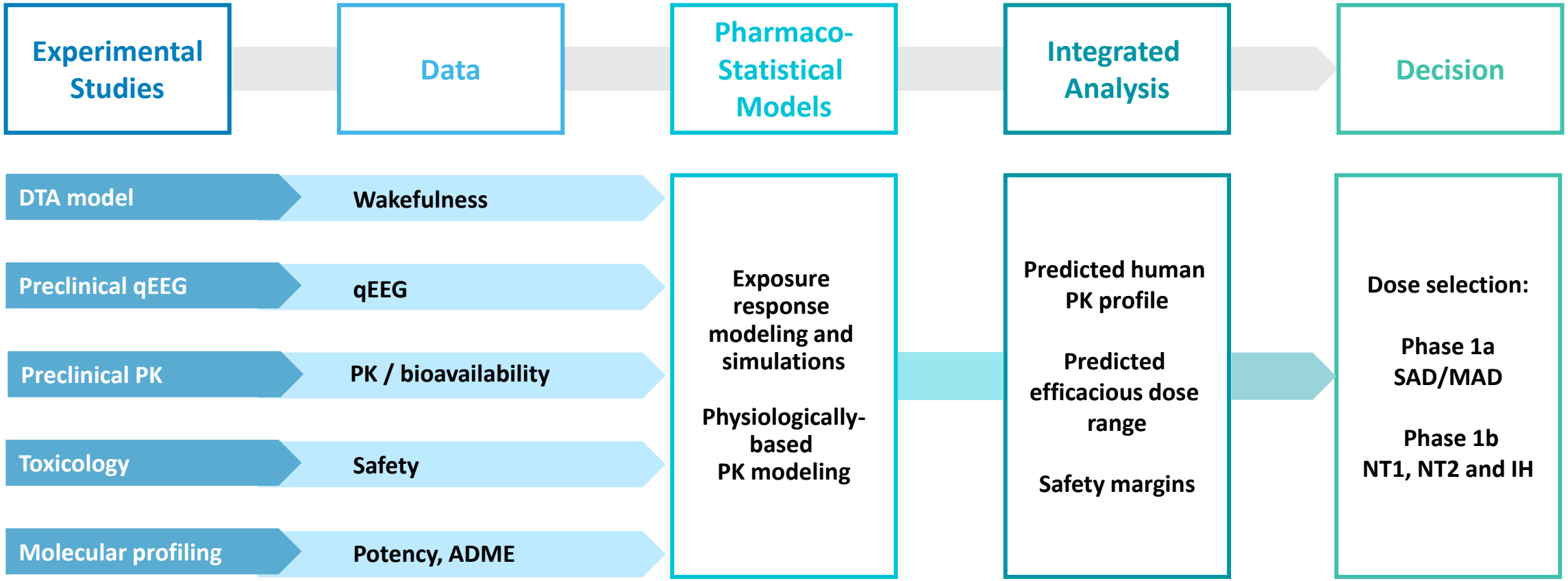
Bhaskar Rege, Ph.D.
Senior Vice President, Pharmaceutical and Early-Stage Development

Alkermes' Data-Driven Approach to Decision Making Across Our Orexin Portfolio



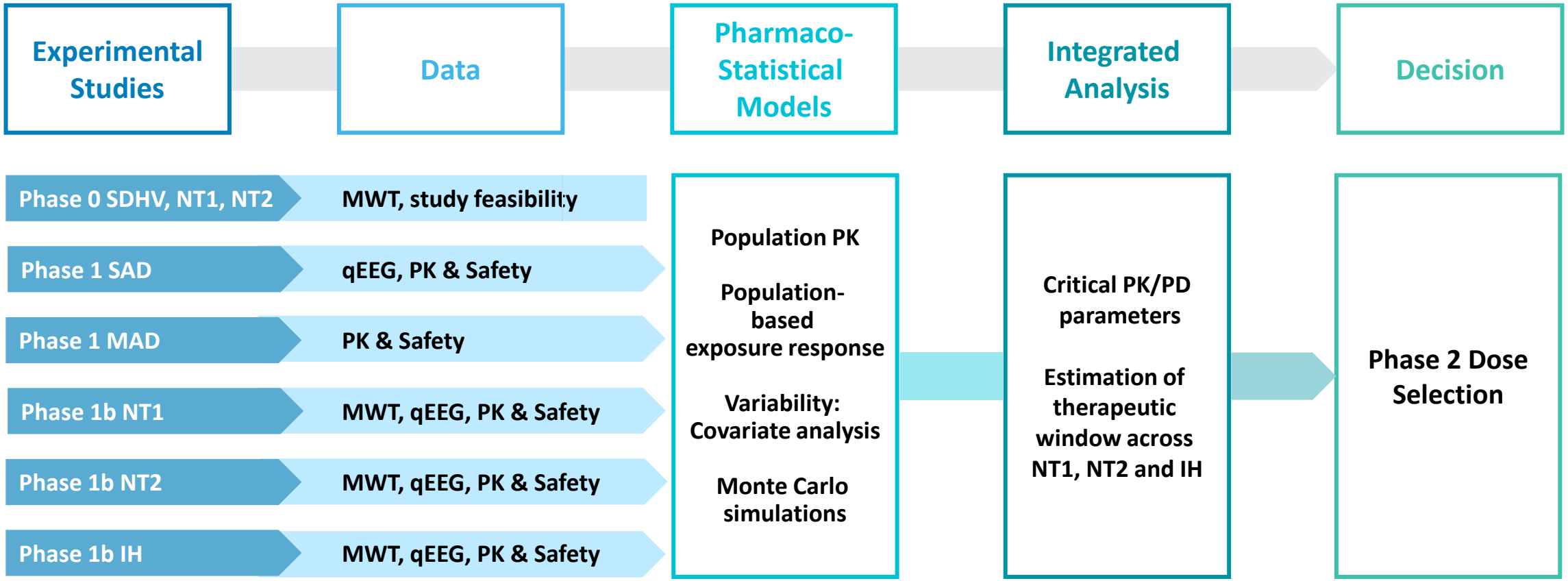
Synthesis of Multiple Data Inputs Improves Clinical Decision Making

Preclinical: Integrated Analysis Designed to Deliver Highly Translatable Data and Enable Efficient Phase 1 Dose Selection



qEEG: quantitative electroencephalography; PK: Pharmacokinetic; ADME: Absorption, distribution, metabolism and excretion;
SAD: Single ascending dose; MAD: Multiple ascending dose; PD: Pharmacodynamic; NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; IH: Idiopathic hypersomnia

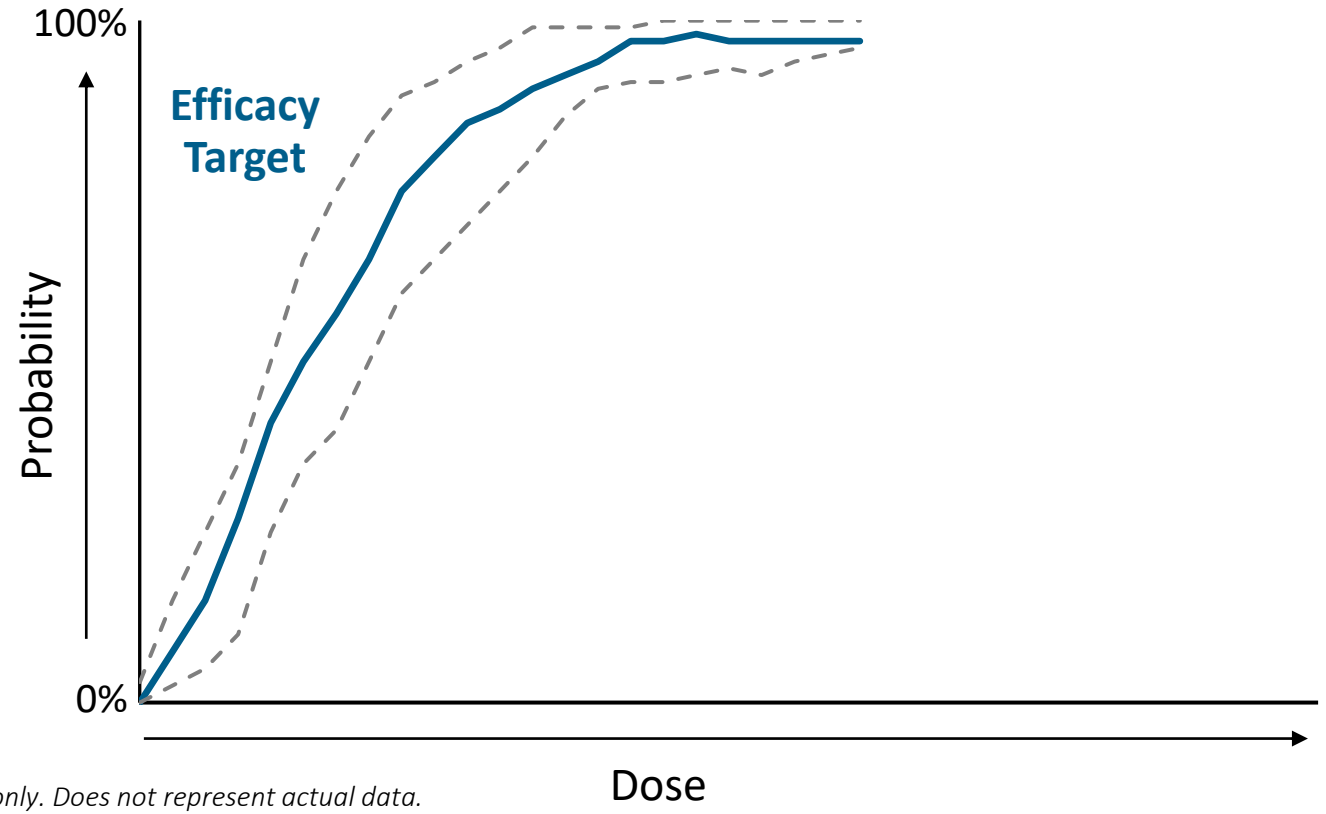
Clinical: Data Intensive Phase 1 Program Designed to Efficiently Deliver Early POC in Patients and Inform Phase 2 Dose Selection



POC: Proof-of-concept; SDHV: Sleep-deprived healthy volunteers; NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; SAD: Single ascending dose; MAD: Multiple ascending dose; qEEG: quantitative electroencephalography; MWT: Maintenance of Wakefulness Test; PK: Pharmacokinetic; PD: Pharmacodynamic; IH: Idiopathic hypersomnia

Model Outputs Enable Data-Driven Dose Selection

Simulated Population-Based Probability Estimates to Achieve Target Profile by Dose



For illustrative purposes only. Does not represent actual data.

Model Outputs Enable Data-Driven Dose Selection

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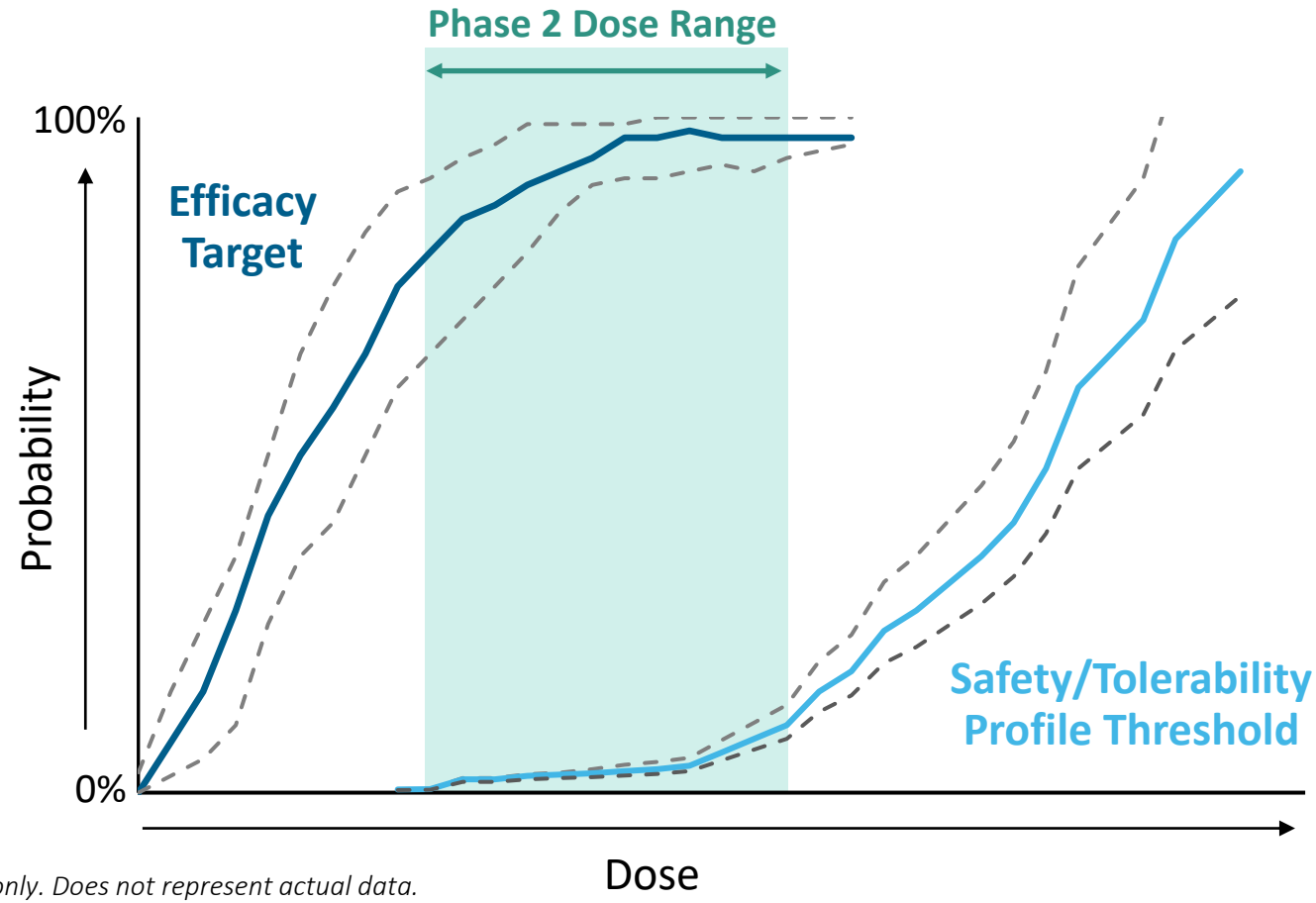
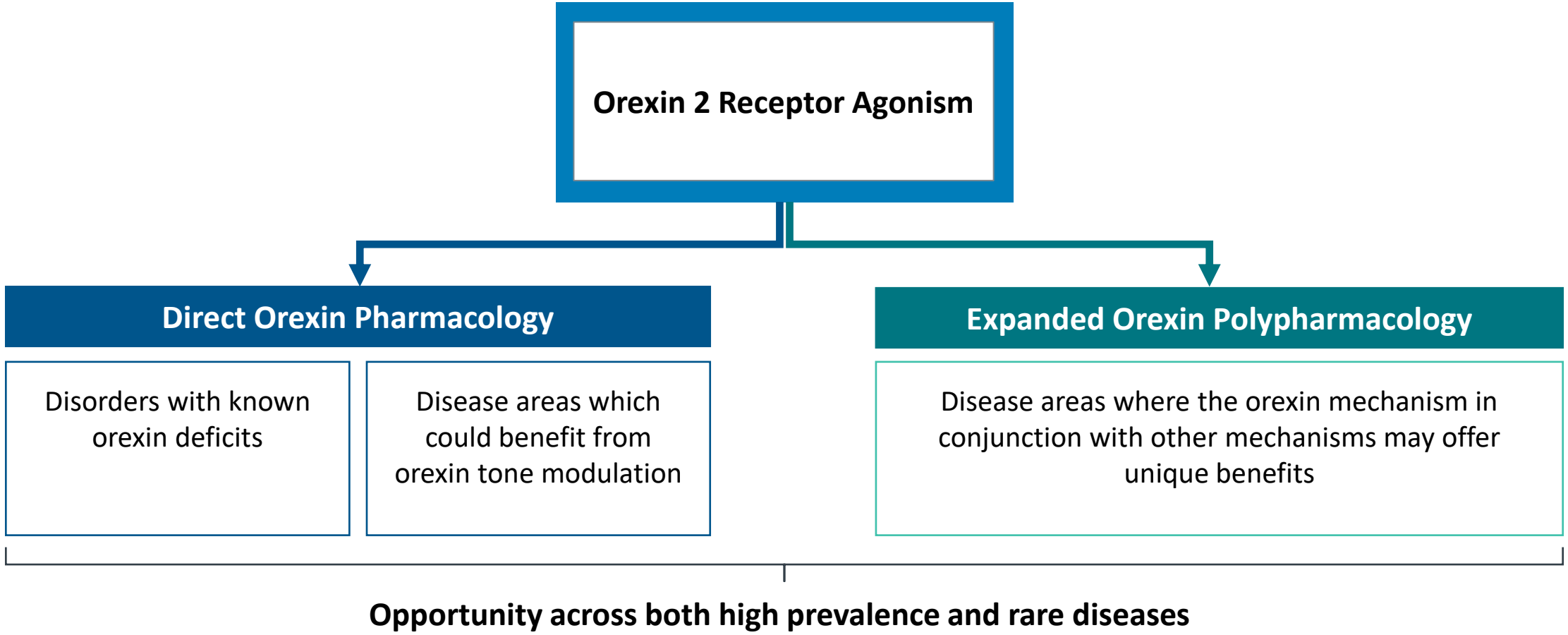


