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): April 22, 2024

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)

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: **+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 7.01 Regulation FD Disclosure

On April 22, 2024, Centessa Pharmaceuticals plc (the "Company") issued a press release announcing that the U.S. Food and Drug Administration (the "FDA") has cleared the Investigational New Drug application (the "IND") to initiate a Phase 1 first-in-human, clinical trial of ORX750 for the treatment of narcolepsy. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and incorporated herein by reference.

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.

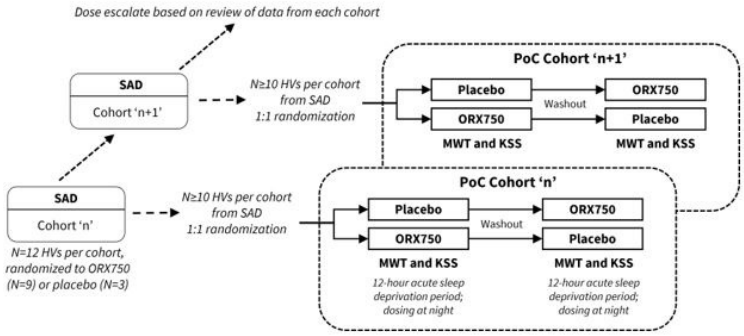
The information under this Item 7.01, including Exhibits 99.1 and 99.2 hereto, is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be 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 Exhibits 99.1 and 99.2.

Item 8.01 Other Events.

On April 22, 2024, the Company announced that the FDA has cleared the IND to initiate a Phase 1 first-in-human, clinical trial of ORX750 for the treatment of narcolepsy.

The Phase 1 study of ORX750 will evaluate the safety, tolerability and pharmacokinetics of single-ascending ("SAD") and multiple-ascending doses of ORX750 in healthy adult subjects. In parallel to the SAD, a cross-over proof-of-concept pharmacodynamic assessment will be performed utilizing the Maintenance of Wakefulness Test (MWT) and Karolinska Sleepiness Scale (KSS) in acutely sleep-deprived healthy adult subjects which is intended to provide proof-of-concept data to enable dose selection for NT1, NT2 and IH indications. The study has a maximum exposure limit specified by the FDA which the Company believes significantly exceeds the predicted efficacious doses of ORX750 in indications associated with or without orexin loss; therefore, the Company does not expect this limit to affect any of the planned clinical development activities for ORX750. The Company expects to commence dosing of the Phase 1 study in healthy volunteers imminently, and proof-of-concept data are anticipated in the second half of 2024.

The Phase 1 study design of ORX750 includes SAD combined with PoC cohorts to assess PD effects of ORX750 by measuring sleep latency with the MWT and subjective sleepiness with the KSS in acutely sleep-deprived healthy subjects.



Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Press Release dated April 22, 2024
99.2	Corporate Presentation as of April 22, 2024
104	Cover Page Interactive Data (embedded within the Inline XBRL document)

Forward Looking Statements

This Current Report on Form 8-K 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 Current Report on Form 8-K 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; the timing of commencement of new studies or clinical trials of ORX750 and other potential orexin agonist candidates; research and clinical development plans and the timing thereof; the Company's ability to differentiate ORX750 and other potential orexin agonist candidates from other treatment options; the development and therapeutic potential of ORX750 and other potential orexin agonist candidates; predicted efficacious doses of ORX750; predicted timing of enrollment in the Company's Phase 1 first-in-human, clinical trial of ORX750, the Company's ability to successfully conduct its clinical development of ORX750 below the maximum exposure limit set by the 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; and other regulatory matters, including the timing and likelihood of success of obtaining authorizations to initiate or continue clinical trials. Any forward-looking statements in this Current Report on Form 8-K are based on the Company's current expectations, estimates 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 and tolerability profile of the Company's product candidates; the Company's ability to protect and maintain its 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 the Company's ongoing and planned clinical trials; the Company's ability to obtain adequate financing, including through its financing facility with Oberland, to fund its 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; future expenditures risks related to its asset-centric corporate model; the risk that any one or more of its product candidates will not be successfully developed and/or commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; geo-political risks such as the Russia-Ukraine war and conflicts in the Middle East. These and other risks concerning the Company's programs and operations are described in additional detail in the Company's Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and its other reports, which are on file with the U.S. Securities and Exchange Commission. The Company's explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

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: April 22, 2024

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

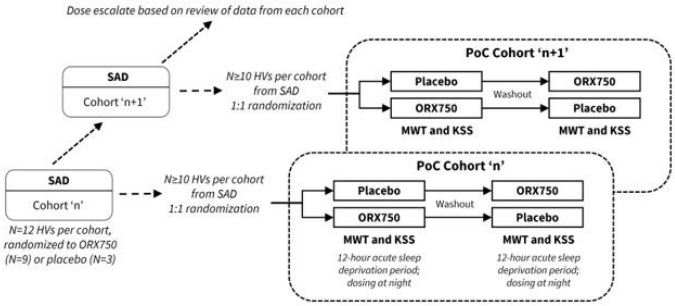
Exhibit 99.1

Centessa Pharmaceuticals Announces Open IND for ORX750;
Proof-of-Concept Data in Sleep-Deprived Healthy Volunteers Planned for 2H 2024

BOSTON & LONDON, April 22, 2024 – Centessa Pharmaceuticals plc (Nasdaq: CNTA), a clinical-stage pharmaceutical company that aims to discover and develop medicines that are transformational for patients, today announced that the U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug application (IND) to initiate a Phase 1 first-in-human, clinical trial of ORX750 for the treatment of narcolepsy. ORX750 is an investigational, orally administered, highly potent and selective orexin receptor 2 (OX2R) agonist designed to directly target the underlying pathophysiology of orexin neuron loss in narcolepsy type 1 (NT1), with potential applicability to narcolepsy type 2 (NT2), idiopathic hypersomnia (IH), and other sleep-wake disorders with normal orexin levels.

The Phase 1 study will evaluate the safety, tolerability and pharmacokinetics of single-ascending doses (SAD) and multiple-ascending doses (MAD) of ORX750 in healthy adult subjects. In parallel to the SAD, a cross-over pharmacodynamic (PD) assessment will be performed utilizing the Maintenance of Wakefulness Test (MWT) and Karolinska Sleepiness Scale (KSS) in acutely sleep-deprived healthy adult subjects which is intended to provide proof-of-concept data to enable dose selection for NT1, NT2 and IH indications. The study has a maximum exposure limit specified by the FDA which the Company believes significantly exceeds the predicted efficacious doses of ORX750 in indications associated with or without orexin loss; therefore, the Company does not expect this limit to affect any of the planned clinical development activities for ORX750. The Company expects to commence dosing of the Phase 1 study in healthy volunteers imminently, and proof-of-concept data are anticipated in the second half of 2024.

The Phase 1 study design of ORX750 includes SAD combined with PoC cohorts to assess PD effects of ORX750 by measuring sleep latency with the MWT and subjective sleepiness with the KSS in acutely sleep-deprived healthy subjects.



