UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (date of earliest event reported): November 5, 2025

CENTESSA PHARMACEUTICALS PLC

(Exact name of Registrant, as specified in its charter)

England and Wales	**001-40445**	**98-1612294**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

3rd Floor **1 Ashley Road** **Altrincham** **Cheshire** **United Kingdom**	**WA14 2DT**
(Address of principal executive offices)	(Zip code)

Registrant's telephone number, including area code: **+1 (617) 468-5770**

Former name or address, if changed since last report:

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Ordinary shares, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC

*Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market, LLC.

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On November 5, 2025, Centessa Pharmaceuticals plc (the "Company") announced its financial results for the quarter ended September 30, 2025. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

Item 7.01 Regulation FD Disclosure.

The Company from time to time presents and/or distributes slide presentations to the investment community at various industry and other conferences to provide updates and summaries of its business. The Company is posting a copy of its current corporate slide presentation to the "Investors" portion of its website at www.centessa.com/events-presentations. These slides are attached to this Current Report on Form 8-K as Exhibit 99.2.

The information in this Current Report on Form 8-K (including Exhibit 99.1 and Exhibit 99.2) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.1 and Exhibit 99.2.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Press Release dated November 5, 2025
99.2	Corporate Presentation as of November 5, 2025
104	Cover Page Interactive Data (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: November 5, 2025

By:	/s/ Saurabh Saha
Name:	Saurabh Saha, M.D., Ph.D.
Title:	Chief Executive Officer

Exhibit 99.1

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

- *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, November 5, 2025 **--** 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.

Contact:

Kristen K. Sheppard, Esq.
SVP of Investor Relations
investors@centessa.com

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


CENTESSA
PHARMACEUTICALS
Corporate Overview
November 2025

Disclaimer and forward looking statements

This presentation has been prepared by Centessa Pharmaceuticals plc (the "Company") for informational purposes only and not for any other purpose. This presentation does not contain all the information that is or may be material to investors or potential investors and should not be considered as advice or a recommendation to investors or potential investors in respect of the holding, purchasing or selling of securities or other financial instruments and does not take into account any investor's particular objectives, financial situation or needs. The communication of this presentation may be restricted by law; it is not intended for distribution to, or use by any person in, any jurisdiction where such distribution or use would be contrary to local law or regulation. This presentation is not directed to or intended for distribution, or transfer, either directly or indirectly to, or use by, any person or entity that is a citizen or resident or located in any locality, state, country or other jurisdiction where such distribution, transfer, publication, availability or use would be contrary to law or regulation or which would require any registration or licensing within such jurisdiction.

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including ORX750, ORX142, and ORX489; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; the Company's ability to successfully conduct its clinical development of ORX750 below the maximum exposure limit set by the U.S. Food and Drug Administration ("FDA") or, in the event the Company plans to exceed the maximum exposure limit, the Company's ability to successfully have the maximum exposure limit removed; enroll subjects in clinical trials; market size and commercial opportunity for our product candidates; and our anticipated cash runway. 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 are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including, without limitation, risks related to our ability to protect and maintain our intellectual property position; business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products 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; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and geo-political risks such as the Russia-Ukraine war, the conflicts in the Middle East, trade wars and imposition of tariffs and other risk factors contained in our filings with the U.S. Securities and Exchange Commission. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. All projections, valuations, market-size forecast (including patient population), statistical analyses and study design illustrations are provided for information purposes only. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward looking statements contained herein to reflect any change in our expectations or any changes in projections, valuations, market-size forecast, statistical analyses, study design events, conditions or circumstances on which any such statement is based, except as may be required by law. They may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, they should not be relied upon as an accurate prediction of future performance.

