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

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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 CNS.[3,4]
- ORX750 is a novel, investigational OX2R agonist in development for the treatment of NT1, NT2, and IH.
- Strong wake-promoting effects of ORX750 were observed in preclinical studies, supporting clinical investigation.[5-7]

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

Methods

Study Design

- Safety, tolerability, and pharmacokinetics (PK) of ORX750 were evaluated as 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, two-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 11pm, with MWT trials at 1am, 3am, 5am, and 7am (*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), C-SSRS scores, and changes from baseline in clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECG).
- Pharmacodynamics:
  - Mean sleep latency on the Maintenance of Wakefulness Test (MWT), averaged across 4 trials
  - Mean Karolinska Sleepiness Scale (KSS) scores, averaged across 4 post-dose assessments

Figure 1: Phase 1 SAD / PoC Study Design Schema

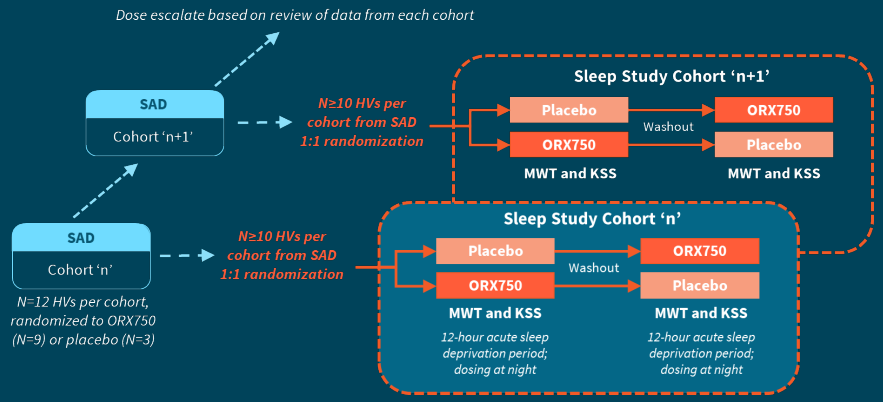
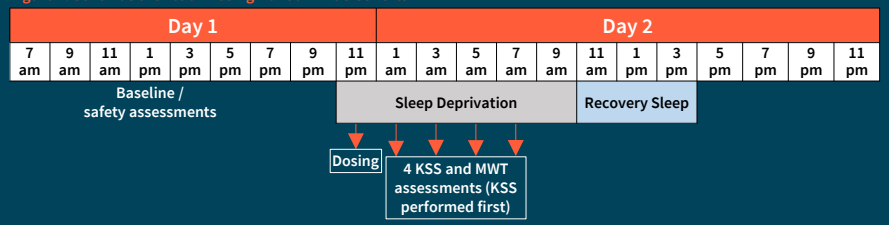


Figure 2: Schematic for each Dosing Period in PoC Cohorts



Results

Participant Enrollment

As of the data cut-off date of December 5, 2024, the following dosing cohorts have completed:

- SAD: 1.0 mg, 2.0 mg, 2.5 mg, 3.5 mg, 5.0 mg
- MAD: 2.0 mg, 3.0 mg, 4.0 mg
- POC: 1.0 mg, 2.5 mg, 3.5 mg, 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 LS mean sleep latencies > 30 minutes in acutely sleep-deprived healthy participants *(Table 1)*.
- Sustained effects (> 30 minutes) were observed throughout the 8-hour post dose observation period *(Figure 3)*.

ORX750 demonstrated dose-dependent improvements in the mean post dose change from pre dose in KSS scores compared to placebo, which were significant at doses ≥ 2.5 mg *(Table 2)*.

- Sustained effects were observed throughout the 8-hour post dose observation period *(Figure 4)*.

