Centessa Pharmaceuticals Reports Financial Results for the Third Quarter of 2025 and Provides Update on Potential Best-in-Class Orexin Receptor 2 (OX2R) Agonist Program

November 5, 2025

- *ORX750: Demonstrated potential best-in-class profile for treatment of narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) in initial cohorts of ongoing Phase 2a study; Data mark first robust demonstration of oral OX2R agonist addressing wakefulness needs of patients across all three indications; Expect to initiate registrational program in Q1 2026*
- *ORX142: Phase 1 data support highly differentiated profile; Expect to initiate patient studies in Q1 2026*
- *ORX489: Advancing in IND-enabling studies; Expect to initiate clinical studies in Q1 2026*

BOSTON and LONDON, Nov. 05, 2025 (GLOBE NEWSWIRE) -- Centessa Pharmaceuticals plc (Nasdaq: CNTA), a clinical-stage pharmaceutical company, today reported financial results for the third quarter ended September 30, 2025 and provided an update on its OX2R agonist program, including Phase 2a data[1] from the initial dosing cohorts within the ongoing CRYSTAL-1 study of ORX750 in NT1, NT2 and IH participants, and Phase 1 data[2] from the ongoing study of ORX142 in healthy volunteers.

"We are thrilled to share significant progress marked by clinical data from our growing OX2R agonist program," said Saurabh Saha MD PhD, Chief Executive Officer of Centessa. "Based on today's update, ORX750 continues to stand out as a potential best-in-class OX2R agonist for the treatment of NT1, NT2 and IH, and potentially as the first OX2R agonist to treat NT2 and IH. Within the Phase 2a's initial cohorts at low doses for all three indications, ORX750 achieved statistically significant, clinically meaningful and dose-dependent results across key measures, including the Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS) and Weekly Cataplexy Rate (WCR). Underpinning these data is a generally favorable safety and tolerability profile observed across the study[1]. These data signal a potentially wide therapeutic window for ORX750 and provide strong mechanistic rationale supporting the potential to further enhance efficacy and dosing flexibility within ongoing dose-escalation cohorts. Given enrollment momentum across these cohorts, we expect to initiate the registrational program for ORX750 in Q1 2026."

Dr. Saha continued, "We are equally excited by the progress of ORX142, where Phase 1 data [2] in healthy volunteers demonstrated a highly differentiated profile characterized by high potency and selectivity, rapid onset of action, differentiated pharmacokinetics (PK), and a generally favorable safety and tolerability profile. Given the strength of this data, we are advancing clinical development with patient studies expected to begin in Q1 2026 for undisclosed indications. In parallel, ORX489, our most potent OX2R agonist drug candidate to date, is advancing through IND enabling studies and, subject to IND clearance, we expect to initiate clinical studies in Q1 2026. With multiple differentiated orexin agonists advancing, we believe we are establishing clear leadership in this emerging class and building a durable, long-term growth platform in neuroscience."

ORX750 Phase 2a Study Update

The Phase 2a data[1] from initial dosing cohorts marks the first robust demonstration of an oral OX2R agonist addressing wakefulness needs across NT1 patients, who lack endogenous orexin, and the broader populations of NT2 and IH patients, who maintain normal to variable orexin levels.

The Phase 2a study update includes a total of 55 participants with NT1, NT2 and IH who completed dosing with ORX750 in the 2-week crossover cohorts as of the September 23, 2025 data cut-off date. ORX750 was observed to be generally well-tolerated at all doses tested across each indication with all treatment-emergent adverse events (TEAEs) being transient and mild to moderate in severity. One participant discontinued from treatment due to urinary urgency in the NT2 cohort. There were no clinically meaningful changes in cardiac, visual, liver or renal function. The most common TEAEs (≥10%) across all completed NT1, NT2 and IH cohorts were pollakiuria (51%), insomnia (22%), dizziness (13%) and headache (11%).

