



# Idorsia – Reaching out for more

We have more passion for science,  
we see more opportunities, and  
we want to help more patients.



The following information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company’s investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company’s existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.

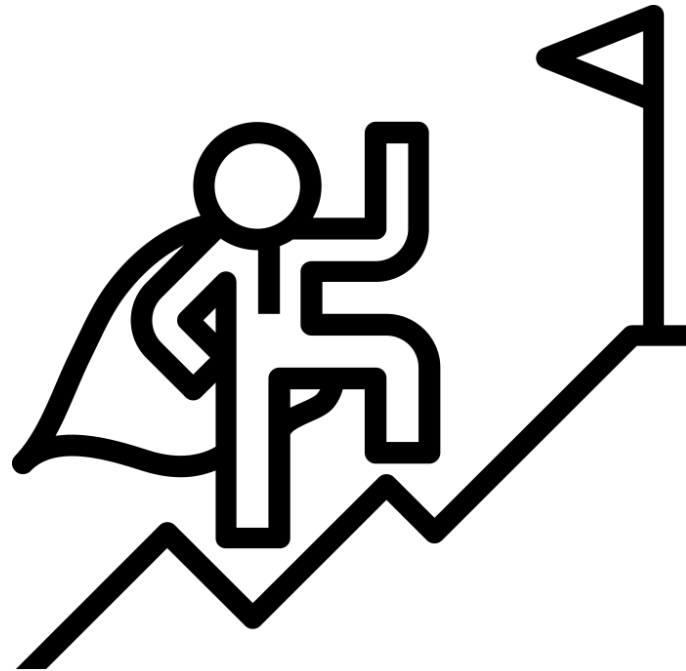
The purpose of Idorsia is to challenge accepted medical paradigms, answering the questions that matter most.

To achieve this, we will discover, develop, and commercialize innovative medicines – either through in-house capabilities or together with partners – and evolve Idorsia into a leading biopharmaceutical company, with a strong scientific core.

**Viatrix collaboration  
for selatogrel and  
cenerimod**

**Restructured  
convertible bond  
debt**

**CHF 150 million  
new funding**



**Highlights  
in 2024 and  
Q1 2025**

**QUVIVIQ unique  
product with rapidly  
growing sales**

**Approval of aprocitentan  
TRYVIO available in the US  
JERAYGO in the EU & UK**

**Advancing early-stage  
innovative assets**

# Securing future operations

Viatrix deal  
restructuring



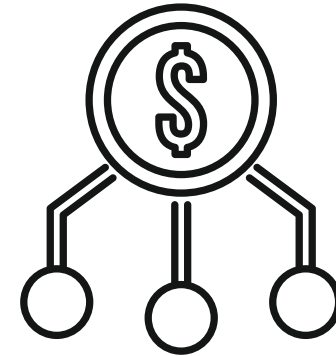
Remove significant  
cash requirements  
in 2025

Funding



Backstopped  
CHF 150 million  
New Money Facility

Balance sheet  
restructuring



Remove  
large debt  
overhang

# Future operations secured

Adapt operations across different divisions to optimize the use of the new money facility



## Partner aprocitentan

Priority remains to find a partner for aprocitentan, preserve and increase the value of aprocitentan with limited launch in the US



## Accelerate QUVIVIQ in EUCAN

Commercial efforts are translating into success – continue to drive sales – expand from specialist prescribers to GP through commercial partnerships



## QUVIVIQ in the US

Maintaining the sales while reducing costs, until descheduling can be achieved and real value in the US market can be unlocked



## Leverage our innovation

Optimize our portfolio within our budget constraint through targeted development and potential partnering

# Idorsia active ingredients

The company is distinguished by our key strengths:

**+ QUVIVIQ**

a different kind of insomnia treatment

**+ Partners**

maximize the value of our portfolio

**+ People**

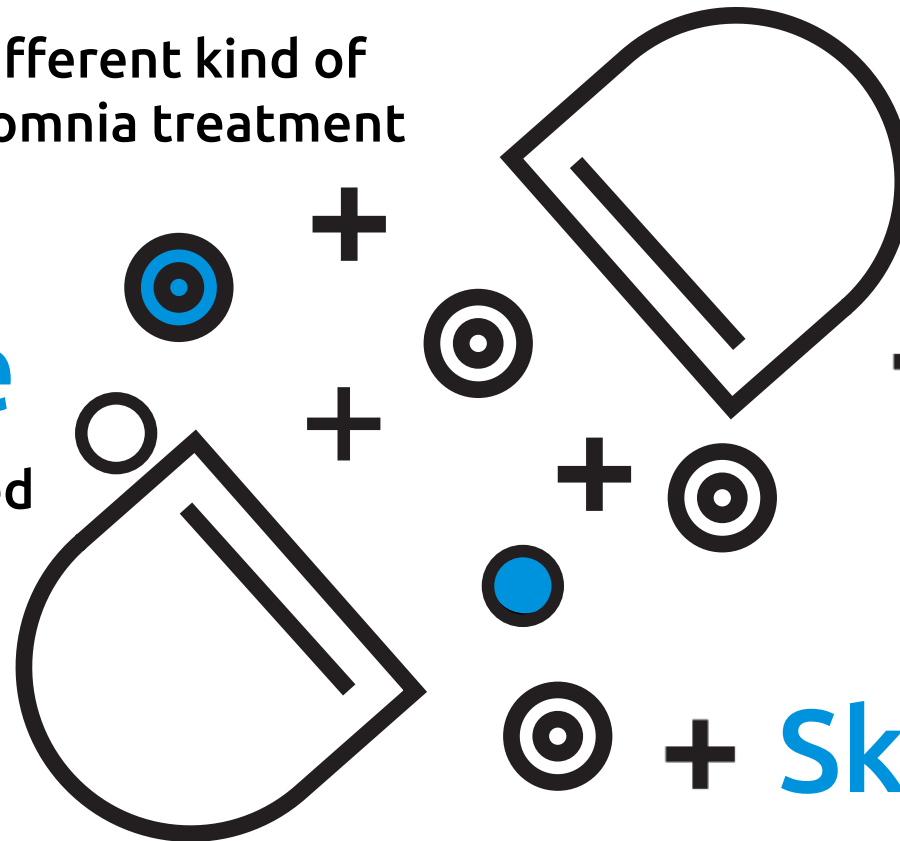
Highly qualified professionals

**+ Pipeline**

Promising in-house assets

**+ Skills**

Specialized Drug Discovery engine





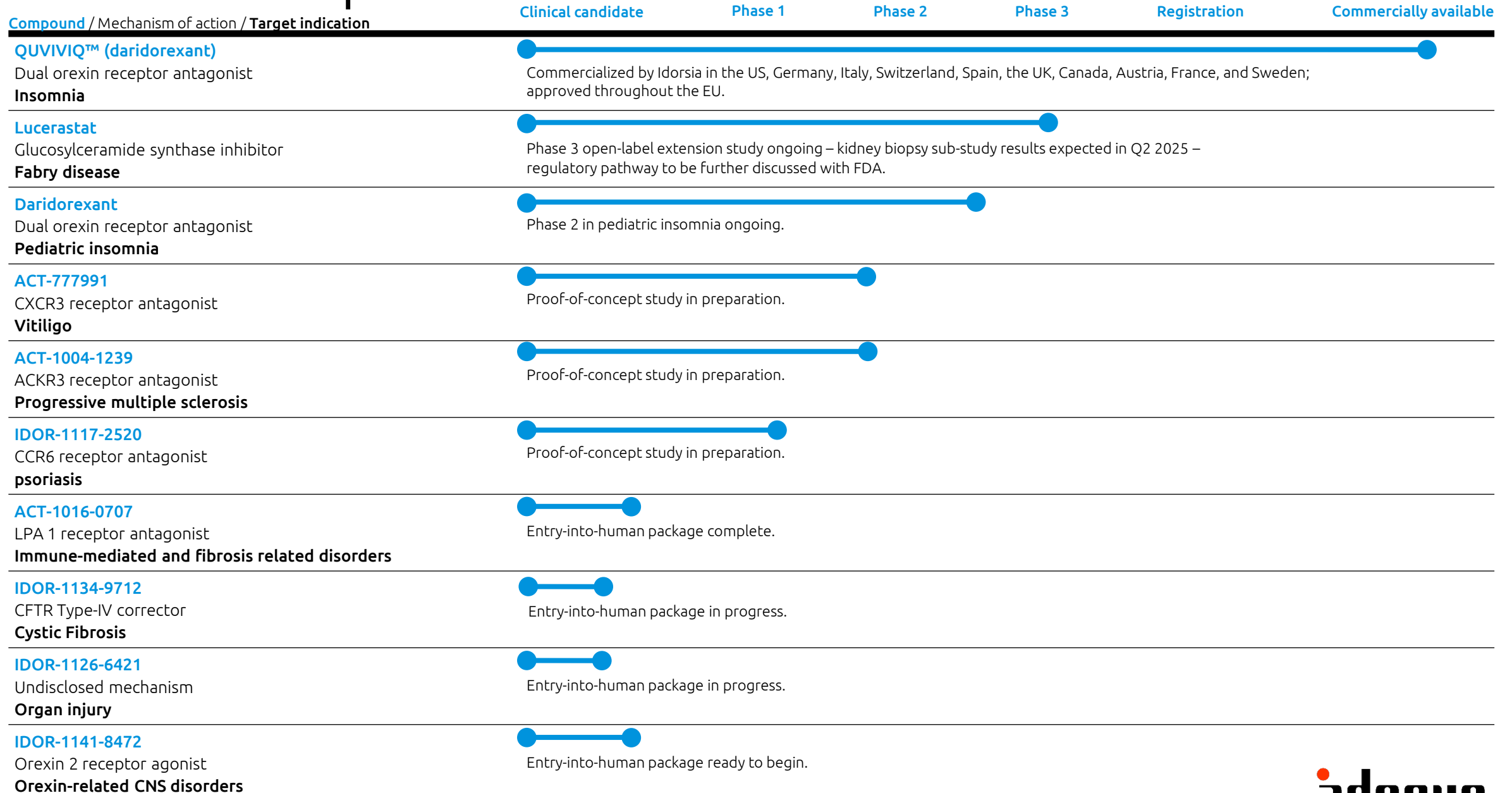


# Our commercial reach



# Idorsia-led portfolio

The company will develop each asset to the next inflection point or seek a partner.



# Idorsia-led portfolio

## Synthetic Glycan Vaccine Platform

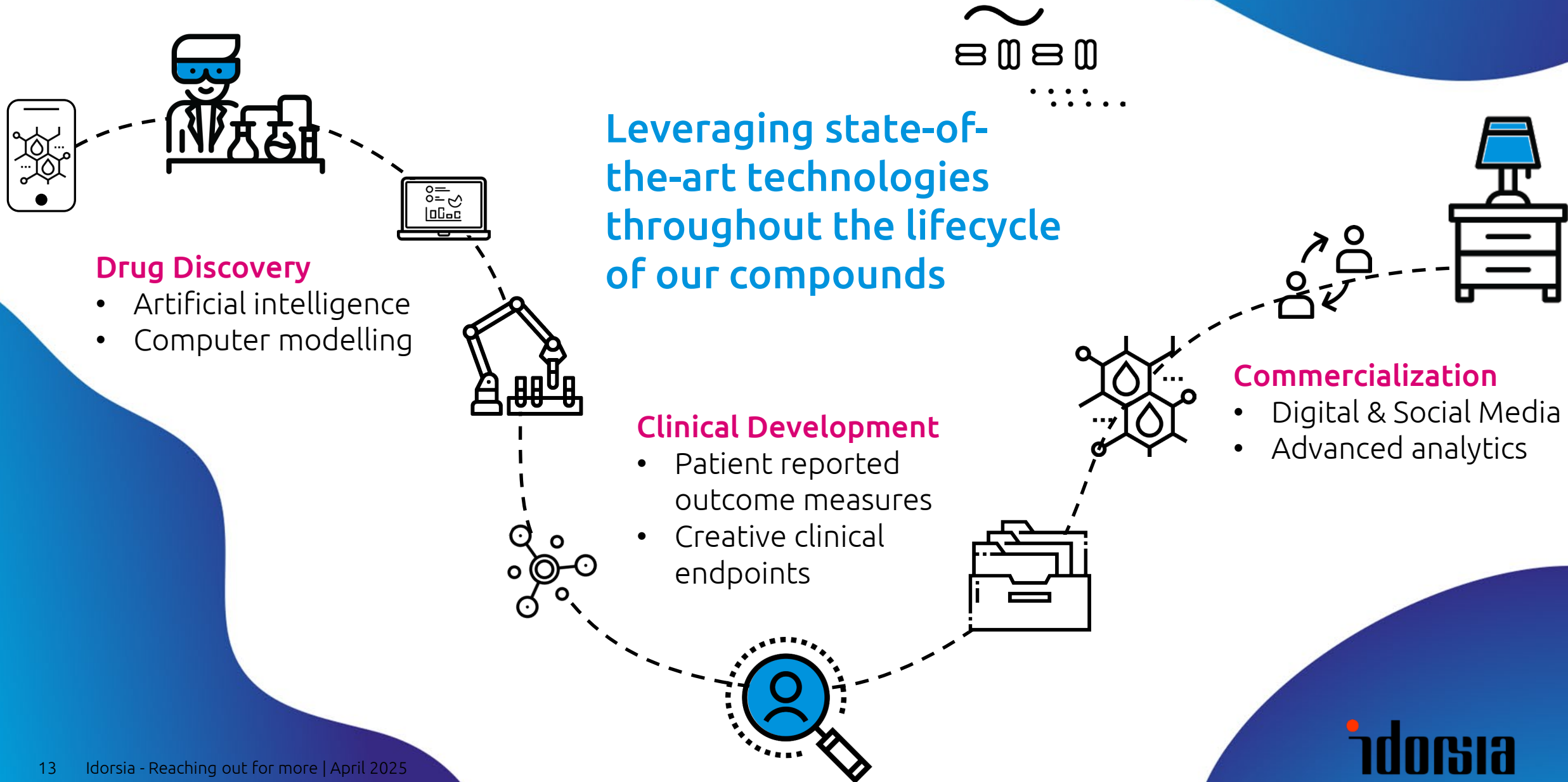
Compound / Mechanism of action / Target indication	Clinical candidate	Phase 1	Phase 2	Phase 3	Registration	Commercially available
<b>IDOR-1134-2831</b> Synthetic glycan vaccine <i>Clostridium difficile</i> infection	●—————●					
	Idorsia is conducting a Phase 1 clinical pharmacology study – results expected in Q2 2025.					
<b>IDOR-1142-0810</b> Synthetic glycan vaccine <i>Klebsiella pneumonia</i> infection	●————●					
	Entry-into-human package in progress.					

- Idorsia will seek a partner for the platform or individual vaccines.

# Partner-led portfolio

Compound / Mechanism of action / Target indication	Partner	Phase 1	Phase 2	Phase 3	Registration	Commercially available
<b>TRYVIO™ (aprocitentan)</b> Dual endothelin receptor antagonist <b>Systemic hypertension in combination with other antihypertensives</b>	To be defined	<p>Worldwide development and commercialization rights. Commercially available in the US.</p>				
<b>JERAYGO™ (aprocitentan)</b> Dual endothelin receptor antagonist <b>Resistant hypertension in combination with other antihypertensives</b>	To be defined	<p>Worldwide development and commercialization rights. Approved in the EU and UK; Marketing authorization applications under review in Canada, and Switzerland.</p>				
<b>QUVIVIQ™ (daridorexant)</b> Dual orexin receptor antagonist <b>Insomnia</b>		<p>License to develop and commercialize for Asia-Pacific region (excluding China). Launched for the treatment of insomnia in Japan; Phase 3 ongoing in South Korea.</p>				
<b>Daridorexant</b> Dual orexin receptor antagonist <b>Insomnia</b>		<p>License to develop and commercialize for Greater China region. NDA submitted in Greater China; approved for the treatment of insomnia in Hong-Kong.</p>				
<b>Selatogrel</b> P2Y <sub>12</sub> inhibitor <b>Acute myocardial infarction</b>		<p>Worldwide development and commercialization rights. Phase 3 "SOS-AMI" program ongoing.</p>				
<b>Cenerimod</b> S1P <sub>1</sub> receptor modulator <b>Systemic lupus erythematosus</b>		<p>Worldwide development and commercialization rights. Phase 3 "OPUS" program ongoing.</p>				
<b>Daridorexant</b> Dual orexin receptor antagonist <b>Posttraumatic stress disorder (PTSD)</b>	US Department of Defense (DOD)	<p>Idorsia is supporting a clinical study sponsored by the US DOD to develop new therapies to treat PTSD.</p>				
<b>ACT-1002-4391</b> EP <sub>2</sub> /EP <sub>4</sub> receptor antagonist <b>Immuno-oncology</b>		<p>Global license to develop and commercialize. Phase 1 ongoing.</p>				

# Innovation from bench to bedside



# Nurturing strong alliances

Commercial and late-stage partnered assets



Development and commercialization rights for Asia-Pacific region (excluding China)



Development and commercialization rights for the Greater China region

Selatogrel



Worldwide development and commercialization rights



Phase 3 study

Cenerimod

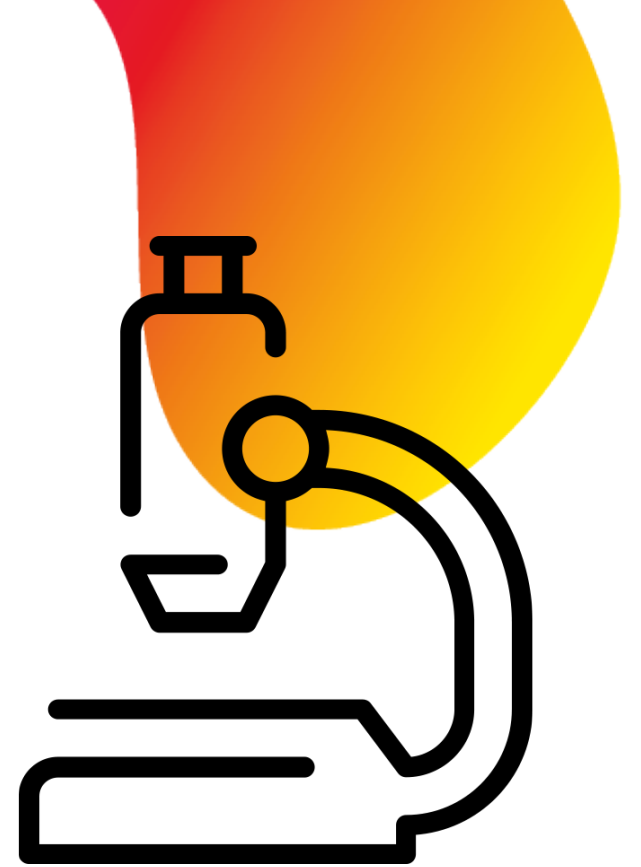


Worldwide development and commercialization rights



Find a comprehensive description of our pipeline assets as follows:

- |   |                           |           |
|---|---------------------------|-----------|
| ① | <b>Daridorexant</b>       | Slide 16  |
| ② | <b>Aprocitentan</b>       | Slide 63  |
| ③ | <b>Lucerastat</b>         | Slide 97  |
| ④ | <b>Early-stage assets</b> | Slide 124 |



# Daridorexant in insomnia

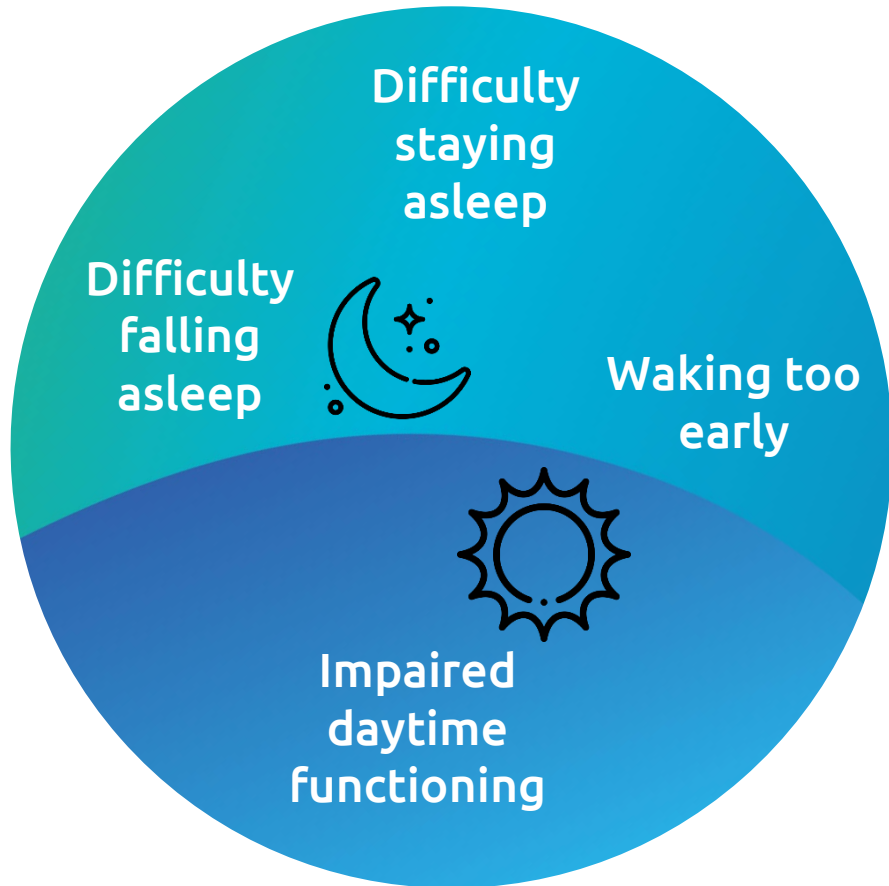


Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.



# Insomnia: A disease of the night and the day

High unmet need for effective, safe medications to treat insomnia



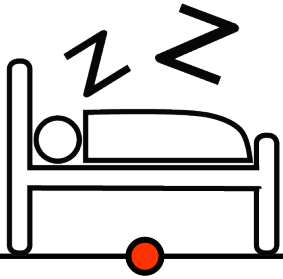
- Combination of difficulty obtaining sufficient sleep and dissatisfaction with sleep **combined with a significant negative impact on daytime functioning**

Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5®)

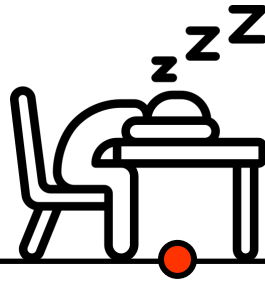
- Estimated approximately 25 million (10%<sup>1</sup>) adults in the US suffer from chronic insomnia

<sup>1</sup> Morin CM, et al. Insomnia disorder. Nat Rev Dis Primers 2015;1:15026

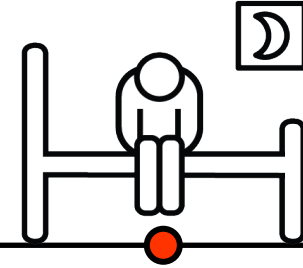
# Insomnia and the importance of sleep



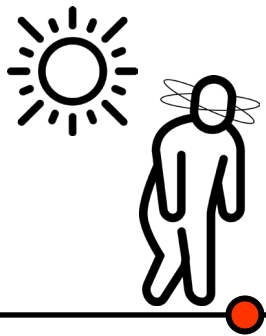
**Sleep is an essential pillar** for good physical and mental health to ensure optimal functioning throughout the day.



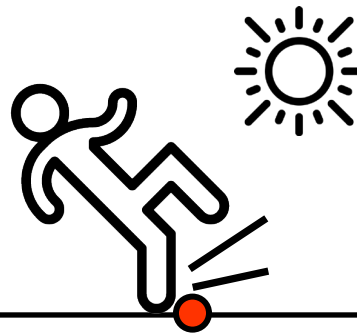
Therefore, **without adequate, quality sleep**, one can face many issues that will impact day-to-day life.



Insomnia disorder, the most common sleep-wake disorder, is **defined by difficulties in initiating or maintaining sleep, and early-morning awakening** with the inability to return to sleep, for **at least 3 months or longer**.



A key symptom of insomnia disorder is the **impairment of daytime functioning**, which is **linked to significant decrements in health status**, such as fatigue, reduced energy, mood alteration and cognitive difficulties.



Poor management of insomnia is associated with **increased risk of motor vehicle accidents, falls, and costly workplace errors**.



**Improving daytime functioning is a critical unmet need** that has not been addressed in a rigorous manner.

# How is insomnia treated, what are the limitations?



## Sleep hygiene

- Active patient participation required



## Cognitive behavioral therapy

- Recommended first-line therapy but inconsistently practiced
- Not easily accessible
- Often not reimbursed
- Active patient participation required



## Pharmacological therapy

- Many have significant limitations
- Insufficient acute effect: lack of sustained effect through the night
- Insufficient long-term effect: lack of continued benefit over time
- Next morning residual effect
- Abuse potential, withdrawal effect, and rebound
- May have significant adverse effects

# Prevalence and impact of insomnia across Europe

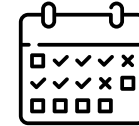
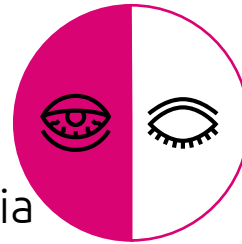
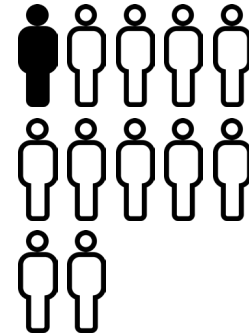
With respect to global burden, insomnia is ranked by the World Health Organization as the

**11th**  
most  
important  
brain disorder\*



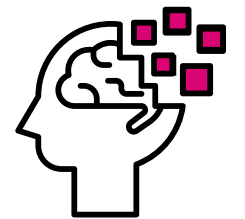
Across Europe, approximately half of all adults are expected to experience some insomnia symptoms, and

**1 in 12 (8.2%) of adults live with chronic insomnia disorder (CID)**



CID is associated to **11/18 days of absenteeism** and **39-45 days of presenteeism** (showing up at work but less productive) leading to an overall, yearly

**45-54 days of loss of productivity\***



\* Source: Roth, Thomas; Insomnia: Definition, Prevalence, Etiology, and Consequences; Journal of Sleep Medicine; Published Online: November 14, 2019;

<https://jcs.m.aasm.org/doi/10.5664/jcs.m.26929>

\*\* \*Hafner M., Romanelli R.J., Yerushalmi E. & Troxel W.M. *The Societal and Economic Burden of Insomnia in Adults: An International Study*. Santa Monica, CA: RAND Corporation, 2023.

# Hidden economic burden of CID (working-age adults)

## Who's affected?

% of adults suffering from CID

Number of adults

Estimated "hidden" annual financial burden across working-age population suffering from CID



7.6%

18.6 million

€92bn



8.8%

2.2 million

Can\$ 10.7bn



7.7%

16.6 million

\$127.1bn

# The US insomnia market is large, highly dissatisfied, and ripe for disruption



## Who's affected?

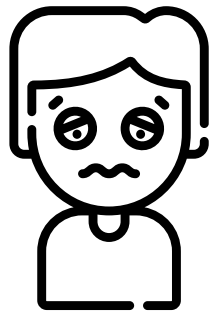
**~25M**

Total insomnia patients

(~10% of US adults)

**12M**

Treated insomnia patients



## Dissatisfaction

In a recent poll of 1001 Americans who struggle with sleep

**70%**

say they are desperate to find a solution to get quality sleep and fully function the next day

## What are the costs?

**\$100B+**

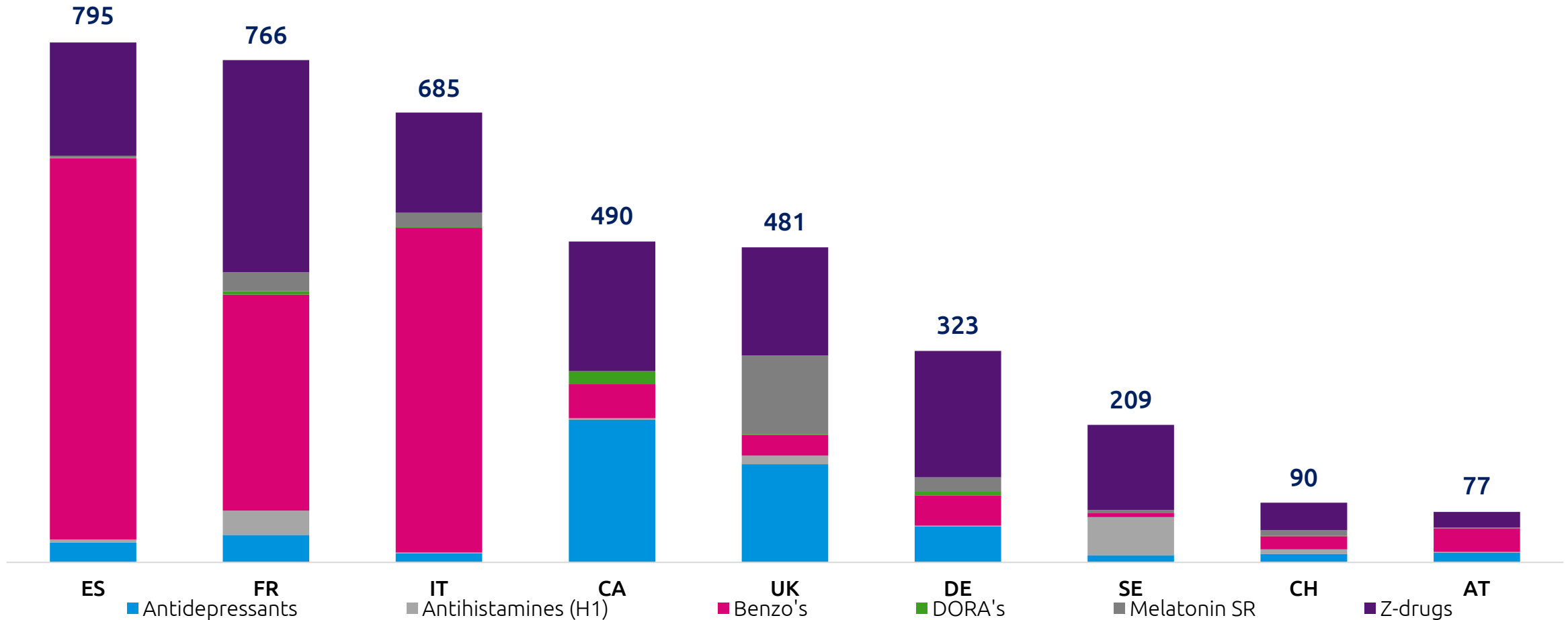
Insomnia related costs per year alone in the US



# High unmet need in EU insomnia market



Estimated insomnia market volume\*, standard units, millions



Sources:

1) IQVIA MIDAS - Monthly Volume in M SU, MAT/Sep/2024 (EU5-CA-CHAT); Sweden MAT/SEP/2020

\*Includes estimated off-label usage of anti-depressants, anti-histamines and benzos to treat insomnia

# The science of sleep

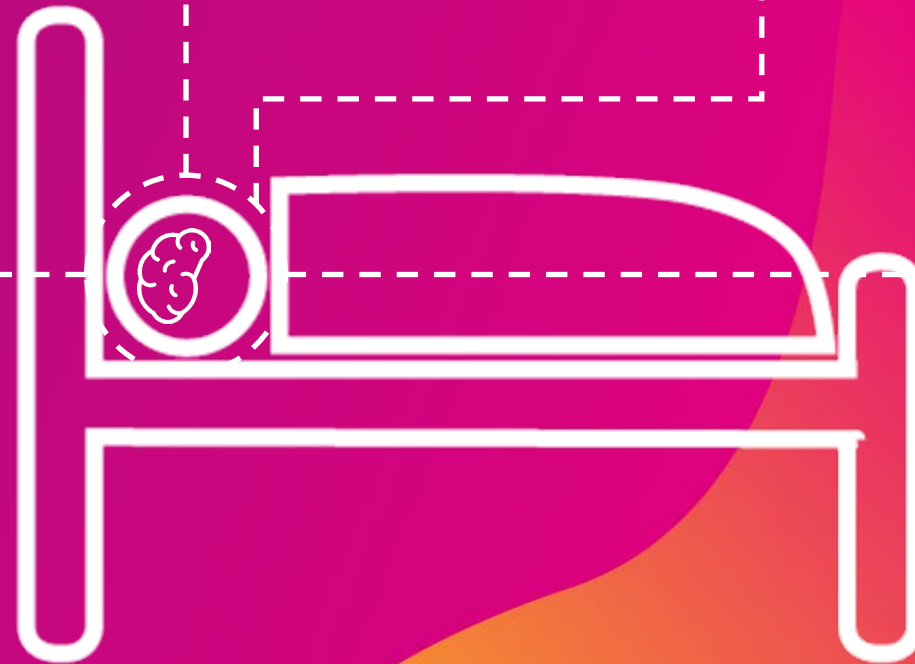
Healthy wake and sleep states are governed by distinct wake and sleep signalling systems in the brain.



