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ORX750 Preclinical Data Presentation: A novel, orally administered, selective orexin receptor 2 (OX2R) agonist for the treatment of narcolepsy and other sleep-wake disorders

October 25, 2023

Agenda

Opening
Kristen K. Sheppard, Esq
Senior Vice President, Investor Relations & Corporate Communications

Overview of Centessa Orexin Agonist Program
Mario Alberto Accardi, PhD
President, Orexin Agonist Program

ORX750 Preclinical Data Presentation*
Sarah Wurts Black, PhD
Head of Biology, Orexin Agonist Program

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As presented in an oral presentation at the World Sleep Congress on October 25, 2023

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Centessa Orexin Agonist Program

Mario Alberto Accardi, PhD
President, Orexin Agonist Program

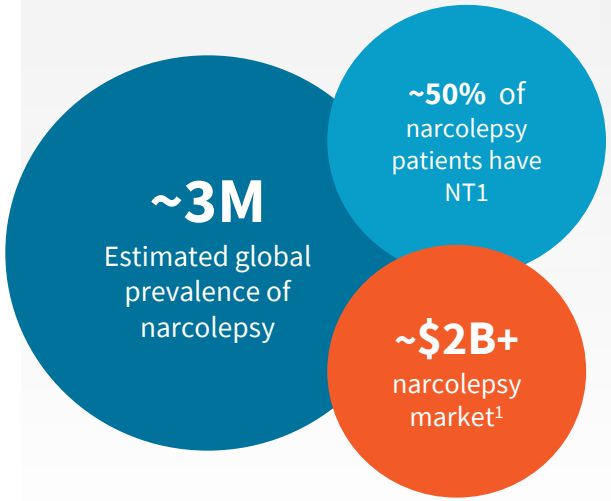
ORX750: Orally administered, selective orexin receptor 2 (OX2R) agonist

In preclinical development for treatment of narcolepsy; IND-enabling activities ongoing

Narcolepsy Type 1 (NT1)

A rare neurological condition that affects the brain's ability to regulate the normal sleep-wake cycle

Caused by a profound loss of orexin neurons in the brain



High unmet need

Current treatments do not restore normal function; symptoms persist despite polypharmacy

75% patients experience EDS[1]

50% patients still have 1-2 cataplexy episodes per day[2]

ORX750 designed to **reactivate orexin signaling** in the brain and treat the underlying cause of NT1

Robust set of preclinical data support **potential best-in-class profile** for treatment of narcolepsy and other sleep-wake disorders[3]

Exploring follow-up orexin agonists for potential expansion opportunities into sleep disorders and broader neurological indications

EDS is excessive daytime sleepiness. In March 2023, ORX750 was announced as the Company's product candidate for the treatment of NT1 with potential expansion into other sleep disorders. 1. Evaluate Pharma 2021. 2. Maski K, et al. J Clin Sleep Med 2017;13;419–25. 3. ORX750 preclinical data as presented at World Sleep on Oct 25, 2023.

Structure-based drug design has enabled the discovery of ORX750 and follow-up agonists as potential orexin signaling ‘replacement therapy’ for narcolepsy and other sleep-wake disorders