For illustrative purposes only. Does not represent actual data.

Phase 2 Dose Selection Objective

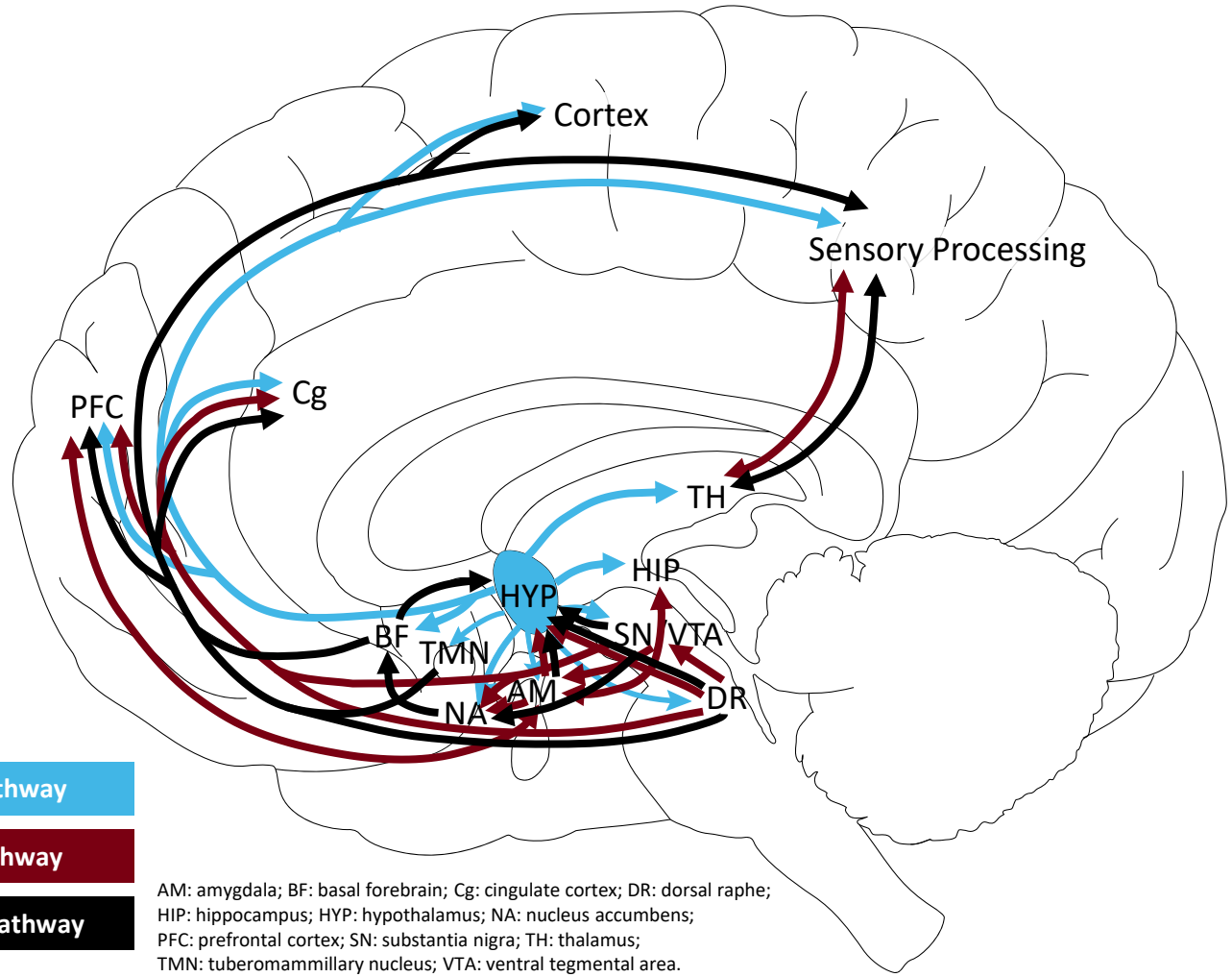
Maximize probability of achieving efficacy target while minimizing probability of crossing desired safety/tolerability threshold

Project Saturn: Opportunity to Apply Orexin Mechanism Across a Range of Indications in Neurology and Psychiatry



Orexin 2 Receptor Pathways and Neurotransmission

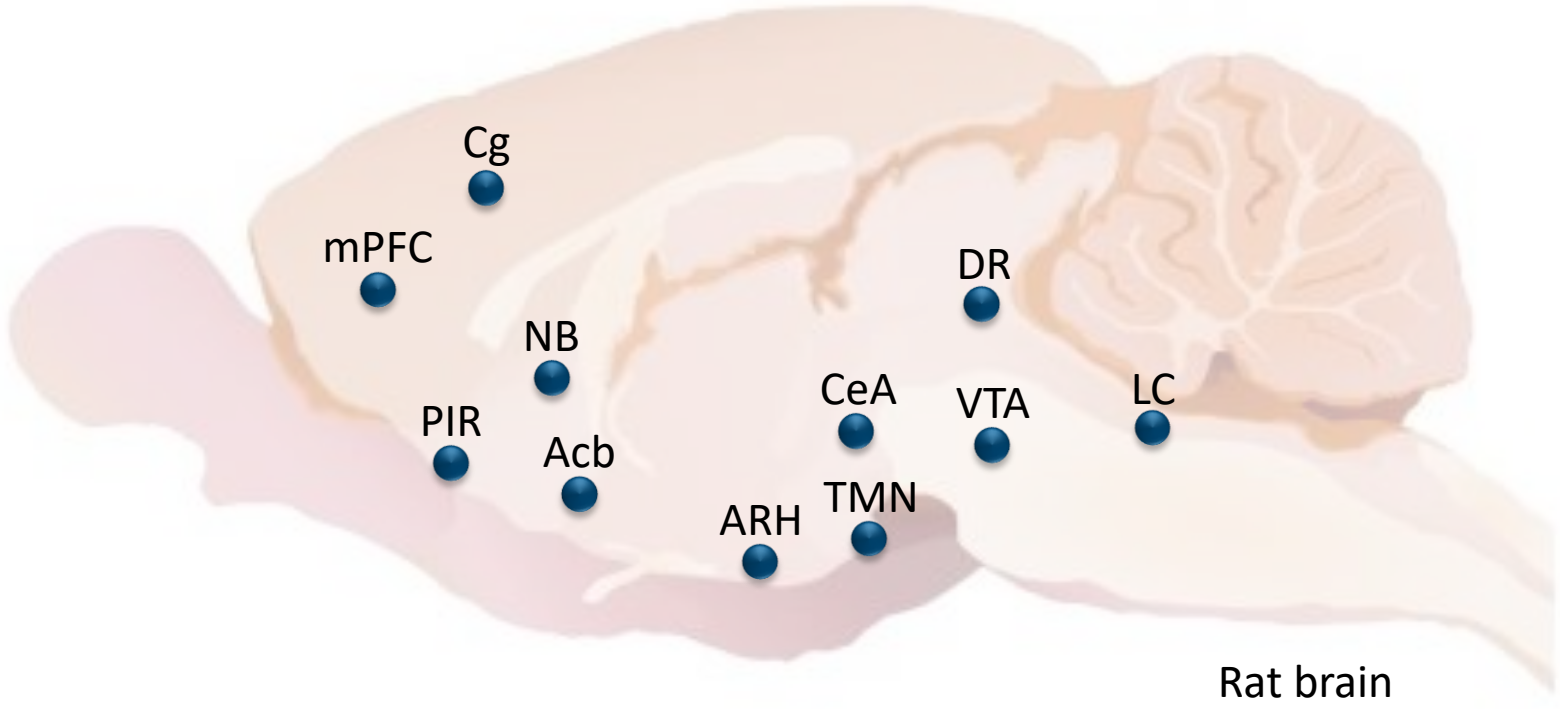
- Orexin neurons project from the hypothalamus into multiple brain regions and modulate an array of downstream neurotransmitters
- These neurons exert central control of **wakefulness**
- Pathways modulated by orexin may also be involved in control of **mood**
- Pathways modulated by orexin may also be involved in control of **attention**



AM: amygdala; BF: basal forebrain; Cg: cingulate cortex; DR: dorsal raphe; HIP: hippocampus; HYP: hypothalamus; NA: nucleus accumbens; PFC: prefrontal cortex; SN: substantia nigra; TH: thalamus; TMN: tuberomammillary nucleus; VTA: ventral tegmental area.

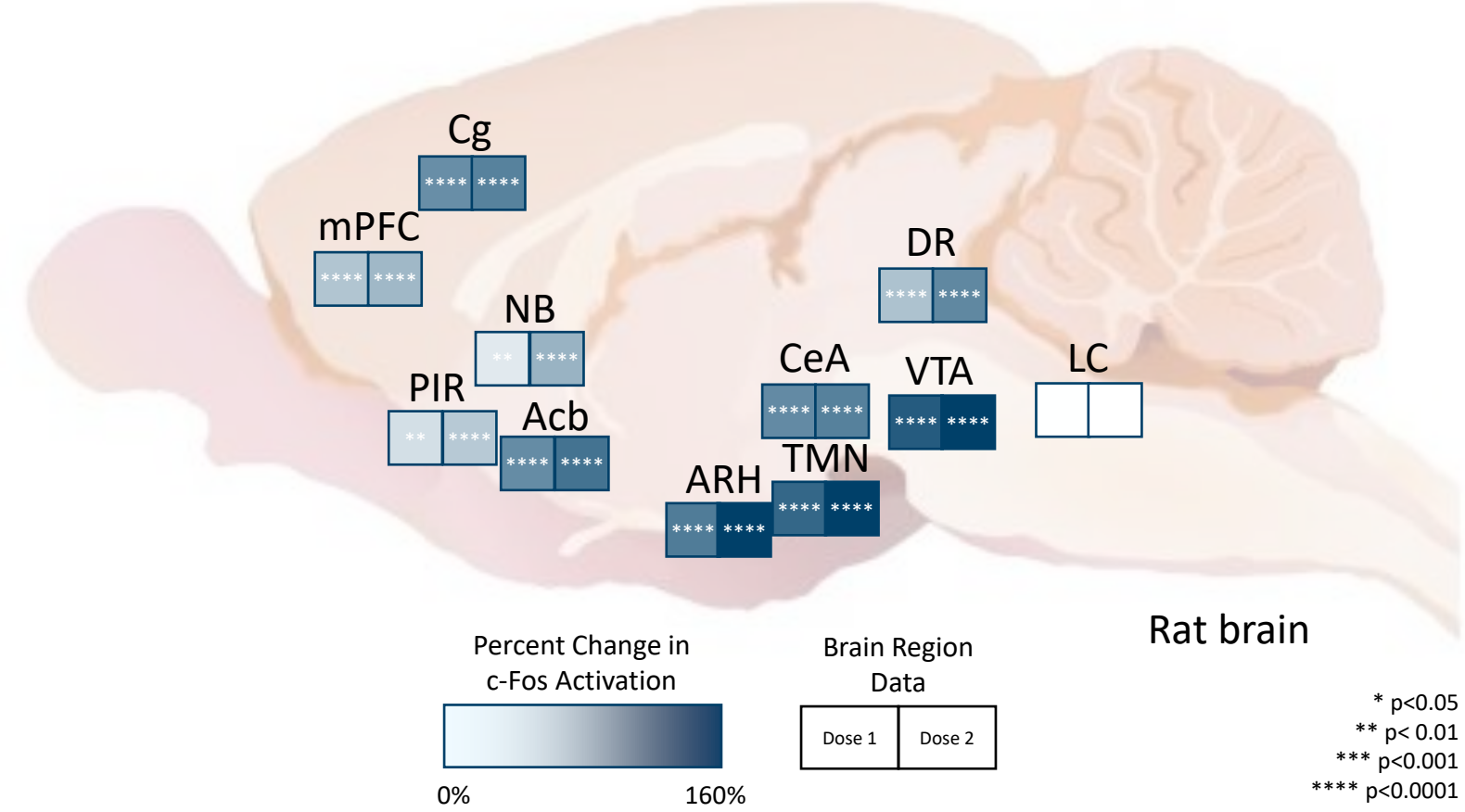
Marcus, et al. *J. Comp. Neurology* 2001.
Alexandre, et al. *Curr. Op. Neurobiology* 2013.
Sarter, et al. *Brain Res. Rev.* 2006.
Katzman & Katzman, *Brain Sci.* 2022.

