Idorsia – Reaching out for more

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 discover, develop, and commercialize innovative medicines to help more patients.

We have more ideas, we see more Opportunities, and we want to transform the horizon of therapeutic options.

Our company history and leadership

Actelion, founded in 1997 by four researchers, changed the lives of thousands of patients living with pulmonary arterial hypertension

1997

2017

Jean-Paul Clozel, MD (Chairman) and Martine Clozel, MD (CSO) bring with them not only drug discovery pedigree as researchers but experience working as doctors to continue their philosophy of building a biopharma company focused on patients

Unique amongst biopharma start-ups, our discovery and clinical development teams have been working together for more than 25 years

Idorsia was created from the demerger of Actelion's drug discovery engine and early-stage clinical pipeline as part of the acquisition by Johnson & Johnson in 2017

A start-up like no other

Idorsia has the ideal constellation for bringing successful medicines to patient

>25-year

Heritage of drug discovery

>10

Idorsia and partner-led assets in our portfolio

>750

Highly qualified professionals

Global

Commercial operations in Europe and North America

What have we achieved in the past 7 years

Brought 3 drugs to the market

Built a global marketing organization

Launched QUVIVIQ in the US and main European countries

Created a late-stage pipeline and continued to discover new drugs

Re-acquired aprocitentan from Johnson & Johnson

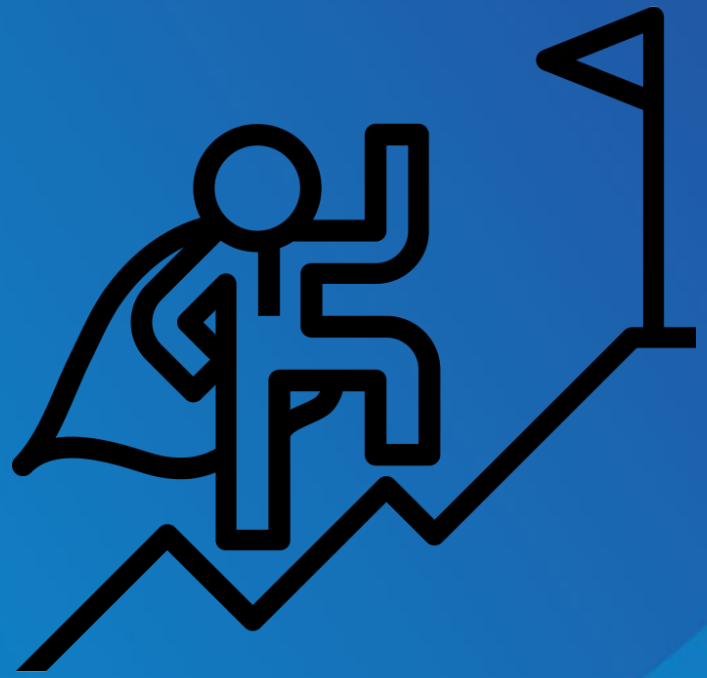
Secured financing for all these achievements

Highlights of H1 2024

Viatris collaboration for selatogrel and cenerimod

Restructured convertible bond – extending cash runway

Adapted governance structure



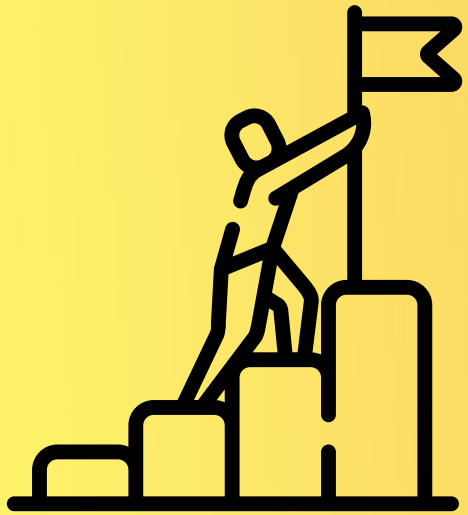
Approval of aprocitentan TRYVIO in the US JERAYGO in the EU

QUVIVIQ NDA submitted in Greater China by Simcere

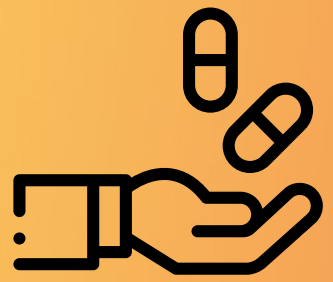
Vaccine for *Clostridium Difficile* advanced into Phase 1

What needs to be done in H2 2024

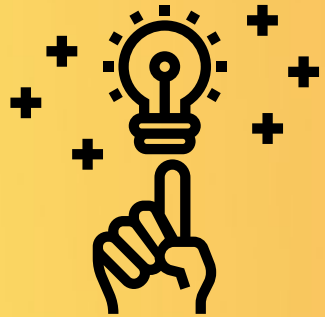
Extend the cash runway



Continue to increase sales of QUVIVIQ



Prepare for the launch of TRYVIO in the US



Continue to innovate

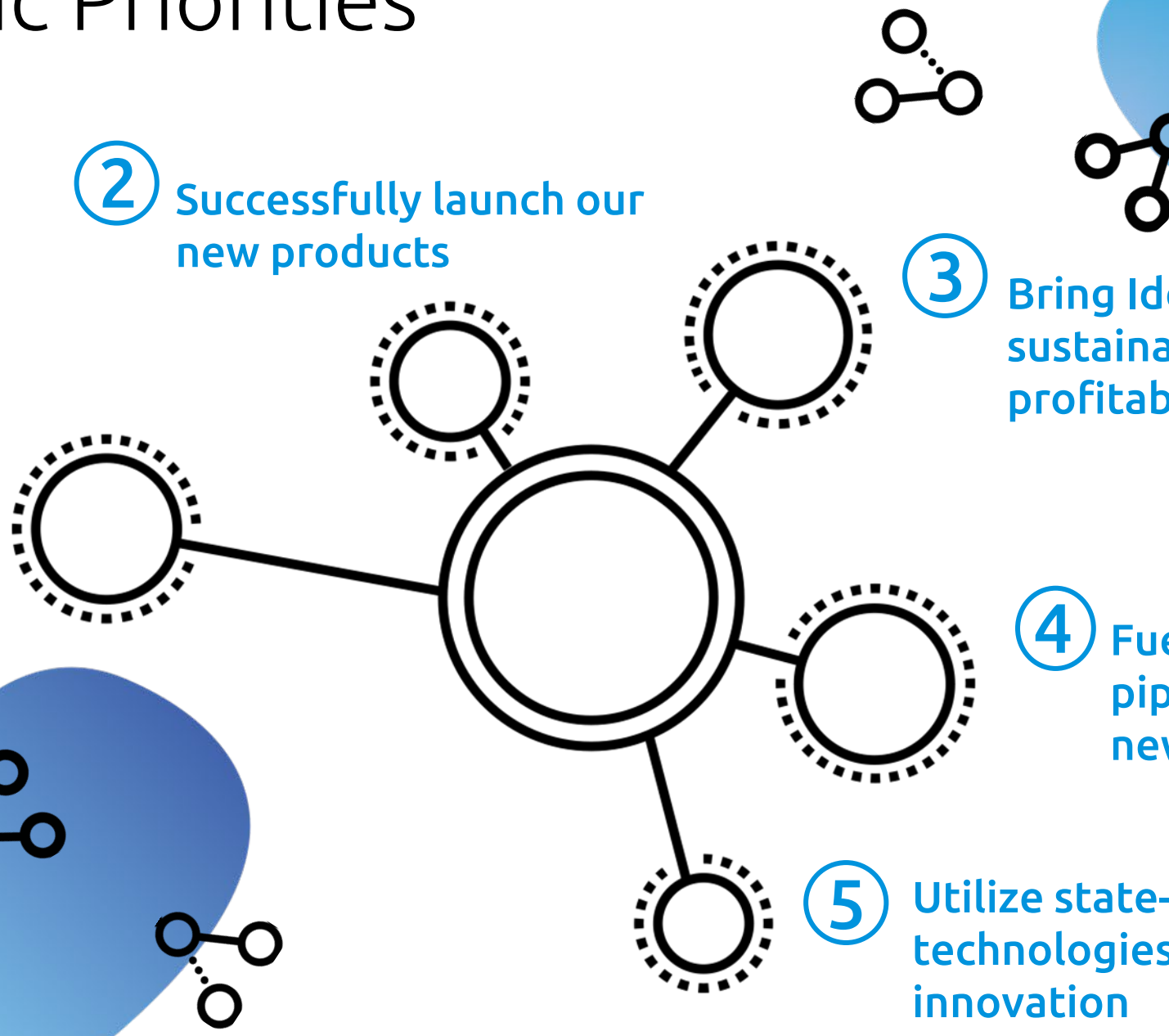
Collaboration and license agreement with Viatris for selatogrel and cenerimod

- Combines Viatris' financial strength and worldwide operational infrastructure with Idorsia's proven, highly productive drug development team and innovative engine.
- Idorsia received an upfront payment of USD 350 million, potential development and regulatory milestone payments, and certain contingent payments of additional sales milestone payments and tiered royalties from mid-single- to low double-digit percentage on annual net sales.
- A joint development committee oversees the development of the ongoing Phase 3 programs for selatogrel and cenerimod through regulatory approval.
- Idorsia transferred to Viatris both clinical programs for selatogrel and cenerimod and all key personnel involved in the development programs.
- The development costs for both programs are shared between Idorsia and Viatris, Idorsia will contribute up to USD 200 million in the next 3 years.
- Viatris will have worldwide commercialization rights for both selatogrel and cenerimod (excluding, for cenerimod only, Japan, South Korea and certain countries in the Asia-Pacific region).
- Includes future optionality to expand collaboration with additional pipeline assets.

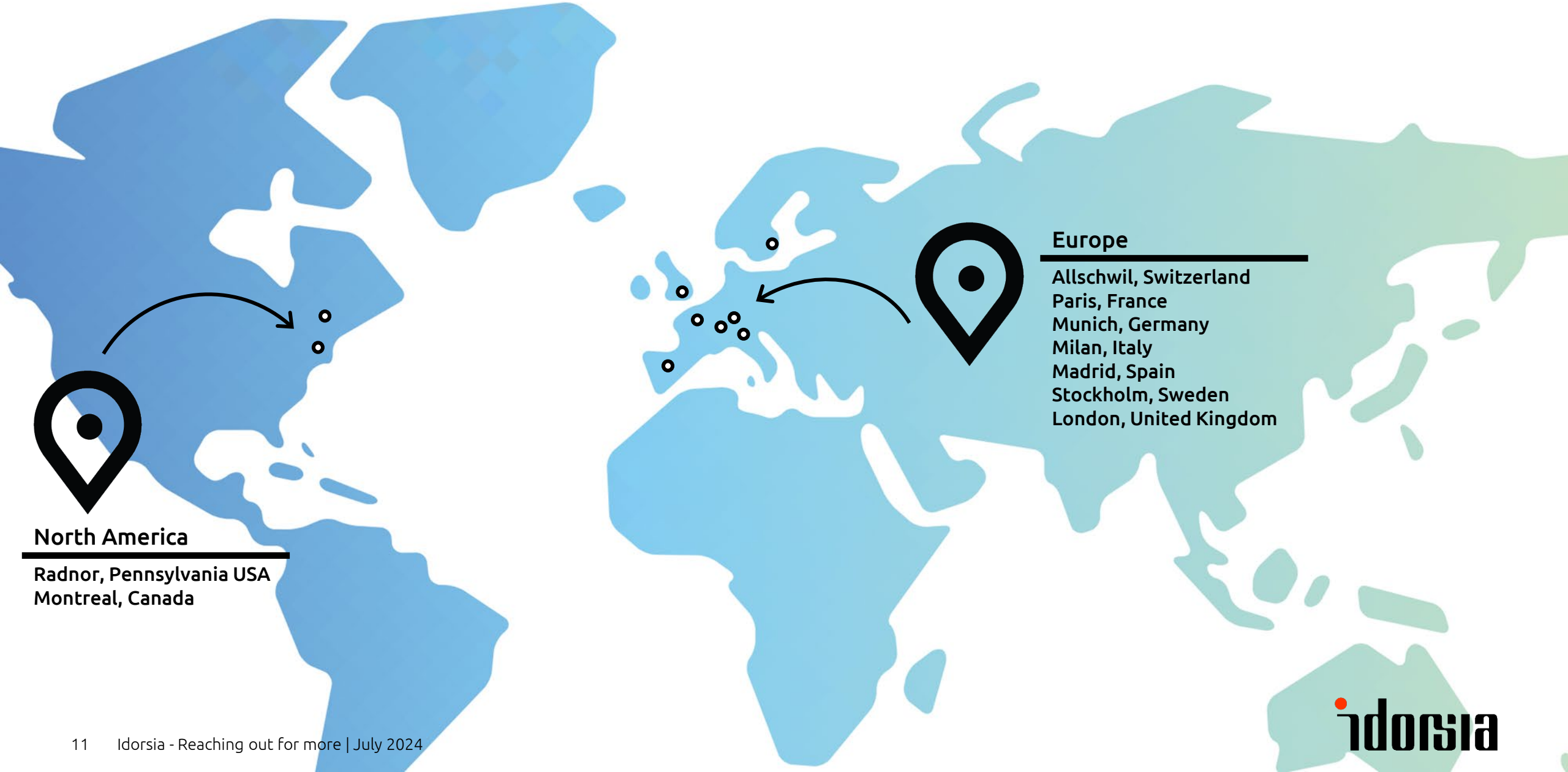
Our Strategic Priorities

Our mid-term key priorities to achieve long-term success:

1. Advance late-stage pipeline
2. Successfully launch our new products
3. Bring Idorsia to sustainable profitability
4. Fuel our pipeline with new discoveries
5. Utilize state-of-the-art technologies to drive innovation



Our commercial reach



North America

Radnor, Pennsylvania USA
Montreal, Canada

Europe

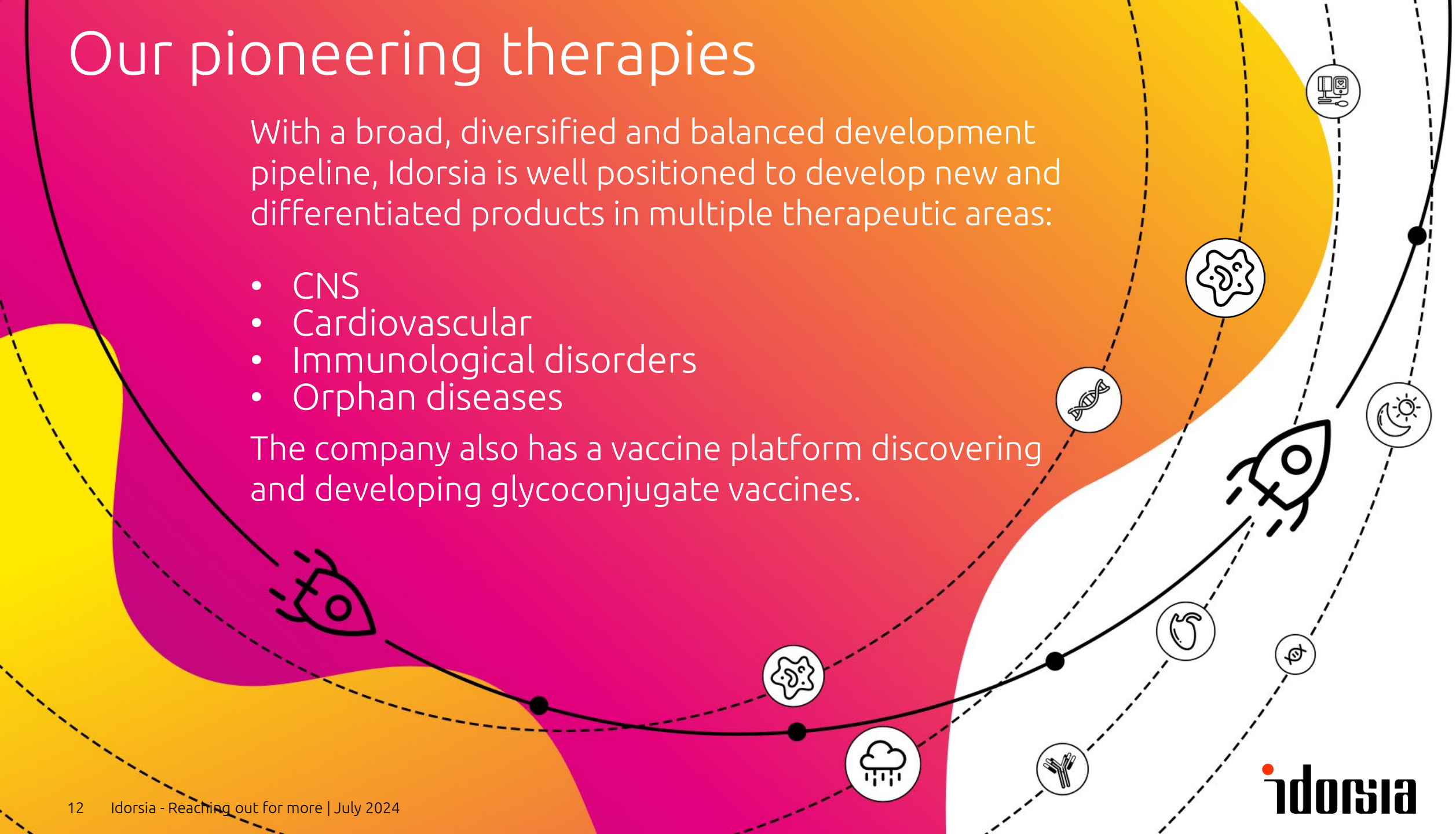
Allschwil, Switzerland
Paris, France
Munich, Germany
Milan, Italy
Madrid, Spain
Stockholm, Sweden
London, United Kingdom

Our pioneering therapies

With a broad, diversified and balanced development pipeline, Idorsia is well positioned to develop new and differentiated products in multiple therapeutic areas:

- CNS
- Cardiovascular
- Immunological disorders
- Orphan diseases

The company also has a vaccine platform discovering and developing glycoconjugate vaccines.



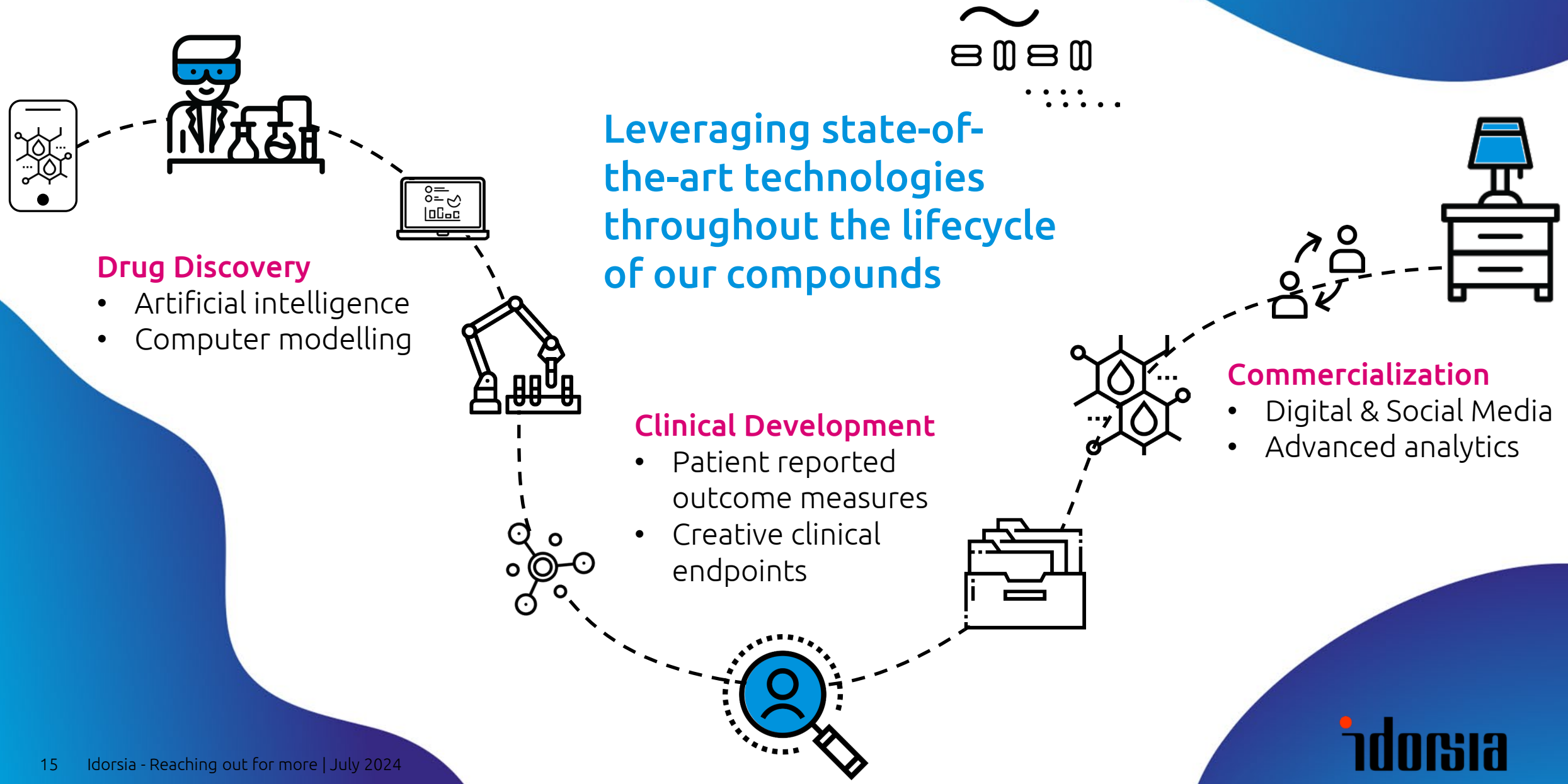
Idorsia-led portfolio

Partner-led portfolio

Compound / Mechanism of action / **Target indication**	**Partner**	Phase 1 / Phase 2 / Phase 3 / Registration / Commercially available
QUVIVIQ™ (daridorexant) Dual orexin receptor antagonist **Insomnia**	Simcere	**Simcere:** Approved for the treatment of insomnia in Hong-Kong
Daridorexant Dual orexin receptor antagonist **Insomnia**	Nxera	**Nxera Pharm:** license to develop and commercialize for Asia-Pacific region (excluding China)* NDA submitted in Japan
Daridorexant Dual orexin receptor antagonist **Insomnia**	Simcere	**Simcere:** license to develop and commercialize for Greater China region NDA submitted in Greater China
Selatogrel $P2Y_{12}$ inhibitor **Acute myocardial infarction**	VIATRIS	**Viatris:** worldwide development and commercialization rights Phase 3 "SOS-AMI" program ongoing
Cenerimod $S1P_1$ receptor modulator **Systemic lupus erythematosus**	VIATRIS	**Viatris:** worldwide development and commercialization rights (excluding Japan, South Korea, and certain countries in the Asia-Pacific region) Phase 3 "OPUS" program ongoing
Daridorexant Dual orexin receptor antagonist **Posttraumatic stress disorder (PTSD)**	US Department of Defense (DOD)	**US Department of Defense (DOD):** Idorsia is supporting a clinical study sponsored by the US DOD to develop new therapies to treat PTSD
ACT-709478 (NBI-827104) T-type calcium channel blocker **Epileptic encephalopathy with continuous spike-and-wave during sleep (CSCW)**	Neurocrine Biosciences	**Neurocrine Biosciences:** global license to develop and commercialize Phase 2 OLE study ongoing
ACT-1002-4391 EP_2/EP_4 receptor antagonist **Immuno-oncology**	OWKIN	**Owkin:** global license to develop and commercialize Phase 1 in preparation

*In Japan, Idorsia has a license agreement with Mochida Pharmaceutical for the supply, co-development and co-marketing of daridorexant. All potential milestones have been assigned to Nxera.