"This is a significant milestone for the development of our potential best-in-class OX2R agonist, ORX750, for the treatment of narcolepsy and other sleep-wake disorders," said Saurabh Saha MD PhD, Chief Executive Officer of Centessa. "We are excited to begin executing what we believe is an elegant, adaptive Phase 1 study aimed at generating early proof-of-concept data for ORX750 in acutely sleep-deprived healthy volunteers in the second half of this year. We expect this study to enable dose selection for planned studies evaluating ORX750 in patients with NT1 and in patient populations with normal orexin levels, including NT2 and IH."

About ORX750

ORX750 is an investigational, orally administered, highly potent and selective orexin receptor 2 (OX2R) agonist designed to directly target the underlying pathophysiology of orexin neuron loss in narcolepsy type 1 (NT1). ORX750 has been shown to potently activate the OX2R with an in vitro EC50 of 0.11 nM and 9,800-fold selectivity over the human orexin receptor (hOX1R). ORX750 is Centessa's first orexin product candidate being developed for the treatment of narcolepsy with potential expansion into narcolepsy type 2 (NT2), idiopathic hypersomnia (IH) and other sleep-wake disorders.

About Centessa Pharmaceuticals

Centessa Pharmaceuticals plc is a clinical-stage pharmaceutical company that aims to discover and develop transformational medicines for patients. Our most advanced programs include a hemophilia program, an orexin agonist program for the treatment of narcolepsy and other sleep-wake disorders and an immuno-oncology program focused on our LockBody® technology platform. We operate with the conviction that each of our programs has the potential to change the current treatment paradigm and establish a new standard of care. 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; the timing of commencement of new studies or clinical trials of ORX750 and other potential orexin agonist candidates; research and clinical development plans and the timing thereof; the Company’s ability to differentiate ORX750 and other potential orexin agonist candidates from other treatment options; the development and therapeutic potential of ORX750 and other potential orexin agonist candidates; predicted efficacious doses of ORX750; the Company’s ability to successfully conduct its clinical development of ORX750 below the maximum exposure limit set by the 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; and other regulatory matters, including the timing and likelihood of success of obtaining authorizations to initiate or continue clinical trials. Any forward-looking statements in this press release are based on our current expectations, estimates 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 and tolerability profile of our product candidates; our ability to 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 Oberland, 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; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and/or commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; geo-political risks such as the Russia-Ukraine war and conflicts in the Middle East. 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.

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


CENTESSA
PHARMACEUTICALS
Corporate Overview
APRIL 22, 2024

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.

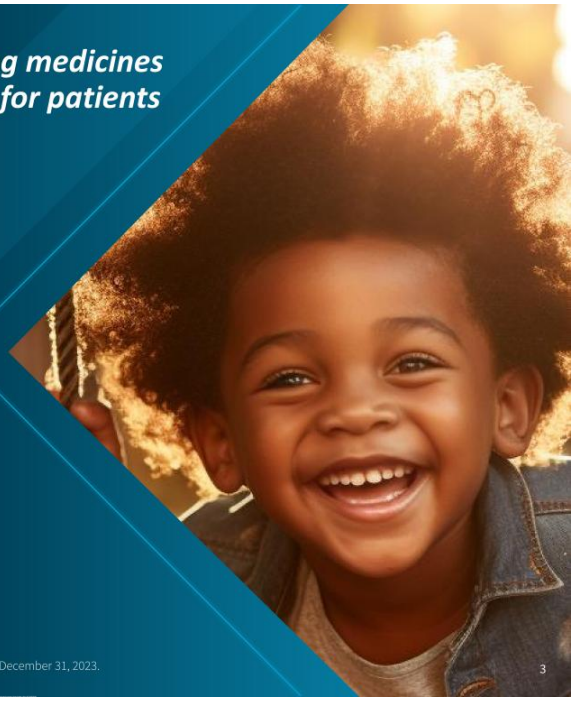
This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements 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 SerpinPC, ORX750 and, LB101; 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 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 Oberland, 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 and the conflicts in the Middle East 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 and statistical analyses 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 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 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.

OUR MISSION

Discovering and developing medicines that are transformational for patients

- Multiple potential blockbuster assets
- Ongoing momentum in 2024 with clinical milestones anticipated across our most advanced programs
- Strong balance sheet



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Centessa reported $256.5 million in cash, cash equivalents and short-term investments as of December 31, 2023.

Our Most Advanced Potential First-in-Class/Best-in-Class Medicines for Patients

ASSET	DISEASE	MECHANISM
SerpinPC	**Hemophilia B**	Activated Protein C Inhibitor
ORX750	**Narcolepsy**	Orexin Receptor-2 (OX2R) Agonist
LB101	**Solid Tumors**	PD-L1xCD47 LockBody®

CENTESSA PHARMACEUTICALS

Centessa has multiple early-stage programs including LB206 and additional orexin agonists and discovery-stage programs not reflected on this slide.

2024 Driving Momentum

ANTICIPATED MILESTONES

HEMOPHILIA PROGRAM

SerpinPC

Registrational study interim analysis expected in **2024**

OREXIN AGONIST PROGRAM

ORX750

Clinical PoC data in healthy volunteers expected in **2H of 2024**

LOCKBODY TECHNOLOGY PLATFORM

LB101

Phase 1/2 study **ongoing**

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Hemophilia Program
Orexin Agonist Program
LockBody Technology Platform
CENTESSA
PHARMACEUTICALS
6

Hemophilia B: Large Growing Market with Unmet Need

~$2.6B+
Hemophilia B Market[1]

- A safe, subcutaneous and effective treatment has the potential to transform care for hemophilia B
- No subcutaneous treatment option currently available for hemophilia B in the US[2]
- Limited options for hemophilia B with inhibitors[2]

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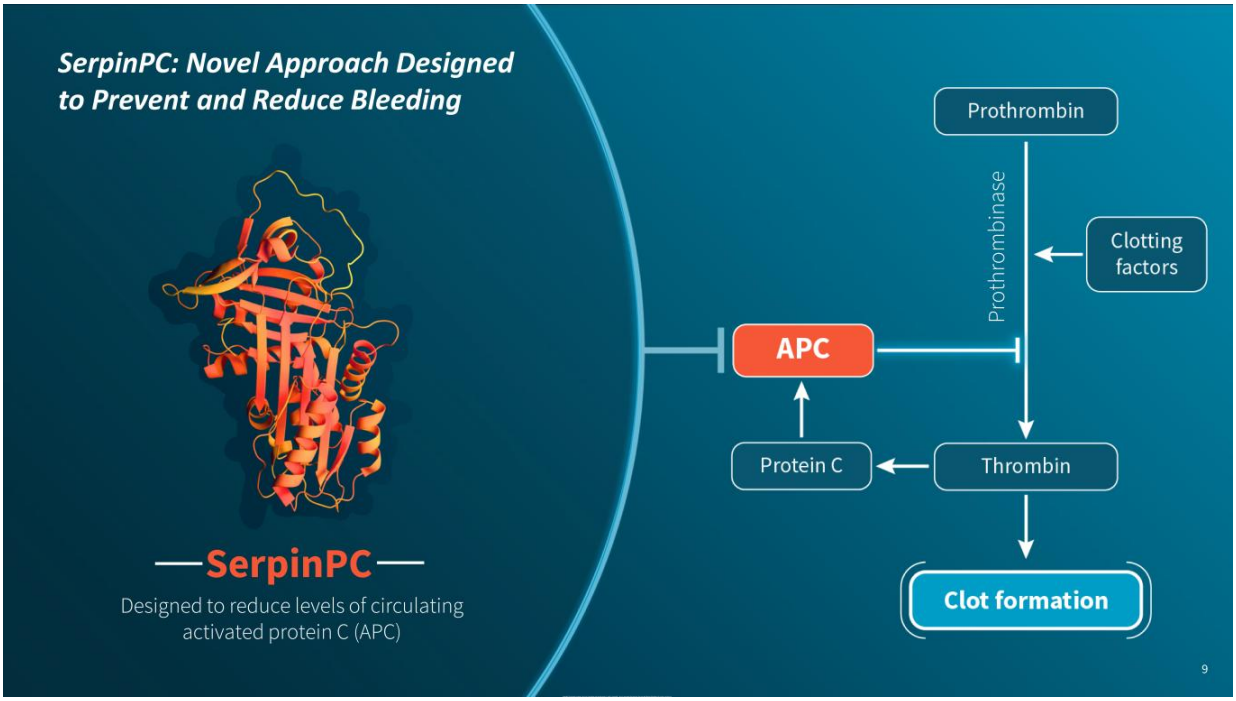
1. Evaluate Pharma Analyst Consensus for 2023. 2. In Canada, a subcutaneous option is available for hemophilia B with inhibitors.

