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): September 10, 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: +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 7.01 Regulation FD Disclosure

On September 10, 2024, Centessa Pharmaceuticals plc (the "Company") issued a press release titled "Centessa Announces Positive Interim Phase 1 Clinical Data with its Novel Orexin Agonist, ORX750, in Acutely Sleep-Deprived Healthy Volunteers." A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The Company from time to time presents and/or distributes to the investment community presentations related to its business. A copy of its most recent presentation is attached hereto as Exhibit 99.2 and incorporated herein by reference.

The information under this Item 7.01, including Exhibits 99.1 and 99.2, 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.

Item 8.01 Other Events.

On September 10, 2024, the Company announced positive interim data from an ongoing Phase 1 trial of its highly potent and selective orexin receptor 2 (OX2R) agonist, ORX750, in acutely sleep-deprived healthy volunteers.

The interim Phase 1 clinical data for ORX750 demonstrated:

- Significantly increased wakefulness in acutely sleep-deprived healthy volunteers compared to placebo at both doses tested. Treatment with ORX750 resulted in statistically significant ($p<0.05$) and clinically meaningful increased sleep latency on the MWT (time to sleep onset over the four sessions performed at ~2, 4, 6, and 8 hours after dosing at 11 p.m., maximum 40 minutes per session) compared to placebo across all doses. Mean sleep latencies, as measured by the MWT, for 1.0 mg dose of ORX750 and placebo were 18 minutes and 10 minutes, respectively (p-value = 0.04) (least squares mean). Mean sleep latencies, as measured by the MWT, for 2.5 mg dose of ORX750 and placebo were 32 minutes and 17 minutes, respectively (p-value = 0.01) (least squares mean). The 2.5 mg dose was shown to restore normative wakefulness with a mean sleep latency of 32 minutes as measured by the MWT.
- Favorable safety and tolerability observed as of the data cutoff date.[1]
    - All observed treatment related AEs were mild and transient with none leading to treatment discontinuation.
    - No observations of frequently reported on-target AEs associated with other OX2R agonists, including urinary frequency, urinary urgency, insomnia, blood pressure increases, and salivary hypersecretion.
    - No cases of hepatotoxicity, visual disturbances or hallucinations were observed. Additionally, there were no clinically meaningful, treatment-emergent changes in hepatic and renal parameters, vital signs, or electrocardiogram (ECG) parameters.
- Acutely sleep-deprived healthy volunteers who received a 2.5 mg dose of ORX750 showed a significant 1.6 point improvement versus placebo in mean KSS score compared to baseline (p-value = 0.03).
- Encouraging linear PK profile supports the use of ORX750 as a once-daily oral dosing regimen with rapid absorption (plasma concentrations of ORX750 peaked at 2h after the first dose). The systemic exposure of ORX750 increased in an approximately dose-proportional manner.

1. Data cutoff date of August 26, 2024.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Press Release, dated September 10, 2024
99.2	Corporate Presentation, dated September 2024
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: September 10, 2024

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

Exhibit 99.1

Centessa Announces Positive Interim Phase 1 Clinical Data with its Novel Orexin Receptor 2 (OX2R) Agonist, ORX750, in Acutely Sleep-Deprived Healthy Volunteers

- *2.5 mg dose restored normative wakefulness with mean sleep latency of 32 minutes as measured by the Maintenance of Wakefulness Test (MWT)*
- *Favorable safety and tolerability profile with no observations of frequently reported on-target adverse events (AEs) associated with other OX2R agonists, visual disturbances or hepatotoxicity as of the data cutoff date [1]*
- *PK profile supports once-daily dosing*
- *Company plans to rapidly initiate Phase 2 studies of ORX750 in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH)*

BOSTON and LONDON, September 10, 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 positive interim data from an ongoing Phase 1 trial of its highly potent and selective orexin receptor 2 (OX2R) agonist, ORX750, in acutely sleep-deprived healthy volunteers. ORX750 showed clinically meaningful and statistically significant improvements in mean sleep latency at the first two doses evaluated (1.0 mg and 2.5 mg) in the Maintenance of Wakefulness Test (MWT) compared to placebo. More specifically, the 2.5 mg dose was shown to restore normative wakefulness[2] with a mean sleep latency of 32 minutes as measured by the MWT. ORX750 was also shown to have a favorable safety and tolerability profile with no observations of frequently reported on-target adverse events (AEs) associated with other OX2R agonists, and no cases of hepatotoxicity or visual disturbances across all three dose levels tested (1.0 mg, 2.0 mg, and 2.5 mg), as of the data cutoff date.[1] Based on the interim data, the Company plans to rapidly advance ORX750 into Phase 2 studies in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) beginning in the fourth quarter of 2024.

“The Phase 1 acutely sleep-deprived healthy volunteer sleep study set a high bar for ORX750, and the early data generated has exceeded our expectations, giving us the confidence to accelerate the program into the next stage of clinical development earlier than anticipated,” said Saurabh Saha MD PhD, Chief Executive Officer of Centessa. “We are very pleased that the data support the potential for ORX750 to

restore normative wakefulness in patients with NT1, NT2, and IH at very low, once-daily oral doses. Underpinning these data is a favorable initial safety and tolerability profile for ORX750, which provides us with the flexibility to explore the therapeutic potential of ORX2 agonists. Given the strength of the data generated to date and the exciting potential opportunities we see with ORX750, we are aggressively pursuing our clinical development plans and expect to initiate Phase 2 studies of ORX750 in patients with NT1, NT2 and IH beginning in the fourth quarter of 2024."

The Phase 1 clinical study is an ongoing first-in-human, randomized, placebo-controlled study designed to evaluate the safety, tolerability and pharmacokinetics (PK) of single-ascending doses (SAD) and multiple-ascending doses (MAD) of ORX750 in healthy adult subjects. In parallel to the SAD, a placebo-controlled cross-over pharmacodynamic (PD) assessment is being performed utilizing the MWT and Karolinska Sleepiness Scale (KSS) in acutely sleep-deprived healthy adult subjects with the goal of rapidly generating early efficacy data to inform dosing for planned studies in patients. As of September 10, 2024, the study has completed three SAD cohorts of healthy volunteers (27 active, 9 placebo) with doses of 1.0 mg, 2.0 mg, and 2.5 mg, and has advanced through two cohorts within the cross-over assessment of acutely sleep-deprived healthy volunteers with doses of 1.0 mg (n=8) and 2.5 mg (n=8), administered as a single oral dose. Dosing in the MAD portion of the study is also ongoing.

Summary of Data:

The interim Phase 1 clinical data for ORX750 demonstrated:

- Significantly increased wakefulness in acutely sleep-deprived healthy volunteers compared to placebo at both doses tested. Treatment with ORX750 resulted in statistically significant ($p<0.05$) and clinically meaningful increased sleep latency on the MWT (time to sleep onset over the four sessions performed at ~2, 4, 6, and 8 hours after dosing at 11 p.m., maximum 40 minutes per session) compared to placebo across all doses. Mean sleep latencies, as measured by the MWT, for 1.0 mg dose of ORX750 and placebo were 18 minutes and 10 minutes, respectively (p-value = 0.04) (least squares mean). Mean sleep latencies, as measured by the MWT, for 2.5 mg dose of ORX750 and placebo were 32 minutes and 17 minutes, respectively (p-value = 0.01) (least squares mean). The 2.5 mg dose was shown to restore normative wakefulness with a mean sleep latency of 32 minutes as measured by the MWT.
- Favorable safety and tolerability observed as of the data cutoff date.[1] All observed treatment related AEs were mild and transient with none leading to treatment discontinuation.

