Development of a Novel, Oral Orexin Receptor 2 Agonist, ORX750, for Treatment of Patients With Narcolepsy (Type 1 and 2) and Idiopathic Hypersomnia

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BACKGROUND

- Narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) are rare, central disorders of hypersomnolence characterized by excessive daytime sleepiness[1]
- Orexin receptor 2 (OX2R) agonists have been shown to increase wakefulness in individuals with NT1,[2] NT2, and IH, who typically have normal levels of orexin in the central nervous system[3,4]
- ORX750 is a novel, investigational OX2R agonist in development for the treatment of NT1, NT2, and IH[5]
- Strong wake-promoting effects of ORX750 were observed in preclinical studies, supporting clinical investigation[6-8]
- The development program is ongoing and includes a first-in-human phase 1 study to evaluate the safety and wake-promoting effects of single and multiple oral doses of ORX750, a phase 2a study (ORX750-0201 [CRYSTAL-1]) in NT1, NT2 and IH patients, and a long-term extension (LTE) study (ORX750-202) for participants who complete ORX750-0201

OBJECTIVE

- **Phase 1:** To evaluate the safety and wake-promoting effects of ORX750 in a first-in-human, phase 1 clinical study

METHODS

Phase 1 Study Design

- The safety, tolerability, and pharmacokinetics (PK) of ORX750 were evaluated using single-ascending doses (SAD) and multiple-ascending doses (MAD) in healthy adult participants
- In each SAD cohort, wake-promoting effects were evaluated in randomized, double-blind, placebo-controlled proof-of-concept (PoC) sleep study cohorts using a single-dose, 2-way crossover design in acutely sleep-deprived participants; dosing occurred at 11:00PM, followed by Maintenance of Wakefulness Test (MWT) trials at 1:00AM, 3:00AM, 5:00AM, and 7:00AM, along with the use of the Karolinska Sleepiness Scale (KSS) (Figure 1)

Phase 1 Study Population

- Eligible participants were healthy males between 18 and 45 years old (females not of childbearing potential were permitted in MAD cohorts)

Phase 1 Key Endpoints

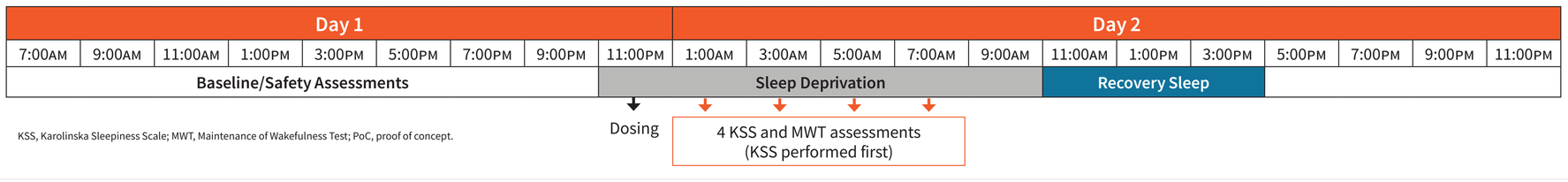
Safety and tolerability

- Incidence of treatment-emergent adverse events (TEAEs)
- Columbia-Suicide Severity Rating Scale scores
- Changes from baseline in clinical laboratory tests
- Changes from baseline in vital signs
- Changes from baseline in 12-lead electrocardiogram (ECG)

Pharmacodynamics

- Mean sleep latency on the MWT averaged across 4 trials
- Mean KSS scores averaged across 4 postdose assessments

Figure 1. Schematic for Each Dosing Period in Phase 1 PoC Cohorts



KSS, Karolinska Sleepiness Scale; MWT, Maintenance of Wakefulness Test; PoC, proof of concept.