***SerpinPC** has the potential to be a **first-in-class subcutaneous** therapy with a **differentiated** safety profile for people with hemophilia B*[1]

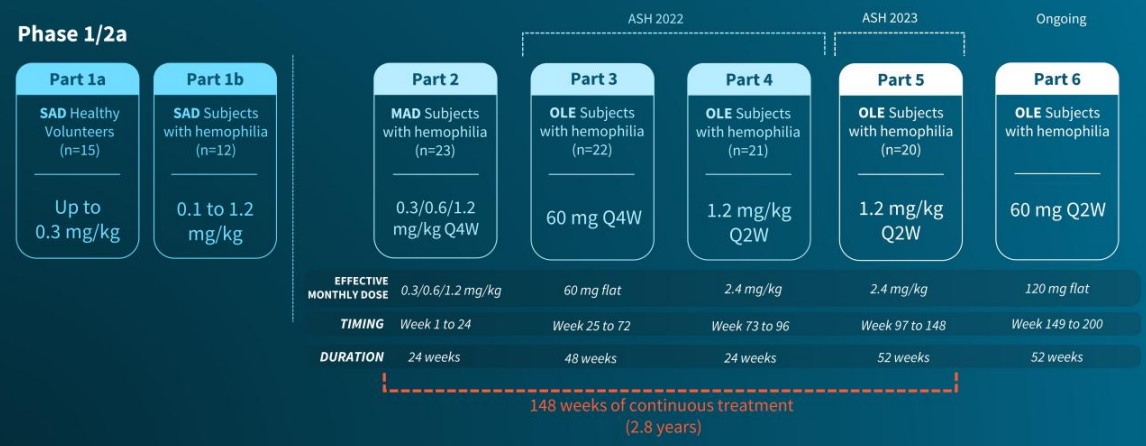
- Novel mechanism of action
- Showed significant reduction in bleeding[1]
- Shown to have a favorable safety and well tolerated profile to date; No thrombosis observed to date[1]

SerpinPC is an investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit activated protein C (APC), that has not been approved by the FDA or any other regulatory authority. ABR is annualized bleed rate. 1. Ongoing Phase 2a Study being conducted in Georgia and Moldova to evaluate safety, tolerability, pharmacokinetics and efficacy of SerpinPC in a population of severe hemophilia A and B subjects not on previous prophylaxis and with a history of frequent bleeding. Part 5: Blood (2023) 142 (Supplement 1): 2619. https://doi.org/10.1182/blood-2023-179969. Part 3-4: Blood (2022) 140 (Supplement 1): 460–461. https://doi.org/10.1182/blood-2022-159631. Additional information on the trial can be accessed at www.clinicaltrials.gov (NCT04073498).


SerpinPC: Novel Approach Designed to Prevent and Reduce Bleeding
SerpinPC
Designed to reduce levels of circulating activated protein C (APC)
Prothrombin
Prothrombinase
Clotting factors
APC
Protein C
Thrombin
Clot formation
9

Phase 2a | Ongoing Study of SerpinPC in Hemophilia

AP-0101 (NCT04073498) | An adaptive, first-in-human study to investigate the safety, tolerability, efficacy, and pharmacokinetics of SerpinPC in male persons with severe hemophilia



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PK=pharmacokinetics; SAD=single ascending dose; MAD=multiple ascending dose; OLE=open-label extension.
Reference: ClinicalTrials.gov. NCT04073498. Accessed January 18, 2024.

Phase 2a Part 5: SerpinPC Achieved a 96% Reduction in Median All-Bleeds ABR[1]

AP-0101 Part 5 all bleed ABR at 1.2 mg/kg Q2W (n=20)[1]

96% Reduction in Bleeding[1]

In Part 5, SerpinPC reduced median all-bleeds ABR to **1.0**, a **96%** reduction from prospective baseline. Subjects in Part 5 participated in Parts 2, 3 and 4 and therefore, received continuous treatment with SerpinPC for approximately 2.8 years.

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ABR is annualized bleeding rate. 1. Part 5 of Phase 2a study as presented at ASH in December 2023. Results reflect approximately 2.8 years of continuous treatment with SerpinPC at dose levels that varied between Parts 2, 3 and 4. Four subjects discontinued during Part 5 (one due to femoral fracture, one due to lengthy travel from study site, and two due to emigration). ABRs calculated based on number of weeks on study drug.

SerpinPC Shown to Have Favorable Safety and Tolerability Profile to Date

No observations of treatment-related adverse events in Part 5

Treatment Emergent Adverse Events (TEAEs)	**Number of subjects (%)** n=20
All TEAEs (total 41 events)	16 (80%)
Related to SerpinPC	**0**
Leading to discontinuation	1 (5%)
Leading to death	0
AEs of special interest	0
Serious adverse events	2 (10%)*
Thromboembolic events	0
Injection site reactions	0
Anti-drug antibodies	1#
Neutralizing anti-drug antibodies	0#

Source: Phase 2a study data of SerpinPC. Part 5: Blood (2023) 142 (Supplement 1): 2619 .
*Two SAEs occurred and were considered unrelated to study drug; (1) traumatic fracture of femur (led to discontinuation) (2) traumatic epididymitis
Preliminary finding.