    - No observations of frequently reported on-target AEs associated with other OX2R agonists, including urinary frequency, urinary urgency, insomnia, blood pressure increases, and salivary hypersecretion.
    - No cases of hepatotoxicity, visual disturbances or hallucinations were observed. Additionally, there were no clinically meaningful treatment-emergent changes in hepatic and renal parameters, vital signs, or electrocardiogram (ECG) parameters.
- Acutely sleep-deprived healthy volunteers who received a 2.5 mg dose of ORX750 showed a significant 1.6 point improvement versus placebo in mean KSS score compared to baseline (p-value = 0.03).
- Encouraging linear PK profile supports the use of ORX750 as a once-daily oral dosing regimen with rapid absorption (plasma concentrations of ORX750 peaked at 2h after the first dose). The systemic exposure of ORX750 increased in an approximately dose-proportional manner.

“With these interim data, we believe we have successfully demonstrated a potential best-in-class profile for ORX750 having achieved normative wakefulness at once-daily low doses in subjects with normal orexin tone, coupled with a favorable safety and tolerability profile,” said Mario Alberto-Accardi PhD, President, Centessa Orexin Program. “Consistent with what we’ve seen preclinically, we believe these data validate our unique structural biology driven orexin research platform and accelerate translation of our growing pipeline of orexin agonists, including the future development of ORX142, our second orexin agonist development candidate. We are excited to leverage these data to expedite the progression of our multi-asset orexin franchise to potentially treat sleep-wake disorders and excessive daytime sleepiness (EDS) across multiple conditions.”

1. Data cutoff date of August 26, 2024.
2. Doghramji K, et al., A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol 1997; 103:554-62.

About Centessa Pharmaceuticals

Centessa Pharmaceuticals plc is a clinical-stage pharmaceutical company that aims to discover and develop medicines that are transformational 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.

About Centessa's Orexin Agonist Program

Orexin is a neuropeptide that regulates the sleep-wake cycle, leading to arousal and promoting wakefulness. Low levels of orexin result in excessive daytime sleepiness (EDS) and poor regulation of rapid eye movement (REM) sleep and, in narcolepsy type 1 (NT1), cataplexy and other symptoms. Centessa is developing a pipeline of potential best-in-class orexin receptor 2 (OX2R) agonists, including ORX750 for the treatment of sleep-wake disorders, including NT1, narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH), and ORX142 for the treatment of EDS in select neurological, neurodegenerative, and psychiatric disorders. The Company's lead asset, ORX750, is in a Phase 1 clinical study. ORX750 and ORX142 have not been approved by the FDA or any other regulatory authority.

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; the timing of commencement of new studies or clinical trials or clinical and preclinical data related to ORX750; its ability to identify, screen, recruit and maintain a sufficient number of or any subjects in its existing and anticipated studies or clinical trials including in respect of ORX750; 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; the Company's ability to differentiate ORX750 from other treatment options; the development, design and therapeutic potential of ORX750; 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 and tolerability profile of our product candidates, including ORX750; whether

ORX750 could be shown to be ineffective; our ability to identify, screen and recruit a sufficient number of or any subjects in our existing and anticipated new studies or clinical trials including ORX750 or within anticipated timelines; our expectations relating to the further clinical development of ORX750 including initiation of phase 2 study and exploration of higher doses in the phase 1 study, including the predicted timing of enrollment, the predicted efficacious doses of ORX750 and our ability to successfully conduct our clinical development of ORX750; whether preclinical and initial clinical results for ORX750 will be predictive of results of further clinical trials; 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; 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 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. 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

Exhibit 99.2

CENTESSA
PHARMACEUTICALS

Corporate Overview

September 10, 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, ORX142 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

CENTESSA PHARMACEUTICALS

Centessa reported $294.8 million in cash, cash equivalents and short-term investments as of June 30, 2024. Cash runway into mid-2026.

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

ASSET	DISEASE/CONDITION	MECHANISM
SerpinPC	**Hemophilia B**	Activated Protein C Inhibitor
ORX750	**Sleep-Wake Disorders** *NT1, NT2 & IH*	Orexin Receptor 2 (OX2R) Agonist
ORX142	**Excessive Daytime Sleepiness (EDS)** *In neurological, neurodegenerative & psychiatric disorders**	Orexin Receptor 2 (OX2R) Agonist
LB101	**Solid Tumors**	PD-L1xCD47 LockBody®

CENTESSA PHARMACEUTICALS

Centessa has multiple early-stage assets not reflected on this slide. NT1 (narcolepsy type 1); NT2 (narcolepsy type 2); IH (idiopathic hypersomnia)
*Select neurological, neurodegenerative and psychiatric disorders with EDS.

2024 Driving Momentum

ANTICIPATED MILESTONES

OREXIN AGONIST PROGRAM

ORX750

Plan to rapidly advance into Phase 2 studies in patients with NT1, NT2, and IH beginning in **Q4 of 2024**

ORX142

Preclinical data to be presented at **Sleep Europe 2024**

HEMOPHILIA PROGRAM

SerpinPC

PRESent-2 Part 1 interim analysis planned in **2024**; Part 1 data planned for **late 2024/early 2025**

