



CENTESSA
P H A R M A C E U T I C A L S

Corporate Overview

November 2025

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ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oxford Finance, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and geo-political risks such as the Russia-Ukraine war, the conflicts in the Middle East, trade wars and imposition of tariffs and other risk factors contained in our filings with the U.S. Securities and Exchange Commission. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. All projections, valuations, market-size forecast (including patient population), statistical analyses and study design illustrations are provided for information purposes only. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward looking statements contained herein to reflect any change in our expectations or any changes in projections, valuations, market-size forecast, statistical analyses, study design events, conditions or circumstances on which any such statement is based, except as may be required by law. They may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, they should not be relied upon as an accurate prediction of future performance.

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MISSION

*Discovering and developing
transformational medicines for patients*

- Potential best-in-class / first-in-class orexin receptor 2 (OX2R) agonist franchise
- Robust series of clinical milestones anticipated across OX2R agonist pipeline in 2026
- Strong balance sheet



2025**Focused Execution****2026****Driving Momentum****ORX750**

Phase 2a data in patients with Narcolepsy Type 1 (NT1), Narcolepsy Type 2 (NT2), and Idiopathic Hypersomnia (IH) in 2025

Registrational program planned for Q1 2026

**ORX142**

Phase 1 data in acutely sleep-deprived healthy volunteers in 2025