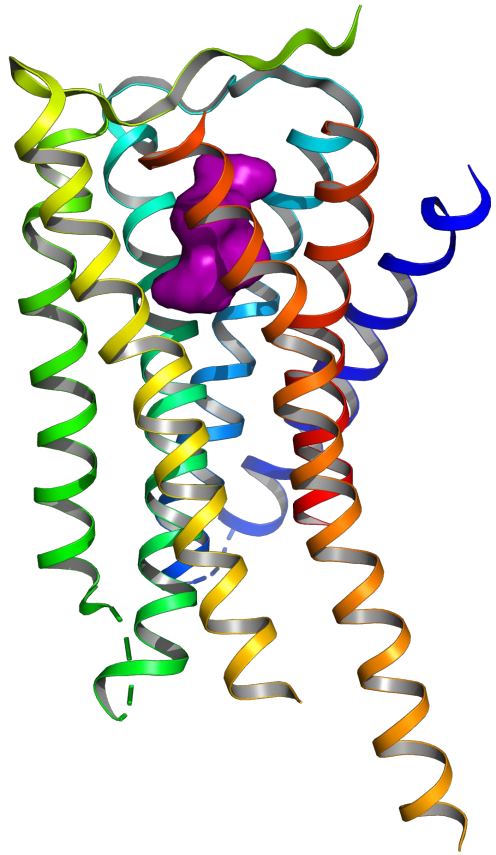


Illustration of OX2R structure
bound to prototype small molecule orexin agonist
(shown in purple)

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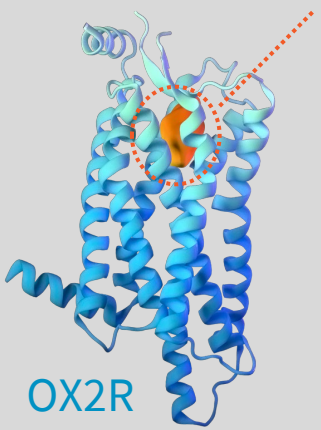
ORX750, an Oral Selective Orexin Receptor 2 Agonist, Promotes Wakefulness and Reduces Cataplexy in the Orexin/Ataxin-3 Mouse

Sarah Wurts Black, PhD

October 25th
World Sleep 2023, Rio de Janeiro, Brazil

Executive summary

- **ORX750 is a novel, full OX2R agonist designed using high resolution crystal and cryo-EM structures**
- **ORX750 potently activated the OX2R with an EC_{50} of 0.11 nM and 9,800-fold selectivity over OX1R**
- **Oral administration of ORX750 achieved maximal wake times in highly predictive Atax and DTA mouse models of narcolepsy type 1**
  - **Activity observed at 0.1 mg/kg,** the lowest dose tested in DTA mice
  - Increased time awake, latency to sleep, latency to cataplexy, and consolidation of wakefulness
  - Suppressed cataplexy occurrences
- **ORX750 showed activity in wild type mice** at the lowest dose tested (1 mg/kg)



We believe ORX750 has the potential to treat narcolepsy and other sleep/wake disorders