Innovation from bench to bedside



Leveraging state-of-the-art technologies throughout the lifecycle of our compounds

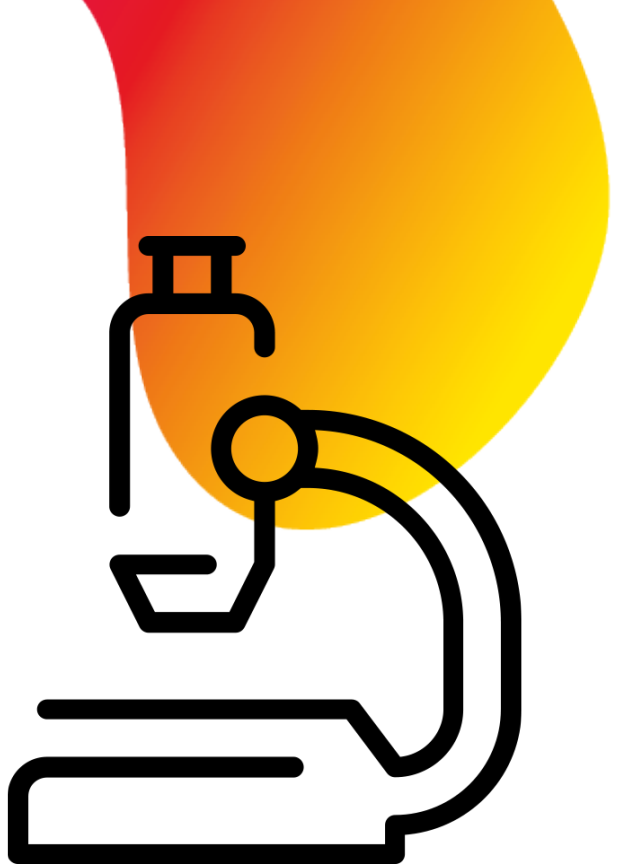
Drug Discovery
- Artificial intelligence
- Computer modelling

Clinical Development
- Patient reported outcome measures
- Creative clinical endpoints

Commercialization
- Digital & Social Media
- Advanced analytics

Find a comprehensive description of our pipeline assets as follows:

1. **Daridorexant** Slide 17
2. **Aprocitentan** Slide 58
3. **Lucerastat** Slide 90
4. **Early-stage assets** Slide 119



Daridorexant in insomnia

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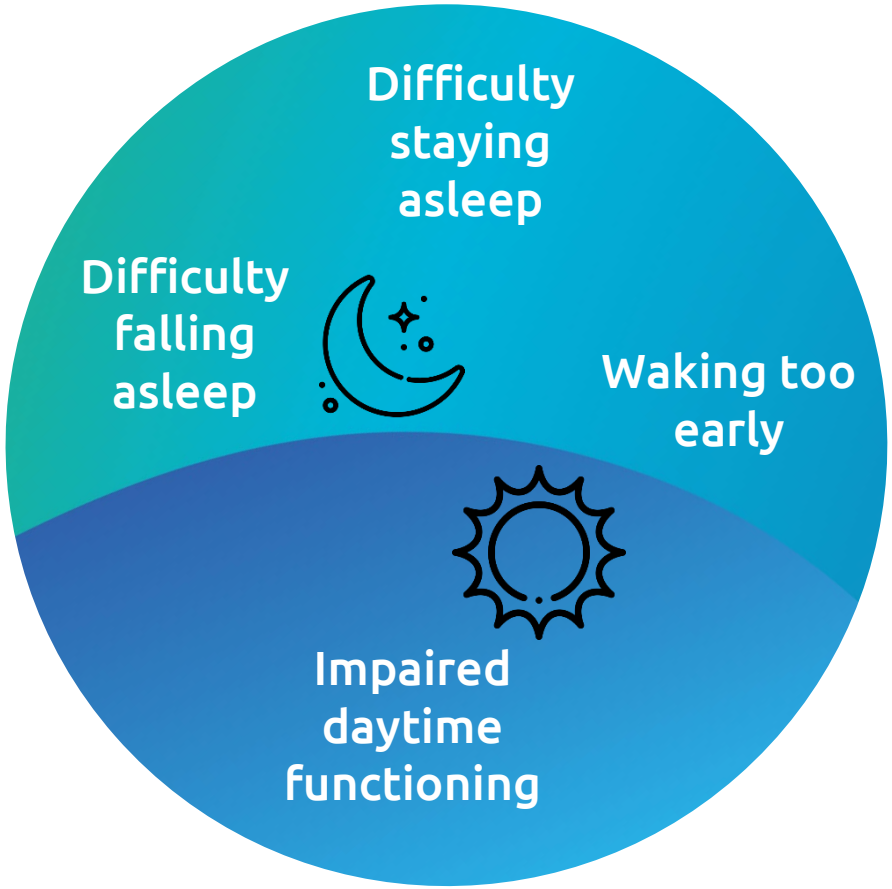
Insomnia: A disease of the night and the day

High unmet need for effective, safe medications to treat insomnia



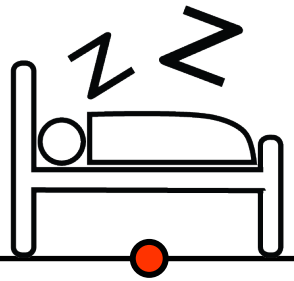
- Combination of difficulty obtaining sufficient sleep and dissatisfaction with sleep **combined with a significant negative impact on daytime functioning**

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

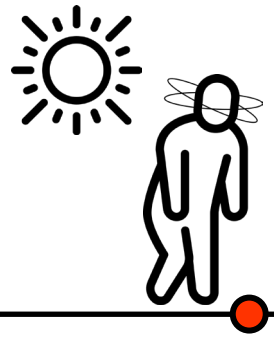
- Estimated approximately 25 million (10%[1]) adults in the US suffer from chronic insomnia

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

Insomnia and the importance of sleep

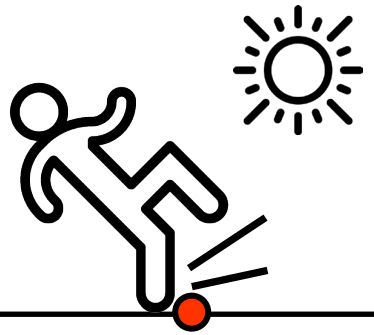


Sleep is an essential pillar for good physical and mental health to ensure optimal functioning throughout the day.

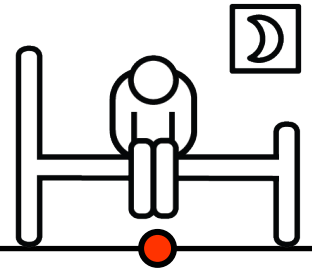


A key symptom of insomnia disorder is the **impairment of daytime functioning**, which is **linked to significant decrements in health status**, such as fatigue, reduced energy, mood alteration and cognitive difficulties.

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



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



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.**

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

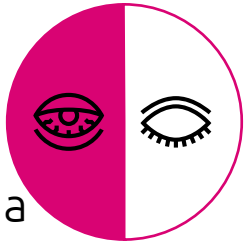
Prevalence and impact of insomnia across Europe

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

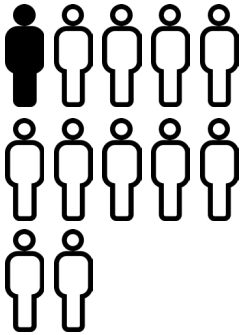
11th

most important brain disorder*

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



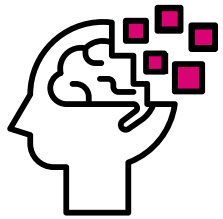
1 in 12 (8.2%) of adults live with chronic insomnia disorder (CID)



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://jcsm.aasm.org/doi/10.5664/jcsm.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?		Estimated "hidden" annual financial burden across working-age population suffering from CID
	% of adults suffering from CID	Number of adults	
	7.6%	18.6 million	€92bn
	8.8%	2.2 million	Can$ 10.7bn
	7.7%	16.6 million	$127.1bn

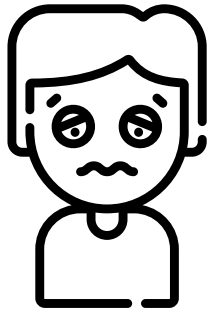
The US insomnia market is large, highly dissatisfied, and ripe for disruption

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

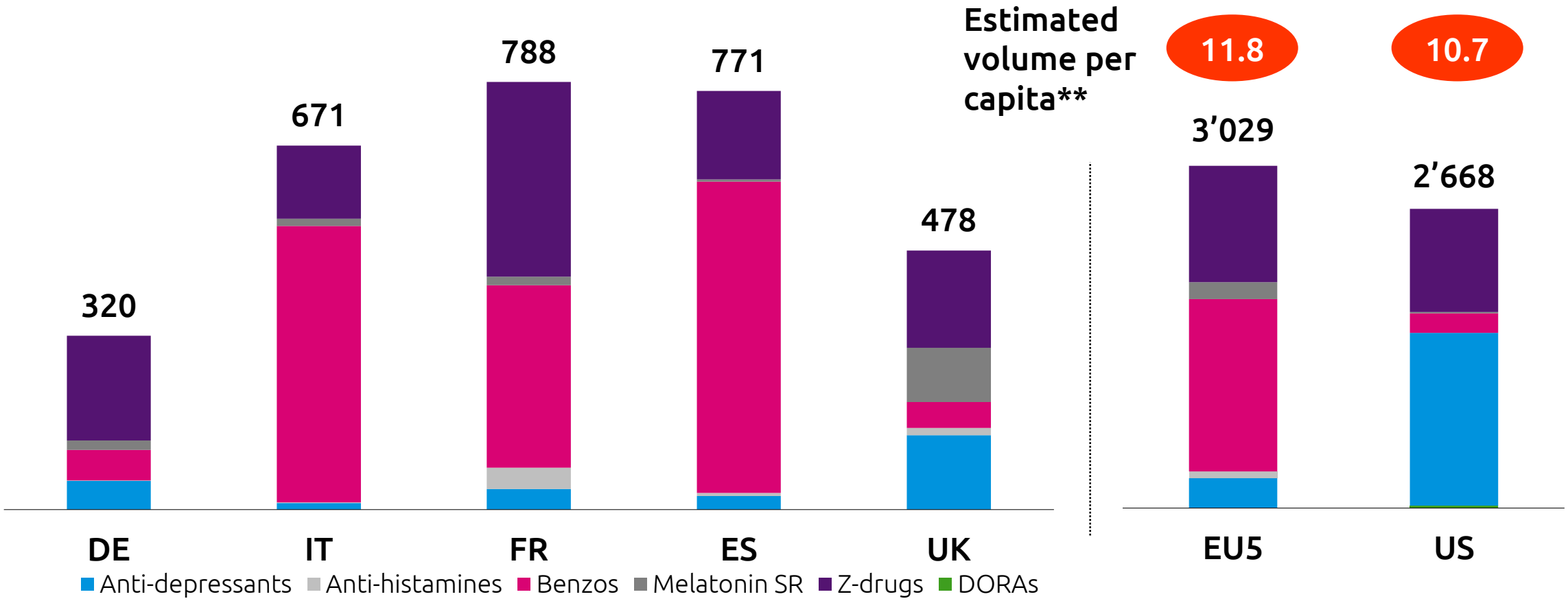
What are the costs?

$100B+

Insomnia related costs per year alone in the US

High unmet need in EU insomnia market

Estimated insomnia market volume*, standard units, millions

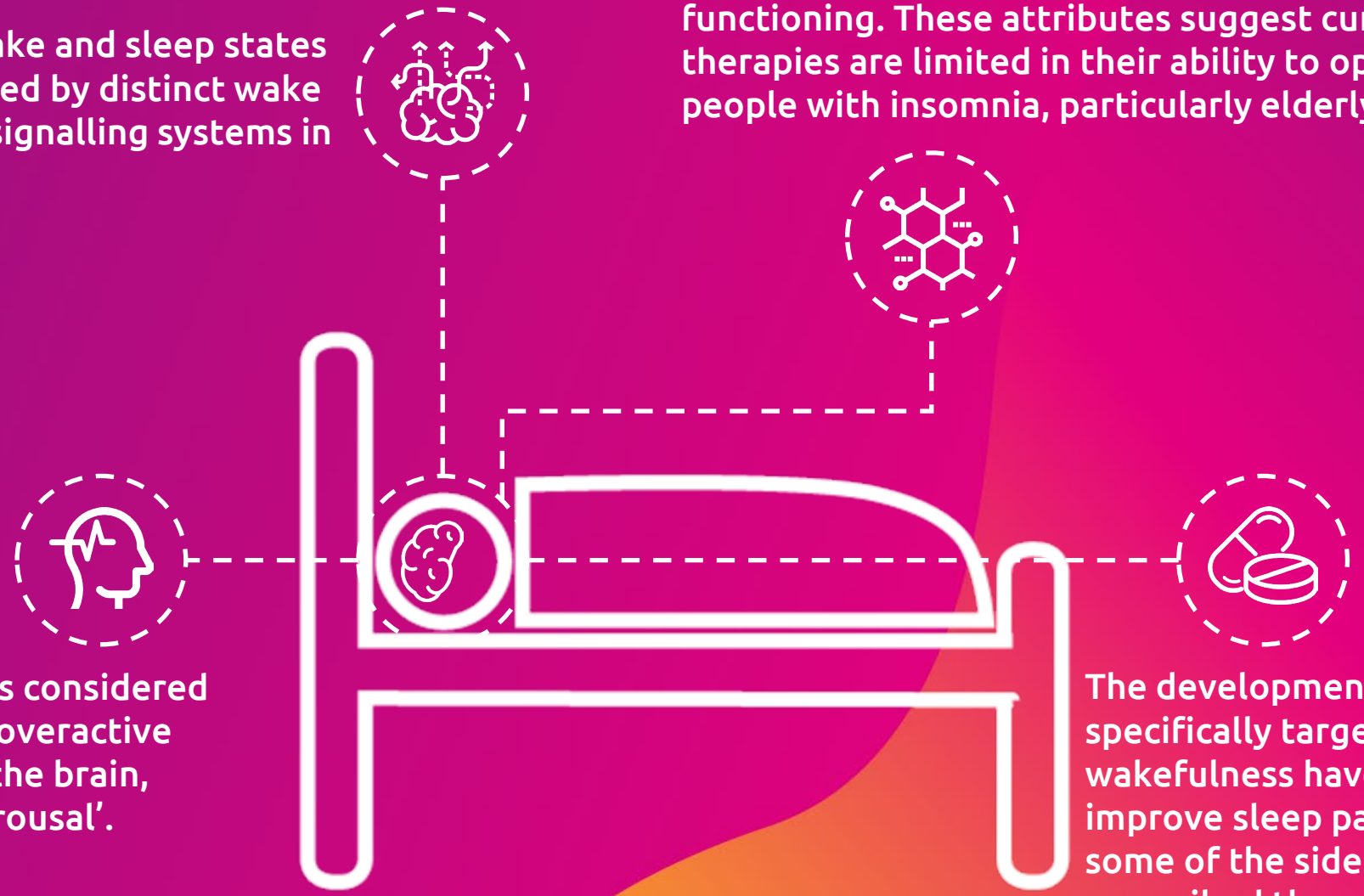


Source: IQVIA MIDAS EU5 – MAT/July 2022; IQVIA US Edition – MAT/August 2022; United Nations population division
* Includes estimated off-label usage of anti-depressants, anti-histamines and benzos to treat insomnia
** Based on adult population

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.



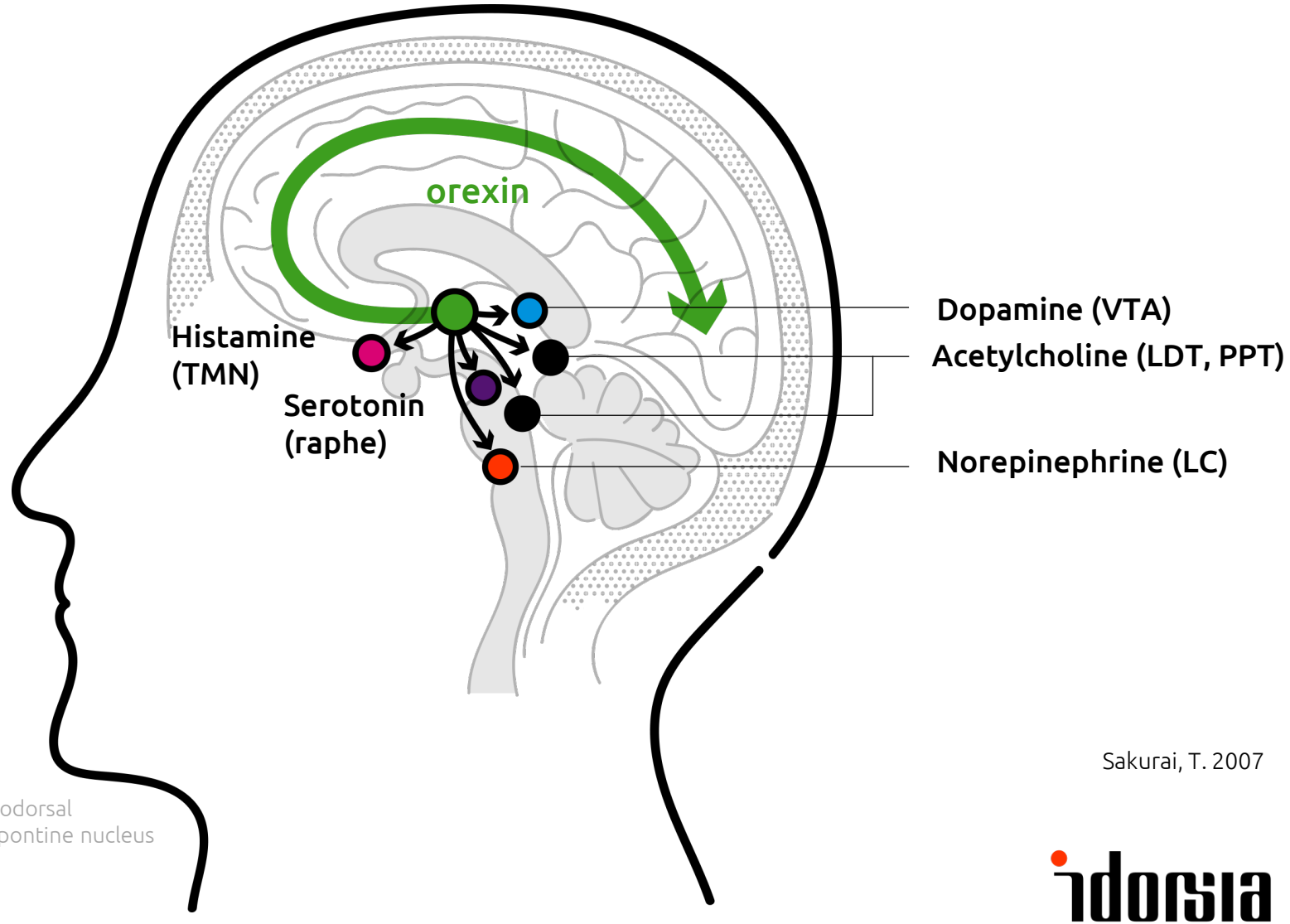
The underlying pathophysiological cause of insomnia is considered to be the result of overactive wake signalling in the brain, also called ‘hyperarousal’.

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_1R
●	**TMN**	OX_2R
●	**Raphe**	OX_1R and OX_2R
●	**LTD / PPT**	OX_1R and OX_2R
●	**VTA**	OX_1R and OX_2R



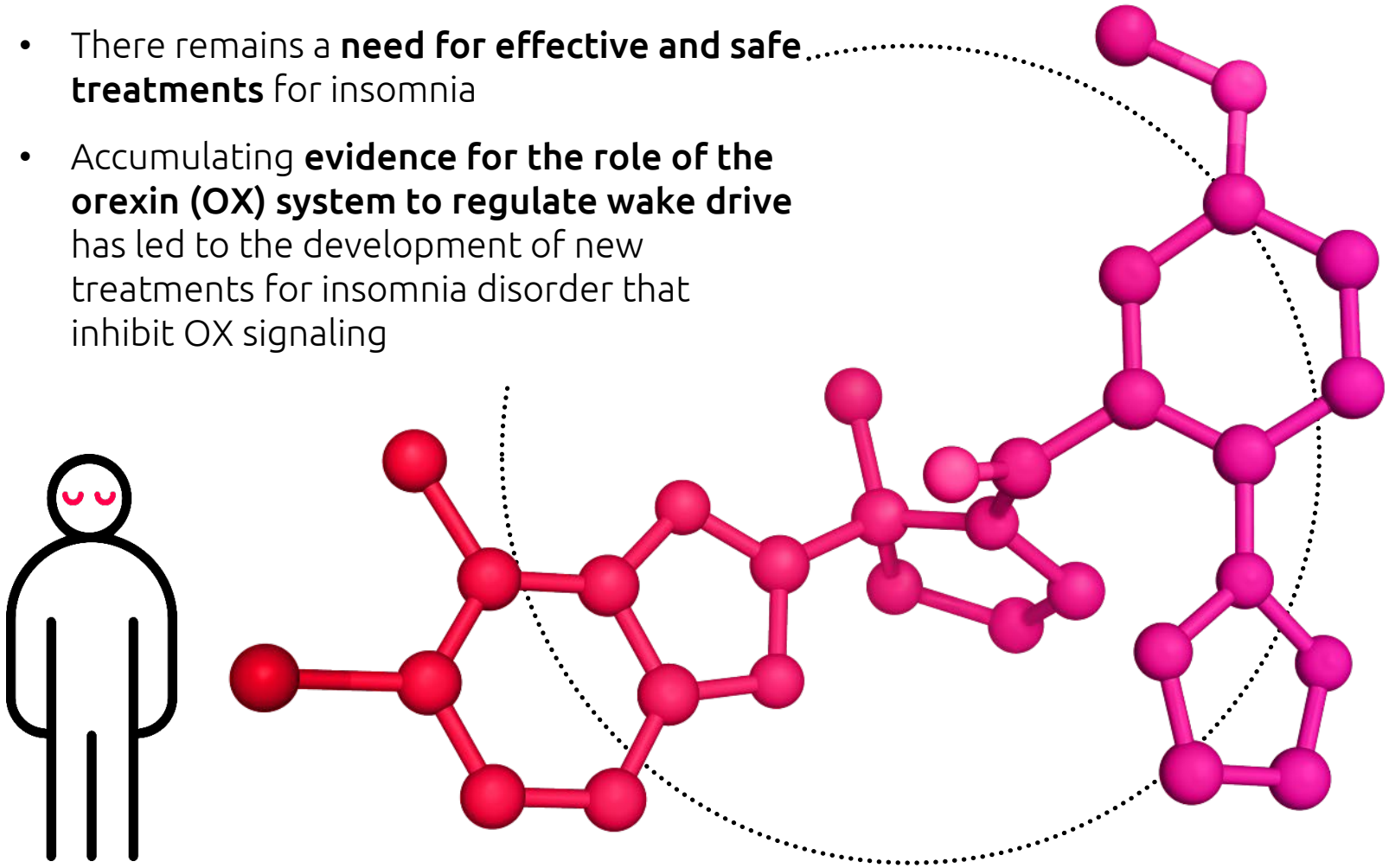
Sakurai, T. 2007

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

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

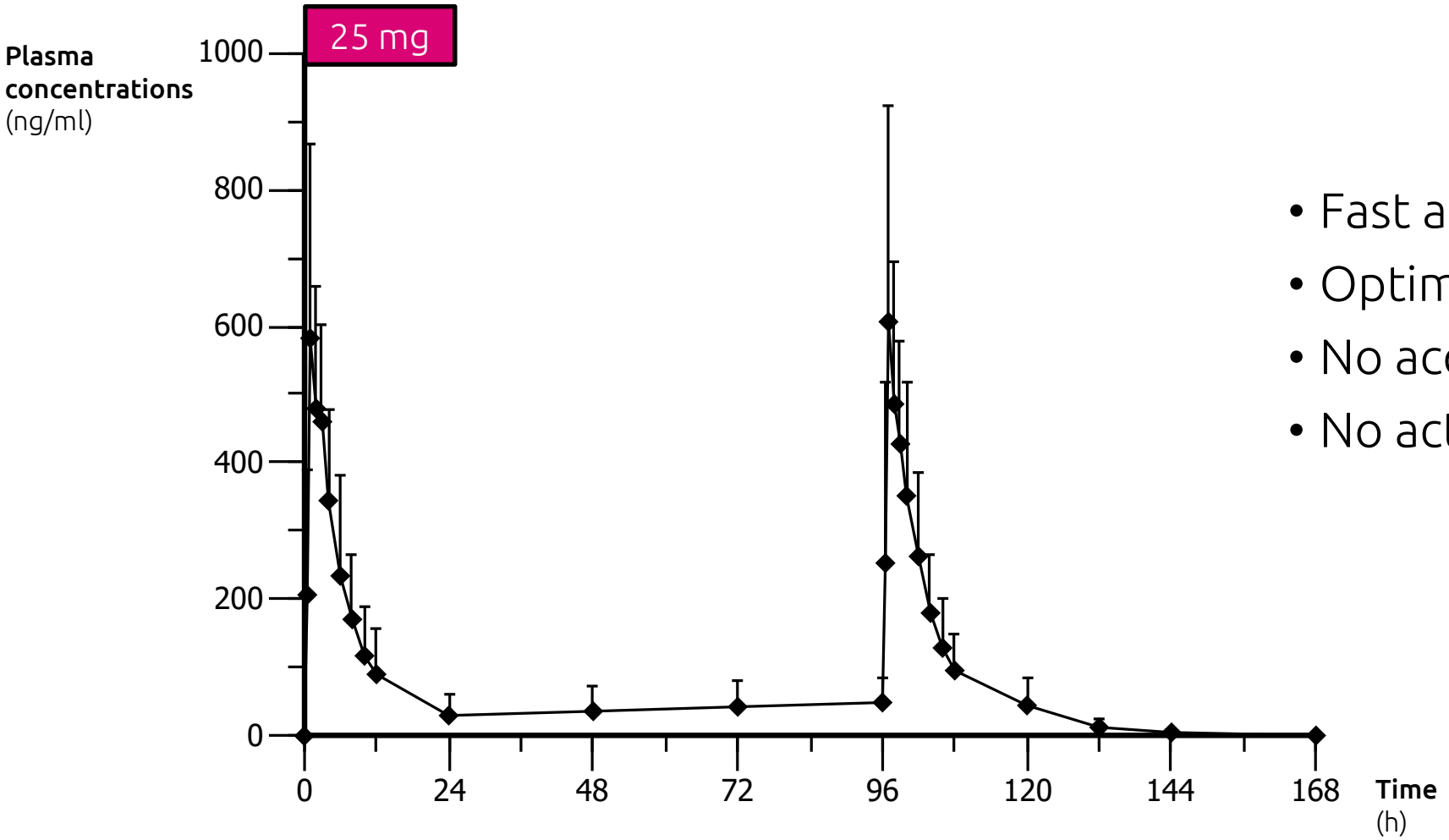
- a **potent and selective** dual orexin receptor antagonist (DORA)
- selected to **promote sleep onset and sleep maintenance, without impairing the next day**