Some therapies may increase somnolence and impair functioning. These attributes suggest current therapies are limited in their ability to optimally treat people with insomnia, particularly elderly patients.



The underlying pathophysiological cause of insomnia is considered to be the result of overactive wake signalling in the brain, also called 'hyperarousal'.



The development of medications that specifically target excessive wakefulness have been shown to improve sleep parameters without some of the side effects of commonly prescribed therapies for insomnia.

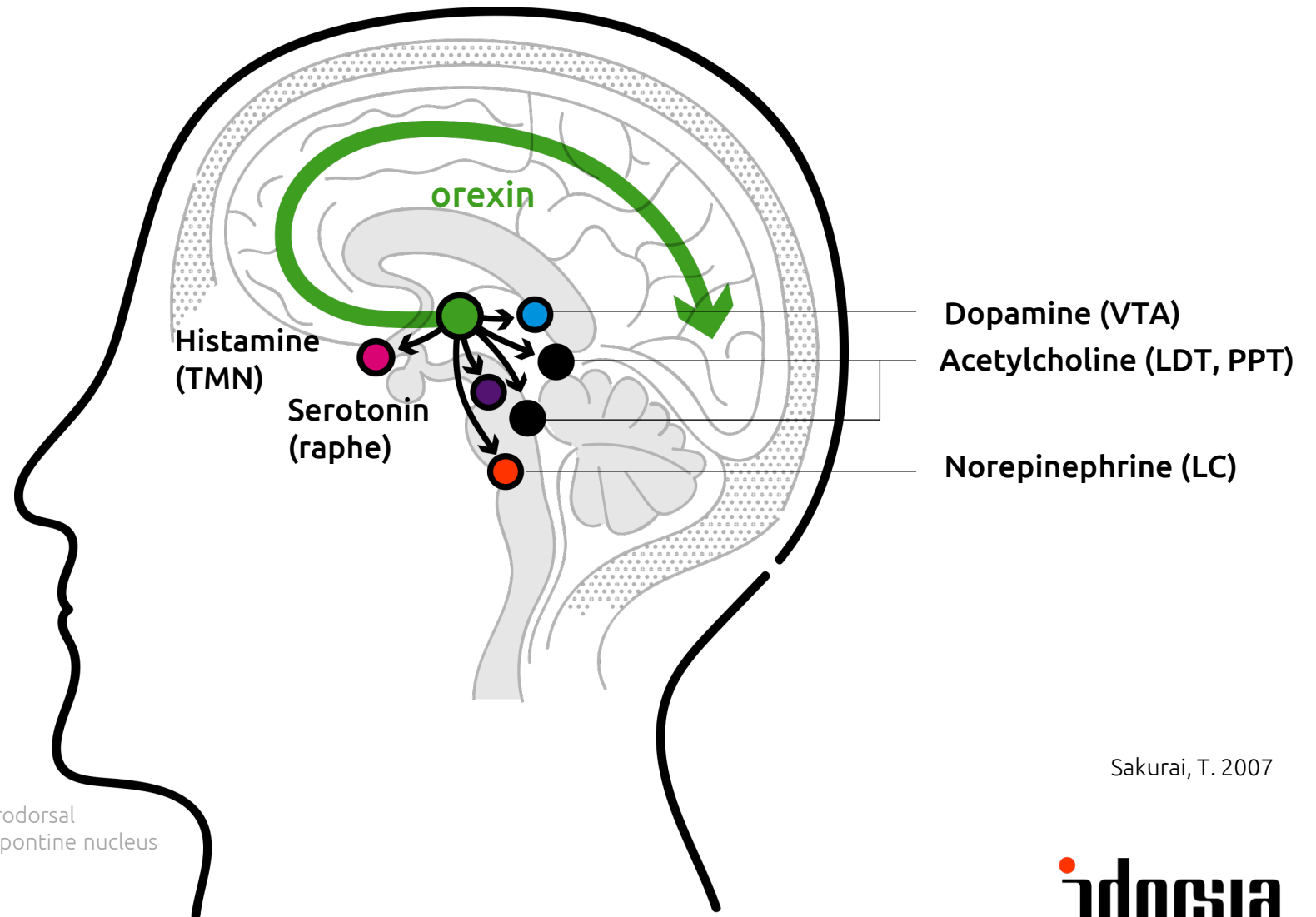




# The orexin system is crucial for the regulation of wakefulness

Orexin stimulates many wake-promoting pathways

- LHA / PH **Orexin**
- LC OX<sub>1</sub>R
- TMN OX<sub>2</sub>R
- Raphe OX<sub>1</sub>R and OX<sub>2</sub>R
- LTD / PPT OX<sub>1</sub>R and OX<sub>2</sub>R
- VTA OX<sub>1</sub>R and OX<sub>2</sub>R



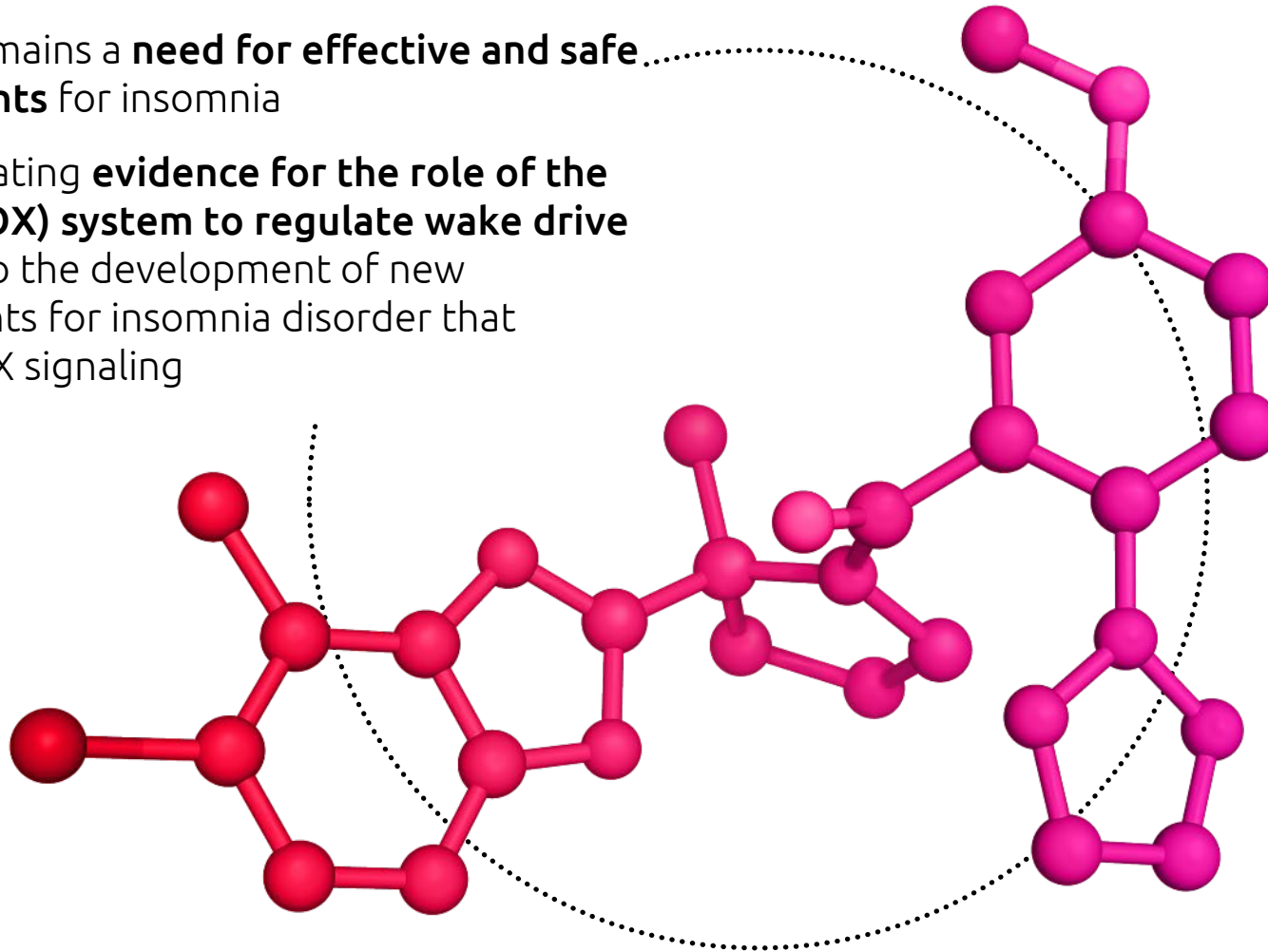
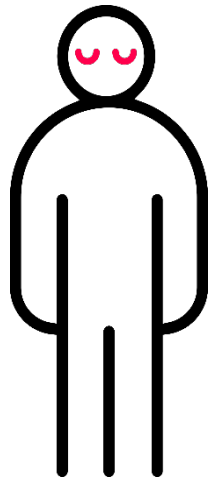
LHA = lateral hypothalamic area; PH = posterior hypothalamus  
LC = locus coeruleus; TMN = tuberomammillary nucleus; LDT = laterodorsal tegmental nucleus; VTA = ventral tegmental area; PPT = pedunculopontine nucleus

Sakurai, T. 2007

# Daridorexant in insomnia

## Rationale

- There remains a **need for effective and safe treatments** for insomnia
- Accumulating **evidence for the role of the orexin (OX) system to regulate wake drive** has led to the development of new treatments for insomnia disorder that inhibit OX signaling



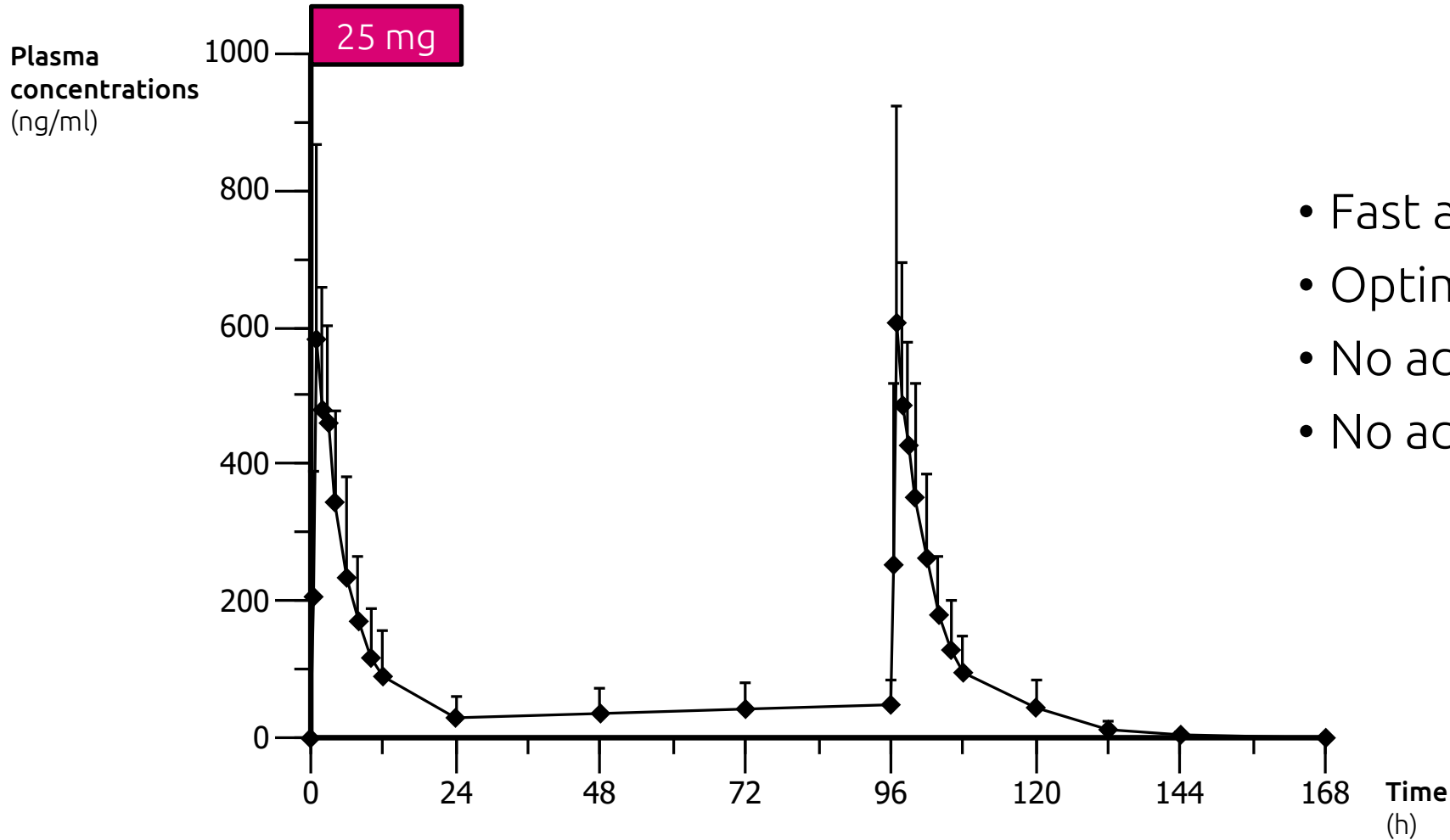
## Daridorexant

- a **potent and selective** dual orexin receptor antagonist (DORA)
- selected to **promote sleep onset and sleep maintenance, without impairing the next day**

Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.

# Different by design – next generation DORA

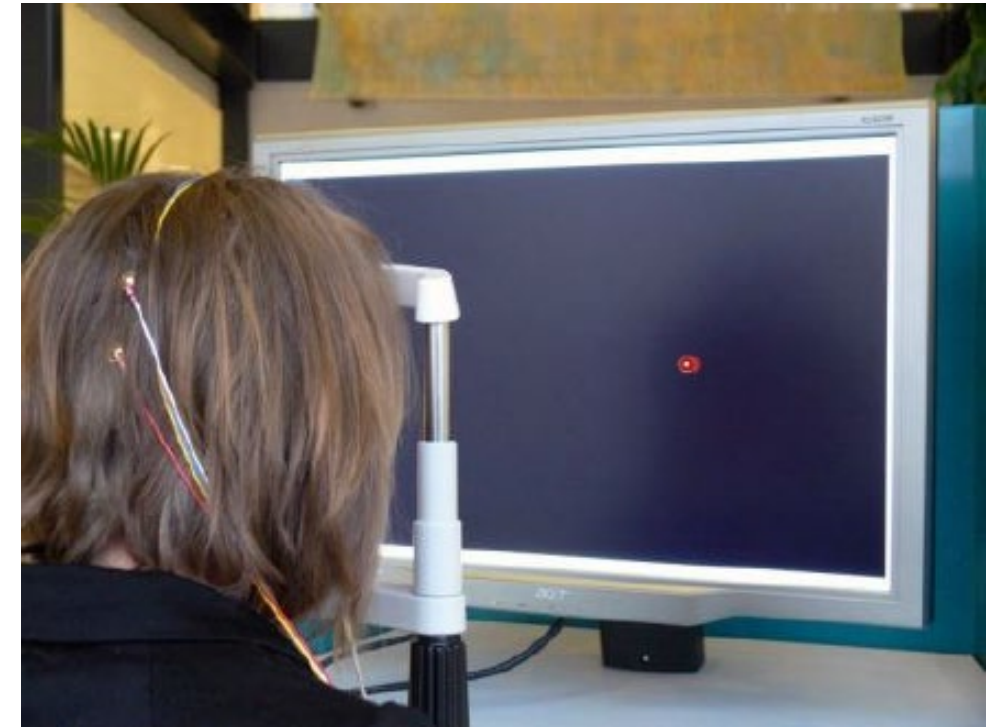
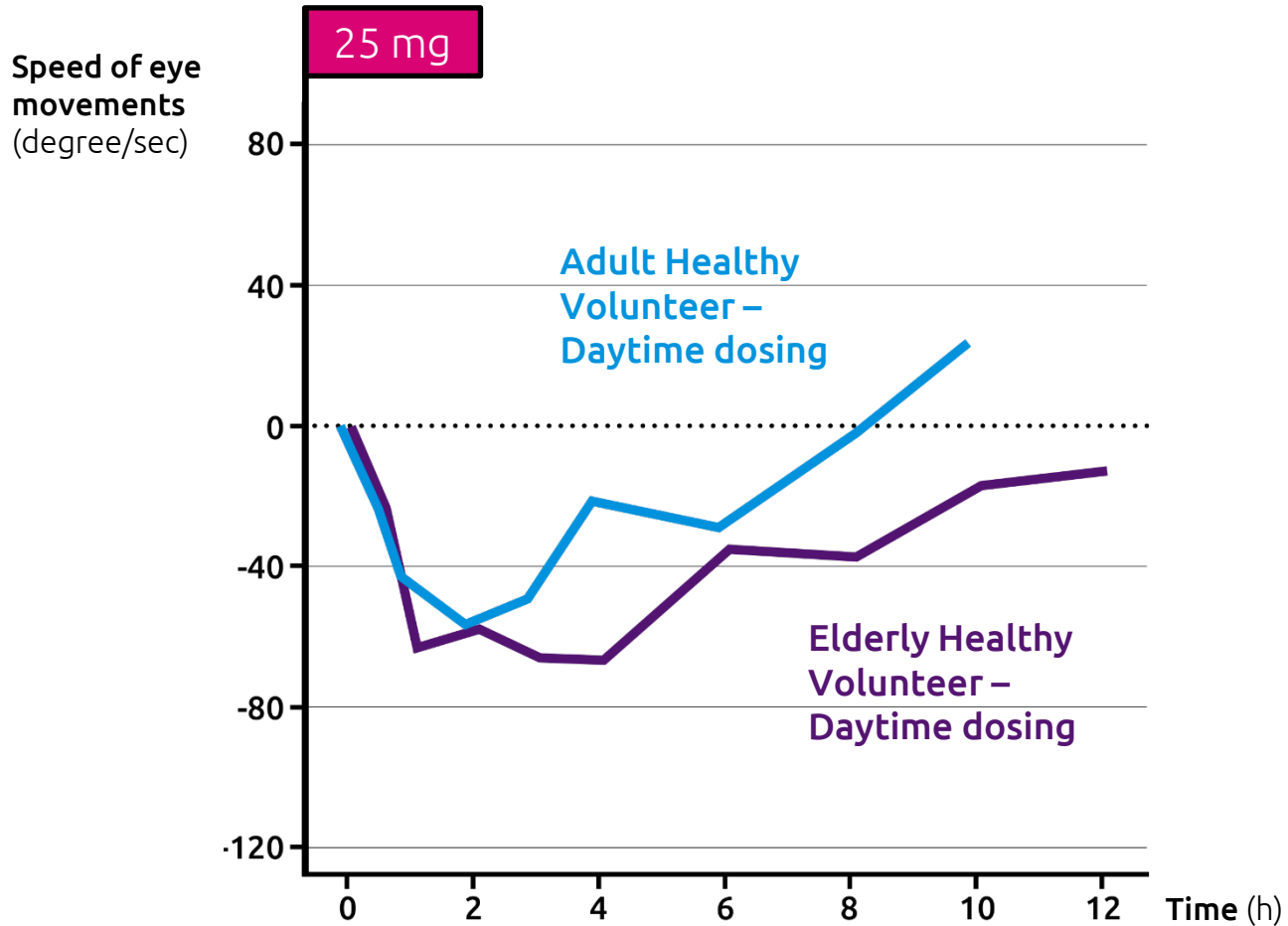
Optimized pharmacokinetic profile



- Fast absorption
- Optimal half-life (8 h)
- No accumulation over time
- No active metabolites

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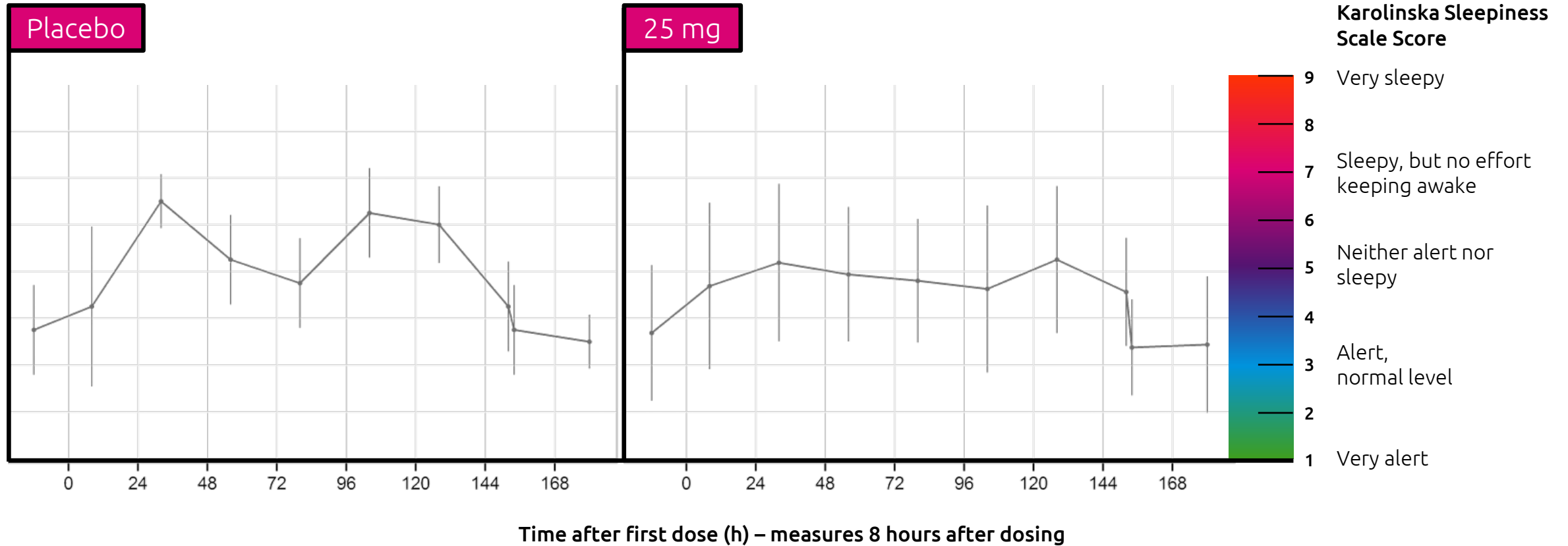
# Fast and time limited pharmacodynamic effect



Person performing eye movement test

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# No pharmacodynamic effect on next morning



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# Daridorexant registration program

Robust program in adult and elderly insomnia patients



**Following completion of Phase 2 studies, two similar pivotal studies of 3-month duration in moderate and severe insomnia**

## **Efficacy**

- Objective and subject sleep parameters (onset and maintenance) by polysomnography (PSG) and sleep diary questionnaire (SDQ)
- Daytime functioning assessed by insomnia daytime symptoms and impact questionnaire (IDSIQ)
- Replicated in two confirmatory studies

## **Safety**

- Adverse events, vital signs, biochemistry and hematology
- Next morning residual “hang-over” effect
- Withdrawal/physical dependence, and rebound insomnia

## **Comprehensive clinical pharmacology program including:**

- Driving performance, interaction (medicines, alcohol), Safety in specific population (COPD, obstructive sleep apnea, liver and renal impairment), drug abuse potential

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# Study objectives

1st study, 50, 25 mg; 2nd study, 25, 10 mg



## Primary objective

- To evaluate the efficacy of daridorexant on objective sleep parameters in patients with insomnia.

## Secondary objective

- To evaluate the efficacy of daridorexant on subjective sleep parameters and daytime functioning in patients with insomnia.

## Safety objective

- To assess the safety and tolerability of daridorexant in patients with insomnia during treatment and upon treatment discontinuation.

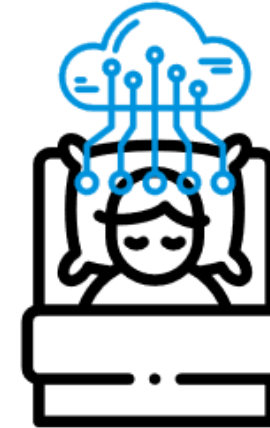
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# Objective sleep assessments

Repeated polysomnography recordings in a sleep lab in all patients



- Assess insomnia objectively
- Ensure well-characterized insomnia patients are randomized
- Establish solid baseline during placebo run-in
- Measure primary endpoint at Month 1 and Month 3
  - **Latency to persistent sleep**
  - **Wakening after sleep onset**
- Asses the potential for rebound
- Collect comprehensive information on total sleep time and sleep architecture



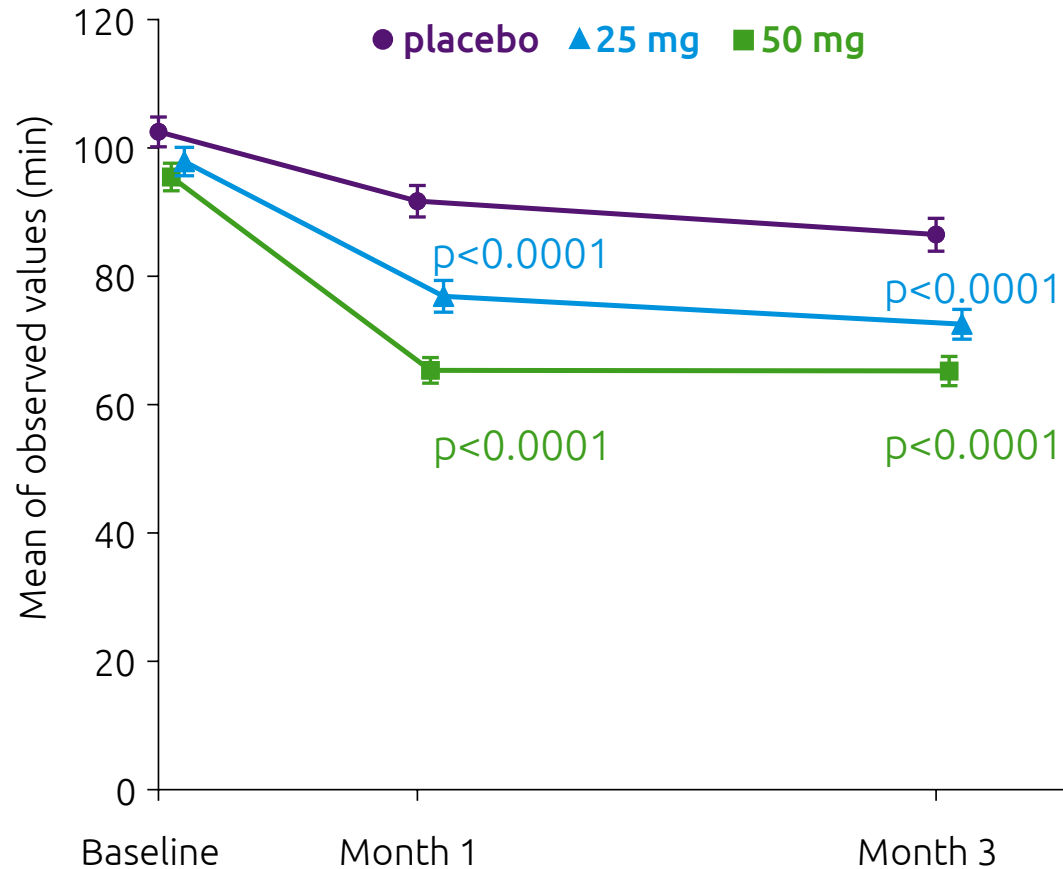
Sensors measure brain activity, eye movements, muscle tone, respiratory, and heart parameters.

Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.