Patient studies planned for Q1 2026

**ORX489**

Advancing in IND-enabling studies

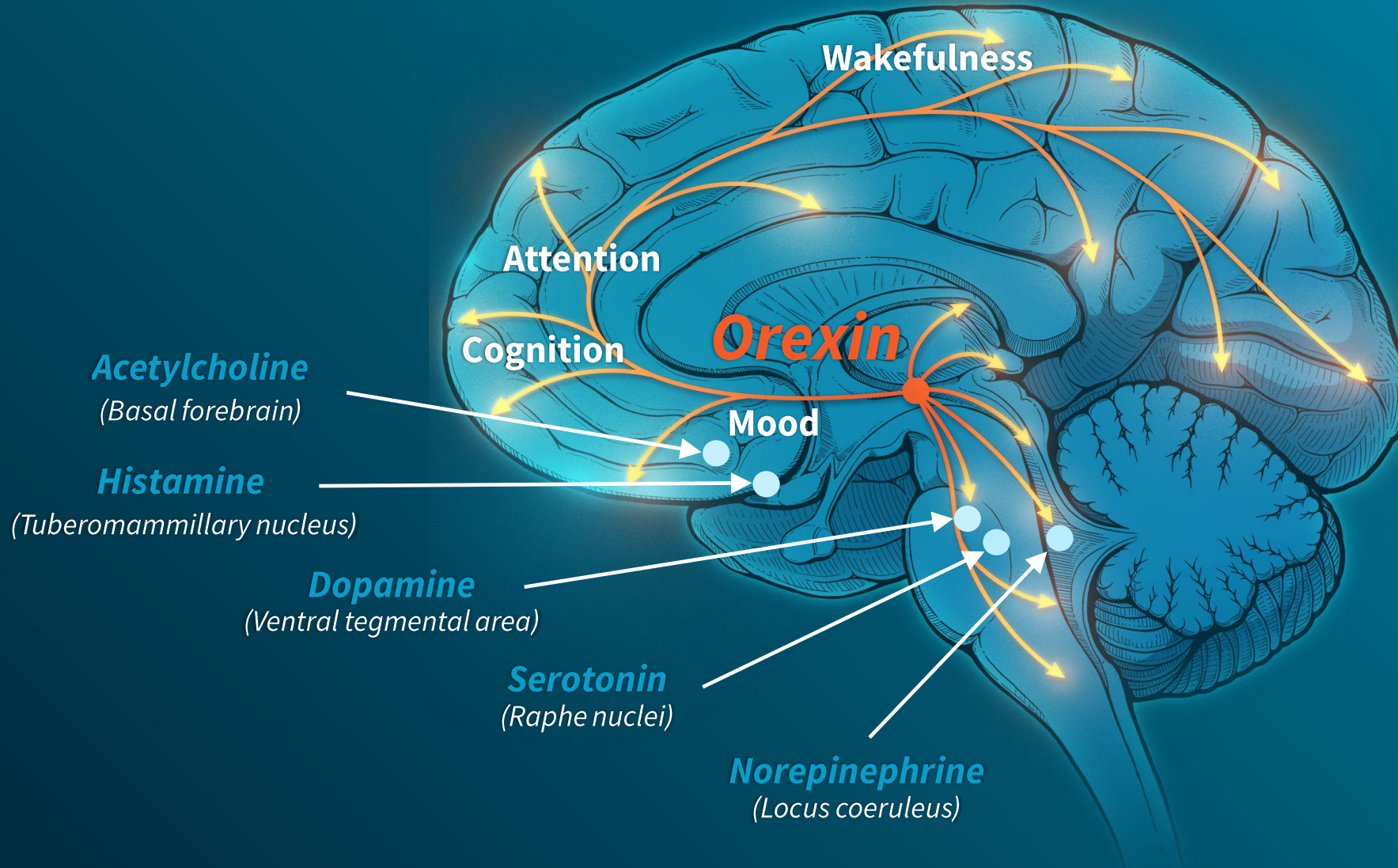
*Clinical studies planned for Q1 2026**

*Orexin agonists have the potential to **transform** the standard of care for individuals with **sleep-wake, neurological, neurodegenerative and neuropsychiatric disorders***



OREXIN

Targeting a key signaling neuropeptide implicated in numerous therapeutic areas



- **ORX750** for the treatment of NT1, NT2 and IH
- **ORX142** for the treatment of neurological and neurodegenerative disorders
- **ORX489** for the treatment of neuropsychiatric disorders
- Earlier stage OX2R agonists and therapeutics for additional potential indications

Molecule	hOX2R EC50 (nM)	Selectivity vs. hOX1R
<i>Native ligand orexin-A (OXA)</i> ¹	0.035	n/a
ORX750 ¹	0.110	9,800x
ORX142 ²	0.069	13,000x
ORX489 ³	0.035	8,800x

OREXIN

Broad and rapidly advancing OX2R agonist pipeline

ASSET	DISEASE/CONDITION	MECHANISM	PRE-CLINICAL	PHASE 1	PHASE 2
ORX750	Narcolepsy Type 1 (NT1)	OXR2 Agonist	████████████████████	████████████████████	████████████████████
ORX750	Narcolepsy Type 2 (NT2)	OXR2 Agonist	████████████████████	████████████████████	████████████████████
ORX750	Idiopathic Hypersomnia (IH)	OXR2 Agonist	████████████████████	████████████████████	████████████████████
ORX142	Neurological & Neurodegenerative Disorders	OXR2 Agonist	████████████████████	████████████████████	
ORX489	Neuropsychiatric Disorders	OXR2 Agonist	████████████████████		
Undisclosed Assets	Undisclosed	Orexin Pathway	████████████████████		

OREXIN

Pipeline of highly potent, selective OX2R agonists enabled by proprietary structural biology insights

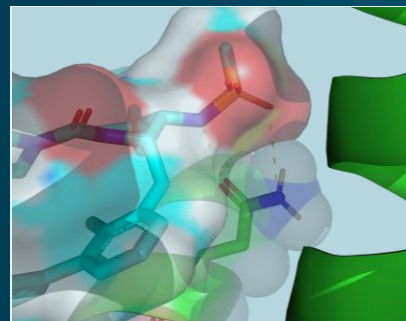
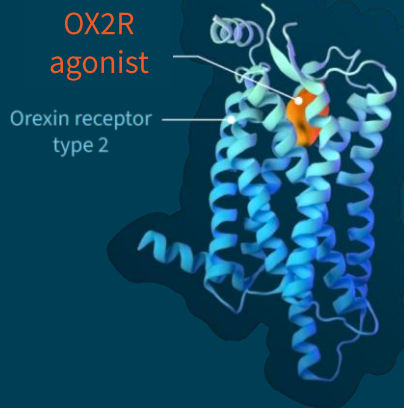
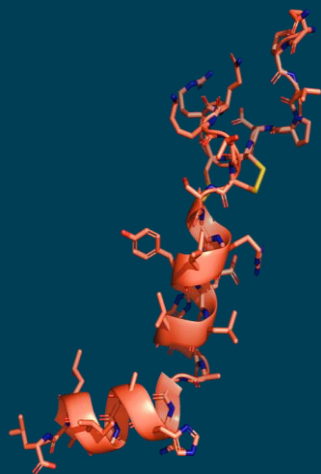
Orexin-A:
Highly Validated
Pathway