RESULTS

Phase 1 Participant Enrollment

- As of the data cutoff date of December 5, 2024, the following dosing cohorts have completed:
  - SAD: 1.0 mg, 2.0 mg, 2.5 mg, 3.5 mg, and 5.0 mg
  - MAD: 2.0 mg, 3.0 mg, and 4.0 mg
  - PoC: 1.0 mg, 2.5 mg, 3.5 mg, and 5.0 mg
- These data are considered interim, as the study is open

Phase 1 Pharmacodynamic Endpoints

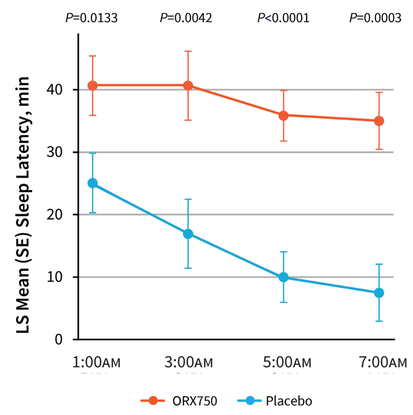
- ORX750 demonstrated dose-dependent and significant improvements in mean sleep latency on the MWT (Table 1)
  - The 2.5 mg, 3.5 mg, and 5.0 mg doses all produced MWT least squares mean sleep latencies >30 minutes in acutely sleep-deprived, healthy participants (Table 1)
  - Sustained effects (>30 minutes) were observed throughout the 8-hour postdose observation period (Figure 2)
- ORX750 demonstrated dose-dependent improvements in the mean postdose change from predose in KSS scores compared with placebo, which were significant at doses ≥2.5 mg (Table 2)
  - Sustained effects were observed throughout the 8-hour postdose observation period (Figure 3)

MWT RESULTS

Table 1. LS Mean Sleep Latency

	LS Mean (95% CI) Sleep Latency, min			
	ORX750	Placebo	Difference ORX750–Placebo	*P*-Value
1.0 mg (n=8)	17.6 (12.1, 23.2)	9.6 (4.1, 15.1)	8.1 (0.3, 15.9)	0.04
2.5 mg (n=8)	32.0 (22.2, 41.8)	16.7 (6.9, 26.5)	15.2 (4.7, 25.8)	0.01
3.5 mg (n=10)	33.6 (27.1, 40.1)	13.4 (6.9, 19.9)	20.2 (15.2, 25.2)	<0.0001
5.0 mg (n=8)	37.9 (31.7, 44.0)	15.3 (9.1, 21.5)	22.6 (17.0, 28.2)	<0.0001

Figure 2. LS Mean Sleep Latency by Time: 5.0 mg Cohort (n=8)



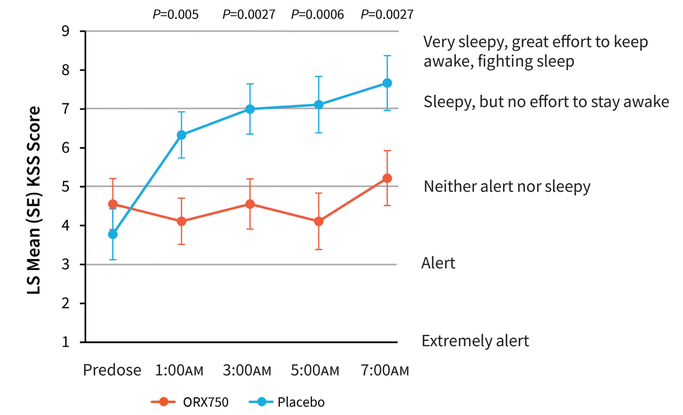
CI, confidence interval; LS, least squares; MWT, Maintenance of Wakefulness Test; SE, standard error.
Analysis used a linear mixed-effects model with repeated measures. Nominal *P*-values were reported by time point. Error bar represents standard error (SE).

KSS RESULTS

Table 2. LS Mean KSS Scores

	LS Mean (95% CI) Sleep Latency, min			
	ORX750	Placebo	Difference ORX750–Placebo	*P*-Value
1.0 mg (n=8)	6.4 (4.9, 7.9)	7.0 (5.5, 8.4)	-0.6 (-2.7, 1.5)	NS
2.5 mg (n=9)	4.9 (3.6, 6.3)	6.7 (5.4, 8.0)	-1.7 (-3.2, -0.3)	0.03
3.5 mg (n=10)	5.0 (4.1, 5.9)	6.9 (6.0, 7.8)	-1.9 (-3.2, -0.7)	0.006
5.0 mg (n=9)	4.4 (3.3, 5.4)	7.3 (6.3, 8.3)	-2.9 (-4.4, -1.5)	0.0012

Figure 3. LS Mean KSS Scores by Time: 5.0 mg Cohort (n=9)



CI, confidence interval; KSS, Karolinska Sleepiness Scale; LS, least squares; NS, not significant; SE, standard error.
Analysis used a linear mixed-effects model with repeated measures. Nominal *P*-values were reported by time point. Error bar represents standard error (SE).