Basic Anatomy and Neurocircuitry in Preclinical Models Similar to Humans



mPFC: medial prefrontal cortex; Cg: cingulate gyrus; Acb: nucleus accumbens; NB: nucleus basalis of Meynert; ARH: arcuate nucleus of the hypothalamus; CeA: central nucleus of the amygdala; PIR: piriform cortex; TMN: tuberomammillary nucleus; VTA: ventral tegmental area; DR: dorsal raphe; LC: locus coeruleus

Alkermes OX2R Molecules Dose-Dependently Engaged Circuits Associated With Wakefulness, Fatigue, Mood & Cognition/Attention



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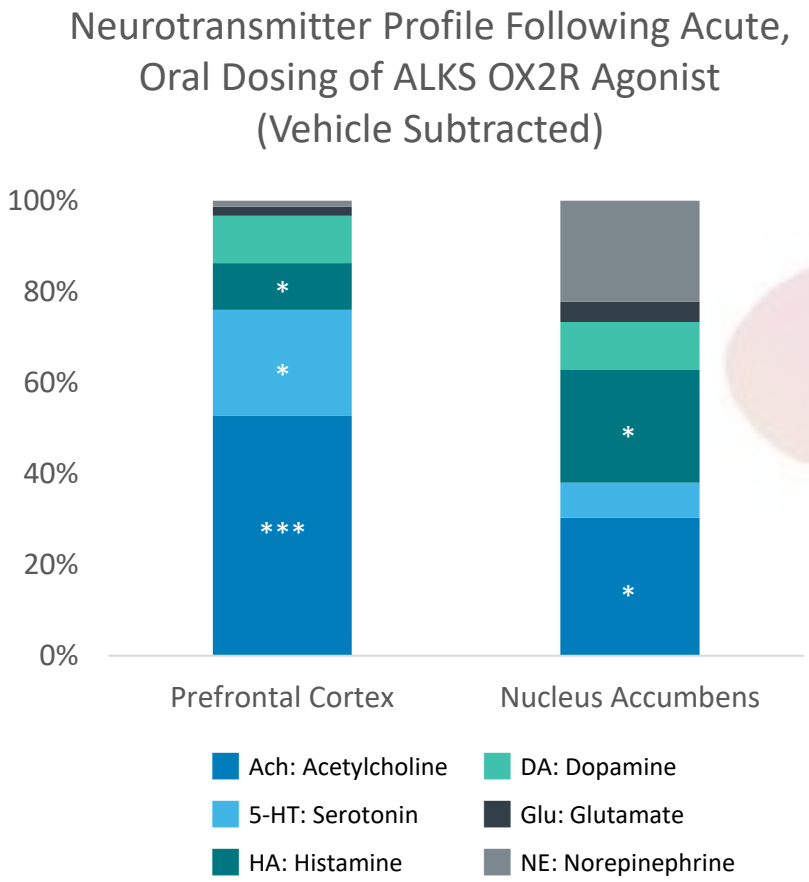
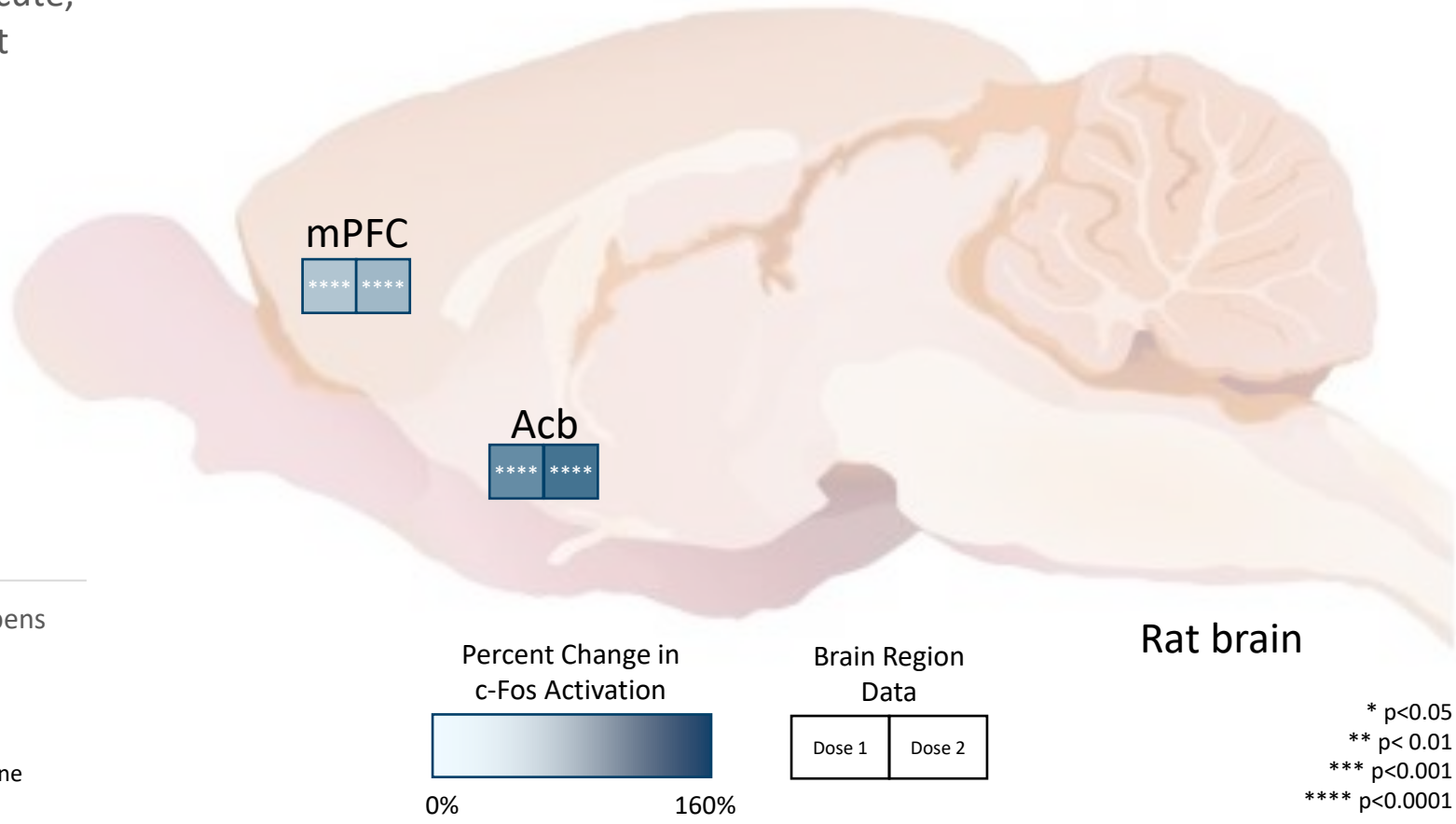
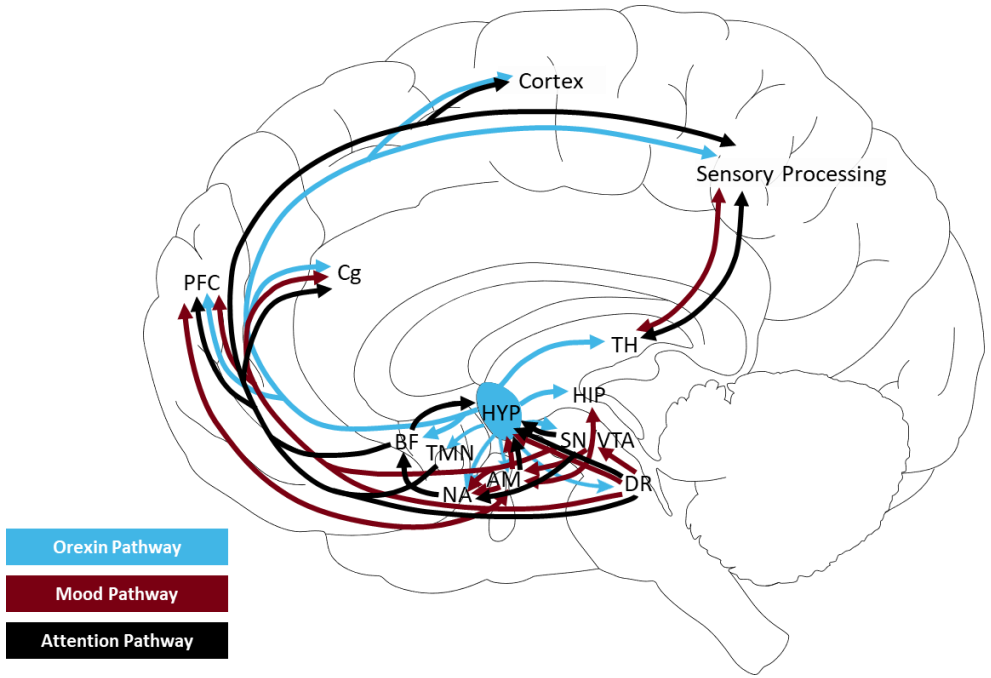
Neurocircuitry Activated by Alkermes OX2R Agonist Increased Key Neurotransmitters





mPFC: medial prefrontal cortex; Acb: nucleus accumbens; 100% defined as total area under the curve for all neurotransmitters measured within experiment

Orexin 2 Receptor Agonist Pathway May Have Potential Applicability in Broad Range of Indications



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Select disease states which intersect across aspects of wakefulness, fatigue, mood and cognition

Neurology

- Attention-deficit/hyperactivity disorder
- Multiple sclerosis fatigue
- Parkinson's disease

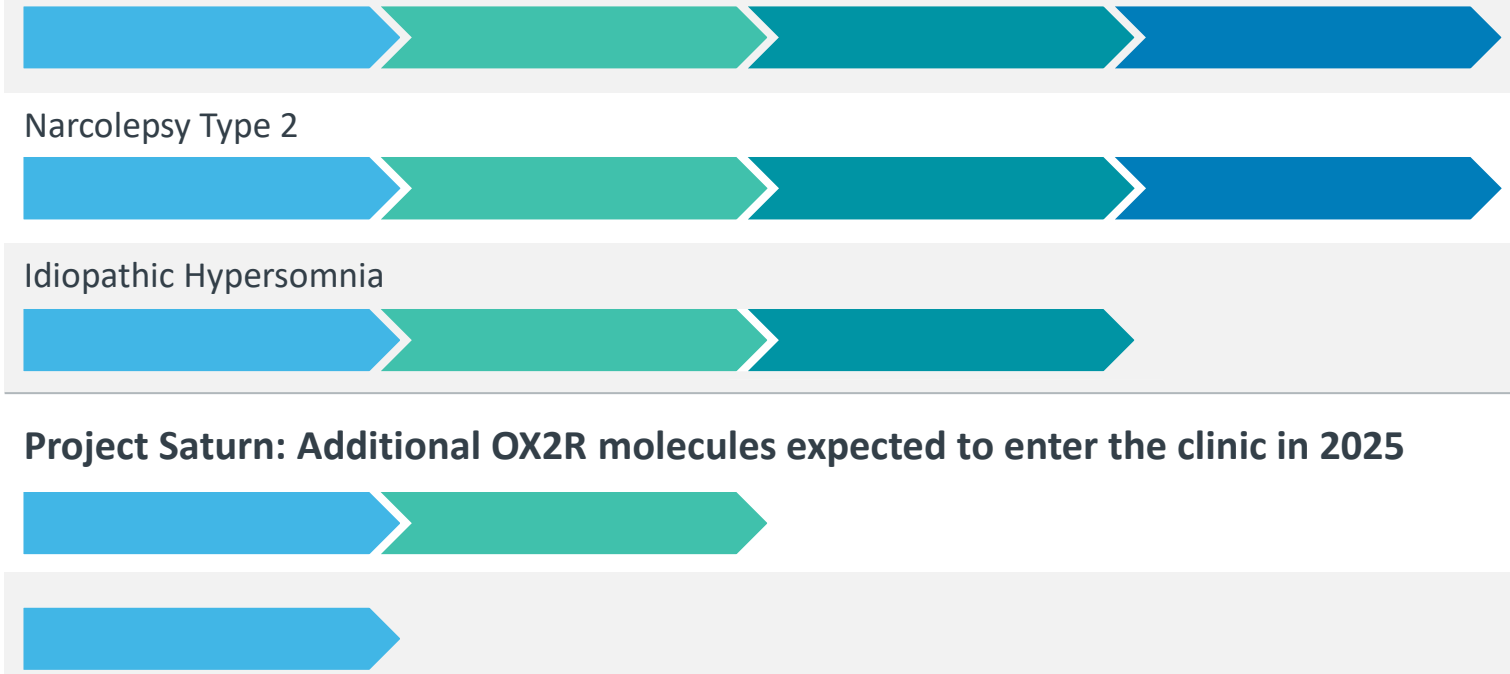
Psychiatry

- Bipolar disorder
- Cognitive impairment in schizophrenia
- Negative symptoms of schizophrenia
- Major depressive disorder
- Seasonal affective disorder

Orphan/ultra-orphan disorders

Advancing Multiple Orexin Development Candidates With Unique Opportunities for Treatment of Neurology & Psychiatry Disorders

Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Next Planned Milestone
ALKS 2680					
Narcolepsy Type 1					Phase 2 data H2 2025
Narcolepsy Type 2					Phase 2 data H2 2025
Idiopathic Hypersomnia					Phase 2 initiation 2025
Project Saturn: Additional OX2R molecules expected to enter the clinic in 2025					
					Phase 1 initiation Mid-2025
					Phase 1 initiation H2 2025



