CENTESSA PHARMACEUTICALS

Corporate Overview

February 2026

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This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including ORX750, ORX142, and ORX489; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; the Company's ability to successfully conduct its clinical development of ORX750 below the maximum exposure limit set by the U.S. Food and Drug Administration ("FDA") or, in the event the Company plans to exceed the maximum exposure limit, the Company's ability to successfully have the maximum exposure limit removed; enroll subjects in clinical trials; market size and commercial opportunity for our product candidates; and our anticipated cash runway. Words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," and variations of these words or similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including, without limitation, risks related to our ability to protect and maintain our intellectual property position; business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our 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 orexin focused 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

Cash runway estimated into mid-2028. Estimated cash runway reflects $619 million in pro forma cash, cash equivalents and investments, based on $349 million as of September 30, 2025, and $270 million in net proceeds from an equity financing that closed on November 14, 2025.

OREXIN

Anticipated milestones

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****

*Subject to IND clearance

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

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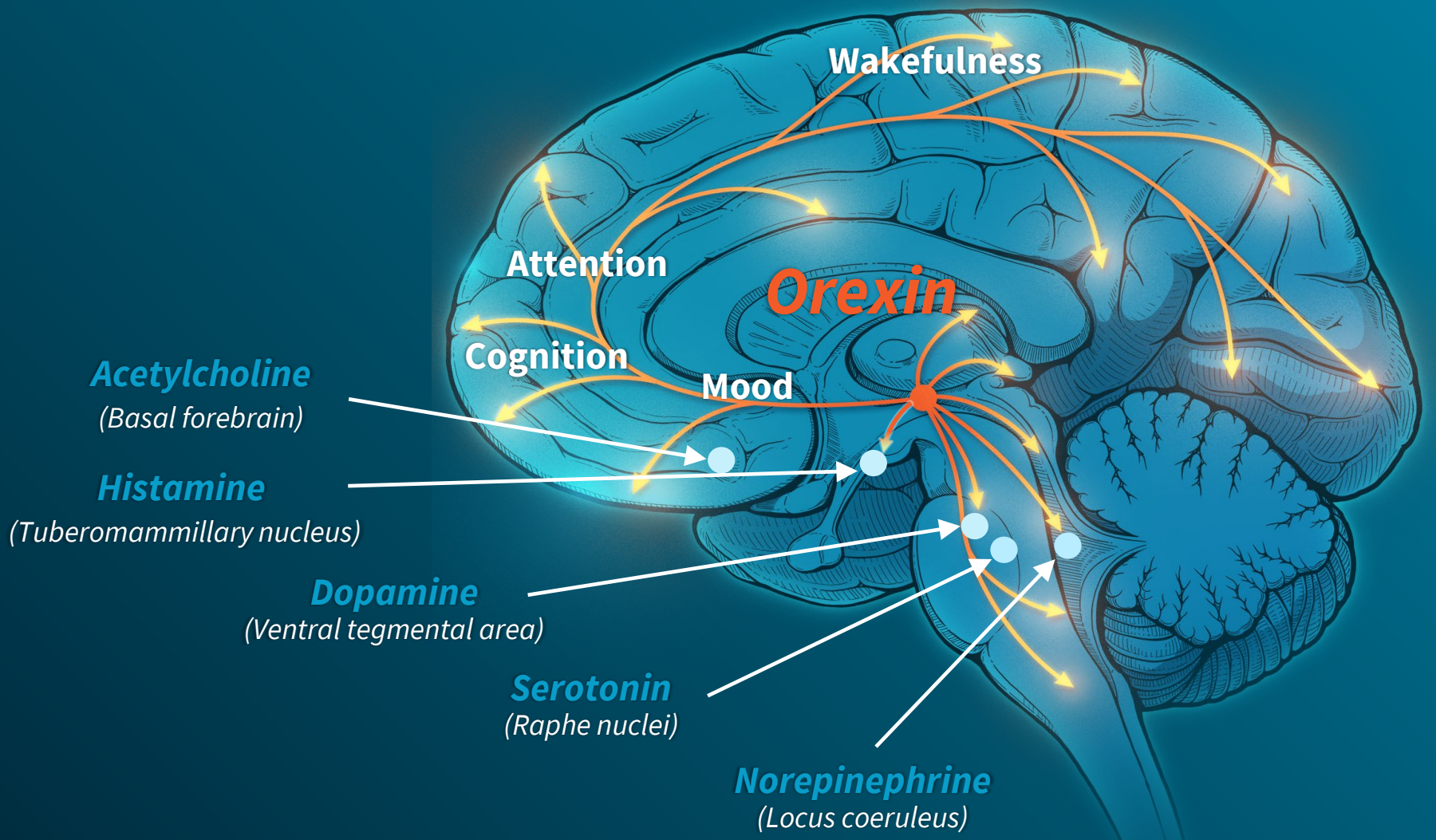
OREXIN