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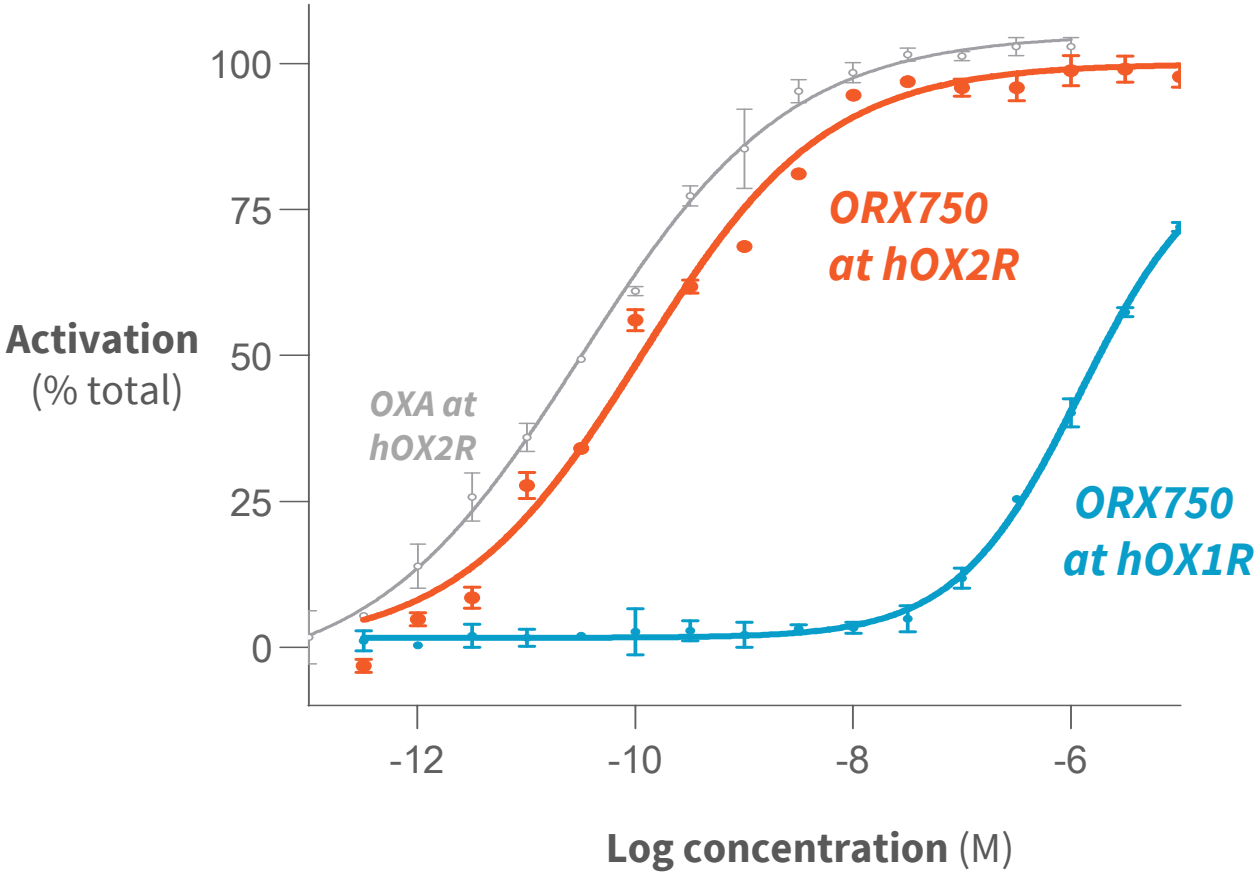
ORX750 showed high *in vitro* potency at OX2R and selectivity vs. OX1R



***EC_{50} 0.11 nM** for hOX2R*

***9,800-fold selectivity** vs. hOX1R*

- Activation pattern was indistinguishable from OXA with lack of biased agonism[1]
- No significant differences in OX2R potency were observed across species[2]