OX2R: Orexin 2 receptor agonist

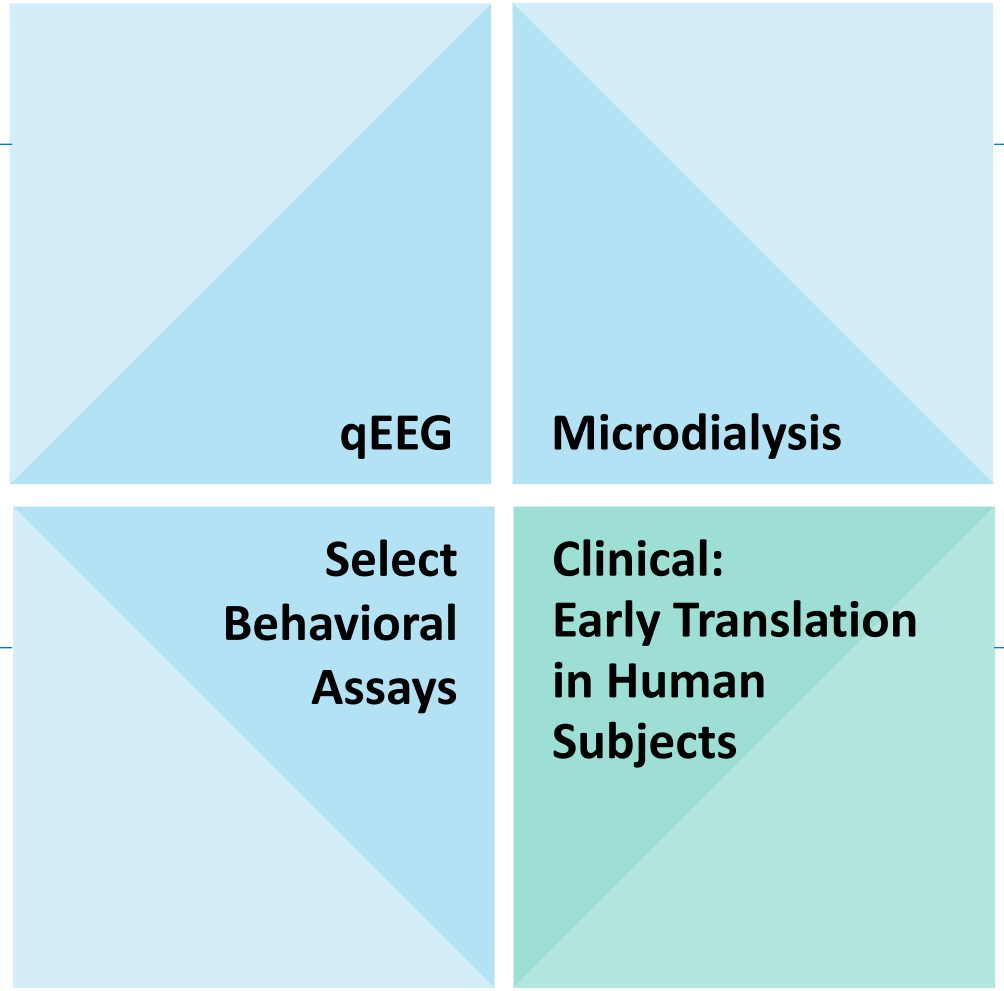
Executing a Rigorous Development Plan to Evaluate Potential Opportunities

Assessment of Brain Wave Activity

- Translational measure of pharmacological engagement
- Gold standard for assessing sleep-wake activity

Measure of Neurotransmitters

- Quantitative measure of pharmacological additivity, synergy or interference



Preclinical Assessment of Effect

- Disease-relevant preclinical models designed to demonstrate pharmacological benefits on specific symptom domains

Clinical Assessment of Effect

- Early clinical demonstration of differentiated profile

Utilizing Multidimensional, Translational Preclinical Research to Identify New Clinical Opportunities for Orexin 2 Receptor Agonists

Julie Brooks, Ph.D.
Director, CNS Disorders

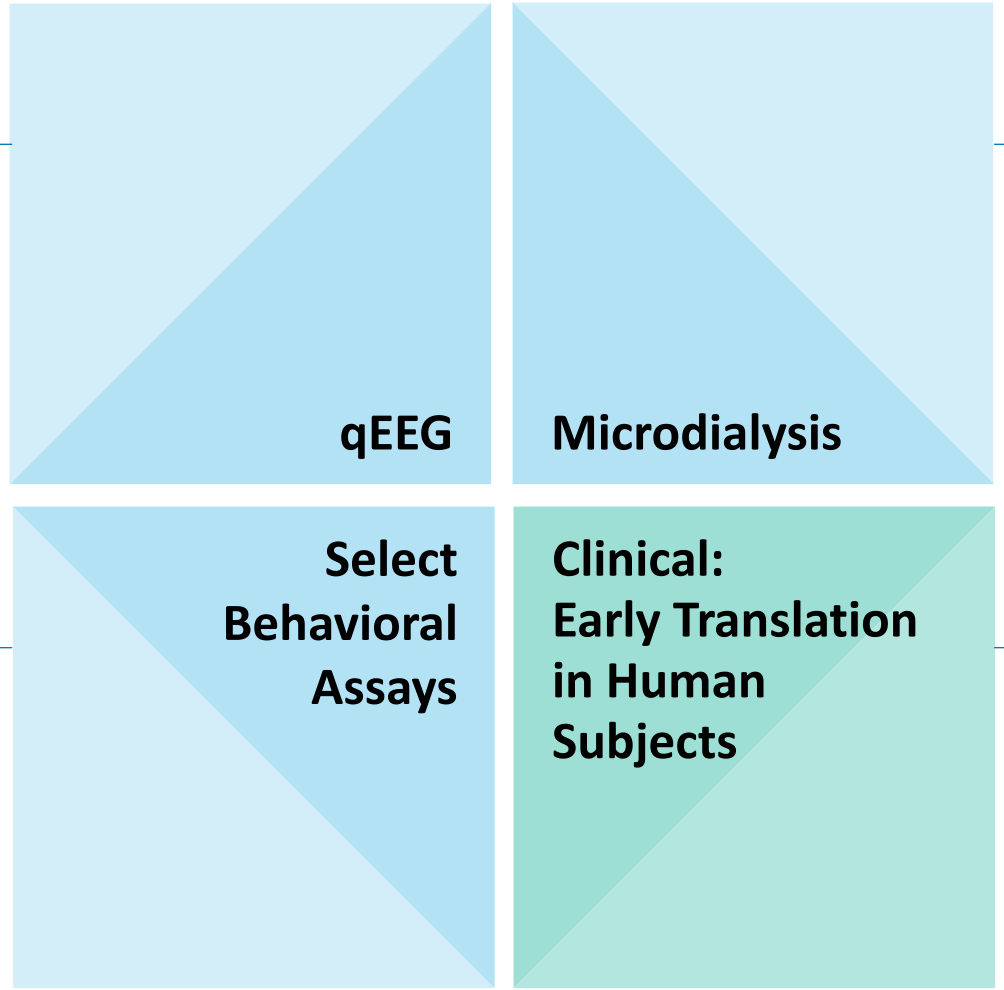
Executing a Rigorous Development Plan to Evaluate Potential Opportunities

Assessment of Brain Wave Activity

- Translational measure of pharmacological engagement
- Gold standard for assessing sleep-wake activity

Measure of Neurotransmitters

- Quantitative measure of pharmacological additivity, synergy or interference



Preclinical Assessment of Effect

- Disease-relevant preclinical models designed to demonstrate pharmacological benefits on specific symptom domains

Clinical Assessment of Effect

- Early clinical demonstration of differentiated profile

Preclinical Pharmacology Strategy in Mood and Stress Disorders

Microdialysis

Measures of Cortical Serotonin

- Measurement of prefrontal cortical serotonin neurotransmission to assess impact of pharmacological interventions
- Deficits in prefrontal cortical serotonin neurotransmission contribute to symptoms of depression

Select Behavioral Assays

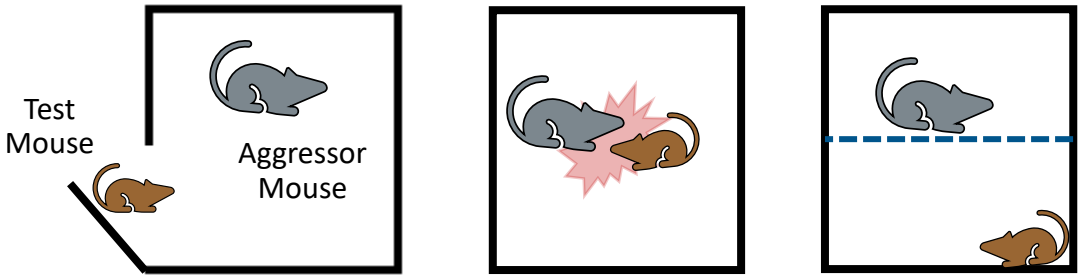
Effects in Chronic Social Defeat Model

- Gold standard rodent model of stress-induced mood disorders
- Translational behavioral assay with strong predictive validity

Chronic Social Defeat Model Induces Robust Depressive-like Phenotype

Chronic Social Defeat Stress
(repeated across 10 days)

Consistently induces enduring physiological and behavioral phenotypes similar to depression



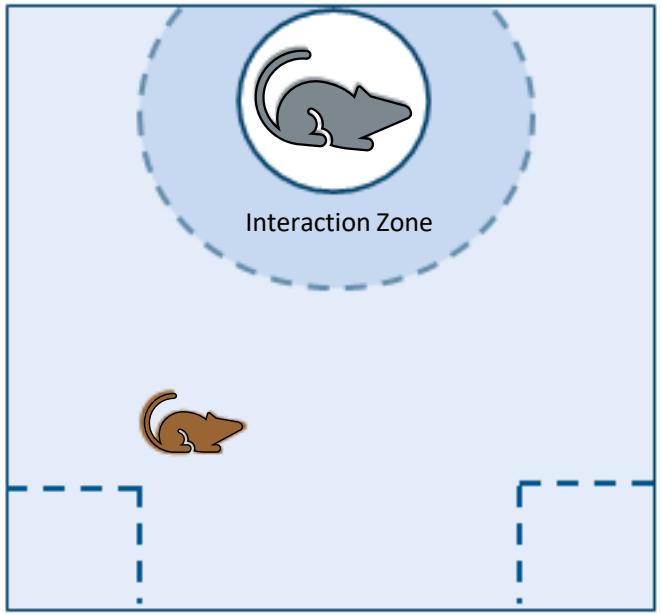
Phase 0:
Test mouse placed in aggressor cage

Phase 1:
Physical Stress (10 minutes)

Phase 2:
Sensory Stress (24 hours)

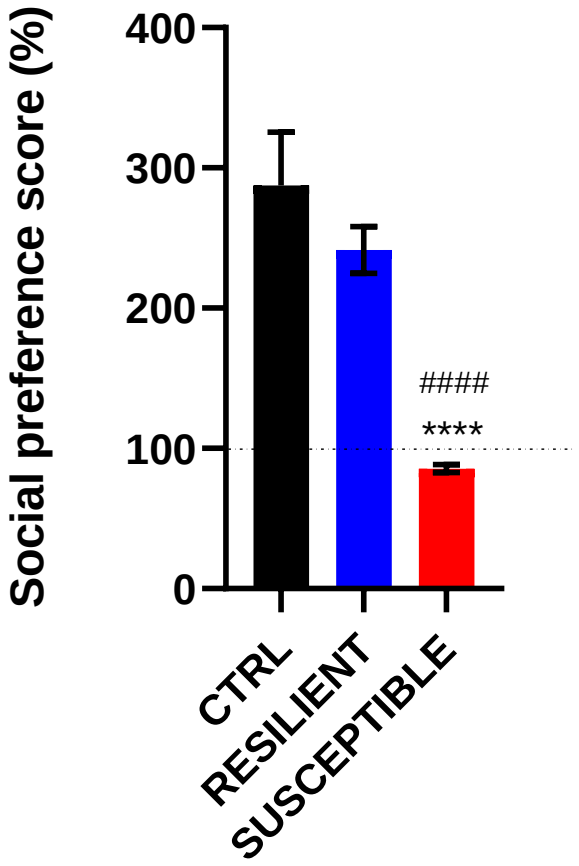
Social Preference (SP) Test

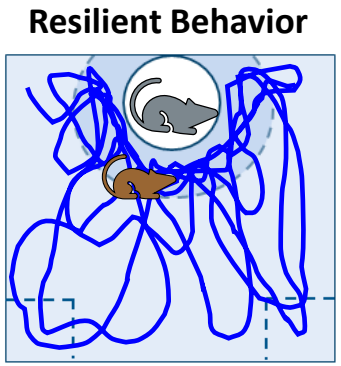
Reliably measures social interaction by calculating time in interaction zone with and without an aggressor mouse present

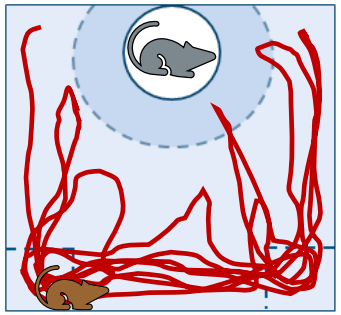


Kim H-D. Testing Depression in Mice: a Chronic Social Defeat Stress Model. *Bio Protoc.* 2017;7(7).

Chronic Social Defeat Model Approximates Individual Variability in Stress Response Observed in Humans







Exposure to chronic social defeat leads to two types of behavioral responses in the social preference test:

Resilient mice maintain social interaction and do not demonstrate a depressive-like phenotype

Susceptible mice develop social avoidance mimicking a depressive-like phenotype; only susceptible mice were used for additional testing

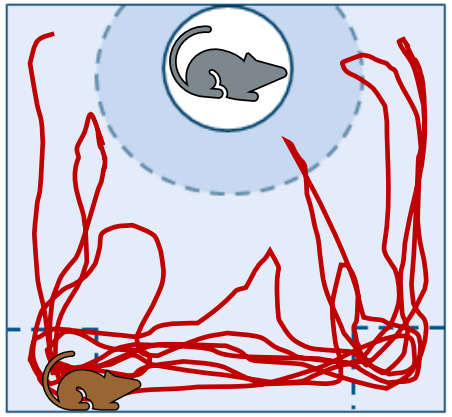
Mean ± SEM ****p<0.0001 vs control (CTRL), ####p<0.0001 vs resilient; Social preference score below 100% associated with susceptible behavior.