LOCKBODY TECHNOLOGY PLATFORM

LB101

Phase 1/2 study **ongoing**

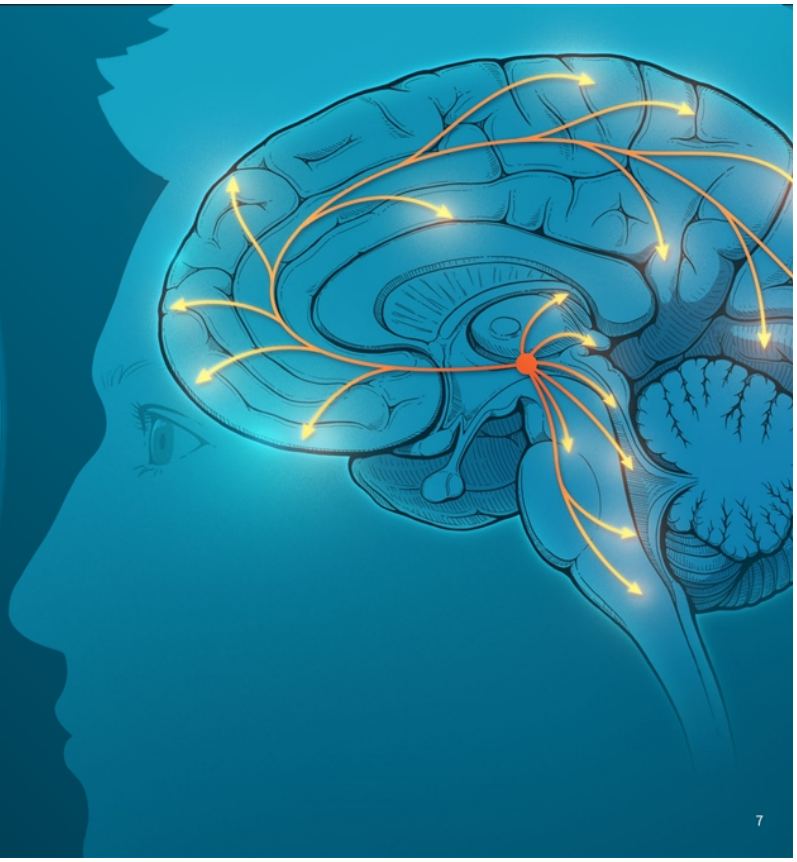
Orexin Agonist Program

Hemophilia Program

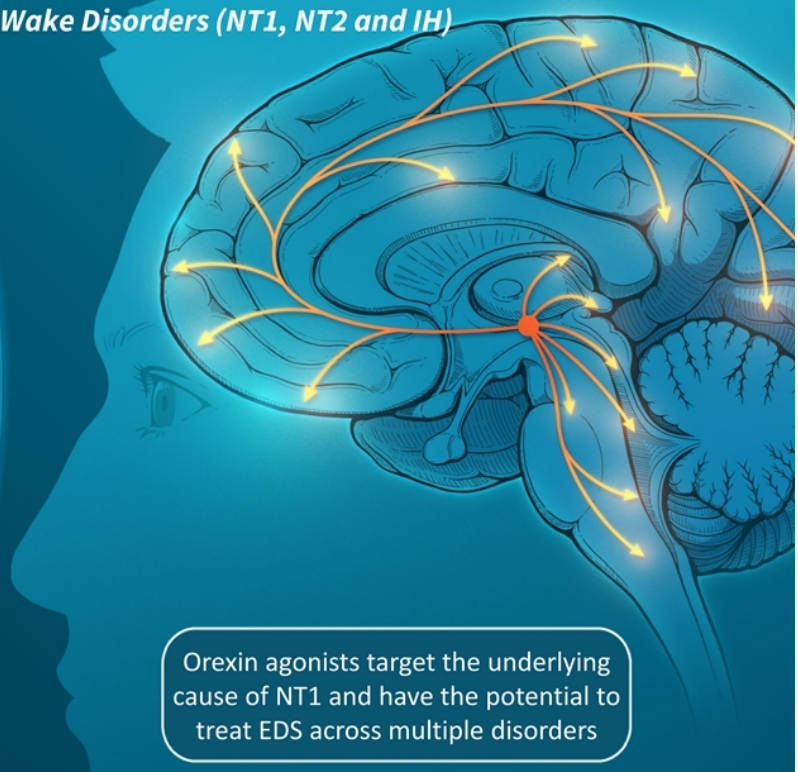
LockBody Technology Platform

CENTESSA PHARMACEUTICALS

Orexin agonists have the potential to transform the standard of care for individuals with sleep-wake disorders and excessive daytime sleepiness (EDS) across select disorders



ORX750: Centessa's Lead OX2R Agonist for Sleep-Wake Disorders (NT1, NT2 and IH)



ORX750

Highly potent, selective orexin receptor type 2 (OX2R) agonist

Orexin agonists target the underlying cause of NT1 and have the potential to treat EDS across multiple disorders

NT1 (narcolepsy type 1); NT2 (narcolepsy type 2); IH (idiopathic hypersomnia)

ORX750 a Potential Best-in-Class Oral OX2R Agonist for the Treatment of Sleep-Wake Disorders (NT1, NT2 and IH)

Highly potent, selective, novel OX2R agonist with linear PK profile to support **once-daily, oral dosing** with rapid absorption[1]

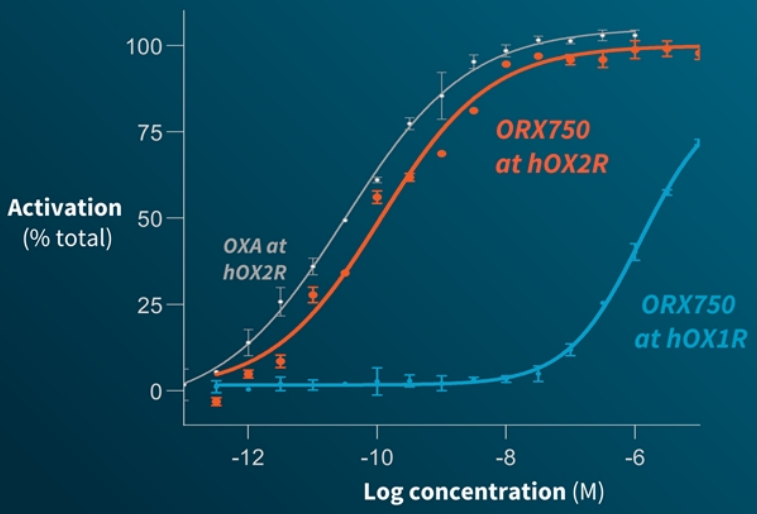
Shown to restore **normative wakefulness**[2] in acutely sleep deprived healthy volunteers with mean sleep latency of **32 mins (MWT)** at **2.5 mg dose**[1]

Favorable safety and tolerability profile;[1] No observations of frequently reported on-target AEs associated with OX2R agonists, hepatotoxicity, visual disturbances or hallucinations, to date[1]

MWT is Maintenance of Wakefulness Test. Phase 1 Study is ongoing,

1. Interim Phase 1 study data reported September 10, 2024. Data cutoff date of August 26, 2024.
2. Doghramji K, et al., "A normative study of the maintenance of wakefulness test (MWT)." *Electroencephalogr Clin Neurophysiol* 1997; 103:554-62.

ORX750 is a Highly Potent and Selective OX2R Agonist



***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

PHASE 1 STUDY

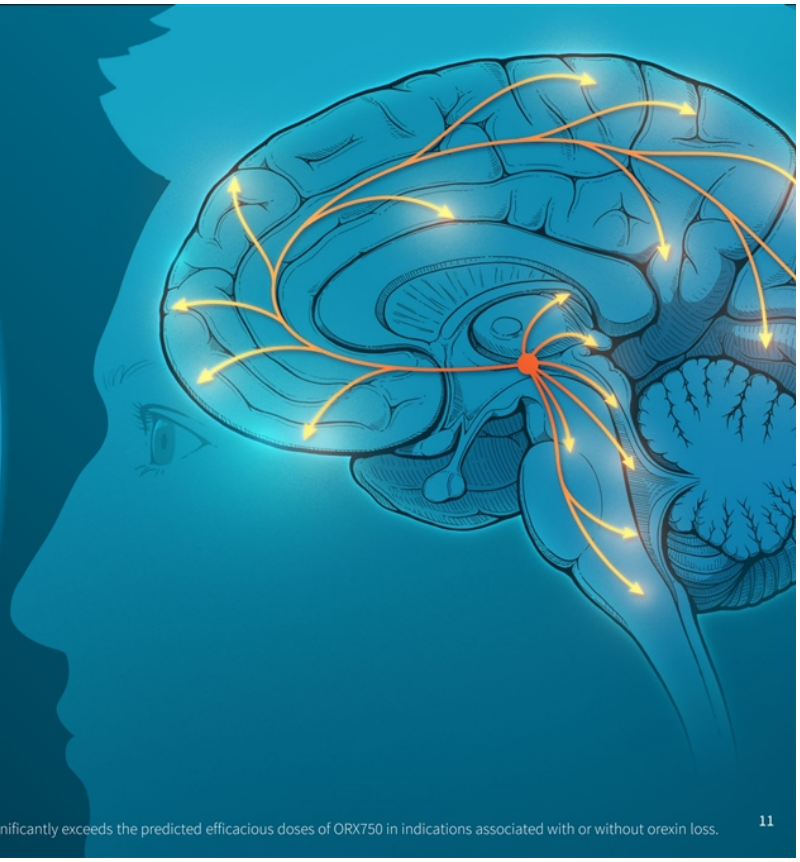
ORX750 First-in-Human Healthy Volunteer (HV) Study

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

- Efficacy assessments are being performed using the **Maintenance of Wakefulness Test (MWT)*** and **Karolinska Sleepiness Scale (KSS)** in acutely sleep-deprived healthy adult subjects

