Poster P-51.423

A Phase 2a, Double-Blind, Placebo-Controlled Study of ORX750 in Participants With Narcolepsy (Type 1 and 2) and Idiopathic Hypersomnia: CRYSTAL-1 Study Design

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BACKGROUND

- Narcolepsy types 1 (NT1) and 2 (NT2) and idiopathic hypersomnia (IH) are rare, debilitating central disorders of hypersomnolence characterized by excessive daytime sleepiness[1,2]
- Individuals with NT1 have a loss of orexin-producing neurons, which are located in the hypothalamus[3,4]
- Orexin receptor 2 (OX2R) agonists have been shown to increase wakefulness not only in individuals with NT1[5,6] but also in individuals with NT2 and IH who typically have normal levels of orexin in the central nervous system[7,8]
- None of the therapies currently available for narcolepsy target the orexin system, which is a core element of wake-promoting circuitries and, specifically, of NT1 pathology[2]
- ORX750 is a novel, investigational OX2R agonist in clinical development for the treatment of NT1, NT2, and IH[9]
- A phase 1 study of ORX750 in healthy participants using single doses up to and including 5.0 mg and multiple doses up to and including 4.0 mg demonstrated the following[9,10]:
  - No serious treatment-emergent adverse events (TEAEs) or TEAEs leading to discontinuation; all TEAEs deemed related to ORX750 were mild in severity, transient, and resolved without intervention[9]
  - In acutely sleep-deprived healthy participants, ORX750 doses of 1.0-5.0 mg demonstrated significant and dose-dependent improvements compared with placebo in mean sleep latency on the Maintenance of Wakefulness Test (MWT) and subjective alertness on the Karolinska Sleepiness Scale[9]
  - Results from the phase 1 study will be presented at SLEEP 2025 as poster P-51.425 on Wednesday, June 11 (10 AM-11:45 AM)
- These phase 1 results support progressing clinical development of ORX750 into patients with NT1, NT2, and IH and informed the phase 2a starting dose

OBJECTIVE

- This phase 2a study (CRYSTAL-1; NCT06752668) will evaluate the safety, tolerability, efficacy, and pharmacokinetics of multiple doses of ORX750 for the first time in participants with NT1, NT2, and IH

STUDY DESIGN

- CRYSTAL-1 is a phase 2a, randomized, double-blind, placebo-controlled, crossover basket study with separate cohorts for participants with NT1, NT2, and IH (**Figure 1**)
- Within dosing cohorts, participants will be randomized to 1 of 2 blinded treatment sequences and receive ORX750 for 4 weeks and placebo for 2 weeks (6-week treatment duration total) in a crossover design (**Figure 2**, **Figure 3**)
- Initially, ORX750 will be dosed once daily at 1.0 mg (NT1 cohort) and 2.0 mg (NT2 cohort and IH cohort), with sequential dose escalation/de-escalation in subsequent cohorts
- This study plans to complete 78 participants (NT1, n=18; NT2, n=24; IH, n=36)
- This crossover study has >87.5% power within each dosing cohort to detect a 15-minute change in mean sleep latency on the MWT relative to placebo (2-sided α=0.05)

Figure 1. Key Eligibility Criteria

Key inclusion criteria

Aged 18-65 years (inclusive)

BMI of 17-37 kg/m^2 (inclusive)