Susceptible Mice Received Therapeutic Intervention and Were Assessed for Restoration of Resilient Behavior

Chronic Social Defeat Stress (10 days)	Baseline SP Test	Treatment Period (14 days)	Post Dosing SP Test

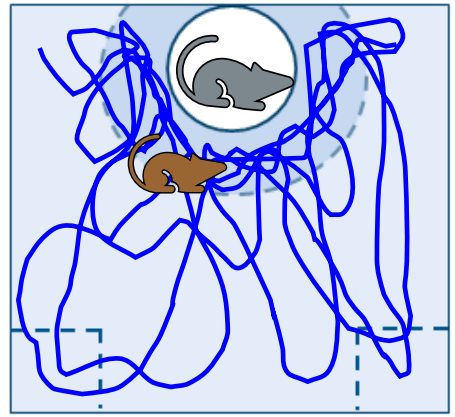
- Ketamine: single dose on day 1
- Fluoxetine: daily dosing for 14 days
- ALKS orexin 2 receptor agonist: daily dosing for 14 days

Susceptible Behavior



Treatment

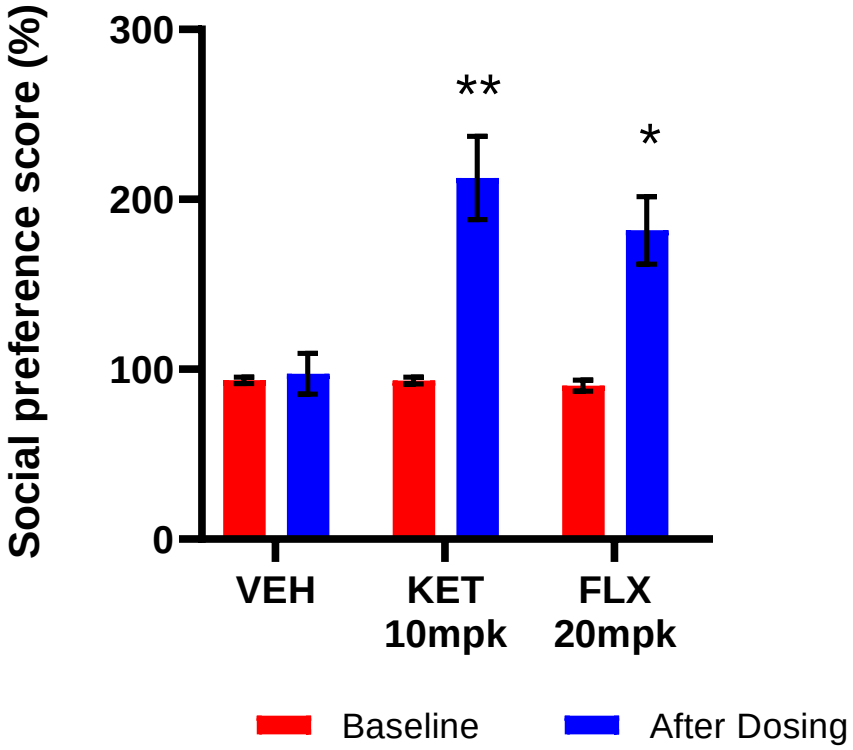
Resilient Behavior



SP: Social preference

Clinically Efficacious Antidepressants Demonstrated Effect in Susceptible Mice

Social Preference Performance in Susceptible Mice



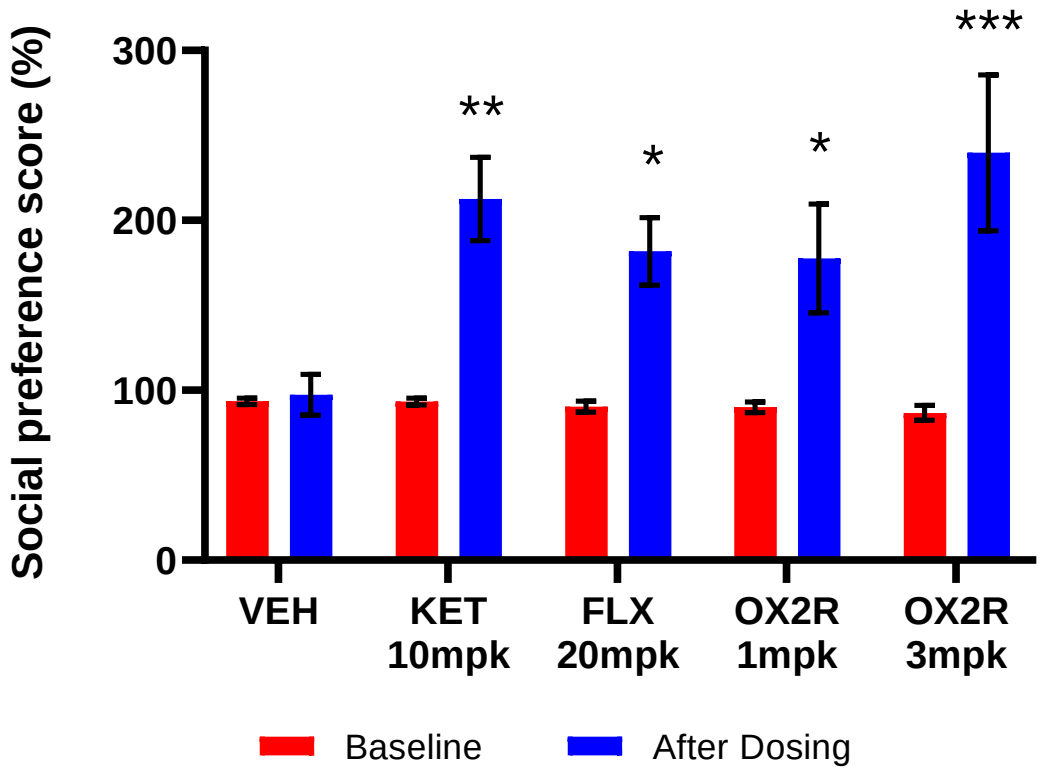
Social Preference Assay demonstrated sensitivity to FDA-approved agents with different mechanisms:

- Fluoxetine: FDA-approved standard SSRI with delayed onset of therapeutic effect
- Ketamine: FDA-approved non-SSRI with rapid onset of therapeutic effect

Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 after treatment vs baseline
VEH: vehicle; KET: Ketamine; FLX: Fluoxetine; SSRI: Selective serotonin reuptake inhibitor

Orexin 2 Receptor Agonist Exhibited Antidepressant-like Effects in Chronic Social Defeat Model

Social Preference Performance in Susceptible Mice



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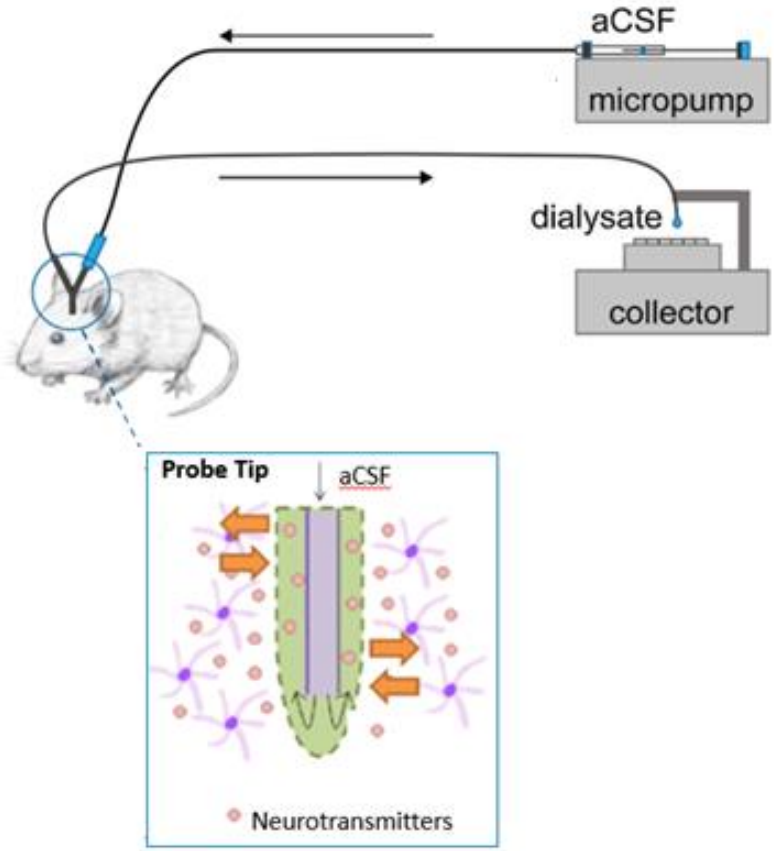
- Fluoxetine: FDA-approved standard SSRI with delayed onset of therapeutic effect
- Ketamine: FDA-approved non-SSRI with rapid onset of therapeutic effect

Alkermes potent orexin 2 receptor agonist demonstrated an antidepressant-like effect similar to fluoxetine and ketamine

Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 after treatment vs baseline
VEH: vehicle; KET: Ketamine; FLX: Fluoxetine; OX2R: Alkermes Orexin 2 receptor agonist; SSRI: Selective serotonin reuptake inhibitor

Microdialysis Enables Quantitative Measurement of Prefrontal Cortical Serotonin

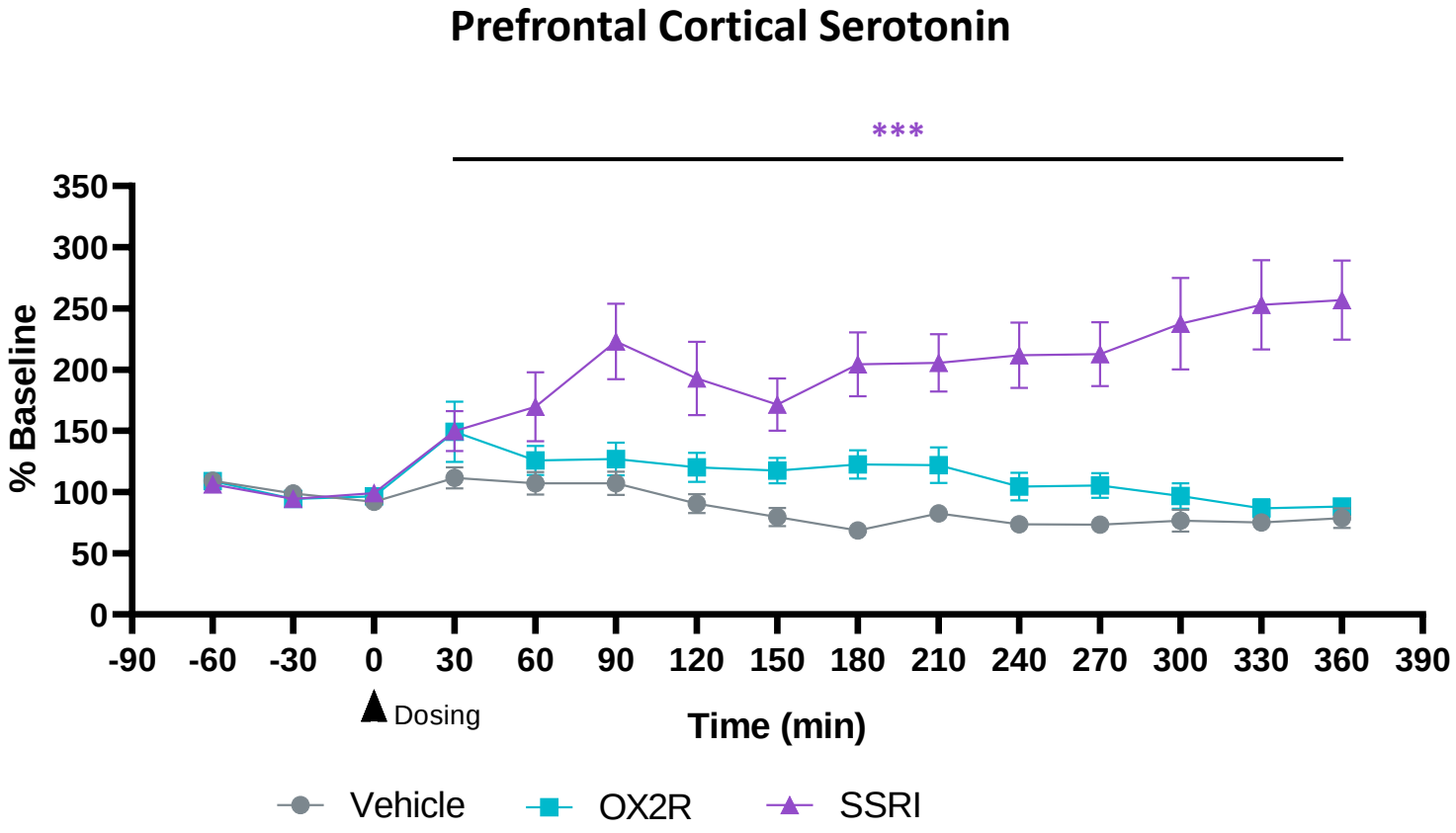
Illustration of Cortical Microdialysis



- Deficits in serotonin neurotransmission contribute to symptoms of depression
- Many treatments for mood disorders restore serotonin neurotransmission
- Symptom domains of interest converge on the prefrontal cortex

Figure adapted from Konig et al., 2018 *JoN Methods* and Sanchez-Dengra et al., 2021 *Animals.* aCSF: artificial cerebral spinal fluid

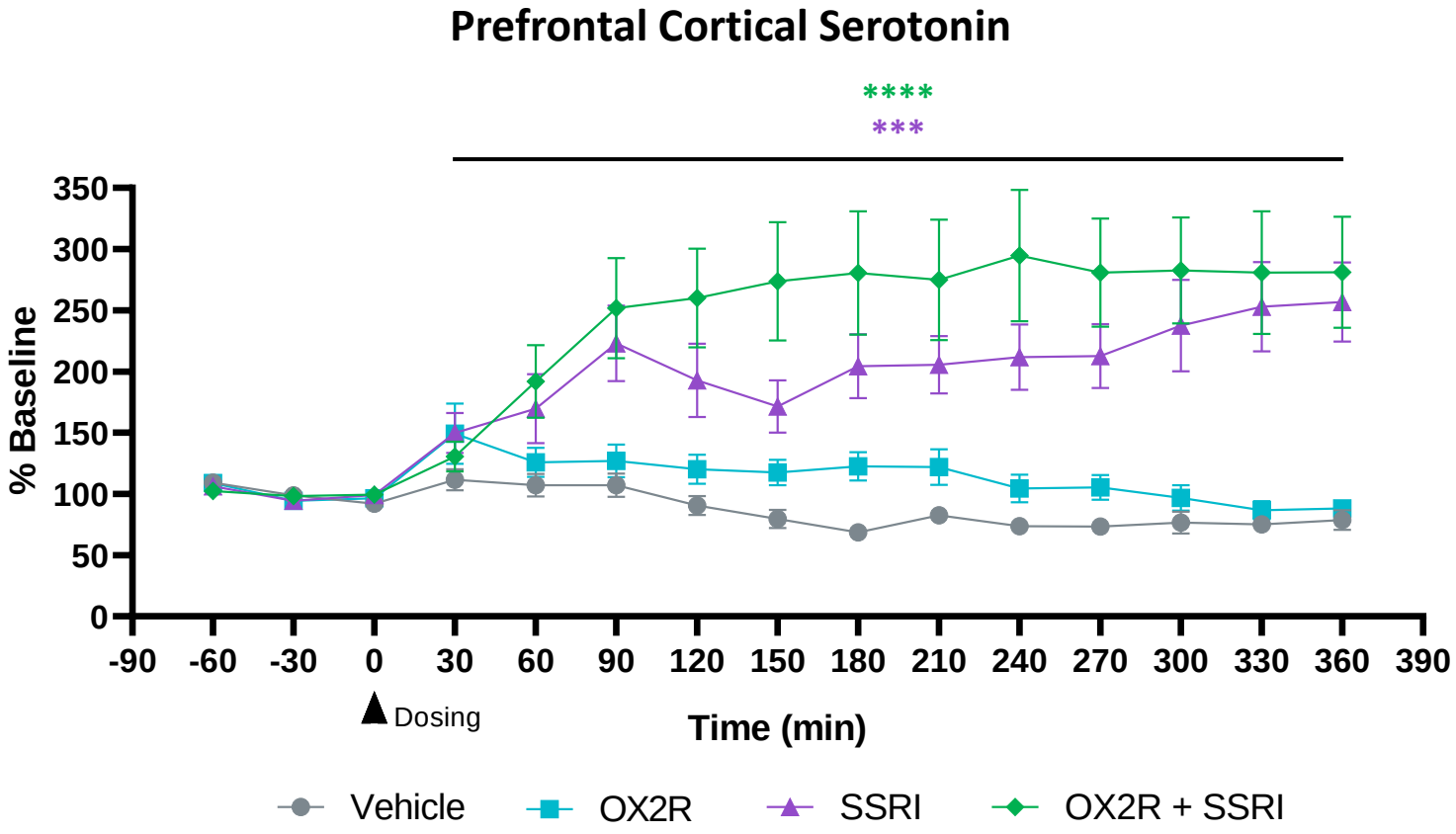
SSRI Significantly Elevated Prefrontal Cortical Serotonin