This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the FDA or any other regulatory agency. No representation or warranty, express or implied, is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Certain information contained in this presentation relates to or is based on studies, publications, surveys, estimates, forecasts, projections and other data obtained from third party sources and the Company's own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation or warranty, express or implied, as to the adequacy, fairness, accuracy or completeness of, any information obtained from third party sources. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

MISSION *Discovering and developing transformational medicines for patients*

- Potential best-in-class / first-in-class orexin receptor 2 (OX2R) agonist franchise
- Robust series of clinical milestones anticipated across OX2R agonist pipeline in 2026
- Strong balance sheet

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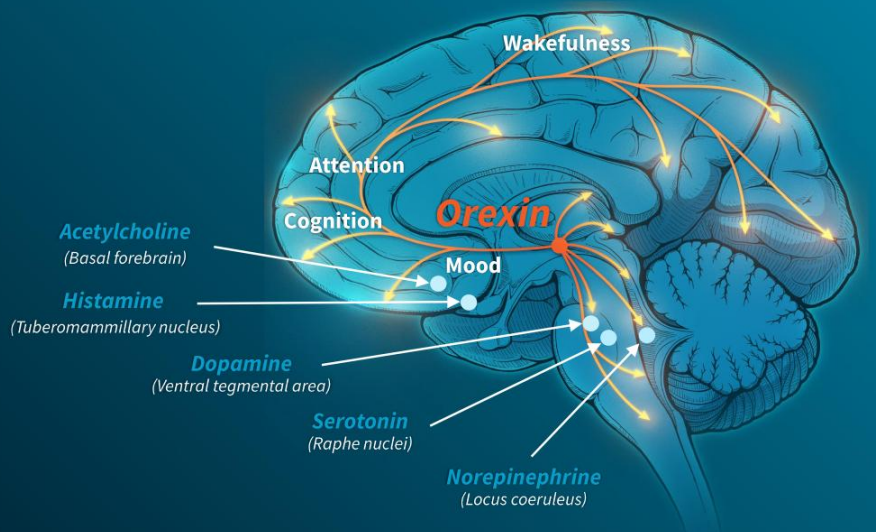
Centessa reported **$349.0 million** in cash, cash equivalents and investments as of September 30, 2025. Cash runway estimated into mid-2027.


OREXIN
Anticipated milestones
2025
Focused Execution
2026
Driving Momentum
ORX750
Phase 2a data in patients with Narcolepsy Type 1 (NT1), Narcolepsy Type 2 (NT2), and Idiopathic Hypersomnia (IH) in 2025
Registrational program planned for Q1 2026
ORX142
Phase 1 data in acutely sleep-deprived healthy volunteers in 2025
Patient studies planned for Q1 2026
ORX489
Advancing in IND-enabling studies
Clinical studies planned for Q1 2026*
CENTESSA
*Subject to IND clearance
4

Orexin agonists have the potential to transform the standard of care for individuals with sleep-wake, neurological, neurodegenerative and neuropsychiatric disorders

CENTESSA PHARMACEUTICALS

OREXIN *Targeting a key signaling neuropeptide implicated in numerous therapeutic areas*



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Sources: Pizza, F et al., J Sleep Res 2022;31(4):e13665; Toor, B et al., Front Neurol Neurosci 2021;45:38 ; Ten-Blanco, M et al., Front Neuroendo 2023;69:101066; and, Yamamoto, H et al., PLoS One, 2022;17(7):e0271901.

OREXIN

Potential best-in-class / first-in-class OX2R agonist therapeutics

- **ORX750** for the treatment of NT1, NT2 and IH
- **ORX142** for the treatment of neurological and neurodegenerative disorders
- **ORX489** for the treatment of neuropsychiatric disorders
- Earlier stage OX2R agonists and therapeutics for additional potential indications

Molecule	hOX2R EC50 (nM)	Selectivity vs. hOX1R
Native ligand orexin-A (OXA)[1]	0.035	n/a
ORX750[1]	**0.110**	**9,800x**
ORX142[2]	**0.069**	**13,000x**
ORX489[3]	**0.035**	**8,800x**

CENTESSA PHARMACEUTICALS

Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing human recombinant OX1R or OX2R.
1. Black et al., World Sleep 2023 Abstract. 2. Black et al., European Sleep Research Society 2024 Abstract. 3. Company data / presentations.