Targeting a key signaling neuropeptide implicated in numerous therapeutic areas



Sources: Pizza, F et al., J Sleep Res 2022;31(4):e13665; Toor, B et al., Front Neurol Neurosci 2021;45:38 ; Ten-Blanco, M et al., Front Neuroendo 2023;69:101066; and, Yamamoto, H et al., PLoS One, 2022;17(7):e0271901.

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OREXIN

Potential best-in-class / first-in-class OX2R agonist therapeutics

- **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

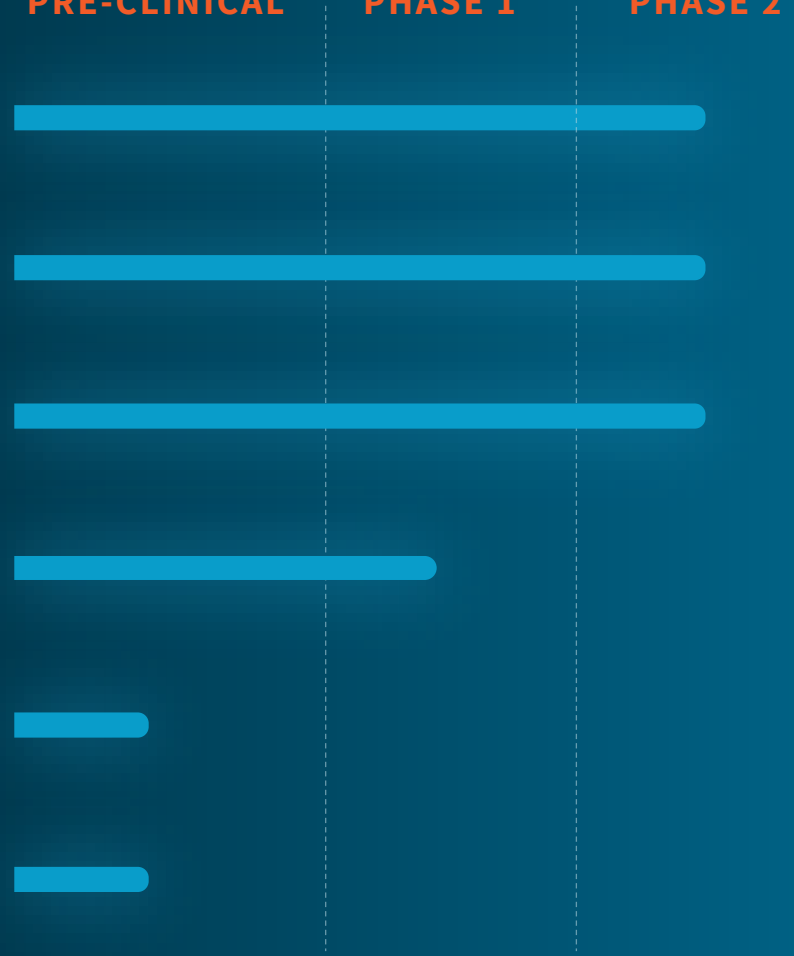
Molecule	hOX2R EC50 (nM)	Selectivity vs. hOX1R
Native ligand orexin-A (OXA)[1]	0.035	n/a
ORX750[1]	**0.110**	**9,800x**
ORX142[2]	**0.069**	**13,000x**
ORX489[3]	**0.035**	**8,800x**

Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing human recombinant OX1R or OX2R.
1. Black et al., World Sleep 2023 Abstract. 2. Black et al., European Sleep Research Society 2024 Abstract. 3. Company data / presentations.

OREXIN

Broad and rapidly advancing OX2R agonist pipeline

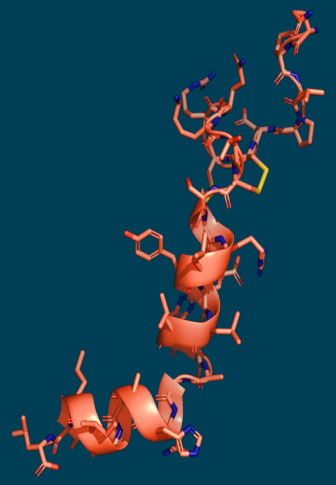
ASSET	DISEASE/CONDITION	MECHANISM
ORX750	Narcolepsy Type 1 (NT1)	OX2R Agonist
ORX750	Narcolepsy Type 2 (NT2)	OX2R Agonist
ORX750	Idiopathic Hypersomnia (IH)	OX2R Agonist
ORX142	Neurological & Neurodegenerative Disorders	OX2R Agonist
ORX489	Neuropsychiatric Disorders	OX2R Agonist
Undisclosed Assets	Undisclosed	Orexin Pathway

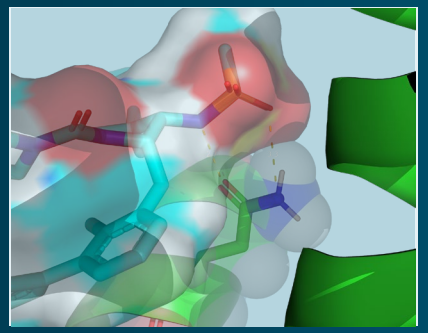


OREXIN

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***





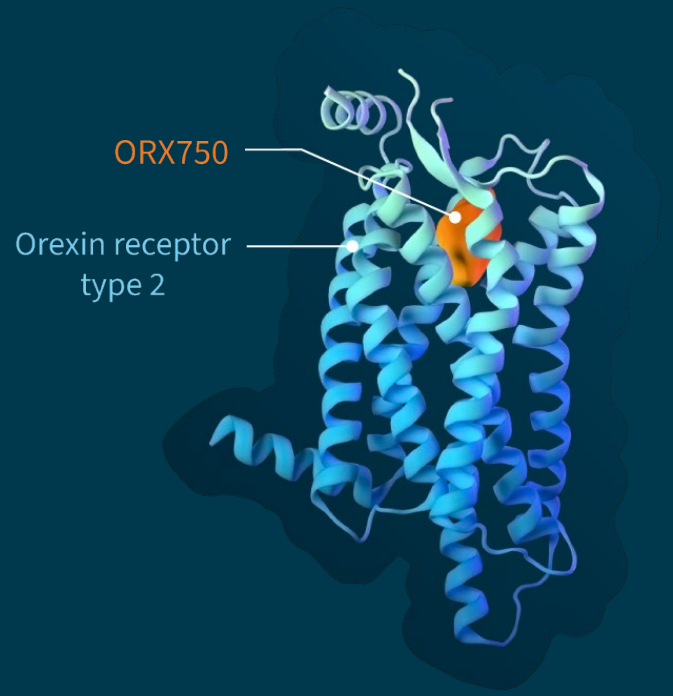
Candidate Selection Criteria for a Best-in-Class Profile

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

*SAR is Structure- Activity Relationship optimization.

