CENTESSA PHARMACEUTICALS

Corporate Overview

January 2025

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This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including ORX750, ORX142, ORX489, 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 Oxford Finance, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and geo-political risks such as the Russia-Ukraine war 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.

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OUR MISSION

Discovering and Developing Transformational Medicines for Patients

- Potential best-in-class / first-in-class orexin receptor 2 (OX2R) agonist franchise
- Robust series of clinical milestones anticipated across OX2R agonist pipeline in 2025
- Strong balance sheet

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Centessa reported **$518.4 million** in cash, cash equivalents and short-term investments as of September 30, 2024. Cash runway estimated into mid-2027.

2025
Focused Execution

ANTICIPATED MILESTONES

ORX750

Phase 2a data in patients with Narcolepsy Type 1 (NT1), Narcolepsy Type 2 (NT2), and Idiopathic Hypersomnia (IH) expected in **2025**

Presentation of Phase 1 data planned for **Q2 2025**

ORX142

Clinical data in acutely sleep-deprived healthy volunteers expected in **2025**

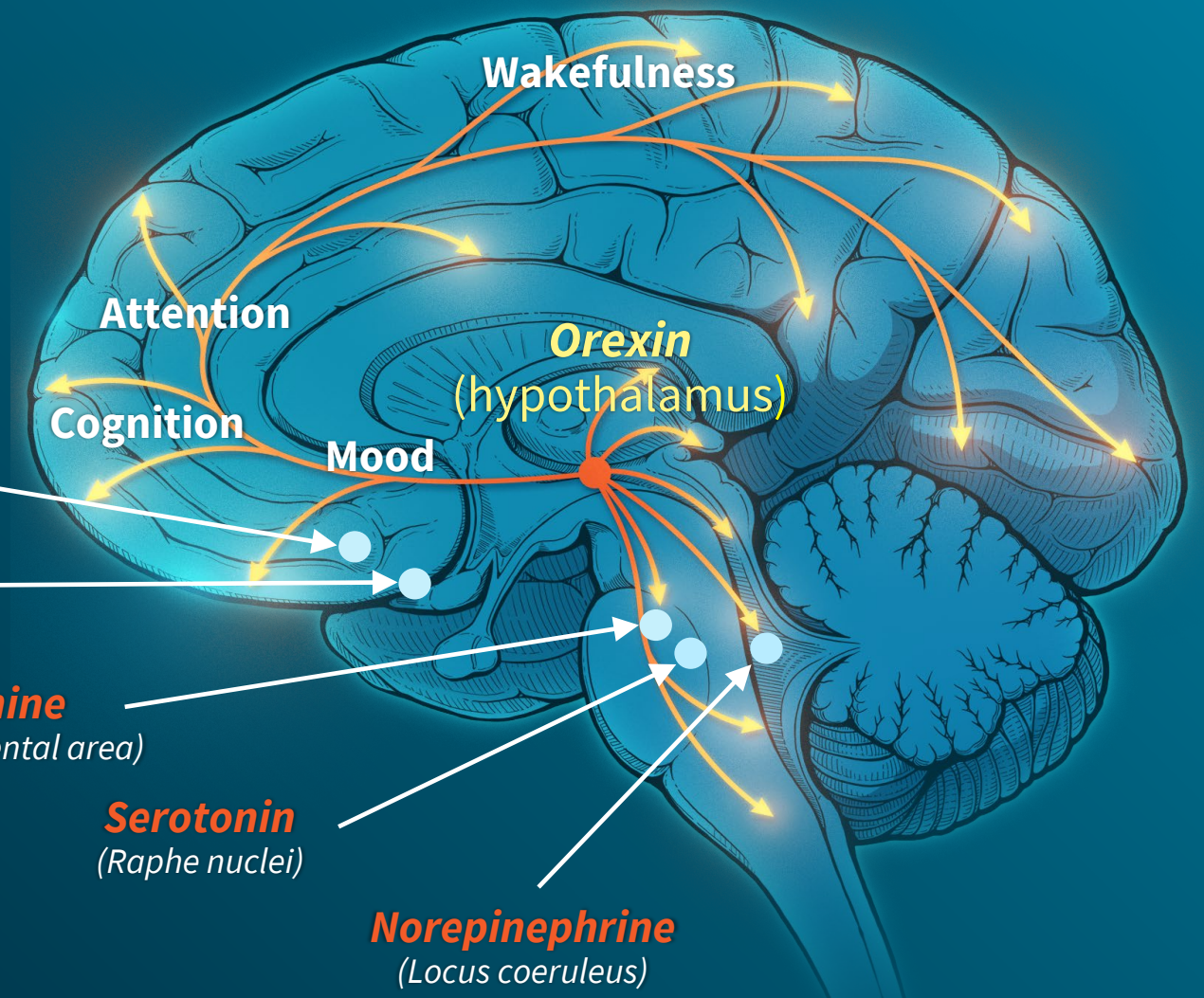
ORX489

Entering IND-enabling studies

OX2R agonists have the potential to transform the standard of care for individuals with sleep-wake, neurological, neurodegenerative and psychiatric disorders