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

Different by design – next generation DORA

Optimized pharmacokinetic profile

Entry into man studies



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

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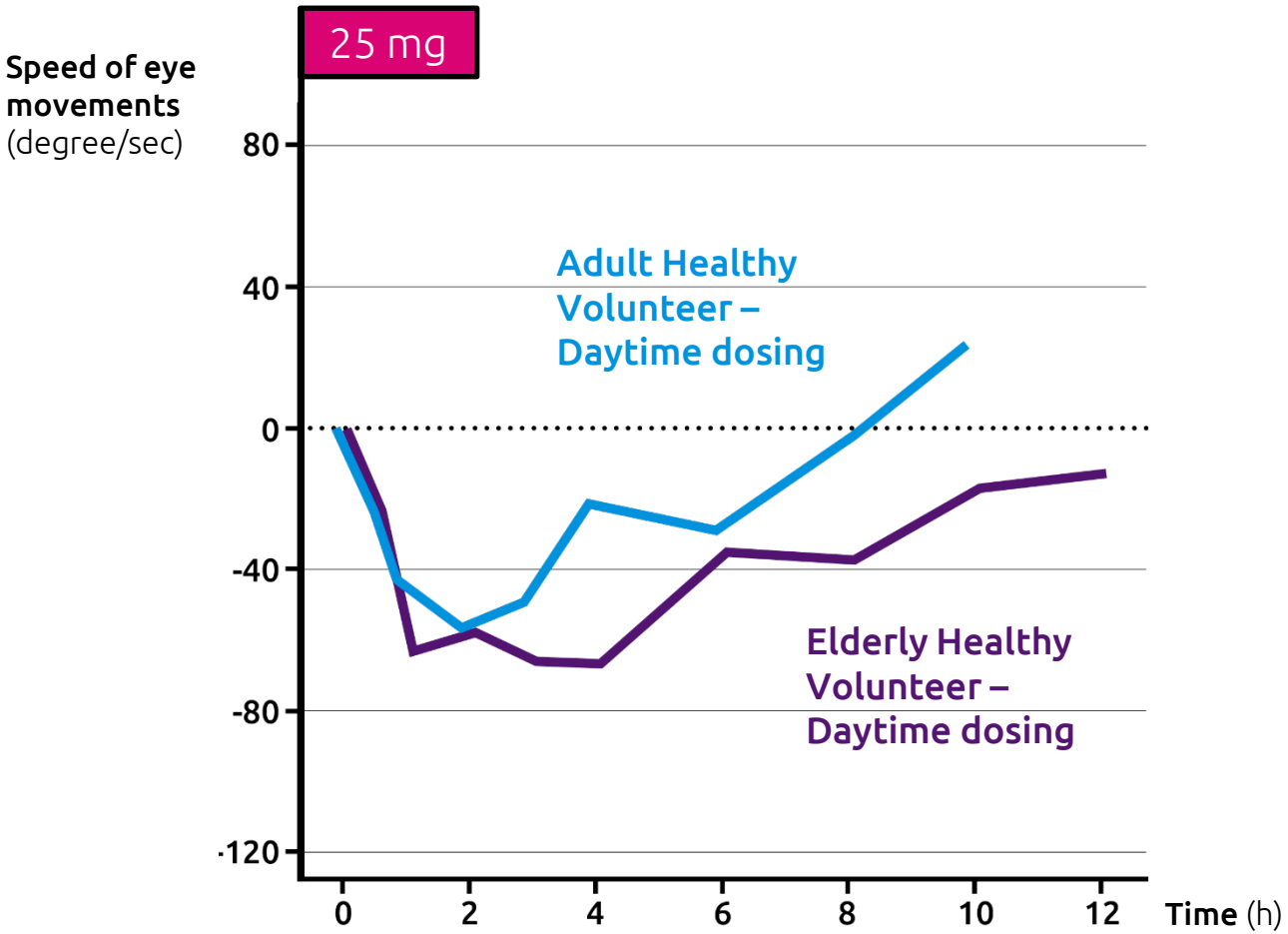
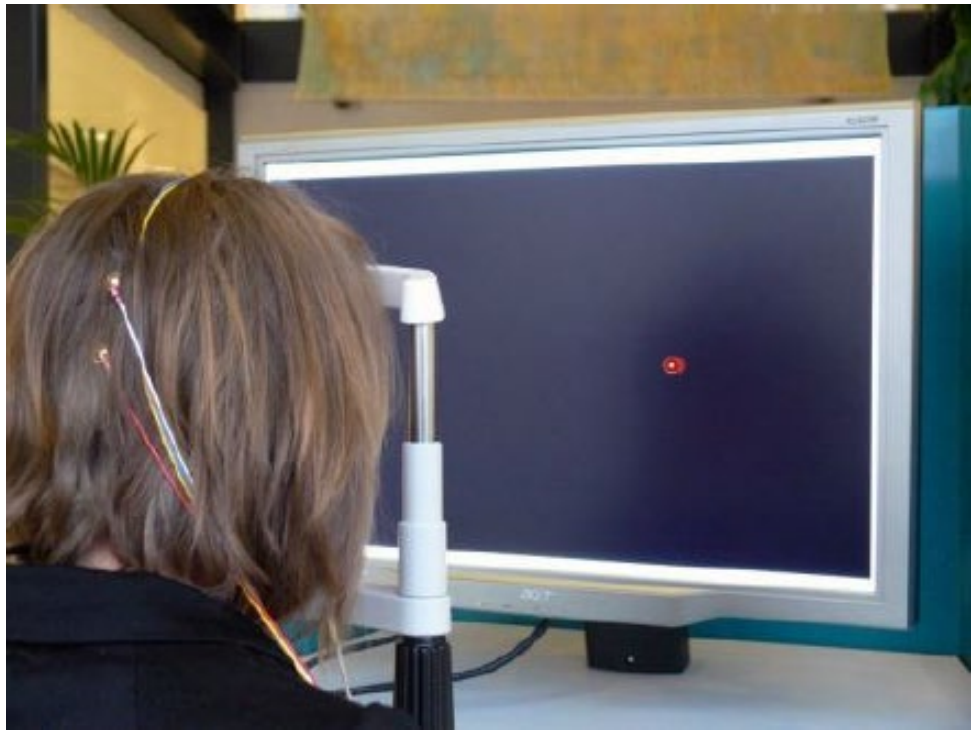
Fast and time limited pharmacodynamic effect





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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In addition, daridorexant is approved throughout the European Union.

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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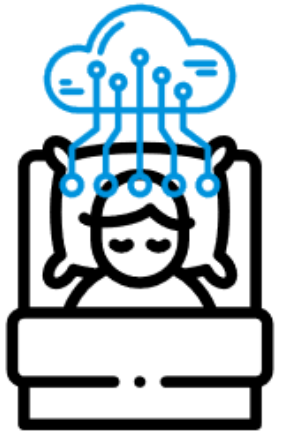
Objective sleep assessments

Repeated polysomnography recordings in a sleep lab in all patients

Phase 3 program

- 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.

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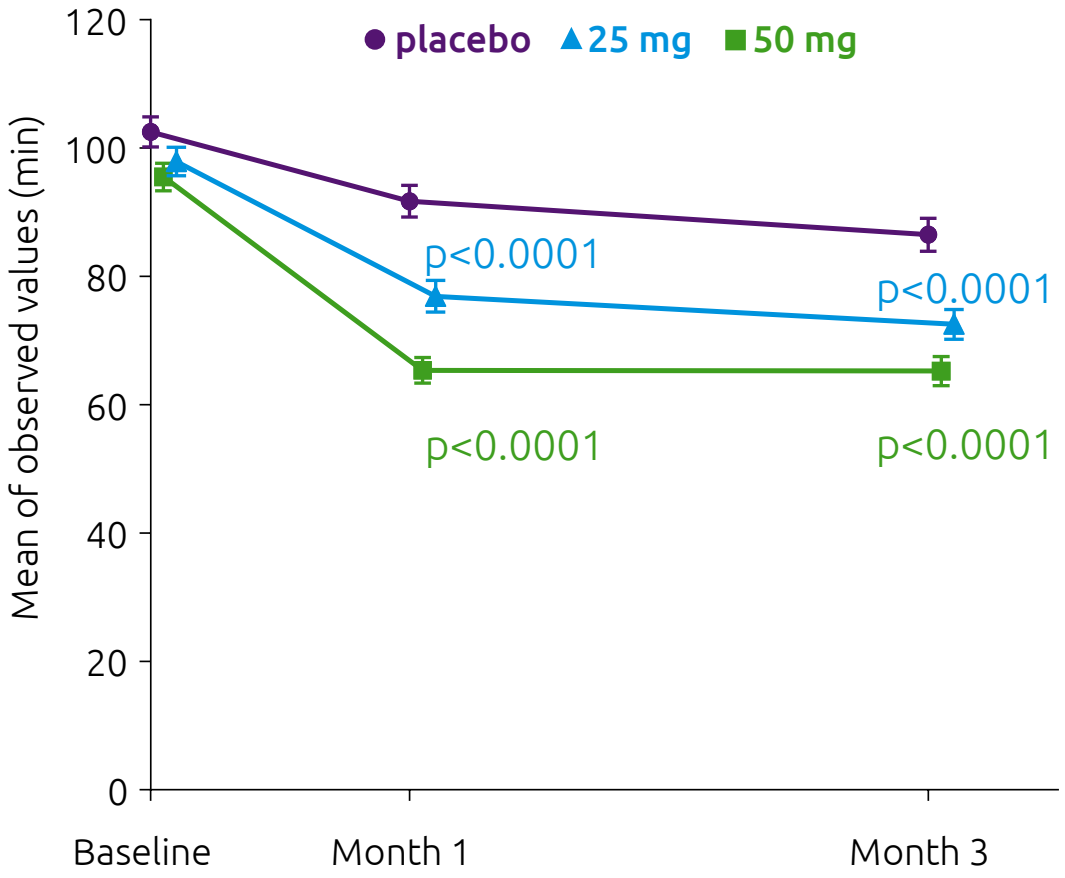
In addition, daridorexant is approved throughout the European Union.

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

CI = confidence interval; LSM = least squares mean

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

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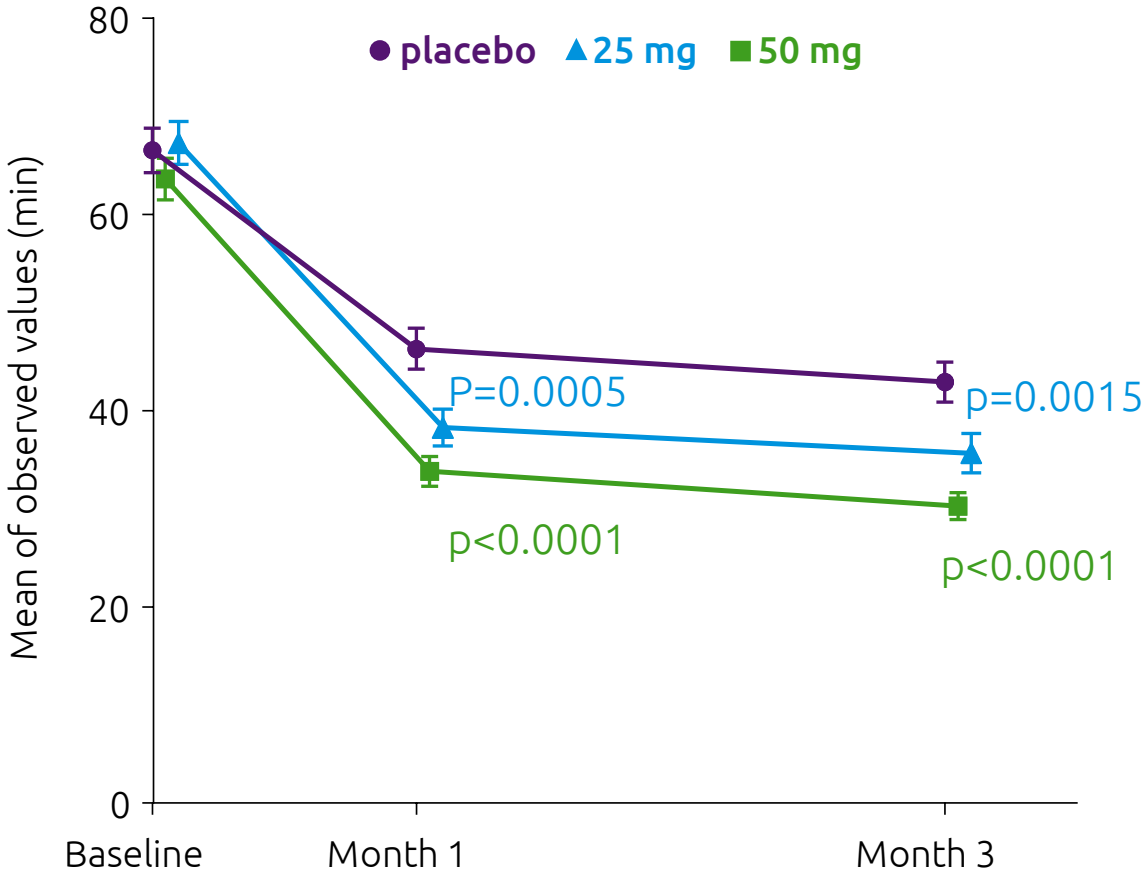
1º endpoint: Latency to persistent sleep (LPS)

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

CI = confidence interval; LSM = least squares mean

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

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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

→ **Total sleep time**
Secondary endpoint

Evening questionnaire

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

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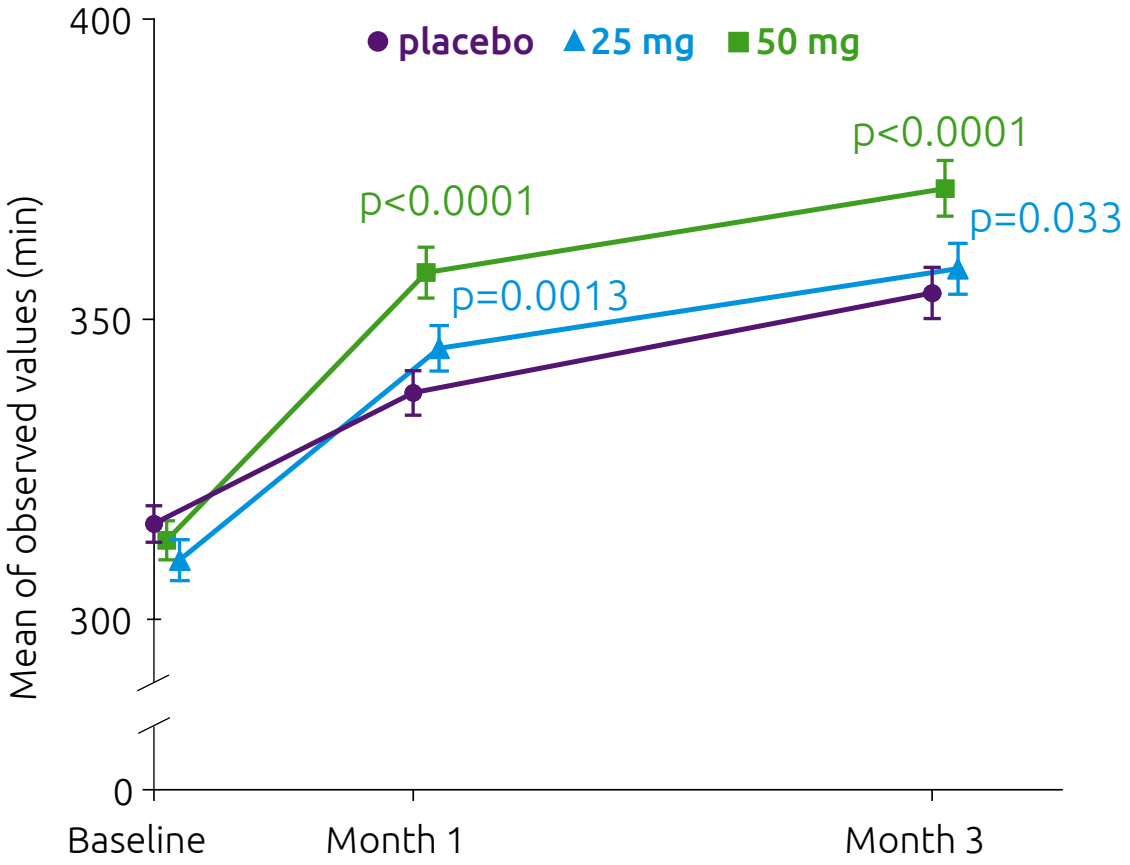
2º endpoint: Subjective Total Sleep Time (sTST)

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

CI = confidence interval; LSM = least squares mean

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

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Subjective assessment of daytime functioning

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)

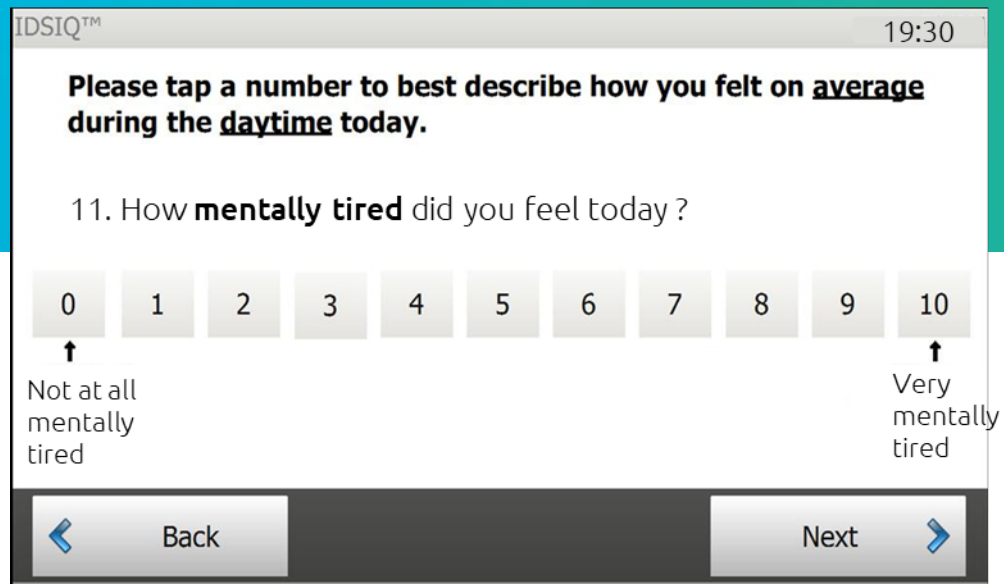
Measures
Item 1. How **clear-headed** did you feel today?
Item 2. How well were you able to **concentrate** today?
Item 3. How **forgetful** did you feel today?
Item 4. How **worried** did you feel today?
Item 5. How **frustrated** by your lack of sleep did you feel today?
Item 6. How **irritable** did 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



Daytime functioning measured by sleepiness domain score
Secondary endpoint

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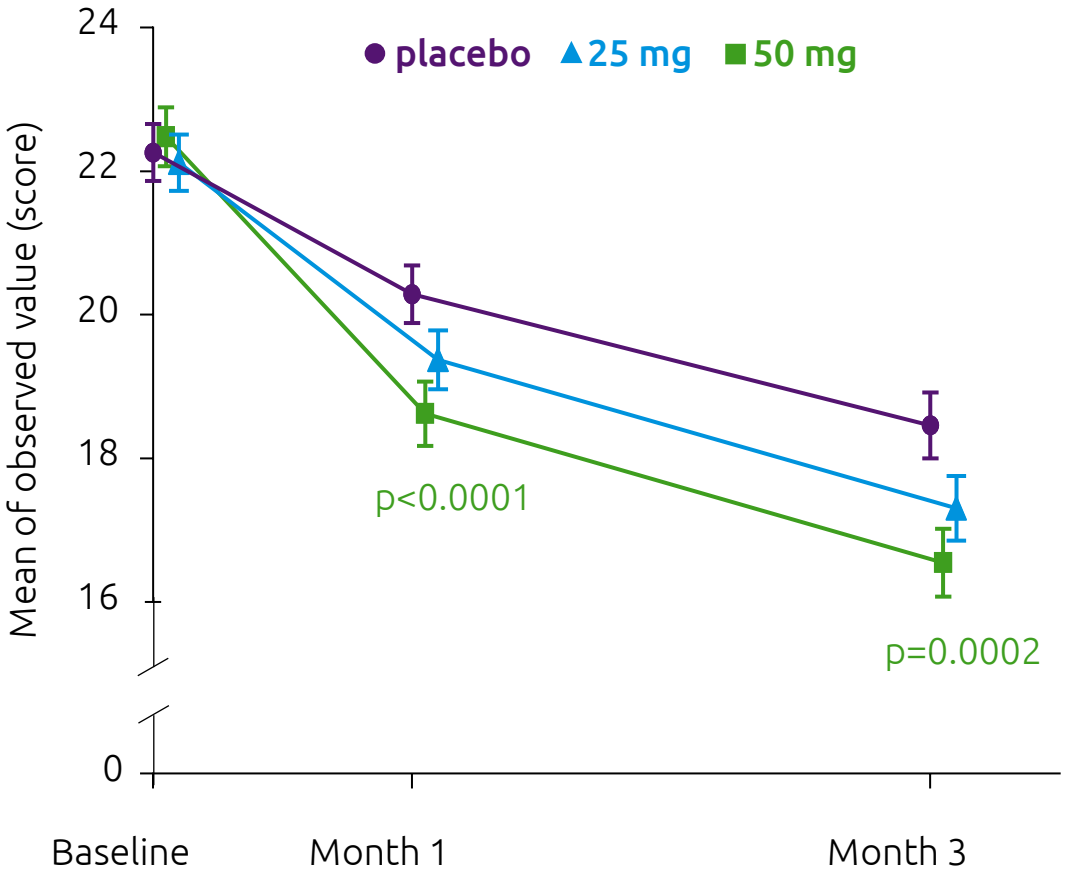
2º endpoint: IDSIQ sleepiness domain

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

CI = confidence interval; LSM = least squares mean

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

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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 ≤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)
Participants with ≥1 adverse event*	116 (38%)	117 (38%)	105 (34%)	121 (39%)	117 (38%)	100 (33%)
Adverse events* leading to treatment discontinuation	3 (1%)	7 (2%)	10 (3%)	4 (1%)	6 (2%)	7 (2%)
Participants with ≥1 serious adverse event	3 (1%)	2 (1%)	7 (2%)	3 (1%)	3 (1%)	4 (1%)
Participants with adverse event* (≥2% in any group)						
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)
Adjudicated adverse events†						
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**

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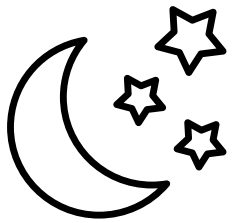
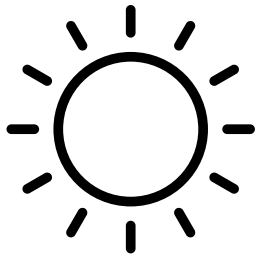
The daridorexant clinical program provides a wealth of evidence



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

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

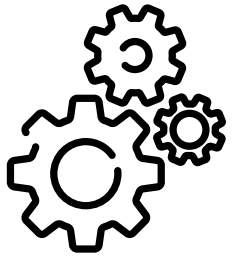


Daytime functioning perceived by patients (50 mg)

- 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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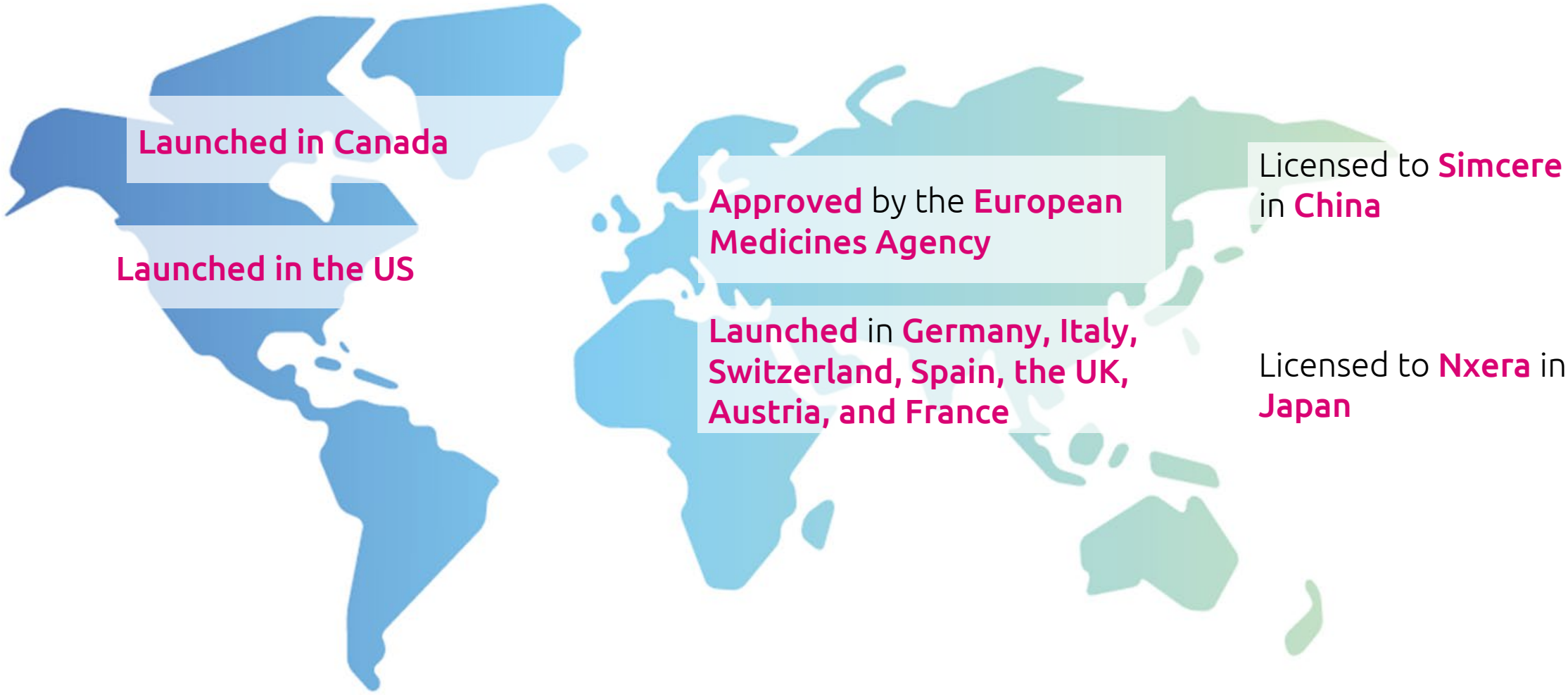
On track to become a global brand

QUVIVIQ daridorexant 25mg, 50mg tablets



Launched in Canada

Launched in the US

Approved by the **European Medicines Agency**

Launched in **Germany, Italy, Switzerland, Spain, the UK, Austria, and France**

Licensed to **Simcere** in **China**

Licensed to **Nxera** in **Japan**

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idorsia

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 & Mochida

Nxera Pharma

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

Mochida

Supply, co-development and co-marketing of daridorexant in Japan

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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.