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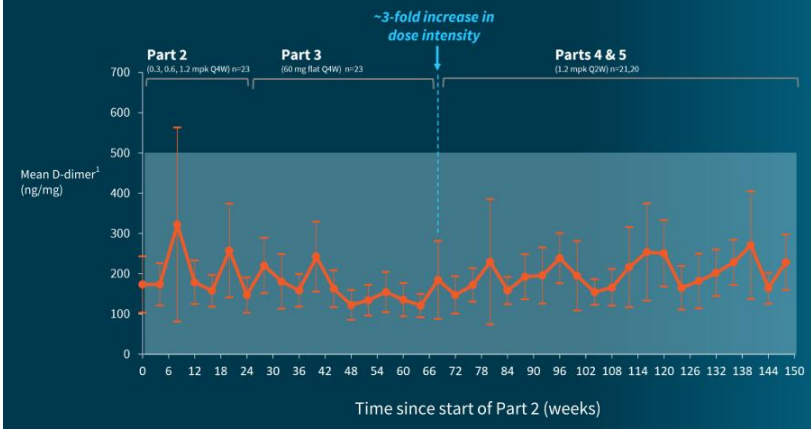
SerpinPC's Potential for Differentiated Safety Profile



- **No observation of thrombosis to date**[2]
  No observations of treatment-related, non-transient elevations in D-dimer across study[2]
- **For Part 5, 96% of D-dimer results were <500 ng/ml**[2]

1. Error bars represent 95% confidence interval. Note: Values from three instances of trauma, cancer and infection determined to represent explained D-dimer elevation and omitted from calculation (Subject 200-012 traumatic hip bleed, week 68 and 72; Subject 300-041 rectosigmoid cancer, Weeks 60-98; Subject 300-032 periodontitis, weeks 128 to 1301. 2.There were no thromboembolic events and no treatment-related sustained elevations of D-dimer observed across the Phase 2a study, to date. D-dimer is a sensitive measure of excessive thrombin generation.

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SerpinPC Ongoing Global Registrational Studies for Hemophilia B

PRESent-2

Hemophilia B without inhibitors (n = 120)

Primary Endpoint: ABR at 24 weeks

PRESent-3

Hemophilia B with inhibitors (n ≥ 12)

Primary Endpoint: ABR at 24 weeks

73 SITES
18 COUNTRIES

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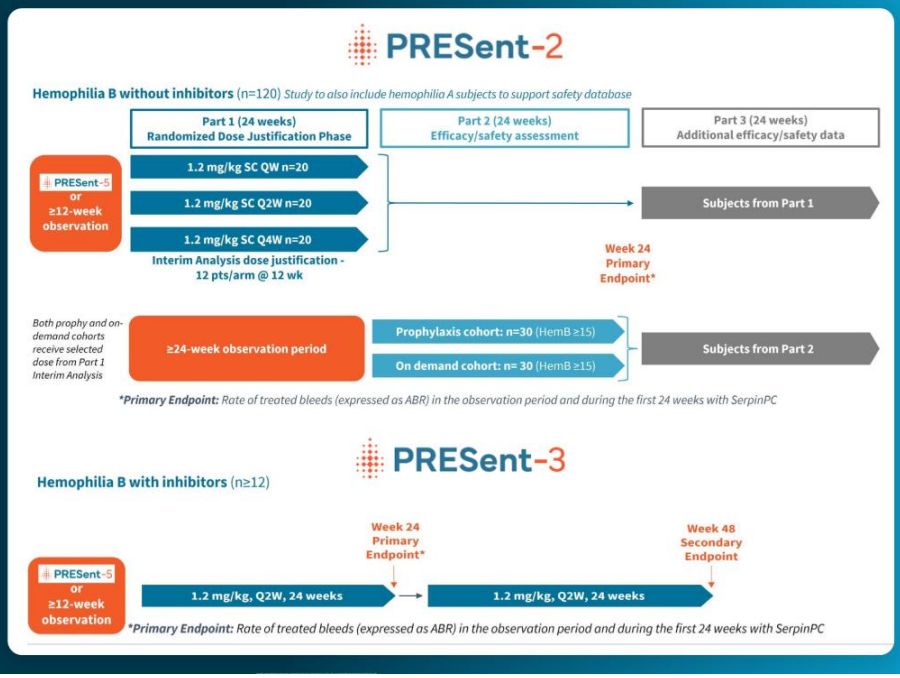
ABR is annualized bleeding rate. Primary endpoint is the rate of treated bleeds (expressed as ABR) during the first 24 weeks of treatment with SerpinPC (Part 2 of PRESent-2) compared to the observation period. Interim Analysis for Part 1 of PRESent -2 Study expected in 2024. Additional information on the registrational program can be accessed at www.clinicaltrials.gov (NCT05605678, NCT05789524, NCT05789537).

SerpinPC

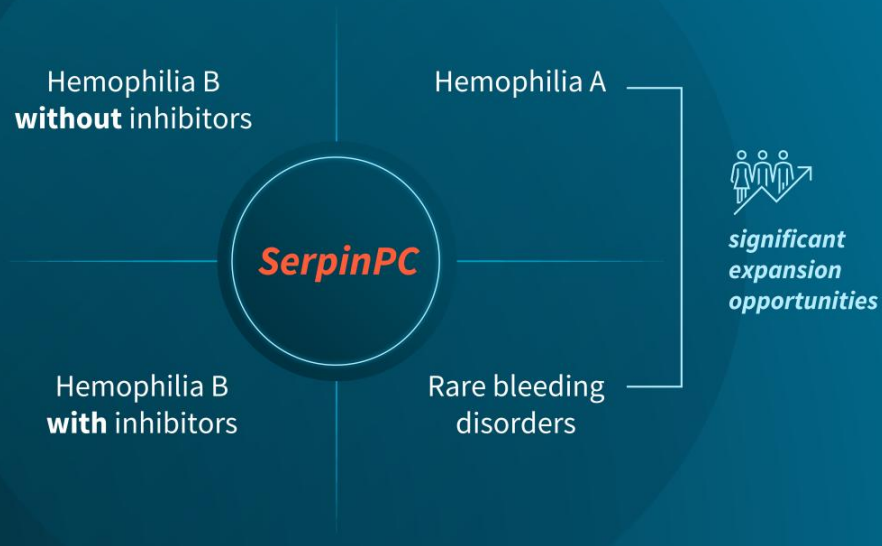
Ongoing Global Registrational Studies for Hemophilia B

- Granted Fast Track designation by the FDA in May 2023
- Granted Orphan Drug Designation by the FDA in Sept. 2022

