Poster P-51.425

Phase 1 Clinical Data With Orexin Receptor 2 (OX2R) Agonist, ORX750, in Acutely Sleep-Deprived Healthy Volunteers

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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. Individuals with NT1 have a loss of orexin-producing neurons, which are located in the hypothalamus[1]
- Orexin receptor 2 (OX2R) agonists have been shown to increase wakefulness not only in individuals with NT1[2] but also in individuals with 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]

OBJECTIVE

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

METHODS

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
- Following each SAD cohort, wake-promoting effects were evaluated in randomized, double-blind, placebo-controlled proof-of-concept (PoC) sleep study cohorts with a single-dose, 2-way crossover design in acutely sleep-deprived participants utilizing the Maintenance of Wakefulness Test (MWT) and Karolinska Sleepiness Scale (KSS) (**Figure 1**)
- Dosing occurred at 11 PM, with MWT trials at 1 AM, 3 AM, 5 AM, and 7 AM (**Figure 2**)

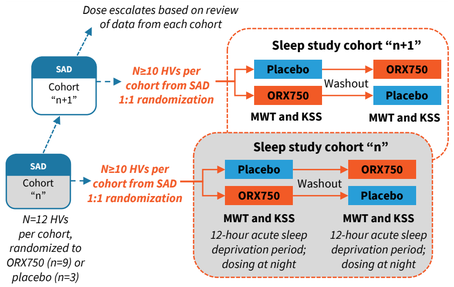
Study Population

- Eligible participants were healthy males between 18 and 40 years old (females not of childbearing potential were permitted in MAD cohorts)

Key Endpoints

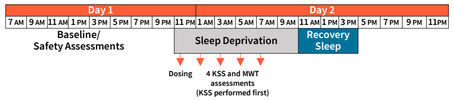
- Safety and tolerability: incidence of treatment-emergent adverse events (TEAEs), Columbia-Suicide Severity Rating Scale scores, and changes from baseline in clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs)
- Pharmacodynamics:
  - Mean sleep latency on the MWT averaged across 4 trials
  - Mean KSS scores averaged across 4 postdose assessments

Figure 1. Phase 1 SAD/PoC Study Design Schema



Study design is for illustrative purposes only.
HV, healthy volunteer; KSS, Karolinska Sleepiness Scale; MWT, Maintenance of Wakefulness Test; PoC, proof of concept; SAD, single-ascending dose.

Figure 2. Schematic for Each Dosing Period in PoC Cohorts



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

RESULTS

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

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 3**)
- 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 4**)

RESULTS (cont.)

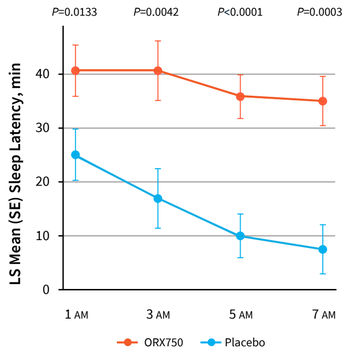
MWT Results

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

CI, confidence interval; LS, least squares.

Figure 3. LS Mean Sleep Latency by Time: 5.0 mg Cohort (n=8)



Analysis was using a linear mixed-effects model with repeated measures. Nominal *P* values were reported by time point. Error bar represents standard error (SE).
LS, least squares.

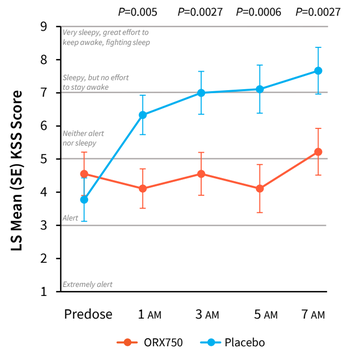
KSS Results

Table 2. LS Mean KSS Scores

	LS Mean (95% CI) Postdose KSS Score			
	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

CI, confidence interval; KSS, Karolinska Sleepiness Scale; LS, least squares; NS, not significant.

Figure 4. LS Mean KSS Scores by Time: 5.0 mg Cohort (n=9)



Analysis was using a linear mixed-effects model with repeated measures. Nominal *P* values were reported by time point. Error bar represents standard error (SE).
KSS, Karolinska Sleepiness Scale; LS, least squares.

Safety

- All TEAEs observed to 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.

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 support continued evaluation of ORX750 for the potential treatment of central disorders of hypersomnolence
  - A phase 2a study, CRYSTAL-1 (ORX750-0201), evaluating the safety, tolerability, efficacy, and PK of ORX750 in patients with NT1, NT2, and IH, is ongoing
  - The phase 2a study design will be presented at SLEEP 2025 as poster P-51.423 on Wednesday, June 11 (10 AM-11:45 AM)

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DISCLOSURES

Deborah Hartman, **Amanda Sterkel**, and **Saurabh Saha** are employees of the sponsor's affiliate, Centessa Pharmaceuticals LLC, **Mario Alberto Accardi** is an employee of the study sponsor, Centessa Pharmaceuticals (UK) Limited, 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. **Emiliangelo Ratti** is a consultant to Centessa and stockholder of Centessa Pharmaceuticals plc.

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