# 1<sup>o</sup> endpoint: Wake after sleep onset (WASO)

A measure of sleep maintenance



Daridorexant 25 mg and 50 mg significantly improved WASO compared to placebo at months 1 and 3

## LSM change from baseline (95% CI)

	Month 1	Month 3
<b>Placebo</b>	<b>-6.2</b> (-9.9 to -2.5)	<b>-11.1</b> (-15.1 to -7.1)
<b>Daridorexant 25 mg</b>	<b>-18.4</b> (-22.1 to -14.7)	<b>-23.0</b> (-27.0 to -19.0)
LSM difference compared with placebo (95% CI)	<b>-12.2</b> (-17.4 to -7.0)	<b>-11.9</b> (-17.5 to -6.2)
<b>Daridorexant 50 mg</b>	<b>-29.0</b> (-32.7 to -25.3)	<b>-29.4</b> (-33.4 to -25.4)
LSM difference compared with placebo (95% CI)	<b>-22.8</b> (-28.0 to -17.6)	<b>-18.3</b> (-23.9 to -12.7)

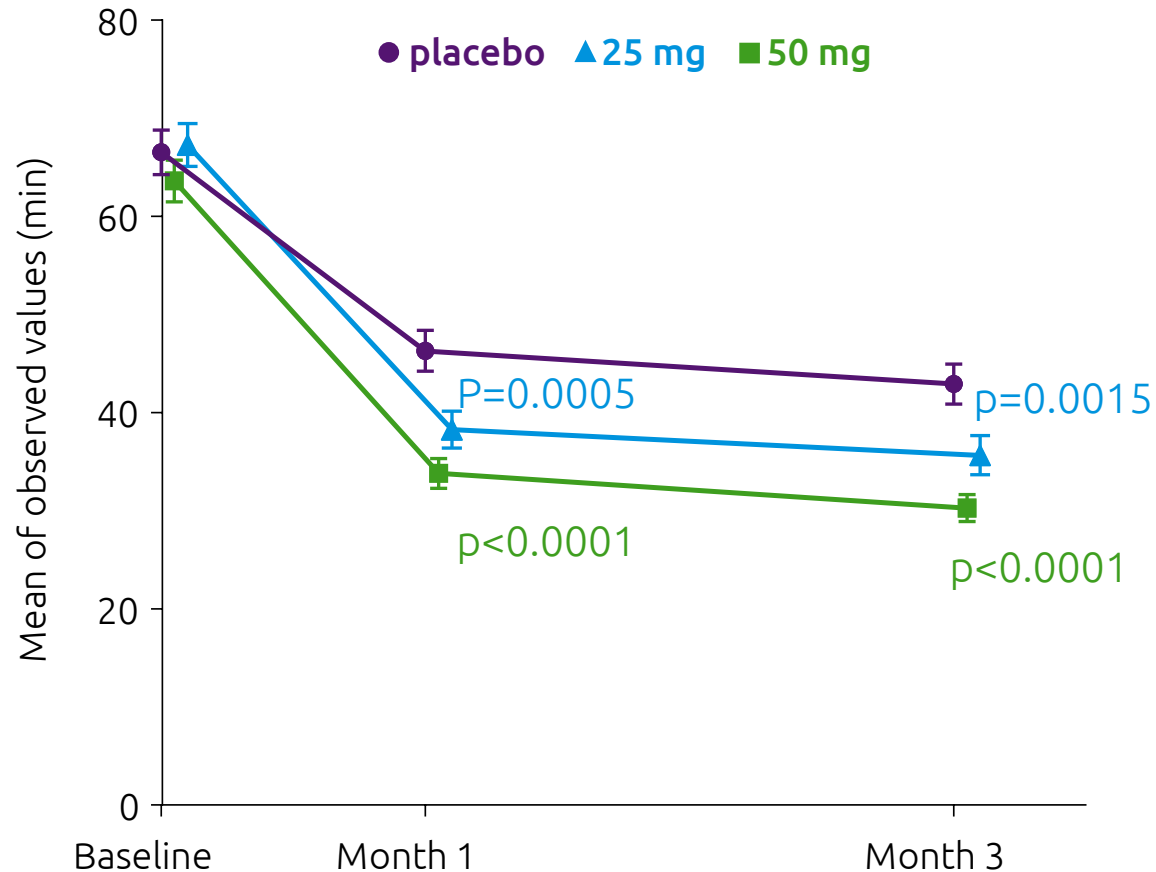
CI = confidence interval; LSM = least squares mean

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Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

# 1<sup>o</sup> endpoint: Latency to persistent sleep (LPS)

A measure of sleep onset



Daridorexant 25 mg and 50 mg significantly improved LPS compared to placebo at months 1 and 3

LSM change from baseline (95% CI)

	Month 1	Month 3
<b>Placebo</b>	<b>-19.9</b> (-23.2 to -16.5)	<b>-23.1</b> (-26.5 to -19.8)
<b>Daridorexant 25 mg</b>	<b>-28.2</b> (-31.5 to -24.8)	<b>-30.7</b> (-34.0 to -27.4)
LSM difference compared with placebo (95% CI)	<b>-8.3</b> (-13.0 to -3.6)	<b>-7.6</b> (-12.3 to -2.9)
<b>Daridorexant 50 mg</b>	<b>-31.2</b> (-34.5 to -27.9)	<b>-34.8</b> (-38.1 to -31.5)
LSM difference compared with placebo (95% CI)	<b>-11.4</b> (-16.0 to -6.7)	<b>-11.7</b> (-16.3 to -7.0)

CI = confidence interval; LSM = least squares mean

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Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

# Sleep diary questionnaire (SDQ)

Daily recording



## Morning questionnaire

- 10 questions related to medication, quantification of sleep, awakenings
- 3 visual analog scales related to quality and deepness of sleep and sleepiness in the morning

## Evening questionnaire

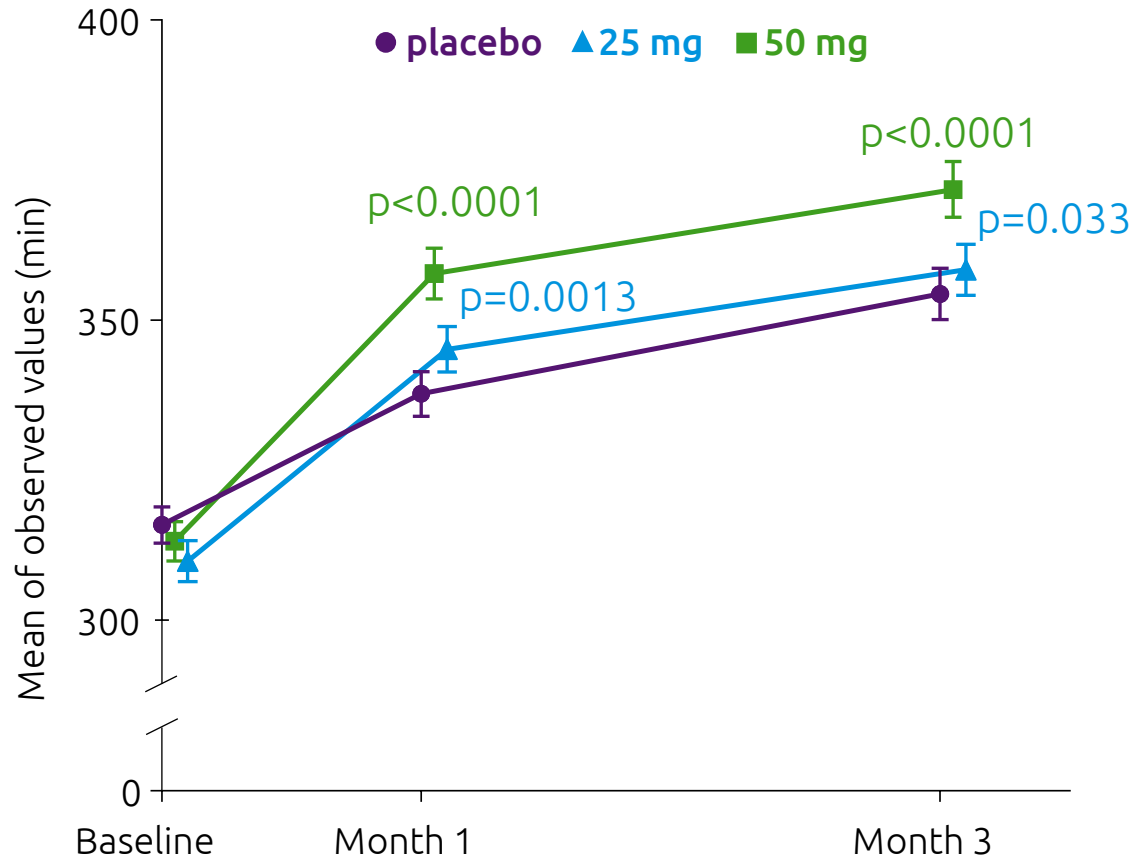
- 2 questions related to napping
- 2 visual analog scales related to alertness and ability to perform

→ **Total sleep time**  
Secondary endpoint

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# 2° endpoint: Subjective Total Sleep Time (sTST)

A measure of how the patient think they slept



Daridorexant 25 mg and 50 mg significantly improved sTST compared to placebo at months 1 and 3

## LSM change from baseline (95% CI)

	Month 1	Month 3
<b>Placebo</b>	<b>21.6</b> (16.1 to 27.0)	<b>37.9</b> (31.4 to 44.4)
<b>Daridorexant 25 mg</b>	<b>34.2</b> (28.7 to 39.6)	<b>47.8</b> (41.3 to 54.3)
LSM difference compared with placebo (95% CI)	<b>12.6</b> (5.0 to 20.3)	<b>9.9</b> (0.8 to 19.1)
<b>Daridorexant 50 mg</b>	<b>43.6</b> (38.2 to 49.1)	<b>57.7</b> (51.2 to 64.2)
LSM difference compared with placebo (95% CI)	<b>22.1</b> (14.4 to 29.7)	<b>19.8</b> (10.6 to 28.9)

CI = confidence interval; LSM = least squares mean

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Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

# Subjective assessment of daytime functioning

## Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)

### Measures

**Item 1.** How **clear-headed** did you feel today?

**Item 2.** How well were you able to **concentrate** today?

**Item 3.** How **forgetful** did you feel today?

**Item 4.** How **worried** did you feel today?

**Item 5.** How **frustrated** by your lack of sleep did you feel today?

**Item 6.** How **irritable** did you feel today?

**Item 7.** How **stressed** did you feel today?

**Item 8.** How **energetic** did you feel today?

**Item 9.** How **much of an effort** was it to perform daily activities (i.e. reading, cleaning, work, school) today?

**Item 10.** How **refreshed** did you feel today?

**Item 11.** How **mentally tired** did you feel today?

**Item 12.** How **physically tired** did you feel today?

**Item 13.** How **sleepy** did you feel today?

**Item 14.** How **awake** did you feel today?

“Alert/cognition”  
domain score  
(0-60)

“Mood”  
domain score  
(0-40)

“Sleepiness”  
domain score  
(0-40)

Items are ranked on a numeric rating scale from 0-10

IDSIQ™ 19:30

Please tap a number to best describe how you felt on **average** during the **daytime** today.

11. How **mentally tired** did you feel today?

0 1 2 3 4 5 6 7 8 9 10

↑ Not at all mentally tired ↑ Very mentally tired

Back Next

Daytime functioning measured by  
sleepiness domain score  
Secondary endpoint

# 2<sup>o</sup> endpoint: IDSIQ sleepiness domain

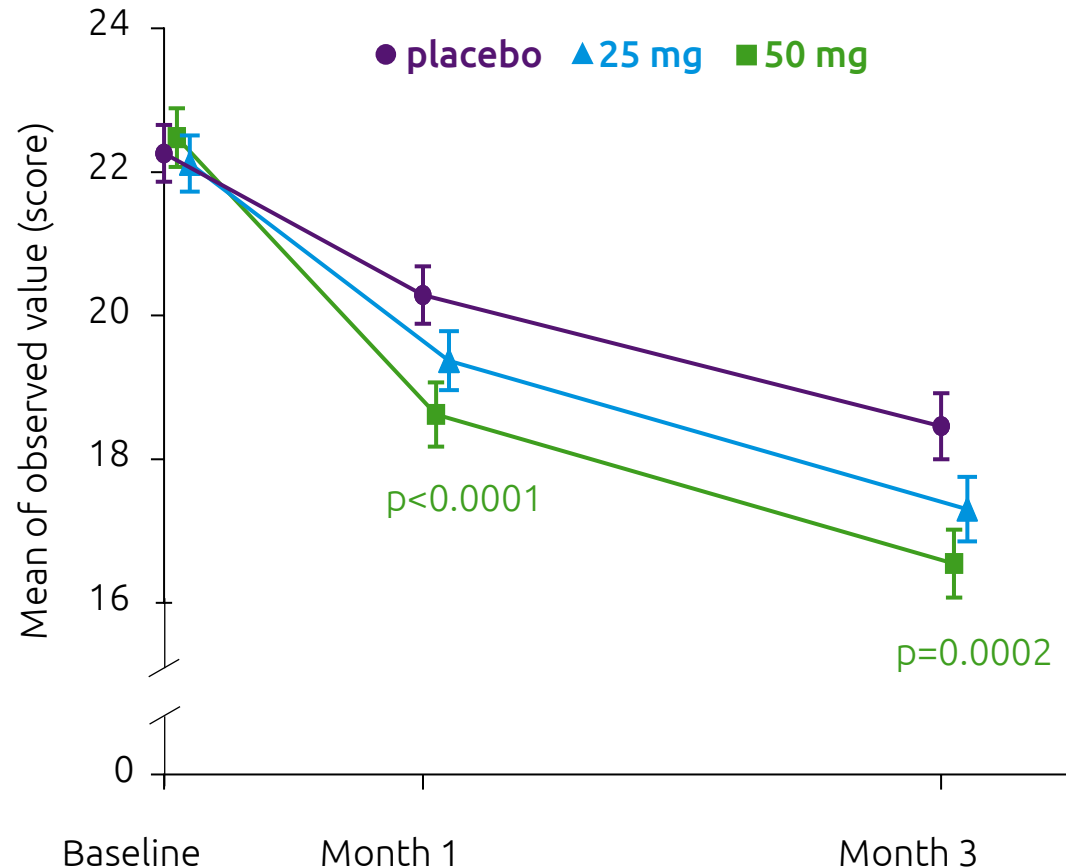
A measure of daytime functioning

How **energetic** did you feel today?

How **mentally tired** did you feel today?

How **physically tired** did you feel today?

How **sleepy** did you feel today?



Daridorexant 50 mg significantly improved IDSIQ sleepiness domain score compared to placebo at months 1 and 3

## LSM change from baseline (95% CI)

	Month 1	Month 3
<b>Placebo</b>	<b>-2.0</b> (-2.6 to -1.5)	<b>-3.8</b> (-4.5 to -3.1)
<b>Daridorexant 25 mg</b>	<b>-2.8</b> (-3.3 to -2.2)	<b>-4.8</b> (-5.5 to -4.1)
LSM difference compared with placebo (95% CI)	<b>-0.8</b> (-1.5 to 0.01)	<b>-1.0</b> (-2.0 to 0.01)
<b>Daridorexant 50 mg</b>	<b>-3.8</b> (-4.3 to -3.2)	<b>-5.7</b> (-6.4 to -5.0)
LSM difference compared with placebo (95% CI)	<b>-1.8</b> (-2.5 to -1.0)	<b>-1.9</b> (-2.9 to -0.9)

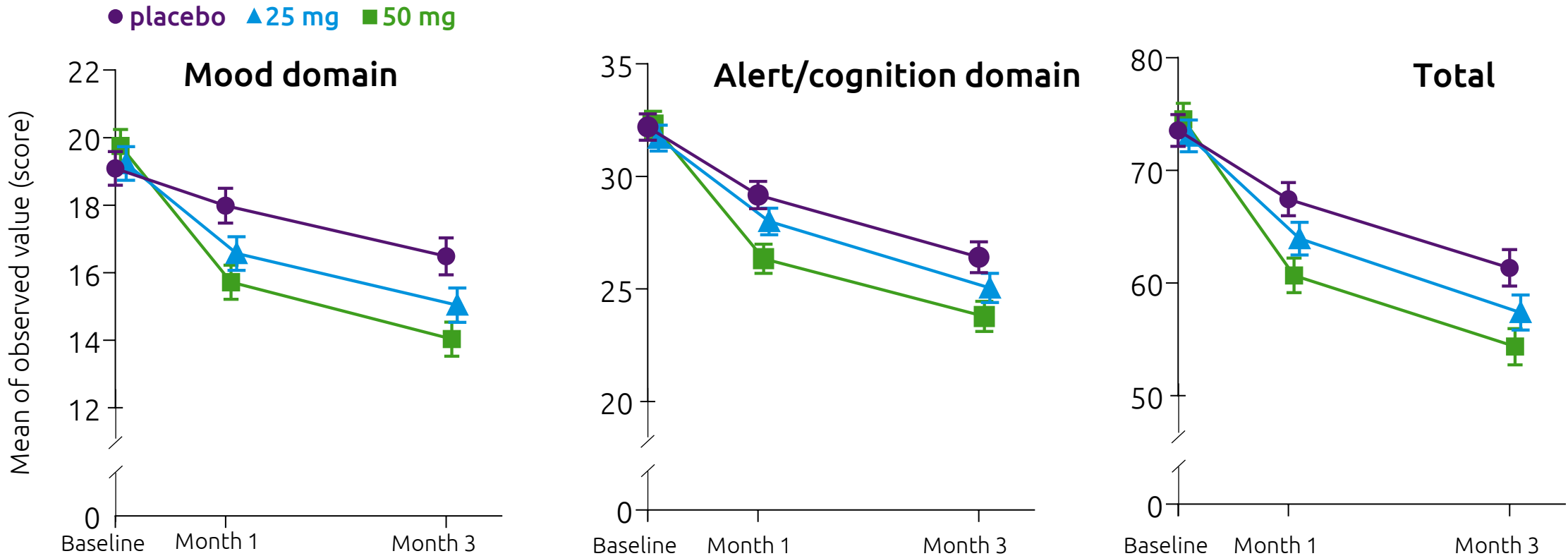
CI = confidence interval; LSM = least squares mean

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Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

# Exploratory endpoints: IDSIQ other scores

A measure of daytime functioning



IDSIQ mood domain, alert/cognition domain, and total scores at both timepoints were reduced (improved) (all nominal p-values for daridorexant 50 mg versus placebo  $\leq 0.0005$ ; not adjusted for multiplicity)

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

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# Adverse events

In the safety analysis population (n=1847)

	Study 1			Study 2		
	Dari 50 mg (n = 308)	Dari 25 mg (n = 310)	Placebo (n = 309)	Dari 25 mg (n = 308)	Dari 10 mg (n = 306)	Placebo (n = 306)
<b>Participants with ≥1 adverse event*</b>	<b>116 (38%)</b>	<b>117 (38%)</b>	<b>105 (34%)</b>	<b>121 (39%)</b>	<b>117 (38%)</b>	<b>100 (33%)</b>
<b>Adverse events* leading to treatment discontinuation</b>	<b>3 (1%)</b>	<b>7 (2%)</b>	<b>10 (3%)</b>	<b>4 (1%)</b>	<b>6 (2%)</b>	<b>7 (2%)</b>
<b>Participants with ≥1 serious adverse event</b>	<b>3 (1%)</b>	<b>2 (1%)</b>	<b>7 (2%)</b>	<b>3 (1%)</b>	<b>3 (1%)</b>	<b>4 (1%)</b>
<b>Participants with adverse event* (≥2% in any group)</b>						
Nasopharyngitis	20 (6%)	21 (7%)	20 (6%)	13 (4%)	32 (10%)	16 (5%)
Headache	19 (6%)	16 (5%)	12 (4%)	15 (5%)	12 (4%)	11 (4%)
Accidental overdose	8 (3%)	4 (1%)	5 (2%)	4 (1%)	4 (1%)	1 (<1%)
Fatigue	7 (2%)	7 (2%)	2 (1%)	11 (4%)	7 (2%)	2 (1%)
Dizziness	7 (2%)	6 (2%)	2 (1%)	6 (2%)	4 (1%)	4 (1%)
Nausea	7 (2%)	1 (<1%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)
Somnolence	5 (2%)	11 (4%)	6 (2%)	10 (3%)	6 (2%)	4 (1%)
Fall	1 (<1%)	1 (<1%)	8 (3%)	3 (1%)	4 (1%)	3 (1%)
Upper respiratory tract infection	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	6 (2%)

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. \*Adverse events that occurred during the double-blind treatment period in the safety population are included in the table and presented with their preferred terms.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

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# Adjudicated adverse events

In the safety analysis population (n=1847)

	Study 1			Study 2		
	Dari 50 mg (n = 308)	Dari 25 mg (n = 310)	Placebo (n = 309)	Dari 25 mg (n = 308)	Dari 10 mg (n = 306)	Placebo (n = 306)
<b>Adjudicated adverse events†</b>						
Excessive daytime sleepiness	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	1 (<1%)	1 (<1%)
Sleep paralysis	1 (<1%)	1 (<1%)	0	2 (1%)	0	0
Hallucinations	0	1 (<1%)	0	1 (<1%)	0	0
Suicidal ideation or self-injury‡	0	0	0	1 (<1%)	1 (<1%)	0

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. †Adjudicated adverse events were reported during the double-blind treatment up to 30 days after the end of treatment or date of enrolment into the extension trial and were adjudicated blindly by an independent safety board. ‡Adjudicated adverse events belonging to the category suicidal ideation or self-injury (preferred term: suicidal ideation) were reported in two participants, one in each daridorexant group in study 2; both patients had pre-existing medical conditions (paranoid schizophrenia or depression) and the independent safety board adjudicated both adverse events as potentially related to trial treatment.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

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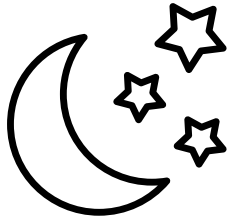
# Further safety observations

**No** adverse events suggested that **drug misuse** might have occurred

**No withdrawal symptoms** were observed during the placebo run-out period, as assessed by adverse events or the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

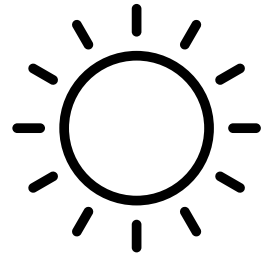
During the placebo run-out period, WASO and LPS were numerically lower, and mean self-reported total sleep time was higher than respective baseline values, indicating **absence of rebound insomnia**

# The daridorexant clinical program provides a wealth of evidence



## Comprehensive sleep efficacy perceived by patients (25 mg & 50 mg)

- Fall asleep faster
- Stay asleep longer
- Time in each sleep stage preserved



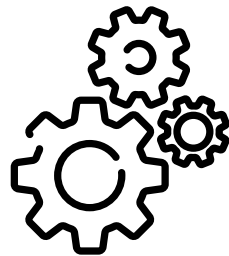
## Daytime functioning perceived by patients (50 mg)

- Improved sleepiness
- Consistent effect on mood and alertness / cognition on exploratory endpoints
- Progressive improvement over time



## Documented safety

- A low overall incidence of adverse events (AE), comparable between treatment groups
- Most common AEs (>5%): nasopharyngitis and headache
- No evidence of tolerance or dependence
- No rebound insomnia or withdrawal effects



## Precision MOA & intrinsic properties of daridorexant

- Targets only the part of the brain that keeps you awake, without broad sedation
- Ideal pharmacological profile

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# Unlocking the value of QUVIVIQ

Advance the science of sleep and insomnia



- Positive results in Phase 4 study in patients with insomnia and comorbid nocturia
- Phase 4 studies in patients with insomnia and comorbid psychiatric and neurological disease
- Phase 2 in pediatric insomnia expected to read out results in Q3 2025
- >10 investigator-initiated studies in preparation or recruiting as a treatment for:
  - mild cognitive impairment and mild to moderate **Alzheimer disease**
  - active-duty service members and veterans with **PTSD**
  - enhancing sleep and **reducing substance use** in patients **dependent on alcohol and opioids**
  - enhancing sleep during **smoking withdrawal**
  - **menopause-related insomnia** symptoms
  - improving **CPAP adherence** in subjects with **co-morbid insomnia and sleep apnea**
  - among others...

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# On track to become a global brand

**QUVIVIQ™**  
daridorexant 25mg, 50mg  
tablets



Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.

# Collaboration with Syneos Health

Commercialization partner to launch daridorexant in the US, Europe, and Canada



- Syneos Health selected as commercialization partner in order to effectively reach the primary care market, which accounts for a large volume of insomnia prescriptions, in the US, Europe, and Canada
- Syneos Health brings a robust customer-facing sales expertise and proven track record in launching new products in these regions
- An innovative, revenue-driven agreement to accelerate and maximize reach to patients
- Together we will lead the transformation and modernization of the insomnia market

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# License agreements with Nxera



## **Nxera Pharma**

Co-exclusive license granted to Nxera for daridorexant in Australia, Brunei, Cambodia, Indonesia, Japan, Laos, Malaysia, Myanmar, New Zealand, Philippines, Singapore, South Korea, Thailand, Taiwan, and Vietnam

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# License agreement with Simcere



Development and commercialization of daridorexant in the Greater China region

- Simcere has an exclusive right to develop and commercialize daridorexant in the Greater China region (Mainland China, Hong Kong, and Macau), one of the world's largest pharmaceutical markets
- Simcere is responsible for the local development program with Chinese patients
- Idorsia receives a US\$ 30 million upfront payment and will be eligible to receive an additional milestone payment of US\$ 20 million upon regulatory approval by the National Medical Products Administration, as well as commercial milestone payments and low double-digit tiered royalties based upon future sales.

Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.



QUVIVIQ® (daridorexant) launched in the US in May 2022



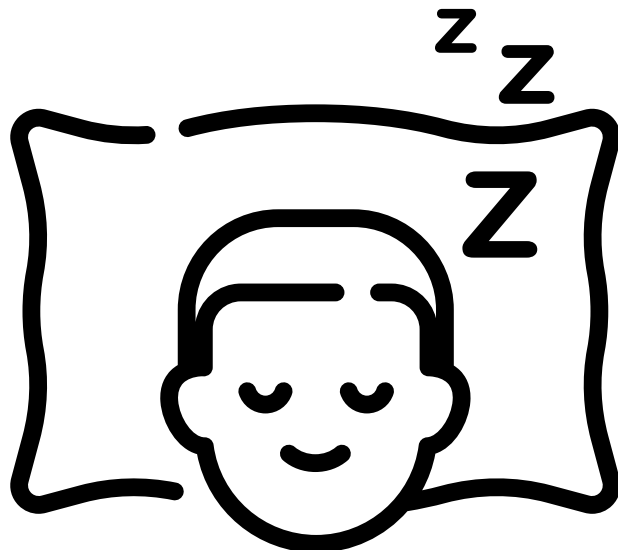
QUVIVIQ®

(daridorexant) (IV) 25mg, 50mg tablets

Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.



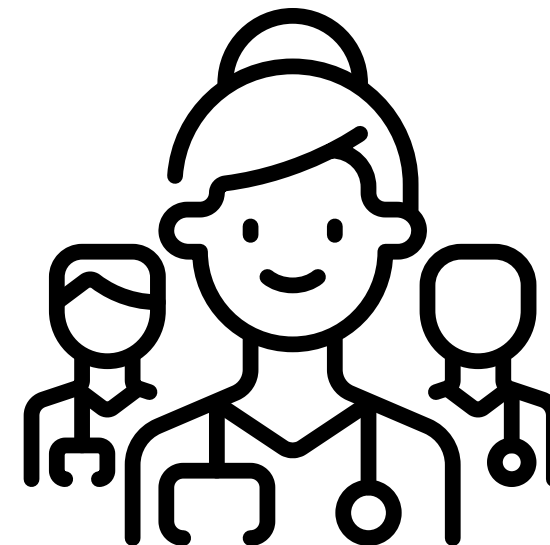
**>180K**  
patients  
treated



**>600K**  
prescriptions  
dispensed



**>50K**  
prescribers



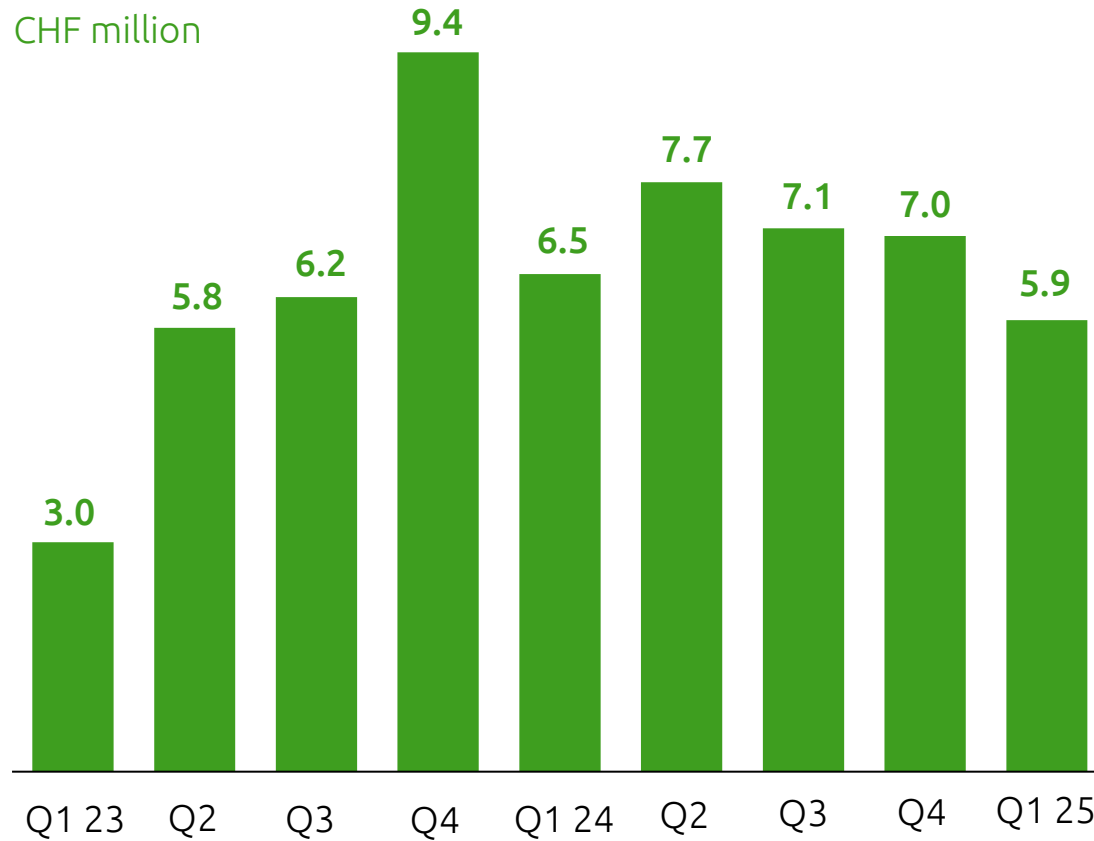
# Unlocking the value of QUVIVIQ

US sales maintained despite field force and OPEX reduction



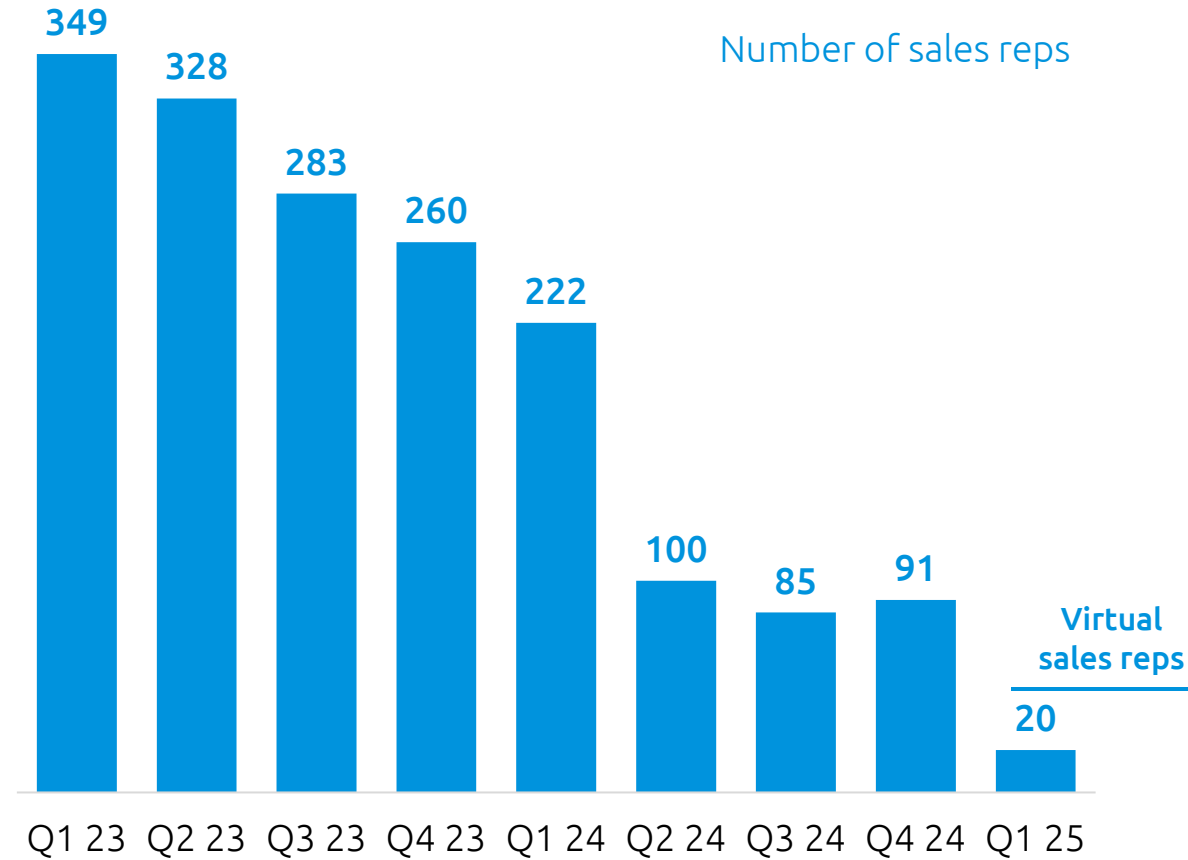
### US net sales

CHF million



### QUVIVIQ field force

Number of sales reps



Idorsia makes daridorexant available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.

“We are still hopeful that descheduling of the DORA class can be achieved and the real value of QUVIVIQ in the US market can be unlocked.”