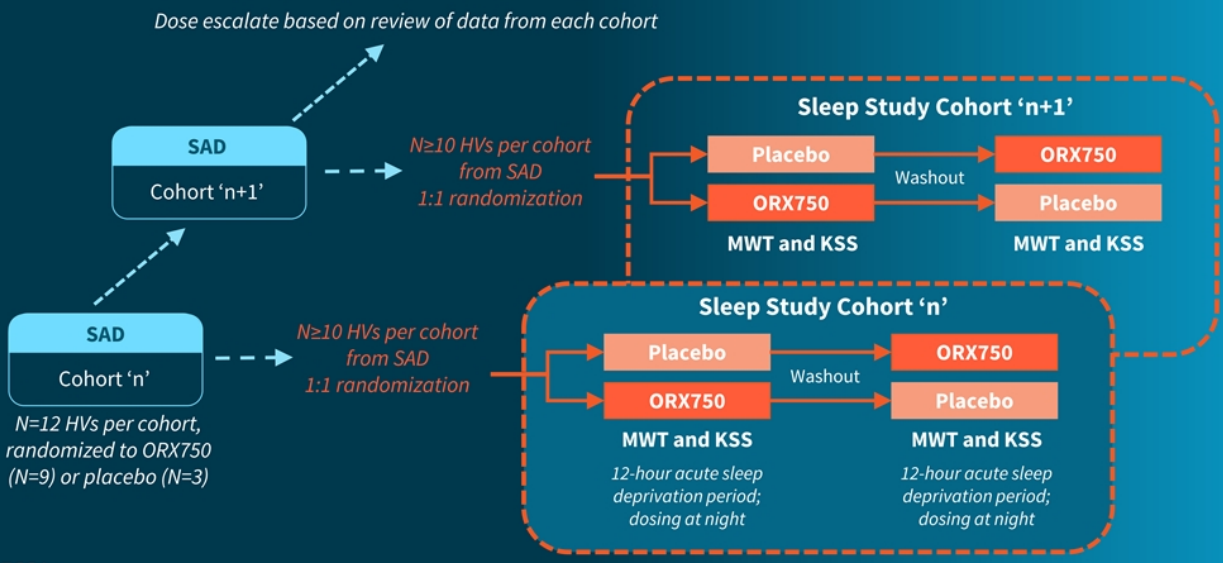


*MWT is an established registrational and objective endpoint in EDS in sleep-wake disorders.
The Phase 1 study has a maximum exposure limit specified by the FDA which the company believes significantly exceeds the predicted efficacious doses of ORX750 in indications associated with or without orexin loss.

PHASE 1 STUDY

SAD Combined with Efficacy Assessment in Acutely Sleep-Deprived HV

PoC-sleep study cohorts to assess efficacy 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



CENTESSA PHARMACEUTICALS

INTERIM PHASE 1

ORX750 Significantly Improved Mean Sleep Onset Latency (measured by MWT) at First Two Doses Compared to Placebo

	Post Dose LS Mean (95% CI) Sleep Onset Latency (Minutes)	LS Mean Difference Compared To Placebo In Mean Sleep Onset Latency (95% CI)	
		Estimate (95% CI)	*P-value*
ORX750 1.0 mg *(n=8)*	**17.6** (12.1, 23.2)	**8.1** (0.3, 15.9)	**0.04**
ORX750 2.5 mg *(n=8)*	**32.0** (22.2, 41.8)	**15.2** (4.7, 25.8)	**0.01**

- The 2.5 mg dose was shown to **restore normative wakefulness**[1] in acutely sleep-deprived healthy volunteers with mean sleep onset latency of **32 minutes** (MWT)
- Acutely sleep-deprived healthy volunteers who received a 2.5 mg dose of ORX750 showed a significant **1.6 point improvement** versus placebo in mean KSS score compared to baseline (p-value = 0.03)

Phase 1 study is ongoing. Interim data cutoff date of August 26, 2024. Least squares (LS) mean.
Consistent with the Phase 1 study design, a sleep study cohort (MWT) is optional at each SAD level, and as of the data cut off date, has been conducted only for 1 mg and 2.5 mg doses.
Mean sleep onset latency on the MWT (time to sleep onset over the four sessions performed at ~2, 4, 6, and 8 h after dosing at 11 p.m.; maximum 40 min per session).
1. Doghramji K, et al., "A normative study of the maintenance of wakefulness test (MWT)." *Electroencephalogr Clin Neurophysiol* 1997; 103:554-62.

CENTESSA PHARMACEUTICALS

INTERIM PHASE 1

ORX750 Demonstrated a Favorable Safety and Tolerability Profile

	Placebo *(n=9)*	ORX750 1.0 mg *(n=9)*	ORX750 2.0 mg *(n=9)*	ORX750 2.5 mg *(n=9)*
Any TEAE, n (%)	3 (33)	4 (44)	3 (33)	2 (22)
Related	2 (22)	1 (11)	2 (22)	1 (11)
Nonrelated	1 (11)	4 (44)	2 (22)	1 (11)
Mild	3 (33)	3 (33)	3 (33)	2 (22)
Moderate	0	1 (11)	0	0
Severe	0	0	0	0
Leading to discontinuation	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0
Most frequent drug-related TEAEs				
Dizziness	1 (11)	1 (11)	0	0
Nausea	1 (11)	0	0	0
Frequently reported AEs associated with other OX2R agonists				
Visual disturbances	0	0	0	0
Hepatotoxicity	0	0	0	0
Insomnia	0	0	0	0
Urinary frequency/urgency	0	0	0	0
Blood pressure increased	0	0	0	0

- No observations of frequently reported on-target AEs associated with OX2R agonists (i.e., urinary frequency/urgency, insomnia, etc.)
- No cases of hepatotoxicity, visual disturbances or hallucinations were observed
- No clinically meaningful, treatment-emergent changes in hepatic and renal parameters, vital signs or electrocardiogram (ECG) parameters

CENTESSA PHARMACEUTICALS

Phase 1 Study is ongoing. Interim data cutoff date of August 26, 2024. Treatment-emergent adverse event (TEAE). Includes safety data from SAD cohorts. Safety data from Sleep Study Cohorts was consistent with SAD. Nonrelated includes unlikely related and not related. Related includes probably and possibly related.

Building a Multi-Asset Orexin Agonist Franchise

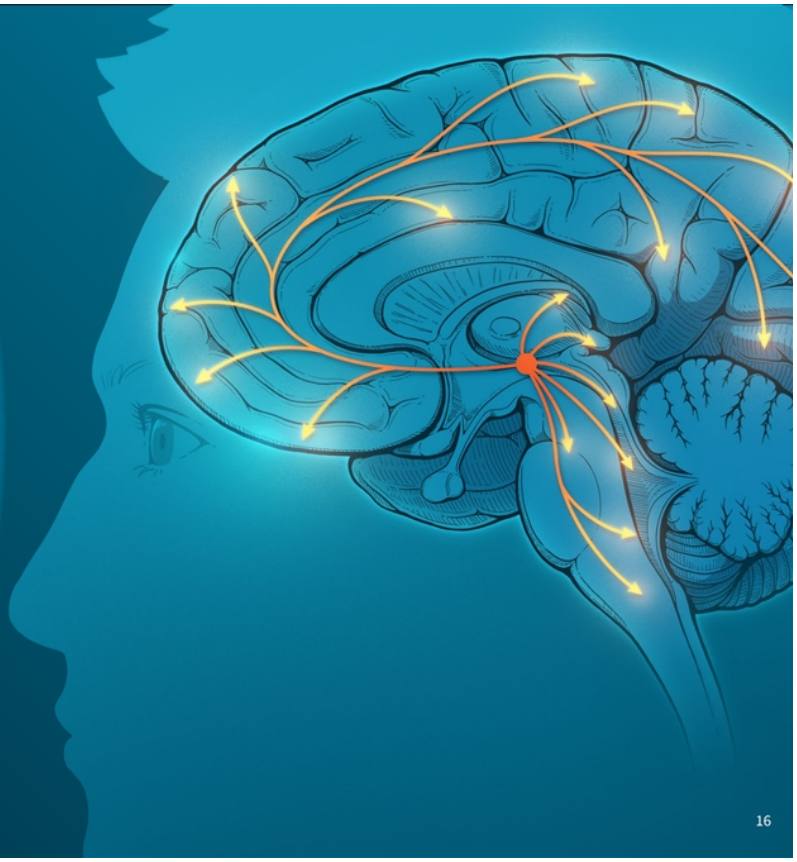
Centessa's orexin pipeline also includes earlier stage orexin agonists and therapeutics