Orexin System is Implicated in Numerous Therapeutic Areas

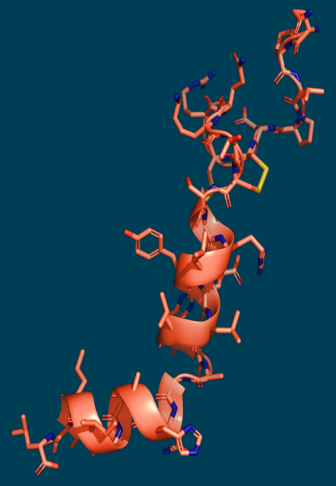
Orexin: a key signaling neuropeptide triggering a cascade of neurotransmitter release

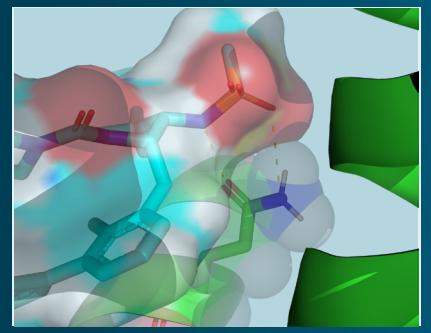


Sources: Pizza, F et al., J Sleep Res 2022;31(4):e13665; Toor, B et al., Front Neurol Neurosci 2021;45:38 ; Ten-Blanco, M et al., Front Neuroendo 2023;69:101066; and, Yamamoto, H et al., PLoS One, 2022;17(7):e0271901.

Pipeline of Highly Potent, Selective OX2R Agonists Enabled by Proprietary Structural Biology Insights

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





Candidate Selection Criteria: Best-in-Class Profile

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

*SAR is Structure- Activity Relationship optimization.

Positioned to be Potential Best-in-Class / First-in-Class in Emerging Category of OX2R Agonist Therapeutics

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

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

Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing human recombinant OX1R or OX2R.

1. Black et al., World Sleep 2023 Abstract.
2. Black et al., European Sleep Research Society 2024 Abstract.
3. Company data / presentations.

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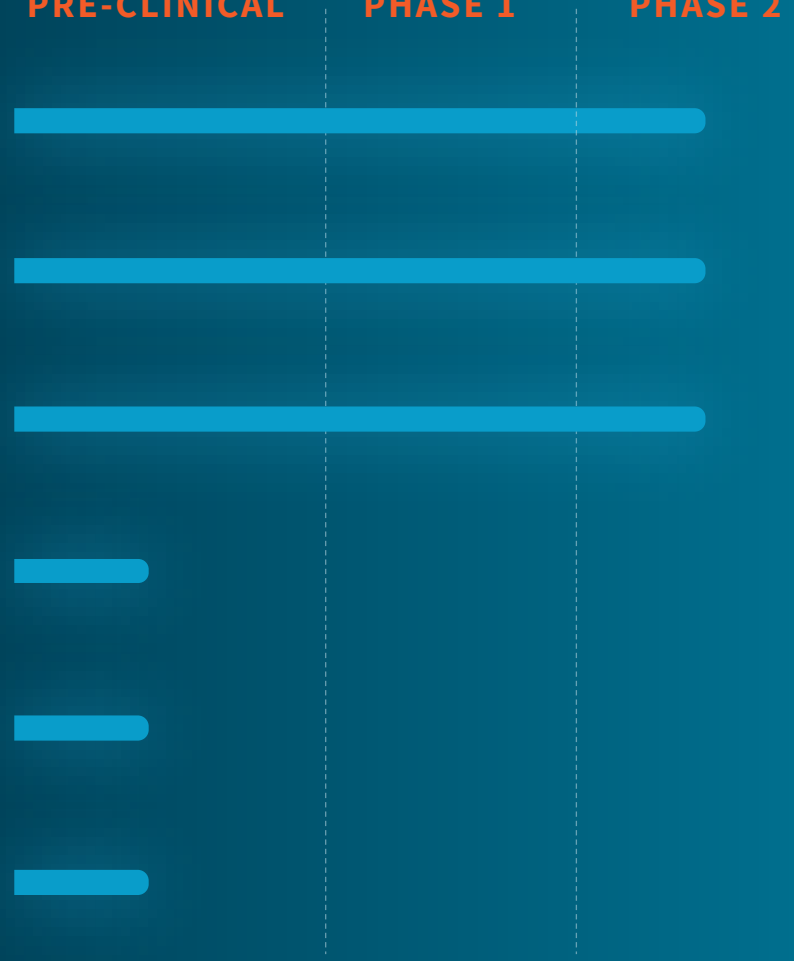
Broad and Rapidly Advancing OX2R Pipeline

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



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Centessa also has multiple early-stage assets including the LockBody® Technology Platform.