- Acute administration of SSRI significantly elevated prefrontal cortical serotonin

Mean ± SEM, n=9-10/group. ***p< 0.001
OX2R: Alkermes Orexin 2 receptor agonist; SSRI: Selective serotonin reuptake inhibitor

Orexin 2 Receptor Agonist Enhanced SSRI-induced Increase in Prefrontal Cortical Serotonin



- Acute administration of SSRI significantly elevated prefrontal cortical serotonin
- **Co-administration of Alkermes orexin 2 receptor agonist further enhanced the SSRI-induced increase in prefrontal cortical serotonin**

Mean ± SEM, n=9-10/group. ***p< 0.001, ****p<0.0001 vs vehicle
OX2R: Alkermes Orexin 2 receptor agonist; SSRI: Selective serotonin reuptake inhibitor

Mood and Stress Data Summary

Preclinical models with strong predictive validity provide translational value and enable decision making

Monotherapy:

- Chronic Social Defeat Model data suggested antidepressant-like effects of orexin 2 receptor agonist

Polypharmacology:

- Early evidence that co-administration of orexin 2 receptor agonist activity enhanced SSRI-induced serotonin neurotransmission suggesting opportunity for additive benefit
- Therapeutic profile varies with choice of mechanistic partner

SSRI: Selective serotonin reuptake inhibitor

Preclinical Pharmacology Strategy in Attention and Impulsivity Disorders

Microdialysis

Measures of Cortical Acetylcholine

- Measurement of cortical acetylcholine neurotransmission to assess impact of pharmacological interventions
- Acetylcholine neurotransmission plays a key role in information processing, attention, and arousal

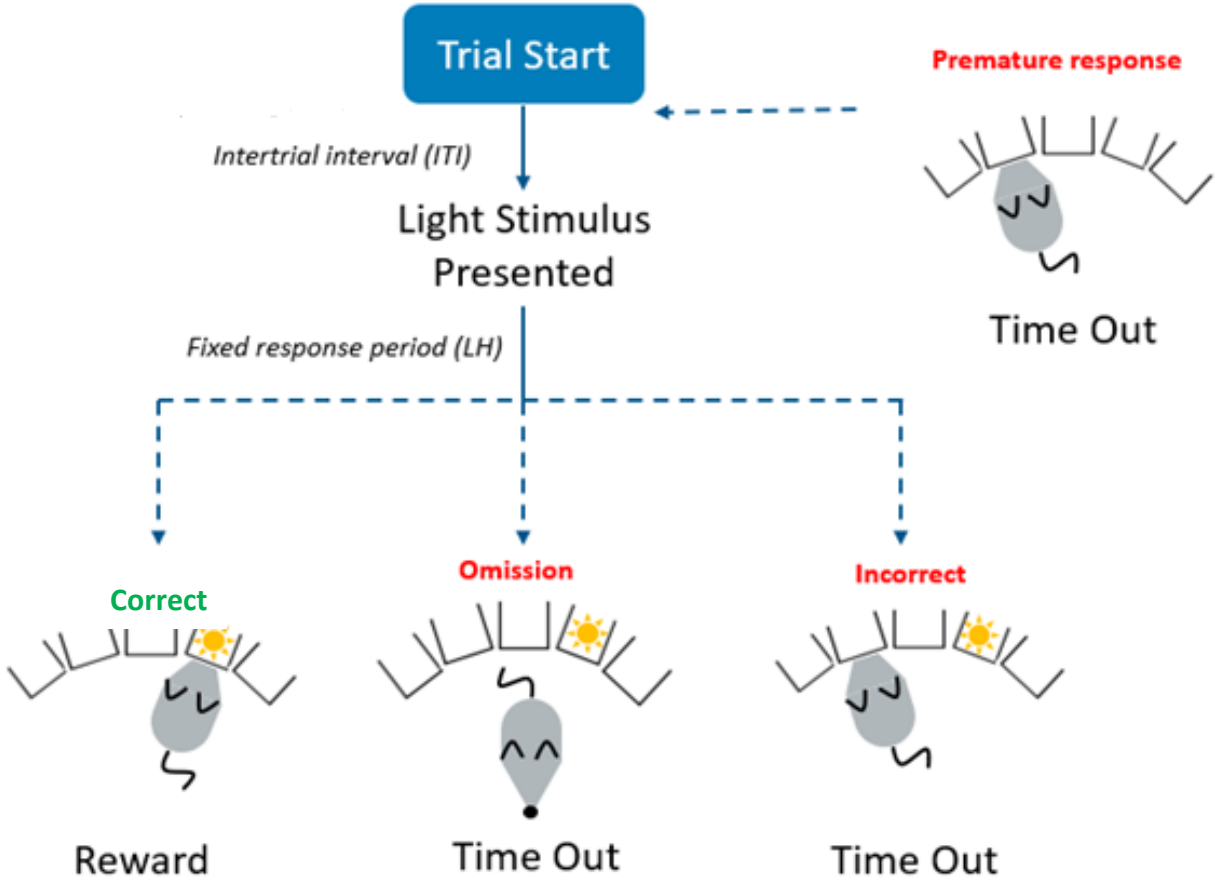
Select Behavioral Assays

Effects in 5-Choice Serial Reaction Time Task

- Gold standard task assessing attention and behavioral impulsivity
- Translational behavioral assay with high predictive validity

5-Choice Serial Reaction Time Task Measures Impulsivity and Attention in Translational Model

Task Trial Phases and Potential Outcomes



Measure of Impulse Control

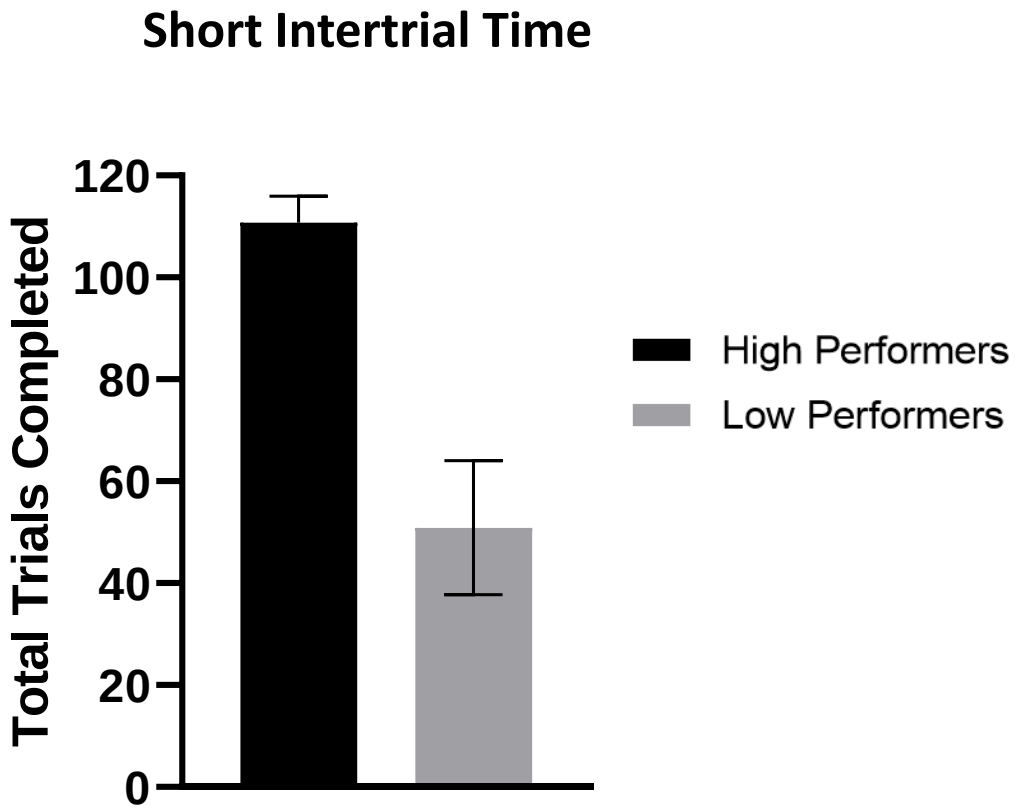
Premature nose-poke responses: Based on number of instances subject fails to withhold response until after light stimulus is presented

Measure of Attention and Task Engagement

Total trials: Based on number of trials completed (correct, incorrect or omitted) for the full duration of the experiment

Higgins GA and Silenieks LB. Rodent Test of Attention and Impulsivity: The 5-Choice Serial Reaction Time Task . *Curr Protoc Pharmacol.* 2017;78(5).

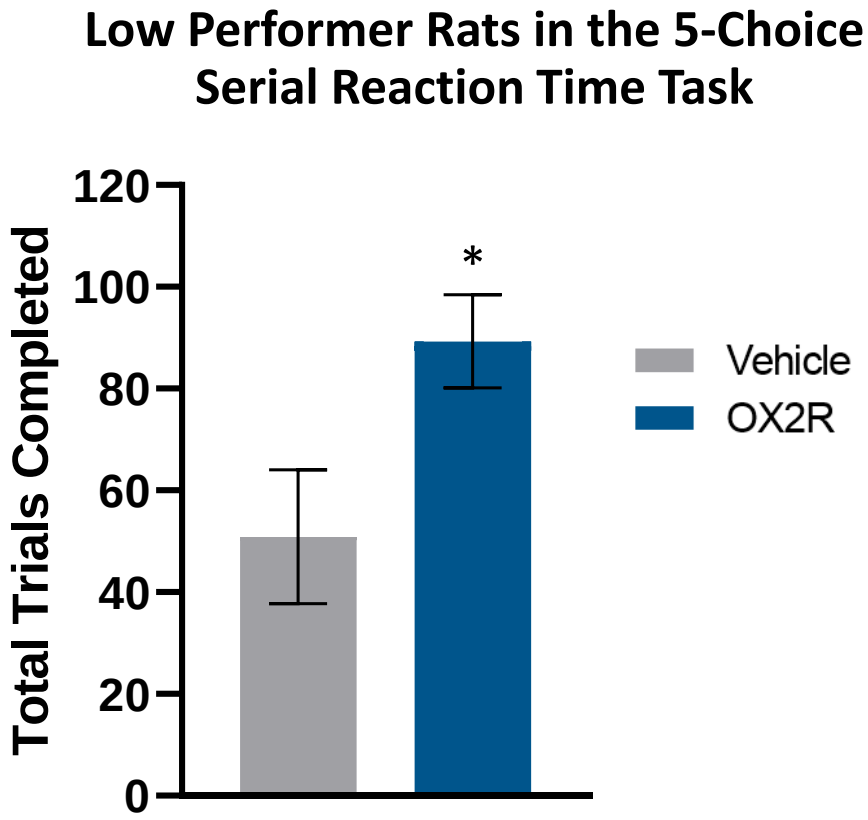
Shortened Intertrial Time Increases Task Cadence Leading to Impaired Attentional Task Performance in a Subgroup of Rats



- Shortening the 5-Choice Serial Reaction Time Task intertrial time **decreases** attentional performance and task engagement in a subgroup of rats (low performers)
- Out of 120 trials possible, low performer rats completed less than half of the total trials possible under the shortened intertrial time condition

Mean ± SEM; n=10/group

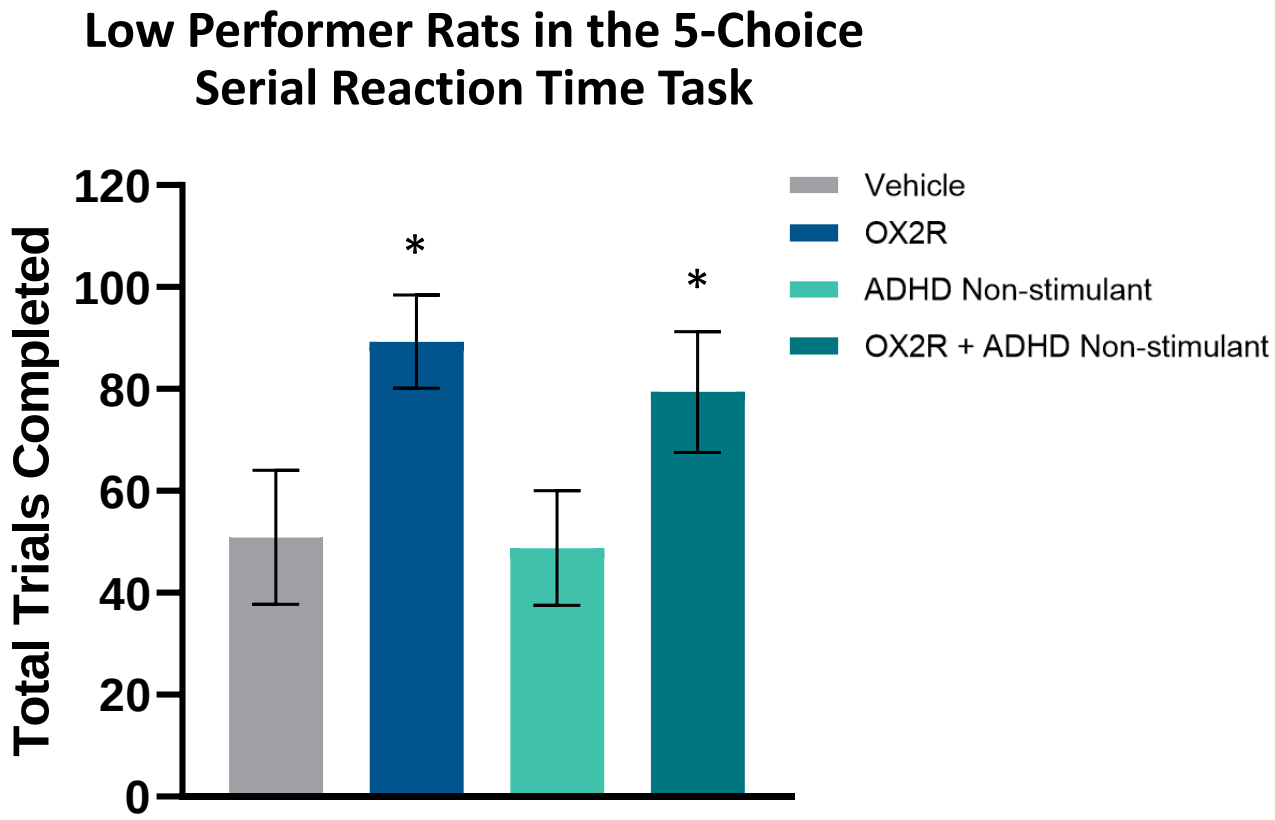
Orexin 2 Receptor Agonist Improved Task Engagement in Low Performer Rats



- Alkermes orexin 2 receptor agonist significantly increased the number of trials completed by low performer rats under the shortened intertrial time condition

Mean ± SEM, n=10 *p<0.05 vehicle vs treatment
OX2R: Alkermes Orexin 2 receptor agonist

Improved Task Performance Following Orexin 2 Receptor Activation was Maintained When Combined With Non-stimulant Treatment