**Michael Moye**  
**President Idorsia US**



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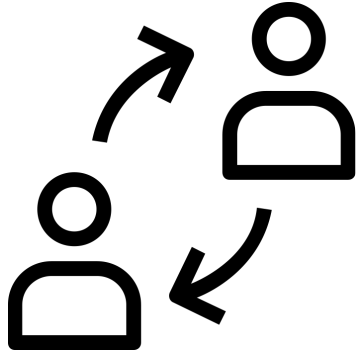
# Scheduling under discussion



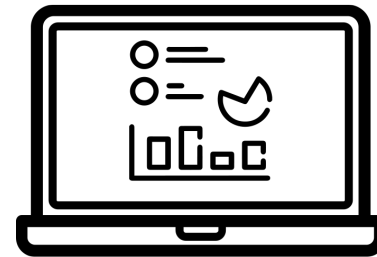
**Citizen's Petition**  
requesting descheduling  
of the DORA class  
of medicines  
**progressing**

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# Collaboration with Syneos Health



Switched to 20 virtual sales reps operating remotely instead of the around 100 field force sales reps



Marketing, digital media, data analytics and market access activities in support of the virtual reps



“Demand has grown by an impressive 50% quarter on quarter, mainly driven by reimbursed markets. Across the EUCAN region, more than 10 million nights of sleep have been prescribed in the first quarter of 2025.”

**Benjamin Limal**

**President of Europe and Canada region**

**QUVIVIQ™**  
daridorexant 25mg, 50mg  
tablets



○○○



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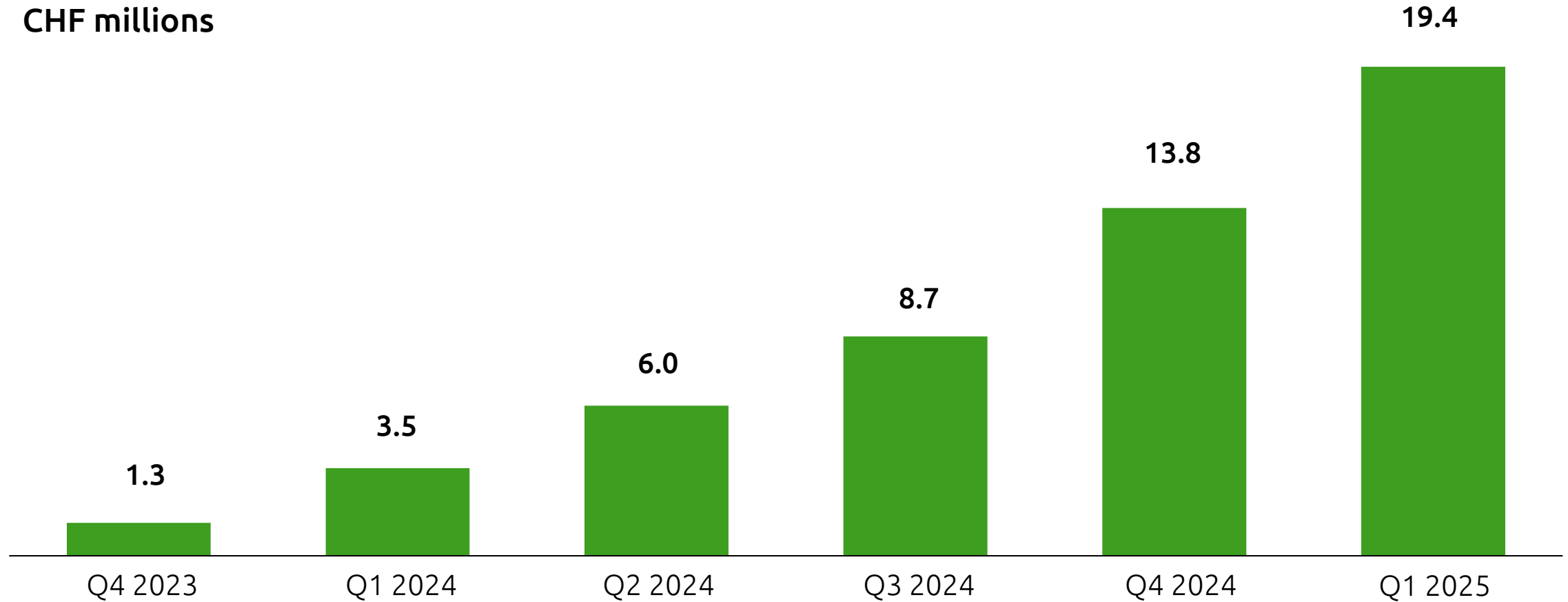
# Accelerating QUVIVIQ sales

Europe & Canada

QUVIVIQ<sup>™</sup>  
daridorexant 25mg, 50mg  
tablets



CHF millions



Daridorexant is available in the US, Germany, Italy, Spain, Switzerland, the UK, Canada, Austria, France, and Sweden under the tradename QUVIVIQ. In addition, daridorexant is approved throughout the European Union.

# Accelerating QUVIVIQ demand

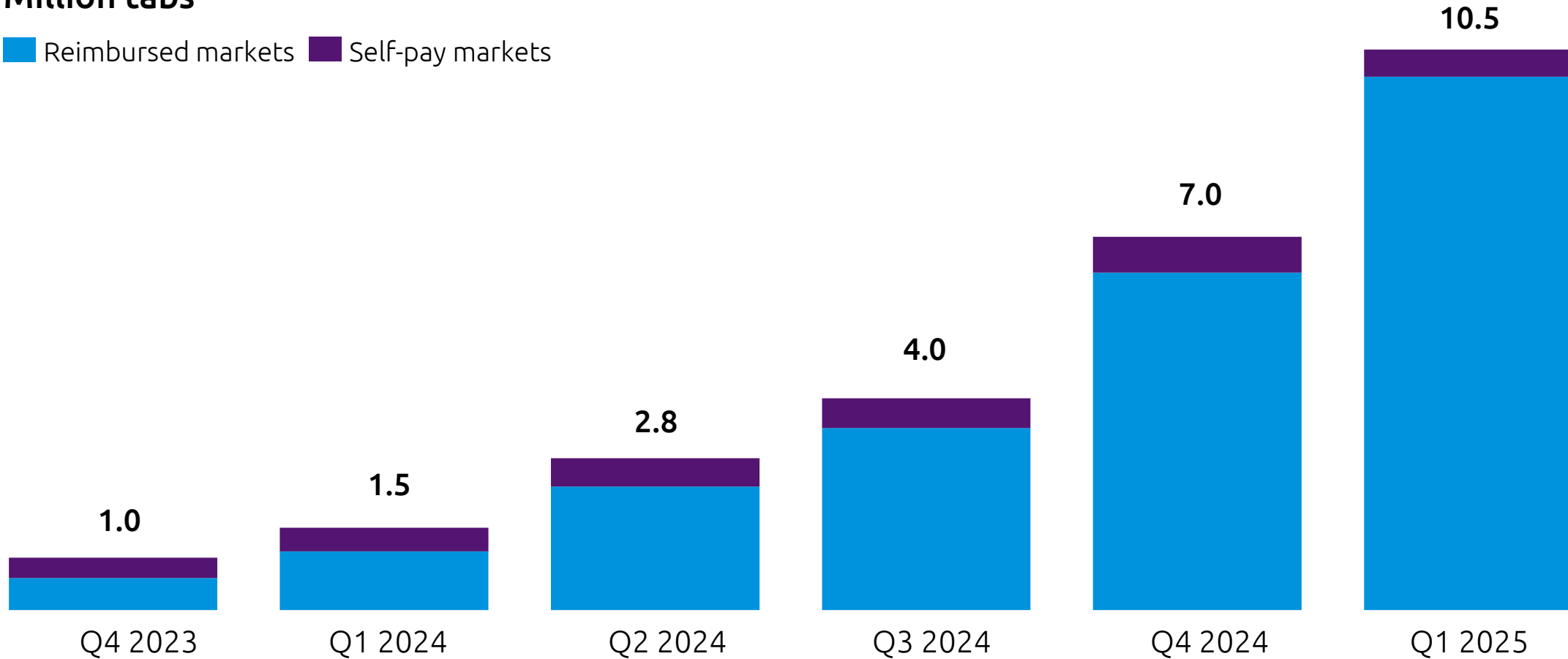
Europe & Canada

QUVIVIQ<sup>™</sup>  
daridorexant 25mg, 50mg  
tablets



## Million tabs

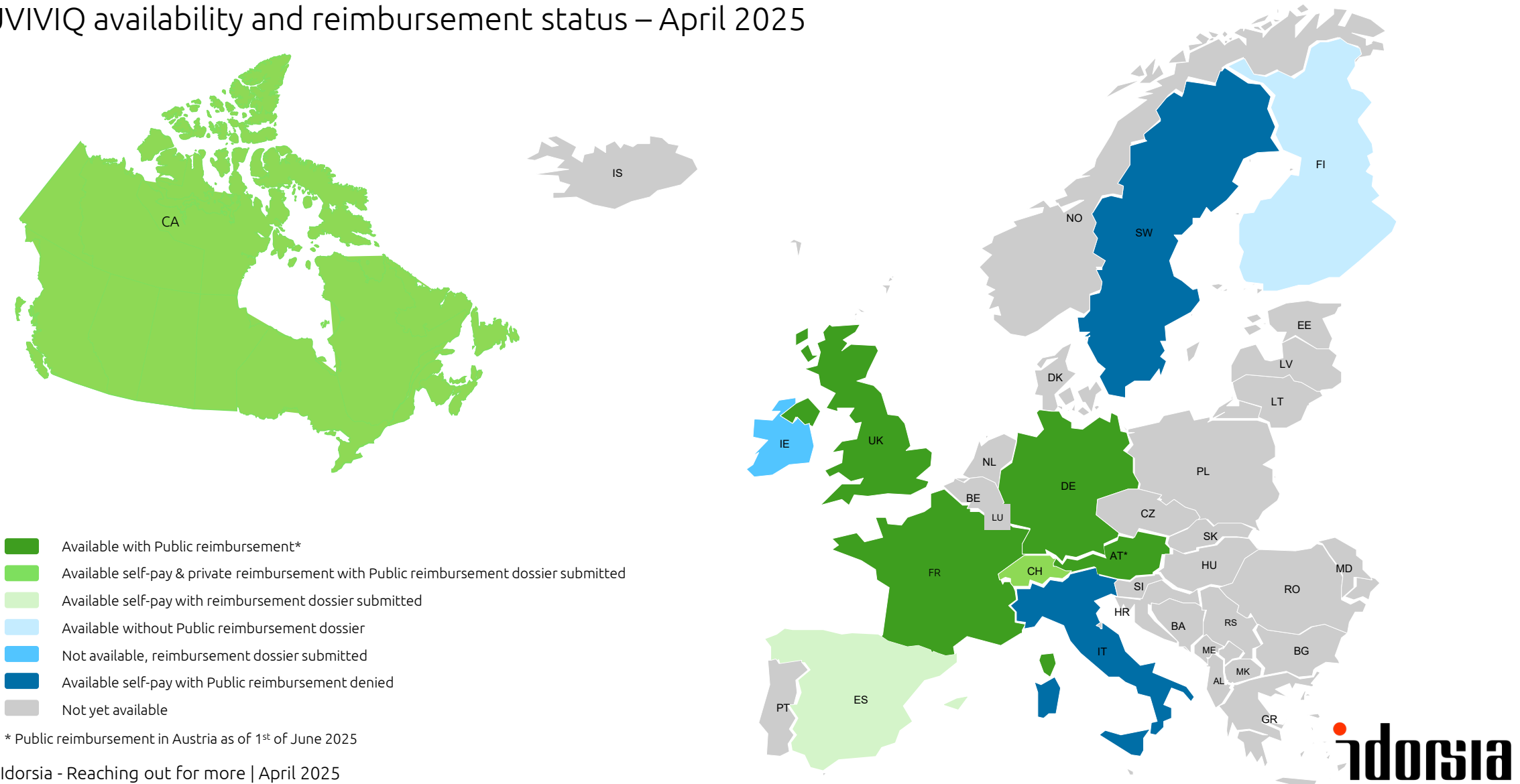
Reimbursed markets Self-pay markets



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# We have secured reimbursement in 6 Countries and are focused to expand public access in EUCAN

QUVIVIQ availability and reimbursement status – April 2025

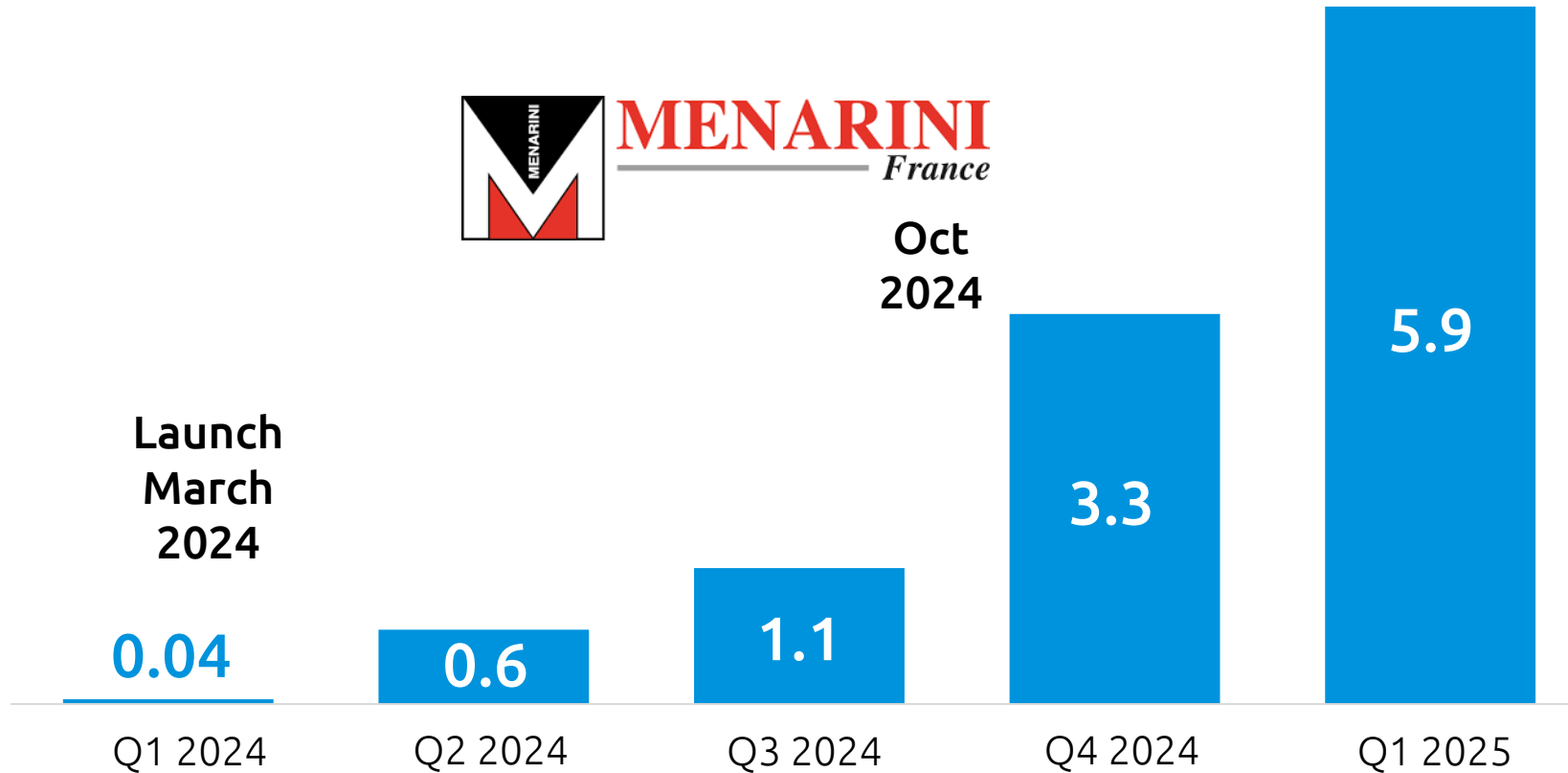


# Expanding our commercial reach to GP prescribers

Immediate impact of commercial partnership with Menarini in France



Million tabs



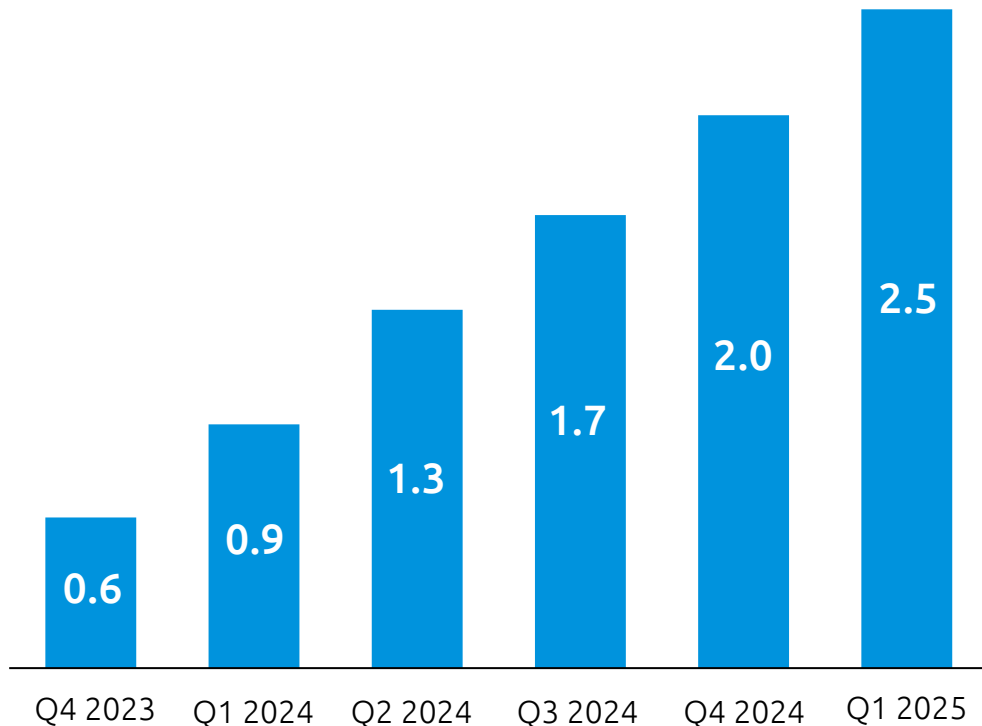
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# Expanding our commercial reach to GP prescribers

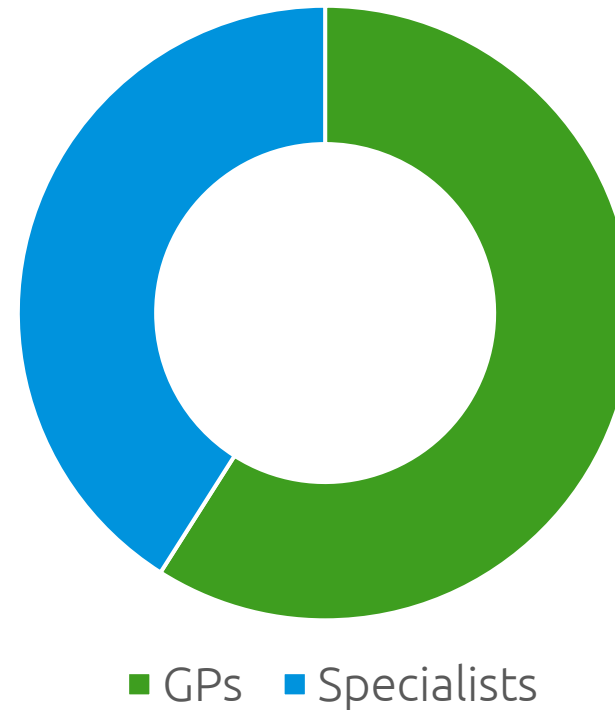
Solid sales growth set to accelerate with new commercial partnership with Berlin-Chemie



Million tabs



Volume share by specialty of the German insomnia market

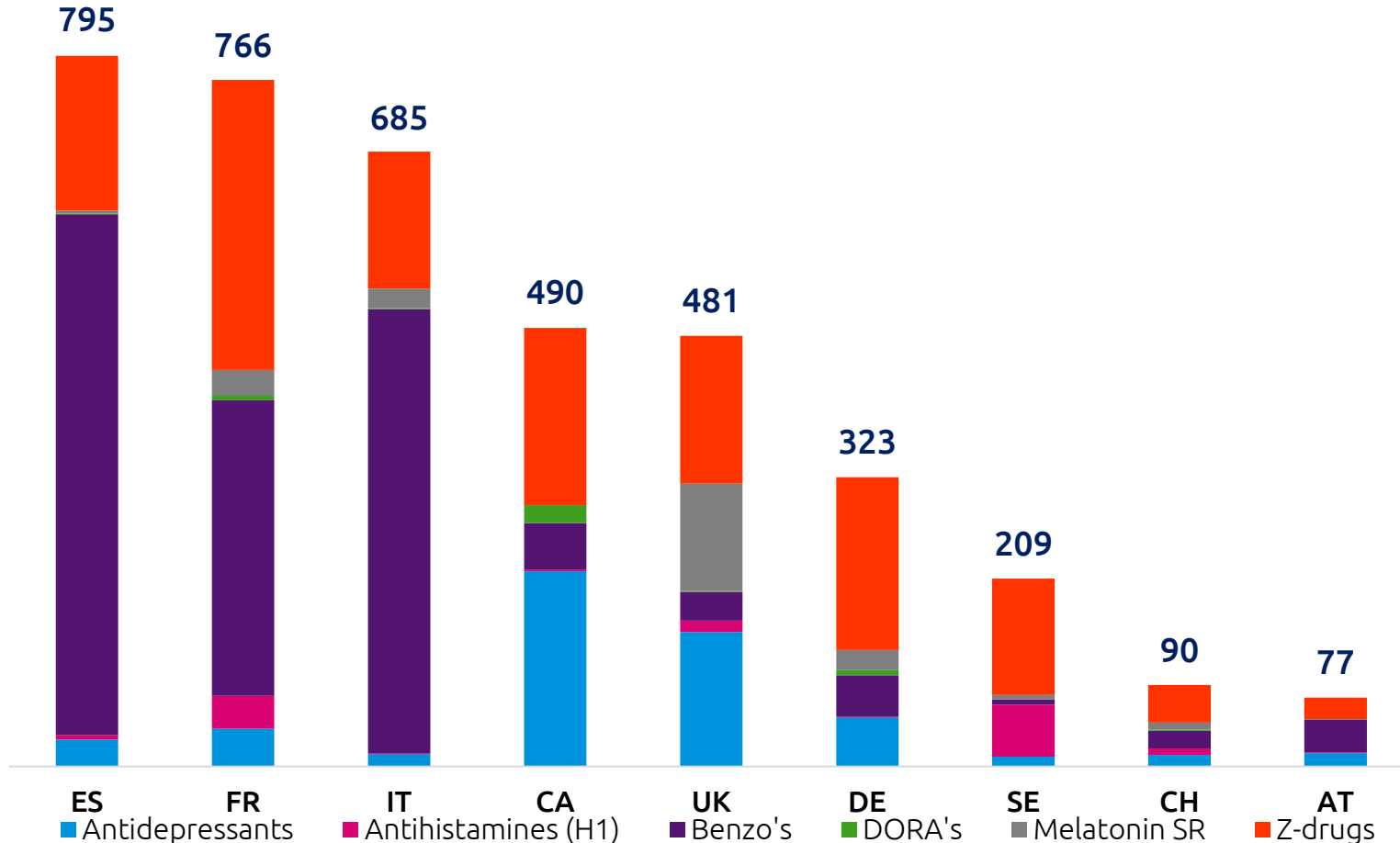


**BERLIN-CHEMIE**  
**MENARINI**

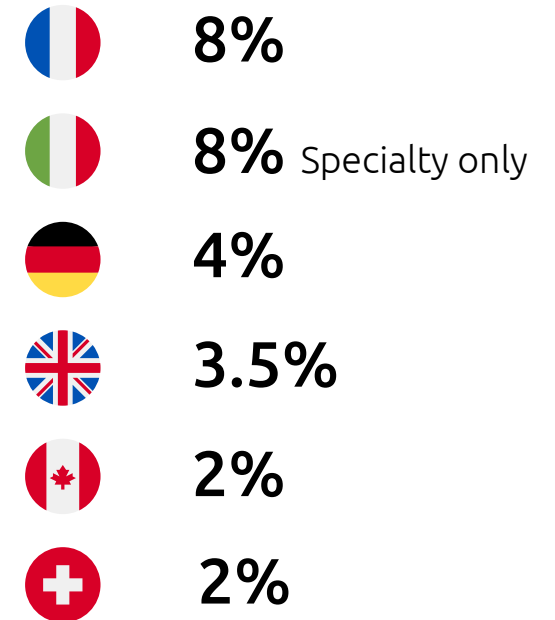
...beginning in  
early April  
2025

# EUCAN represents a massive market opportunity

Estimated insomnia market volume\*, standard units, millions



QUVIVIQ patient NBRx\*\*



\*\* LRx - Nov 2024 for FR, IT, DE & CA. Oct 2024 for CH

Sources:

1) IQVIA MIDAS - Monthly Volume in M SU, MAT/Sep/2024 (EU5-CA-CHAT); Sweden MAT/SEP/2020

\*Includes estimated off-label usage of anti-depressants, anti-histamines and benzos to treat insomnia



# Aprocitentan in systemic hypertension

Aprocitentan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.

# Aprocitentan: Innovative and highly differentiated drug for uncontrolled hypertension



**TRYVIO**™

(aprocitentan) 12.5mg tablets



TRYVIO™ (aprocitentan)  
12.5 mg **approved** in  
March 2024



**JERAYGO**™

aprocitentan



JERAYGO™ (aprocitentan)  
12.5 mg & 25 mg **approved** in the EU  
in July 2024 and UK in January 2025

Idorsia makes aprocitentan available in the US under the tradename TRYVIO. In addition, aprocitentan is approved throughout the European Union and in the UK under the tradename JERAYGO. Marketing authorization applications are under review in Canada and Switzerland.



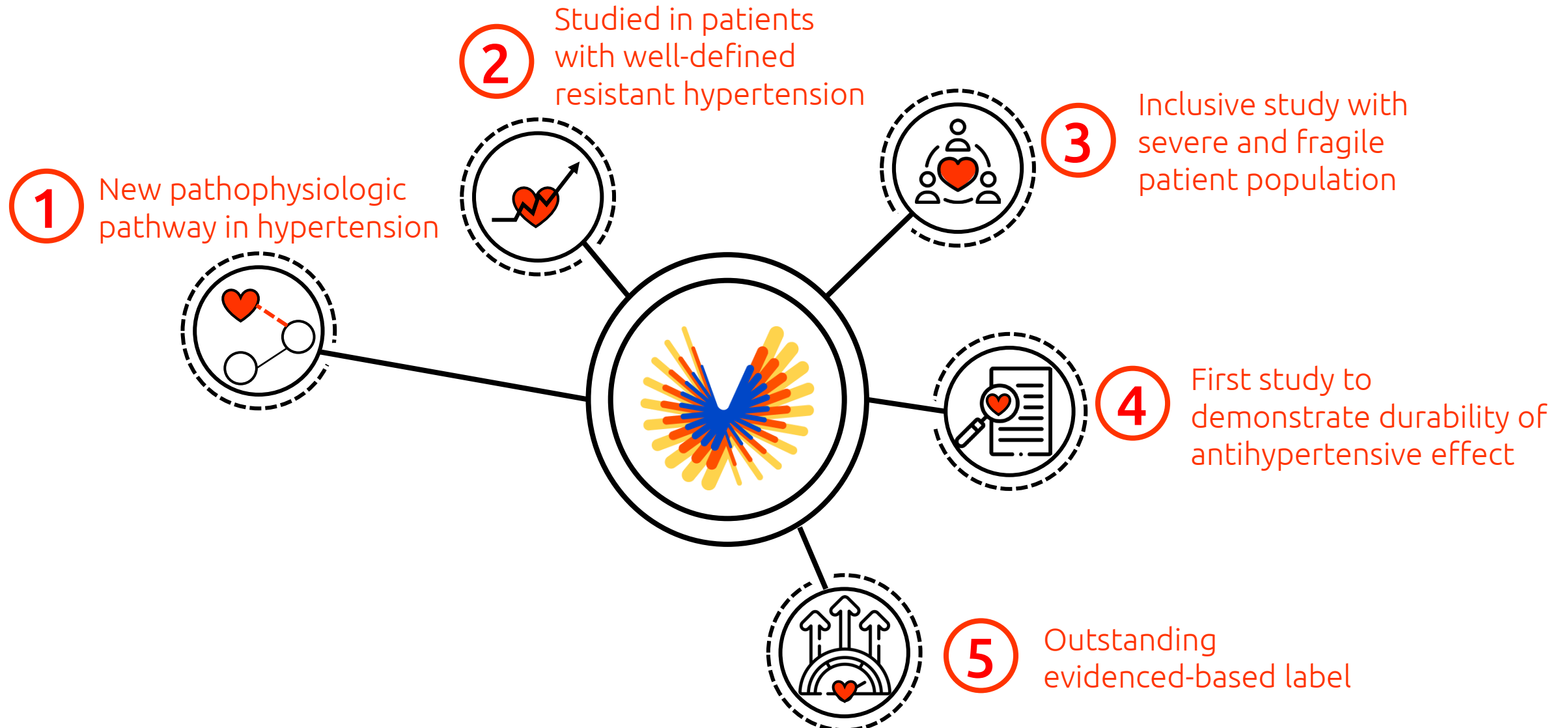


“Today, there are millions of Americans whose blood pressure is not well-controlled despite existing therapy. This is a major public health issue leading to a high incidence of cardiovascular events.”

**Jean-Paul Clozel**  
Chairman of the Board of Directors



# A unique compound with unique data



Aprocitentan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.