Proprietary Structure
Based Drug Design

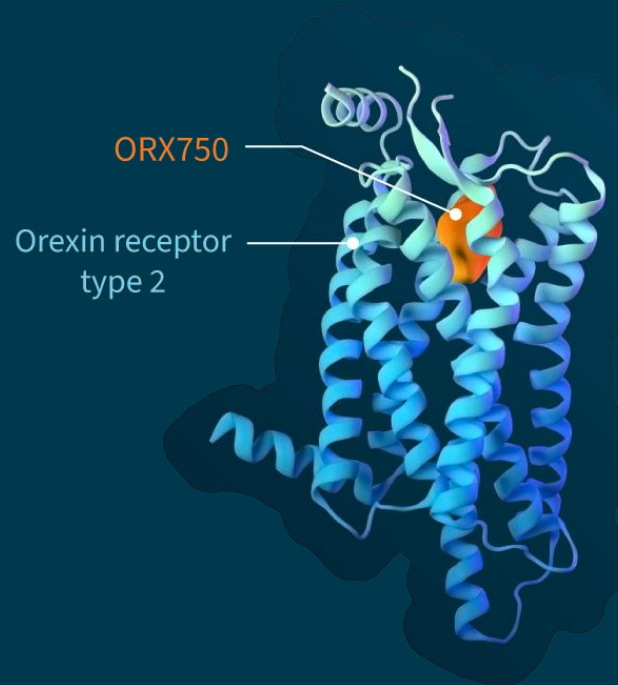


Medicinal
Chemistry SAR*



Candidate Selection Criteria for a Best-in-Class Profile

- Highly potent and highly selective
- Optimal predicted PK profile
- Low predicted human doses
- Fast onset of action



ORX750

Highly potent, selective
OX2R agonist

- **High unmet medical need** in NT1, NT2 and IH
- Phase 2a data from initial low dose cohorts demonstrate **potential best-in-class profile across all three indications**¹
- Expect to initiate **registrational studies in Q1 2026**
- **Significant commercial opportunity** as potential treatment for all three indications

The logo for the CRYSTAL-1 STUDY, featuring a stylized blue and orange starburst icon to the left of the text "CRYSTAL-1" in a large, bold, blue font, with "STUDY" in a smaller, blue font below it.

Evaluate safety, tolerability, and PK in NT1, NT2, and IH patients

Efficacy assessment registrational endpoints: **Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), weekly cataplexy rate** (NT1 patients only), and overall symptom improvement*

Exploratory efficacy assessments will measure sleep, **cognition, attention, memory,** and general health

First robust demonstration of oral OX2R agonist addressing wakefulness needs of patients across NT1, NT2 and IH...

- ✓ **Generally favorable safety and tolerability profile**
- ✓ **Statistically significant, clinically meaningful and dose-dependent efficacy**
- ✓ **Dose escalation** across ongoing and future cohorts with **once-daily and split-dose regimens**, enabled by Phase 1 data

...Expect to initiate registration program in Q1 2026

<https://clinicaltrials.gov/study/NCT06752668>

MWT and ESS are established registrational endpoints for EDS in sleep-wake disorders and weekly cataplexy rate is an established registration endpoint for cataplexy in NT1.

* Measured by Narcolepsy Severity Scale (NSS) and Idiopathic Hypersomnia Severity Scale (IHSS).

ORX750 has been observed to be generally well-tolerated at all doses tested across each indication with all treatment-emergent adverse events (TEAEs) being transient and mild to moderate in severity.

**55 participants
with NT1, NT2 and IH**

who have been dosed with ORX750 in the 2-week crossover dose cohorts completed as of the data cut-off date

The most common TEAEs ($\geq 10\%$) across all completed NT1, NT2 and IH cohorts

pollakiuria
51%

insomnia
22%

dizziness
13%

headache
11%

NT1

>20-minute change

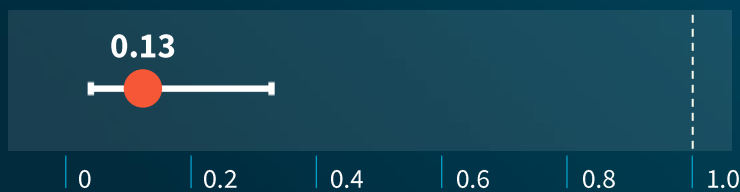
from baseline in MSL compared with placebo on MWT with 1.5 mg dose | *p-value*=0.0026, n=6