ORX750

Potential to redefine the standard of care for patients with sleep-wake disorders



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 program in Q1 2026**
- **Significant commercial opportunity** as potential treatment for all three indications

1. As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750 in 2-week crossover dose cohorts ; Data are considered preliminary, as the study is ongoing

ORX750

Positive Phase 2a topline data from initial low dose cohorts demonstrate potential best-in-class profile across NT1, NT2 and IH[1]

CRYSTAL-1 STUDY

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

Summary

Positive Phase 2a Topline Data from Initial Low Dose Cohorts[1]

- Generally favorable safety and tolerability profile
- Statistically significant, clinically meaningful and dose-dependent efficacy[2]
- 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

1. As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750 in 2-week crossover dose cohorts ; Data are considered preliminary, as the study is ongoing
2. As measured by maintenance of wakefulness test (MWT), Epworth Sleepiness Scale scores (ESS), and for NT1 only the weekly cataplexy rates (WCR)

https://clinicaltrials.gov/study/NCT06752668

ORX750

Demonstrated a generally favorable safety and tolerability profile

CRYSTAL-1

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 (≥10%) across all completed NT1, NT2 and IH cohorts

pollakiuria	insomnia	dizziness	headache
51%	22%	13%	11%

Data cutoff as of September 23, 2025; Data are considered preliminary, as the study is ongoing

ORX750

Achieved statistically significant, clinically meaningful and dose-dependent improvements

CRYSTAL-1

NT1

>20-minute change

from baseline in MSL compared with placebo on **MWT**

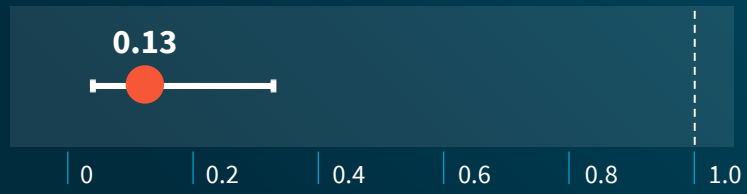
with 1.5 mg dose | ***p-value***=0.0026, n=6

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

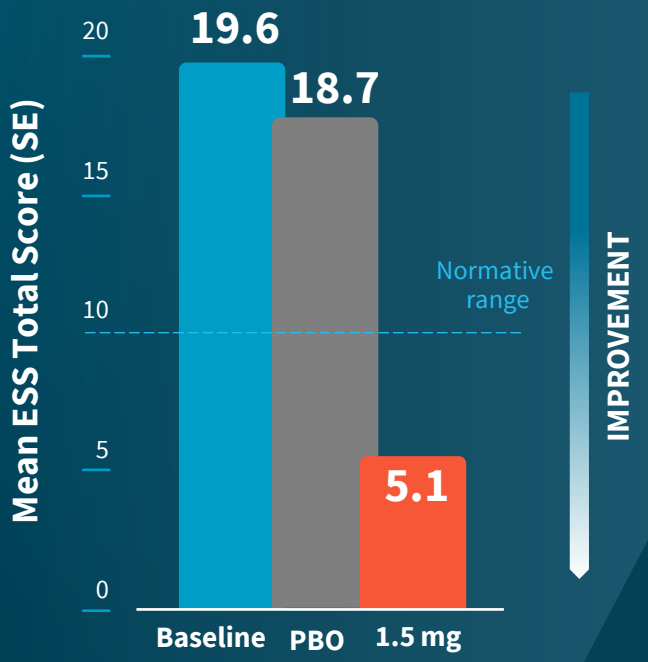
WCR Incidence Rate Ratio Relative to Placebo



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 ongoing within a 4-week parallel design