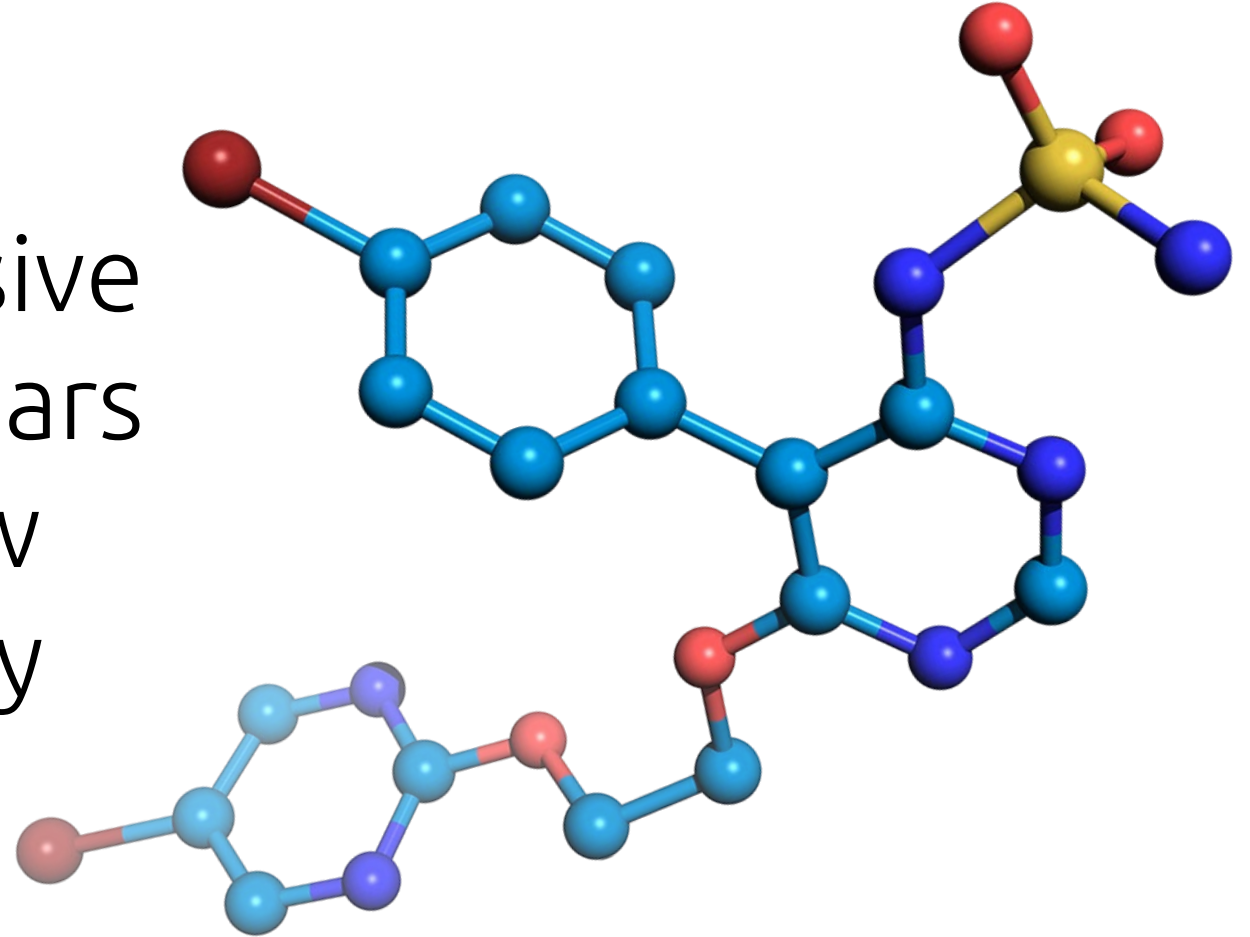
“Since the endothelin pathway was not yet tackled, we selected aprocitentan, an endothelin receptor antagonist with the ideal properties for use with patients whose hypertension is not adequately controlled with other antihypertensives.”

**Martine Clozel**  
**Chief Scientific Officer**

Aprocitentan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.



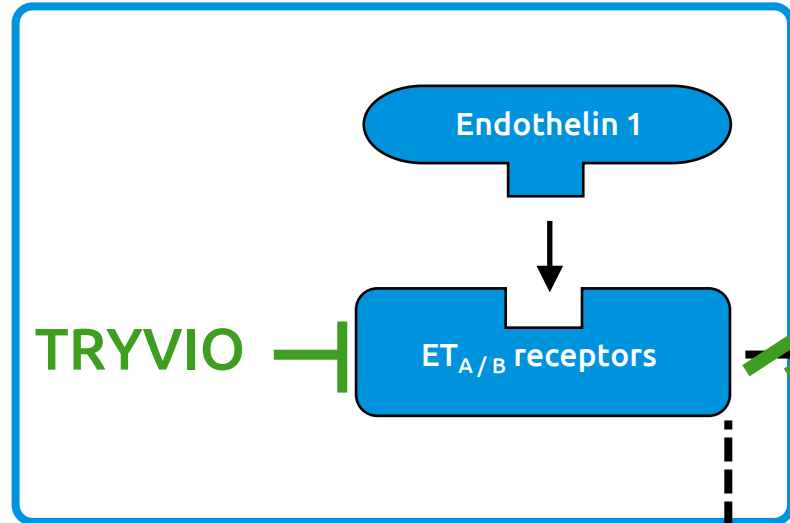
The first anti-hypertensive therapy in almost 40 years which works on a new physiological pathway



Aprocitentan is only available in the US under the tradename TRYVIO<sup>™</sup> and is approved in the European Union and the UK under the tradename JERAYGO<sup>™</sup>. Market authorization is under review in Canada and Switzerland.

# Targeting a new pathway in hypertension

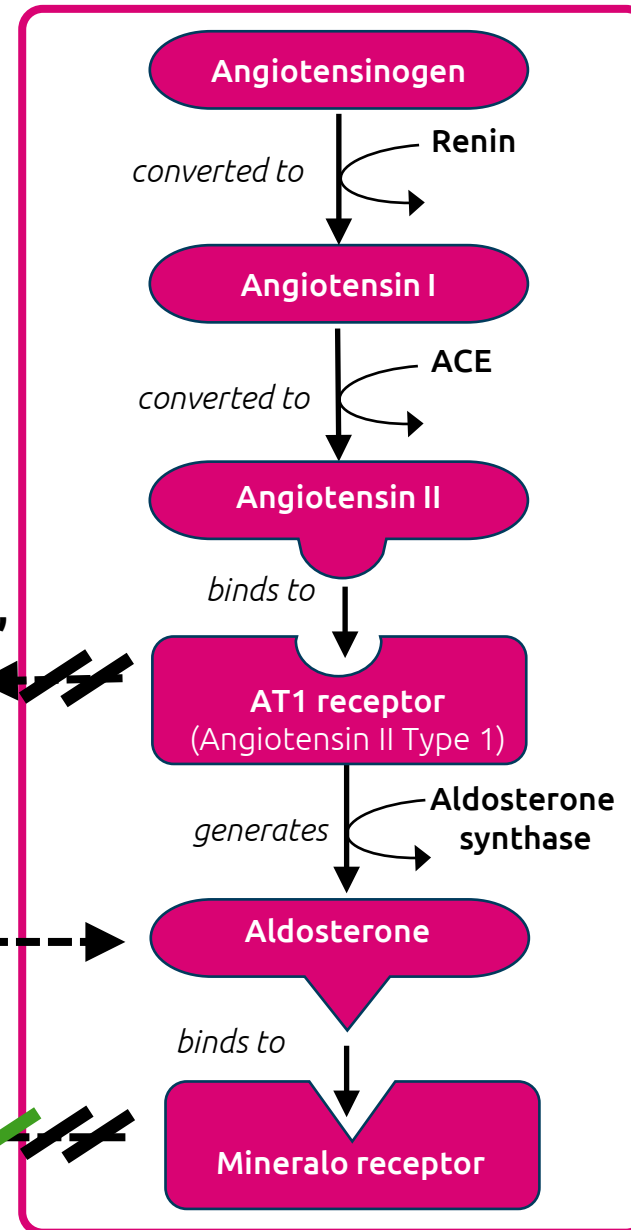
## Endothelin Pathway



Vasoconstriction, hypertrophy and remodeling

Sodium and water retention

## RAAS Pathway



Aprocintentan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.

# >30 years of researching the endothelin system

**1988**

Endothelin-1  
identified

**1990**

ET<sub>A</sub> and ET<sub>B</sub> receptors  
identified

**1993**

First proof of the  
role of ERA  
published in *Nature*

**1998**

First evidence of  
dual ERA effect in  
hypertension  
published in *New  
England Journal of  
Medicine*

**2007**

Failed attempt  
by competition  
in resistant  
hypertension  
with selective  
ERA

**2022**

**Aprocitentan –  
positive Phase 3  
in resistant  
hypertension**

**2024**

**TRYVIO™  
(aprocitentan)  
approved by  
US FDA**

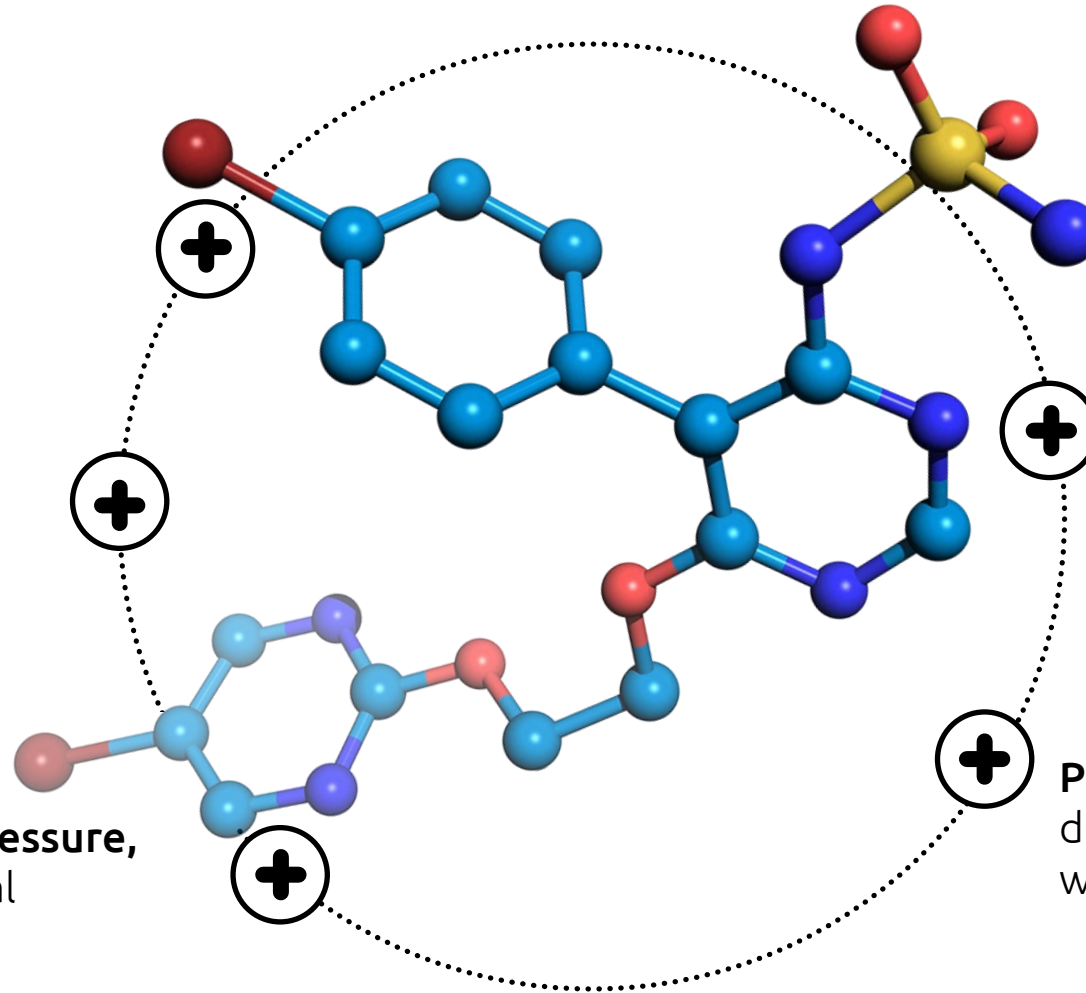
**JERAYGO™  
(aprocitentan)  
approved by  
EMA**

# Aprocitantan selected for its ideal properties

Orally-active, potent dual  $ET_A$  and  $ET_B$  receptor antagonist

Synergistic effect with other antihypertensive drugs (RAAS blockers) in animal models

Demonstrated efficacy on blood pressure, renal and cardiac protection in animal models



Low potential for drug-drug interaction

Phase 2 study shows blood pressure decrease as monotherapy in patients with hypertension

Aprocitantan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.

“Aprocitentan demonstrated a clear and consistent effect across all endpoints of blood pressure measurement and in key sub-populations.”

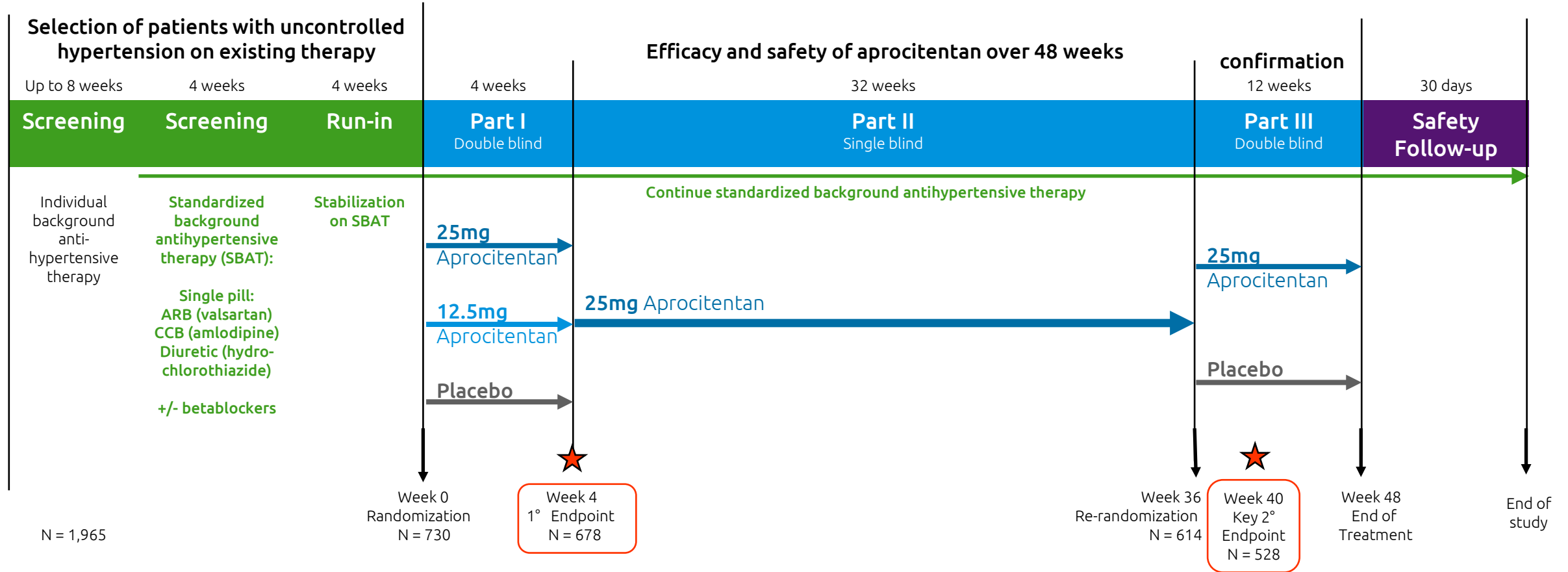
**Alberto Gimona**  
**Head of Global Clinical  
Development**

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# PRECISION investigated durability of BP reduction



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# Frail population with multiple co-morbidities

Total: N = 730 [n (%)]

Age (years)		
Mean (SD)	61.7	(10.6)
18 to <65	409	(56.0)
<b>65 - &lt;75</b>	<b>249</b>	<b>(34.1)</b>
<b>≥75</b>	<b>72</b>	<b>(9.9)</b>
Race		
White	605	(82.9)
<b>Black or African American</b>	<b>82</b>	<b>(11.2)</b>
Asian	38	(5.2)
Other	5	(0.7)
BMI# (kg/m <sup>2</sup> )		
<b>Mean (SD)</b>	<b>33.7</b>	<b>(6.2)</b>
SiSBP / SiDBP (mmHg)*		
Mean (SD)	153.3 (8.9)	/ 87.6 (9.7)

Antihypertensive therapies#		
3	269	(36.8)
4	337	(46.2)
≥ 5	123	(16.8)
UACR [mg/g]*		
< 30	453	(63.2)
<b>30–300</b>	<b>174</b>	<b>(24.3)</b>
<b>&gt; 300</b>	<b>90</b>	<b>(12.6)</b>
missing	13	
eGFR [mL/min]*		
<b>&lt; 30</b>	<b>21</b>	<b>(2.9)</b>
<b>30 – &lt; 45</b>	<b>48</b>	<b>(6.6)</b>
<b>45 – &lt; 60</b>	<b>93</b>	<b>(12.7)</b>
≥ 60	568	(77.8)

Medical history		
<b>Diabetes mellitus</b>	<b>395</b>	<b>(54.1)</b>
<b>Congestive heart failure</b>	<b>143</b>	<b>(19.6)</b>
Sleep apnea syndrome	103	(14.1)
Stroke	57	(7.8)
Myocardial infarction	51	(7.0)

BMI: body mass index

eGFR: estimated glomerular filtration rate

RHT: resistant hypertension

SD: standard deviation

SiDBP: sitting diastolic blood pressure

SiSBP: sitting systolic blood pressure

UACR: urine albumin-to-creatinine ratio

\* at baseline

# at screening

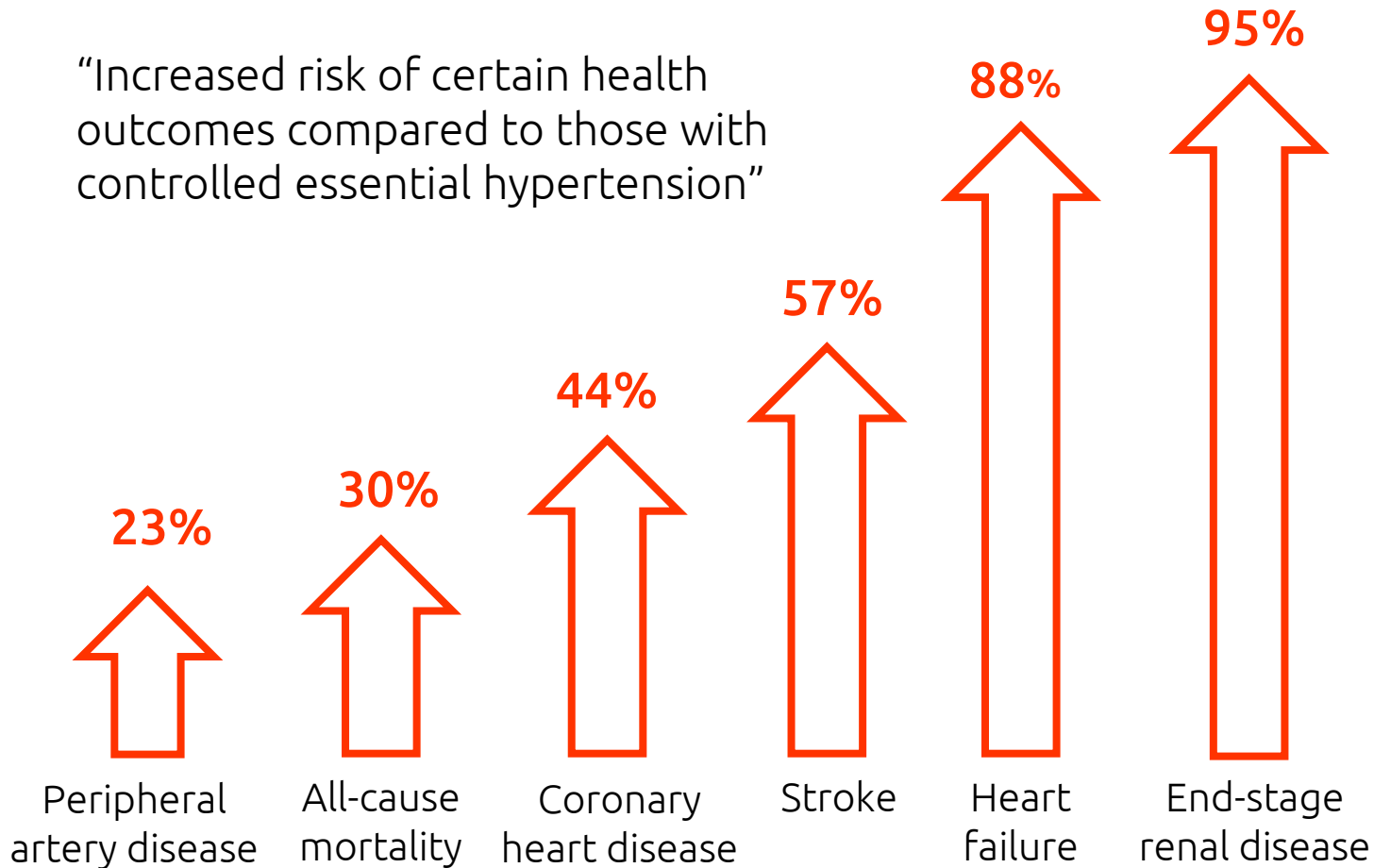
Danaietash P et al., *J Clin Hypertens* 2022 Jul; 24(7):804-813

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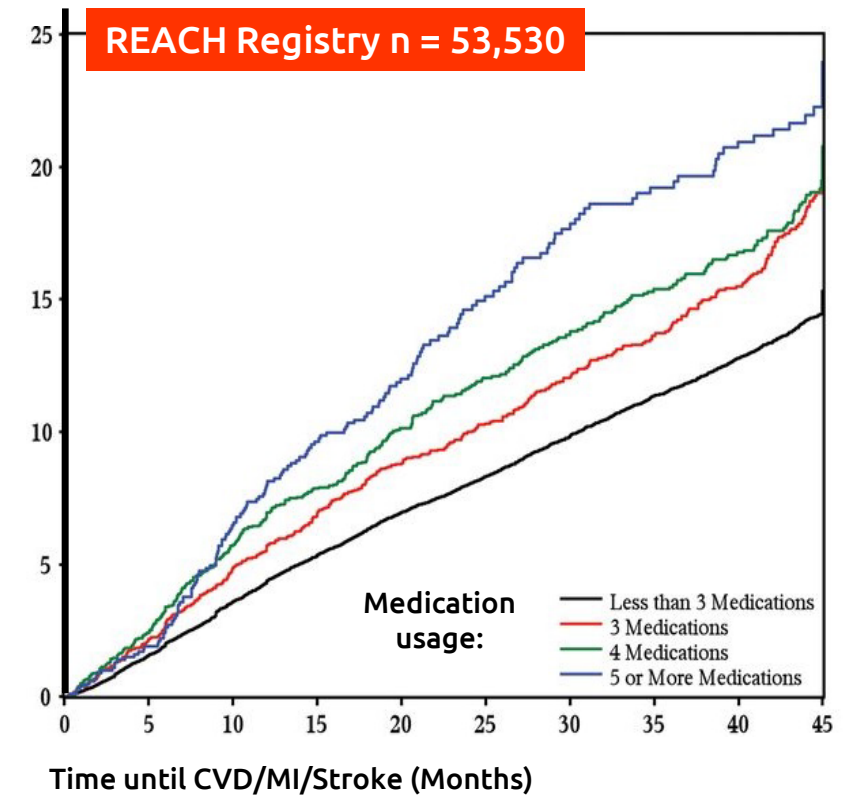
# Disease burden when hypertension is uncontrolled

“Increased risk of certain health outcomes compared to those with controlled essential hypertension”



Muntner et al., 2014

Higher incidence of major cardiovascular events



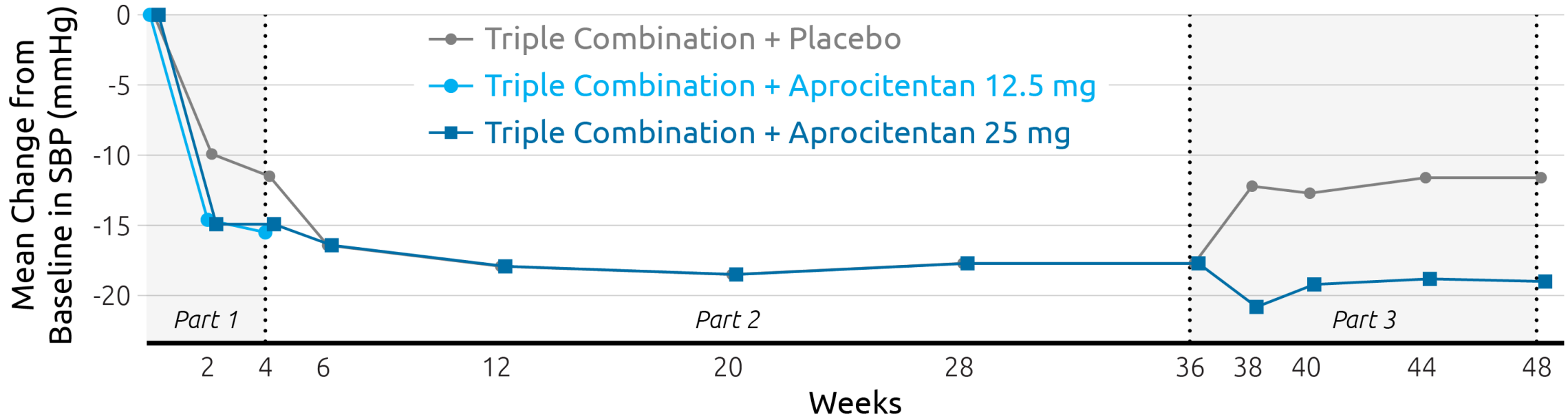
European Heart Journal, 2013

Idorsia

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# Significant and sustained BP reduction

Absolute BP reduction of 15 mmHg



## Primary endpoint

12.5 mg vs placebo: -3.8 mmHg, P=0.0042  
25 mg vs placebo: - 3.7 mmHg, P=0.0046

## Key secondary endpoint

25 mg vs placebo: - 5.8 mmHg P<0.0001

Triple combination: single pill ARB (valsartan), CCB (amlodipine) , diuretic (hydrochlorothiazide) +/- beta blockers

Schlaich MP, et al. The Lancet, 2022; Dec 3;400(10367):1927-1937.

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# USPI Highlights: Indication and Usage



## -----INDICATIONS AND USAGE-----

TRYVIO is an endothelin receptor antagonist indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

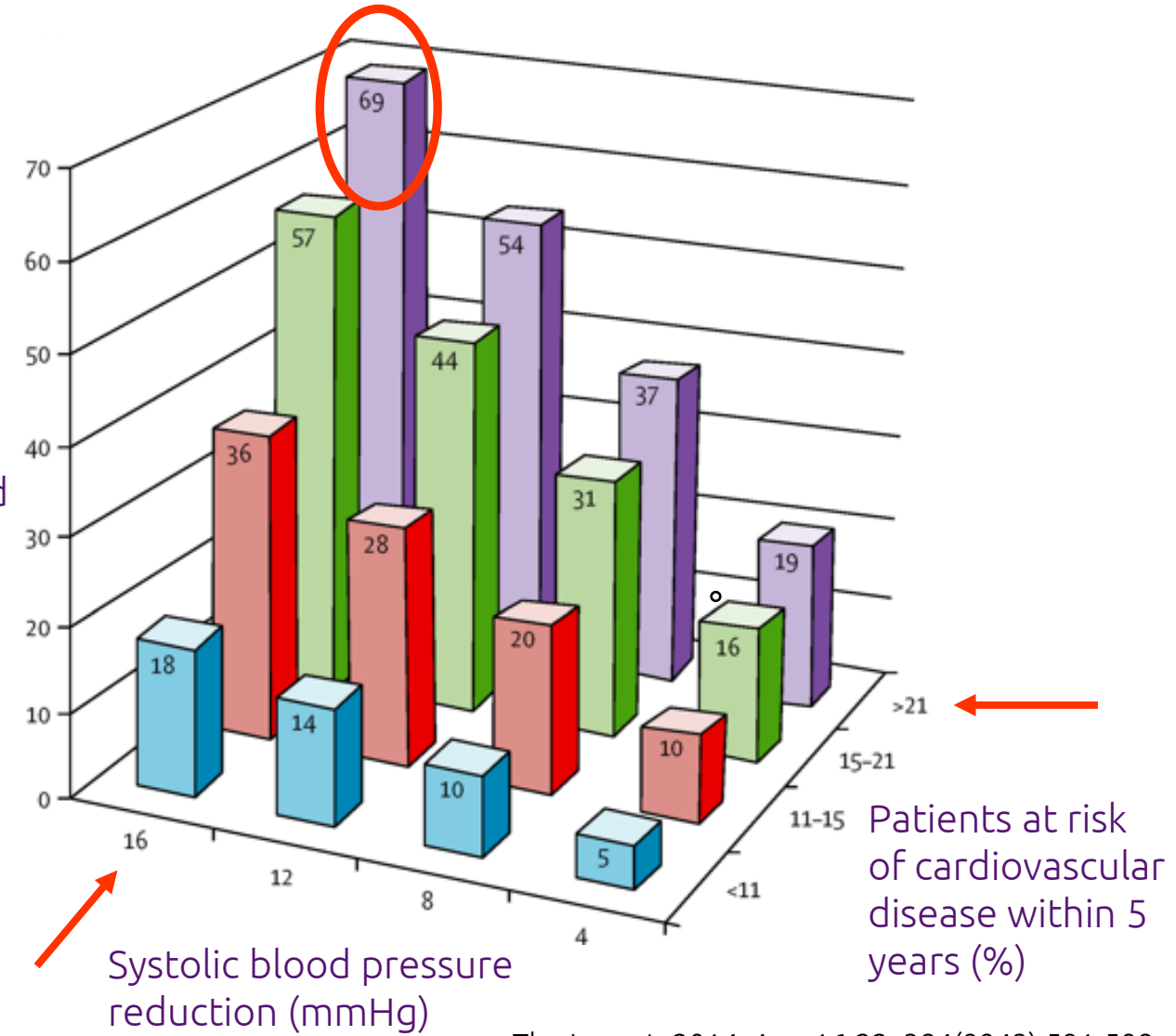
Aprocitentan is only available in the US under the tradename TRYVIO™ and is approved in the European Union and the UK under the tradename JERAYGO™. Market authorization is under review in Canada and Switzerland.

# Reduction in BP will prevent CV events

16-mmHg (uAOBPM) reduction in SBP vs baseline would avoid approximately 70 CV events per 1000 patients over the following 5 years

Cardiovascular events avoided per 1000

NB: There are no controlled trials demonstrating reduction of risk of these events with TRYVIO



Systolic blood pressure reduction (mmHg)

Patients at risk of cardiovascular disease within 5 years (%)

The Lancet, 2014; Aug 16-22; 384(9943):591-598.

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# USPI Highlights: Dosage and Administration



## -----DOSAGE AND ADMINISTRATION-----

- The recommended dosage of TRYVIO is 12.5 mg orally once daily, with or without food. (2.1)

## USPI Section 14: Clinical Studies

### TRYVIO long-term sustained effect

The persistence of the BP-lowering effect of TRYVIO was demonstrated in part 3 of the trial, in which patients on aprocitentan were re-randomized to placebo or 25 mg aprocitentan following a period during which all patients were treated with 25 mg. In patients re-randomized to placebo, the mean SiSBP increased, whereas in patients re-randomized to 25 mg aprocitentan the mean effect on SiSBP was maintained and was statistically superior to placebo at Week 40. The treatment effect was consistent for SiDBP.

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# USPI Section 14: Clinical Studies



TRYVIO consistent **effect in subgroups** and across **measures**

Most of the BP-lowering effect occurred within the first two weeks of treatment with TRYVIO.