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

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Educational campaigns to prime the US market

The Alliance for Sleep

Top sleep experts drive education, awareness and research to medical community and consumers

Seize the Night & Day

Partnering with **Jennifer Aniston** to drive awareness and education

Wake up America Sleep Survey

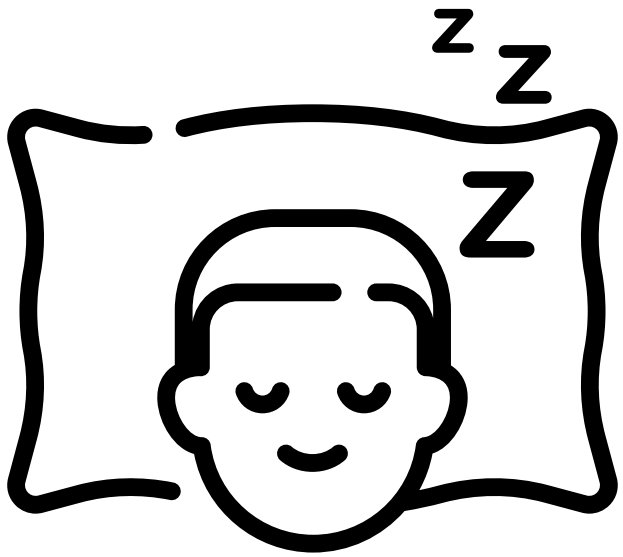
Consumer and HCP survey to reveal views and patient unmet needs

The Quest for Sleep

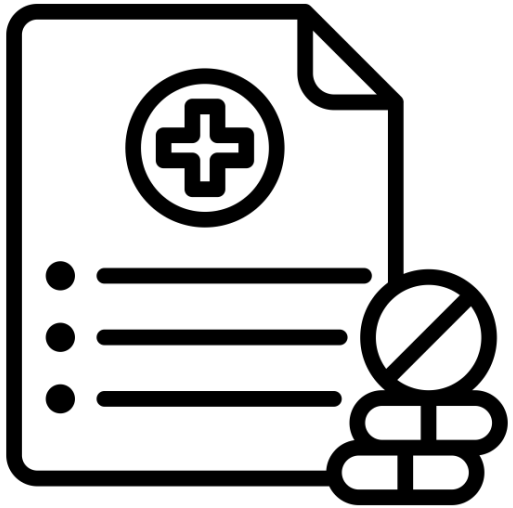
Documentary Film using storytelling to raise awareness of insomnia, and bring the science of sleep to life

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

>155K
patients
treated



~450K
prescriptions
dispensed



>45K
prescribers

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idorsia

“We have streamlined the US operations for 2024 with the mindset **‘Achieving more with less’**. For example, our dynamic digital marketing campaign is the #1 driver of traffic to the QUVIVIQ website so it will replace DTC TV commercials realizing substantial cost savings.”

Tosh Butt
President Idorsia US

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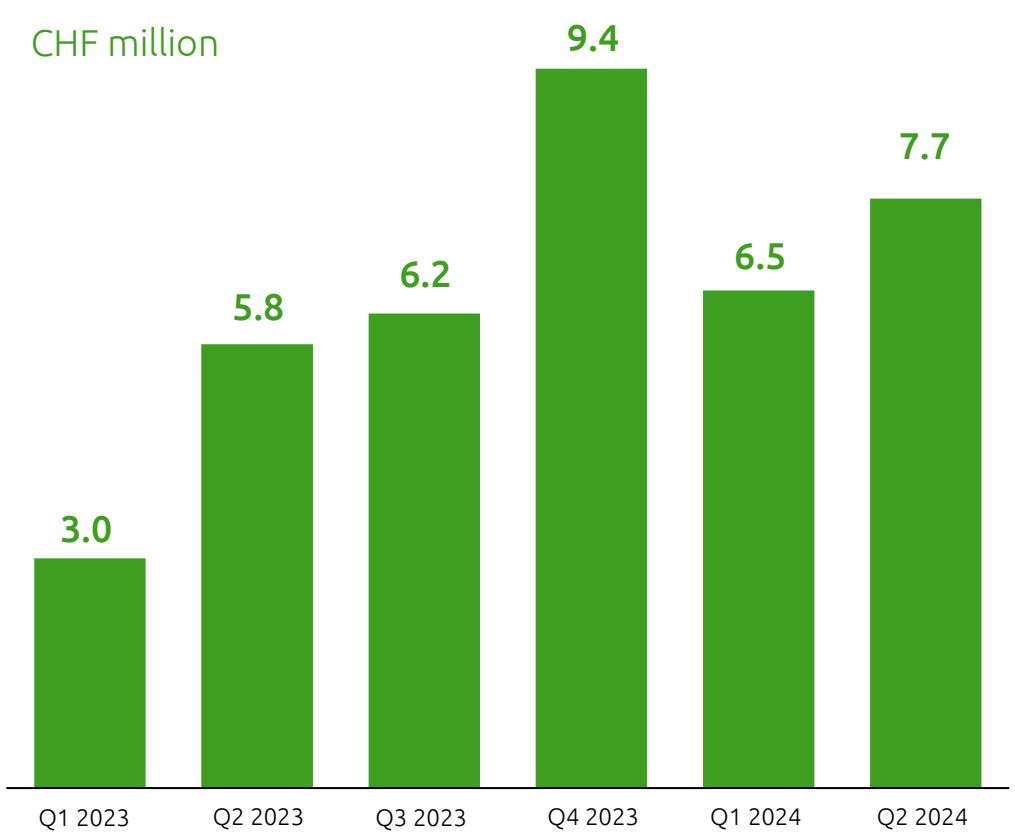
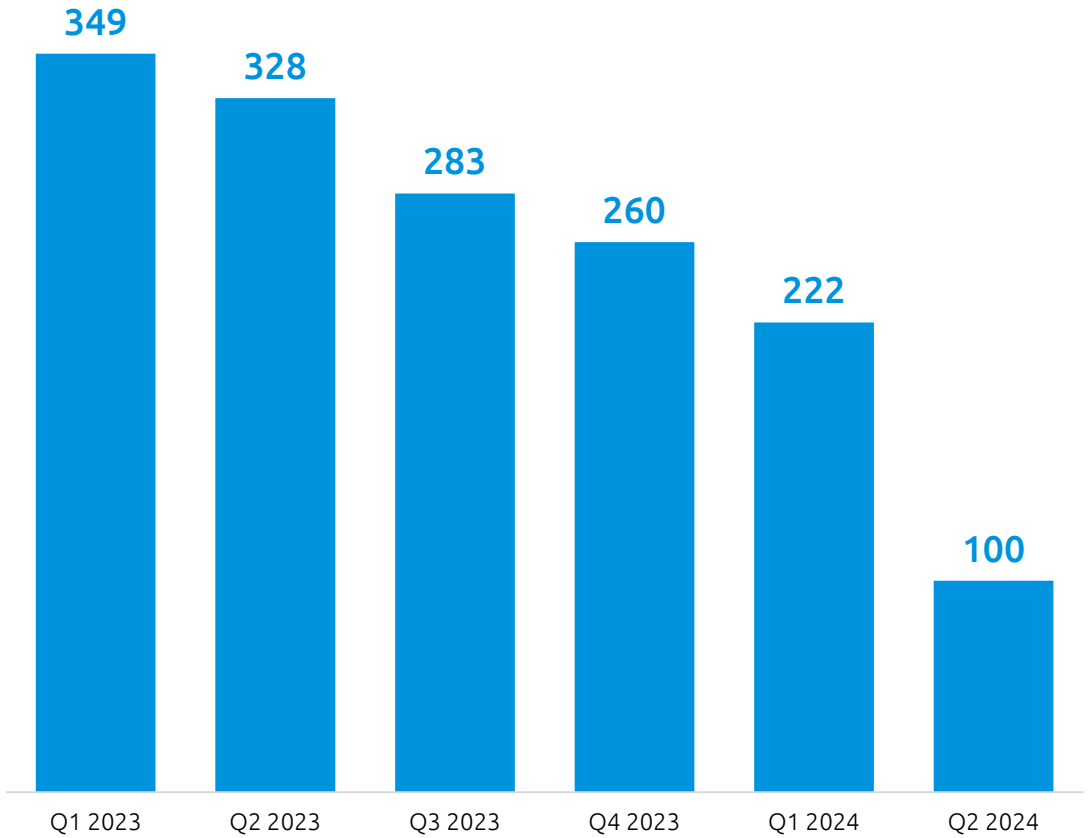
US sales outpaces field force changes

US net sales



QUVIVIQ field force



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Scheduling under discussion

Citizen's Petition
requesting de-scheduling
of the DORA class
of medicines
progressing

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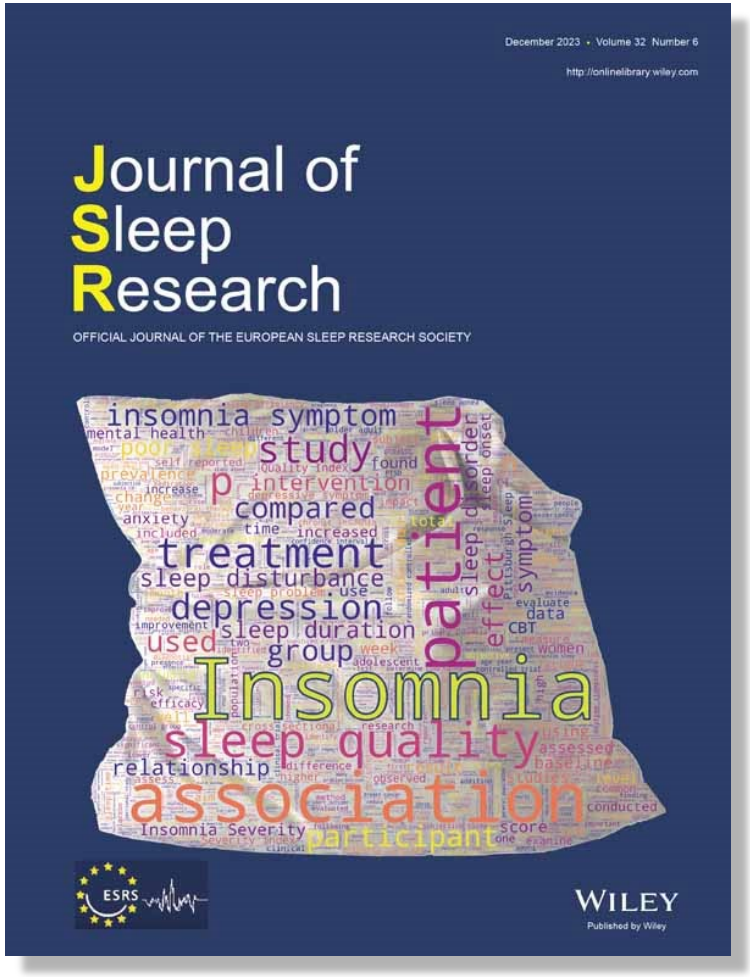
The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023

"The introduction of DORAs has probably been the most significant recent development in the pharmacological treatment of insomnia..."



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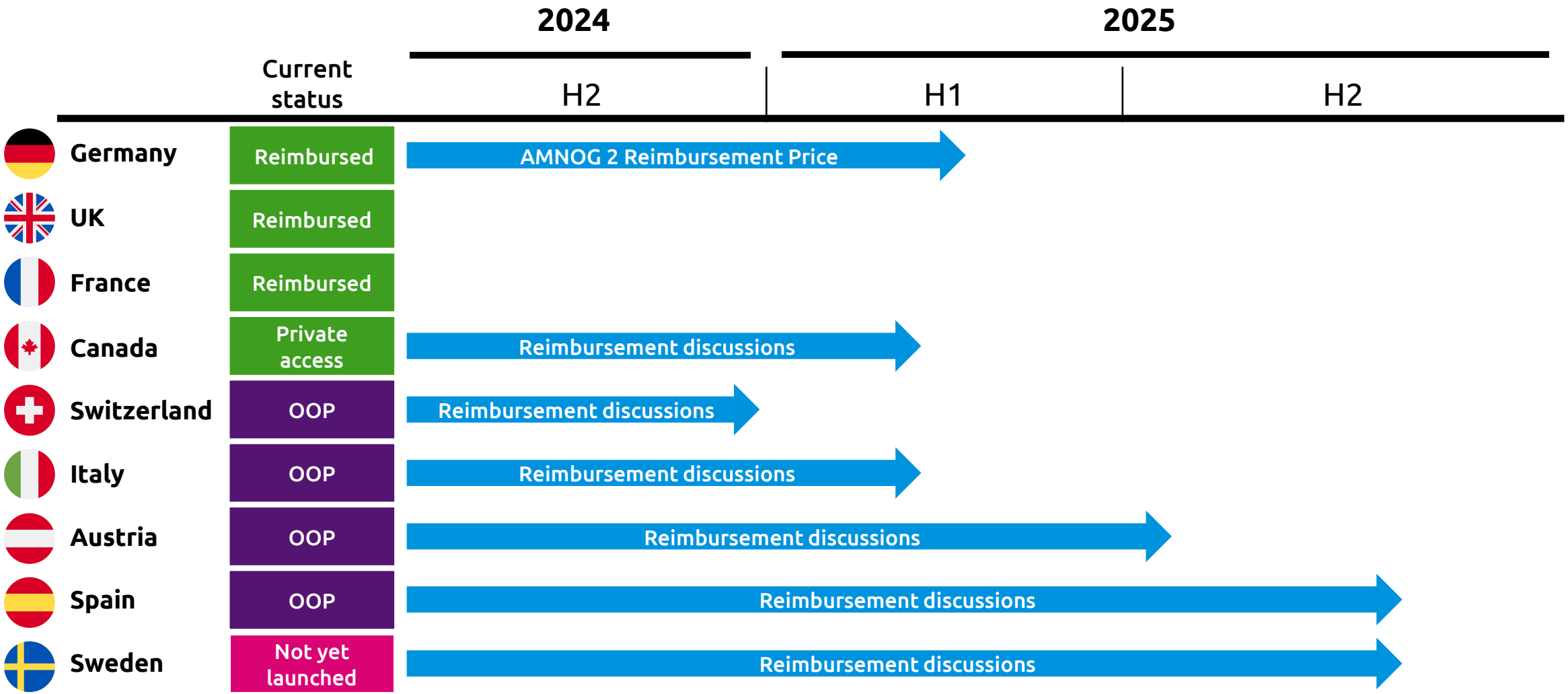
EUCAN reimbursement status



OOP = Out of pocket

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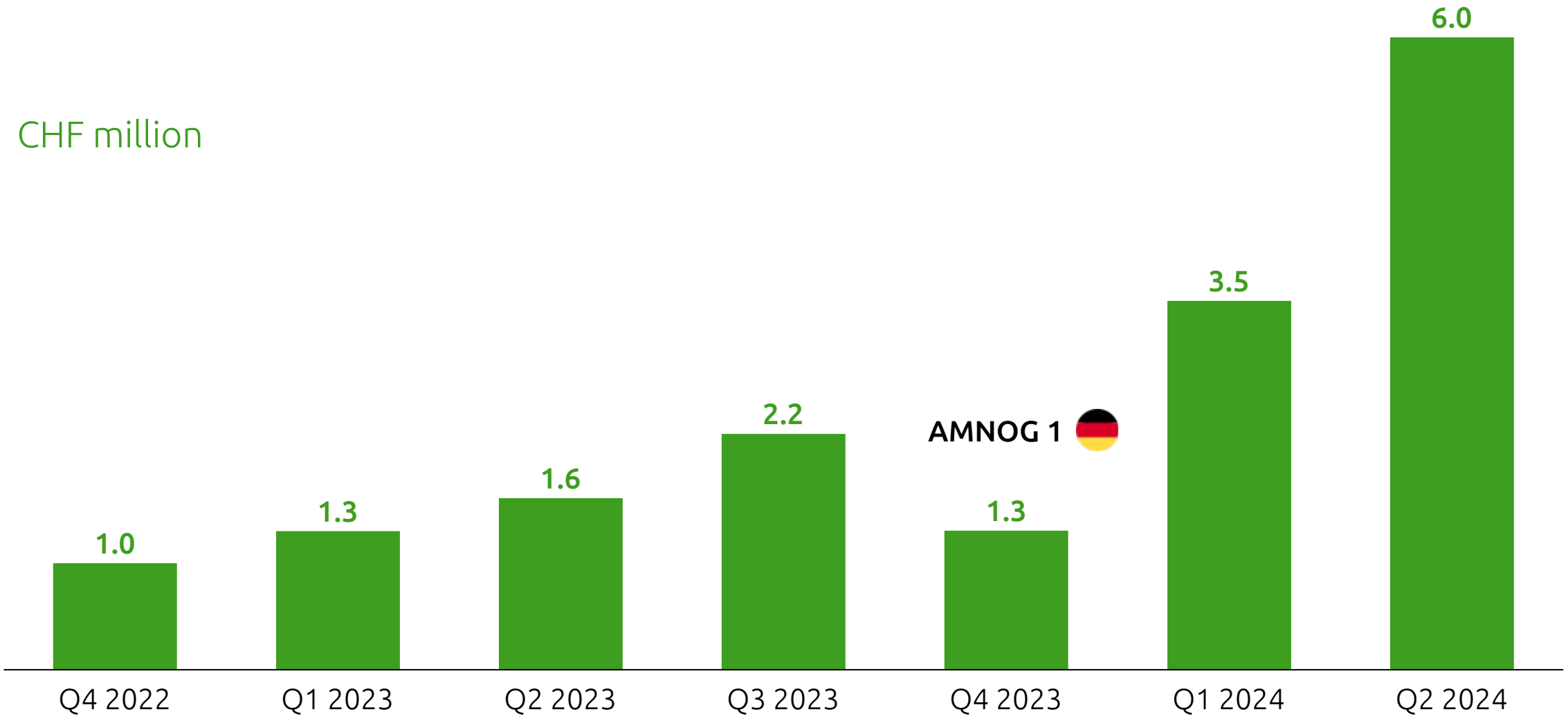
EUCAN net sales growth



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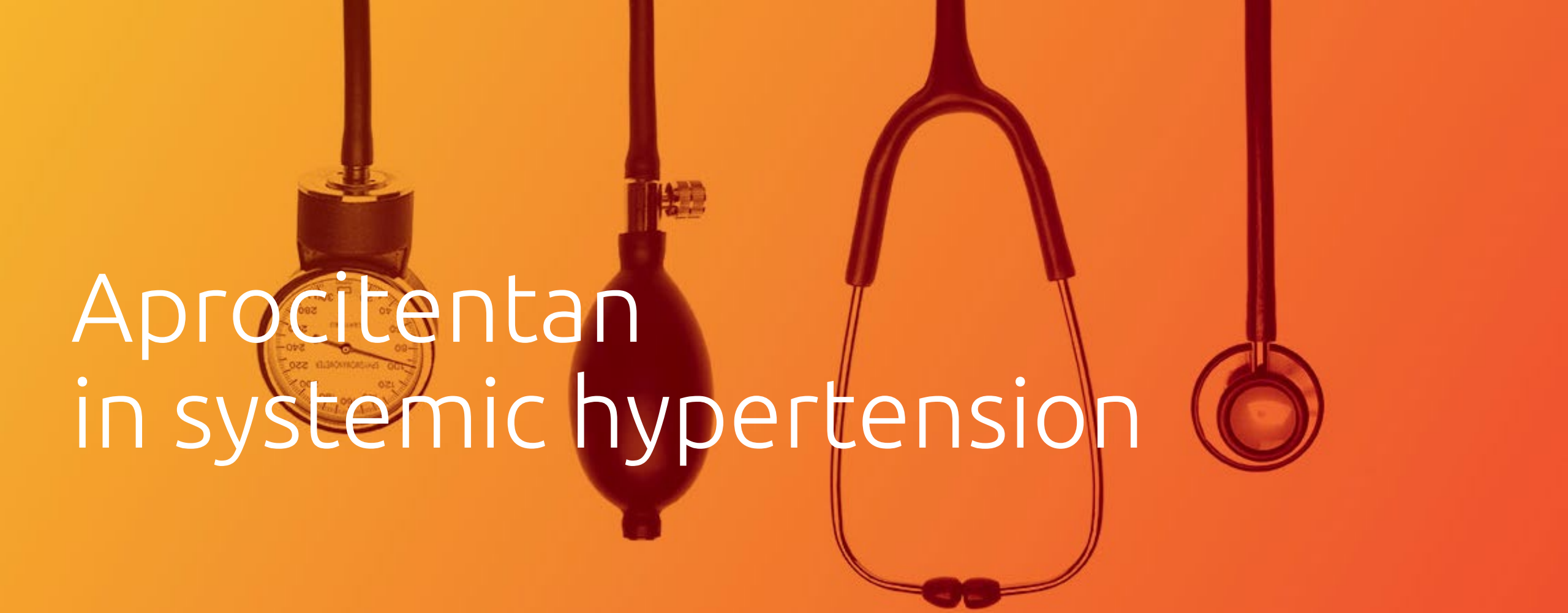


Aprocitentan in systemic hypertension

Aprocitentan is only approved in the US under the tradename TRYVIO™ where it will be made available later in 2024, and in Europe under the tradename JERAYGO™. Market authorization is under review in other countries.