- Alkermes orexin 2 receptor agonist significantly increased the number of trials completed by low performer rats under the shortened intertrial time condition
- ADHD non-stimulant did not improve total trials completed by low performer rats
- Effect of Alkermes orexin 2 receptor agonist was maintained when co-administered with ADHD non-stimulant treatment

Mean ± SEM, n=10 *p<0.05 vehicle vs treatment
OX2R: Alkermes Orexin 2 receptor agonist

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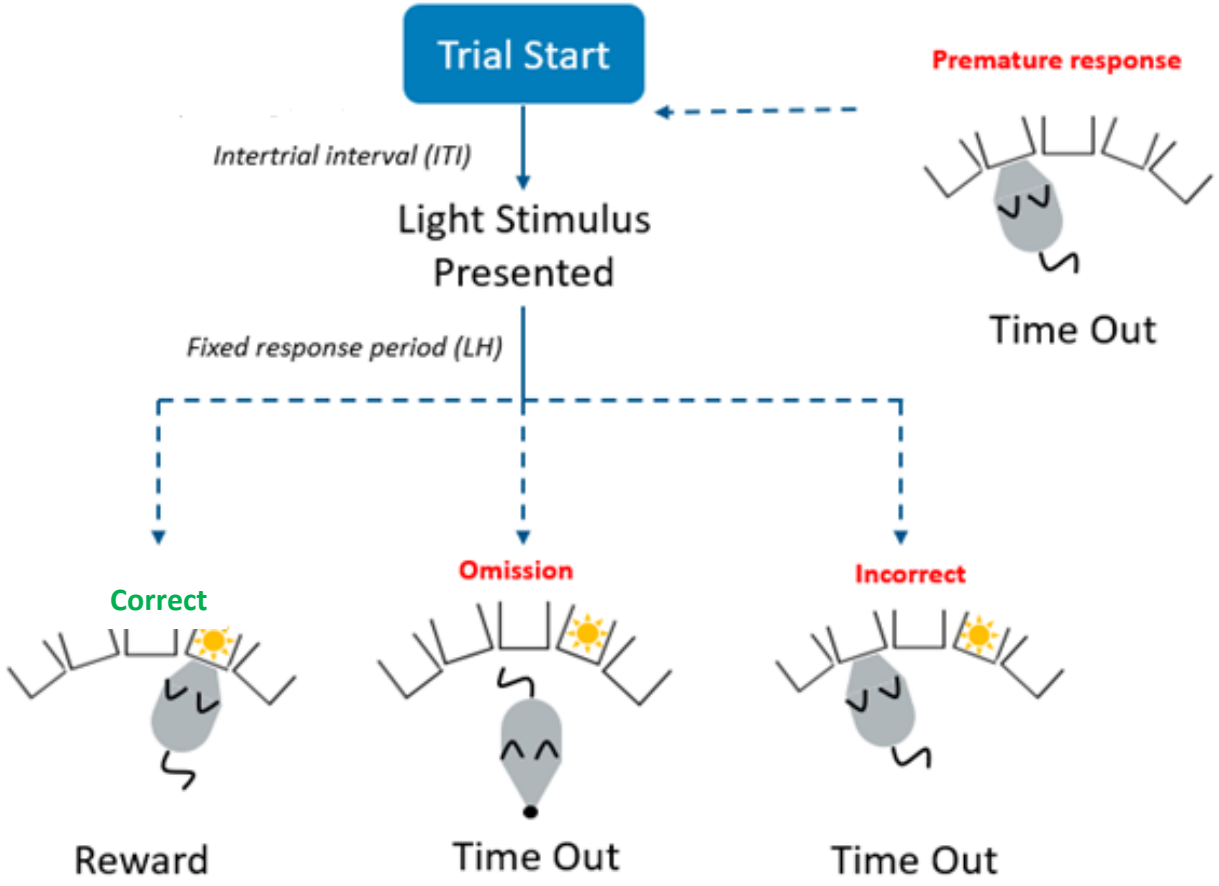

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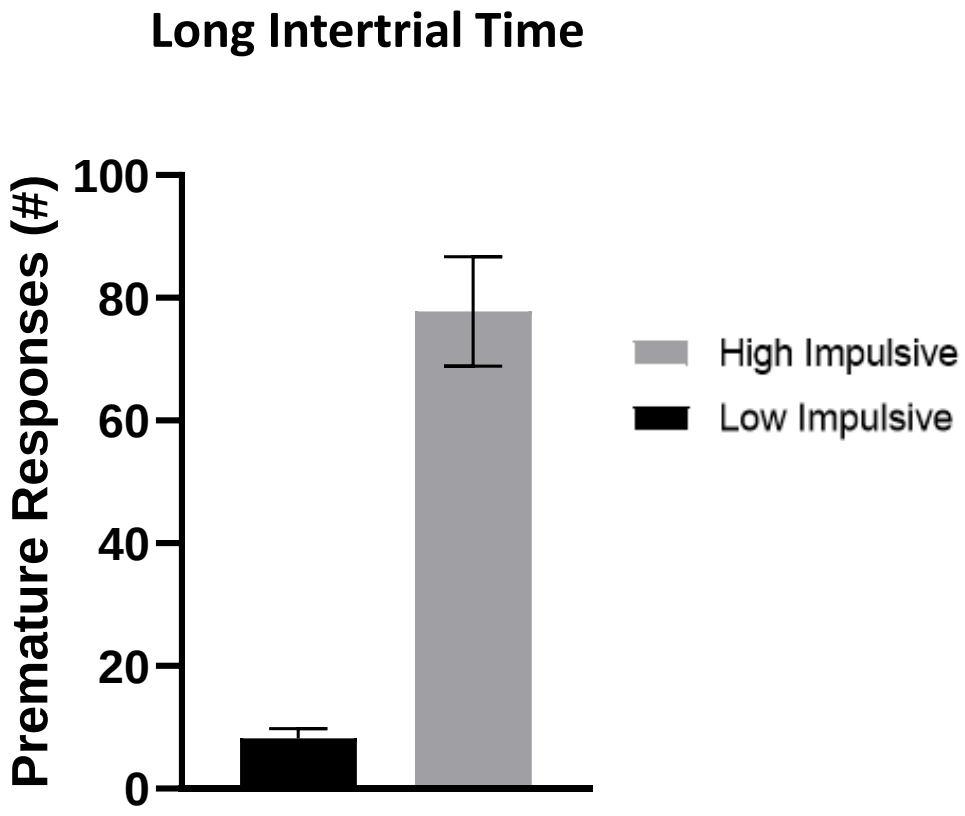
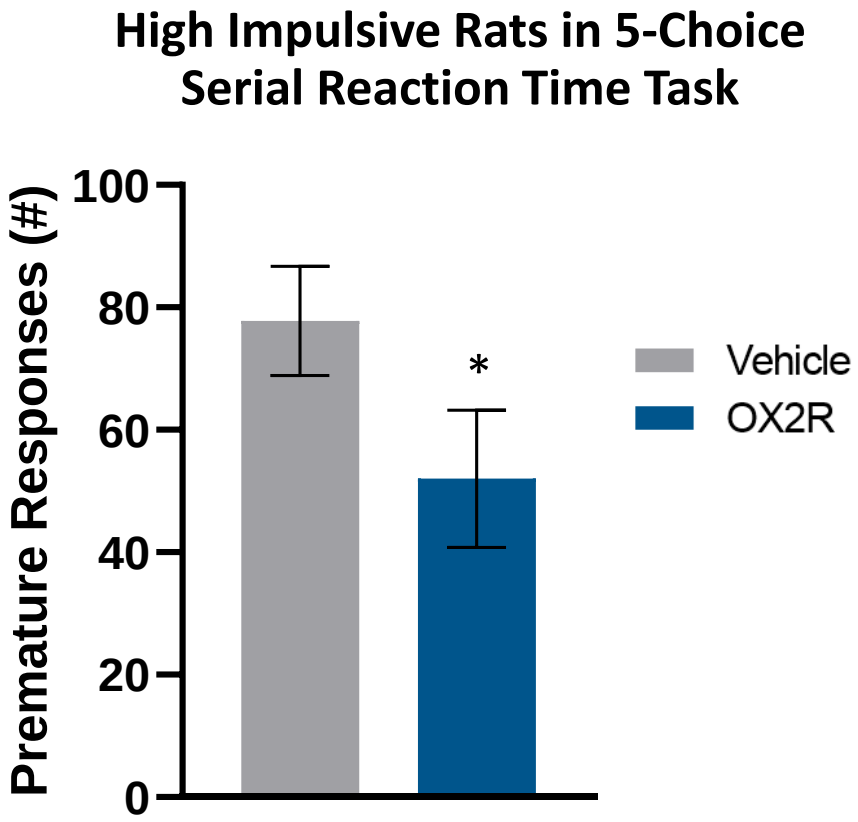
Long Intertrial Time Slows Task Cadence Leading to Increased Impulsivity in a Subgroup of Rats



- Extending the 5-Choice Serial Reaction Time Task intertrial time leads to an **increase** in impulsivity in a subset of rats (High Impulsive)
- High impulsive rats made an exceptionally high number of premature responses under the long intertrial time condition

Mean ± SEM; n=10/group

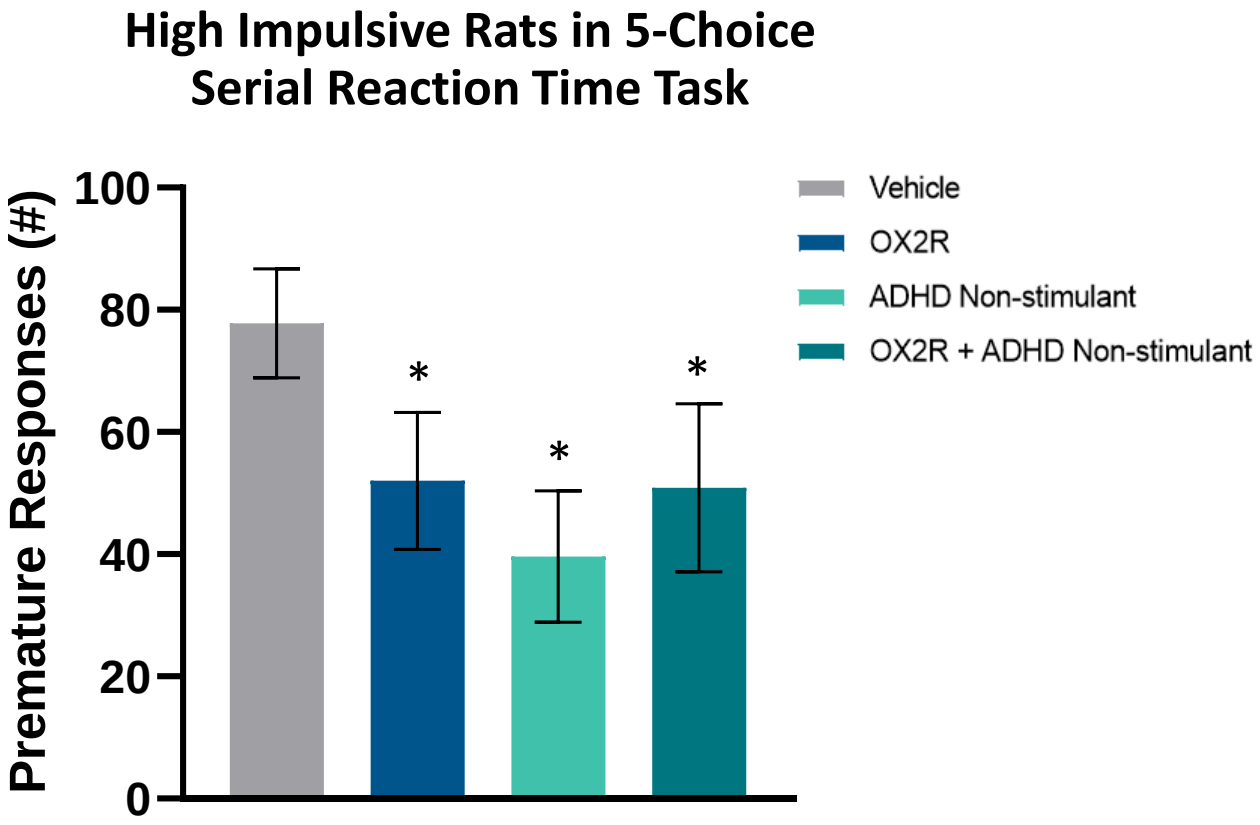
Orexin 2 Receptor Agonist Decreased Impulsivity in High Impulsive Rats



- Alkermes orexin 2 receptor agonist significantly lowered the number of impulsive premature responses made by high impulsive rats under the long intertrial time condition

Mean ± SEM, n=10 *p<0.05 vehicle vs treatment
OX2R: Alkermes Orexin 2 receptor agonist

Orexin 2 Receptor Agonist Maintained Impulse Control Efficacy of Non-stimulant Treatment in High Impulsive Rats

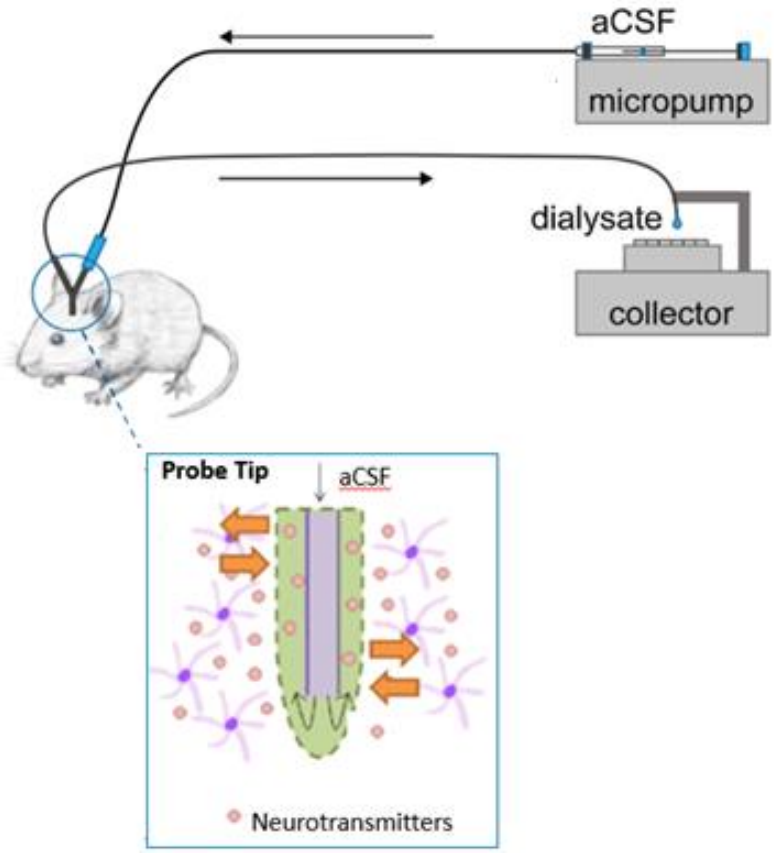


- ADHD non-stimulant treatment significantly lowered the number of impulsive premature responses made by high impulsive rats under the long intertrial time condition
- Co-administration of Alkermes orexin 2 receptor agonist did not interfere with the impulse control effects of ADHD non-stimulant treatment