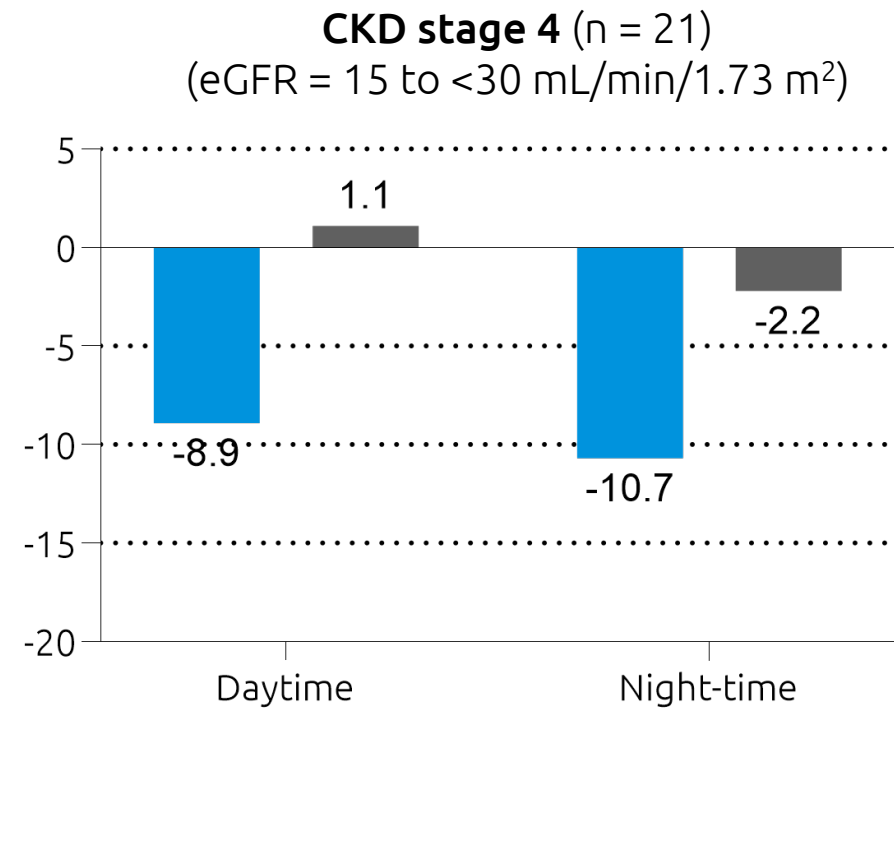
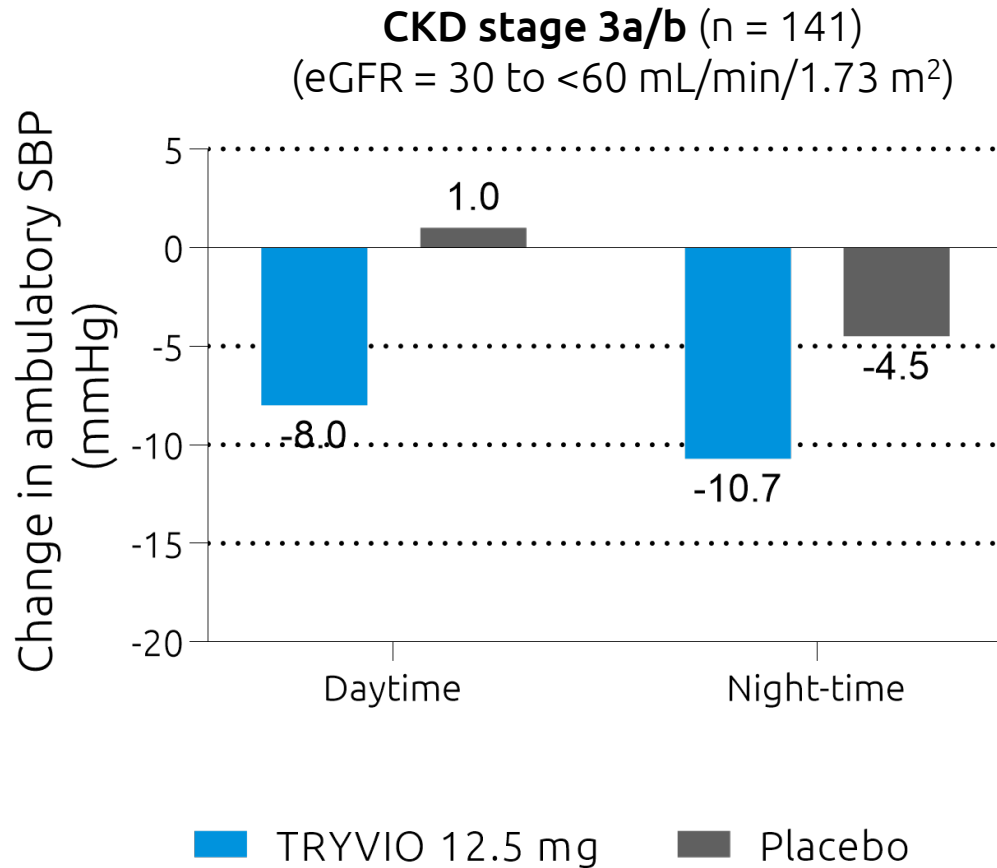
TRYVIO's BP-lowering effect appeared **consistent among subgroups** defined by age, sex, race, BMI, **baseline eGFR, baseline UACR**, medical history of diabetes, and between BP measurement methodologies (uAOBP and **ambulatory BP measurements**).

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# Consistent effect among subgroups: E.g., Patients with chronic kidney disease



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# USPI Section 6: Adverse Reactions

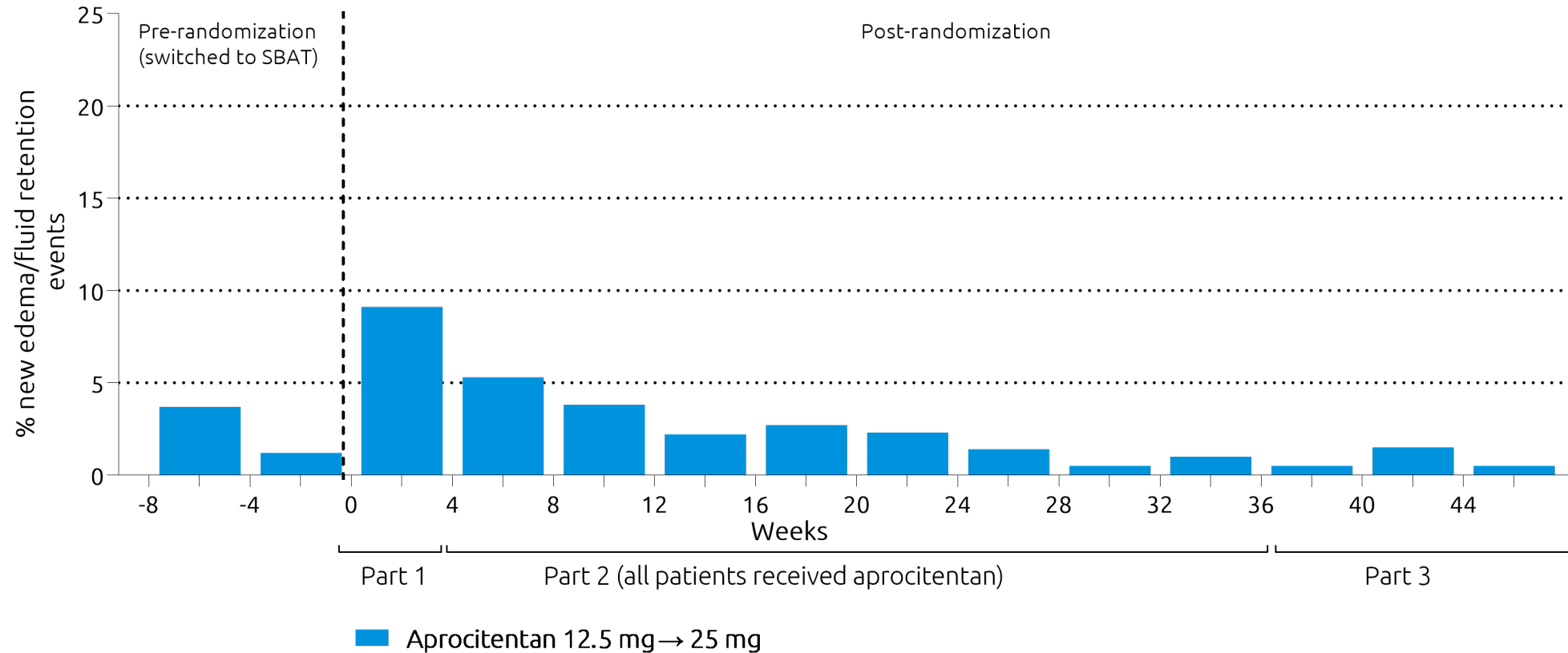
**Table 1 Adverse reactions reported with a frequency of  $\geq 2\%$  in TRYVIO-treated patients and greater ( $\geq 1\%$ ) than in placebo-treated patients during the initial 4-week double-blind placebo-controlled treatment (part 1)**

	<b>12.5 mg N = 243</b>	<b>Placebo N = 242</b>
<b>Adverse Reaction</b>	<b>%</b>	<b>%</b>
Edema/fluid retention	9.1	2.1
Anemia	3.7	0

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# Incidence of edema

Returns to levels observed before randomization 8 weeks after treatment



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# USPI Section 5.2: TRYVIO REMS

## 5.2 TRYVIO REMS

TRYVIO is available only through a restricted program under the TRYVIO REMS because of the risk of embryo-fetal toxicity. For more information, see the TRYVIO REMS (4.1), Warnings and Precautions (5.1), Use in Specific Populations (6.1), and Clinical Studies (7.1).

Important requirements of the TRYVIO REMS include the following:

- Prescribers must be certified with the TRYVIO REMS by enrolling and completing training.

Pharmacies that dispense TRYVIO must be certified with the TRYVIO REMS.

For further information is available at [www.TRYVIOREMS.com](http://www.TRYVIOREMS.com) or 1-866-429-8964.

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“We are eager to provide physicians and patients with a novel medicine working in a new pathway in uncontrolled hypertension that can provide additional blood pressure control”

**Michael Moye**  
**President Idorsia US**

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# Hypertension is the leading modifiable risk factor for early death and disability



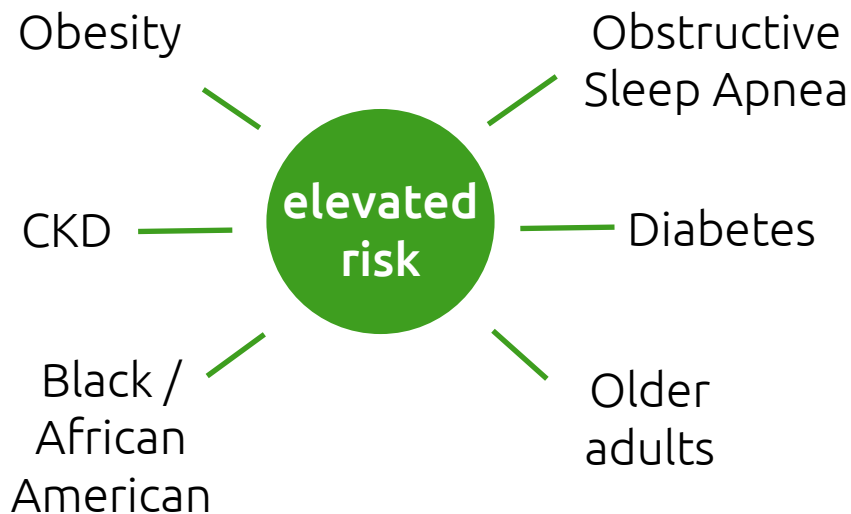
The importance of treating hypertension is well established

The risk of developing uncontrolled hypertension is elevated in certain subgroups of patients

**2-6x**  
Greater Risk

especially for uncontrolled patients at high risk of cardio- and neurovascular events

**5 mmHg reduction in SBP = ~10% reduction in the risk of major cardiovascular events**



Uncontrolled hypertension patients have a **greater risk** for CV events and end-stage renal disease

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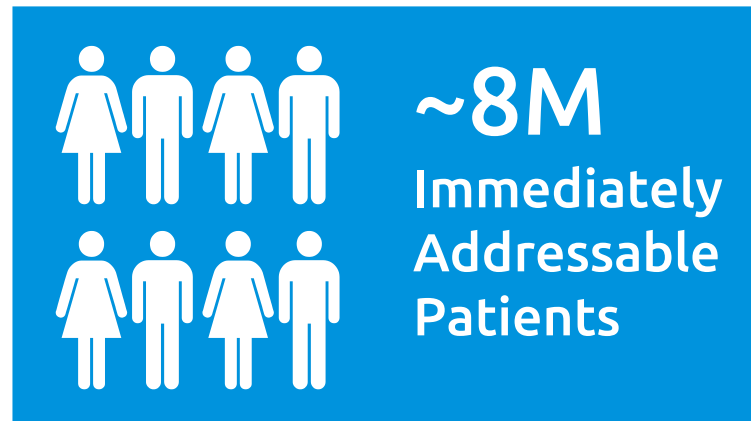
# ~8M patients immediately addressable at launch\* – most with multiple comorbidities



**3.5M Patients**  
on 3 meds for  
hypertension are  
not controlled



**4.6M Patients**  
on 4+ meds for  
hypertension



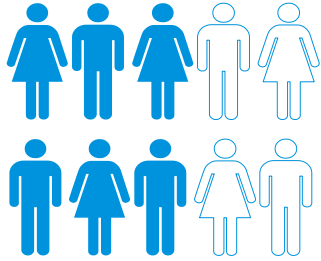
*90% of these patients  
have comorbidities and  
are taking branded meds*

\* in line with Phase 3 criteria

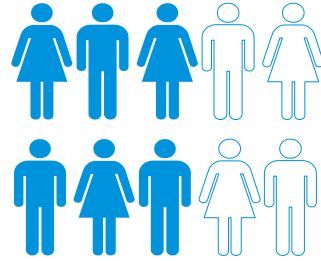
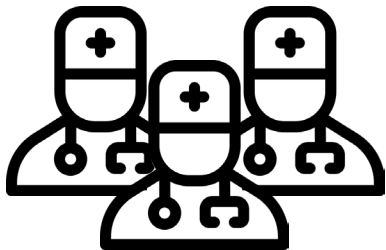
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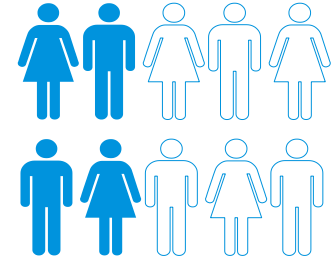
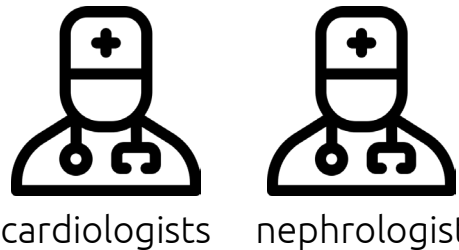
# Prescribers span several specialties – often more than one HCP involved



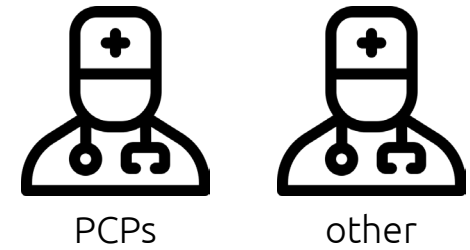
**60% of Patients**  
on 3+ Meds were treated  
by 2 or more HCPs



**50-60% of patients**  
on 3+ Meds were treated  
by cardiologists and  
nephrologists



**30-40% of patients**  
on 3+ Meds were treated  
by primary care physicians  
(PCPs)/other



Source: Komodo claims; 3-Year Dx: Sep'20 - Aug'23; 1-Year Rx: Sep'22 - Aug'23

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# Early dialogues with Payers suggest an overall favorable reaction to TRYVIO clinical profile



Recognize the unmet patient need of uncontrolled hypertension



Favorable reaction to Phase 3 trial design



Perceive efficacy as favorable, highlighting BP differences vs placebo clinically meaningful



Product available through med exception process until the NTM / NDC Blocks removed

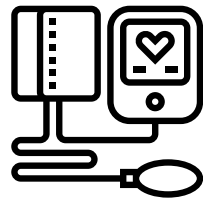
NTM: New To Market; NDC: National Drug Code

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# First to target the endothelin pathway bringing the power of an ERA to systemic hypertension



**Easy** for patients to **use**



**Easy** for HCPs to **prescribe**

...even for **high-risk, frail** population



Broad indication, evidence-based label



Strong and sustained efficacy with good safety and tolerability



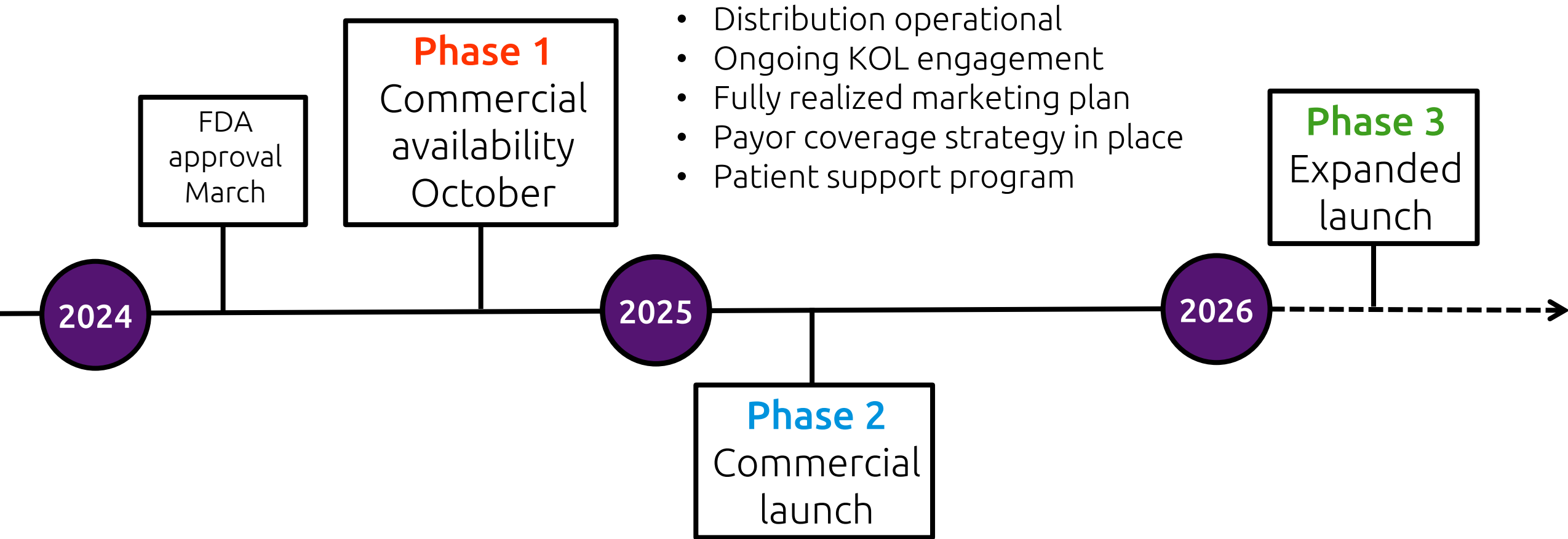
Once-daily oral, single dose

Idorsia makes aprocitentan available in the US under the tradename TRYVIO. In addition, aprocitentan is approved throughout the European Union and in the UK under the tradename JERAYGO. Marketing authorization applications are under review in Canada and Switzerland.



**TRYVIO™**  
(aprocitantan) 12.5mg tablets

# US launch



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“The approval of TRYVIO heralds a new era of endothelin research beyond hypertension, where we intend to investigate the utility of aprocitentan for first-in-class applications in new indications.”

**Martine Clozel**  
**Chief Scientific Officer**

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# JERAYGO™ (aprocitentan) for resistant hypertension in the EU

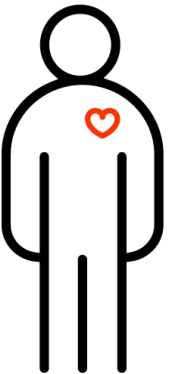
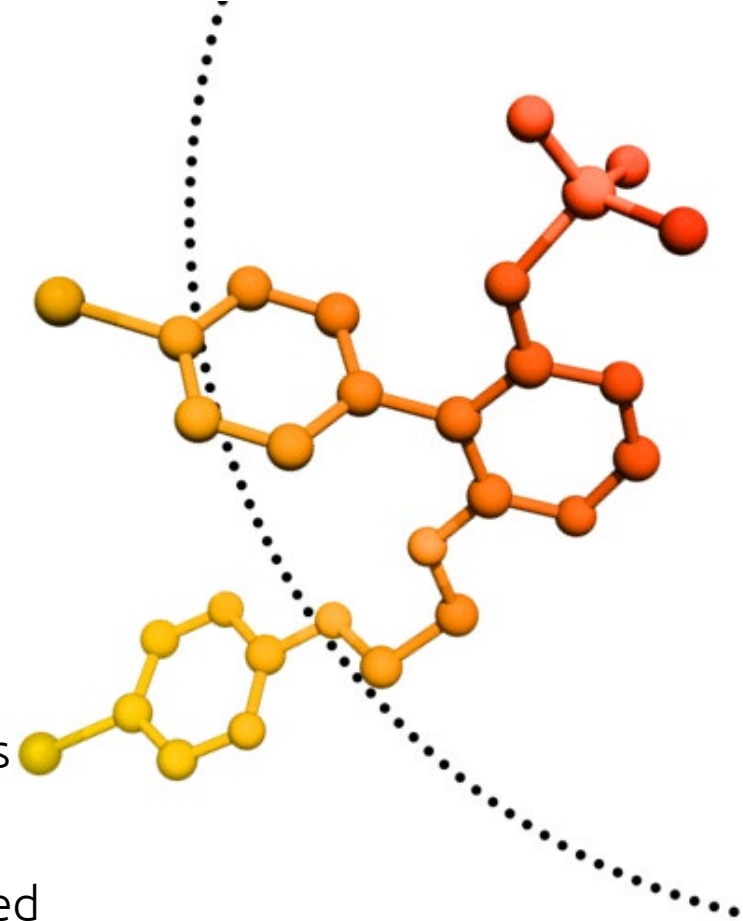
New mode of action in systemic hypertension



**JERAYGO™**  
aprocitentan

## Current status

- In June 2024, Idorsia received approval from the European Commission (EC) for JERAYGO™ (aprocitentan) as the first and only endothelin receptor antagonist (ERA) for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products.
- The recommended dose is 12.5 mg orally once daily. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter blood pressure (BP) control.



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# Lucerastat in Fabry disease

Lucerastat is investigational, in development and not approved or marketed in any country.

# Fabry disease



Fabry disease is a **rare inherited lysosomal storage disorder** in which a particular **lipid** (a fat-like substance) can't be broken down by the body, leading to its build-up in the cells of the body organs which results in cell and organ damage

Fabry disease is often undetected or misdiagnosed

As the disease is progressive, **early diagnosis is essential** to manage the symptoms as soon as possible and reduce the risk of developing serious complications

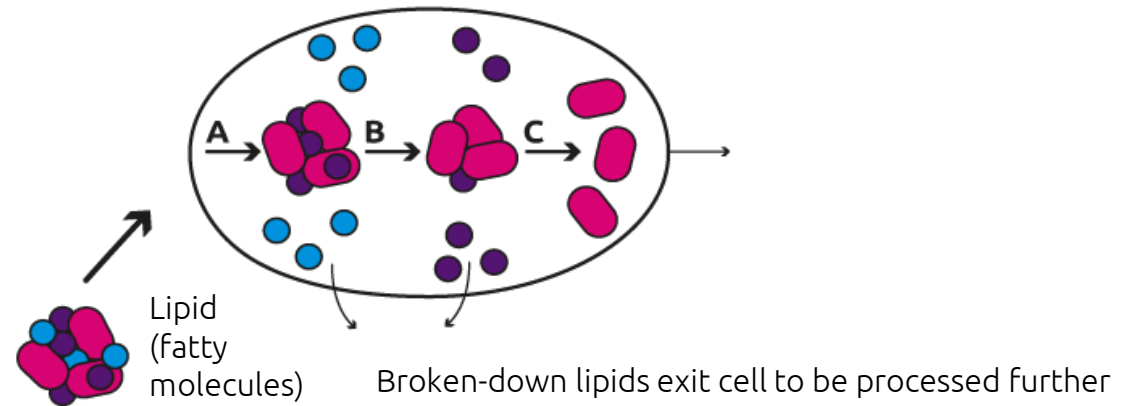


# What is the role of lipids in the body?

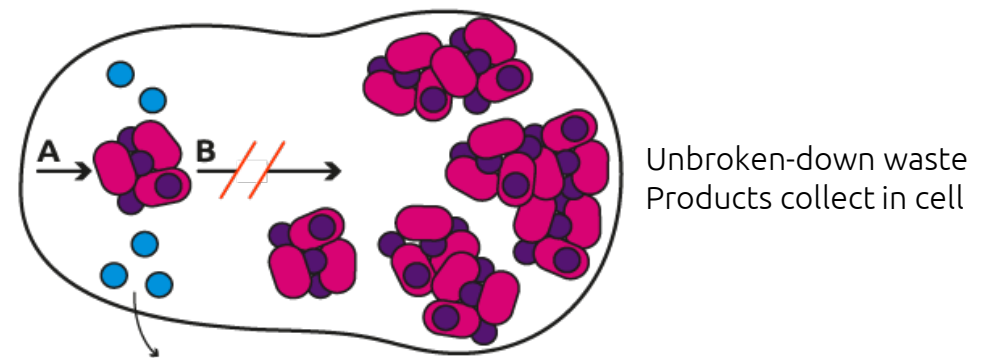
- Lipids are fat-like substances such as fatty acids, oils, waxes and steroids. A well-known example is cholesterol
- Lipids are stored naturally in the body's cells and organs and are vital to their healthy functioning
- Normally, the body is able to process lipids effectively, which keeps them within healthy levels

## What happens in patients with lysosomal storage disorders?

Normal breakdown of lipids

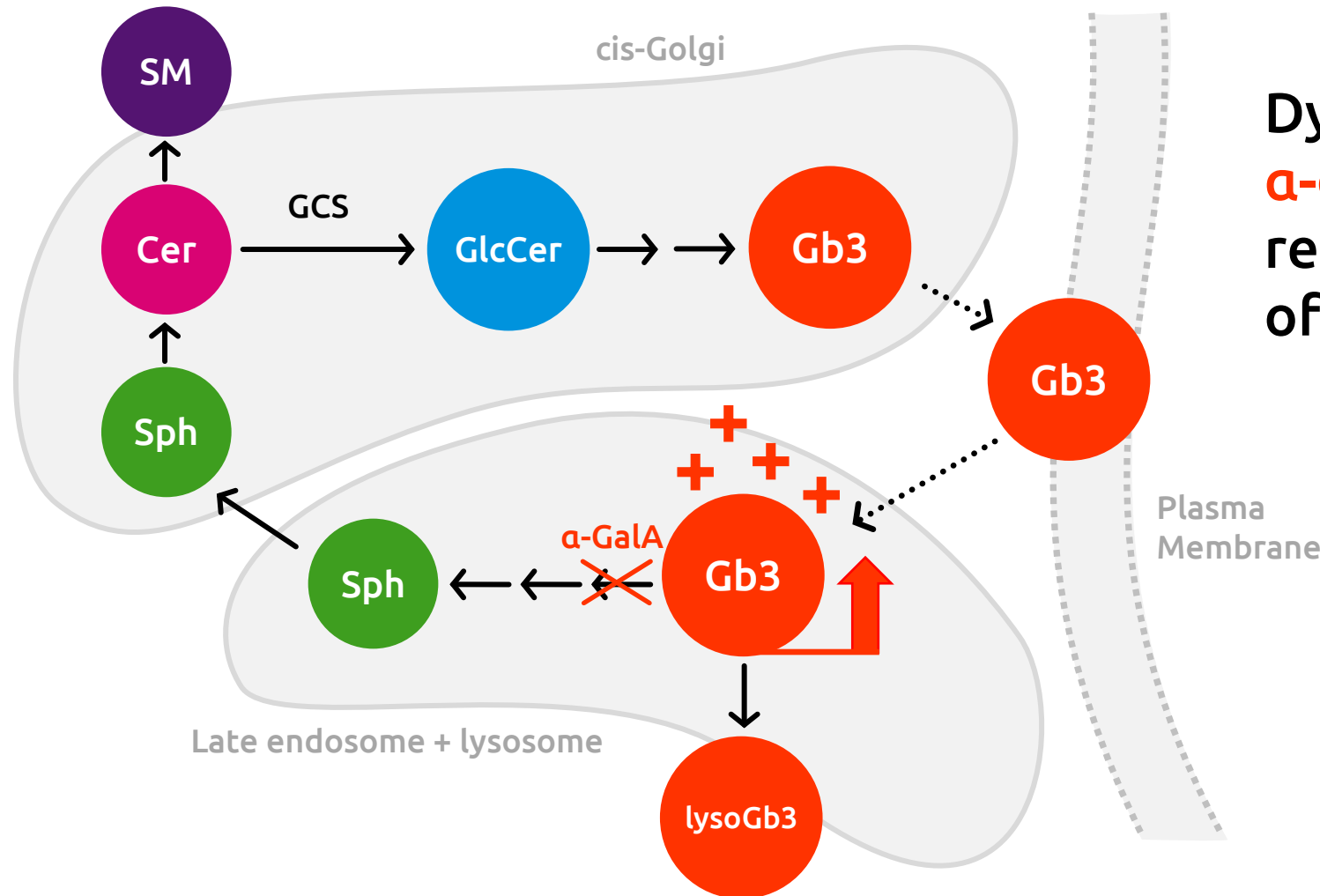


When enzyme to break down lipid is deficient



# Fabry disease

## Biochemical mechanism



Dysfunctional or absent  **$\alpha$ -galactosidase A** results in accumulation of **Gb3** in various organs

<b>Cer</b>	ceramide
<b>GCS</b>	glucosylceramide synthase
<b>GlcCer</b>	glucosylceramide
<b>Gb3</b>	globotriaosylceramide
<b>lysoGb3</b>	globotriaosylsphingosine
<b><math>\alpha</math>-GalA</b>	$\alpha$ -galactosidase A
<b>SM</b>	sphingomyelin
<b>Sph</b>	sphingosine

# Inheritance pattern in Fabry disease

## X-linked recessive genetic disease

- GLA gene mutation results in **defective lysosomal enzyme  $\alpha$ -GalA**
- In turn, this results in **Gb3 accumulation**



## Random X-inactivation in Fabry female 'carriers': both genders affected



Male have generally classical phenotype

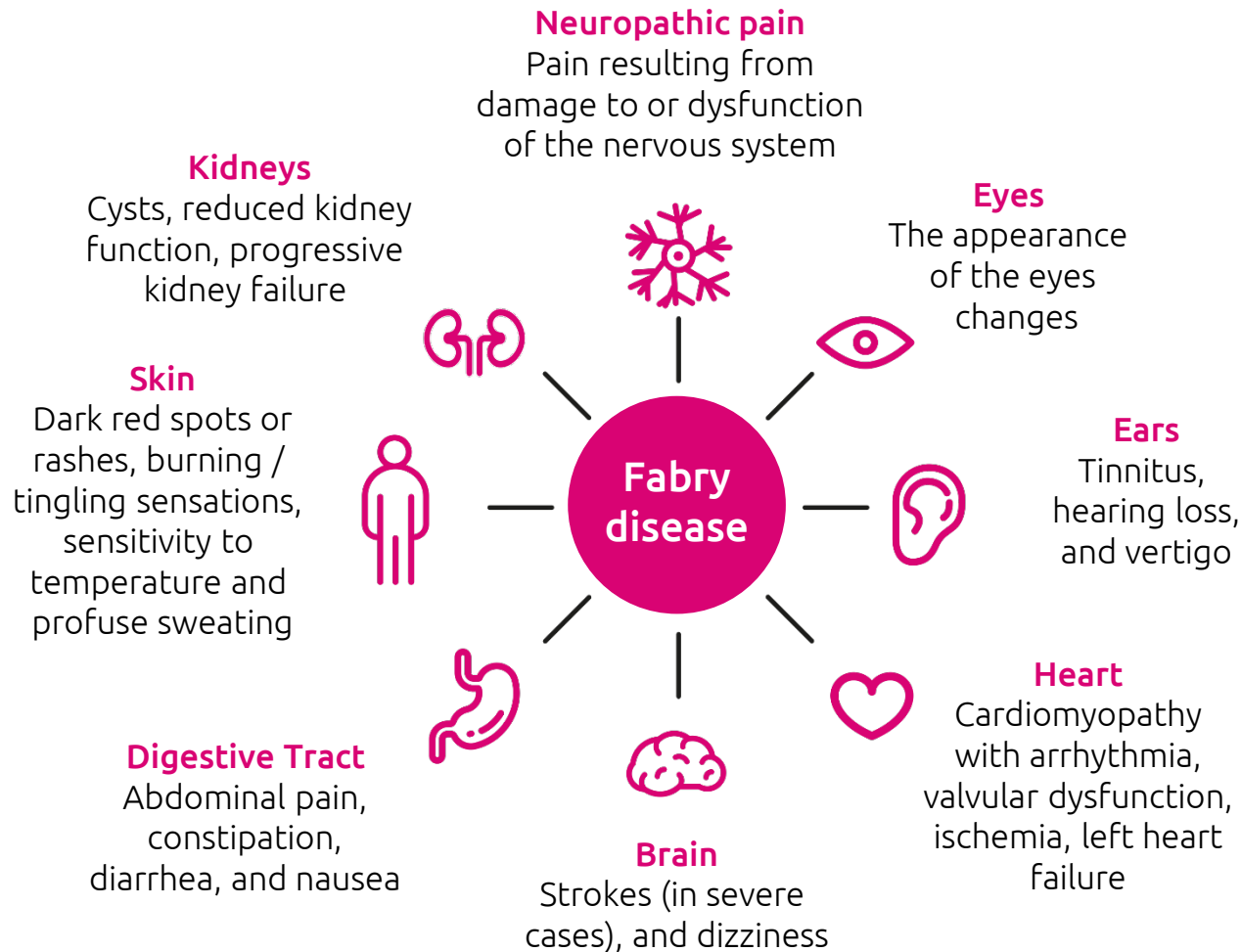


Females have higher residual level enzyme and

- are affected later
- progress slower
- have more variable phenotype

# Clinical manifestations of Fabry disease

## Large spectrum of clinical, heterogeneous manifestations



- **Gradually progressing** in severity from childhood to adulthood
- **Major impact on quality of life**
- **Slow progressive damage** to vital organs over decades
- **Earlier death**