Initial NT1 dose cohorts included 1.0 mg and 1.5 mg doses administered once daily in the randomized 2-week crossover. For NT1, ORX750 achieved:

- Statistically significant, clinically meaningful and dose-dependent improvements from baseline compared with placebo in mean sleep latency on the MWT at both doses. In the 1.5 mg cohort (n=6), ORX750 achieved a >20 minute change from baseline in mean sleep latency compared with placebo on the MWT at Week 2 (p-value =0.0026), with half the participants achieving >30 minutes in mean sleep latency on the MWT. Dose escalation is progressing with both once-daily and split-dose regimens.
- Statistically significant, clinically meaningful and dose-dependent improvements from baseline in ESS total score compared with placebo at both doses. In the 1.5 mg cohort (n=7), participants had a mean ESS total score of 5.1 with ORX750 compared to a mean ESS total score of 18.7 with placebo at Week 2 (p-value =0.0001). Participants had a mean ESS total score of 19.6 at baseline.
- Statistically significant, clinically meaningful and dose-dependent reductions in Weekly Cataplexy Rate (WCR) at both doses. In the 1.5 mg cohort (n=7), participants with ORX750 had an 87% relative reduction in WCR compared with placebo, with an estimated incidence rate ratio of 0.13 at Week 2 (p-value = 0.0025).

Initial NT2 dose cohorts included 2.0 mg and 4.0 mg doses administered once daily in the randomized 2-week crossover. For NT2, ORX750 achieved:

- Statistically significant, clinically meaningful and dose-dependent improvements from baseline compared with placebo in mean sleep latency on the MWT at both doses. In the 4.0 mg cohort (n=10), ORX750 achieved a >10 minute change from baseline in mean sleep latency compared with placebo on the MWT at Week 2 (p-value = 0.0193). Dose escalation is progressing with both once-daily and split-dose regimens.
- Statistically significant, clinically meaningful and dose-dependent improvements from baseline in ESS total score compared with placebo at both doses. In the 4.0 mg cohort (n=10), participants had a mean ESS total score of 8.1 with ORX750 compared to a mean ESS total score of 15.9 with placebo at Week 2 (p-value =0.0023). Participants had a mean ESS total score of 17.3 at baseline.

The initial IH dose cohort included a 2.0 mg dose administered once daily in the randomized 2-week crossover. At this dose (n=17), ORX750 achieved statistically significant and clinically meaningful improvements from baseline compared with placebo on multiple efficacy measures including mean sleep latency on the MWT (p-value =0.0213). Dose escalation is progressing.

“In these early cohorts, ORX750 has already achieved notable improvements on MWT, ESS and WCR- key measures of symptom normalization in NT1- translating clinical efficacy into meaningful, real-world gains in wakefulness and daily functioning. In addition, ORX750’s distinct PK profile contributed to generally favorable safety and tolerability, along with a prolonged duration of action throughout the day,” stated Mario Alberto-Accardi PhD, President, Centessa Orexin Program. “ORX750 also achieved clinically meaningful wake promotion in NT2 with observed improvements to date that could potentially establish ORX750 as the new standard of care in NT2. And, for IH, ORX750 is the first OX2R agonist to demonstrate statistically significant and clinically meaningful improvements on multiple efficacy measures including on the MWT. With more than 50 participants across ongoing cohorts, we expect to further enhance efficacy and dosing flexibility across all indications. We are deeply grateful to the patients, investigators and clinical site teams for their continued partnership and support in the successful execution of this study.”

ORX142 Phase 1 Study Update

The Phase 1 study update includes a total of 89 healthy adult volunteers who were dosed with ORX142 as of the October 3, 2025 data cut-off date. ORX142 demonstrated a rapid onset of action, differentiated pharmacokinetics and was observed to be generally well-tolerated at all doses tested. In addition, ORX142 achieved statistically significant and dose-dependent improvements from baseline compared to placebo in mean sleep latency on the MWT at all doses tested in acutely sleep-deprived healthy volunteers. Based on the totality of the Phase 1 data for ORX142, patient studies are planned for undisclosed indications.

OX2R Agonist Pipeline and Anticipated Upcoming Milestones

- **ORX750**: Phase 2a *CRYSTAL-1* study is ongoing. Expect to initiate registrational program in Q1 2026.
- **ORX142**: Phase 1 first-in-human study is ongoing. Expect to initiate patient studies in Q1 2026.
- **ORX489**: Advancing in IND-enabling studies. The Company is focused on obtaining IND clearance and initiating clinical studies in Q1 2026.