Meets ICSD-3-TR diagnostic criteria for NT1, NT2, or IH

Discontinue all medications used to treat narcolepsy or IH

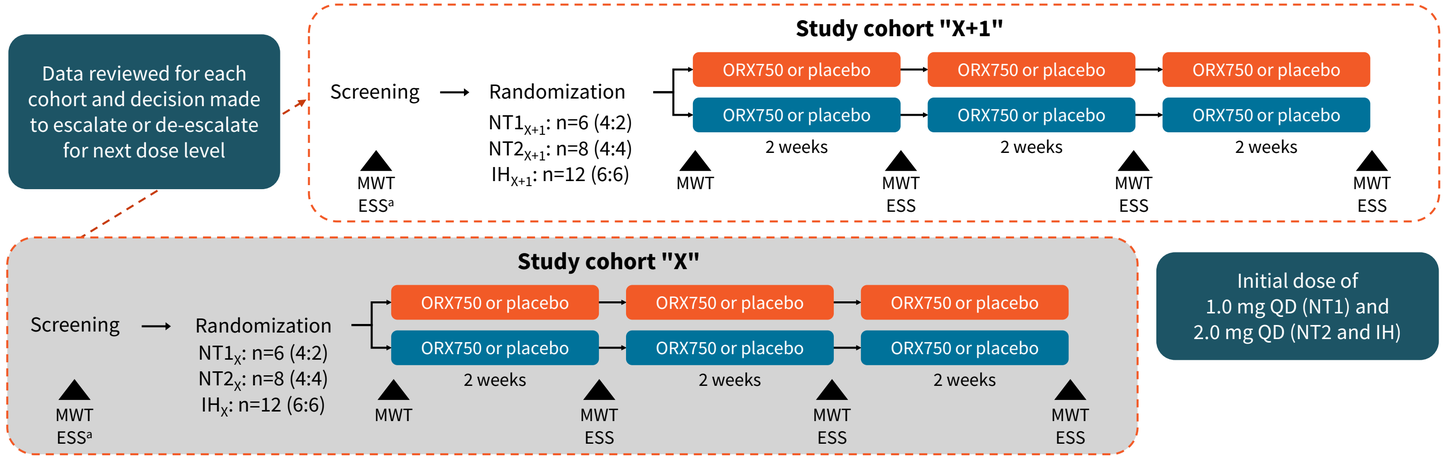
Key exclusion criteria

Medical disorder associated with EDS other than NT1, NT2, or IH

Presence of significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, hematologic, endocrine, neurologic, or psychiatric disease or malignancy

BMI, body mass index; EDS, excessive daytime sleepiness; ICSD-3-TR, International Classification of Sleep Disorders, 3rd edition, text revision; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

Figure 2. CRYSTAL-1 Study Design



Study design is for illustrative purposes only.
[a]Baseline MWT and ESS assessments are conducted after washout of medications used for narcolepsy or IH.
ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; QD, once daily.

Figure 3. Key Endpoints

Primary endpoints	• Safety and tolerability
Secondary endpoints	• Pharmacokinetic parameters of ORX750 • Efficacy on measures of excessive daytime sleepiness: – Objective: Maintenance of Wakefulness Test (MWT) – Subjective: Epworth Sleepiness Scale (ESS)
Exploratory endpoints	• Weekly cataplexy rate (NT1 only) • Narcolepsy Severity Scale (NSS/NSS2) or Idiopathic Hypersomnia Severity Scale (IHSS) • Karolinska Sleepiness Scale (KSS) • Additional efficacy assessments of cognition, attention, memory, and general health

NT1, narcolepsy type 1.

CURRENT STATUS AND FUTURE DIRECTIONS

- The CRYSTAL-1 study is currently recruiting at participating sites in the United States, Canada, and the European Union
- Data from this study are expected in 2025
- This will be the first time ORX750 is evaluated in participants with NT1, NT2, and IH, and the results will inform future clinical studies

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DISCLOSURES

Yves Dauvilliers is a consultant for and has participated in advisory boards for Avadel, Bioprojet, Centessa, Harmony Biosciences, Idorsia, Takeda, Theranexus, and UCB. **Giuseppe Plazzi** serves on advisory boards for Alkermes, Bioprojet Pharma, Centessa, Idorsia, Jazz, Takeda, and UCB. **David T. Plante** has served as consultant/advisor for or received funding or speaking/lecture fees from Aditum Bio, Alkermes, Alzheimer's Association, American Academy of Sleep Medicine, American Academy of Sleep Medicine Foundation, Centessa, Harmony Biosciences, Jazz, National Institutes of Health, Teva Pharmaceutical Australia, and the Wisconsin Alumni Research Foundation; and has received royalties from Cambridge University Press. **Emmanuel Mignot** has received consulting fees and is an investigator of research contracts or funded clinical trials sponsored by Alkermes, Avadel, Centessa Pharmaceuticals plc, Eisai, Jazz, Takeda, and Vanda; and owns equity in Centessa. **Thomas Roth** is a consultant for Avadel, Centessa, Eisai, Idorsia, Jazz, Merck, Orexo, and Takeda. **Mario Alberto Accardi** is an employee of the study sponsor, Centessa Pharmaceuticals (UK) Limited, **Amanda Sterkel, Deborah Hartman,** and **Saurabh Saha** are employees of the sponsor's affiliate, Centessa Pharmaceuticals LLC, and each person is a stockholder of the sponsor's parent company, Centessa Pharmaceuticals plc. **Jennifer Kong** and **Ellie Im** are former employees of the sponsor's affiliate, Centessa Pharmaceuticals LLC, and during the course of employment received stock of the sponsor's parent company, Centessa Pharmaceuticals plc.

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