# Diagnosis of Fabry disease

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## Clinical symptoms

Neuropathic pain, GI, hearing loss, hypohydrosis

## Clinical events

Stroke, cardiac and renal events

## Pedigree analysis

Family members (between children and parents)



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## Enzyme assay

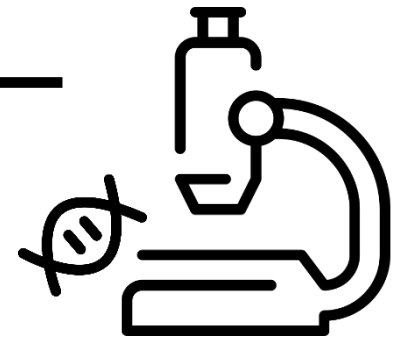
Leukocyte  $\alpha$ -GalA

## Genotyping

>830 mutations

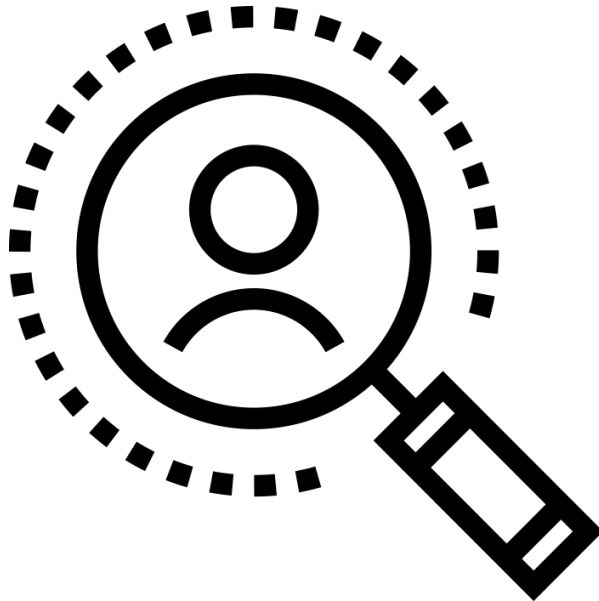
## Biomarkers

Gb3 in plasma and urine



# Epidemiology of Fabry disease

**Patients diagnosed with Fabry disease**  
in 7 major markets (US, EU-4 and UK, and  
Japan) in 2020 and forecasted out to 2034



	2020	2034
<b>EU-4 + UK</b>	<b>6,251</b>	<b>8,248</b>
UK	1,340	1,769
Italy	1,325	1,748
Germany	2,000	2,638
France	800	1,056
Spain	786	1,037
<b>US</b>	<b>8,288</b>	<b>11,710</b>
<b>Japan</b>	<b>1,658</b>	<b>1,778</b>
<b>Total</b>	<b>16,197</b>	<b>21,736</b>

Delveinsight, Fabry Disease – Market Insight, Epidemiology and Market Forecast – 2034 (March 2025)

# Current therapies in Fabry disease

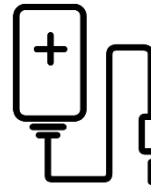
No curative therapy

Symptomatic treatments not satisfactory

Etiological therapies limited

## Enzyme replacement therapy

- Fabrazyme (agalsidase beta) (US and EU)
- Replagal (agalsidase alfa) (EU only)
- i.v. infusion, bi-weekly
- Immunogenicity
- Partial efficacy

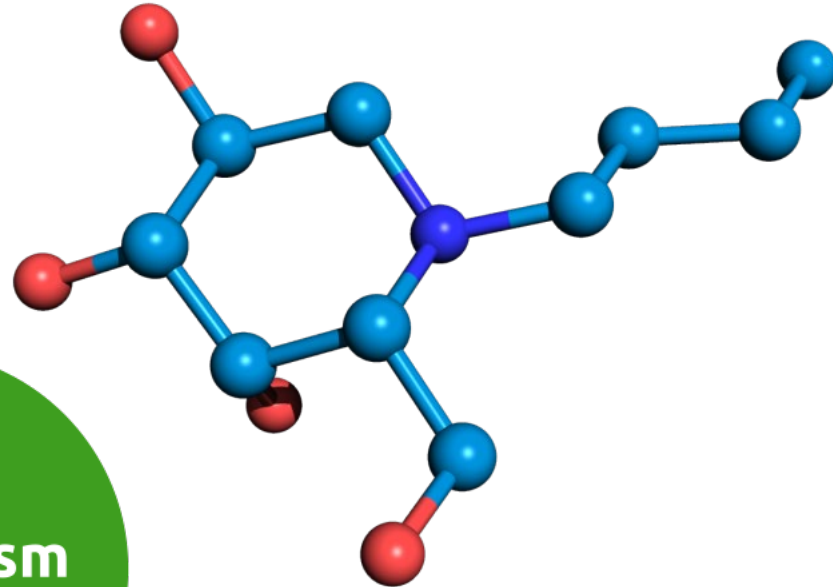


## Chaperone therapy

- Galafold (migalastat) for patients with amenable mutation
- 1 capsule orally, fasted, every other day



# Lucerastat in Fabry disease



**Novel  
mechanism  
of action**



## **Bioavailability**

Orally available, highly soluble small molecule with rapid and complete absorption



## **Tissue penetration**

Access to most tissues, including peripheral and central nervous system



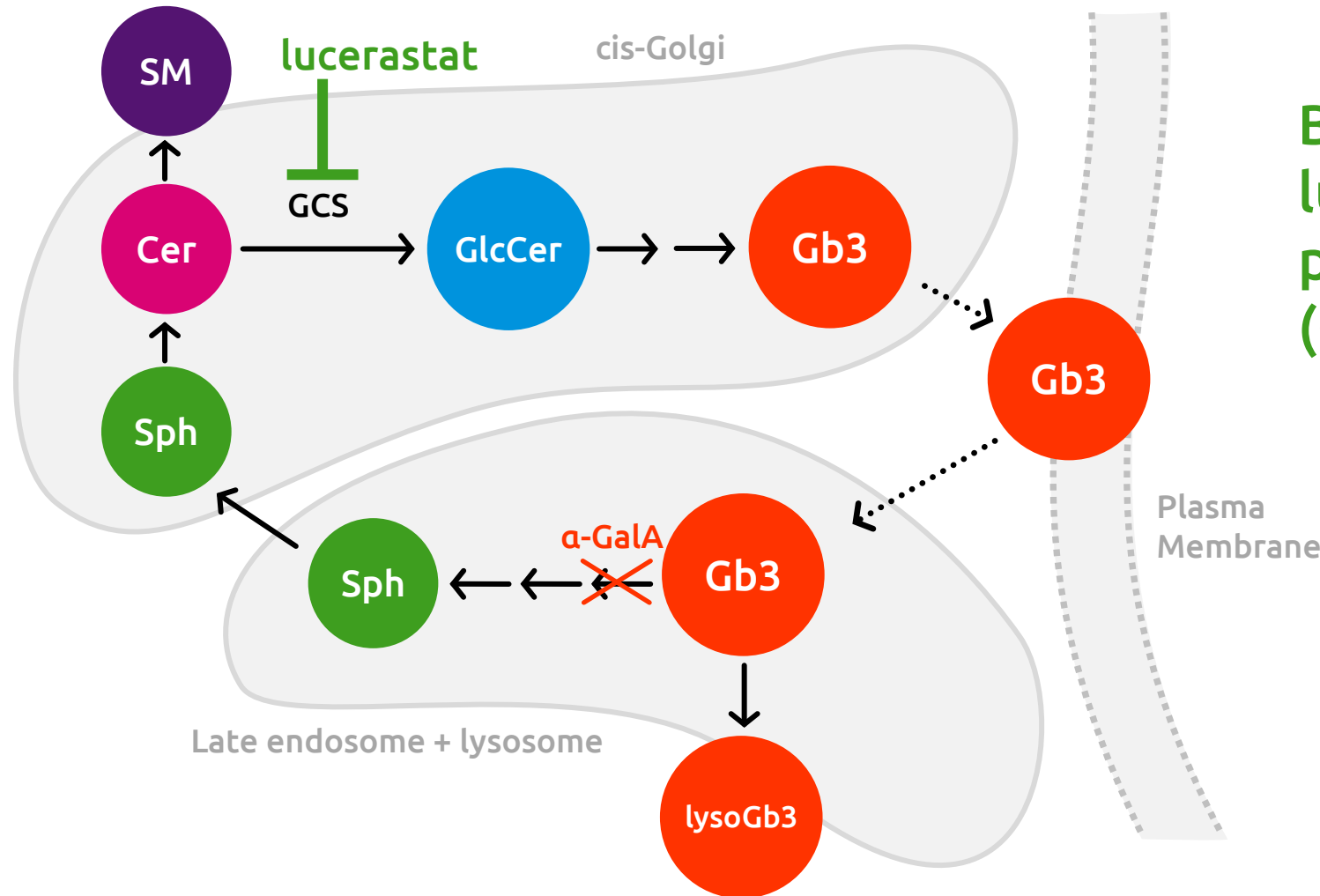
## **For all mutations**

Potential to treat all Fabry patients irrespective of the underlying enzyme mutation



# Lucerastat in Fabry disease

Mode of action



By inhibiting GCS, lucerastat reduces the precursor of Gb3 (GlcCer) and Gb3 itself

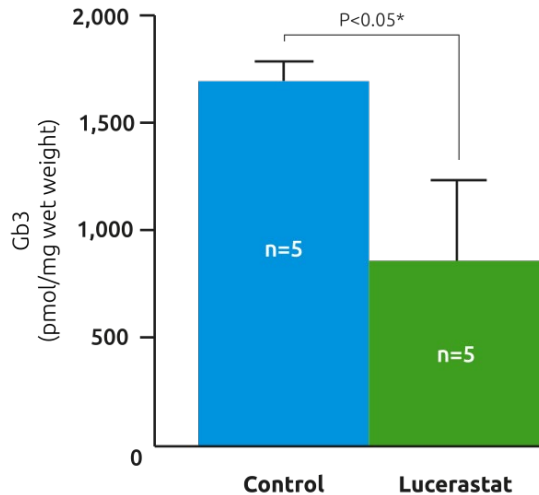
<b>Cer</b>	ceramide
<b>GCS</b>	glucosylceramide synthase
<b>GlcCer</b>	glucosylceramide
<b>Gb3</b>	globotriaosylceramide
<b>lysoGb3</b>	globotriaosylsphingosine
<b><math>\alpha</math>-GalA</b>	$\alpha$ -galactosidase A
<b>SM</b>	sphingomyelin
<b>Sph</b>	sphingosine

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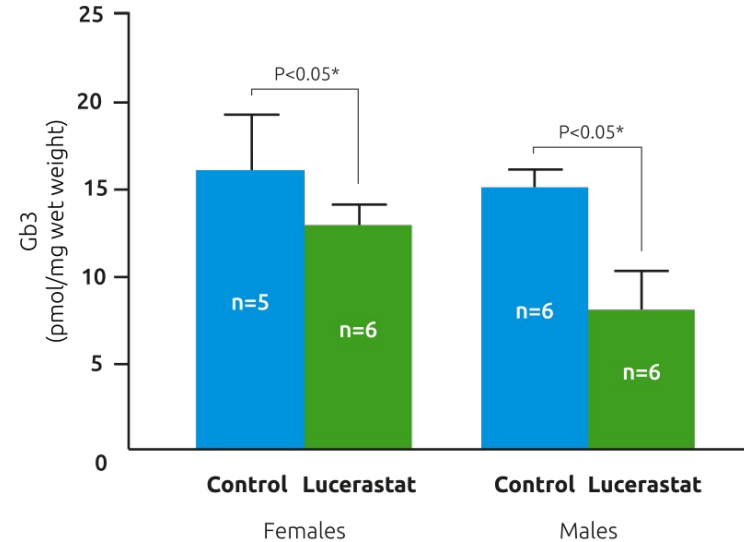
# Lucerastat has the potential to reduce Gb3 levels in target organs



Dorsal root ganglia



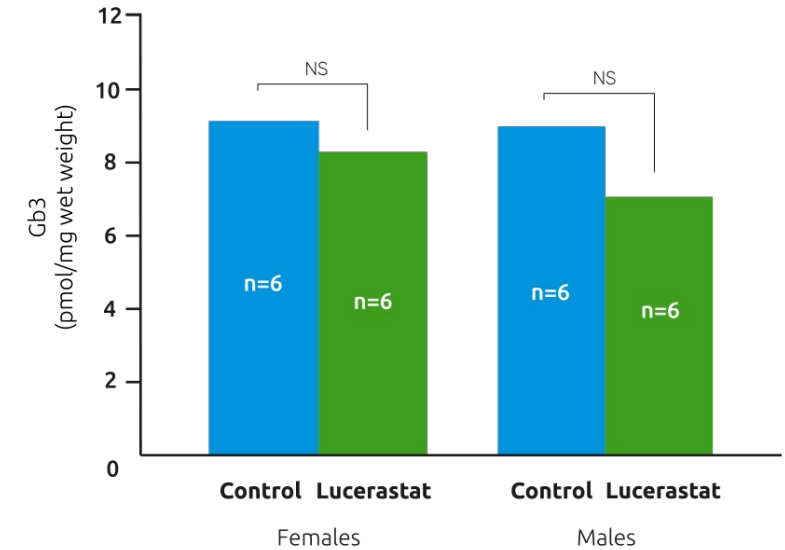
Kidneys



\*ANOVA with Bonferroni's multiple testing correction.



Heart



Male and female Fabry mice treated for 20 weeks with lucerastat at 1200 mg/kg/day as food admix and compared to non-treated controls

Lucerastat is investigational, in development and not approved or marketed in any country.

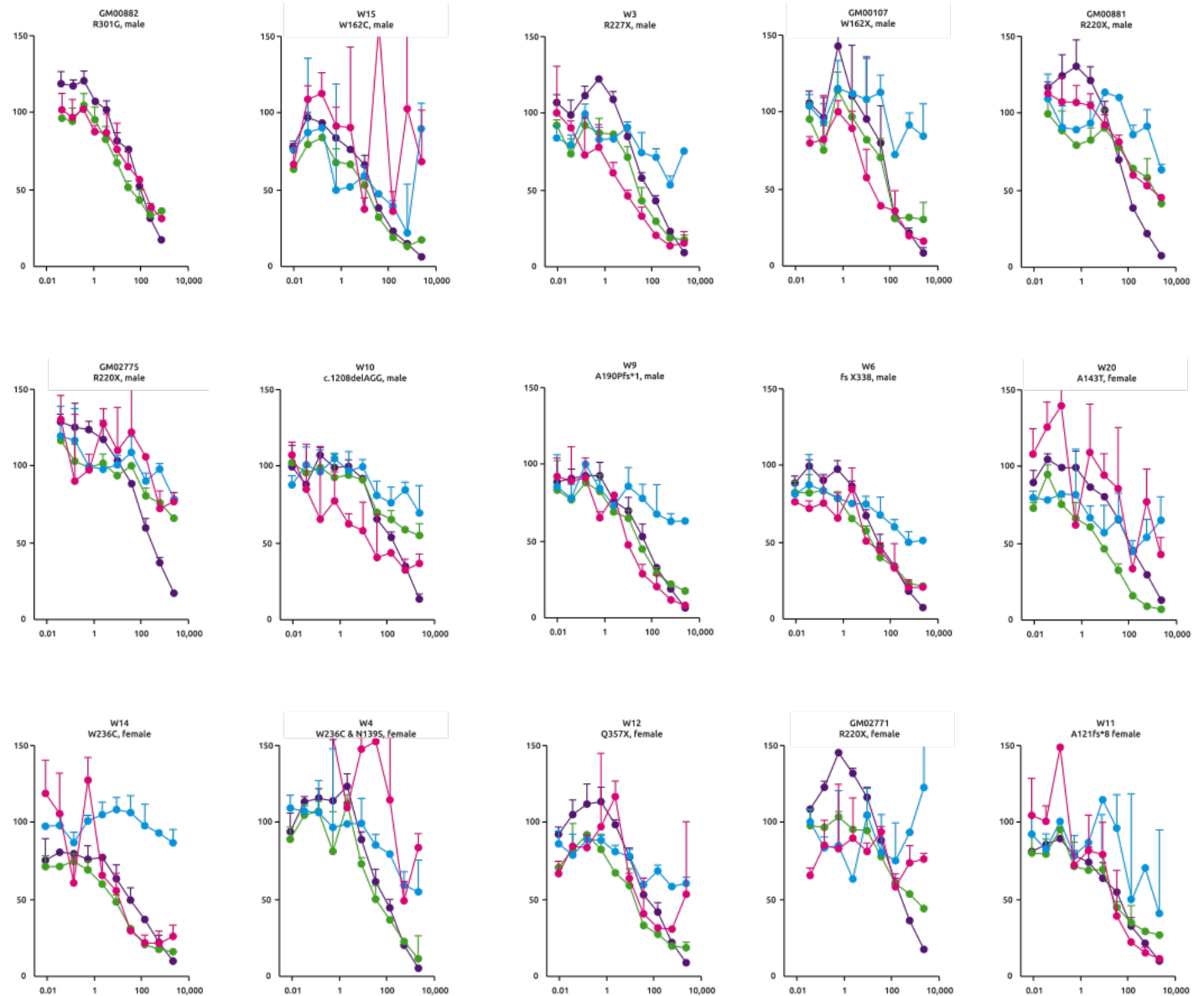
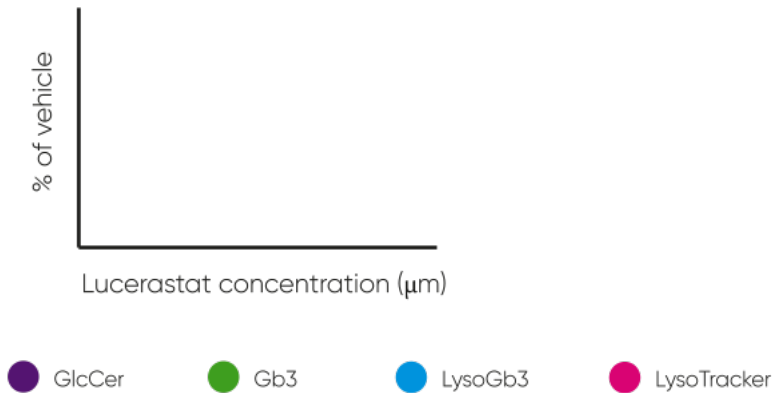
Idorsia data on file. Data collected in animal models does not necessarily predict human clinical effect.

# Mutation sensitivity

Proven reduction in Gb3 in all tested mutation types

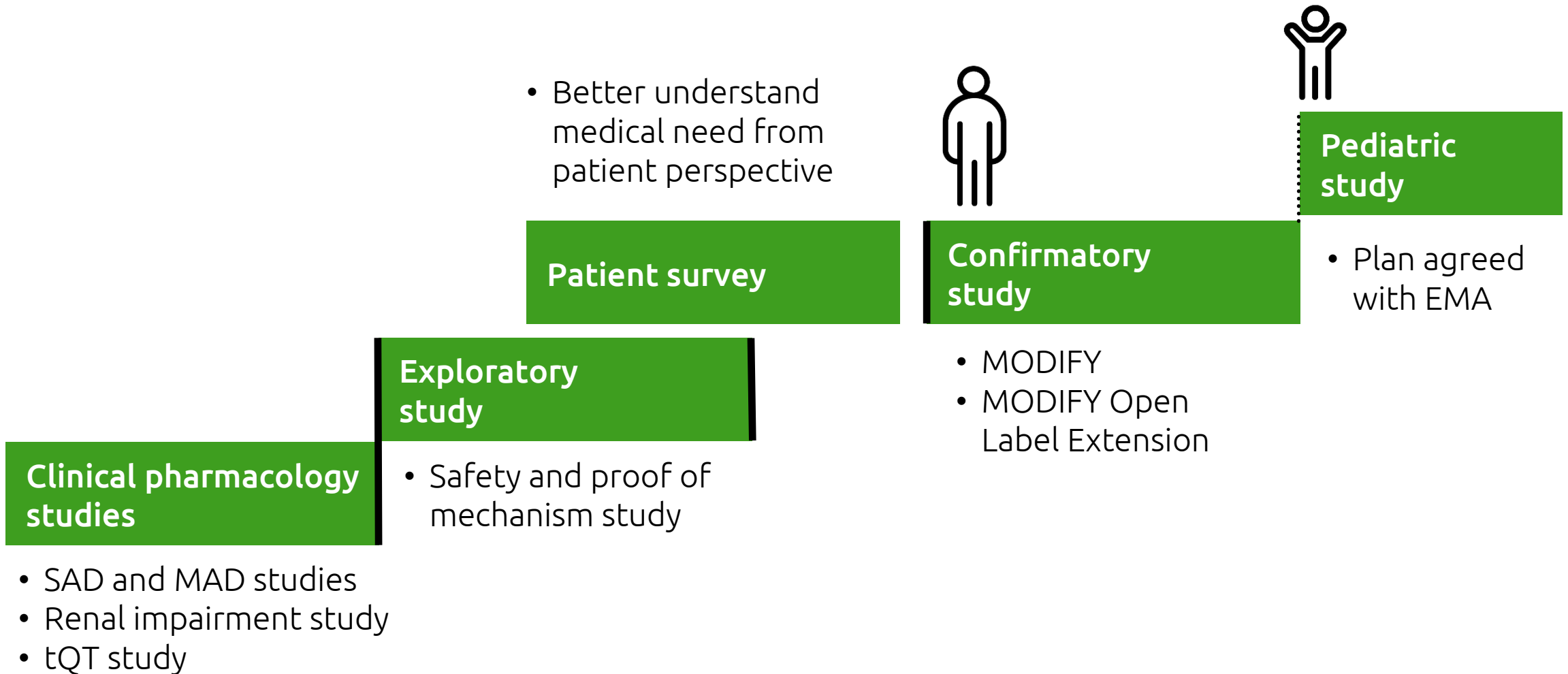
Effect of different concentrations of lucerastat on GlcCer, Gb3, lysoGb3 lipid levels, and LysoTracker staining in cultured Fabry patients' fibroblasts after 9 days of treatment.

Each point is the mean of duplicates ( $\pm$ SD)



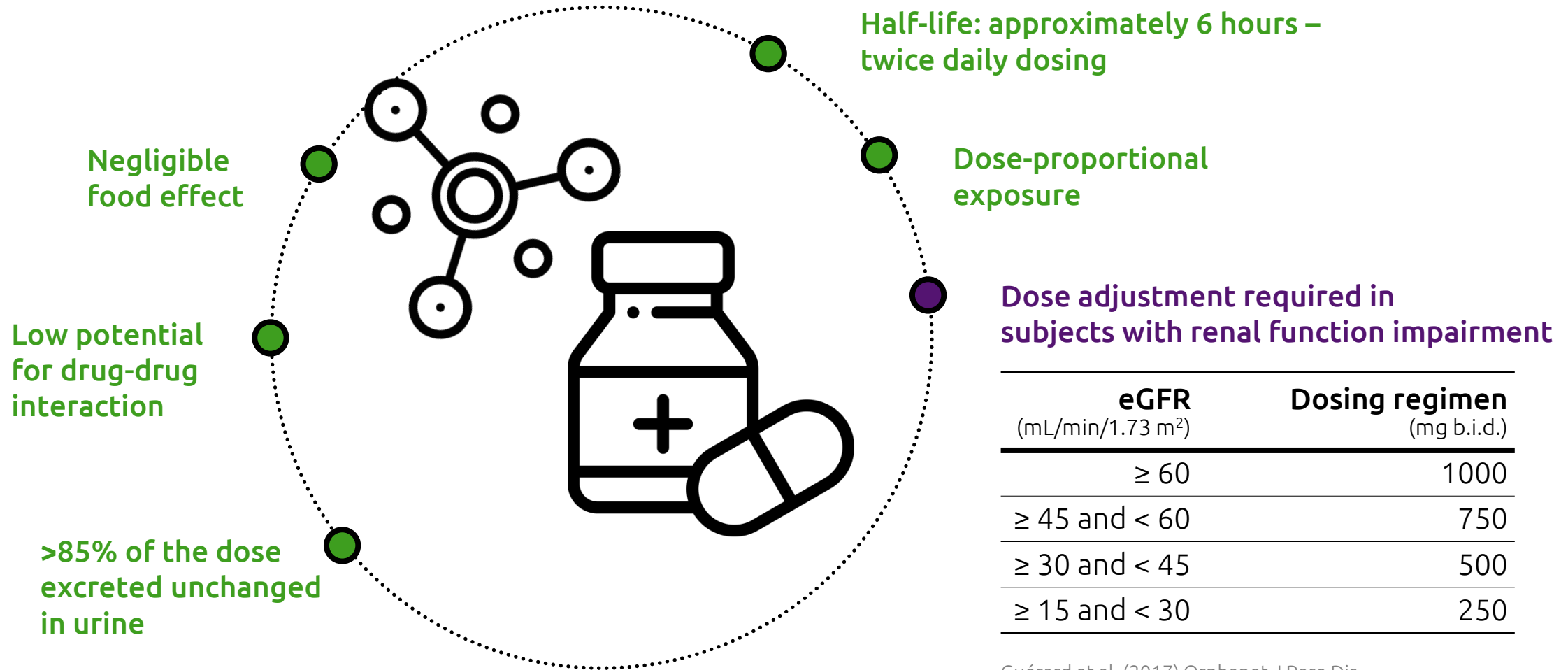
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# Lucerastat clinical development plan



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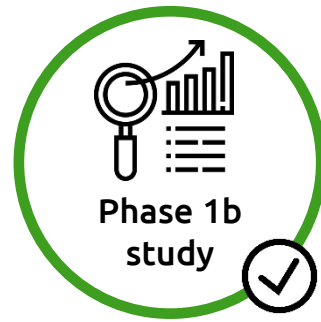
# Lucerastat clinical pharmacology



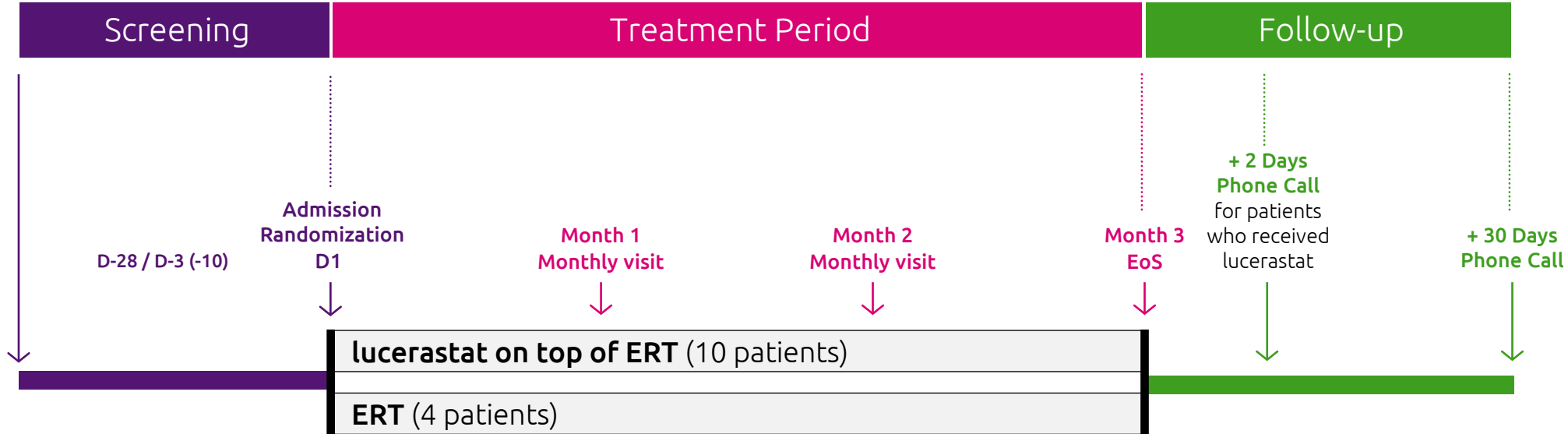
Lucerastat is investigational, in development and not approved or marketed in any country.