- No significant pharmacological activity observed in GPCR selectivity and in vitro safety panels[3]

Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing recombinant human OX1R or OX2R; **OXA EC50 at hOX2R = 0.035 nM; ORX750 EC50 at hOX1R = 1100 nM**

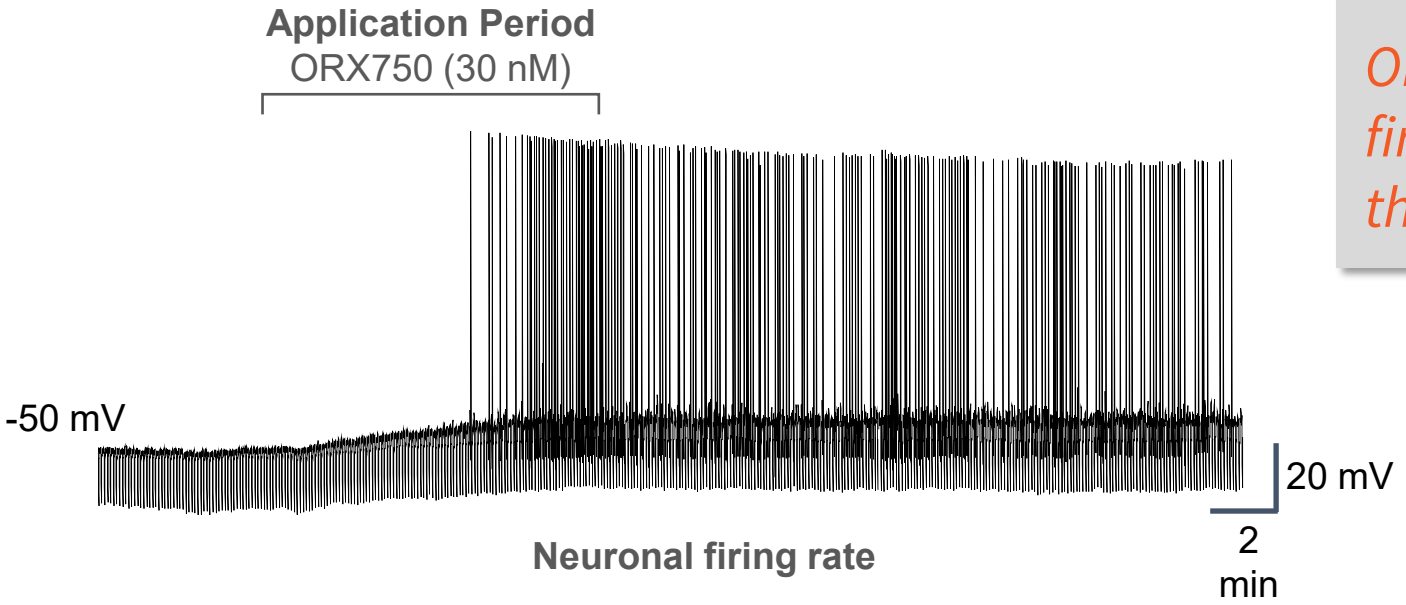
1 Pathhunter β-arrestin recruitment assay with CHO cells co-expressing ProLink™ (PK)-tagged OX2R and Enzyme Acceptor (EA)-tagged β-arrestin