Mean ± SEM, n=10 *p<0.05 vehicle vs treatment
OX2R: Alkermes Orexin 2 receptor agonist

Microdialysis Enables Quantitative Measurement of Prefrontal Cortical Acetylcholine

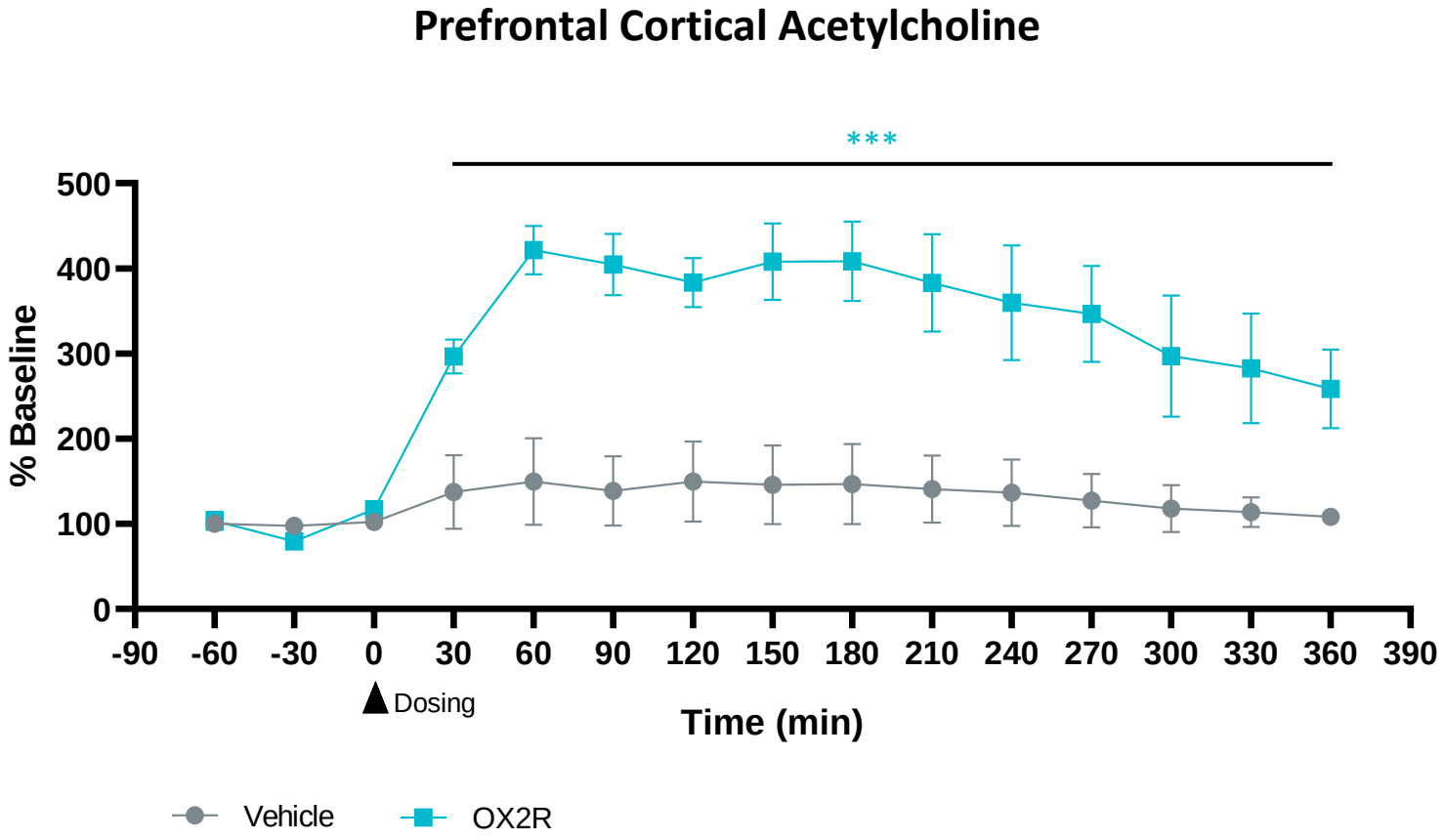
Illustration of Cortical Microdialysis



- Acetylcholine neurotransmission plays a key role in information processing, attention and arousal
- Enhancing acetylcholine neurotransmission contributes to effective attentional performance
- Symptom domains of interest converge on the prefrontal cortex

Figure adapted from Konig et al., 2018 *JoN Methods* and Sanchez-Dengra et al., 2021 *Animals* aCSF: artificial cerebral spinal fluid

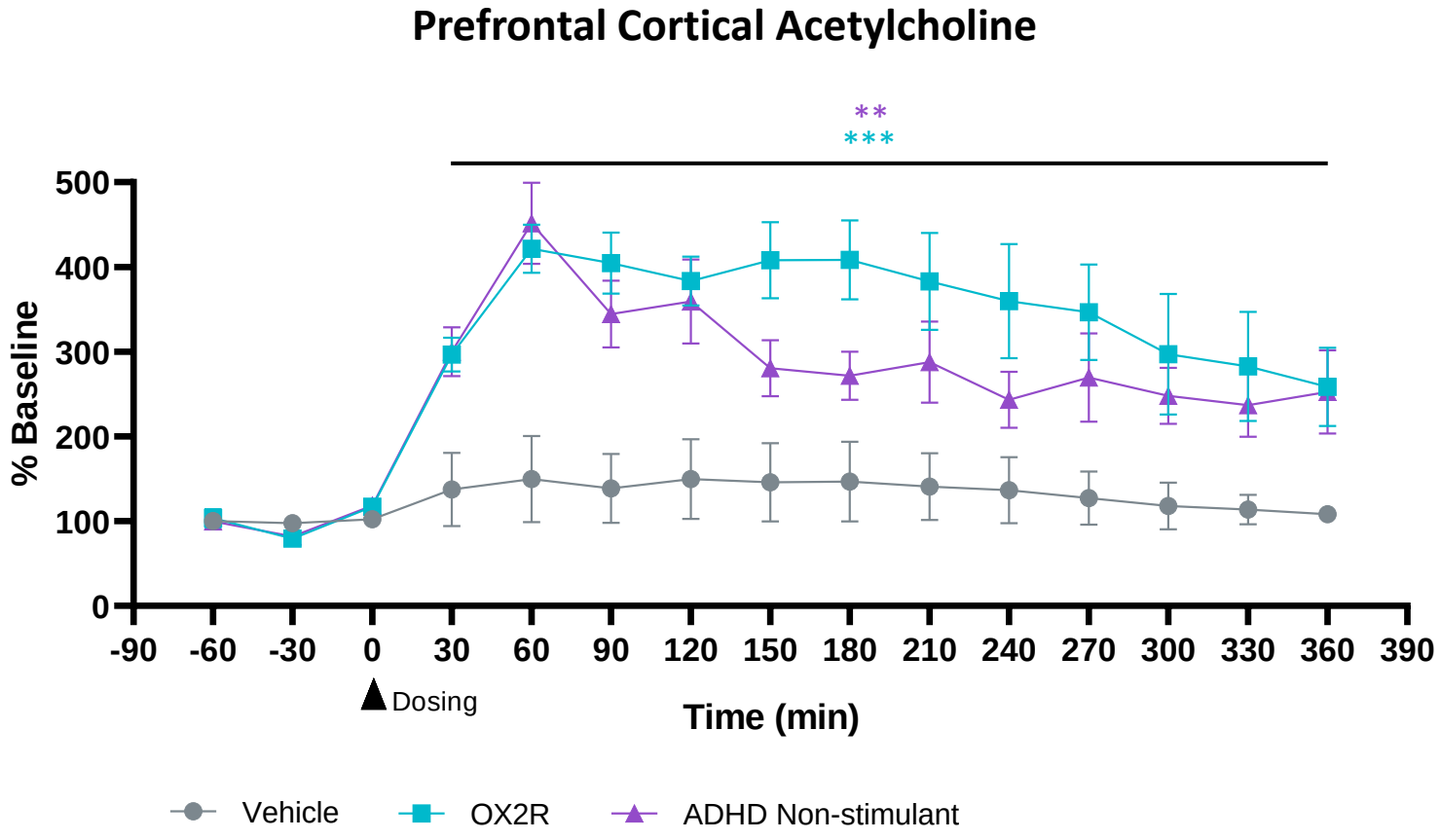
Orexin 2 Receptor Agonist Significantly Increased Prefrontal Cortical Acetylcholine Release



- Alkermes orexin 2 receptor agonist significantly increased prefrontal cortical acetylcholine

Mean ± SEM, n=9-10/group. ***p<0.001, OX2R vs vehicle
OX2R: Alkermes Orexin 2 receptor agonist

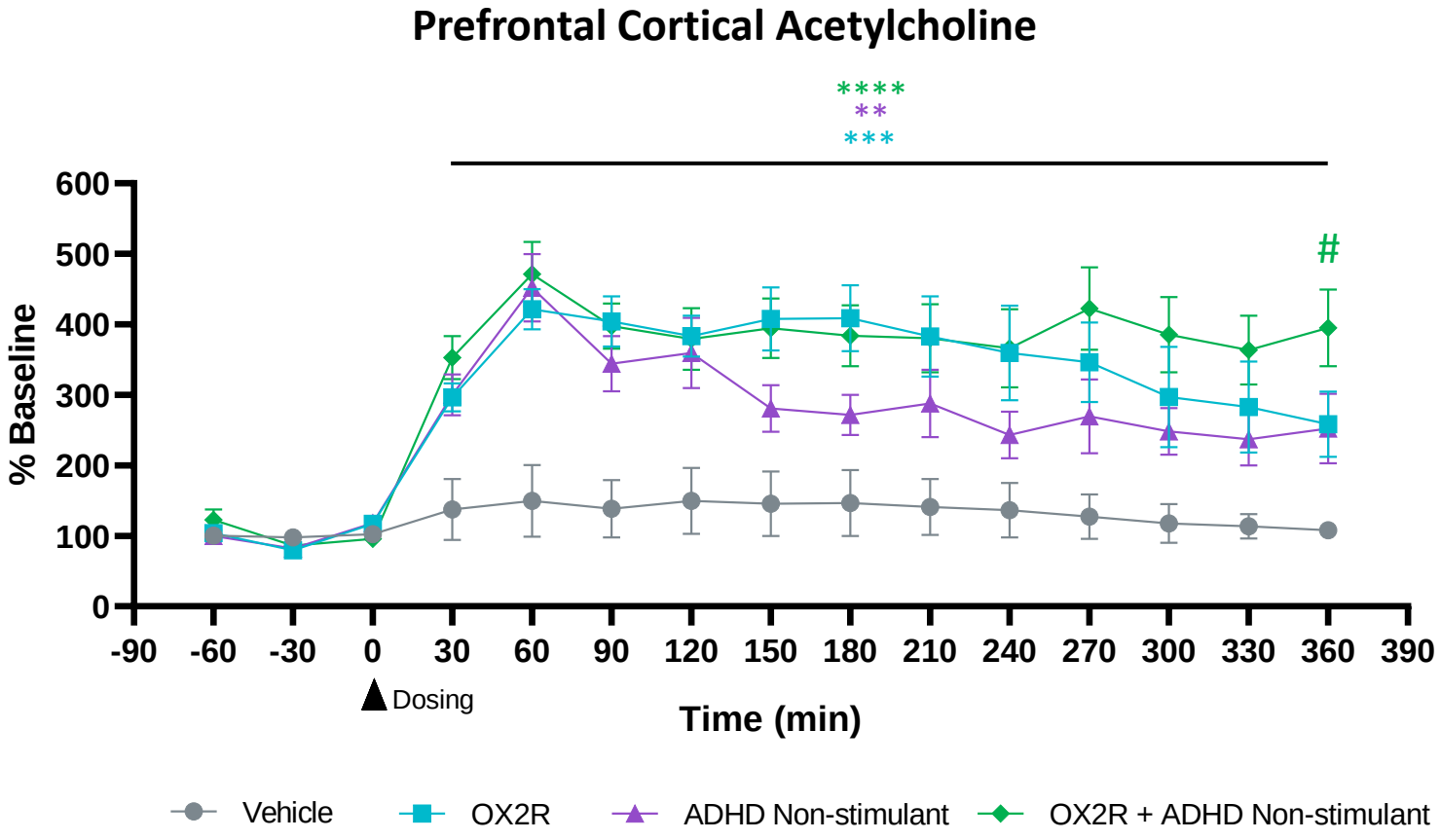
ADHD Non-stimulant Treatment Significantly Increased Prefrontal Cortical Acetylcholine



- Alkermes orexin 2 receptor agonist significantly increased prefrontal cortical acetylcholine
- ADHD non-stimulant treatment significantly increased prefrontal cortical acetylcholine

Mean ± SEM, n=9-10/group. **p<0.01, ***p<0.001, ****0.0001 OX2R or ADHD Non-stimulant vs vehicle
OX2R: Alkermes Orexin 2 receptor agonist

Prolonged Elevation of Prefrontal Cortical Acetylcholine Observed Following Co-administration of OX2R Agonist and ADHD Non-stimulant Treatment



- Alkermes orexin 2 receptor agonist significantly increased prefrontal cortical acetylcholine
- ADHD non-stimulant treatment significantly increased prefrontal cortical acetylcholine
- **Co-administration of orexin 2 receptor agonist and ADHD non-stimulant treatment maintained elevated prefrontal cortical acetylcholine for duration of study**

Mean ± SEM, n=9-10/group. **p<0.01, ***p<0.001, ****p< 0.0001 OX2R, ADHD Non-stimulant, or Combination vs vehicle;
# p<0.5 Combination vs OX2R at Time 360 min OX2R: Alkermes Orexin 2 receptor agonist

Attention and Impulsivity Data Summary

Preclinical models with strong predictive validity provide translational value and enable decision making

Monotherapy:

- 5-Choice Serial Reaction Time Task data suggest orexin 2 receptor agonist improved measures of attention and task engagement and decreased behavioral impulsivity

Polypharmacology:

- Orexin 2 receptor agonist may be complementary to ADHD non-stimulant agents providing additional dimensionality for this class
- Early evidence that orexin 2 receptor agonist prolonged elevation in prefrontal cortical acetylcholine following co-administered with ADHD non-stimulant suggesting opportunity for additive benefit

Validated Preclinical Models Provide Translational Value and Enable Data-driven Decision Making

- Orexin 2 receptor agonist demonstrated significant effects across prefrontal cortical neurotransmission, cortical arousal, and symptom-relevant behavioral assays
- Orexin pharmacology coupled with credentialed existing pharmacology may open new opportunities to address unmet need in a broad range of neuropsychiatric disorders
- Choice of clinical candidates and indication selection derive from strength, consistency and reliability of preclinical assessments