CENTESSA PHARMACEUTICALS



Potential Multi-Billion-Dollar Market Opportunities

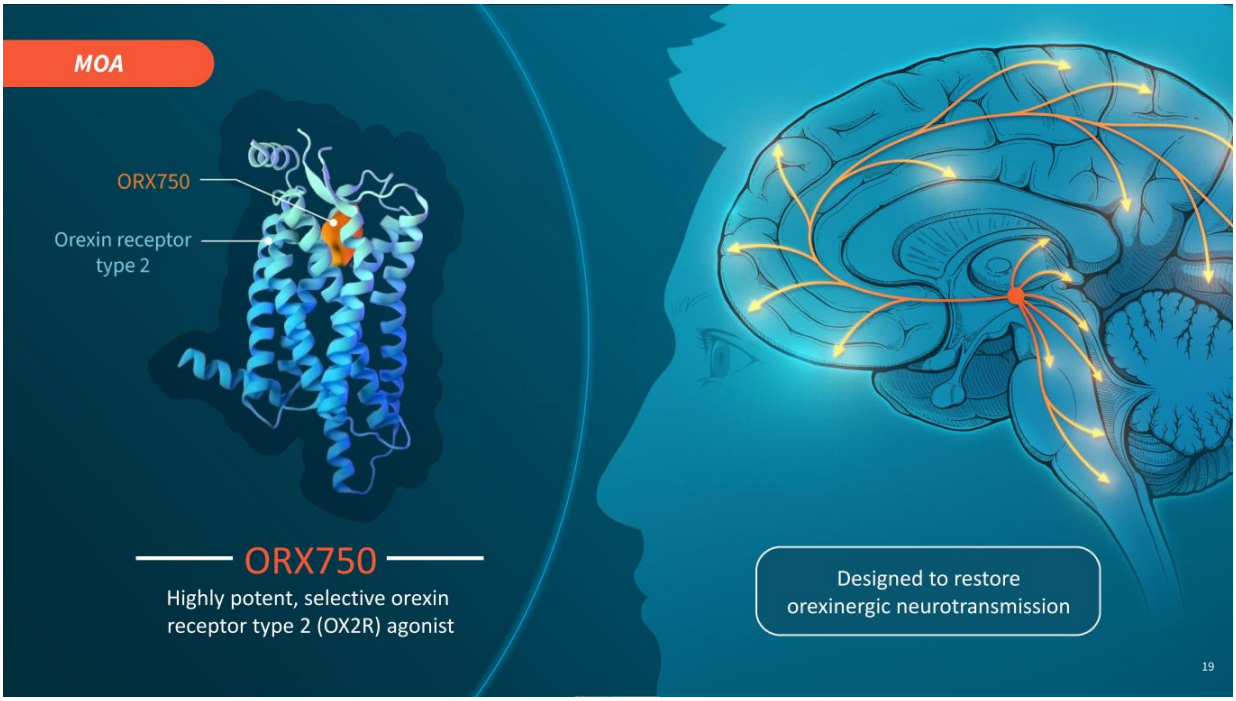


CENTESSA PHARMACEUTICALS

Evaluate Pharma Analyst Consensus for 2023.


Hemophilia Program
Orexin Agonist Program
LockBody Technology Platform
CENTESSA
17

Orexin agonists have the potential to transform standard of care for individuals with sleep-wake disorders


MOA
ORX750
Orexin receptor type 2
ORX750
Highly potent, selective orexin receptor type 2 (OX2R) agonist
Designed to restore orexinergic neurotransmission
19

ORX750 a Potential Best-in-Class Oral OX2R Agonist for the Treatment of Narcolepsy and Other Sleep-Wake Disorders

Highly potent, selective, novel OX2R agonist that closely **mimics function of endogenous peptide**[1]

Achieved **maximal wake times** and **cataplexy suppression** in highly predictive, translational narcolepsy type 1 mouse models[1]

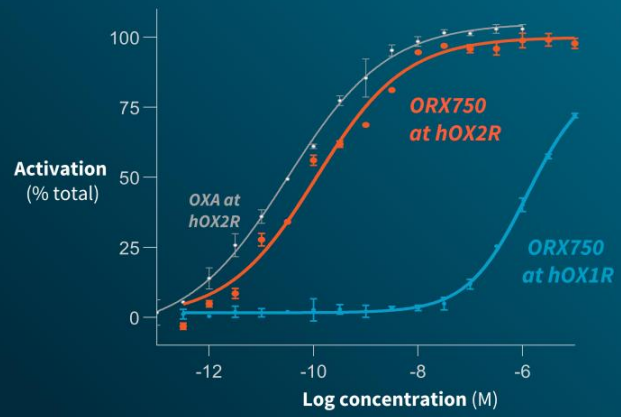
Preclinical data support potential **expansion** into **broader sleep-wake disorders**, including narcolepsy type 2 and idiopathic hypersomnia[1]

CENTESSA PHARMACEUTICALS

Investigational New Drug (IND) application open.
1. ORX750 preclinical data presentation at World Sleep Congress, Oct. 25, 2023. https://investors.centessa.com/static-files/7377defd-f7b4-49fe-8806-e86c31e8e5de.

PRECLINICAL DATA

ORX750 Showed High In Vitro Potency at OX2R and Selectivity vs. OX1R



***EC_{50} 0.11 nM** for hOX2R*

***9,800-fold selectivity** vs. hOX1R*

- Activation pattern was indistinguishable from OXA with lack of biased agonism[1]
- No significant differences in OX2R potency were observed across species[2]
- No significant pharmacological activity observed in GPCR selectivity and in vitro safety panels[3]

Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing recombinant human OX1R or OX2R; OXA EC50 at hOX2R = 0.035 nM; ORX750 EC50 at hOX1R = 1100 nM.

1 Pathhunter β-arrestin recruitment assay with CHO cells co-expressing ProLink™ (PK)-tagged OX2R and Enzyme Acceptor (EA)-tagged β-arrestin.

2 HumSafetyan, mouse, rat, dog, monkey recombinant receptors *in vitro*.

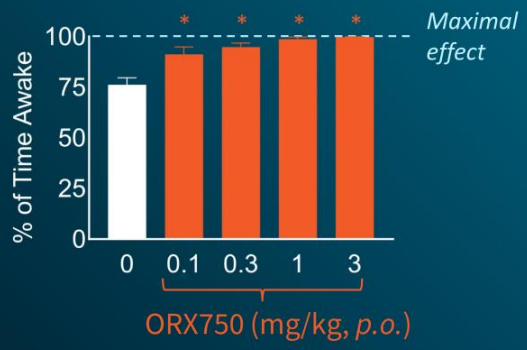
3 Safety 47 and GPCRMax168 from >60 receptor families.

CENTESSA PHARMACEUTICALS

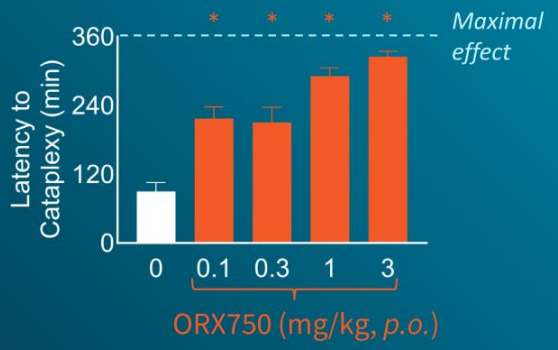
PRECLINICAL DATA

ORX750 Increased Wakefulness and Suppressed Cataplexy in NT1 Mice

Wakefulness



Latency to Cataplexy

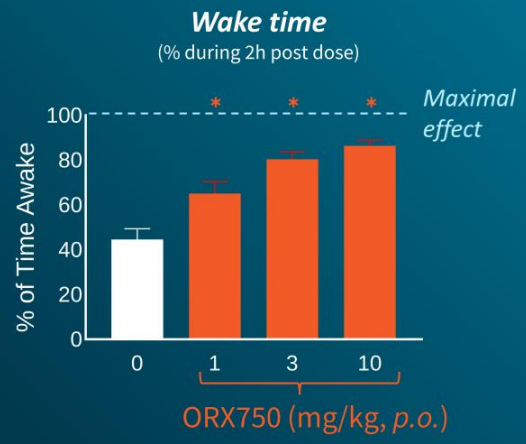


NT1 is Narcolepsy Type 1.
% of Time Awake refers to time spent awake in the first 3 hours after oral dosing.
ORX750 preclinical data presentation at World Sleep Congress, Oct. 25, 2023. NT1 model shown is orexin/tTA;tetO diphtheria toxin fragment A (DTA) mice. Age at first dose 23-27 wks (7 wks after removal of doxycycline chow); 16 males used; EEG, EMG recorded using intraperitonially implanted telemeters with video and manually scored in 10-sec epochs; dosing at start of dark period (active phase). *For all doses $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following repeated-measures analysis of variance in counterbalanced design.