MWT RESULTS

Table 1. LS Mean Sleep Latency

	ORX750 LS Mean (95% CI) Sleep Latency (min)	Placebo LS Mean (95% CI) Sleep Latency (min)	LS Mean Difference vs placebo (95% CI)	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)	p=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)	p=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)	p<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)	p<0.0001

KSS RESULTS

Table 2. LS Mean KSS Scores

	ORX750 LS Mean (95% CI) post dose KSS score	Placebo LS Mean (95% CI) post dose KSS score	LS Mean Difference vs placebo (95% CI)	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)	p=NS
2.5 mg (n=9)	4.9 (3.6, 6.3)	6.7 (5.4, 8.0)	-1.7 (-3.2, -0.3)	p=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)	p=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)	p=0.0012

NS = not significant

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

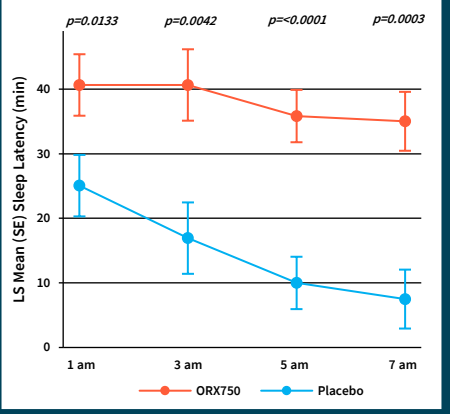
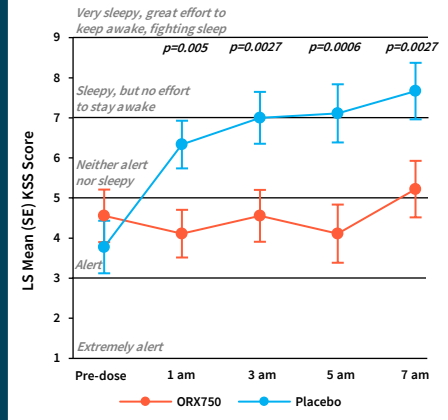


Figure 4. 5.0 mg Cohort (n=9) LS Mean KSS Score by Time



LS, least squares. Analysis was using a linear mixed-effects model with repeated measures. Nominal p-values were reported by timepoint. Error bar represents standard error.

Safety

- All treatment emergent adverse events (TEAEs) observed to date were mild or moderate in severity, 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 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 Nonrelated	4 (27) 1 (7)	0 3 (33)	2 (22) 2 (22)	1 (11) 0	0 0	2 (22) 2 (22)	1 (17) 3 (50)	4 (50) 2 (25)	2 (25) 2 (25)	5 (63) 3 (38)
Mild Moderate Severe	4 (27) 0 0	3 (33) 0 0	3 (33) 0 0	1(11) 0 0	0 0 0	3 (33) 0 0	3 (50) 0 0	4 (50) 0 0	4 (50) 0 0	4 (50) 2 (25) 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

Treatment-emergent adverse event (TEAE) are reported by maximum severity. Nonrelated includes unlikely related and not related. Related includes probably and possibly related. 2 moderate AEs were reported at 4.0 mg (toothache and vasovagal syncope); both were deemed unrelated.

Conclusion

- There were no serious TEAEs, no 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 to 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, ORX750-0201, evaluating the safety, tolerability, efficacy, and PK of ORX750 in patients with NT1, NT2, and IH is ongoing.

References: [1]Scammell TE. N Engl J Med 2015;373:2654-62. [2]Dauvilliers et al., NEJM 2023;389; [3]Evans et al, PNAS 2022; [4]Mignot E et al., Sleep 2023;46(9); [5]Black, SW et al., J Sleep Res 2022;31(S1):P001; [6]Black, SW et al., Sleep Med 2024;115(S1):S2902; [7]Black et al., European Sleep Research Society 2024 Abstract.

Acknowledgments: Sponsored by Centessa Pharmaceuticals (UK) Limited. We thank Dr. Yves Dauvilliers for scientific input throughout the study conduct and Dr. Mandy Sterkel for writing support.

Disclosures: Mario Accardi is an employee of the study sponsor, Centessa Pharmaceuticals (UK) Limited, and Deborah Hartman, Jennifer Kong, Saurabh Saha, and Ellie Im 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. Emiliangelo Ratti is a consultant to the study sponsor and stockholder of Centessa Pharmaceuticals plc.

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