2 Human, mouse, rat, dog, monkey recombinant receptors *in vitro*

3 Safety 47 and GPCRMax168 from >60 receptor families

ORX750 activated endogenous OX2R in mouse *ex vivo* brain slice

Whole cell recordings of histaminergic neurons in ventral TMN in mouse brain slices



High potency at native mouse OX2R

ORX750 depolarized[1] and increased firing rates[2] of histaminergic neurons in the TMN

- ORX750 EC_{50} 5 nM; OXA EC_{50} 32 nM
- TMN=tuberomammillary nucleus, area enriched in OX2R and a component of the orexinergic wake-promoting neurocircuitry (Mignot, E., et al., Front Neurol Neurosci, 2021;45:103)

1. Performed in presence of tetrodotoxin
2. Performed in absence of tetrodotoxin

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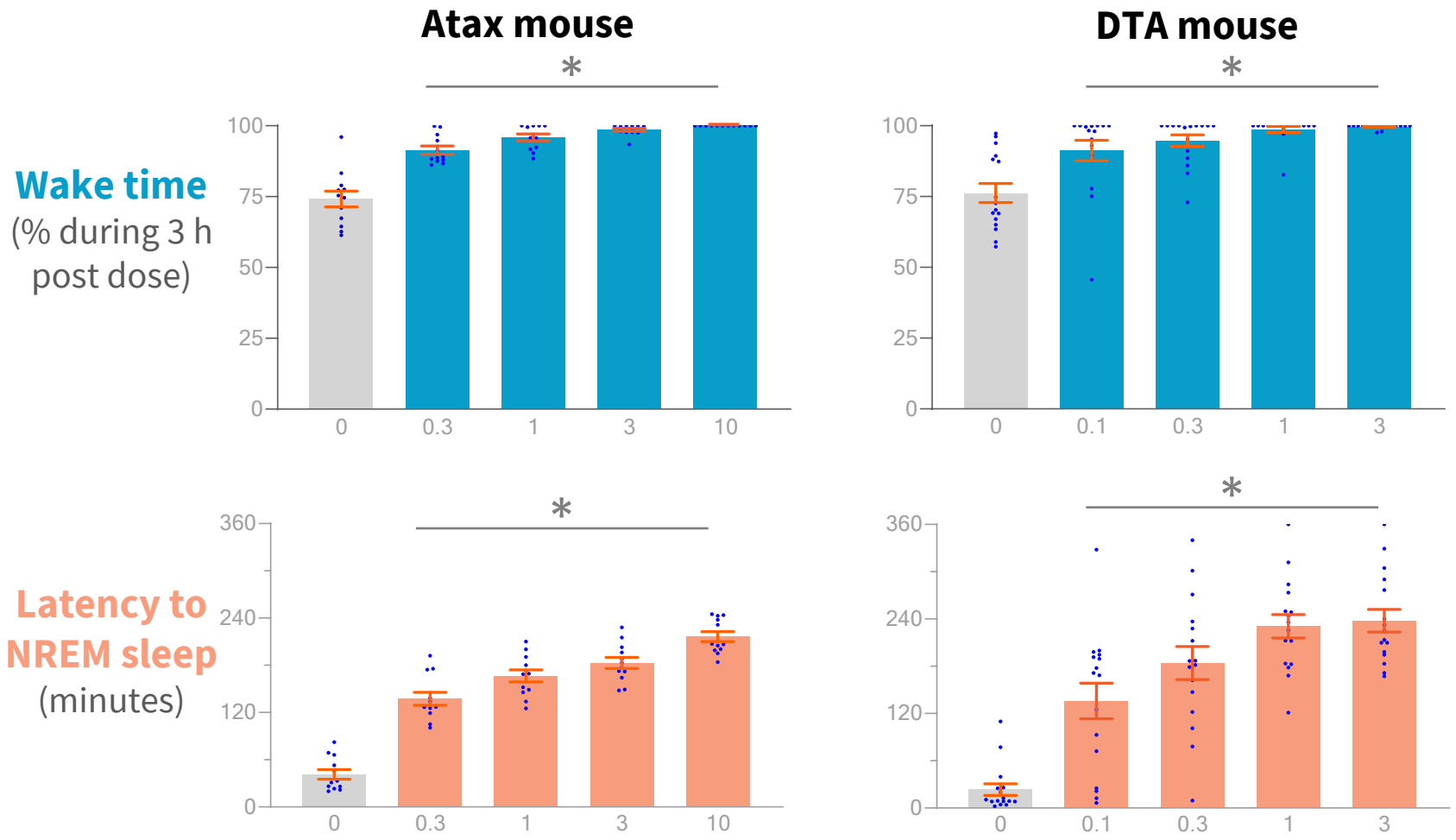
ORX750 promoted wakefulness in NT1 mouse models during the active phase in the EEG/EMG/video assay



***Time awake increased at ≥ 0.1 mg/kg** (lowest dose tested in DTA mice)*

***Latency to sleep increased at ≥ 0.1 mg/kg** (lowest dose tested in DTA mice)*

- Age at first dose 20-22 wks in orexin/ataxin-3 (Atax) and 23-27 wks (7 wks after removal of doxycycline chow) in orexin/tTA;tetO diphtheria toxin fragment A (DTA) mice; males used
- EEG, EMG recorded using intraperitonially implanted telemeters with video and manually scored in 10-sec epochs; dosing at start of dark period
- *For all doses, all models $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following repeated-measures analysis of variance (RM-ANOVA) per mouse model in counterbalanced design