SAFETY

- All *Phase 1* TEAEs observed as of cutoff date were mild or moderate in severity (Table 3), transient, and resolved without intervention
  - Only 2 moderate TEAEs were observed, and both were deemed unrelated to study drug
- There were no clinically significant treatment-emergent changes in hepatic or renal parameters, vital signs, or ECG parameters
- No cases of hepatotoxicity, cardiotoxicity, visual disturbances, or hallucinations were observed
- Safety data from PoC cohorts were consistent with those from SAD cohorts

Table 3. Summary of TEAEs

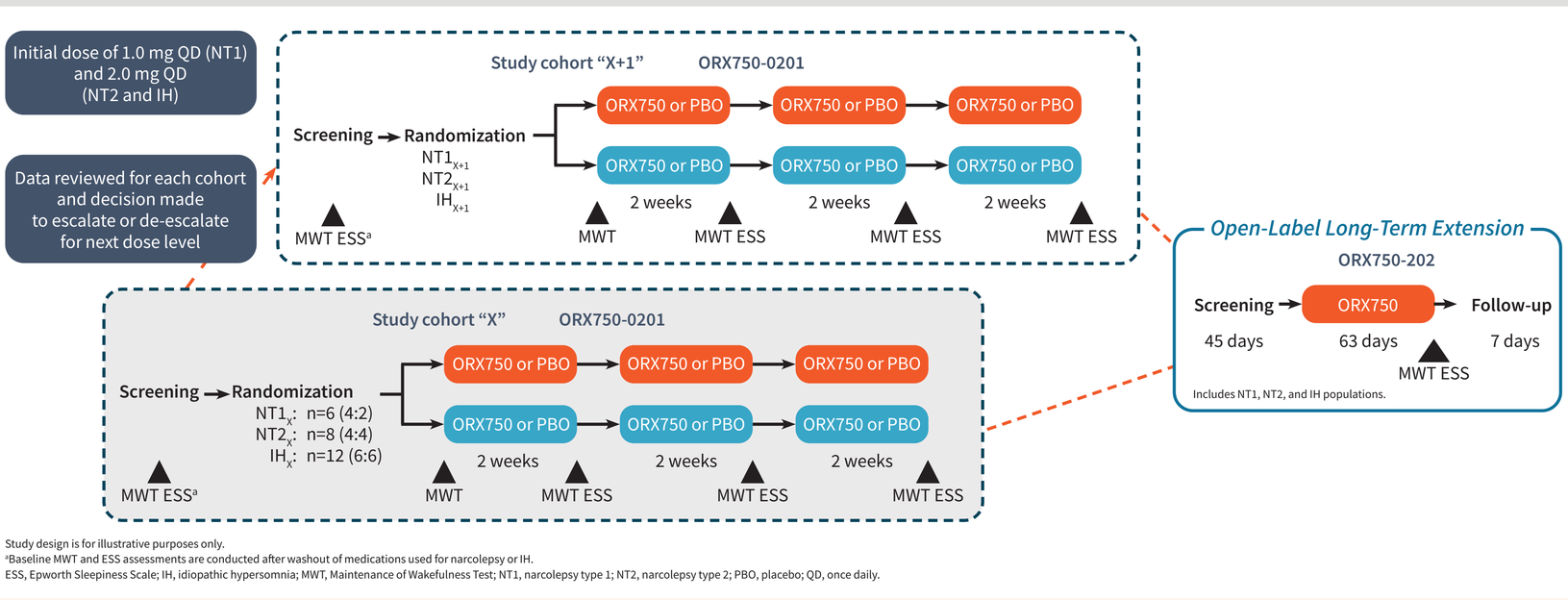
	SAD Cohorts						MAD Cohorts			
	Placebo (n=15)	ORX750 1.0 mg (n=9)	ORX750 2.0 mg (n=9)	ORX750 2.5 mg (n=9)	ORX750 3.5 mg (n=9)	ORX750 5.0 mg (n=9)	Placebo (n=6)	ORX750 2.0 mg (n=8)	ORX750 3.0 mg (n=8)	ORX750 4.0 mg (n=8)
Any TEAE, n (%)	4 (27)	3 (33)	3 (33)	1 (11)	0	3 (33)	3 (50)	4 (50)	4 (50)	6 (75)
Related	4 (27)	0	2 (22)	1 (11)	0	2 (22)	1 (17)	4 (50)	2 (25)	5 (63)
Nonrelated	1 (7)	3 (33)	2 (22)	0	0	2 (22)	3 (50)	2 (25)	2 (25)	3 (38)
Mild	4 (27)	3 (33)	3 (33)	1 (11)	0	3 (33)	3 (50)	4 (50)	4 (50)	4 (50)
Moderate	0	0	0	0	0	0	0	0	0	2 (25)
Severe	0	0	0	0	0	0	0	0	0	0
TEAEs leading to discontinuation, n (%)	0	0	0	0	0	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0	0	0	0	0