OREXIN

Broad and rapidly advancing OX2R agonist pipeline

ASSET	DISEASE/CONDITION	MECHANISM	PRE-CLINICAL	PHASE 1	PHASE 2
ORX750	Narcolepsy Type 1 (NT1)	OXR2 Agonist			
ORX750	Narcolepsy Type 2 (NT2)	OXR2 Agonist			
ORX750	Idiopathic Hypersomnia (IH)	OXR2 Agonist			
ORX142	Neurological & Neurodegenerative Disorders	OXR2 Agonist			
ORX489	Neuropsychiatric Disorders	OXR2 Agonist			
Undisclosed Assets	Undisclosed	Orexin Pathway			

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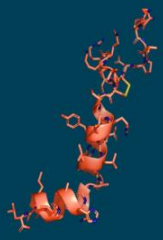
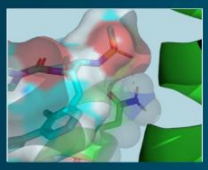
Pipeline of highly potent, selective OX2R agonists enabled by proprietary structural biology insights

Orexin-A: Highly Validated Pathway → **Proprietary Structure Based Drug Design** → **Medicinal Chemistry SAR***





Candidate Selection Criteria for a Best-in-Class Profile

- Highly potent and highly selective
- Optimal predicted PK profile
- Low predicted human doses
- Fast onset of action

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*SAR is Structure- Activity Relationship optimization.

ORX750 *Potential to redefine the standard of care for patients with sleep-wake disorders*

ORX750

Highly potent, selective OX2R agonist

- **High unmet medical need** in NT1, NT2 and IH
- Phase 2a data from initial low dose cohorts demonstrate **potential best-in-class profile across all three indications**[1]
- Expect to initiate **registrational studies in Q1 2026**
- **Significant commercial opportunity** as potential treatment for all three indications

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1. As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750; Data are considered preliminary, as the study is ongoing

ORX750 *CRYSTAL-1 Phase 2a study in NT1, NT2 and IH*

CRYSTAL-1 STUDY

Evaluate safety, tolerability, and PK in **NT1, NT2, and IH patients**

Efficacy assessment registrational endpoints: **Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), weekly cataplexy rate** (NT1 patients only), and overall symptom improvement*

Exploratory efficacy assessments will measure sleep, **cognition, attention, memory,** and general health

***First robust demonstration** of oral OX2R agonist addressing wakefulness needs of patients across NT1, NT2 and IH…*

- **Generally favorable safety and tolerability profile**
- **Statistically significant, clinically meaningful and dose-dependent efficacy**
- **Dose escalation** across ongoing and future cohorts with **once-daily and split-dose regimens**, enabled by Phase 1 data

…Expect to initiate registration program in Q1 2026

https://clinicaltrials.gov/study/NCT06752668
MWT and ESS are established registrational endpoints for EDS in sleep-wake disorders and weekly cataplexy rate is an established registration endpoint for cataplexy in NT1.
*Measured by Narcolepsy Severity Scale (NSS) and Idiopathic Hypersomnia Severity Scale (IHSS).

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ORX750 *Demonstrated a generally favorable safety and tolerability profile*

CRYSTAL-1

ORX750 has been 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.

55 participants
with NT1, NT2 and IH

who have been dosed with ORX750 in the 2-week crossover dose cohorts completed as of the data cut-off date

The most common TEAEs (≥10%) across all completed NT1, NT2 and IH cohorts	pollakiuria 51%	insomnia 22%	dizziness 13%	headache 11%

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Data cutoff as of September 23, 2025; Data are considered preliminary, as the study is ongoing

ORX750 *Achieved statistically significant, clinically meaningful and dose-dependent improvements: MWT, ESS and WCR*

CRYSTAL-1

NT1

>20-minute change

from baseline in MSL compared with placebo on MWT

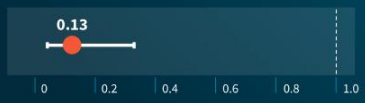
with 1.5 mg dose | ***p-value***=0.0026, n=6

50% of participants achieved **>30 minutes** in MSL on MWT

87% relative reduction in weekly cataplexy rate

with 1.5 mg dose | ***p-value***=0.0025, n=7

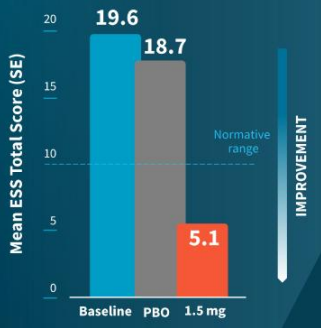
WCR Incidence Rate Ratio Relative to Placebo