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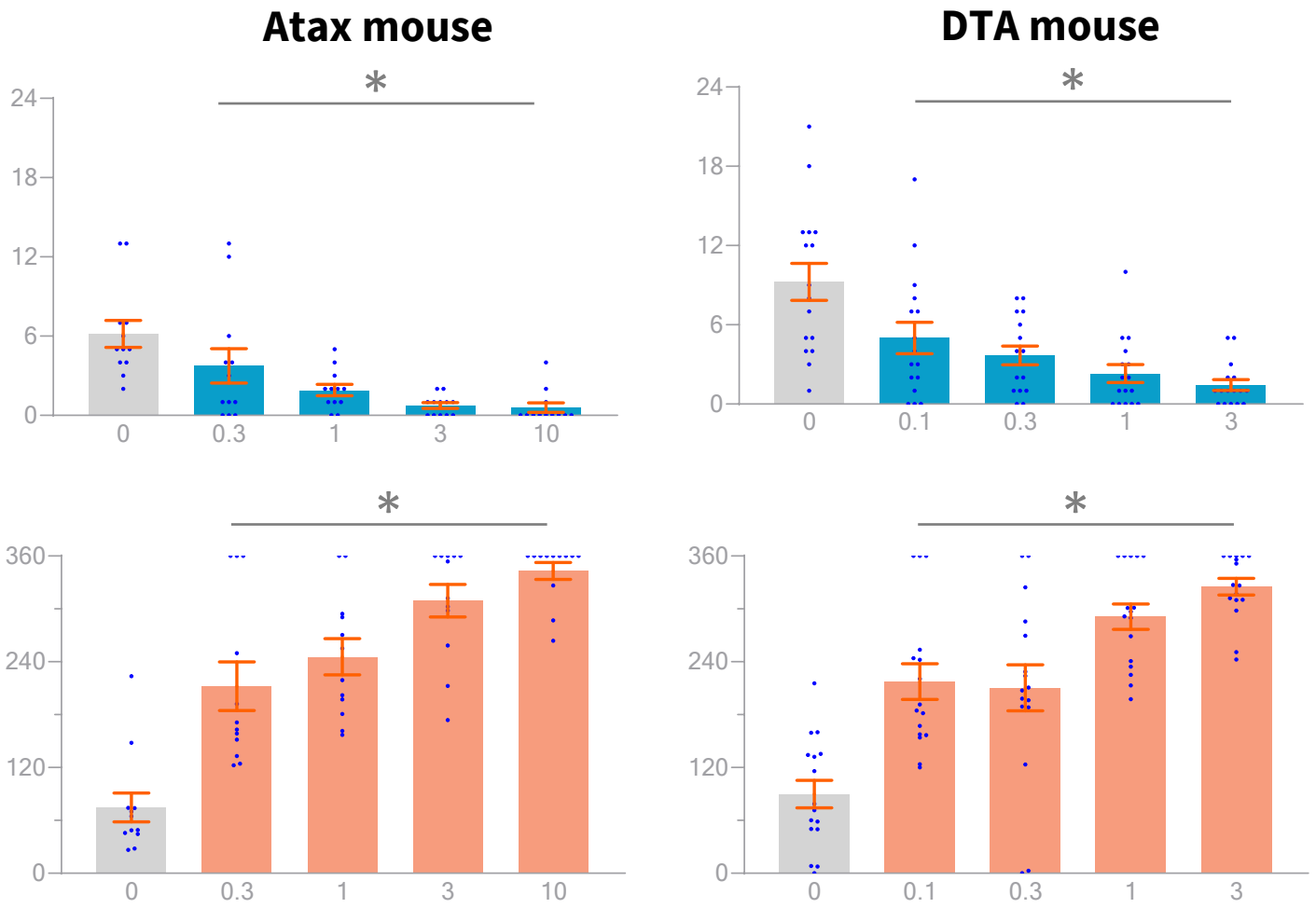
ORX750 suppressed cataplexy in NT1 mouse models during the active phase in the EEG/EMG/video assay



Cataplexy occurrences decreased at ≥ 0.1 mg/kg *(lowest dose tested in DTA mice)*

Latency to cataplexy increased ≥ 0.1 mg/kg *(lowest dose tested in DTA mice)*

- Manually scored 10-sec epochs by consensus criteria (Scammell, T et al., SLEEP 2009;32(1):111) in mice housed with running wheels; dosing at start of dark period
- If no cataplexy was observed during the 6 h test window, the maximum possible latency was assigned (360 min); mice without cataplexy in baseline were excluded from analysis
- For all doses, all models vs. vehicle, $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA per mouse model in counterbalanced design