50% of participants achieved >30 minutes in MSL on MWT

87% relative reduction in weekly cataplexy rate

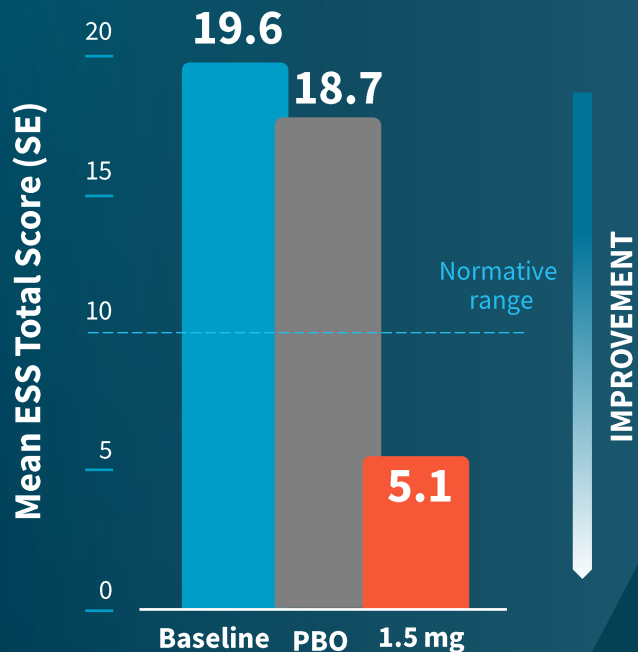
with 1.5 mg dose | *p-value*=0.0025, n=7

WCR Incidence Rate Ratio Relative to Placebo



ESS Score

achieved normative range with 1.5 mg dose | *p-value*=0.0001, n=7



Potential Best-in-Class Profile

- Generally favorable safety and tolerability profile
- Clinically meaningful improvements across multiple efficacy measures
- Dose escalation across ongoing and future cohorts within a 4-week parallel design¹

ORX750

Demonstrated clinically meaningful improvements on multiple efficacy measures;
Data has the potential to establish ORX750 as the new standard of care for NT2



NT2

>10-minute change
from baseline in MSL compared with
placebo on MWT

with 4 mg dose | *p-value*=0.0193, n=10

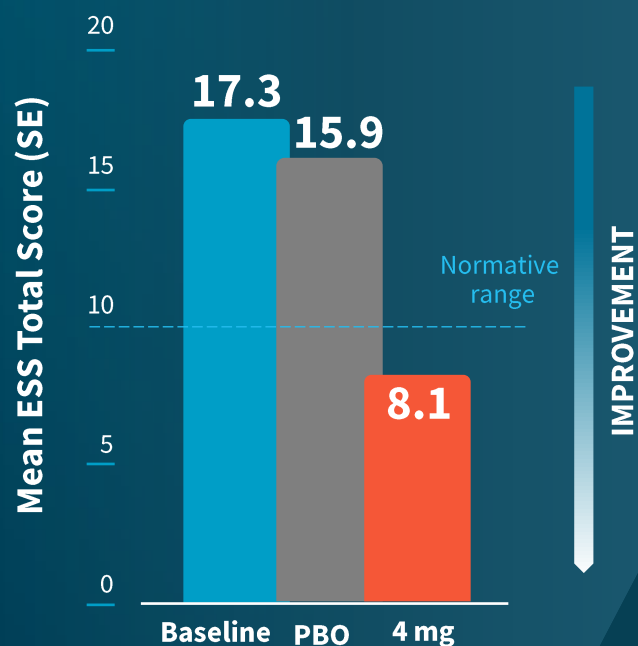
IH

Statistically significant and clinically
meaningful improvements from
baseline on multiple efficacy measures,
including MSL on MWT

with 2 mg dose | *p-value* =0.0213, n=17

ESS Score

for NT2 achieved normative range
with 4 mg dose | *p-value*=0.0023, n=10



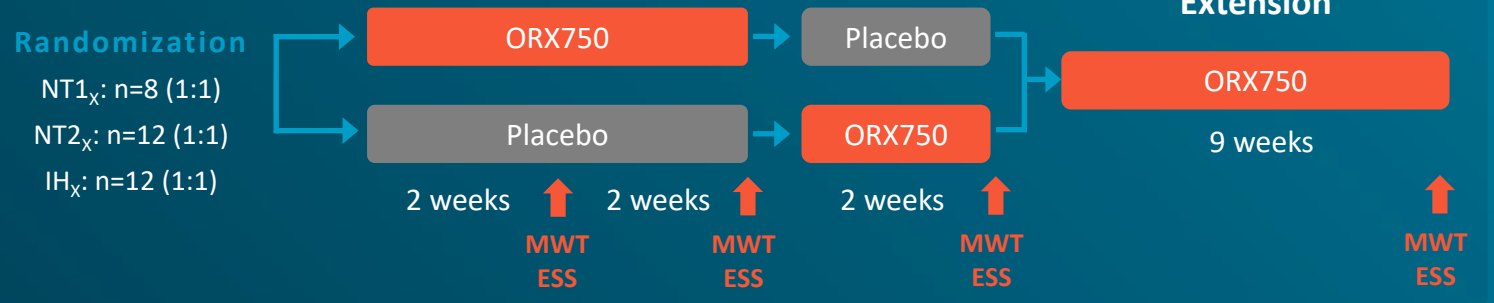
Potential Best-in-Class / First-in-Class Profile