ESS Score

achieved normative range

with 1.5 mg dose | ***p-value***=0.0001, n=7



Potential Best-in-Class Profile

- **Generally favorable safety and tolerability** profile
- **Clinically meaningful improvements** across multiple efficacy measures
- **Dose escalation across ongoing and future cohorts** within a 4-week parallel design[1]

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MWT, Maintenance of Wakefulness Test; MSL, Mean Sleep Latency; ESS, Epworth Sleepiness Scale; PBO, Placebo; SE, Standard Error; MWT and ESS analysis used a linear mixed model to estimate the treatment effect with the Least Square Mean (LS Mean); WCR analysis used a generalized linear mixed model (Poisson) to estimate the incidence rate ratio. The incidence rate ratio was calculated by dividing the adjusted incidence of the ORX750 group with the adjusted incidence of the placebo group; As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750; Data are considered preliminary, as the study is ongoing; 1. Ongoing QD dose in 2 week crossover design

ORX750 *Demonstrated clinically meaningful improvements on multiple efficacy measures; Data has the potential to establish ORX750 as the new standard of care for NT2*

CRYSTAL-1

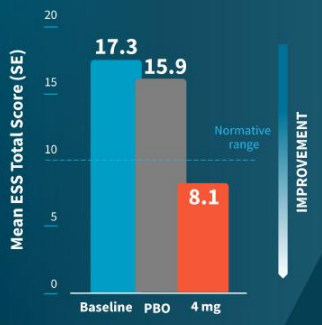
NT2

>10-minute change
from baseline in MSL compared with placebo on MWT
with 4 mg dose | ***p-value***=0.0193, n=10

IH

Statistically significant and clinically meaningful improvements from baseline on multiple efficacy measures, including MSL on MWT
with 2 mg dose | ***p-value*** =0.0213, n=17

ESS Score
for NT2 achieved normative range
with 4 mg dose | ***p-value***=0.0023, n=10



Potential Best-in-Class / First-in-Class Profile

- **Generally favorable safety and tolerability** profile
- **Clinically meaningful improvements** across multiple efficacy measures
- **Dose escalation across ongoing and future cohorts** within a 4-week parallel design

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MWT, Maintenance of Wakefulness Test; MSL, Mean Sleep Latency; ESS, Epworth Sleepiness Scale; PBO, Placebo; SE, Standard Error; MWT and ESS analysis used a linear mixed model to estimate the Least Square Mean (LS Mean); As of the September 23, 2025 data cut-off date for the Phase 2a study of ORX750; Data are considered preliminary, as the study is ongoing.

ORX750 *Randomized, double-blind, placebo-controlled basket study of ORX750 in patients with NT1, NT2, and IH ongoing*

CRYSTAL-1

CRYSTAL-1 STUDY

- Innovative design with potential to enable **well-powered** and efficient data generation
- Optimal number of patients to allow **efficient recruitment**
- Potential for **optimized dose selection**
- **4-week placebo-controlled** data at target doses
- Dosing started at **1.0 mg in NT1** and **2.0 mg in NT2 and IH once-daily**
- **Open-label extension** study initiated

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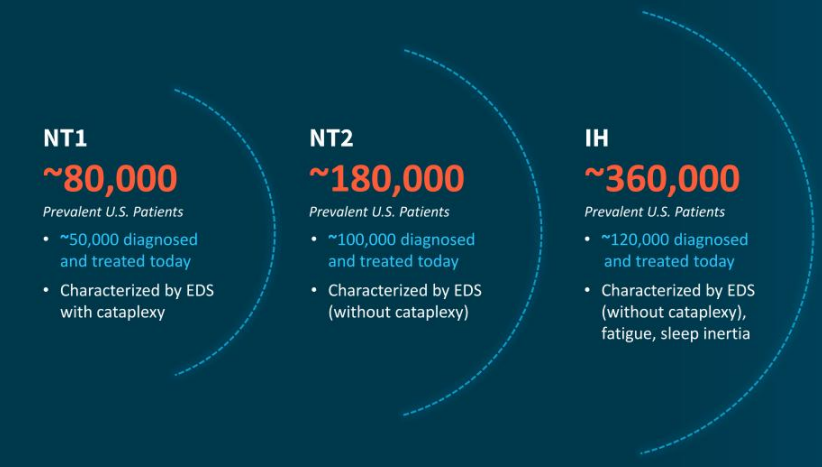
Note: Study design for illustrative purposes only.