Potential $15B+ Market Opportunity Across Multiple Therapeutic Areas

Sleep-Wake Disorders

NT1, NT2, IH

$5B+

potential market size

Excessive Daytime Sleepiness and Fatigue

Neurological, Neurodegenerative and Psychiatric Disorders

$10B+

potential market size

Additional Opportunity in Cognition, Attention, and Mood

Neurological, Neurodegenerative and Psychiatric Disorders

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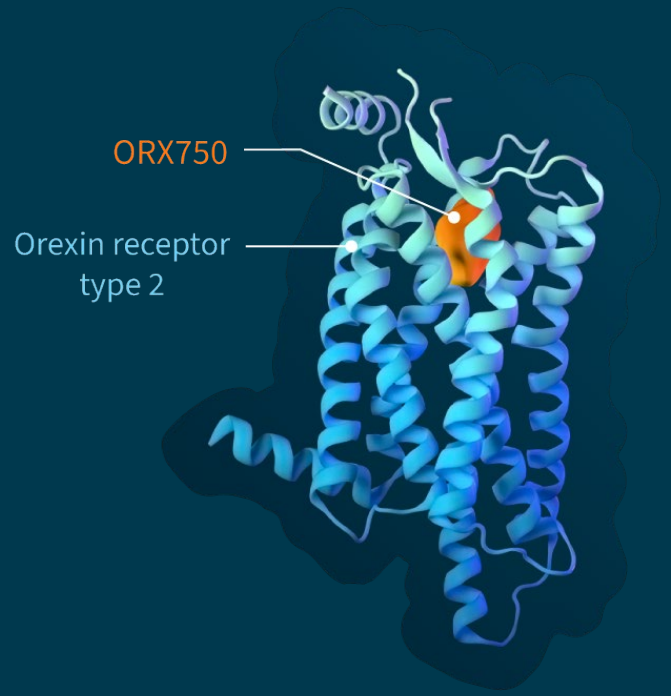
Source: Evaluate Pharma 2030 projected sales for narcolepsy – sales are not risk adjusted; projections for other disorders based on internal market research.

ORX750: Potential to Redefine the Standard of Care for Patients with Sleep-Wake Disorders



ORX750

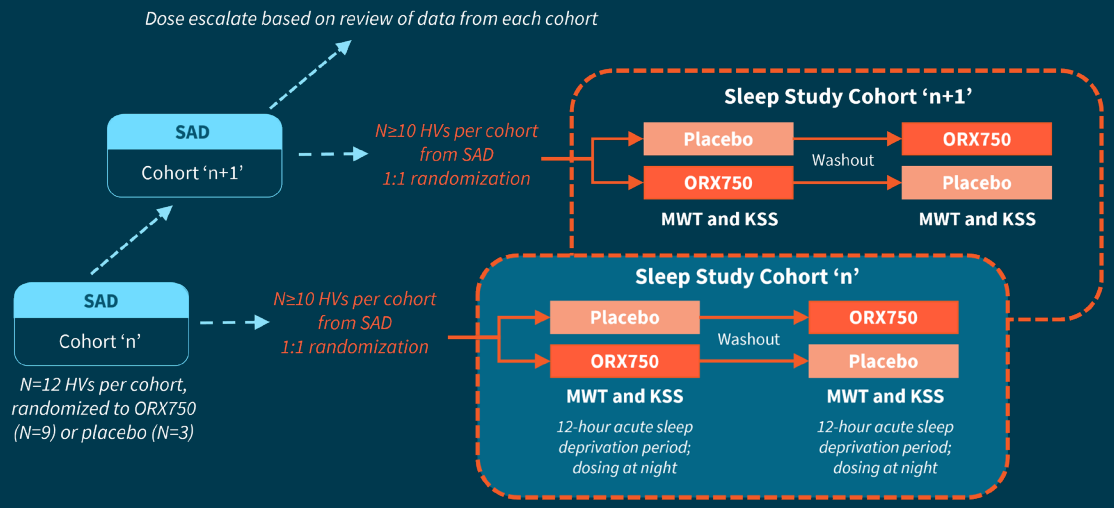
Highly potent, selective OX2R agonist

- **High unmet medical need** in NT1, NT2 and IH
- **Proof-of-concept achieved** and asset clinically **derisked** in Phase 1 study of acutely sleep-deprived healthy volunteers
- **Advancing Phase 2a studies** in patients with NT1, NT2 and IH; **Data expected across all three indications in 2025**
- **Significant commercial opportunity** as potential treatment for all three indications