CENTESSA PHARMACEUTICALS

PRECLINICAL DATA

ORX750 Increased Wakefulness in Wild Type (WT) Mice



- In WT mice *(ie: orexin system is intact and functional)*, wake time increased at **≥ 1 mg/kg** (lowest dose tested)

Data collected using PiezoSleep, in which wakefulness readouts based on movement & breath rate highly correlate with EEG/EMG measures (Black, et al., ESRS2022 presentation). Age at first dose was 16-20 wks in male C57BL/6J mice; mice dosed at 5 h after lights on * $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA in counterbalanced design.

IND OPEN

ORX750 First-in-Human Healthy Volunteer (HV) PoC Study

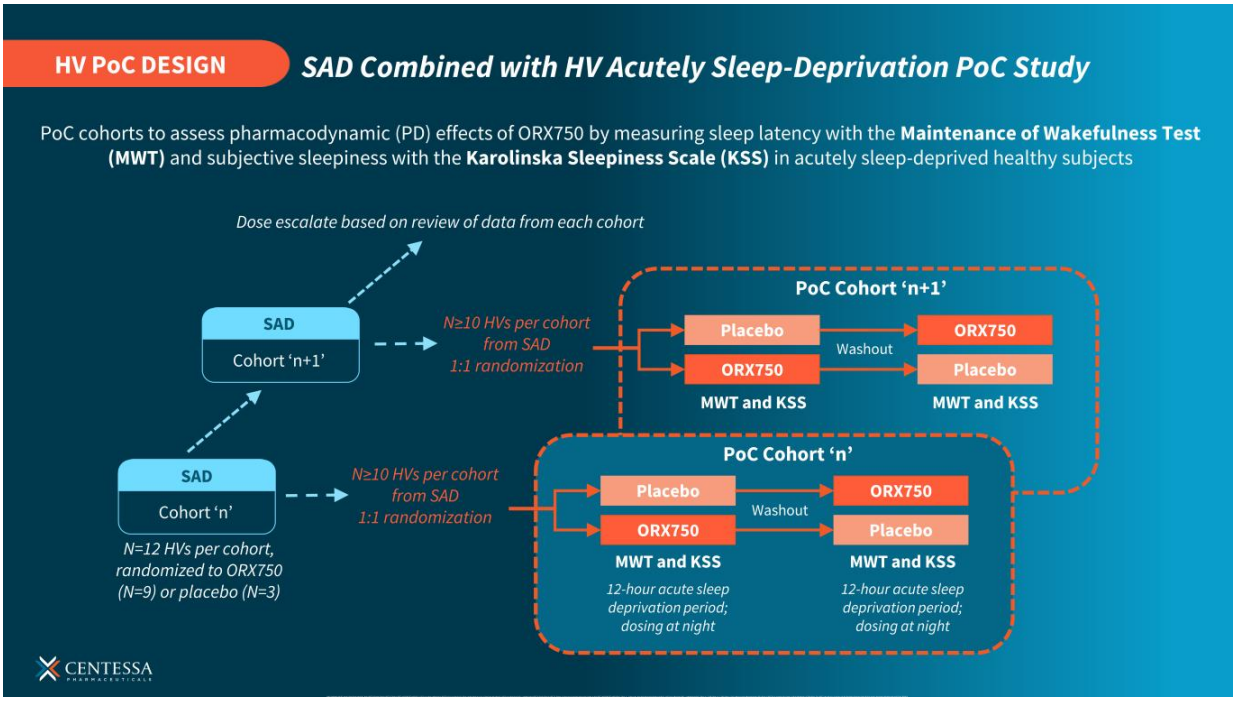
Phase 1 clinical study of ORX750:

- Evaluate the safety, tolerability and pharmacokinetics (PK) of single-ascending and multiple-ascending doses in healthy adult subjects

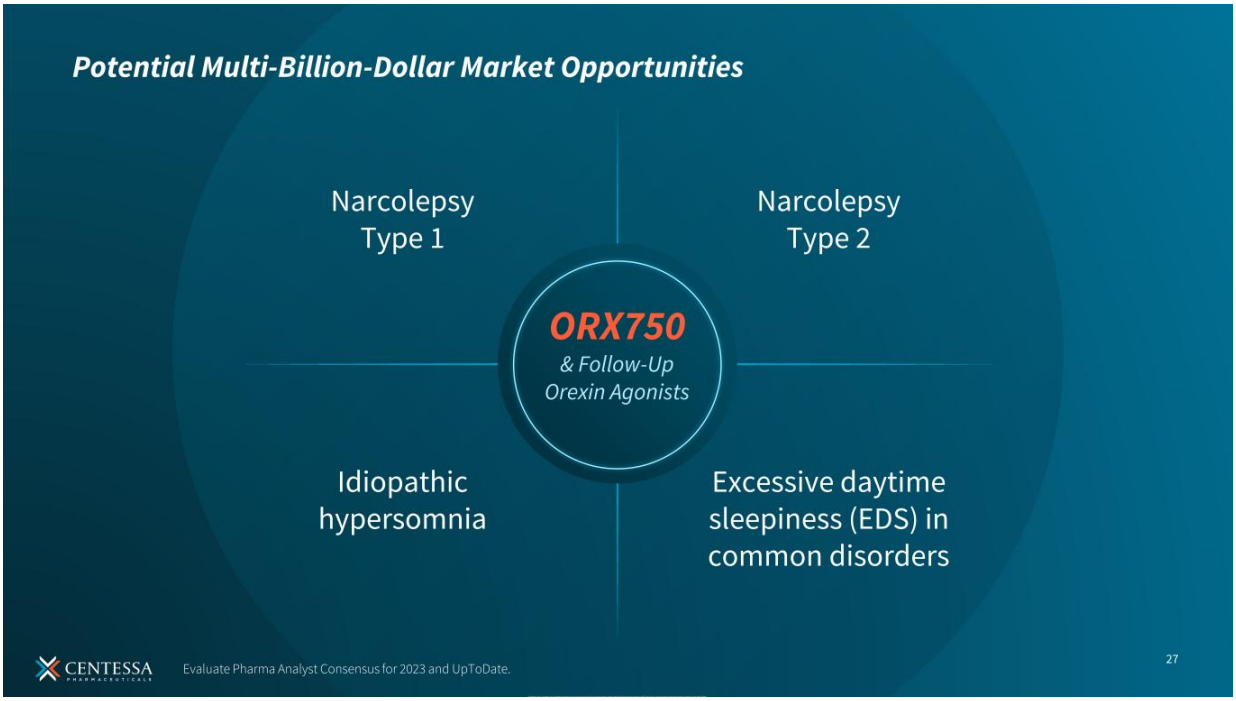
In parallel

- A cross-over PoC portion of the study to assess pharmacodynamics (PD) using the **Maintenance of Wakefulness Test (MWT)** and **Karolinska Sleepiness Scale (KSS)** in acutely sleep-deprived healthy adult subjects

The Phase 1 study has a maximum exposure limit specified by the FDA which the company believes significantly exceeds the predicted efficacious doses of ORX750 in indications associated with or without orexin loss.