Unlocking value for Idorsia

Exploring best avenues to maximize aprocitentan value

TRYVIO™ (aprocitentan) 12.5 mg approved in March 2024

JERAYGO™ (aprocitentan) 12.5 mg & 25 mg approved in June 2024

TRYVIO™ (aprocitentan) 12.5mg tablets

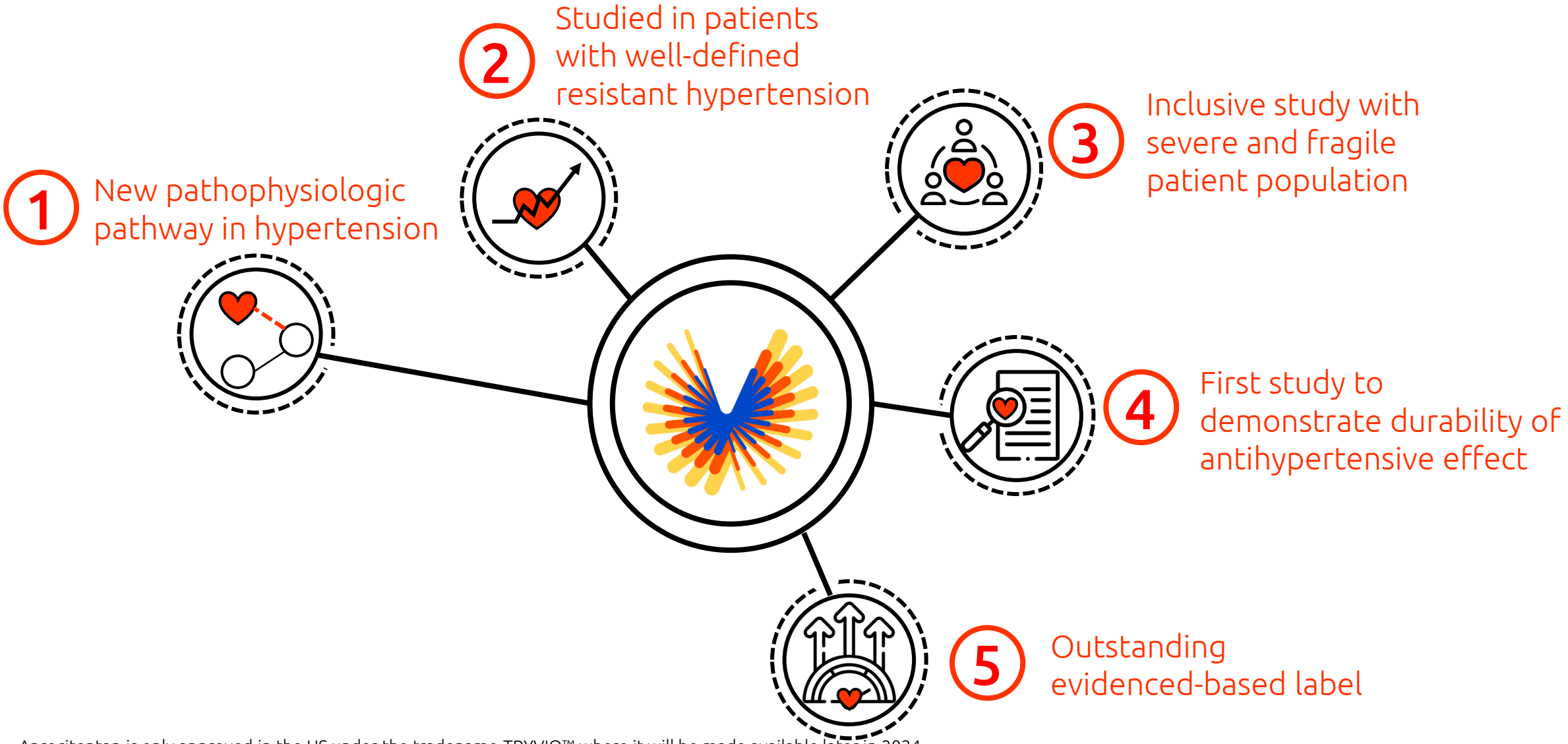
JERAYGO™ aprocitentan

Aprocitentan is only approved in the US under the tradename TRYVIO™ where it will be made available later in 2024, and in Europe under the tradename JERAYGO™. Market authorization is under review in other countries.

"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 approved in the US under the tradename TRYVIO™ where it will be made available later in 2024, and in Europe under the tradename JERAYGO™. Market authorization is under review in other countries.

“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.”

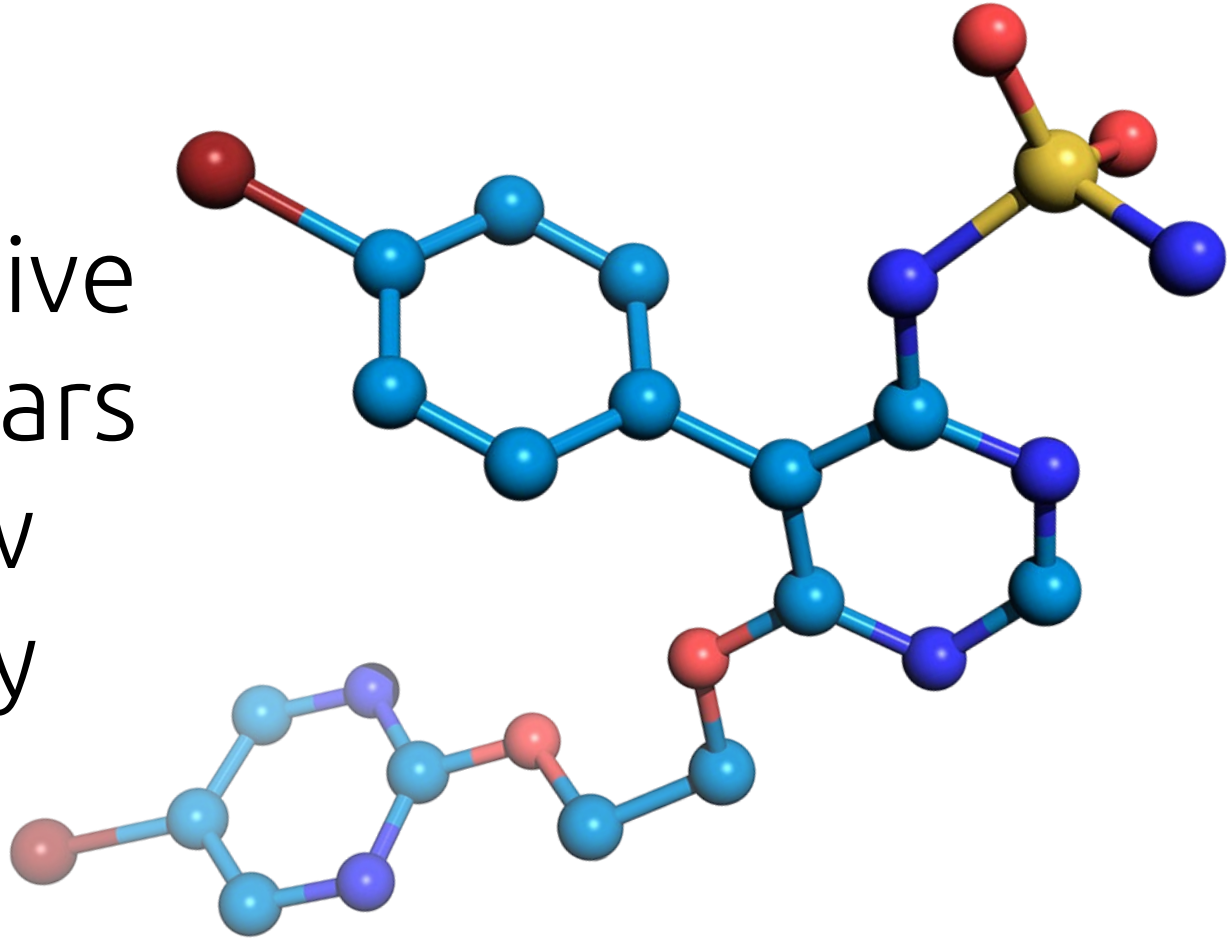
Martine Clozel
Chief Scientific Officer

Aprocitentan is only approved in the US under the tradename TRYVIO™ where it will be made available later in 2024, and in Europe under the tradename JERAYGO™. Market authorization is under review in other countries.

TRYVIO™
(aprocitentan) 12.5mg tablets

JERAYGO™
aprocitentan

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



Aprocitentan is only approved in the US under the tradename TRYVIO™ where it will be made available later in 2024, and in Europe under the tradename JERAYGO™. Market authorization is under review in other countries.

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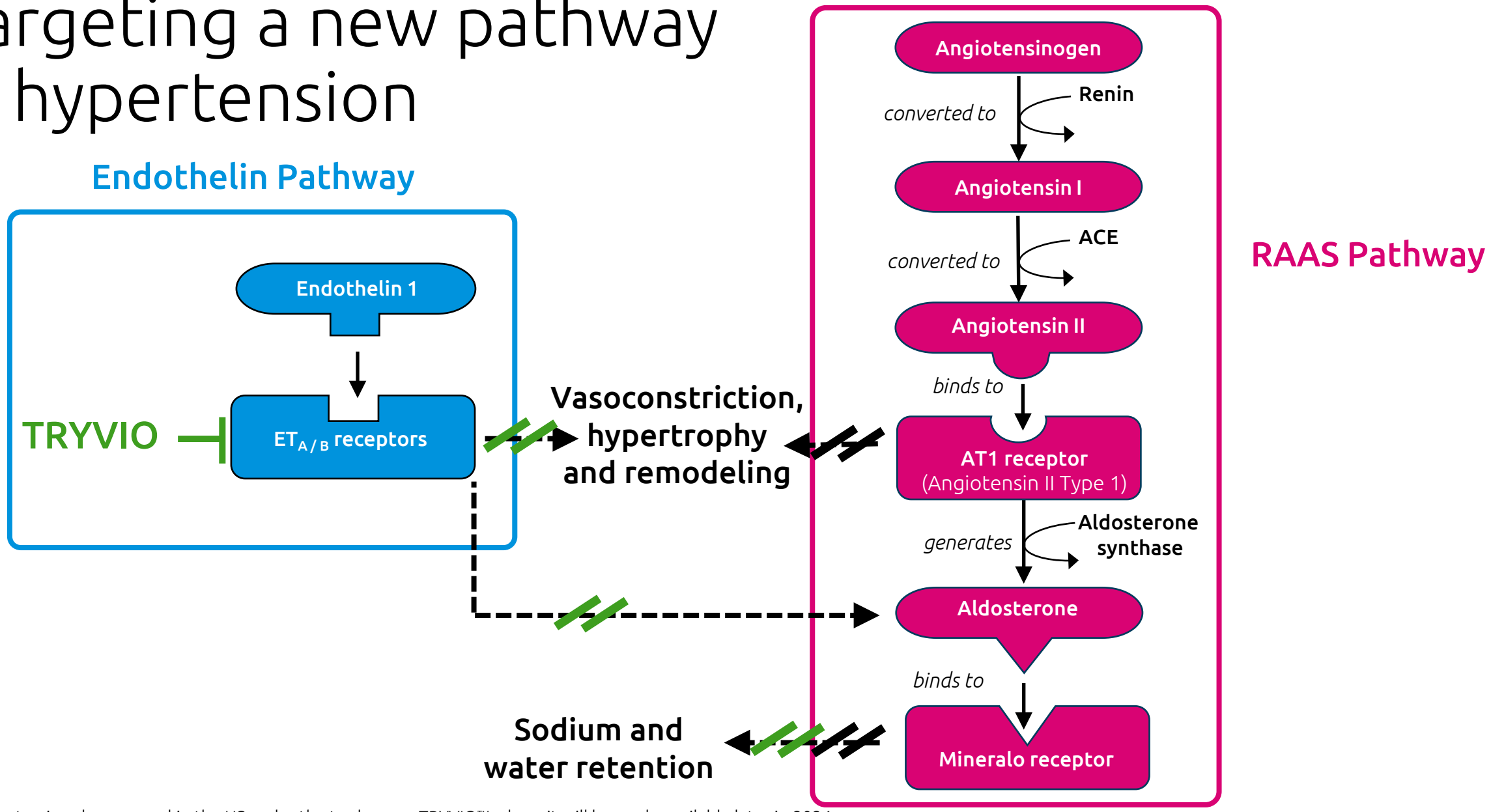
Targeting a new pathway in hypertension



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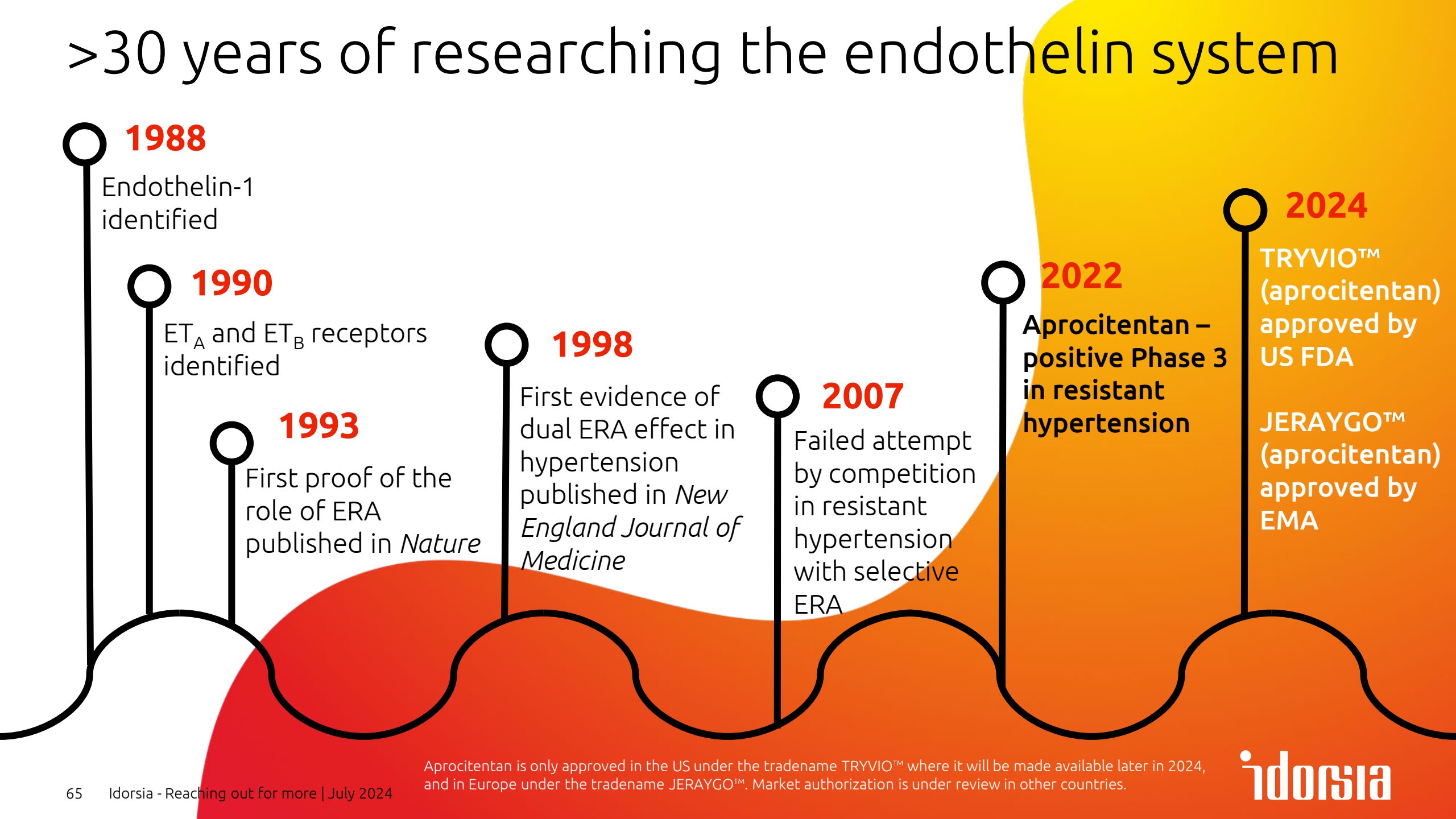
>30 years of researching the endothelin system



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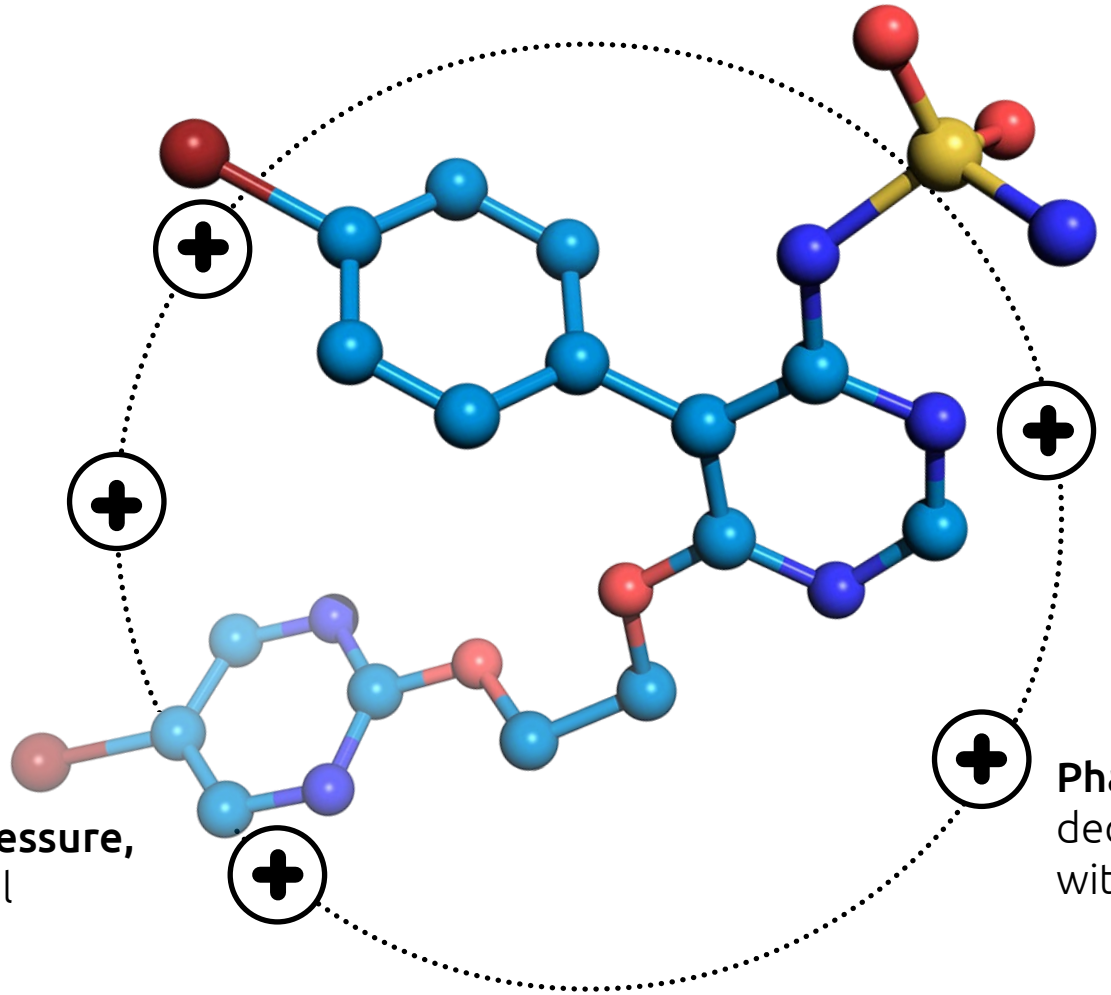
Aprocitentan selected for its ideal properties

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

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“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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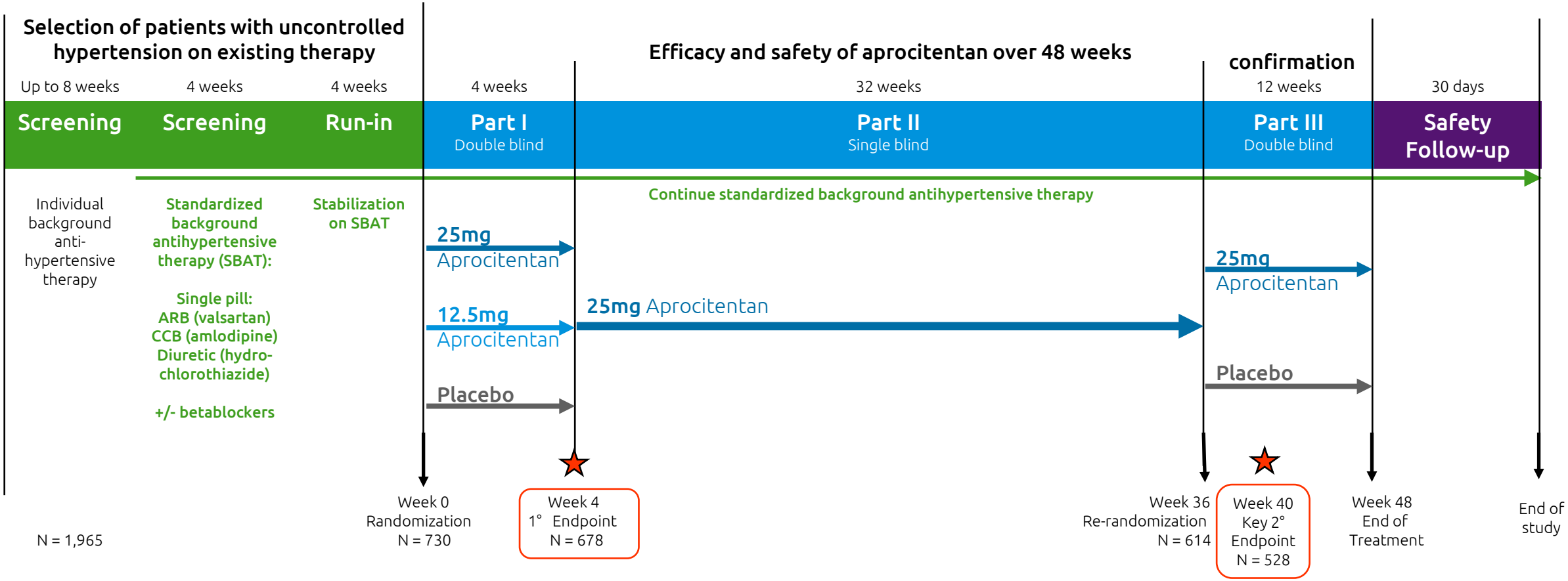
PRECISION investigated durability of BP reduction



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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)
65 - <75	**249**	**(34.1)**
≥75	**72**	**(9.9)**
Race		
White	605	(82.9)
Black or African American	**82**	**(11.2)**
Asian	38	(5.2)
Other	5	(0.7)
BMI# (kg/m^2)		
Mean (SD)	**33.7**	**(6.2)**
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)
30–300	**174**	**(24.3)**
> 300	**90**	**(12.6)**
missing	13	
eGFR [mL/min]*		
< 30	**21**	**(2.9)**
30 – < 45	**48**	**(6.6)**
45 – < 60	**93**	**(12.7)**
≥ 60	568	(77.8)