MWT, Maintenance of Wakefulness Test; MSL, Mean Sleep Latency; ESS, Epworth Sleepiness Scale; PBO, Placebo; SE, Standard Error; MWT and ESS analysis used a linear mixed model to estimate the treatment effect with the Least Square Mean (LS Mean); WCR analysis used a generalized linear mixed model (Poisson) to estimate the incidence rate ratio. The incidence rate ratio was calculated by dividing the adjusted incidence of the ORX750 group with the adjusted incidence of the placebo group; As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750 in 2-week crossover dose cohorts ; Data are considered preliminary, as the study is ongoing;

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ORX750

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

CRYSTAL-1

NT2

>10-minute change

from baseline in MSL compared with placebo on **MWT** at Week 2*

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

25-minute change at Day 1** | ***p-value=<0.0001, n=5)

IH

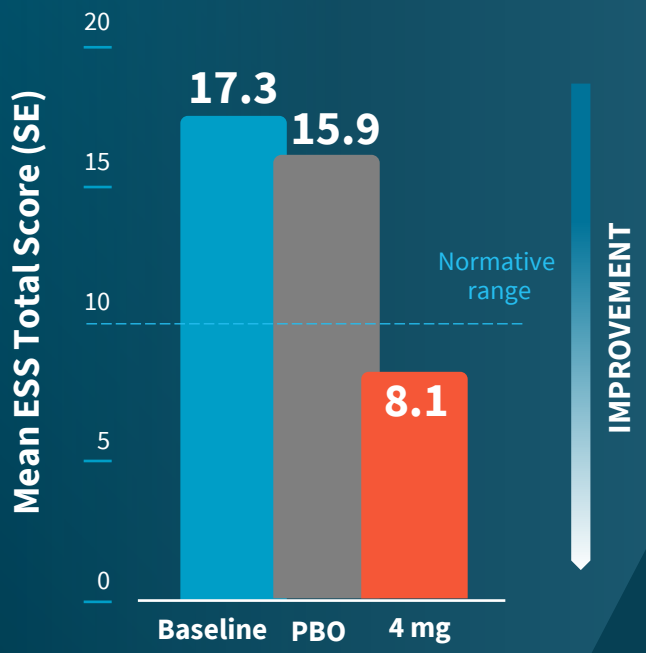
Statistically significant and clinically meaningful improvements from baseline on multiple efficacy measures, including MSL on **MWT**

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
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MWT, Maintenance of Wakefulness Test; MSL, Mean Sleep Latency; ESS, Epworth Sleepiness Scale; PBO, Placebo; SE, Standard Error; MWT and ESS analysis used a linear mixed model to estimate the Least Square Mean (LS Mean); As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750 in 2-week crossover dose cohorts ; Data are considered preliminary, as the study is ongoing.

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ORX750

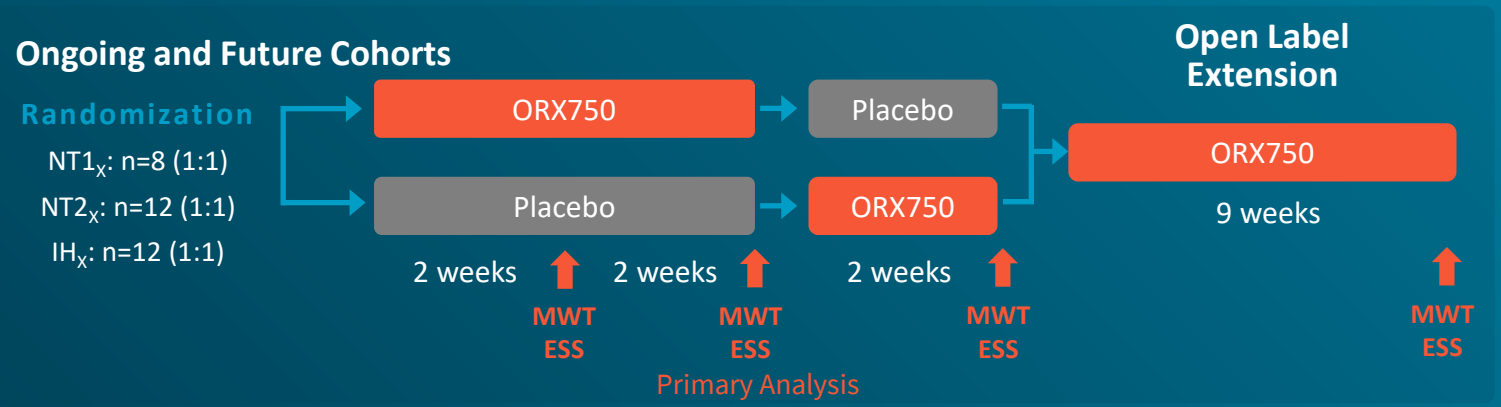
Randomized, double-blind, placebo-controlled basket study of ORX750 in patients with NT1, NT2, and IH ongoing