ORX750 *NT1, NT2, and IH represent large addressable patient populations*



NT1

~80,000

Prevalent U.S. Patients

- ~50,000 diagnosed and treated today
- Characterized by EDS with cataplexy

NT2

~180,000

Prevalent U.S. Patients

- ~100,000 diagnosed and treated today
- Characterized by EDS (without cataplexy)

IH

~360,000

Prevalent U.S. Patients

- ~120,000 diagnosed and treated today
- Characterized by EDS (without cataplexy), fatigue, sleep inertia

ORX750
Addressable Patient Population
NT1, NT2, and IH

~620,000
Prevalent U.S. Patients

~270,000
Diagnosed and Treated U.S. Patients

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EDS is excessive daytime sleepiness.
Source of prevalent patient estimates: Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Centessa market research.
Source of diagnosed and treated patient estimates: Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Ohayon et al. Sleep Med X. 2023.

ORX750 *Large, well defined commercial opportunity for ORX750 as potential treatment for NT1, NT2 and IH*

LARGE MARKET OPPORTUNITY

ADDRESSABLE PATIENT POPULATION IN NT1, NT2 AND IH

~620,000
Prevalent U.S. patients[1]

~270,000
Diagnosed and treated U.S. patients[1]

HIGH UNMET NEED

CURRENT APPROVED THERAPIES HAVE SIGNIFICANT LIMITATIONS

Suboptimal Efficacy[2]

- Slightly increased sleep onset latencies in patients as measured by MWT
- Do not adequately address EDS, cataplexy or brain fog

Poor Tolerability[3]

- Potential for significant side effects leading to treatment discontinuations
- Challenges dealing with complex medication regimens

3 INDICATIONS IN 1

ORX750 HAS BEST-IN-CLASS POTENTIAL FOR THE TREATMENT OF NT1, NT2 AND IH

Flexible dosing supports potential to meet the needs of patients across 3 closely related indications

EFFICIENT GO TO MARKET

CONCENTRATED CALL POINTS IN U.S.[5]

~7,500 sleep specialists
~2,500 sleep centers

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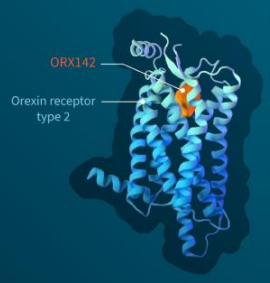
Source: 1. Acquavella *et al.*, J Clin Sleep Med 2020; Saad *et al.*, Sleep 2023; and Centessa Market Research; 2. Prescribing information for current standard of care therapies; 3. FDA, "The Voice of the Patient: Narcolepsy" 2014; 4. Maski *et al.*, J Clin sleep Med 2017; 5. American Association of Sleep Medicine (AASM) 2022

ORX142

Advancing pipeline molecule characterized by high potency and differentiated pharmacokinetics

ORX142



- **>13,000-fold selectivity vs. hOX1R**; EC_{50} 0.069 nM for hOX2R
- Rapid **onset of action** and **differentiated pharmacokinetics**
- Planned for the treatment of **neurological and neurodegenerative disorders**

Phase 1
89 healthy adult volunteers

Generally well-tolerated at all doses tested
with all AEs being self-limited and either mild or moderate intensity

- **Statistically significant**
- **Clinically meaningful**
- **Dose-dependent**

▶ Improvements from baseline compared to placebo in mean sleep latency on the MWT at all doses tested

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As of the October 3, 2025 data cut-off date for the Phase 1 study of ORX142 in healthy volunteers. Data are considered preliminary, as the study is ongoing.

OREXIN

Building a class-leading franchise

ORX750

Registrational program planned for Q1 2026

ORX142

Patient studies planned for Q1 2026

ORX489

Advancing in IND-enabling studies;
Clinical studies planned for Q1 2026*

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*Subject to IND clearance

MISSION *Discovering and developing transformational medicines for patients*

- Potential best-in-class / first-in-class orexin receptor 2 (OX2R) agonist franchise
- Robust series of clinical milestones anticipated across OX2R agonist pipeline in 2026
- Strong balance sheet

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Centessa reported **$349.0 million** in cash, cash equivalents and investments as of September 30, 2025. Cash runway estimated into mid-2027.


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