HV PoC DESIGN
SAD Combined with HV Acutely Sleep-Deprivation PoC Study
PoC cohorts to assess pharmacodynamic (PD) effects of ORX750 by measuring sleep latency with the Maintenance of Wakefulness Test (MWT) and subjective sleepiness with the Karolinska Sleepiness Scale (KSS) in acutely sleep-deprived healthy subjects
Dose escalate based on review of data from each cohort
SAD
Cohort 'n+1'
N≥10 HVs per cohort from SAD 1:1 randomization
PoC Cohort 'n+1'
Placebo
ORX750
Washout
ORX750
Placebo
MWT and KSS
MWT and KSS
SAD
Cohort 'n'
N=12 HVs per cohort, randomized to ORX750 (N=9) or placebo (N=3)
N≥10 HVs per cohort from SAD 1:1 randomization
PoC Cohort 'n'
Placebo
ORX750
Washout
ORX750
Placebo
MWT and KSS
MWT and KSS
12-hour acute sleep deprivation period; dosing at night
12-hour acute sleep deprivation period; dosing at night
CENTESSA

ORX750 Clinical PoC data in sleep-deprived healthy volunteers expected in 2H of 2024


Potential Multi-Billion-Dollar Market Opportunities
Narcolepsy Type 1
Narcolepsy Type 2
ORX750
& Follow-Up Orexin Agonists
Idiopathic hypersomnia
Excessive daytime sleepiness (EDS) in common disorders
CENTESSA PHARMACEUTICALS
Evaluate Pharma Analyst Consensus for 2023 and UpToDate.
27


Hemophilia Program
Orexin Agonist Program
LockBody Technology Platform
CENTESSA
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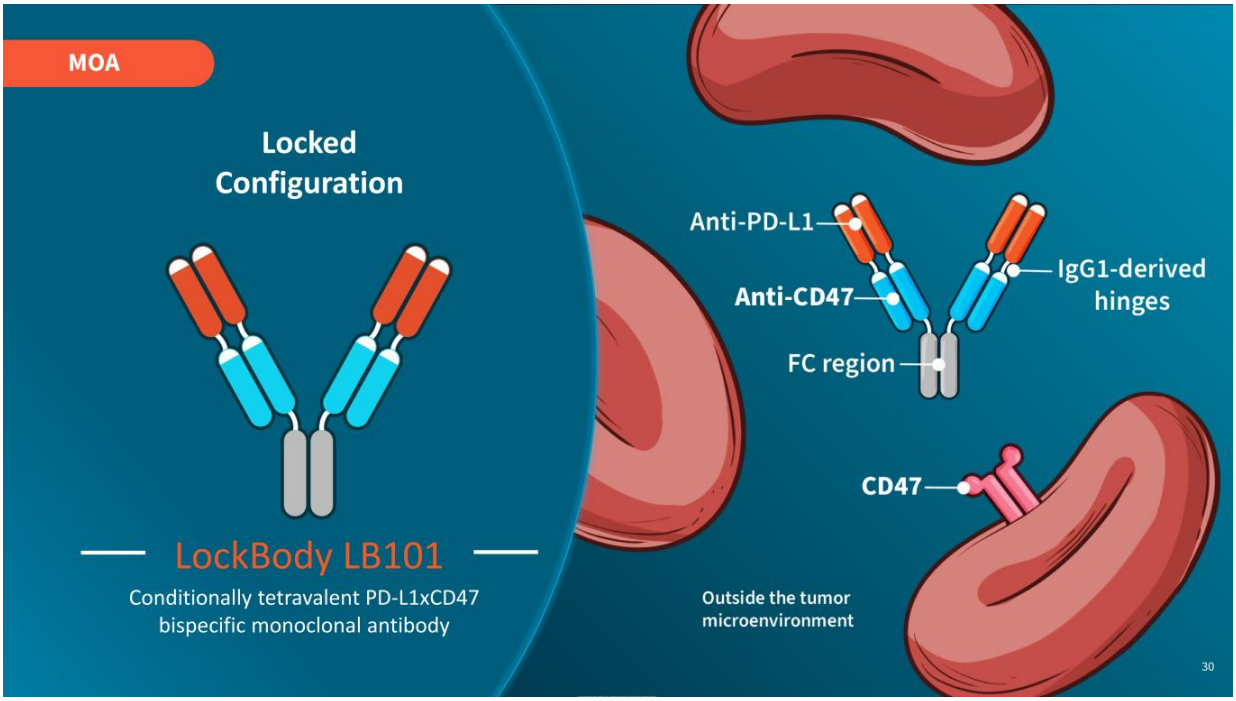
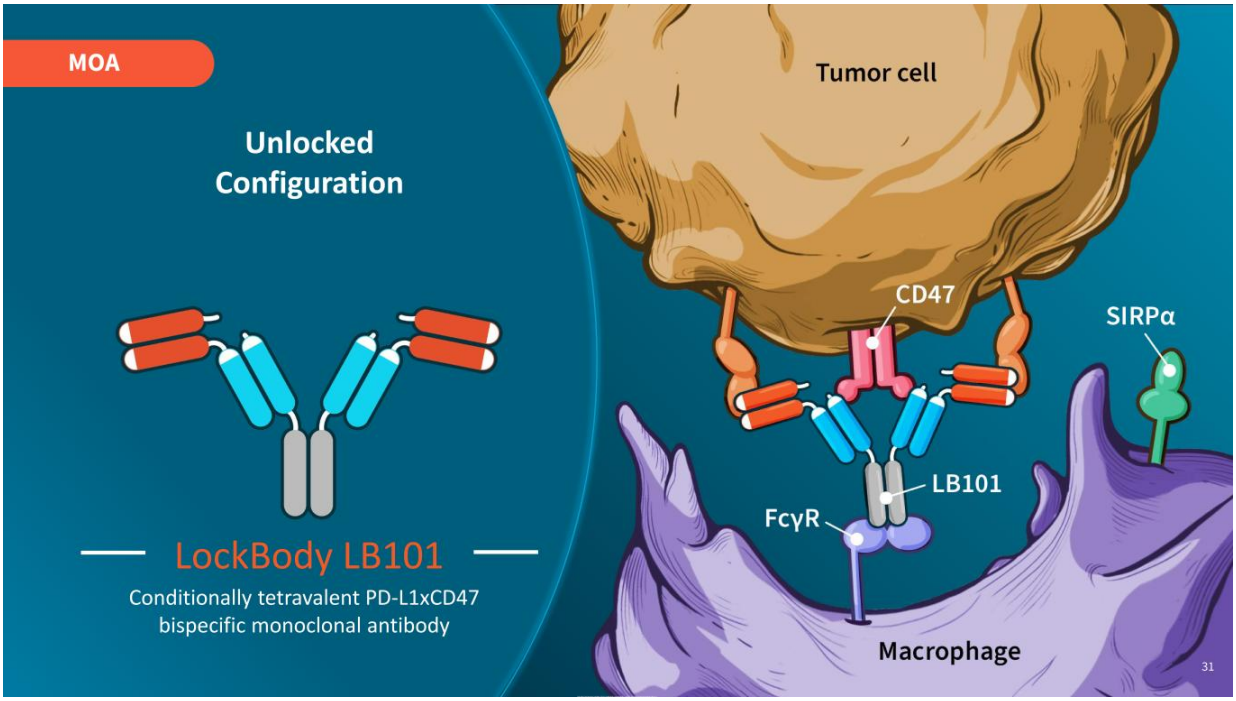
LockBody Technology Platform aims to redefine immuno-oncology treatment