Medical history		
Diabetes mellitus	**395**	**(54.1)**
Congestive heart failure	**143**	**(19.6)**
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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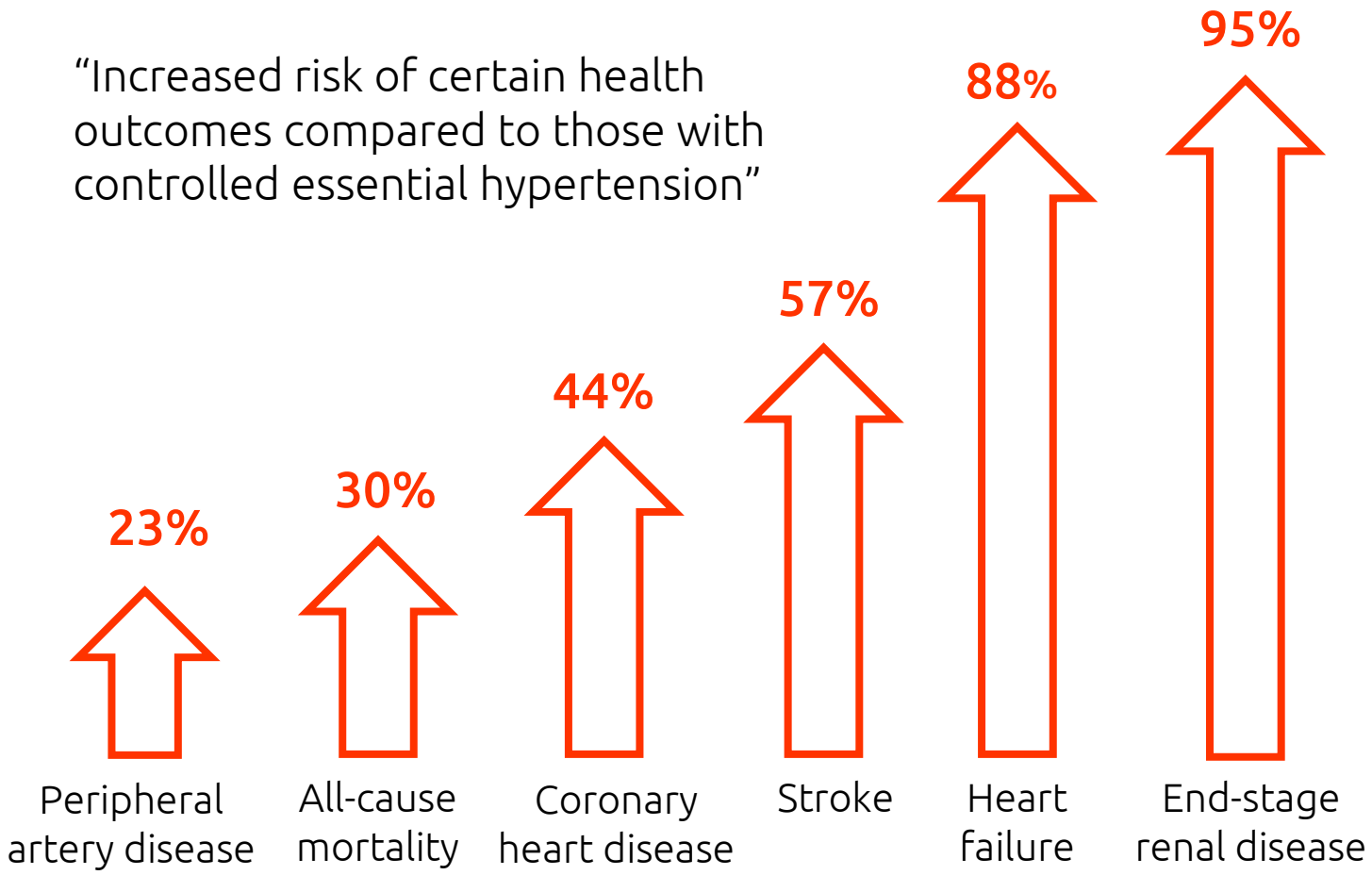
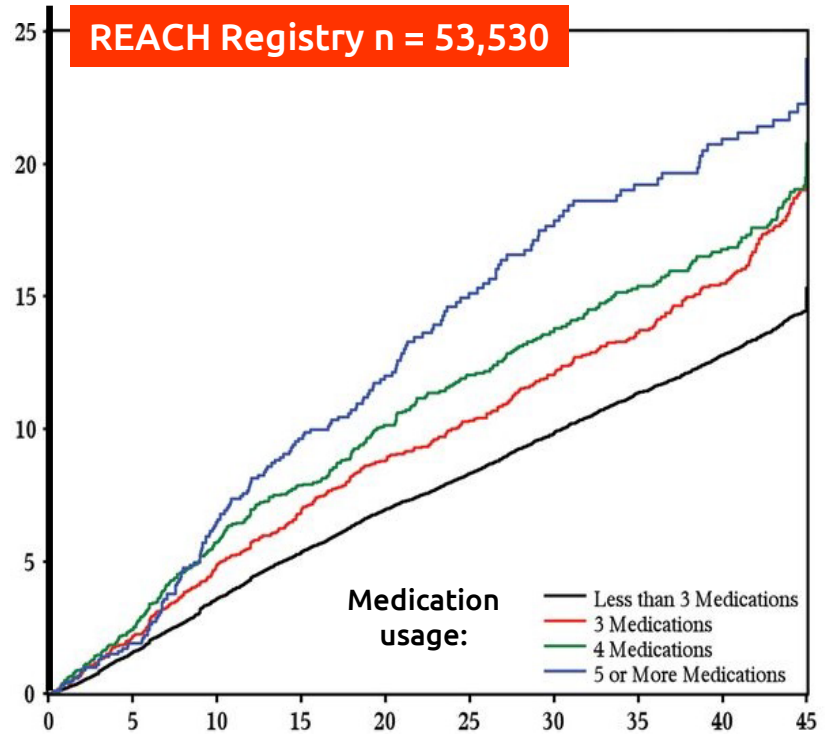
Disease burden when hypertension is uncontrolled

"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

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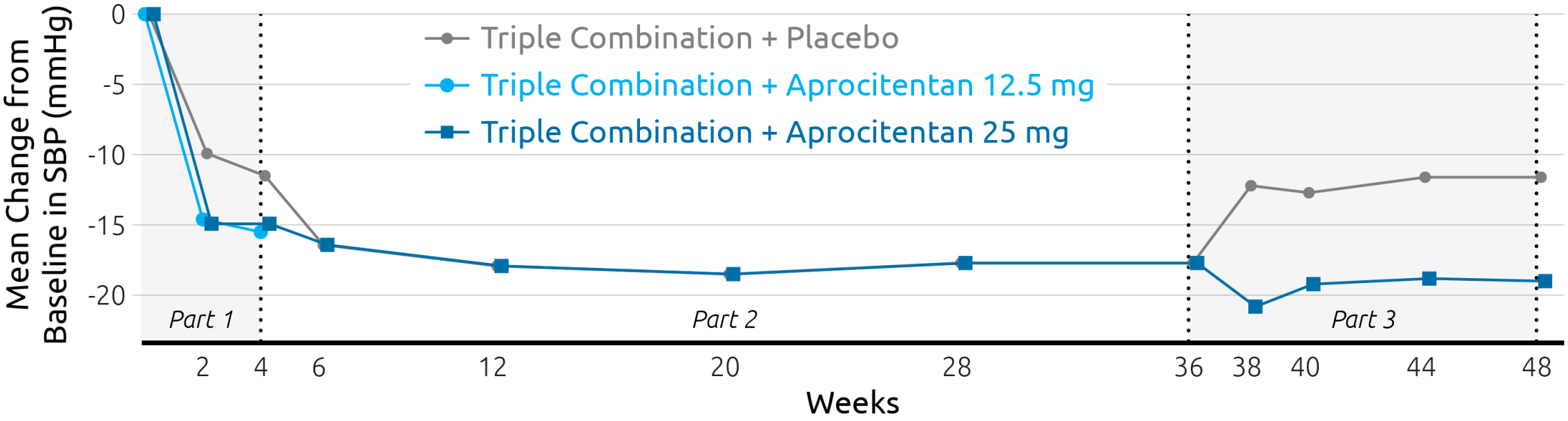
Significant and sustained BP reduction

Absolute BP reduction of 15 mmHg

TRYVIO™ (aprocitentan) 12.5mg tablets



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

TRYVIO™ (aprocitentan) 12.5mg tablets

----------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)

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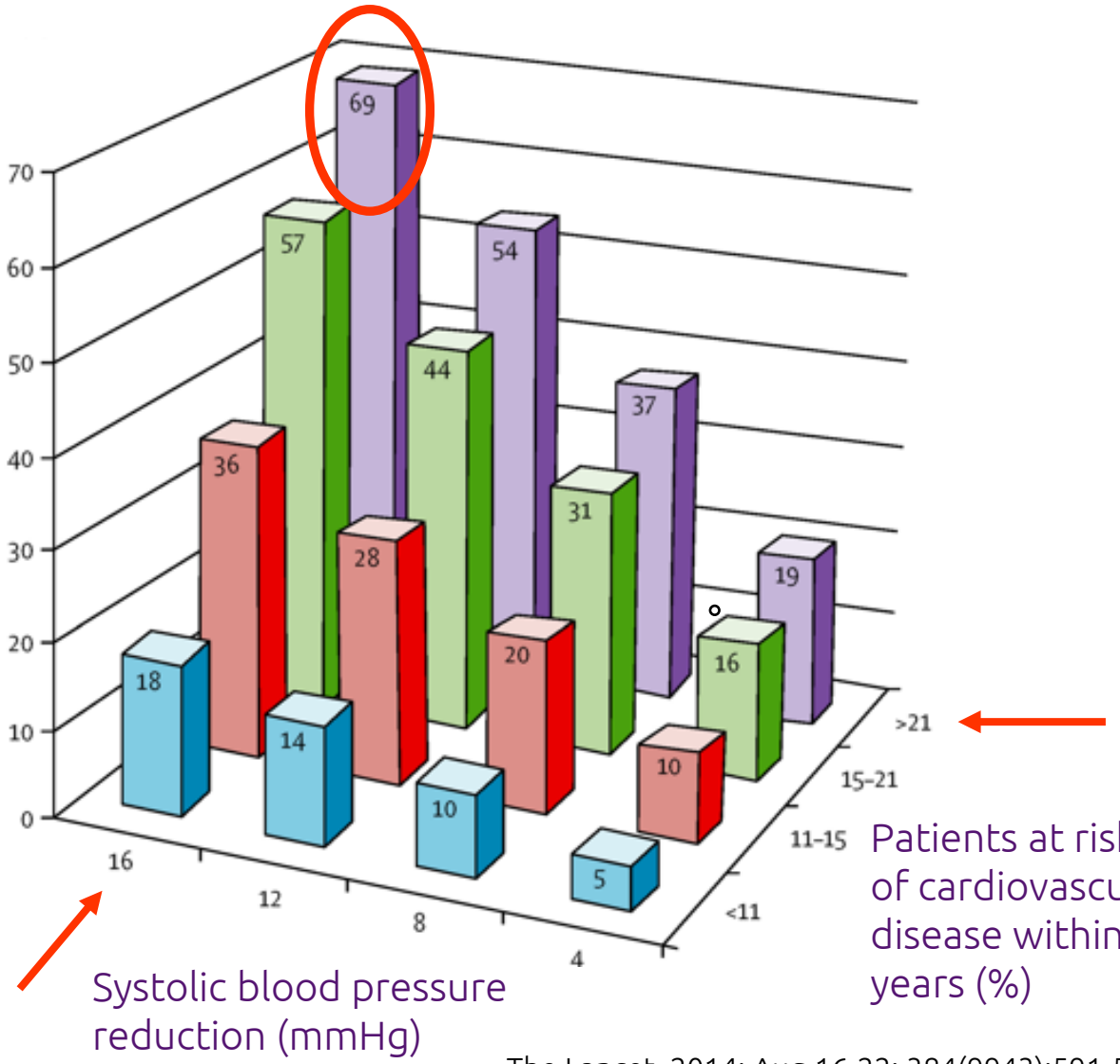
Reduction in BP will prevent CV events

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



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

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

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USPI Highlights: Dosage and Administration

TRYVIO™ (aprocitentan) 12.5mg tablets

----------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**

TRYVIO™ (aprocitentan) 12.5mg tablets

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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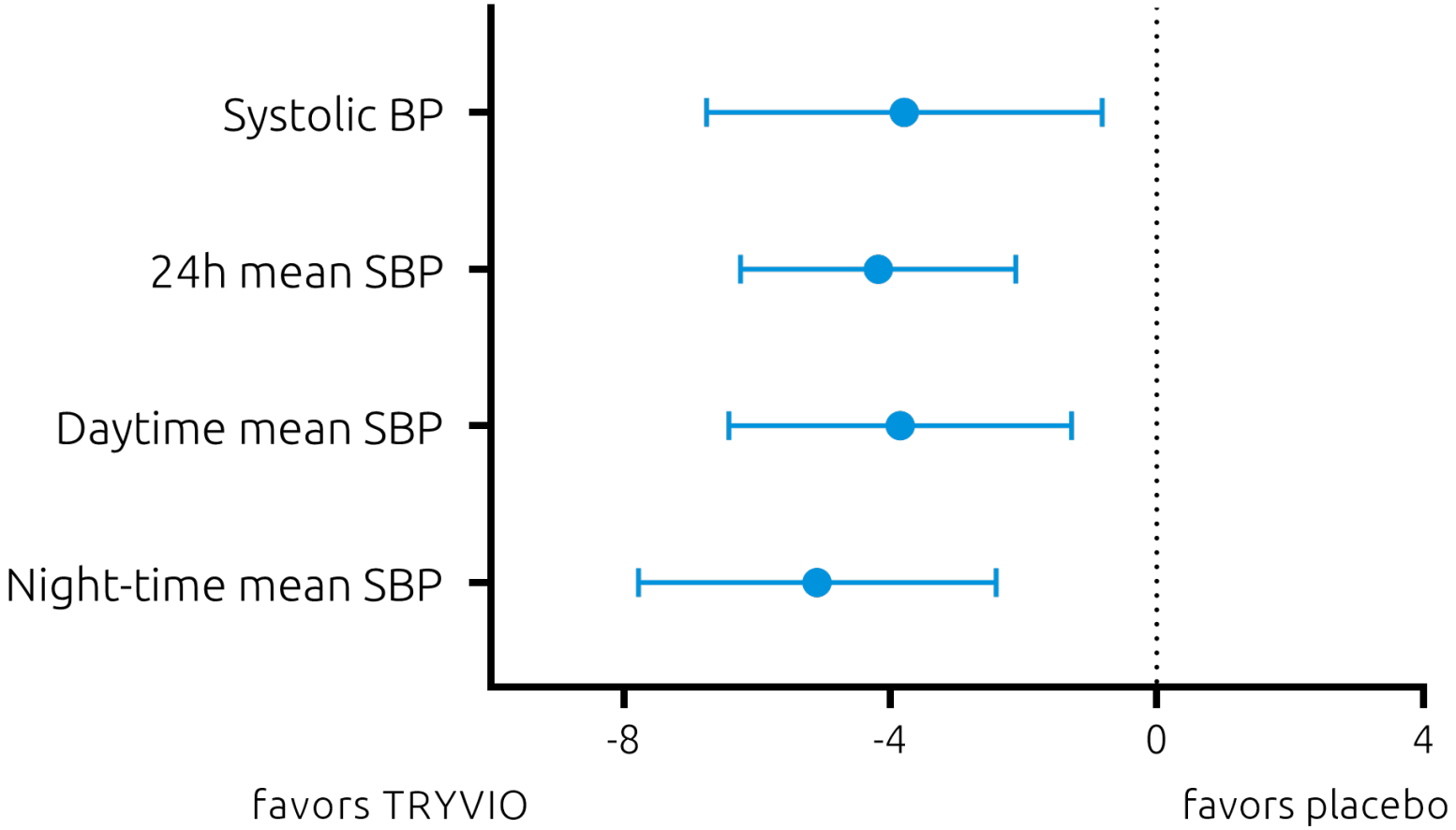
Consistent effect between BP measurement methodologies

TRYVIO™ (aprocitentan) 12.5mg tablets



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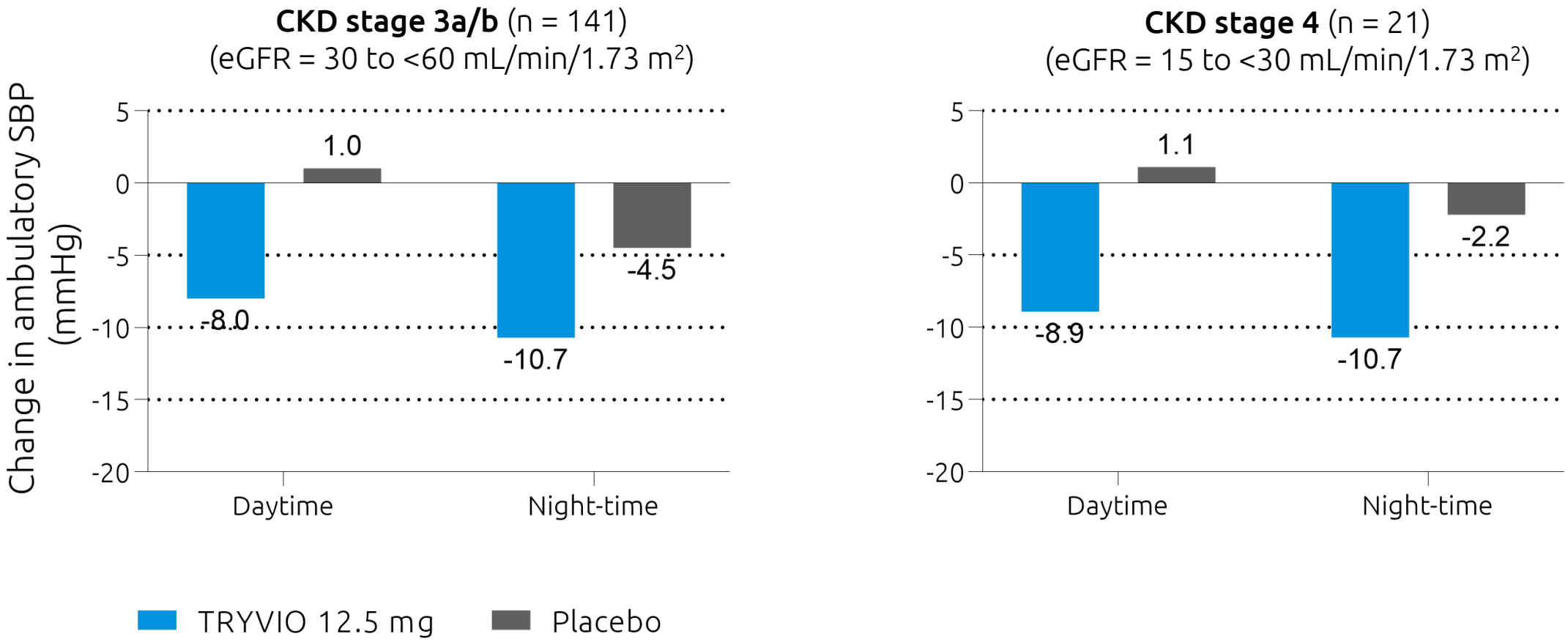
Consistent effect among subgroups: E.g., Patients with chronic kidney disease

TRYVIO™ (aprocitentan) 12.5mg tablets



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USPI Section 6: Adverse Reactions

TRYVIO™ (aprocitentan) 12.5mg tablets

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

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

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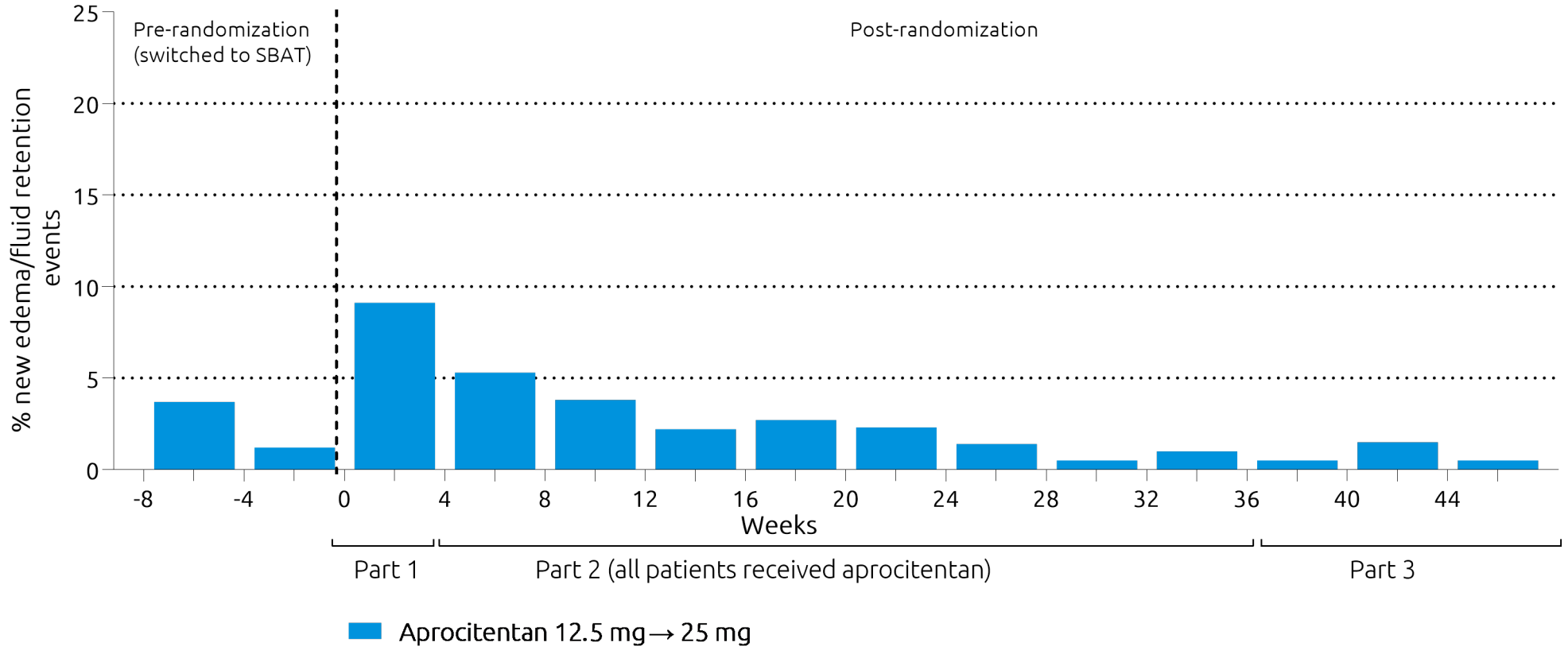
Incidence of edema

TRYVIO™ (aprocitentan) 12.5mg tablets

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 a REMS called the TRYVIO REMS because of the risk of embryo-fetal toxicity *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)]*.

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.

Further information is available at 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”

Tausif ‘Tosh’ Butt
President Idorsia US

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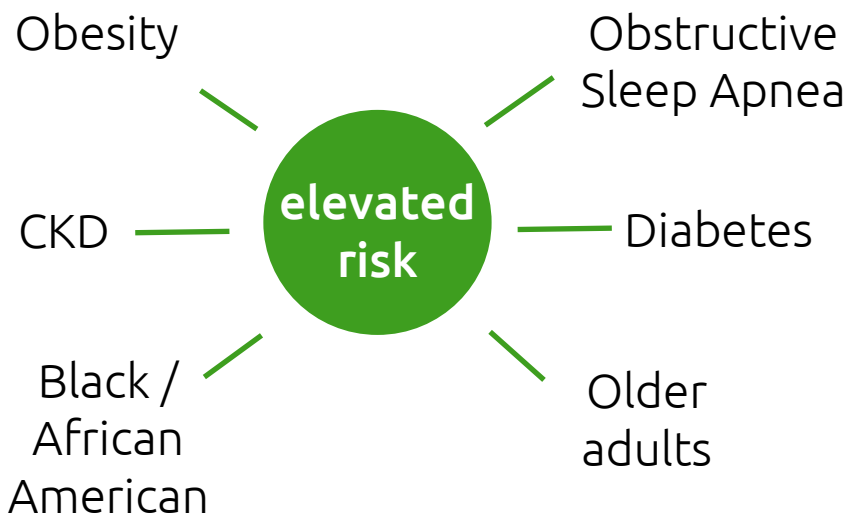
Hypertension is the leading modifiable risk factor for early death and disability

The importance of treating hypertension is well established

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

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



2-6x
Greater Risk

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

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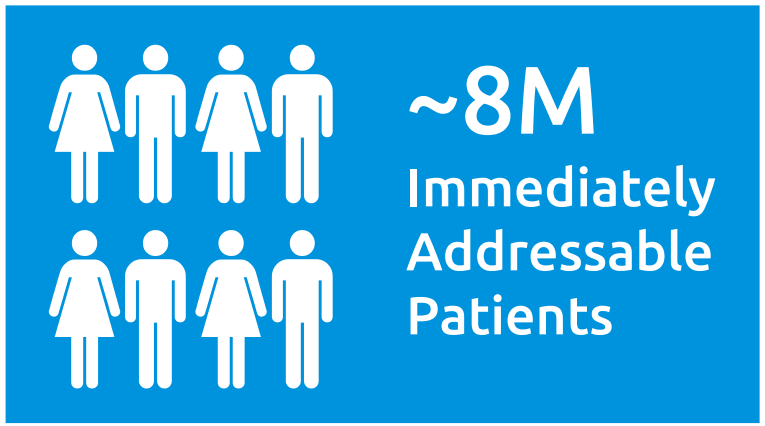
~8M patients immediately addressable at launch* – most with multiple comorbidities

TRYVIO™ (aprocitentan) 12.5mg tablets

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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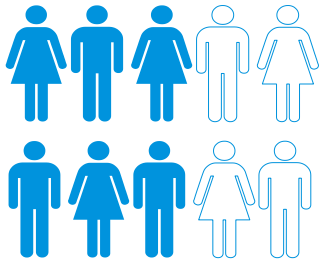
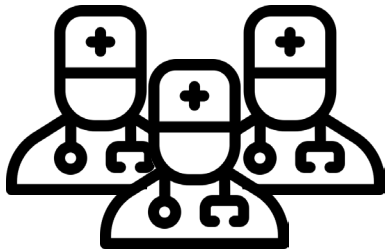
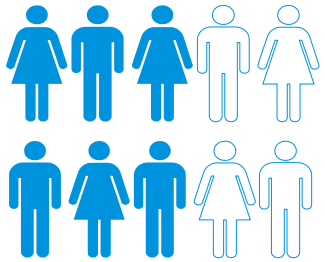
Prescribers span several specialties – often more than one HCP involved

