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): August 22, 2023

CENTESSA PHARMACEUTICALS PLC

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

England and Wales	**001-04321**	**98-1612294**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

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

Registrant's telephone number, including area code: **+44 7391 789784**

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 8.01 Other Events.

On August 22, 2023, the World Sleep Congress 2023 released an abstract submitted by Centessa Pharmaceuticals Plc. (the "Company") containing preclinical data on ORX750, the Company's orally administered, selective orexin receptor 2 (OX2R) agonist in development for the treatment of narcolepsy and other sleep disorders. The Company will present the abstract in an oral presentation on Wednesday, October 25, 2023 at 10:45am (local time). A copy of the Company's abstract is filed as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Abstract released by World Sleep 2023 on August 22, 2023
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: August 23, 2023

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

Exhibit 99.1

ORX750, an oral selective orexin receptor 2 agonist, promotes wakefulness and reduces cataplexy in the orexin/ataxin-3 mouse

S.W. Black, T. Steinfeld, K. Gibson, G.R. Ott, E. Ratti, D. Grainger, M.A. Accardi, D.S. Hartman

Centessa Pharmaceuticals, Inc., Boston, MA, United States, Centessa Pharmaceuticals (Orexia) Limited, Altrincham, Cheshire, United Kingdom, Centessa Pharmaceuticals (UK) Limited, Altrincham, Cheshire, United Kingdom

Introduction: Narcolepsy Type 1 (NT1) is a rare neurological disease caused by the profound loss of orexin-producing neurons. Orexin (also called hypocretin) is a neurotransmitter that regulates wakefulness, arousal, and energy homeostasis via activation of Orexin Receptor-1 (OX1R) and -2 (OX2R). Orexin agonists are designed to directly address the underlying disease pathology of NT1 to restore orexin neurotransmission in the brain. The orexin/ataxin-3 (Atax) mouse model of NT1 recapitulates key features of the human disorder, such as orexin loss, inability to sustain wakefulness, and cataplexy (emotionally triggered, transient loss of muscle tone). Here we present ORX750, a novel, orally available, brain penetrant, OX2R selective agonist. ORX750 was developed using structure-based drug design with an OX2R stabilized receptor (StaR®) protein and high-resolution protein crystallography.

Materials and Methods: In vitro calcium mobilization (FLIPR), β-arrestin recruitment, and inositol-phosphate accumulation assays were performed in Chinese hamster ovary (CHO) cells stably expressing human recombinant OX1R or OX2R. Electrophysiological recordings were performed on slices of the ventral tuberomammillary nucleus (TMN) from mouse hypothalamus; effects on membrane potential were measured in the presence of 1 micromolar tetrodotoxin to block neuron firing. In vivo efficacy for enhancing wakefulness was evaluated in wild type (WT) and Atax mice during their rest phase using PiezoSleep, a rapid, non-invasive method for classifying sleep and wakefulness by unsupervised machine learning on physiologically relevant readouts, including body movement and breath rate. Electroencephalogram (EEG), electromyogram (EMG), and video recordings were used in Atax mice during their active phase to evaluate effects at 0.3-10 mg/kg on arousal states and cataplexy.

Results: ORX750 behaved as a potent full agonist at human OX2R (EC50=0.11 nM) relative to the native ligand orexin A (OXA; EC50=0.035 nM) and showed 9,800-fold selectivity over human OX1R (EC50=1100 nM) in the FLIPR assay. Biased agonism was not detected by measurement of b-arrestin recruitment at OX2R in comparison to OXA. ORX750 depolarized membrane potential (EC50=5.0 nM, max DmV=9.5) in whole cell current-clamp recordings in the TMN. In the PiezoSleep assay, in which wakefulness readouts are highly correlated with EEG/EMG-defined wakefulness, ORX750 increased time awake and the consolidation of wakefulness vs. vehicle in a dose-related manner when administered to WT and Atax mice during the rest phase. Increased sensitivity to these wake-promoting effects was observed in Atax vs. WT mice. In Atax mice, ORX750 increased time awake; consolidated wakefulness; increased EEG gamma power during wakefulness; reduced cataplexy occurrences; and increased latencies to sleep and cataplexy in a dose-related manner during the active phase using the EEG/EMG/video assay. At the lowest dose tested (0.3 mg/kg) and compared to vehicle, the latency to sleep was 2.3 h vs. 0.69 h and the latency to cataplexy was 2.7 h vs. 1.3 h.

Conclusions: ORX750 is an oral, highly potent, and selective OX2R agonist with the potential to treat patients with primary symptoms of NT1, as well as reduce excessive sleepiness in those presenting sleep/wake disorders with normal orexin levels.

Acknowledgements: Sponsored by Centessa Pharmaceuticals. We thank Dr. Emmanuel Mignot for scientific input.