- Generally favorable safety and tolerability profile
- Clinically meaningful improvements across multiple efficacy measures
- Dose escalation across ongoing and future cohorts within a 4-week parallel design

CRYSTAL-1 STUDY

- Innovative design with potential to enable **well-powered** and efficient data generation
- Optimal number of patients to allow **efficient recruitment**
- Potential for **optimized dose selection**
- **4-week placebo-controlled** data at target doses
- Dosing started at **1.0 mg in NT1** and **2.0 mg in NT2 and IH once-daily**
- **Open-label extension** study initiated

Ongoing and Future Cohorts



NT1

~80,000

Prevalent U.S. Patients

- ~50,000 diagnosed and treated today
- Characterized by EDS with cataplexy

NT2

~180,000

Prevalent U.S. Patients

- ~100,000 diagnosed and treated today
- Characterized by EDS (without cataplexy)

IH

~360,000

Prevalent U.S. Patients

- ~120,000 diagnosed and treated today
- Characterized by EDS (without cataplexy), fatigue, sleep inertia

ORX750

Addressable Patient Population
NT1, NT2, and IH

~620,000

Prevalent U.S. Patients

~270,000

Diagnosed and Treated U.S. Patients

ORX750

Large, well defined commercial opportunity for ORX750 as potential treatment for NT1, NT2 and IH

LARGE MARKET OPPORTUNITY

ADDRESSABLE PATIENT POPULATION IN NT1, NT2 AND IH



~620,000

Prevalent U.S. patients¹

~270,000

Diagnosed and treated U.S. patients¹

HIGH UNMET NEED

CURRENT APPROVED THERAPIES HAVE SIGNIFICANT LIMITATIONS

Suboptimal Efficacy²

- Slightly increased sleep onset latencies in patients as measured by MWT
- Do not adequately address EDS, cataplexy or brain fog

Poor Tolerability³

- Potential for significant side effects leading to treatment discontinuations
- Challenges dealing with complex medication regimens

3 INDICATIONS IN 1

ORX750 HAS BEST-IN-CLASS POTENTIAL FOR THE TREATMENT OF NT1, NT2 AND IH



Flexible dosing supports potential to meet the needs of patients across 3 closely related indications

EFFICIENT GO TO MARKET

CONCENTRATED CALL POINTS IN U.S.⁵

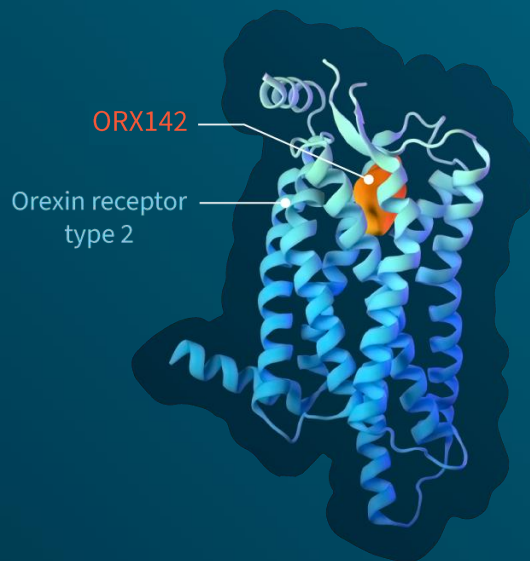
~7,500 sleep specialists
~2,500 sleep centers



ORX142

Advancing pipeline molecule characterized by high potency and differentiated pharmacokinetics

ORX142



- **>13,000-fold selectivity vs. hOX1R**; EC₅₀ 0.069 nM for hOX2R
- Rapid **onset of action** and **differentiated pharmacokinetics**
- Planned for the treatment of **neurological and neurodegenerative disorders**

Phase 1 89 healthy adult volunteers

Generally well-tolerated at all doses tested with all AEs being self-limited and either mild or moderate intensity

- **Statistically significant**
- **Clinically meaningful**
- **Dose-dependent**

▶ Improvements from baseline compared to placebo in mean sleep latency on the MWT at all doses tested

OREXIN

Building a class-leading franchise

ORX750

Registrational program planned for Q1 2026

ORX142

Patient studies planned for Q1 2026

ORX489

Advancing in IND-enabling studies;
Clinical studies planned for Q1 2026*



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