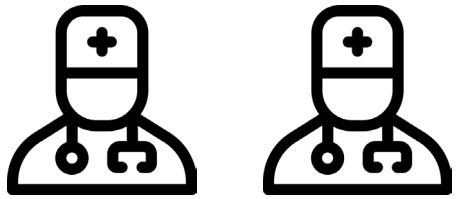


60% of Patients
on 3+ Meds were treated by 2 or more HCPs

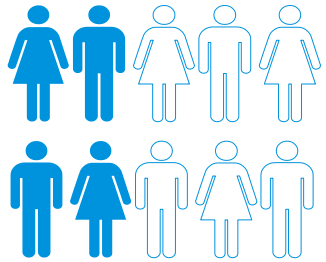




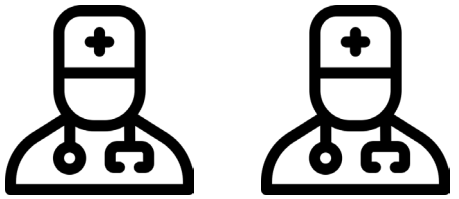
50-60% of patients
on 3+ Meds were treated by cardiologists and nephrologists



cardiologists nephrologist



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



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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Important aspects of TRYVIO for US market

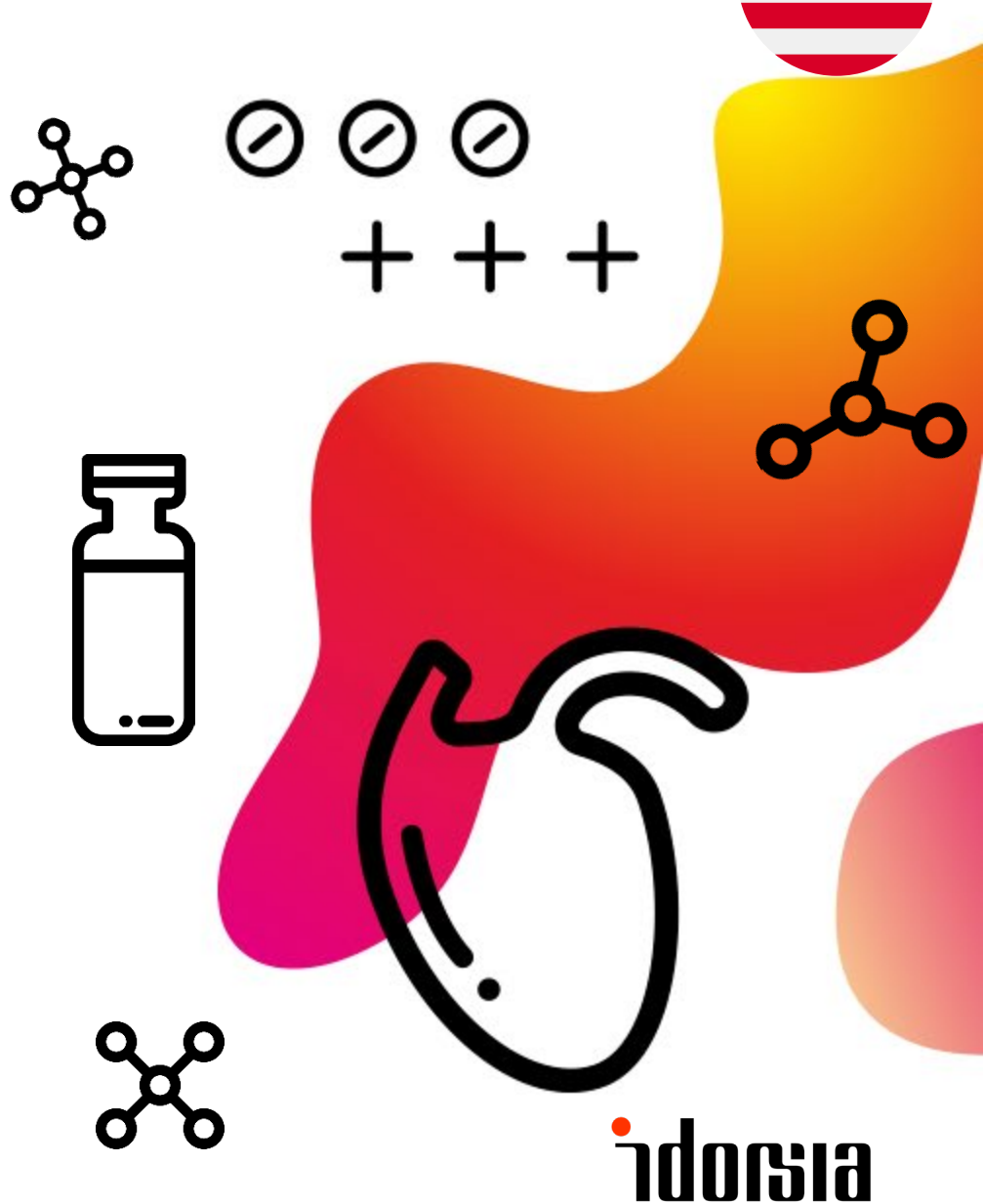
TRYVIO™
(aprocitentan) 12.5mg tablets

Easy to prescribe

- **One dose** for all patients
- No clinically relevant drug-drug interactions
- Manageable side-effect profile
- One-time REMS certification for HCP and Pharmacy only

Easy to use

- **Oral** once-daily tablet, with or without food
- **Long half-life** (approx. 41 hours)



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Preparing the TRYVIO US launch

Re-acquisition of aprocitentan from J&J in September 2023

TRYVIO™ (aprocitentan) 12.5mg tablets

- **Target product availability in Q4 2024**
  - Distribution network setup
  - WAC price published: $775 per month
  - REMS program being establishing
  - Access: payer discussions initiated
  - Hiring and training of MSLs underway

ACC 2024, Atlanta, April 6-8, 2024

Commercial launch
Q1 2025

Congress presence 2024
September: AHA-HTN
October: ASN Kidney Week
November: AHA

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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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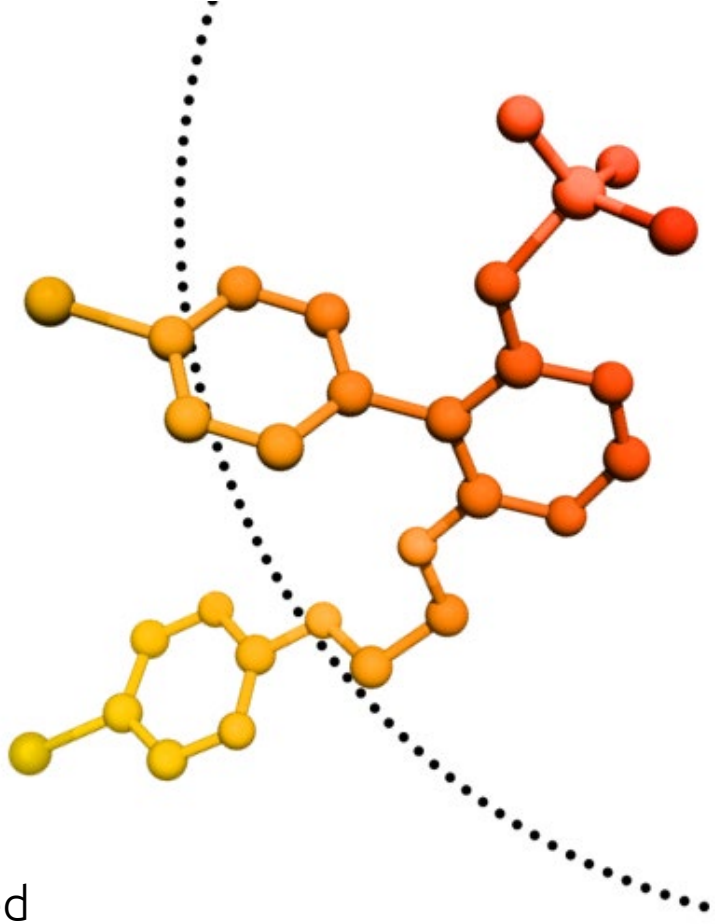
JERAYGO™ (aprocitentan) for resistant hypertension in the EU

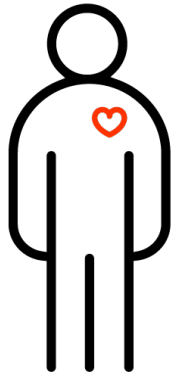
New mode of action in systemic hypertension

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

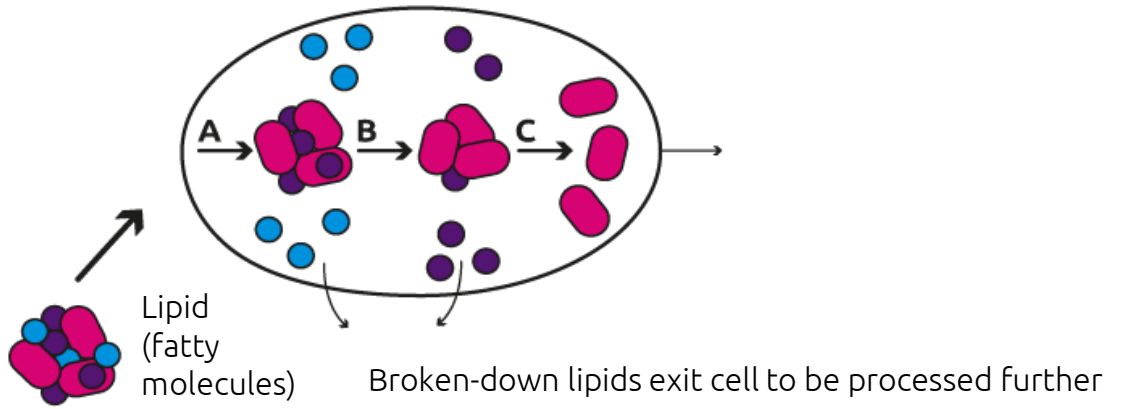
As the disease is progressive, **early diagnosis is essential** to manage the symptoms as soon as possible and reduce the risk of developing serious complications

What is the role of lipids in the body?

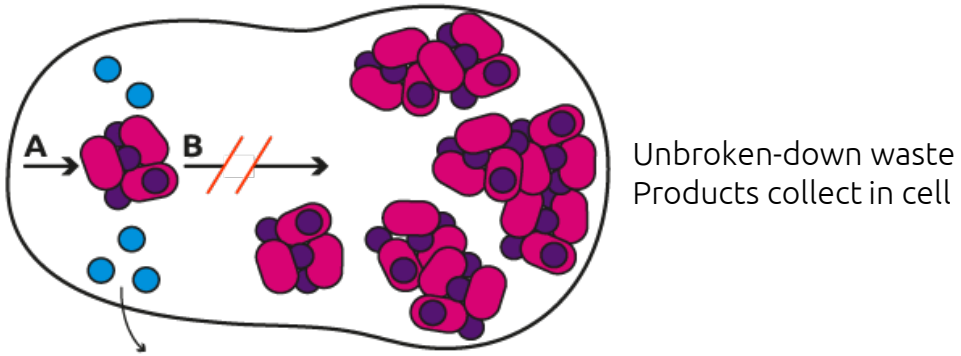
- Lipids are fat-like substances such as fatty acids, oils, waxes and steroids. A well-known example is cholesterol
- Lipids are stored naturally in the body's cells and organs and are vital to their healthy functioning
- Normally, the body is able to process lipids effectively, which keeps them within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

What happens in patients with lysosomal storage disorders?

Normal breakdown of lipids



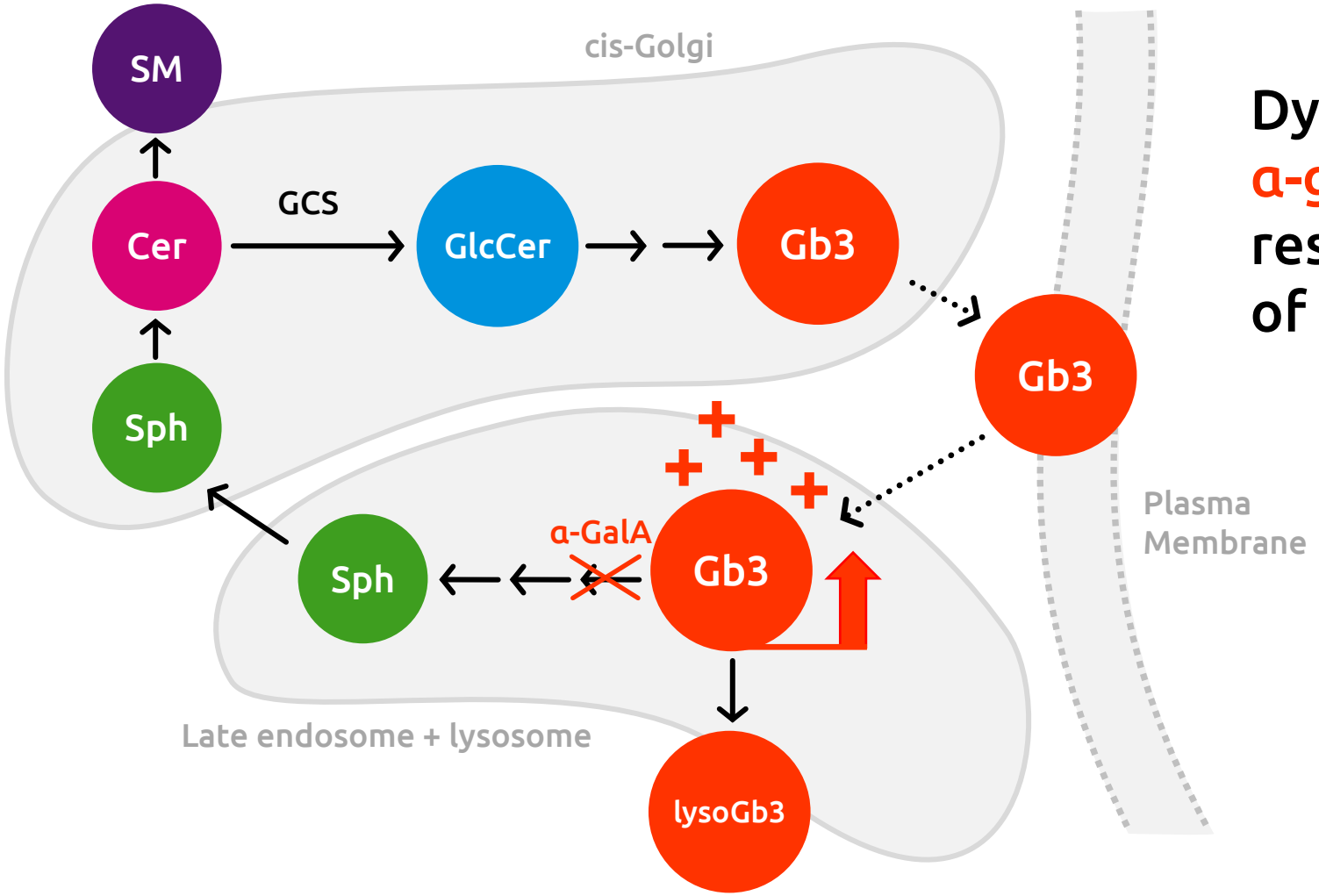
When enzyme to break down lipid is deficient



Lipids can't be processed and build up in cell

Fabry disease

Biochemical mechanism



Dysfunctional or absent α-galactosidase A results in accumulation of Gb3 in various organs

Cer	ceramide
GCS	glucosylceramide synthase
GlcCer	glucosylceramide
Gb3	globotriaosylceramide
lysoGb3	globotriaosylsphingosine
α-GalA	α-galactosidase A
SM	sphingomyelin
Sph	sphingosine

Inheritance pattern in Fabry disease

X-linked recessive genetic disease

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

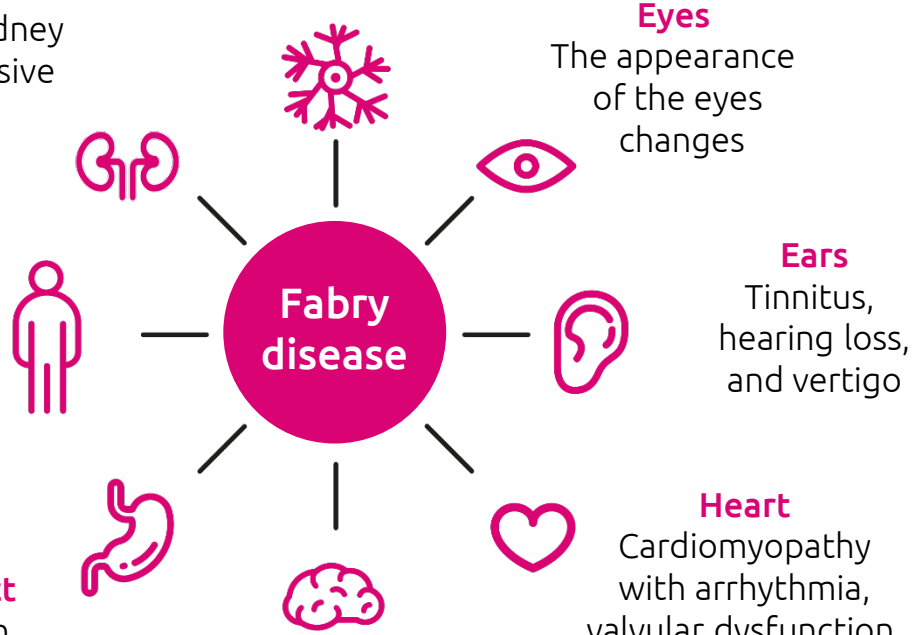
Random X-inactivation in Fabry female 'carriers': both genders affected

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



Neuropathic pain
Pain resulting from damage to or dysfunction of the nervous system

Kidneys
Cysts, reduced kidney function, progressive kidney failure

Eyes
The appearance of the eyes changes

Skin
Dark red spots or rashes, burning / tingling sensations, sensitivity to temperature and profuse sweating

Ears
Tinnitus, hearing loss, and vertigo

Heart
Cardiomyopathy with arrhythmia, valvular dysfunction, ischemia, left heart failure

Digestive Tract
Abdominal pain, constipation, diarrhea, and nausea

Brain
Strokes (in severe cases), and dizziness

- **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

Clinical symptoms

Neuropathic pain, GI, hearing loss, hypohydrosis

Clinical events

Stroke, cardiac and renal events

Pedigree analysis

Family members

(between children and parents)

Enzyme assay

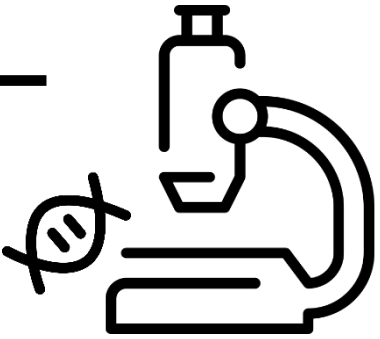
Leukocyte α-GalA

Genotyping

>830 mutations

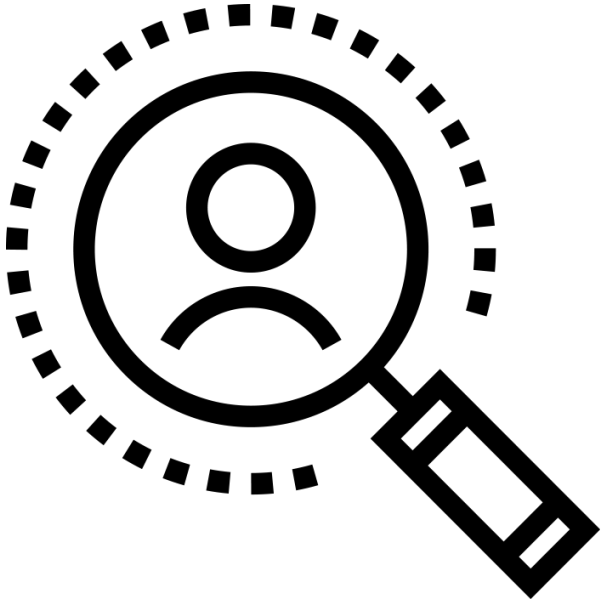
Biomarkers

Gb3 in plasma and urine



Epidemiology of Fabry disease

Patients diagnosed with Fabry disease
in EU-5 and US in 2018



2018	patients, n
EU-5	**3,507**
UK	890
Italy	828
Germany	692
France	562
Spain	535
US	**3,875**
Total	**7,382**

Delveinsight, Fabry Disease – Market Insight, Epidemiology and Market Forecast – 2028

Current therapies in Fabry disease

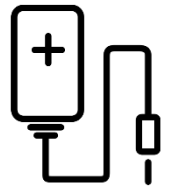
No curative therapy

Symptomatic treatments not satisfactory

Etiological therapies limited

Enzyme replacement therapy

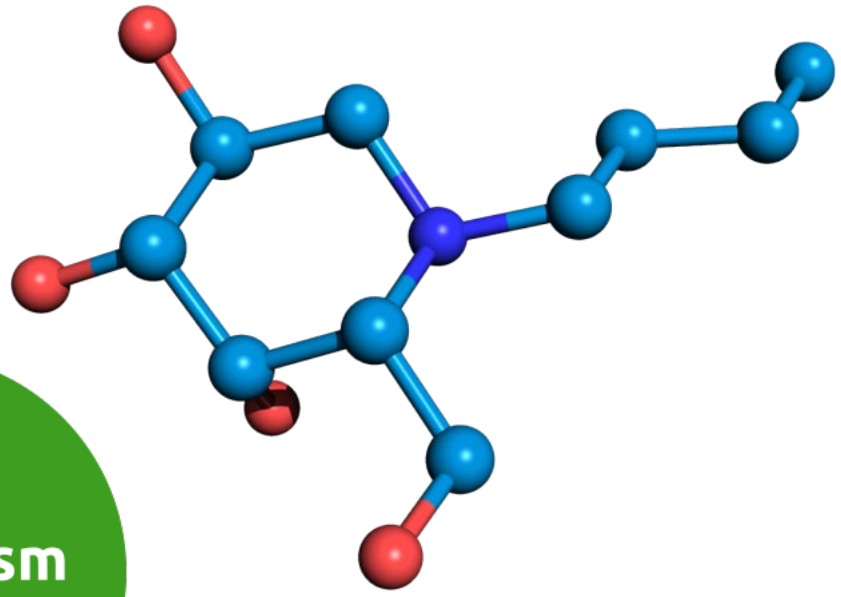
- Fabrazyme (agalsidase beta) (US and EU)
- Replagal (agalsidase alfa) (EU only)
- i.v. infusion, bi-weekly
- Immunogenicity
- Partial efficacy



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

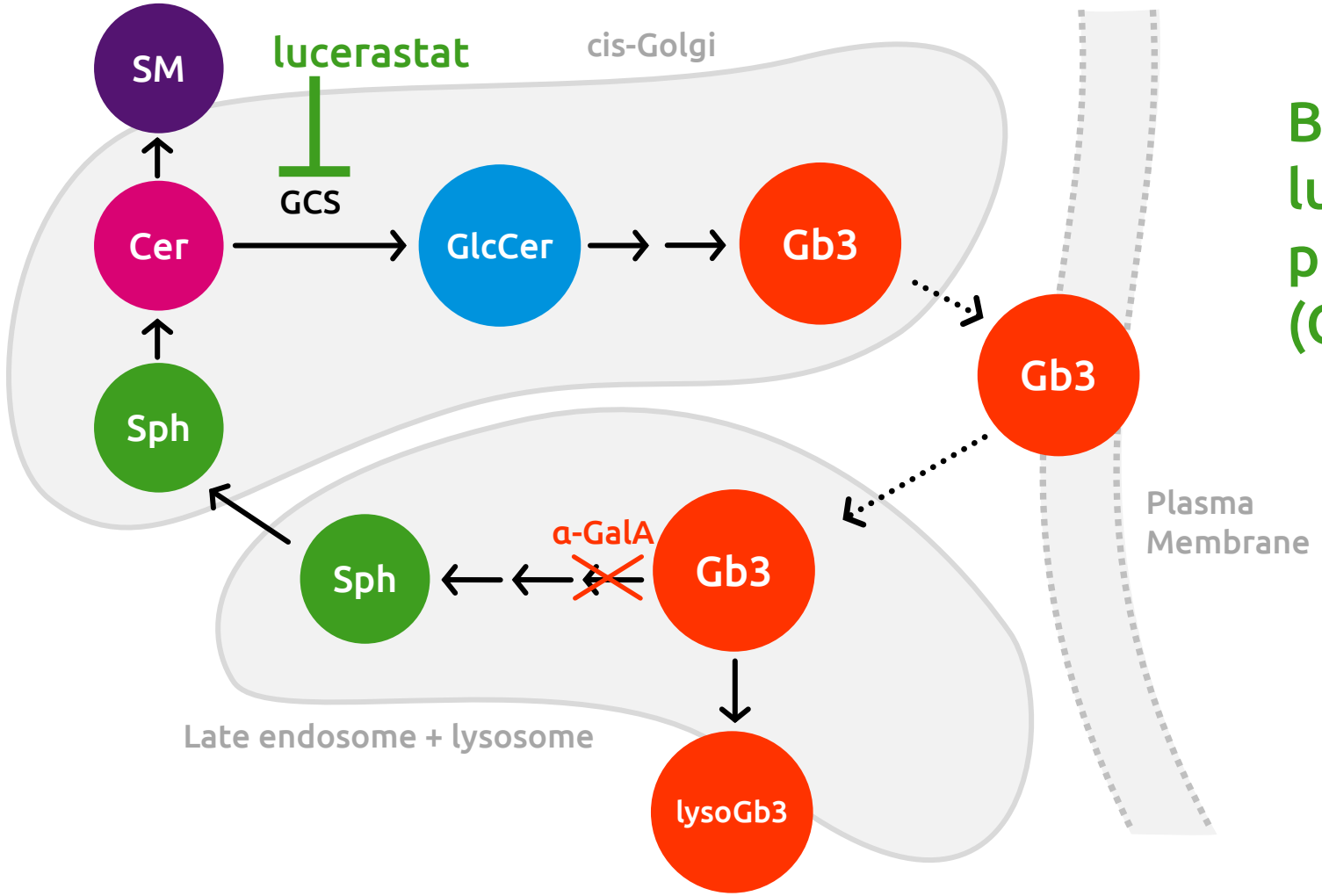
Tissue penetration
Access to most tissues, including peripheral and central nervous system