CENTESSA PHARMACEUTICALS

Source: Evaluate Pharma 2030 projected sales for narcolepsy – sales are not risk adjusted; projections for EDS in other disorders based on internal market research

Plan to rapidly advance ORX750 into Phase 2 studies in patients with NT1, NT2 and IH beginning in Q4 of 2024

ORX142 preclinical data to be presented at Sleep Europe 2024



Orexin Agonist Program

Hemophilia Program

LockBody Technology Platform

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]

CENTESSA PHARMACEUTICALS

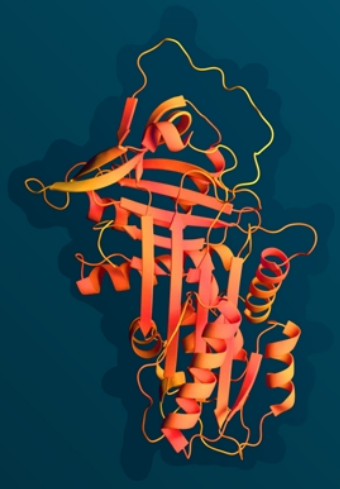
1. Evaluate Pharma Analyst Consensus for 2023. 2. In Canada, a subcutaneous option is available for hemophilia B with inhibitors.

***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]

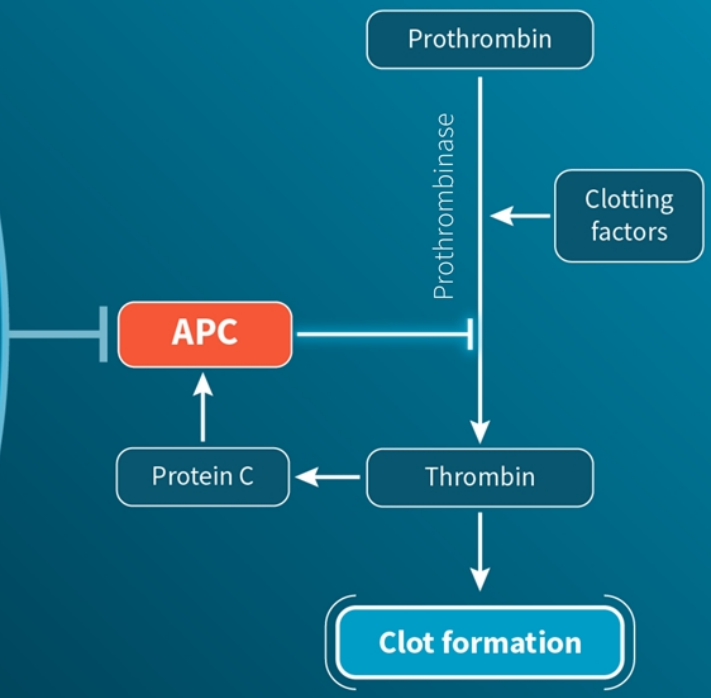
SerpinPC is an investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit activated protein C (APC), that has not been approved by the FDA or any other regulatory authority. ABR is annualized bleed rate. 1. Ongoing Phase 2a Study being conducted in Georgia and Moldova to evaluate 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



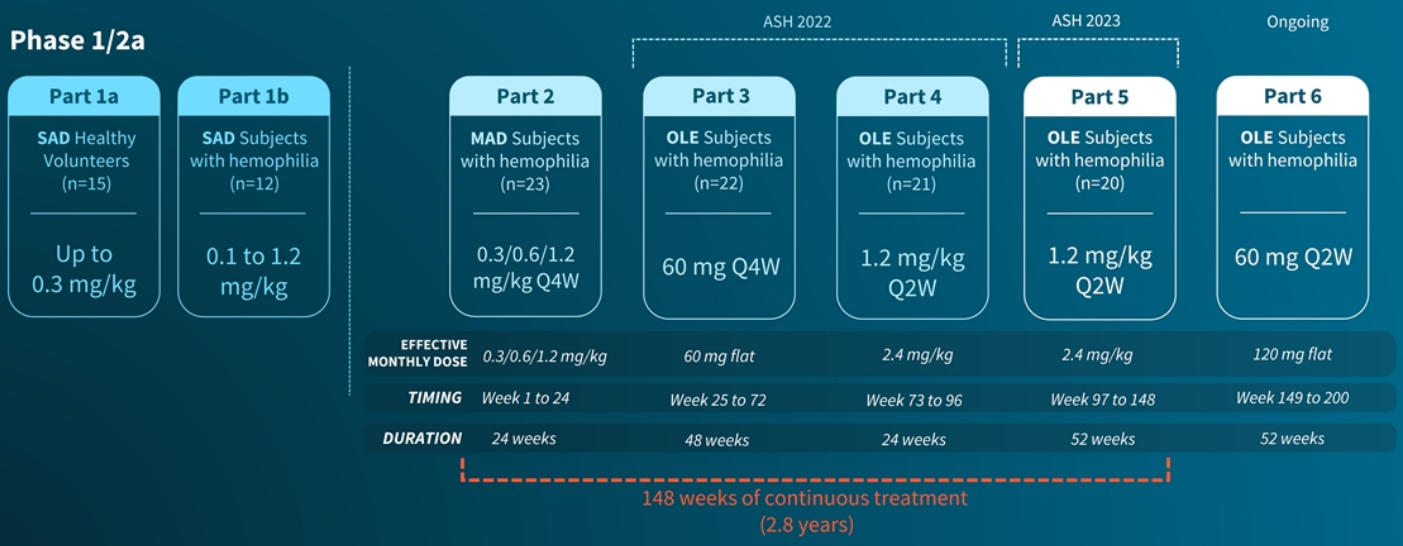
SerpinPC

Designed to reduce levels of circulating activated protein C (APC)



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

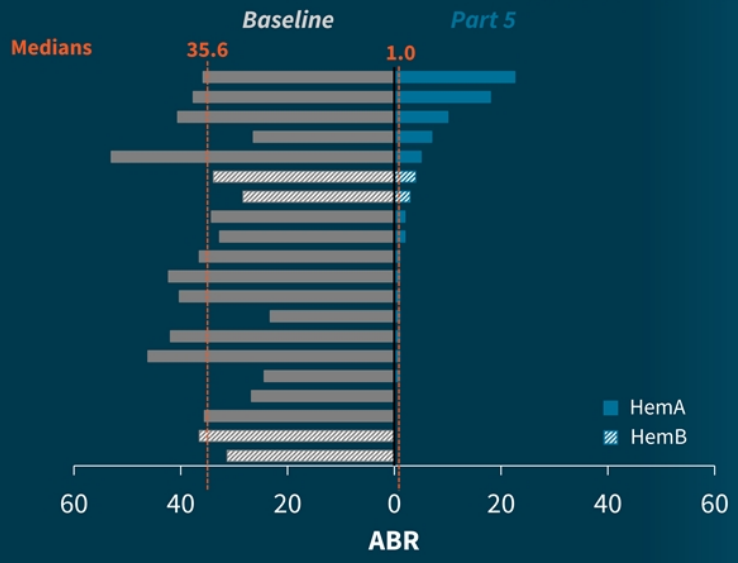


CENTESSA PHARMACEUTICALS

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.