INTERIM PHASE 1 DATA

ORX750 Phase 1 Interim Data Supports Potential Best-in-Class Profile for the Treatment of NT1, NT2 and IH

Phase 1 Clinical Study Design



The Phase 1 clinical study of ORX750 evaluates the safety, tolerability and pharmacokinetics (PK) of single-ascending and multiple-ascending doses (SAD and MAD) 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 .

Summary of Interim Phase 1 Data

- Shown to **restore normative wakefulness**[1] at **low doses** in acutely sleep-deprived healthy volunteers[2]
- **Favorable safety and tolerability profile**;[2] No observations of hepatotoxicity, cardiotoxicity, visual disturbances or hallucinations[2]
- **Linear PK profile** supports once-daily, oral dosing with rapid absorption[2]

*MWT is an established registrational and objective endpoint in EDS in sleep-wake disorders.
Phase 1 study ongoing.

1. Doghramji K, et al., "A normative study of the maintenance of wakefulness test (MWT)." *Electroencephalogr Clin Neurophysiol* 1997; 103:554-62.
2. Interim Phase 1 study data as of Dec. 5, 2024 data cutoff date.

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INTERIM PHASE 1 DATA

ORX750 Demonstrated Dose-Dependent and Significant Improvements in Mean Sleep Latency

	ORX750 LS Mean (95% CI) Sleep Latency (Minutes)	**Placebo** LS Mean (95% CI) Sleep Latency (Minutes)	**LS Mean Difference** Compared to Placebo (95% CI)	**p-value**
1.0 mg (n=8)	**18** (12, 23)	**10** (4, 15)	**8** (0, 16)	p=0.04
2.5 mg (n=8)	**32** (22, 42)	**17** (7, 27)	**15** (5, 26)	p=0.01
3.5 mg (n=10)	**34** (27, 40)	**13** (7, 20)	**20** (15, 25)	p<0.0001
5.0 mg (n=8)	**38** (32, 44)	**15** (9, 21)	**23** (17, 28)	p<0.0001

- 2.5, 3.5 and 5.0 mg doses were shown to **restore normative wakefulness**[1] in acutely sleep-deprived healthy volunteers

As of December 5, 2024 data cutoff date. Phase 1 study ongoing. Least squares (LS) mean.
Per the Phase 1 study design, a sleep study cohort (MWT) is optional at each SAD level, and has been conducted for 1 mg, 2.5 mg, 3.5 mg and 5.0 mg doses.
Mean sleep onset latency in 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.

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INTERIM PHASE 1 DATA

ORX750 Demonstrated a Favorable Safety and Tolerability Profile with 95 Unique Subjects Exposed

	SAD Cohorts						MAD Cohorts			
	Placebo *(n=15)*	**ORX750 1.0 mg** *(n=9)*	**ORX750 2.0 mg** *(n=9)*	**ORX750 2.5 mg** *(n=9)*	**ORX750 3.5 mg** *(n=9)*	**ORX750 5.0 mg** *(n=9)*	**Placebo** *(n=6)*	**ORX750 2.0 mg** *(n=8)*	**ORX750 3.0 mg** *(n=8)*	**ORX750 4.0 mg** *(n=8)*
Any TEAE, n (%)	**4 (27)**	**3 (33)**	**3 (33)**	**1 (11)**	**0**	**3 (33)**	**3 (50)**	**4 (50)**	**4 (50)**	**6 (75)**
Related	**4 (27)**	**0**	**2 (22)**	**1 (11)**	**0**	**2 (22)**	**1 (17)**	**4 (50)**	**2 (25)**	**5 (63)**
Nonrelated	**1 (7)**	**3 (33)**	**2 (22)**	**0**	**0**	**2 (22)**	**3 (50)**	**2 (25)**	**2 (25)**	**3 (38)**
Mild	**4 (27)**	**3 (33)**	**3 (33)**	**1(11)**	**0**	**3 (33)**	**3 (50)**	**4 (50)**	**4 (50)**	**4 (50)**
Moderate	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2 (25)**
Severe	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
TEAEs leading to discontinuation, n (%)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Serious TEAEs, n (%)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Frequently reported AEs associated with other OX2R agonists										
Insomnia	**0**	**0**	**0**	**0**	**0**	**0**	**1 (17)**	**2 (25)**	**0**	**0**
Urinary frequency/urgency	**1 (7)**	**0**	**0**	**0**	**0**	**1 (11)**	**0**	**1 (12)**	**1 (12)**	**2 (25)**
Visual disturbances	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Hepatotoxicity	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Blood pressure increased	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