- **Novel pharmacology** combining tumor enrichment with activation of effector function
- Designed as **single agent** systemic treatment
- Potential **wide therapeutic index**[1]

CENTESSA PHARMACEUTICALS

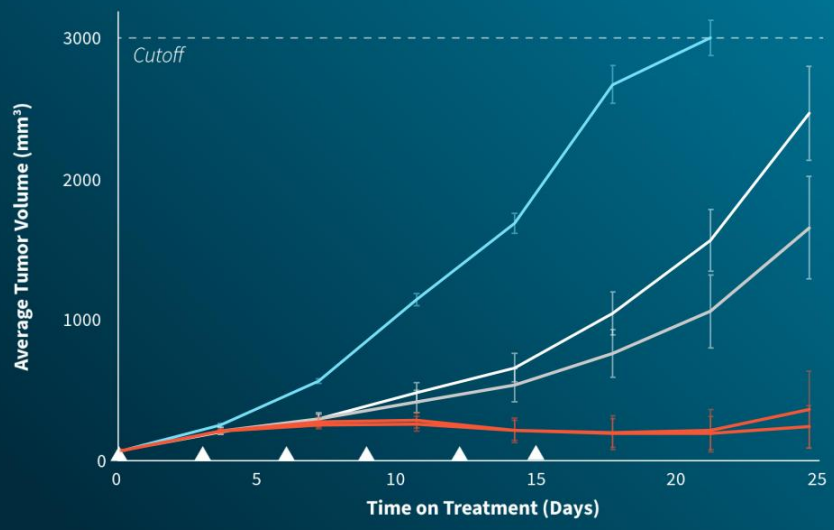
LB101 is an investigational agent that has not been approved by the FDA or any other regulatory authority. Information on the Phase 1/2a trial of LB101 can be accessed at www.clinicaltrials.gov (NCT05821777). 1. LB101 *in-vivo* preclinical data: MC38 hPD-L1+ syngeneic model in mouse, and in non-human primates where LB101 was delivered IV at 5, 20, 50mg/kg (q7d x 4).


MOA
Locked Configuration
LockBody LB101
Conditionally tetravalent PD-L1xCD47 bispecific monoclonal antibody
Anti-PD-L1
Anti-CD47
IgG1-derived hinges
FC region
CD47
Outside the tumor microenvironment
30


MOA
Unlocked Configuration
LockBody LB101
Conditionally tetravalent PD-L1xCD47 bispecific monoclonal antibody
Tumor cell
CD47
SIRPα
LB101
FcγR
Macrophage
31

PRECLINICAL DATA

Significant Tumor Regression Observed In-Vivo with LB101



IgG1 isotype control
0/16 regressed

Atezolizumab 5 mg/kg
1/16 regressed

Atezolizumab 10 mg/kg
3/16 regressed

LB101 8.5 mg/kg
14/16 regressed

LB101 17 mg/kg
12/16 regressed

CENTESSA PHARMACEUTICALS

Source: *In vivo*- 5 mg/kg of atezolizumab is equivalent to 8.5 mg/kg of LB101. Data presented at ASCO in June 2022. https://investors.centessa.com/static-files/2f9bffb4-97a6-4320-8885-70f12aa4d036. MC38 hPD-L1+ syngeneic model in mouse. Triangles indicate dosing schedule.

PRECLINICAL DATA

Observed to be Well Tolerated in Non-Human Primates (NHPs) with LB101 Doses up to 50mg/kg

No anemia/ thrombocytopenia

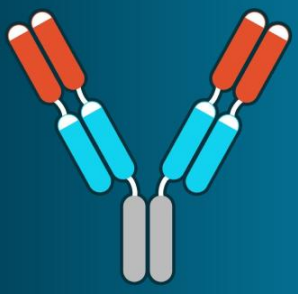
No weight loss

No change in red blood cell or hemoglobin

CENTESSA PHARMACEUTICALS

Source: *In-vivo*- LB101 delivered IV at 5, 20, 50mg/kg (q7d x 4) in non-human primates.

Dosing subjects in ongoing Phase 1/2a first-in-human clinical trial of LB101



CENTESSA PHARMACEUTICALS

2024 Driving Momentum

ANTICIPATED MILESTONES

HEMOPHILIA PROGRAM

SerpinPC

Registrational study interim analysis expected in **2024**

OREXIN AGONIST PROGRAM

ORX750

Clinical PoC data in healthy volunteers expected in **2H of 2024**

LOCKBODY TECHNOLOGY PLATFORM

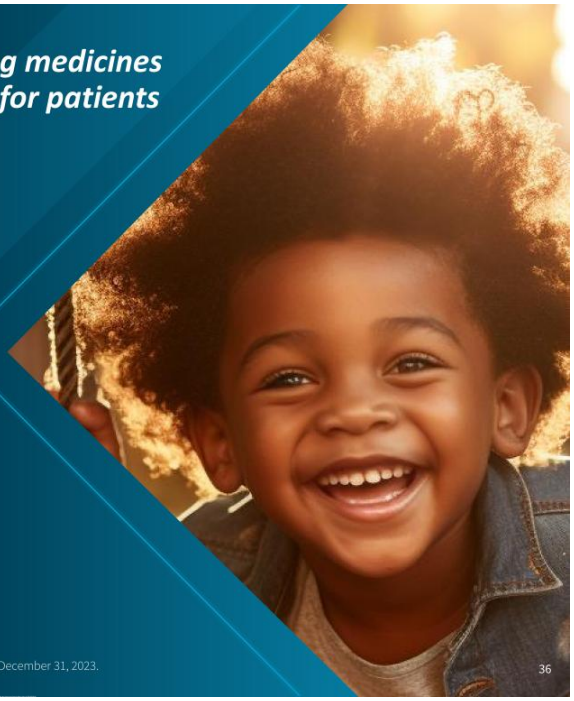
LB101

Phase 1/2 study **ongoing**

OUR MISSION

Discovering and developing medicines that are transformational for patients

- Multiple potential blockbuster assets
- Ongoing momentum in 2024 with clinical milestones anticipated across our most advanced programs
- Strong balance sheet



CENTESSA PHARMACEUTICALS

Centessa reported $256.5 million in cash, cash equivalents and short-term investments as of December 31, 2023.


CENTESSA
PHARMACEUTICALS