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

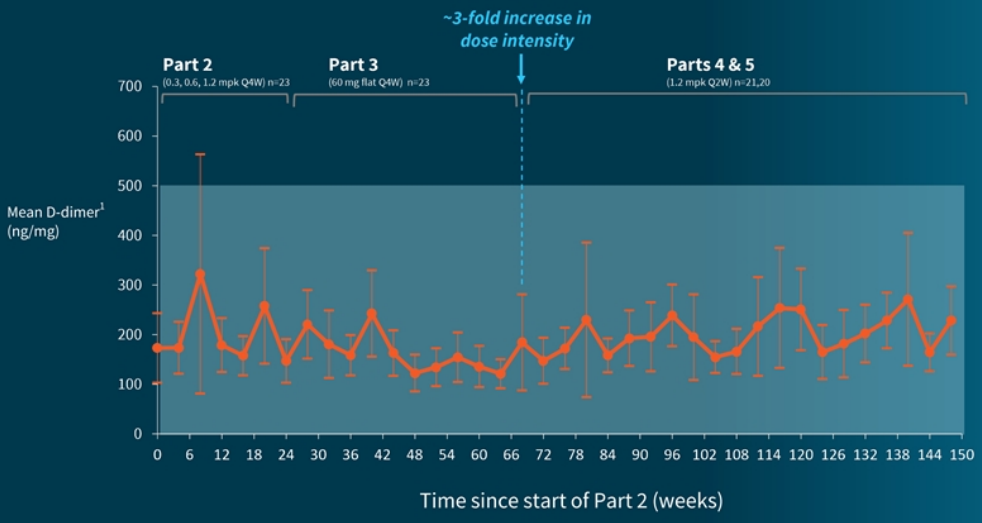
No observations of treatment-related adverse events in Part 5

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.

CENTESSA PHARMACEUTICALS

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.

CENTESSA PHARMACEUTICALS

SerpinPC Ongoing Global Registrational Program 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

>50 SITES
>15 COUNTRIES

CENTESSA PHARMACEUTICALS

ABR is annualized bleeding rate. The primary endpoint for PRESent-2 is measured in Part 2 and is the rate of treated bleeds (expressed as ABR) for hemophilia B subjects who previously received on-demand therapy compared to their prospective baseline ABR. Additional information on the PRESent studies can be accessed at www.clinicaltrials.gov (NCT05605678, NCT05789524, NCT05789537).

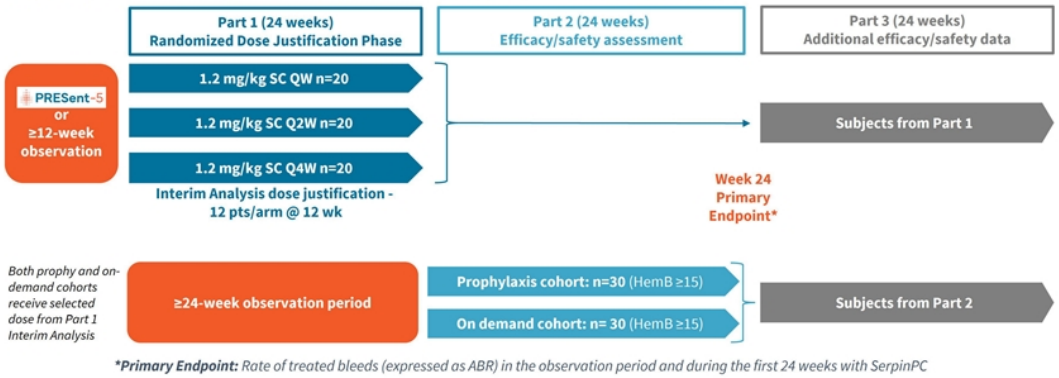
SerpinPC

Ongoing Global Registrational Program for Hemophilia B

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

PRESent-2

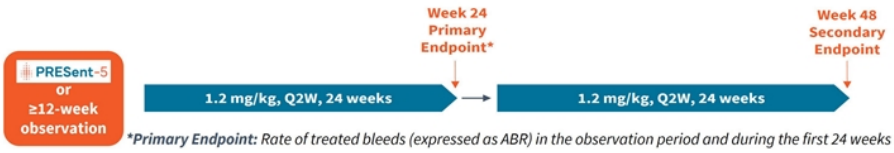
Hemophilia B without inhibitors (n=120) *Study to also include hemophilia A subjects to support safety database*



***Primary Endpoint:** Rate of treated bleeds (expressed as ABR) in the observation period and during the first 24 weeks with SerpinPC*

PRESent-3

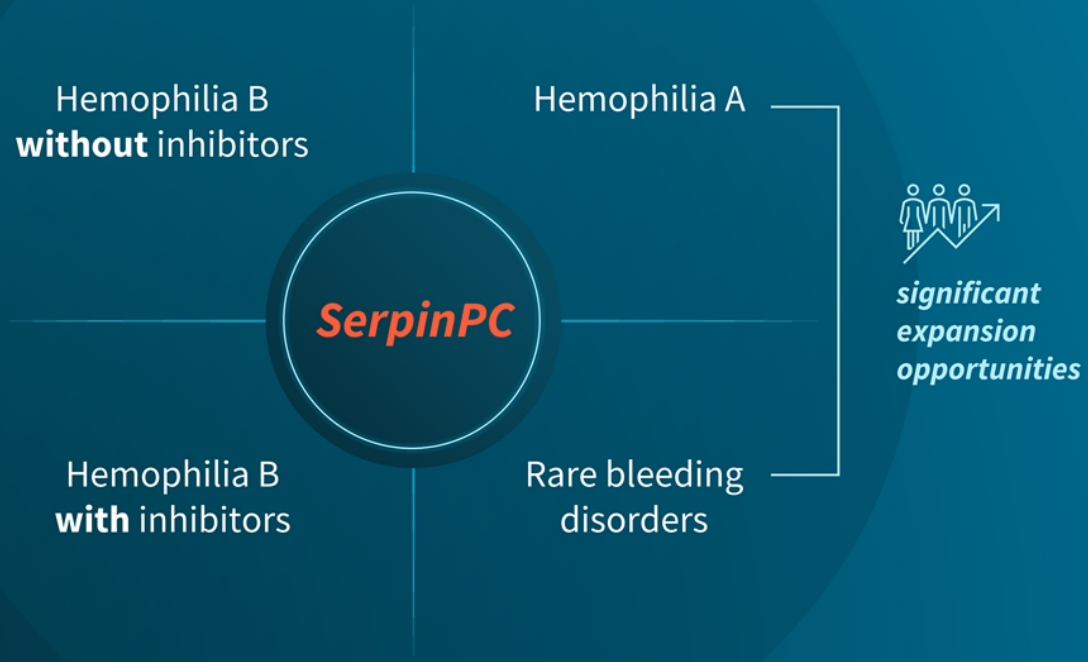
Hemophilia B with inhibitors (n≥12)



***Primary Endpoint:** Rate of treated bleeds (expressed as ABR) in the observation period and during the first 24 weeks with SerpinPC*

CENTESSA PHARMACEUTICALS

Potential Multi-Billion-Dollar Market Opportunities



CENTESSA PHARMACEUTICALS

Evaluate Pharma Analyst Consensus for 2023.