Third Quarter 2025 Financial Results

- **Cash, Cash Equivalents and Investments**: Cash, cash equivalents and investments totaled $349.0 million as of September 30, 2025. The Company expects its cash, cash equivalents and investments as of September 30, 2025 will fund operations into mid-2027.
- **Research & Development (R&D) Expenses**: R&D expenses were $41.6 million for the third quarter ended September 30, 2025, compared to $33.9 million for the third quarter ended September 30, 2024.
- **General & Administrative (G&A) Expenses**: G&A expenses were $12.2 million for the third quarter ended September 30, 2025, compared to $12.5 million for the third quarter ended September 30, 2024.
- **Net Loss**: Net loss was $54.9 million for the third quarter ended September 30, 2025, compared to $42.6 million for the third quarter ended September 30, 2024.

About the CRYSTAL-1 Study

The ongoing CRYSTAL-1 Study is a Phase 2a adaptive, randomized, double-blind, placebo-controlled study of ORX750 in the central disorders of hypersomnolence. The goals of the study are to demonstrate the safety and tolerability of ORX750, evaluate pharmacokinetics (PK) and pharmacodynamic (PD) measures, and identify the optimal dose(s) of ORX750 in each indication for a registrational program. For initial dose cohorts, independent cohorts with NT1, NT2, and IH patients were recruited to receive both ORX750 and placebo treatment randomized in a crossover manner (all participants received both 2 weeks of ORX750 and 2 weeks of placebo for comparison purposes and all patients served as their own control). Safety and tolerability were evaluated using standard adverse event (AE) collection, labs, ECG and vital signs. Efficacy was assessed by the change from baseline in mean sleep latency on the MWT and excessive daytime sleepiness on the ESS, each compared with placebo, and, for NT1 participants, by the incidence rate ratio for WCR compared with placebo. After completion of each indication cohort, a new dose was selected and reviewed by the Safety Review Committee based on observed safety, tolerability, exposure and efficacy.

Following the initial dose cohorts, the study was adapted to a 4-week parallel design enrolling at least eight participants with NT1 and at least twelve participants with NT2 or IH per cohort. Under this design, participants in ongoing and future cohorts are randomized to one of two blinded treatment sequences and receive 4 weeks of treatment with either ORX750 or placebo, followed by a 2-week crossover to the other treatment. Efficacy is assessed after the initial 4-week treatment period. Following completion of *CRYSTAL-1*, participants may enroll into an ongoing 9-week open-label

long-term extension (LTE) of ORX750 with separate cohorts for each condition. Information about the trial can also be found at ClinicalTrials.gov (NCT06752668 and NCT07096674).

About the Phase 1 Study of ORX142 in Healthy Volunteers

The Phase 1 clinical study is an ongoing first-in-human, randomized, placebo-controlled study designed to evaluate the safety, tolerability and PK of single-ascending doses (SAD) and multiple-ascending doses (MAD) of ORX142 in healthy adult participants. In parallel to the SAD, a placebo-controlled crossover PD assessment is being performed in acutely sleep-deprived healthy adult participants with the goal of generating early efficacy data to inform dosing for planned patient studies. Information about the trial can also be found at ClinicalTrials.gov (NCT07082829).

About Centessa Pharmaceuticals and Our OX2R Agonist Program

Centessa Pharmaceuticals, plc is a clinical-stage pharmaceutical company with a mission to discover, develop and ultimately deliver medicines that are transformational for patients. We are pioneering a new class of potential therapies within our OX2R agonist program for the treatment of EDS, impaired attention, cognitive deficits and fatigue across neurological, neurodegenerative and neuropsychiatric disorders. ORX750, ORX142 and ORX489 are investigational candidates and have not been approved by the FDA or any other regulatory authority. For more information, visit www.centessa.com, which does not form part of this release.