- No cases of hepatotoxicity, cardiotoxicity, visual disturbances or hallucinations observed
- No clinically significant treatment-emergent changes in hepatic and renal parameters, vital signs or electrocardiogram (ECG) parameters

As of December 5, 2024 data cutoff date. Phase 1 Study is ongoing with 95 subjects exposed across the full study. Treatment-emergent adverse event (TEAE). Safety data from Sleep Study Cohorts was consistent with SAD. TEAEs are reported by maximum severity. Nonrelated includes unlikely related and not related. Related includes probably and possibly related. 2 moderate AEs were reported at 4.0 mg (toothache and vasovagal syncope); both were deemed unrelated. 4.0 mg MAD dose has comparable drug exposure to 5.0 mg SAD dose.

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PHASE 2a STUDY

Phase 2a study of ORX750 in patients with NT1, NT2, IH underway

Data expected in 2025

- Evaluate safety, tolerability, and PK in NT1, NT2, and IH patients
- Efficacy assessments will evaluate excessive daytime sleepiness using the **Maintenance of Wakefulness Test (MWT)*** and **Epworth Sleepiness Scale (ESS)***, **weekly cataplexy rate*** (NT1 patients only), and overall symptom improvement**
- Exploratory efficacy assessments will measure sleep, **cognition, attention, memory,** and general health

https://clinicaltrials.gov/study/NCT06752668

* MWT and ESS are established registrational endpoints for EDS in sleep-wake disorders and weekly cataplexy rate is an established registration endpoint for cataplexy in NT1.

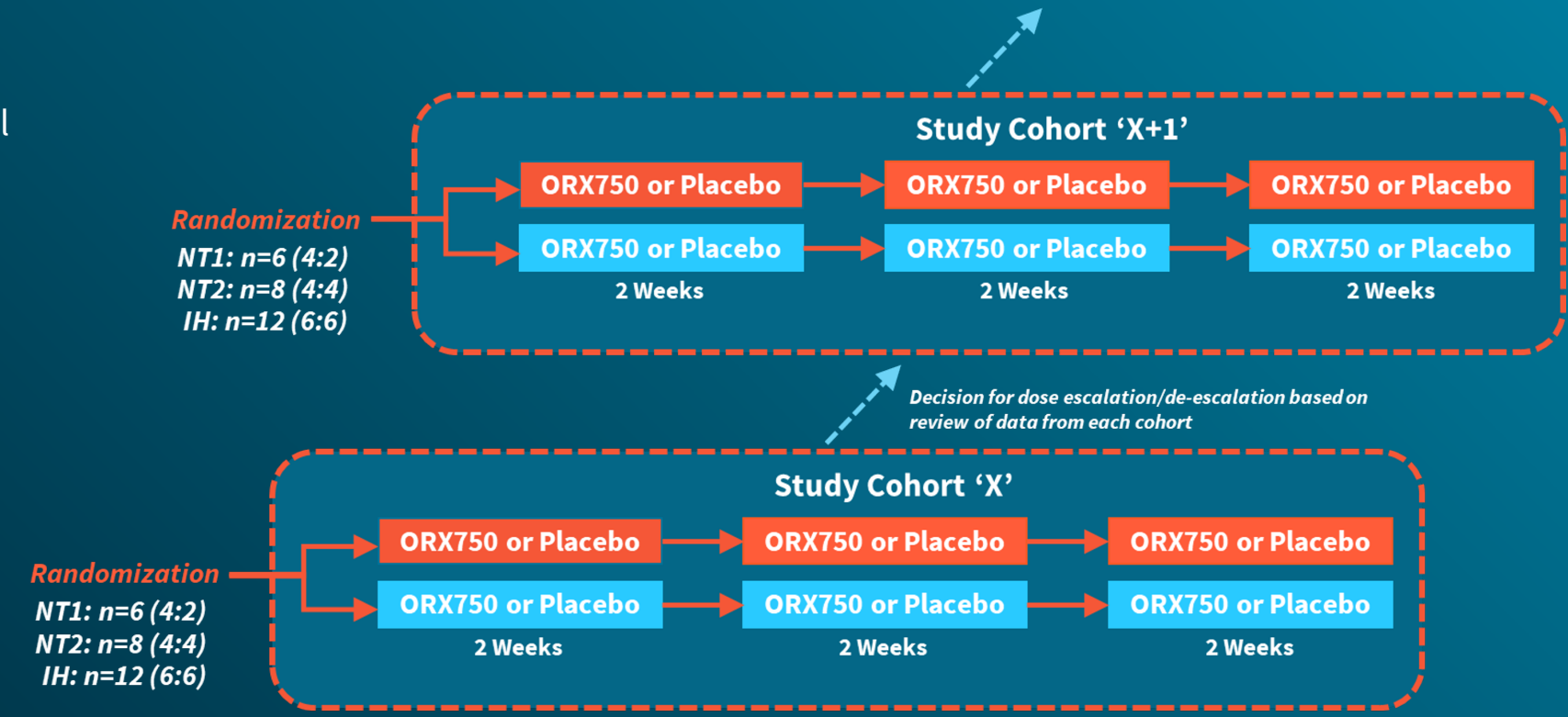
** Measured by Narcolepsy Severity Scale (NSS) and Idiopathic Hypersomnia Severity Scale (IHSS).