Guérard et al. (2017) Orphanet J Rare Dis  
Guérard et al. (2017) J Clin Pharmacol  
Guérard et al. (2018) Clin Pharmacol Ther

# Lucerastat exploratory study design

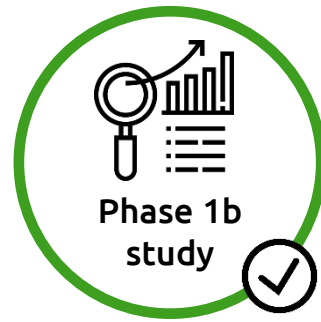


**Prospective, single-center, open-label, randomized,** study in 14 male/female adult patients with Fabry disease receiving enzyme replacement therapy (ERT)



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# Lucerastat exploratory study



## Primary objective

- **To assess the safety and tolerability** of lucerastat 1000 mg b.i.d. for 12 weeks

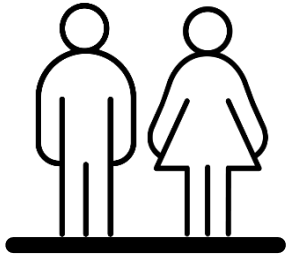
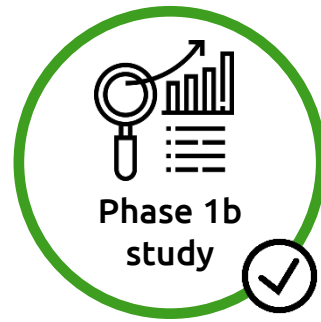
## Secondary objectives

- To investigate the effect of lucerastat on plasma biomarker levels following a 12-week treatment
- To assess the effect of lucerastat on renal and cardiac function
- To determine the 12-hour pharmacokinetic profile of lucerastat at steady state
- To identify metabolites in plasma

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# Lucerastat exploratory study

## Patient demographics

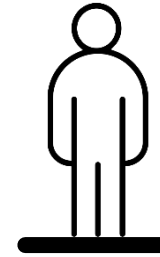


### Lucerastat group

- 6 females, 4 males
- Mean age (SD): 47.7 (15.0), range from 18 to 67
- Mean ERT duration in years (SD): 4.5 (2.6)

### Medical history:

- All patients had comorbidities, most of them manifestations of Fabry disease
- None of these affected eligibility for the study
- Overall balanced between groups



### Control group

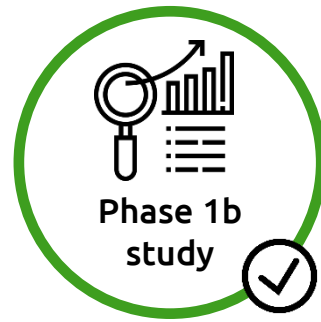
- 4 males
- Mean age (SD): 39.8 (19.1), range from 21 to 62
- Mean ERT duration in years (SD): 6.3 (4.2)

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# Lucerastat exploratory study

## Safety results



**Lucerastat was safe and well tolerated in patients with Fabry disease over 12 weeks on top of ERT**

### **One Serious Adverse Event, unrelated to lucerastat:**

Re-occurrence of atrial fibrillation in a patient with underlying hypertrophic cardiomyopathy

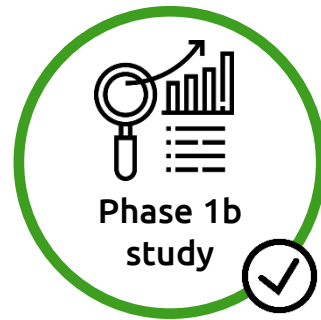
**No specific pattern** in the nature and distribution of Treatment-Emergent Adverse Events

**No trends for changes** from baseline in:  
Vital signs, body weight, ECG recordings, clinical laboratory parameters

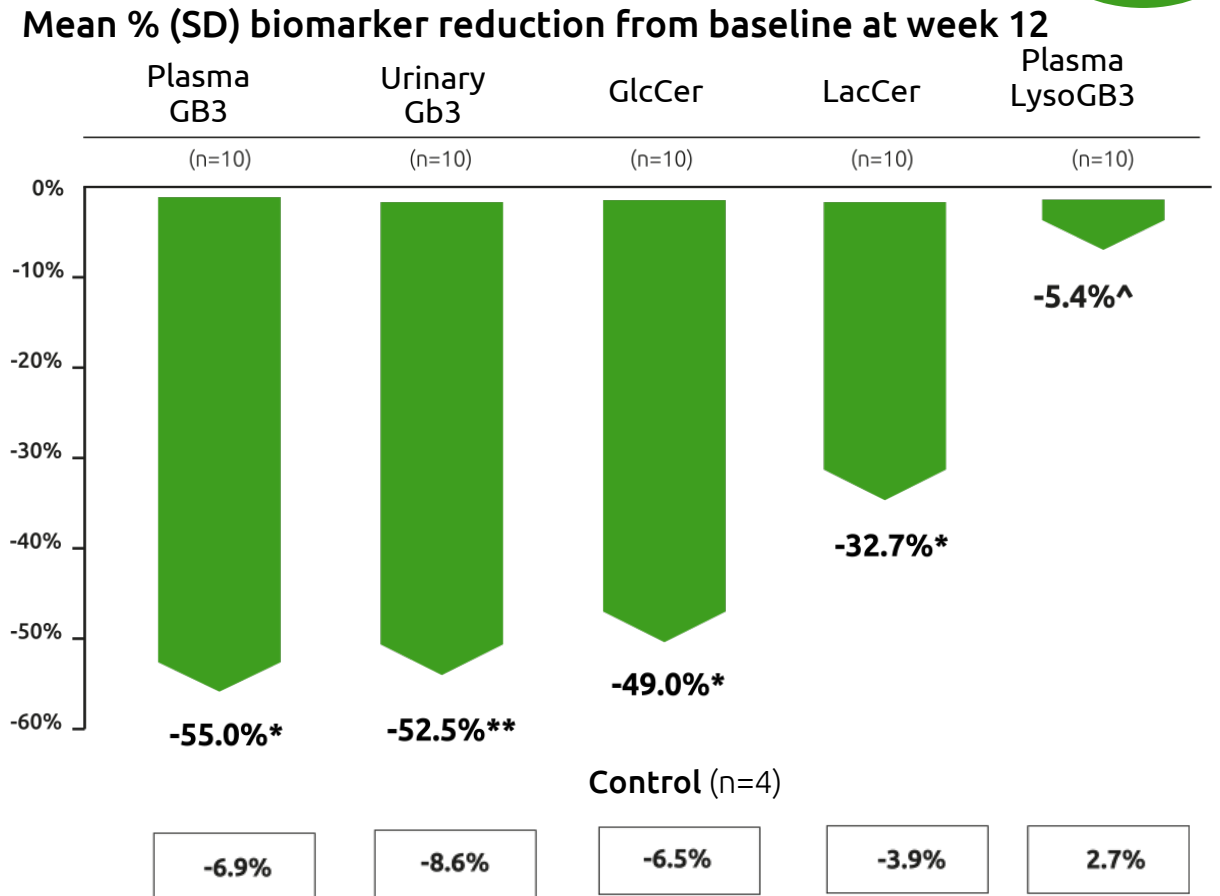
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# Lucerastat exploratory study

Results: rapid and additional reduction in Gb3 when added to enzyme replacement therapy



- ✓ **Lucerastat was safe and well tolerated** in patients with Fabry disease over 12 weeks on top of ERT
- ✓ **Pharmacokinetic findings consistent** with previous studies in healthy subjects
- ✓ **Proof of mechanism achieved with lucerastat:** Lucerastat significantly reduced Fabry disease-elevated Gb3 and other relevant biomarkers



\*P<0.0001, \*\*statistical significance not calculated, ^non-significant

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# Fabry patients survey

## Goals

**Better understand** patients' disease and needs from the patient perspective

1

**Investigate key aspects** of Phase 3 study MODIFY with respect to symptoms: neuropathic pain and gastrointestinal symptoms

2

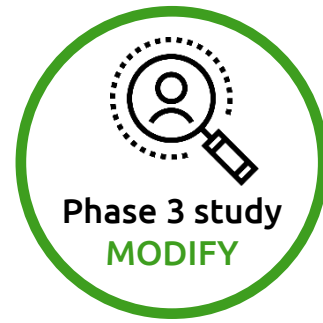
**Complement existing information/data** from the literature

3

### **In addition, collect information on:**

- Use of enzyme replacement therapy (ERT)
- Impact on daily life
- Participation in clinical trials

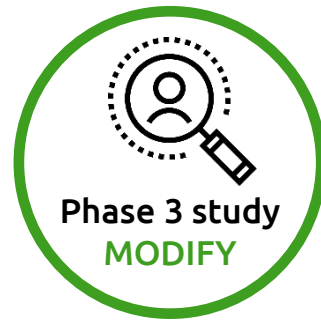
# Designing the confirmatory study: MODIFY



- **Informed design** based on patients survey
- **Development of endpoint measurement** – neuropathic pain, based on Brief Pain Inventory instrument, modified for Fabry's neuropathic pain according to FDA guidelines for PRO
- **Development and validation of electronic tool** to collect pain and gastro-intestinal daily data
- **Input from patient organization and from specialists**
- **Input from regulatory agencies including FDA,** and in Europe through scientific advice and the VHP procedure

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# MODIFY: Objectives



## Primary objective

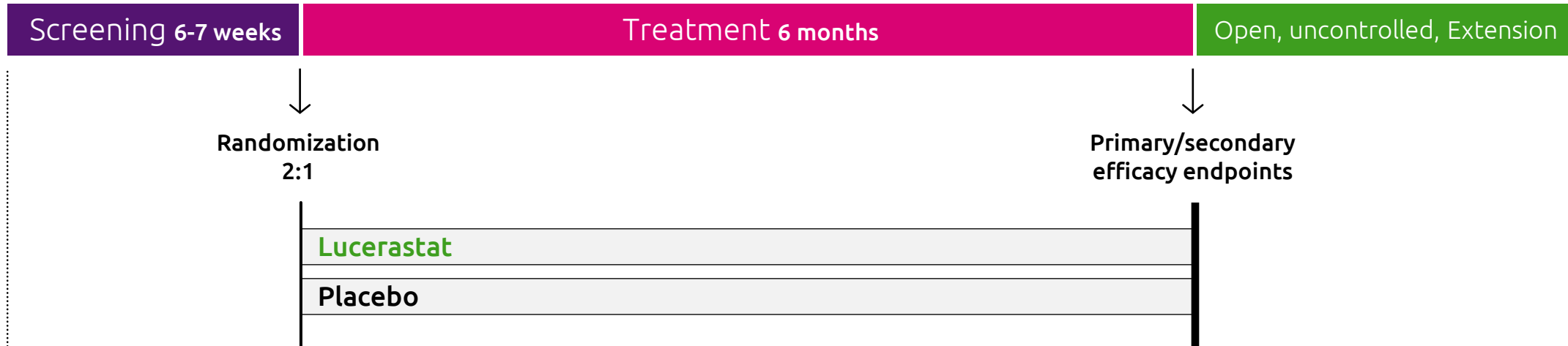
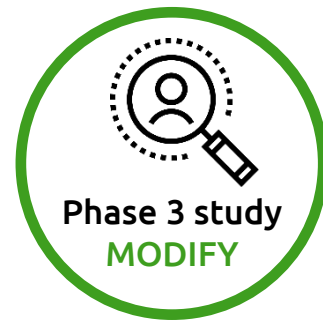
- **To determine the effect of lucerastat on neuropathic pain** in patients with Fabry disease

## Secondary objectives

- **To determine the effect of lucerastat on gastro-intestinal symptoms** (abdominal pain and diarrhea) in patients with Fabry disease and GI symptom(s) at baseline
- **To confirm the effect of lucerastat on biomarkers** of Fabry disease
- **To determine the safety and tolerability** of lucerastat in patients with Fabry disease

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# MODIFY: Study design



## Site visits

Screening, Randomization, Months 1, 2 (phone), 3, 4 (phone), 5, 6 + 2 FU visits (phone)

## Stratification by

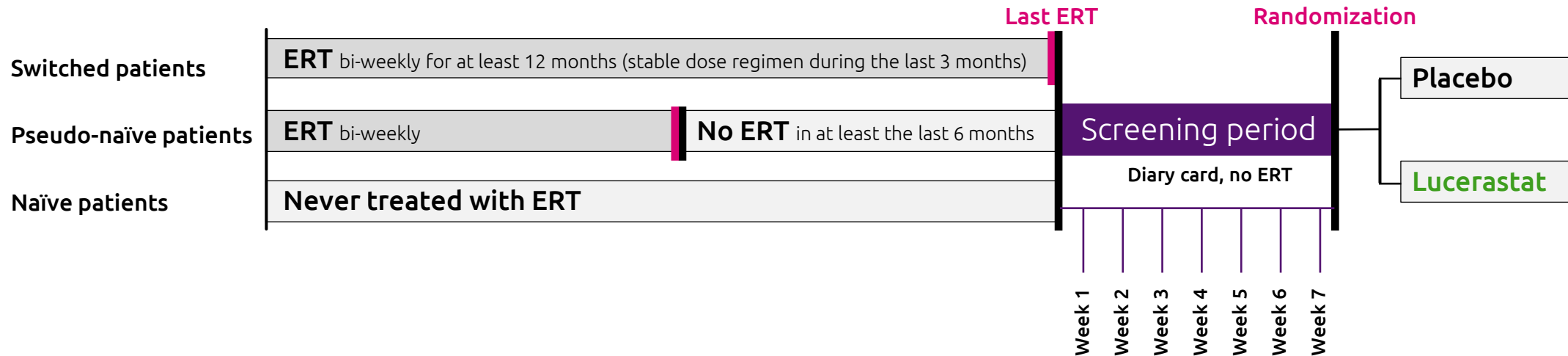
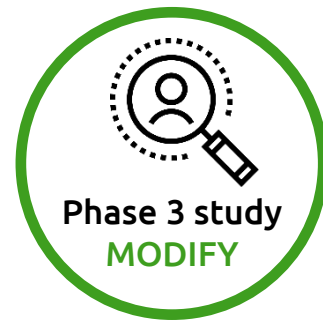
- Sex
- ERT use (on ERT at screening vs never treated/previously treated)

## Lucerastat dose

- 1000 mg b.i.d.
- Adjusted in subjects with moderate renal failure

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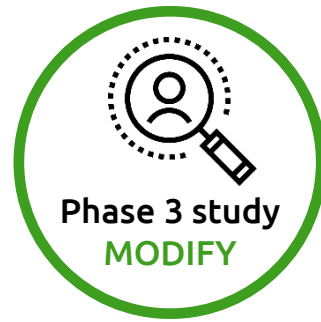
# MODIFY: Patient population



- Confirmed Fabry disease – presence of at least 1 mutation in GLA (the gene coding for  $\alpha$ -galactosidase A) as measured with genetic test
- Neuropathic pain in the last 3 months preceding the screening period
- Three options for ERT status at baseline

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# MODIFY: Study endpoints



## Primary efficacy endpoint

- The primary efficacy endpoint is a response to study treatment on neuropathic pain, defined as a reduction from baseline to Month 6 of at least 30% in the “modified” BPI-SF3 score of “neuropathic pain at its worst in the last 24 hours”.

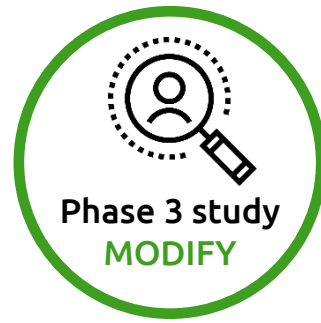
## Secondary efficacy endpoints

- Change from baseline to Month 6 in the average daily 11-point Numerical Rating Scale (NRS-11) score of “abdominal pain at its worst in the last 24 hours” in subjects with GI symptoms at baseline.
- Change from baseline to Month 6 in the number of days with at least one stool of a Bristol Stool Scale (BSS) consistency Type 6 or 7 in subjects with GI symptoms at baseline;
- Change from baseline to Month 6 in plasma globotriaosylceramide (Gb3).

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# MODIFY: Results



- October 2021 MODIFY did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo
- Substantial and consistent reduction of plasma Gb3 – confirming the pharmacological activity of lucerastat
- Based on historical patient data, mean estimated glomerular filtration rate (eGFR) – a measure of kidney function – was decreasing prior to the study. During the 6 months of the MODIFY study, eGFR increased in both arms of the study (as measured by the eGFR slope), with a slightly higher increase observed in the lucerastat group than in the placebo group.
- Lucerastat was well tolerated
- Lucerastat will therefore be further characterized in the Open label extension (OLE) study

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# MODIFY: Open label extension study

- To determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical effects on renal and cardiac function in adult patients with Fabry disease over an additional period of up to 72 months
- October 2022: Interim analysis of the OLE study – all patients continuing in the study have now been treated with lucerastat for at least 12 months
- The analysis corroborated the long-term effect on the reduction of plasma Gb3 and showed that the signal seen on kidney function after 6 months of treatment is still observed after the longer treatment duration, supporting a potential positive long-term effect on kidney function
- The analysis also showed a safety and tolerability profile consistent with that observed during the 6-month randomized treatment period

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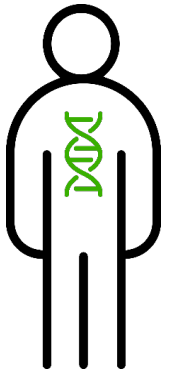
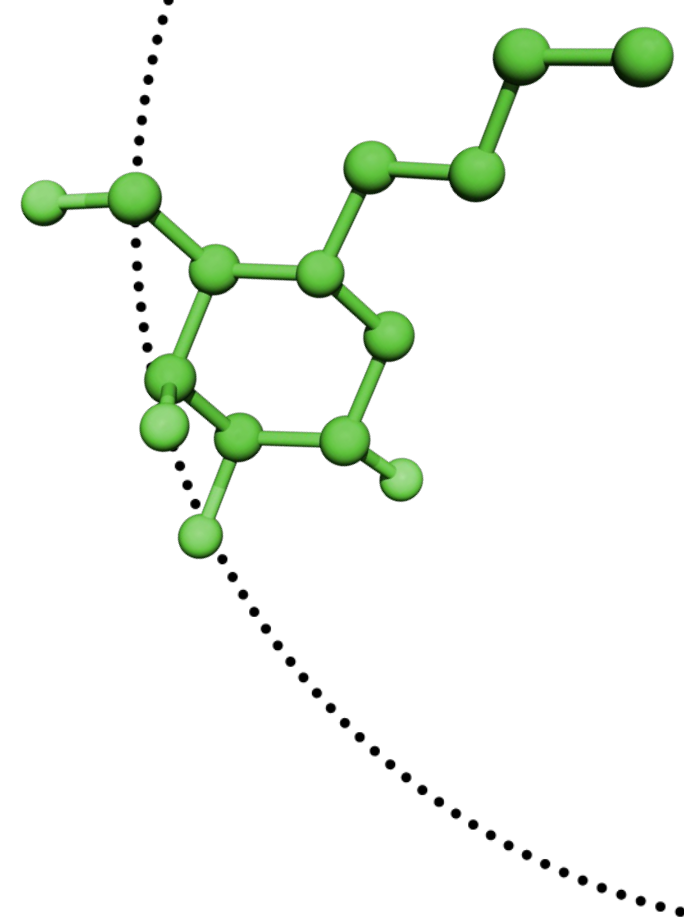
# Lucerastat for Fabry disease

Glucosylceramide synthase inhibitor

An oral substrate reduction therapy investigated for the treatment of adult patients with Fabry disease.

- Lucerastat for Fabry disease has received orphan drug designation in the US and the EU
- MODIFY did not meet the primary endpoint
- Observations on renal function which, if confirmed with longer-term data, would indicate a treatment effect on the main organs affected by the disease
- Interim analysis showed that the signal seen on kidney function after 6 months of treatment is still observed after the longer treatment duration
- The company is conducting a kidney biopsy sub-study within a subset of patients currently participating in the OLE study – results are expected in Q2 2025
- Regulatory pathway to then be discussed with the US FDA

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# Idorsia-led early stage clinical development assets

# Leveraging our innovative pipeline – Early-stage

Idorsia exploring potential collaboration or option deals until the next inflection point

## ACKR3 antagonist

**Progressive multiple sclerosis**

Proof-of-concept in preparation

**Unique** combination of re-myelination and anti-inflammatory effect with decreased inflammatory cell infiltration.

## CXCR3 antagonist

**Vitiligo**

Proof-of-concept in preparation

**First-in-class** inhibition of CXCR3+ CD8+ T-cells for effective and safer treatment of immuno-dermatology and autoimmune disorders.

## CCR6 antagonist

**Psoriasis**

Proof-of-concept in preparation

**Unique** potential as a **first-in-class**, oral, targeted systemic therapy for effective treatment of Th17-driven immuno-dermatology and autoimmune disorders.

# Leveraging our innovative pipeline – Preclinical

Idorsia exploring potential collaboration or option deals until the next inflection point

## LPA 1 receptor antagonist

**Immune-mediated and fibrosis related disorders**

Entry-in-human package complete

Potential **best-in-class** due to insurmountable binding mode – proven inhibitory activity in preclinical models of inflammation and fibrosis

## Orexin 2 receptor agonist

**Narcolepsy, Hypersomnia**

Entry-in-human package ready to begin

Potential **best-in-class** – sustained chronic efficacy in a preclinical model of narcolepsy

## Undisclosed mechanism

**Organ injury / fibrosis**

Entry-in-human package in progress

Broad potential of undisclosed mechanism for inhibiting organ injury and fibrosis – proven effectiveness (i.v. & oral) in several preclinical models of organ injury

## CFTR type-IV corrector

**Cystic Fibrosis**

Entry-in-human package in progress

A unique corrector targeting an Idorsia-identified binding site on the Cystic Fibrosis Transmembrane regulator (CFTR) protein. Potential synergy with other molecules

# Leveraging our innovative pipeline – Vaccines

Idorsia exploring potential collaboration

## Synthetic glycan vaccine platform

Transforming vaccines from biologics to medicinal chemistry:  
fast approach to find new optimized vaccines for bacterial, fungal, oncological threats,  
substantially reducing costs in development

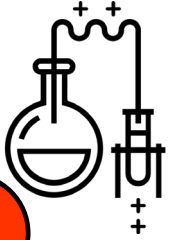
### ***Clostridium difficile* infection vaccine**

Idorsia is conducting a Phase 1 clinical pharmacology study which will test the immune response of the vaccine and evaluate its safety and tolerability.  
Results expected in Q2 2025.

### **Pentavalent *Klebsiella pneumoniae* infection vaccine**

Entry-in-human package in progress

# More knowledge – Powered by science



## Focus on small molecules

- Based on organic chemistry
- Suitable for acute and chronic diseases
  - Suitable for oral use
  - Clear patent protection



## Industry leading talent

- Highly experienced and motivated team
- Medical expertise in multiple therapeutic areas

## Vaccine platform

- Discovering and developing glycoconjugate vaccines
- Containing synthetic antigenic glycan molecules
- +/- carrier protein to prevent infection



## Target selection

- High medical need – patient focused
- Therapeutic novelty



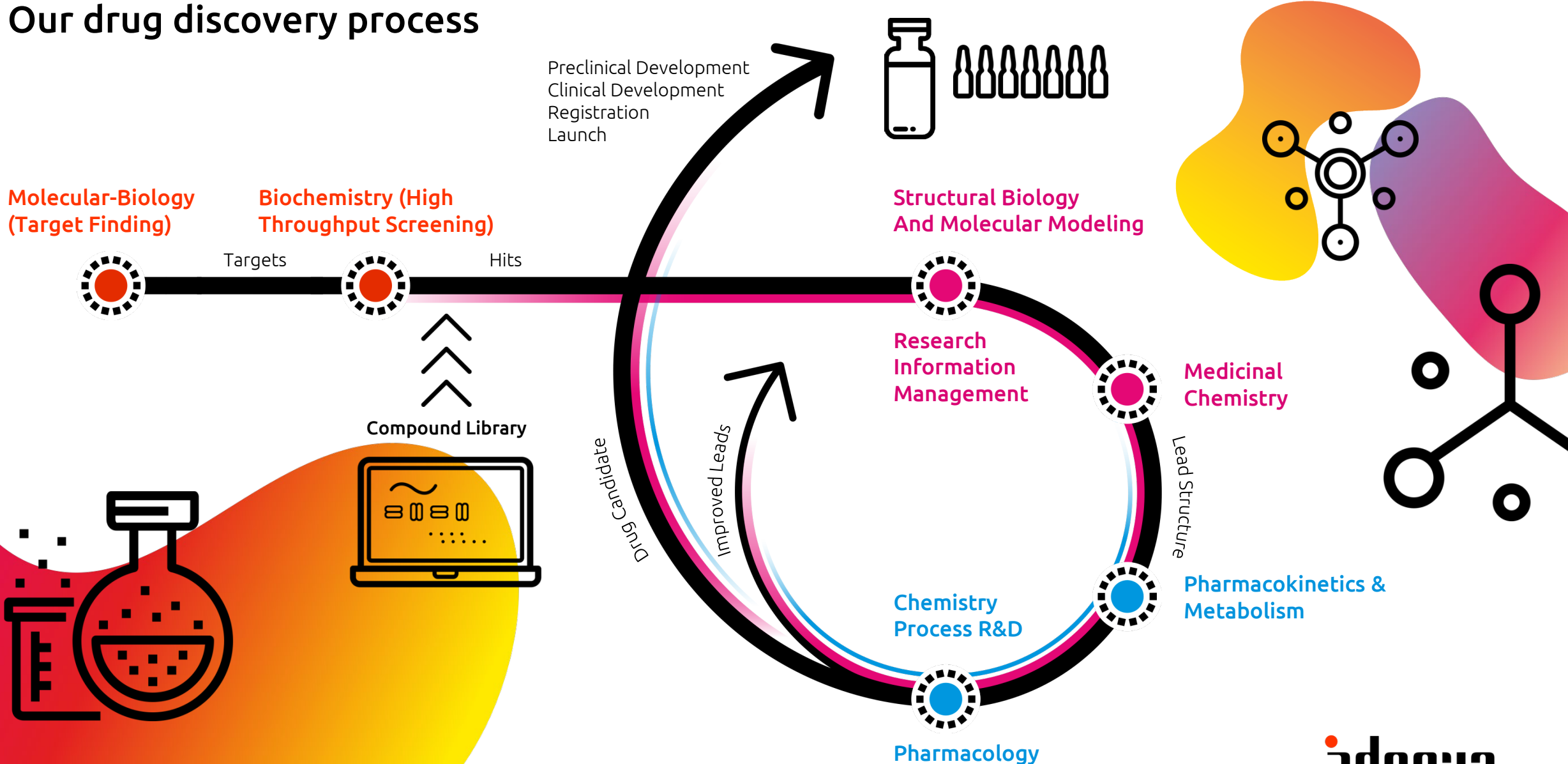
## State-of-the-art technologies

- Artificial intelligence
- Computer modelling
- High throughput screening



# More joy – Transforming the horizon

## Our drug discovery process

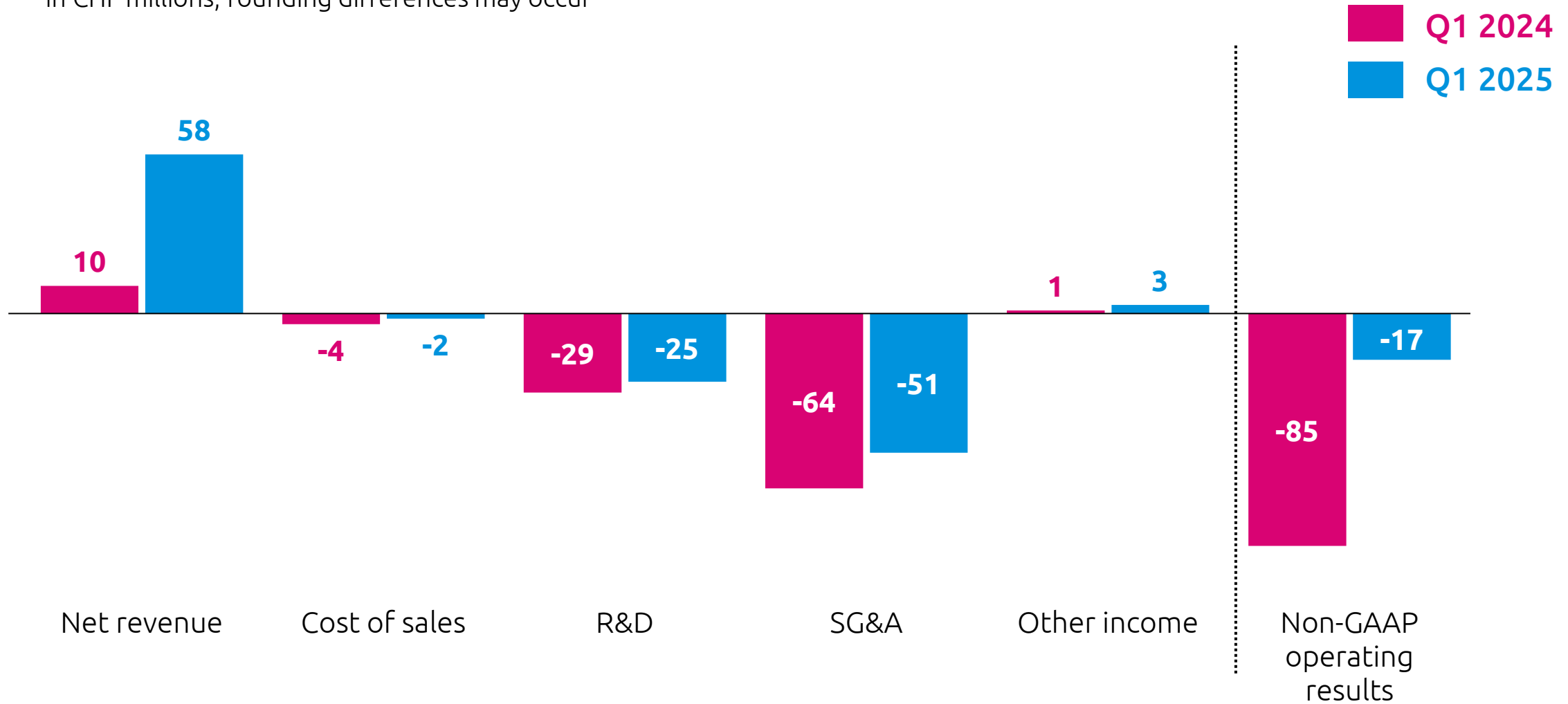


# Financial information

## Q1 2025

# Non-GAAP operating results

in CHF millions, rounding differences may occur



Financial results as of March 31, 2025



# Q1 2024 vs Q1 2025 operating performance

	Q1 2024			Q1 2025		
in CHF millions, rounding differences may occur	Idorsia business	Partnered business	Global Business	Idorsia business	Partnered business	Global Business
REVENUE	10	-	10	25	33	58
COGS	-4	-	-4	-2	-0	-2
SG&A OPEX	-64	-	-64	-51		-51
R&D OPEX	-29	-	-29	-25		-25
Other	0	-	0	3		3
<b>Non-GAAP EBIT</b>	<b>-85</b>	<b>-</b>	<b>-85</b>	<b>-50</b>	<b>33</b>	<b>-17</b>
D&A	-4	-	-4	-4		-4
SBC	-5	-	-5	-2		-2
Other	-1	125	124	-1	91	90
<b>US-GAAP EBIT</b>	<b>-95</b>	<b>125</b>	<b>31</b>	<b>-57</b>	<b>124</b>	<b>67</b>

# Q1 2025 cash development

in CHF millions, rounding differences may occur



# Financial outlook

# Financial outlook

Status: April 2025

## Idorsia-led business

CHF million	2023 proforma*	2024 as reported	2025 guidance**
REVENUE	32	61	110
COGS	-4	-6	-15
SG&A OPEX	-358	-263	-210
R&D OPEX	-262	-128	-100
Other	-	6	-
<b>Non-GAAP EBIT</b>	<b>-591</b>	<b>-330</b>	<b>-215</b>

\* Excluding the business sold as part of the Nxera deal

\*\* Excluding unforeseen events

- Accelerate sales
- Reduce cost-base

# Financial outlook

Status: April 2025

## Guidance for 2025

CHF million	Idorsia-led business	Partner-led business	Global Business
REVENUE	110	45	155
COGS	-15	-	-15
SG&A OPEX	-210	-	-210
R&D OPEX	-100	-	-100
<b>Non-GAAP EBIT</b>	<b>-215</b>	<b>45</b>	<b>-170</b>
D&A	-20	-	-20
SBC	-15	-	-15
Other	-10	90	80
<b>US-GAAP EBIT</b>	<b>-260</b>	<b>135</b>	<b>-125</b>



Idorsia has a **strong and visionary leadership team** with the power and drive to create more remarkable innovations and more new medicines

# Idorsia Executive Committee



**Alberto Gimona**  
Head of Global Clinical  
Development & Medical Affairs

**Julien Gander**  
Group General Counsel

**André C. Muller**  
Chief Executive Officer

**Martine Clozel**  
Chief Scientific Officer

**Arno Groenewoud**  
Chief Financial Officer

# Idorsia Leadership Team



**Olivier Lambert**  
Head of Technical  
Operations

**Kerstin Niggemann**  
Head Pharmacological  
Sciences

**Gaby Scherer**  
Head of Global  
Human Resources

**Eva Caroff**  
Head Chemical  
Sciences

**Andrew Jones**  
Head of Corporate Communications  
& Investor Relations

**idorsia**

Be prepared  
for more