14 days of treatment did not attenuate the effect of ORX750

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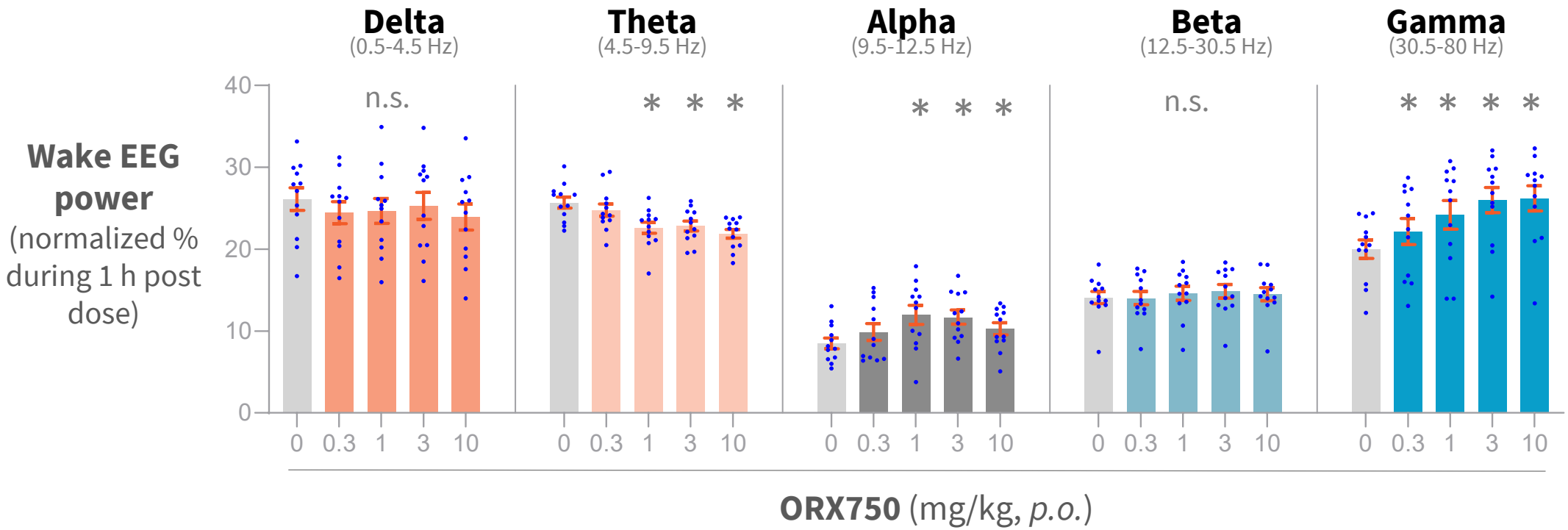
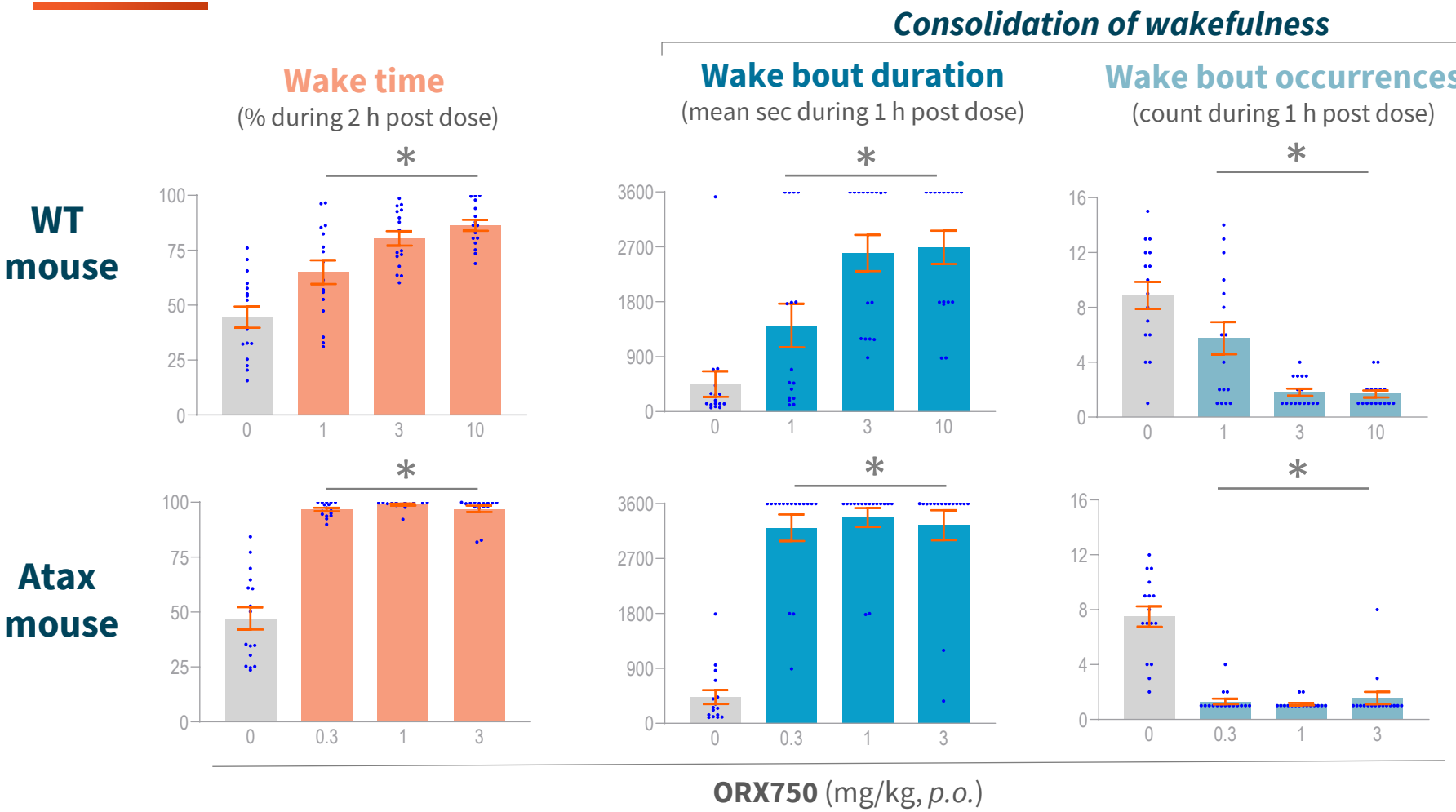
ORX750 altered EEG power during wakefulness during the active phase in Atax mice