Orexin Agonist Program

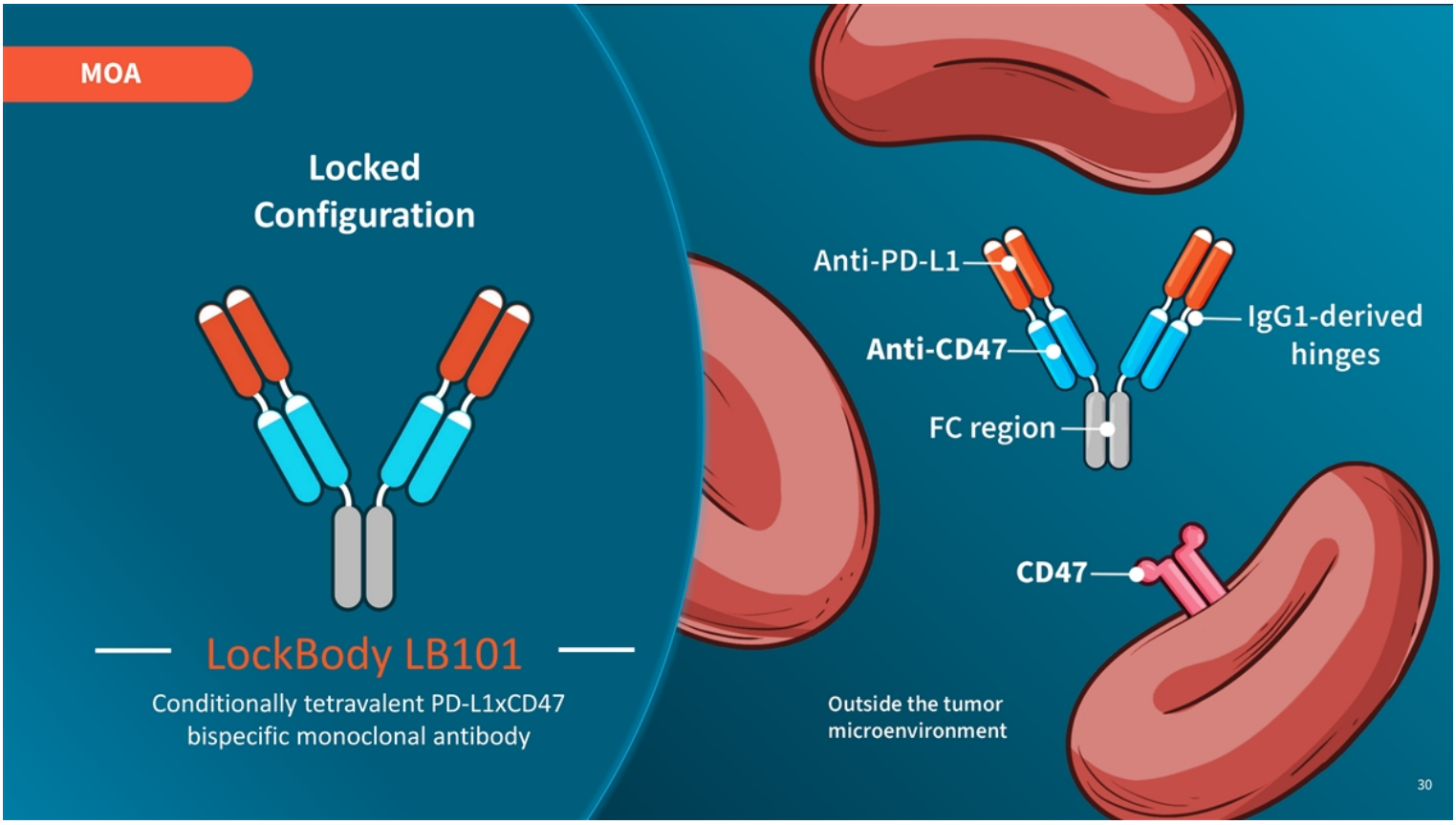
Hemophilia Program

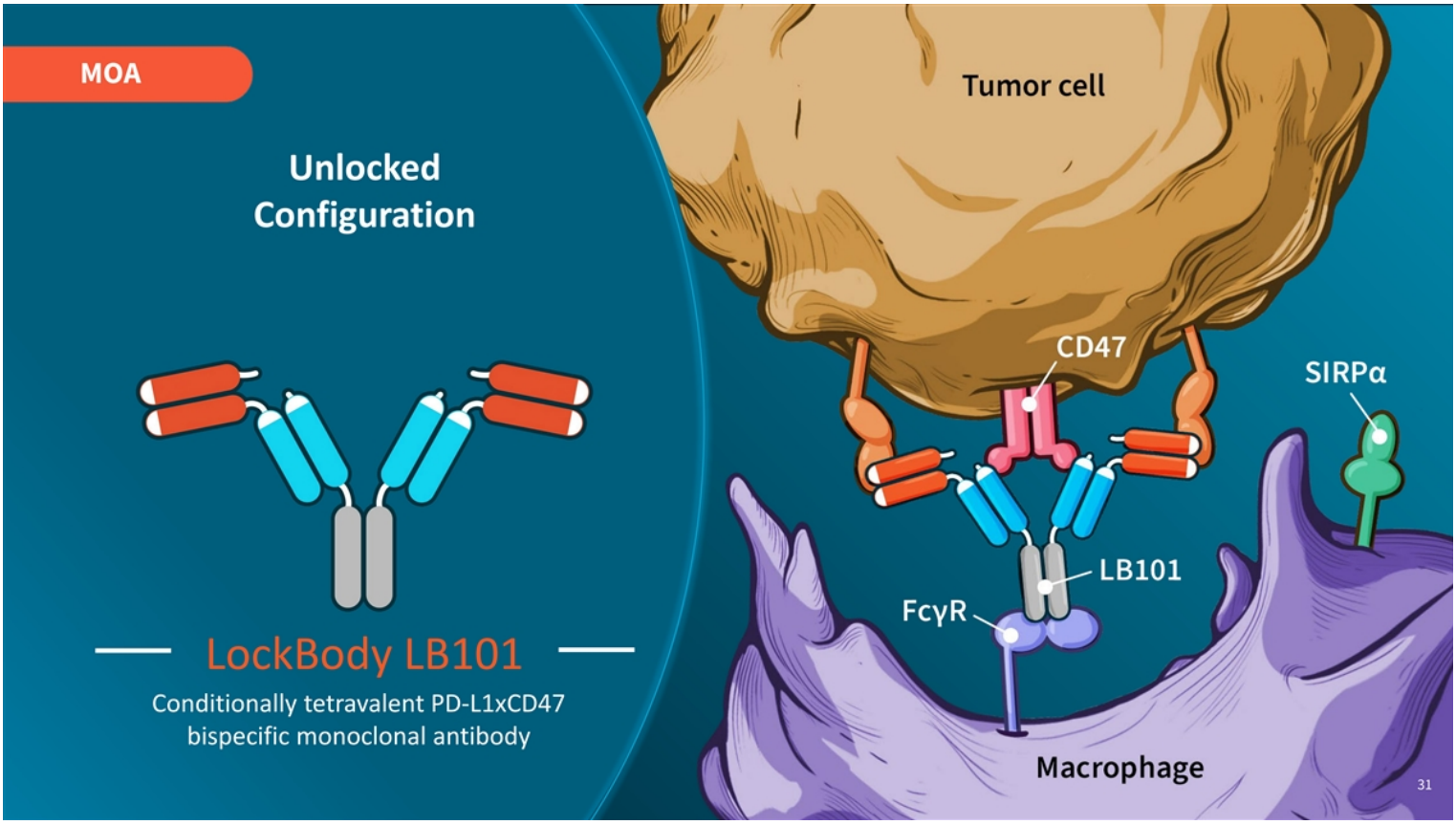
LockBody Technology Platform

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]