CRYSTAL-1

CRYSTAL-1 STUDY

- Adapted to **4-week parallel design** for each ongoing and future dose cohort across NT1, NT2 and IH with potential to enable efficient data generation
- Optimal number of patients to allow **efficient recruitment**
- Potential for **optimized dose selection**
- **4-week placebo-controlled** data at target doses
- Ongoing **open-label extension** study

4- Week Parallel Design



Note: Study design for illustrative purposes only.

ORX750

NT1, NT2, and IH represent large addressable patient populations

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

EDS is excessive daytime sleepiness.
Source of prevalent patient estimates: Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Centessa market research.
Source of diagnosed and treated patient estimates: Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Ohayon et al. Sleep Med X. 2023.

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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. patients[1]

~270,000

Diagnosed and treated U.S. patients[1]

HIGH UNMET NEED

CURRENT APPROVED THERAPIES HAVE SIGNIFICANT LIMITATIONS

Suboptimal Efficacy[2]

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

Poor Tolerability[3]

- 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

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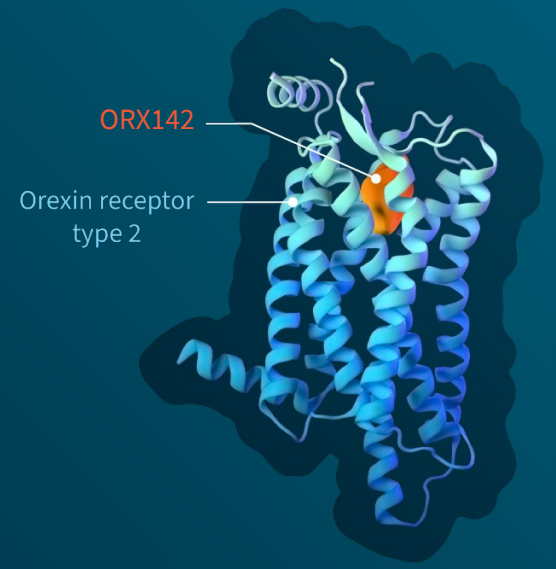
Source: 1. Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Centessa Market Research; 2. Prescribing information for current standard of care therapies; 3. FDA, "The Voice of the Patient: Narcolepsy" 2014; 4. Maski *et al.*, J Clin sleep Med 2017; 5. American Association of Sleep Medicine (AASM) 2022.

ORX142

Advancing pipeline molecule characterized by high potency and differentiated pharmacokinetics

ORX142



- >13,000-fold selectivity vs. hOX1R; EC_{50} 0.069 nM for hOX2R
- Rapid onset of action and differentiated pharmacokinetics
- Planned for the treatment of neurological and neurodegenerative disorders

Summary of Phase 1 Study

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

As of the October 3, 2025 data cut-off date for the Phase 1 study of ORX142 in healthy volunteers. Data are considered preliminary, as the study is ongoing.

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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