Forward Looking Statements

This press release contains forward-looking statements. These statements may be identified by words such as “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue,” “ongoing,” “aim,” “seek,” and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements, including statements related to the Company’s ability to discover and develop transformational medicines for patients; its expectations for executing on the Company's pipeline; its expectations on its anticipated cash runway; the timing of commencement of new studies or clinical trials or clinical and preclinical data related to ORX750, ORX142, ORX489 and other OX2R agonist molecules; its ability to identify, screen, recruit and maintain a sufficient number of or any participants in its existing and anticipated studies or clinical trials of ORX750, ORX142, ORX489 and other OX2R agonist molecules; its expectations on executing its research and clinical development plans and the timing thereof; its expectations as to the potential results, and impact of each of its clinical programs and trials; its statements and expectations regarding the safety, tolerability and efficacy of ORX750, ORX142, ORX489 and other OX2R agonist molecules based on topline and interim results and/or clinical updates; the Company’s ability to differentiate ORX750, ORX142, ORX489 and other OX2R agonist molecules from other existing or in-development treatment options including standard of care; the development, design and therapeutic potential of ORX750, ORX142, ORX489 and other OX2R agonist molecules; and regulatory matters, including the timing and likelihood of success of obtaining regulatory clearance, obtaining authorizations to initiate or continue clinical trials. Any forward-looking statements in this press release are based on our current expectations, estimates, assumptions and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the safety, tolerability and efficacy profile of our product candidates including ORX750, ORX142, ORX489 and other OX2R agonist molecules; our ability to identify, screen, recruit and retain a sufficient number of or any participants in our existing and anticipated new studies or clinical trials of ORX750, ORX142, ORX489 or within anticipated timelines; our expectations relating to the clinical trials of ORX750, ORX142 and ORX489, including the predicted timing of enrollment, the predicted efficacious doses of each of ORX750, ORX142 and ORX489 respectively and our ability to successfully conduct our clinical development of ORX750, ORX142 and ORX489, our ability to prosecute, protect and maintain our intellectual property position; business (including commercial viability), regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing product candidates and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oxford Finance, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; our operating costs and use of cash, including cash runway, cost of development activities and conducting clinical trials, future expenditures risks; the risk that any one or more of our product candidates will not be successfully developed and/or commercialized; the risk that the historical results of preclinical studies or clinical studies, including interim or topline results or updates will not be predictive of future results in ongoing or future studies; economic risks to the United States and United Kingdom banking systems; and geo-political risks such as the Russia-Ukraine war or the Middle East conflicts or trade wars. These and other risks concerning our programs and operations are described in additional detail in our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and our other reports, which are on file with the U.S. Securities and Exchange Commission (SEC). We explicitly disclaim any obligation to update any forward-looking statements except to the extent required by law.

1. As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750.
2. As of the October 3, 2025 data cut-off date for the Phase 1 study of ORX142.

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Centessa Pharmaceuticals plc
Consolidated Statements of Operations and Comprehensive Loss
(unaudited)
(amounts in thousands except share and per share data)

	Three Months Ended September 30, 2025	Three Months Ended September 30, 2024	Nine Months Ended September 30, 2025	Nine Months Ended September 30, 2024
License and other revenue	$ —	$ —	$ 15,000	$ —
Operating expenses:				
Research and development	41,563	33,903	117,747	89,370
General and administrative	12,227	12,502	36,473	37,105
Loss from operations	(53,790)	(46,405)	(139,220)	(126,475)
Interest and investment income	3,765	3,340	16,035	9,171
Interest expense	(2,890)	(2,557)	(8,651)	(7,611)

Other non-operating income (expense), net	(1,810)	3,664	2,808	2,281
Loss before income taxes	(54,725)	(41,958)	(129,028)	(122,634)
Income tax expense	166	608	2,341	1,794
Net loss	(54,891)	(42,566)	(131,369)	(124,428)
Other comprehensive (loss) income:				
Foreign currency translation adjustment	691	(412)	855	(498)
Unrealized (loss) gain on available for sale marketable securities, net of reclassification adjustment and tax	318	912	(2,468)	1,100
Other comprehensive (loss) income	1,009	500	(1,613)	602
Total comprehensive loss	$ (53,882)	$ (42,066)	$ (132,982)	$ (123,826)
Net loss per ordinary share - basic and diluted	$ (0.41)	$ (0.37)	$ (0.98)	$ (1.15)
Weighted average ordinary shares outstanding - basic and diluted	134,163,492	116,253,902	133,627,043	108,571,742

Centessa Pharmaceuticals plc
Condensed Consolidated Balance Sheets
(unaudited)
(amounts in thousands)

	September 30, 2025	December 31, 2024
Total assets:		
Cash and cash equivalents	$ 50,811	$ 383,221
Investments in marketable securities	298,228	98,956
Other assets	99,261	94,621
Total assets	$ 448,300	$ 576,798
Total liabilities		
Other liabilities	$ 36,910	$ 66,313
Long term debt	109,816	108,940
Total liabilities	146,726	175,253
Total shareholders' equity	301,574	401,545
Total liabilities and shareholders' equity	$ 448,300	$ 576,798