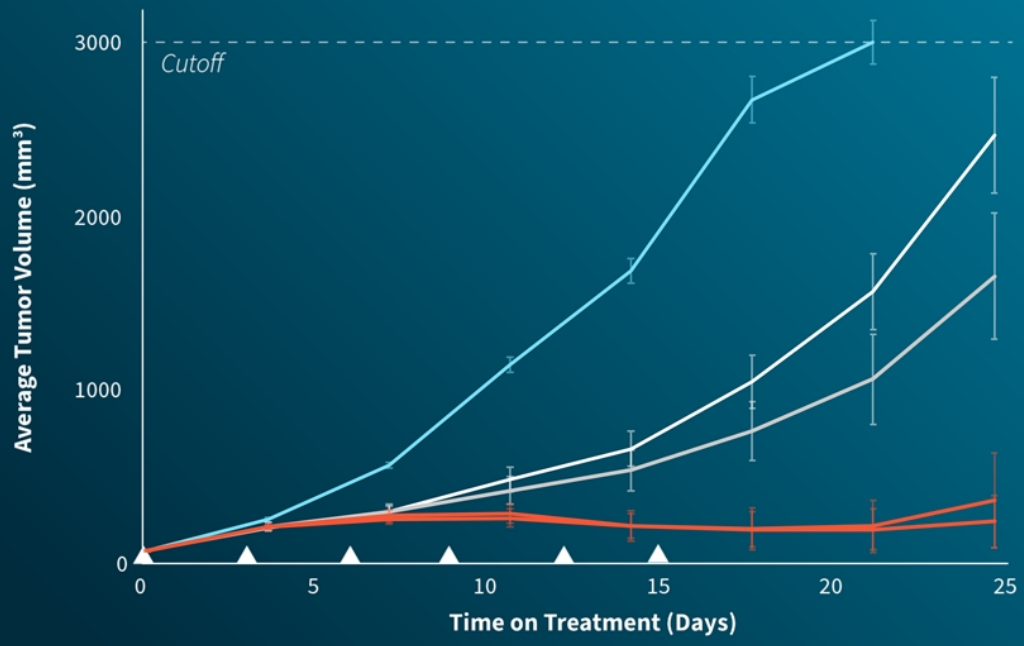
LB101 is an investigational agent that has not been approved by the FDA or any other regulatory authority. Information on the Phase 1/2a trial of LB101 can be accessed at www.clinicaltrials.gov (NCT05821777). 1. LB101 *in-vivo* preclinical data: MC38 hPD-L1+ syngeneic model in mouse, and in non-human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

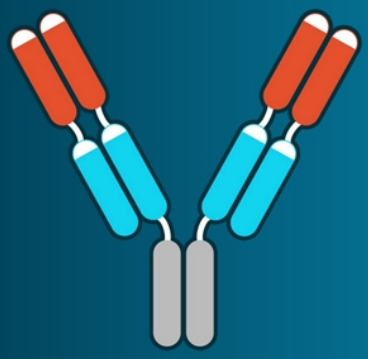
No weight loss

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.

LB101 is in an ongoing Phase 1/2a first-in-human clinical trial



CENTESSA PHARMACEUTICALS

2024 Driving Momentum

ANTICIPATED MILESTONES

OREXIN AGONIST PROGRAM

ORX750

Plan to rapidly advance into Phase 2 studies in patients with NT1, NT2, and IH beginning in **Q4 of 2024**

ORX142

Preclinical data to be presented at **Sleep Europe 2024**

HEMOPHILIA PROGRAM

SerpinPC

PRESent-2 Part 1 interim analysis planned in **2024**; Part 1 data planned for **late 2024/early 2025**

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

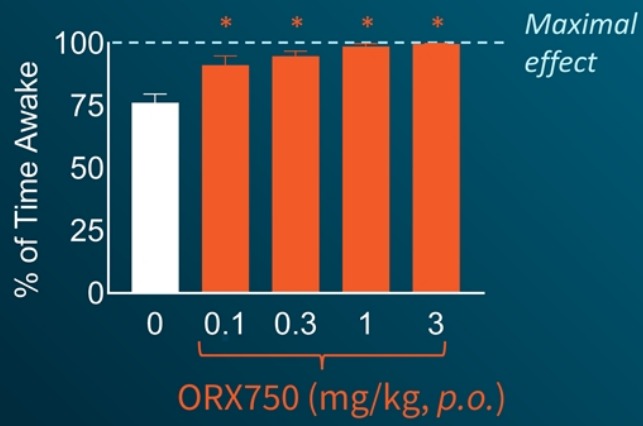
Centessa reported $294.8 million in cash, cash equivalents and short-term investments as of June 30, 2024. Cash runway into mid-2026.


CENTESSA
PHARMACEUTICALS

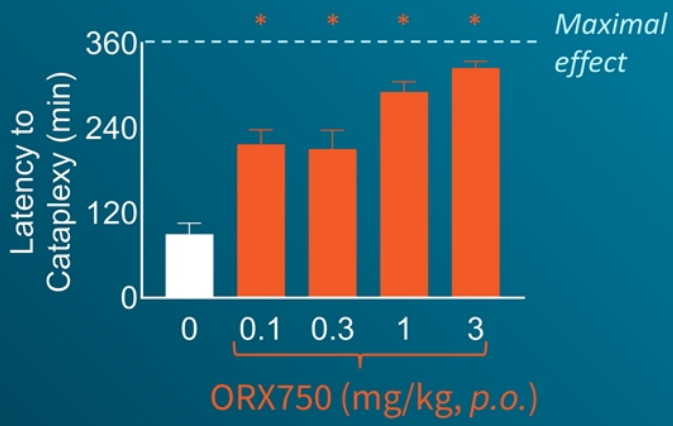
PRECLINICAL DATA

ORX750 Increased Wakefulness and Suppressed Cataplexy in NT1 Mice

Wakefulness



Latency to Cataplexy

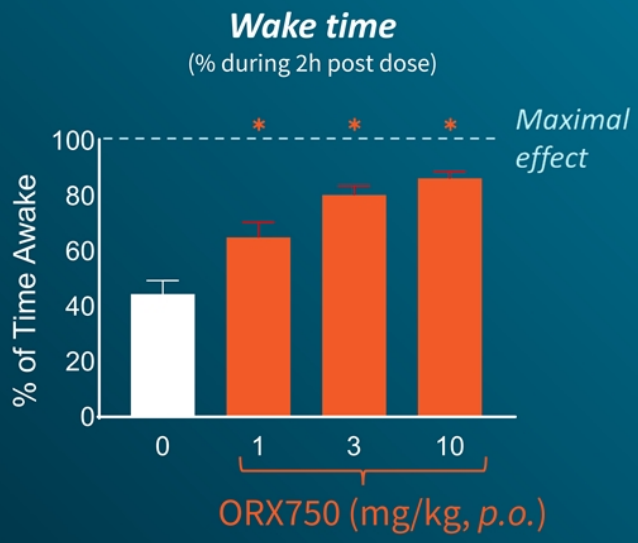


NT1 is Narcolepsy Type 1.
% of Time Awake refers to time spent awake in the first 3 hours after oral dosing.
ORX750 preclinical data presentation at World Sleep Congress, Oct. 25, 2023. NT1 model shown is orexin/tTA;tetO diphtheria toxin fragment A (DTA) mice. Age at first dose 23-27 wks (7 wks after 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.