PHASE 2a STUDY

Randomized, Double-blind, Placebo-Controlled Basket Study of ORX750 in Patients with NT1, NT2, and IH is Underway

Data expected in all three indications in 2025

- Innovative design with potential to enable **well-powered** and efficient data generation
- All patients to receive ORX750 for **at least 4 weeks**
- Optimal number of patients to allow **efficient recruitment**
- Potential for **optimized dose selection**



After each 2-week period, treatment assignment (ORX750 or Placebo) may change

OX2R AGONIST PROGRAM

ORX750

Initiated Phase 2a study in patients with NT1, NT2, and IH; Data expected in **2025**

Presentation of Phase 1 data planned for **Q2 2025**

ORX142

IND-enabling studies ongoing; Clinical data in acutely sleep-deprived healthy volunteers expected in **2025**

ORX489

Entering IND-enabling studies

LockBody Technology Platform

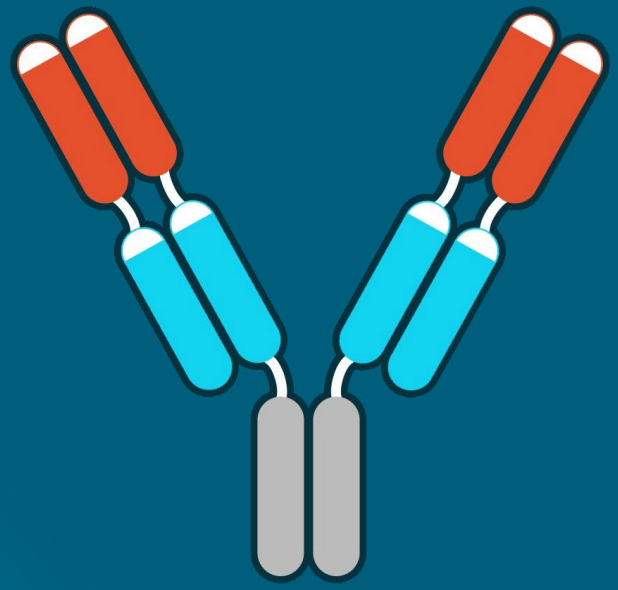
***LockBody* Technology Platform aims to *redefine* immuno-oncology treatment**

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

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).
LB101 is an investigational agent that has not been approved by the FDA or any other regulatory authority.