TEAEs are reported by maximum severity. Nonrelated includes unlikely related and not related. Related includes probably and possibly related. Two moderate AEs were reported at 4.0 mg (toothache and vasovagal syncope); both were deemed unrelated.
AE, adverse event; MAD, multiple-ascending dose; SAD, single-ascending dose; TEAE, treatment-emergent adverse event.

PHASE 2a AND LTE STUDY DESIGN

- ORX750-0201 (CRYSTAL-1) is a phase 2a adaptive, randomized, double-blind, placebo-controlled crossover basket study that will evaluate the safety, tolerability, efficacy, and PK of multiple doses of ORX750 in participants with NT1, NT2, and IH; the study includes an open-label long-term extension study with separate cohorts for each condition
- Within dosing cohorts, participants will be randomized to 1 of 2 blinded treatment sequences and receive ORX750 or placebo in a crossover design
- Additional endpoints assessed in relevant cohorts include the Epworth Sleepiness Scale (ESS) and the change from baseline in weekly cataplexy rate (WCR), Narcolepsy Severity Scale (NSS), Narcolepsy Severity Scale-2 (NSS-2), and Idiopathic Hypersomnia Severity Scale (IHSS)
- 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
- Participants currently enrolled will have the opportunity to enroll in the open-label extension upon completion of the double-blind treatment sequence
- This study plans to enroll approximately 96 participants
- An open-label LTE study (ORX750-202) for participants who complete ORX750-0201 is ongoing
- The LTE includes screening (returning participants only; up to 45 days), a 9-week treatment period (Days 1–63), and a 7-day (±2) safety follow-up (Figure 4)

Figure 4: CRYSTAL-1 and Long-Term Extension 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; PBO, placebo; QD, once daily.

PHASE 1 CONCLUSIONS

- **There were no serious TEAEs or TEAEs leading to discontinuation, and all TEAEs deemed related to ORX750 were mild in severity, transient, and resolved without intervention**
- **ORX750 demonstrated significant and dose-dependent improvements in mean sleep latency on the MWT and subjective alertness on the KSS compared with placebo in acutely sleep-deprived, healthy male participants**
- **ORX750 doses ≥2.5 mg produced MWT mean sleep latencies >30 minutes**
- **These results supported progressing clinical development of ORX750 into patients with NT1, NT2, and IH**

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DISCLOSURES

Giuseppe Plazzi serves on advisory boards for Alkermes, Bioprojet Pharma, Centessa, Idorsia, Jazz, Takeda, and UCB.

Yves Dauvilliers is a consultant for and has participated in advisory boards for Avadel, Bioprojet, Centessa, Harmony Biosciences, Idorsia, Takeda, Theranexus, 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, Eisai, Jazz, Takeda, and Vanda; and owns equity in Centessa Pharmaceuticals plc.

Thomas Roth is a consultant for Avadel, Centessa, Eisai, Idorsia, Jazz, Merck, Orexo, and Takeda.

Amanda Sterkel, **Eileen Leary**, **Deborah Hartman**, **Saurabh Saha**, and **Stephen Kanes** 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.

Mario Alberto Accardi is an employee of the study sponsor, Centessa Pharmaceuticals (UK) Limited.

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