ORX750 increased EEG power during wakefulness in the alpha and gamma bands and decreased power in the theta band

- Increase in EEG power in gamma frequency associated with enhanced alertness (Cantero, J.L., et al., NeuroImage, 2004;22:1271)
- Data normalized as the percent of the mean power across all frequency bands in 6 h recording from 10-sec, artifact-free wakefulness epochs of manually scored EEG
- * $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA in counterbalanced design

ORX750 increased wake time and consolidation in wild type (WT) and an NT1 mouse model during the rest phase in the PiezoSleep assay



In healthy WT mice, wake time and consolidation increased at ≥ 1 mg/kg (lowest dose tested)

NT1 mouse models were more sensitive to OX2R agonism than WT mice

- Data collected using PiezoSleep, in which wakefulness readouts based on movement & breath rate highly correlate with EEG/EMG measures (Black, et al., ESRS2022 presentation)
- Age at first dose was 16-20 wks in male Atax mice and WT colony mates; mice dosed at 5 h after lights on
- * $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA per mouse model in counterbalanced design

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Summary and conclusion

- **ORX750 is a novel, full OX2R agonist designed using high resolution crystal and cryo-EM structures**
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- **Oral administration of ORX750 achieved maximal wake times in highly predictive Atax and DTA mouse models of narcolepsy type 1**
  - **Activity observed at 0.1 mg/kg,** the lowest dose tested in DTA mice
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- **ORX750 showed activity in wild type mice** at the lowest dose tested (1 mg/kg)

We believe these results support further progression of ORX750 as a potential best-in-class treatment for narcolepsy and other sleep/wake disorders

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Thank you

Please contact investors@centessa.com with any questions.