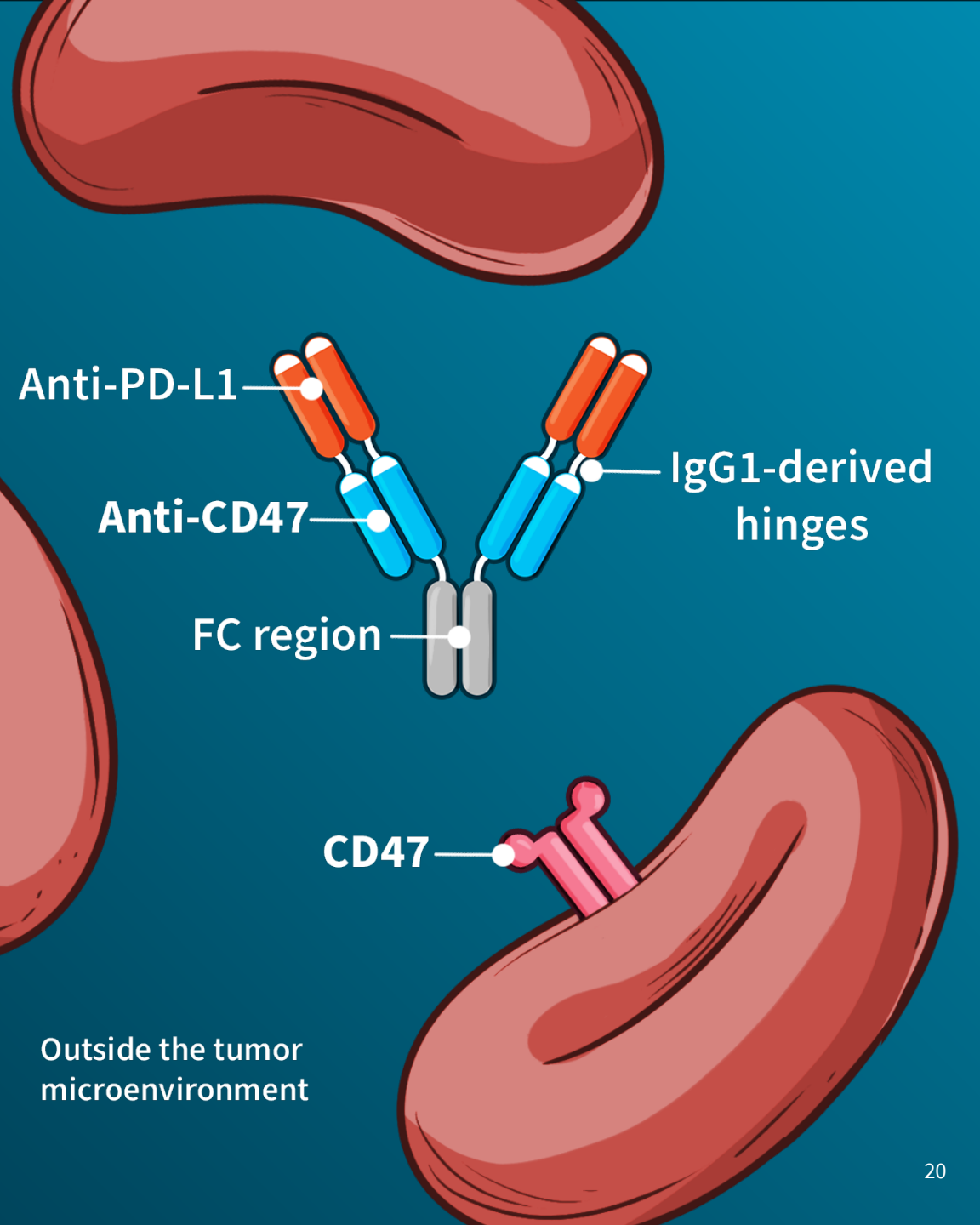
MOA

Locked Configuration



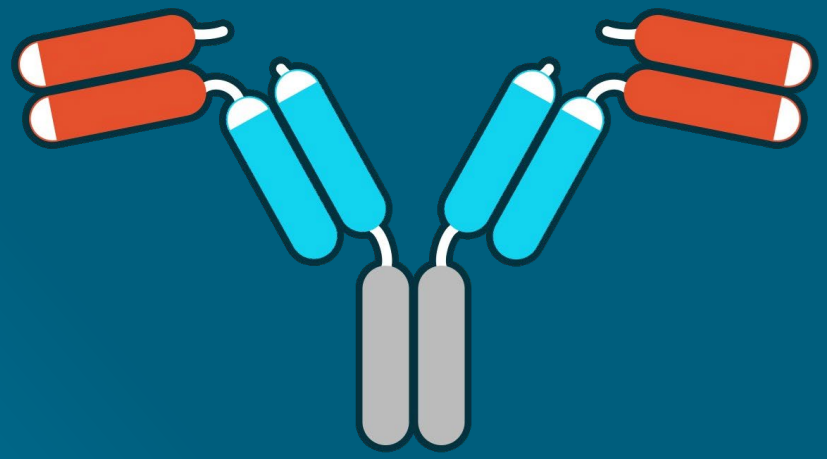
LockBody LB101

Conditionally tetravalent PD-L1xCD47 bispecific monoclonal antibody



MOA

Unlocked Configuration



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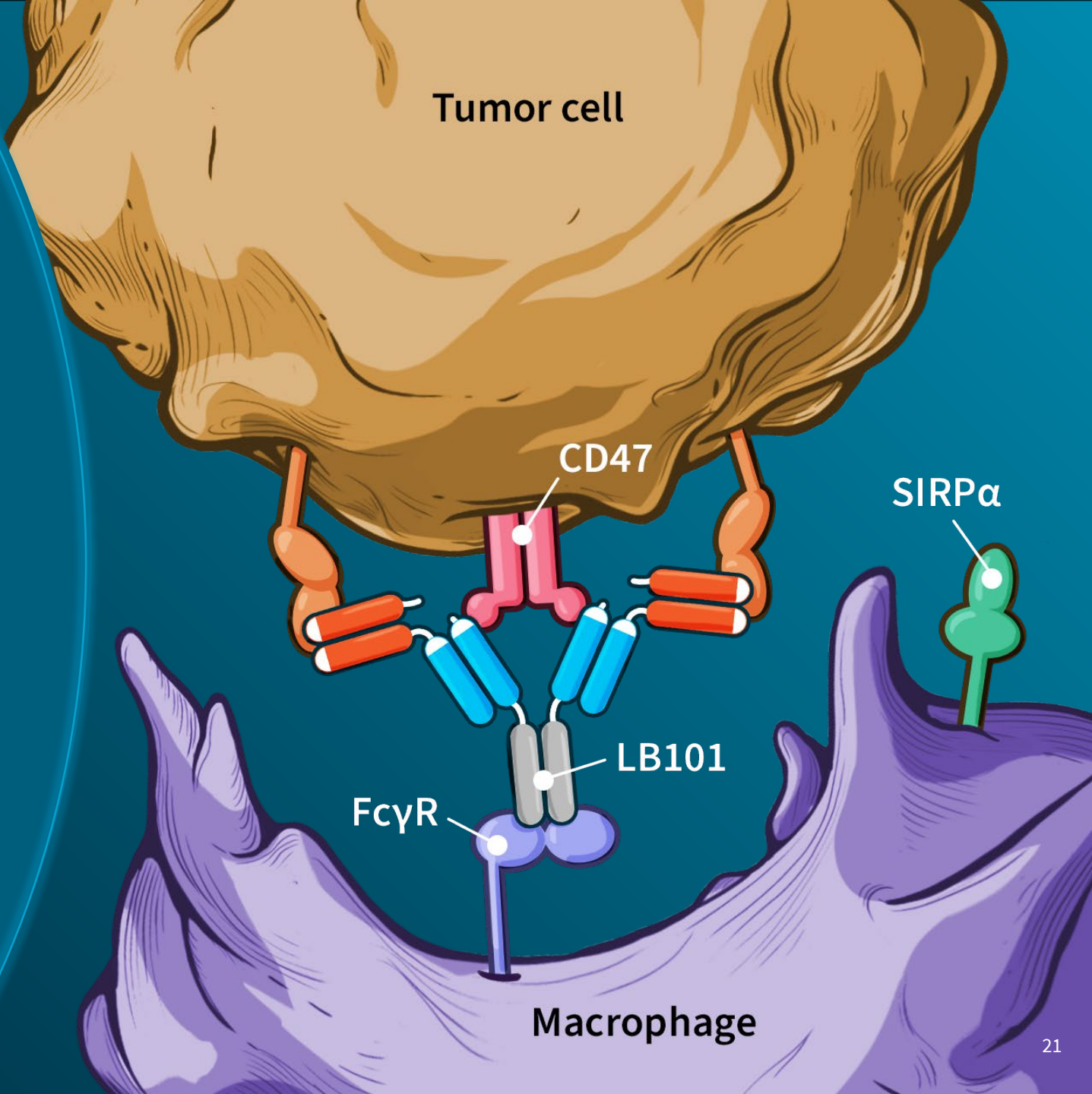


PRECLINICAL DATA

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

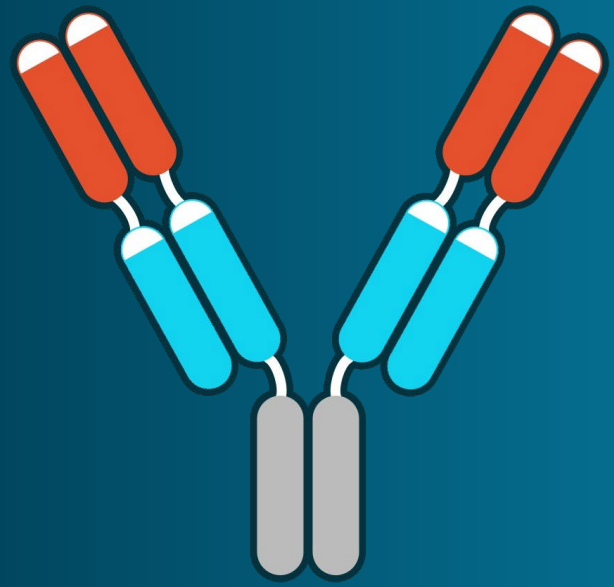
No anemia/ thrombocytopenia

No weight loss

No change in red blood cell or hemoglobin

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

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



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