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

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

Lucerastat in Fabry disease

Mode of action



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

Cer	ceramide
GCS	glucosylceramide synthase
GlcCer	glucosylceramide
Gb3	globotriaosylceramide
lysoGb3	globotriaosylsphingosine
α-GalA	α-galactosidase A
SM	sphingomyelin
Sph	sphingosine

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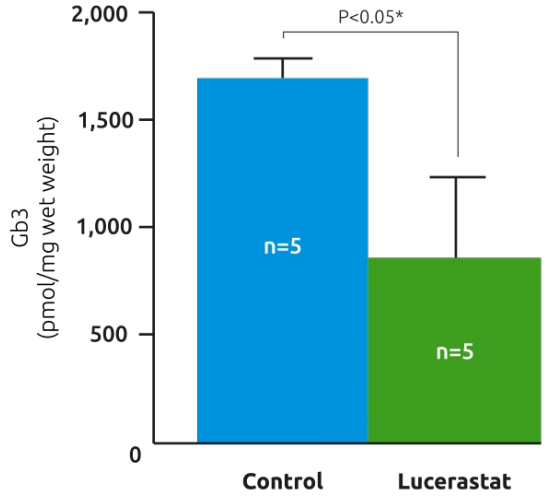
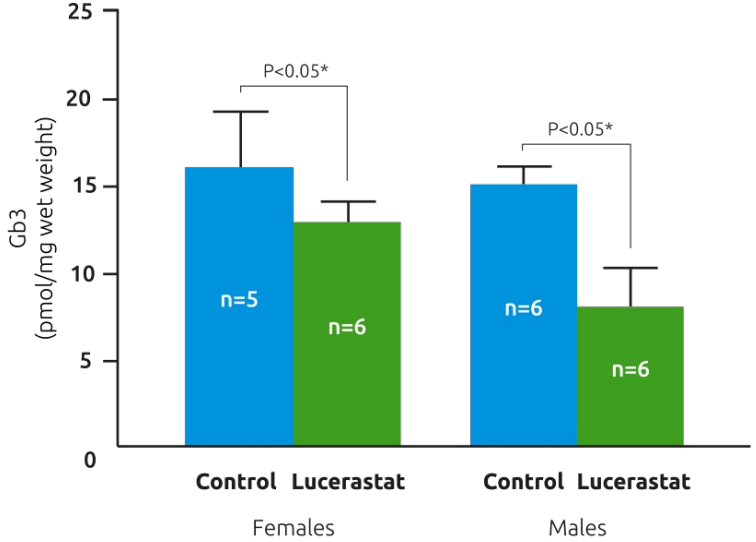
Lucerastat has the potential to reduce Gb3 levels in target organs

Dorsal root ganglia

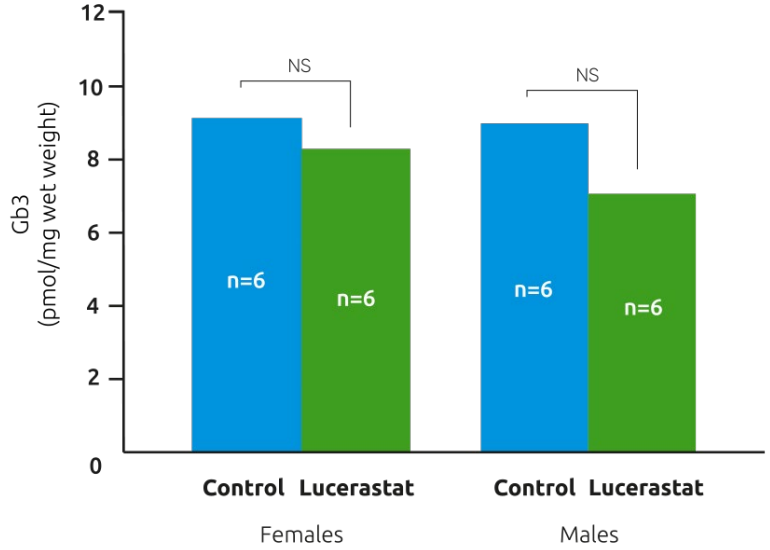


Kidneys



*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

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

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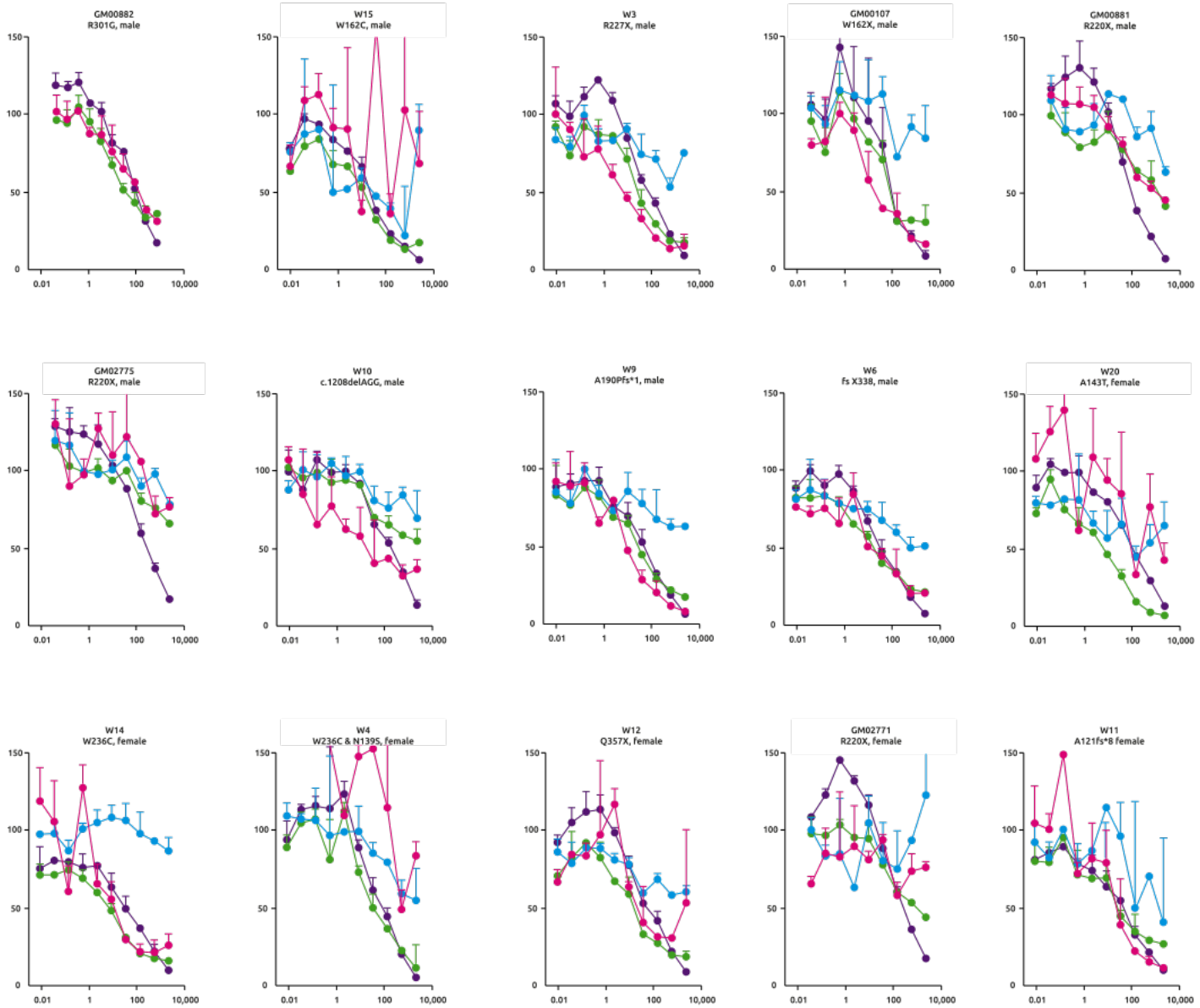
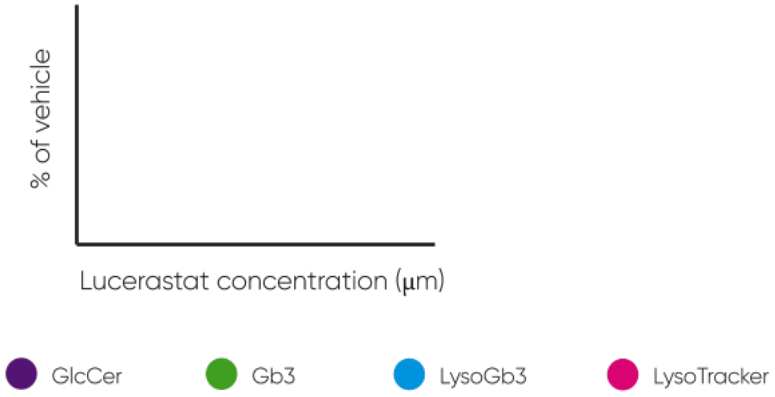
Mutation sensitivity

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.

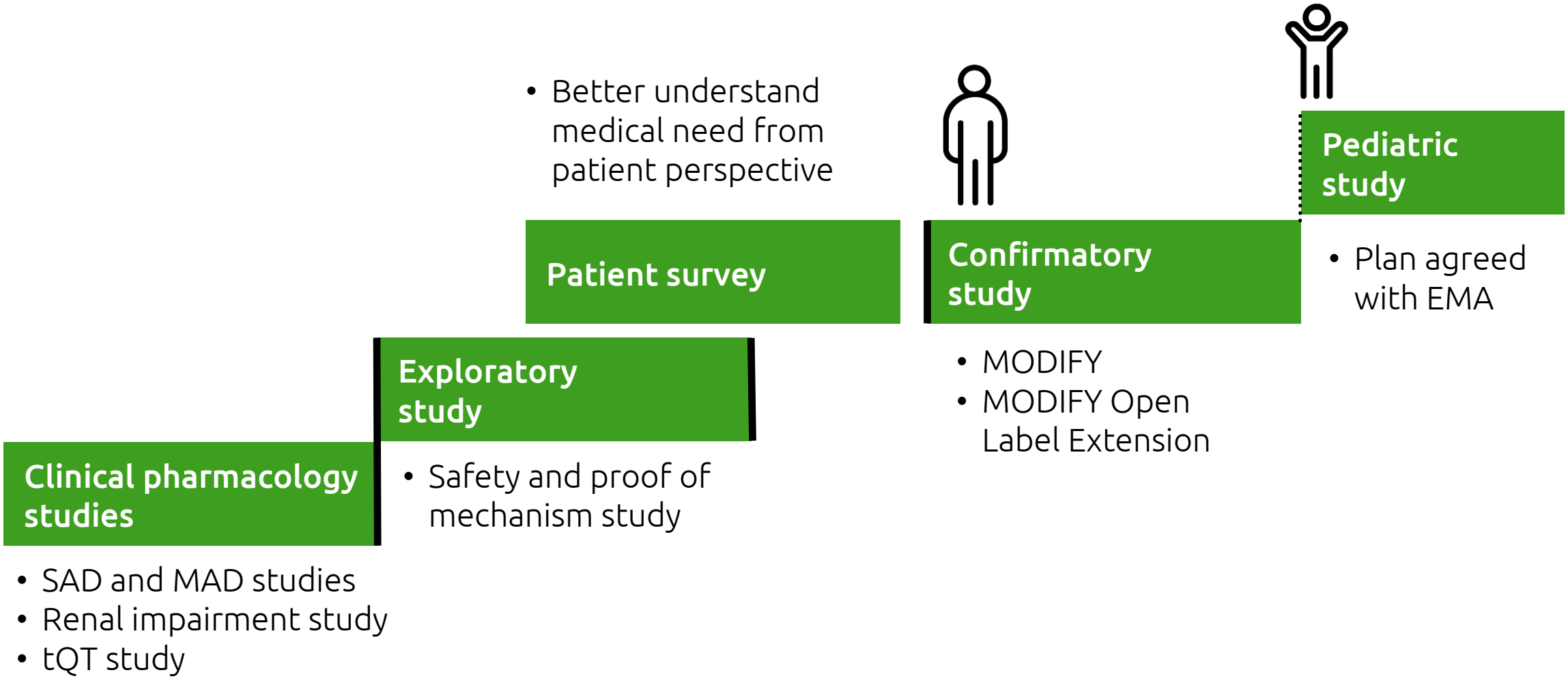
Each point is the mean of duplicates (±SD)





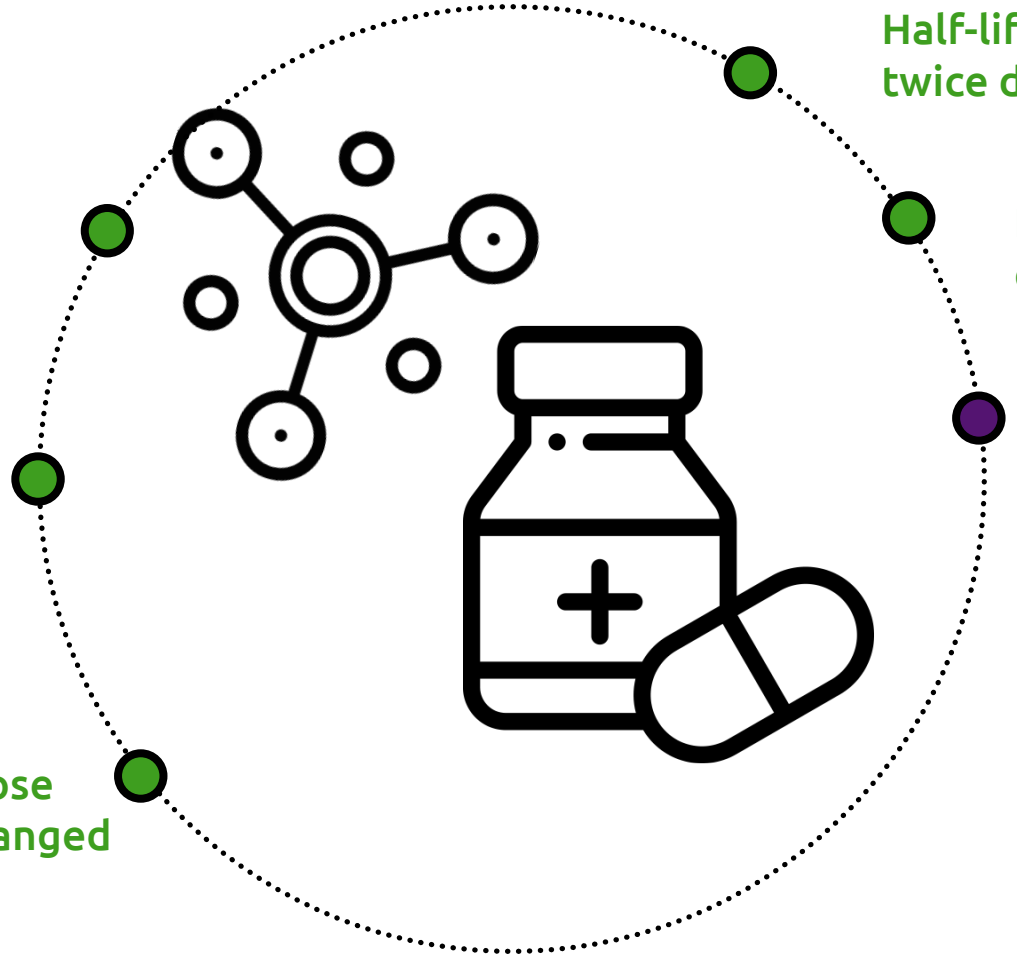
Lucerastat is investigational, in development and not approved or marketed in any country.

Lucerastat clinical development plan



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

Lucerastat clinical pharmacology



Half-life: approximately 6 hours – twice daily dosing

Dose-proportional exposure

Dose adjustment required in subjects with renal function impairment

Negligible food effect

Low potential for drug-drug interaction

>85% of the dose excreted unchanged in urine

eGFR (mL/min/1.73 m^2)	Dosing regimen (mg b.i.d.)
≥ 60	1000
≥ 45 and < 60	750
≥ 30 and < 45	500
≥ 15 and < 30	250

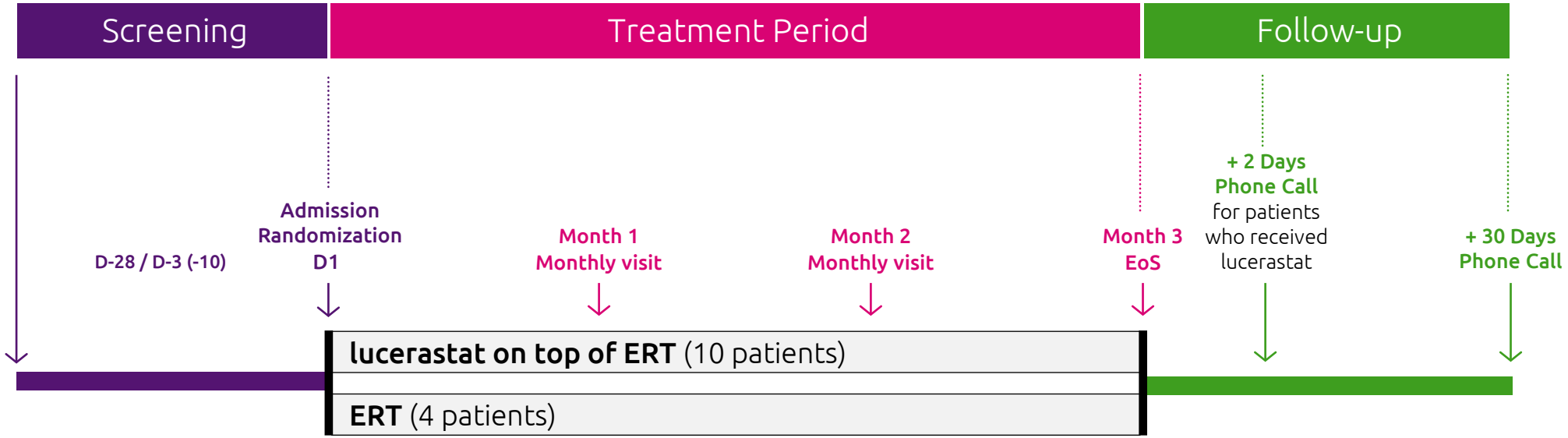
Guérard et al. (2017) Orphanet J Rare Dis
Guérard et al. (2017) J Clin Pharmacol
Guérard et al. (2018) Clin Pharmacol Ther

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

Lucerastat exploratory study design

Phase 1b study

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



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

Lucerastat exploratory study

Primary objective

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

Secondary objectives

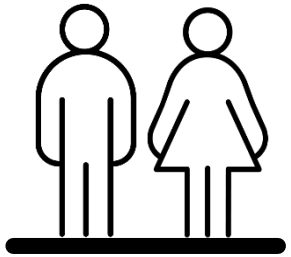
- To investigate the effect of lucerastat on
  plasma biomarker levels following a 12-week treatment
- To assess the effect of lucerastat on renal and cardiac function
- To determine the 12-hour pharmacokinetic profile
  of lucerastat at steady state
- To identify metabolites in plasma

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

Lucerastat exploratory study

Patient demographics

Phase 1b study

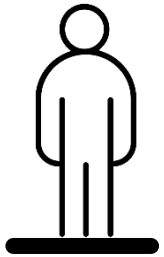


Lucerastat group

- 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)

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

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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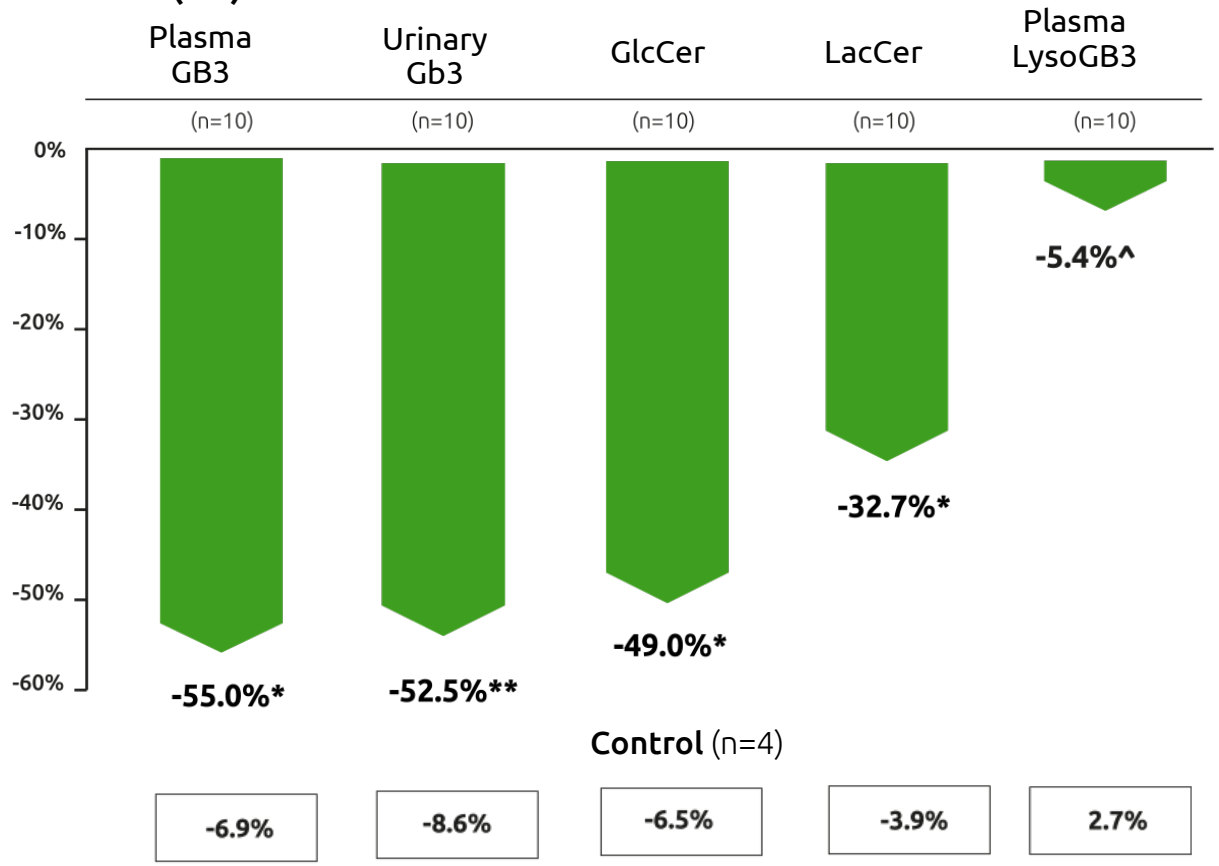
Lucerastat exploratory study

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

Phase 1b study

- **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

Mean % (SD) biomarker reduction from baseline at week 12



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

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

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

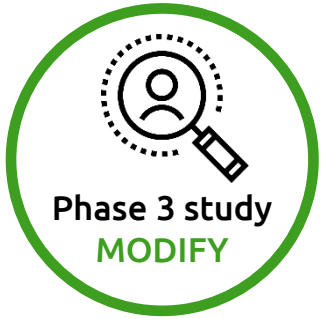
Complement existing information/data from the literature

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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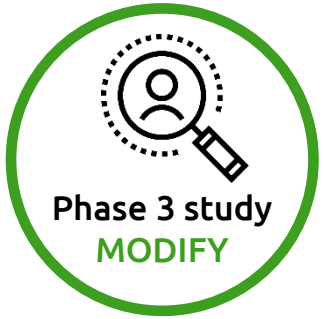
MODIFY: Objectives



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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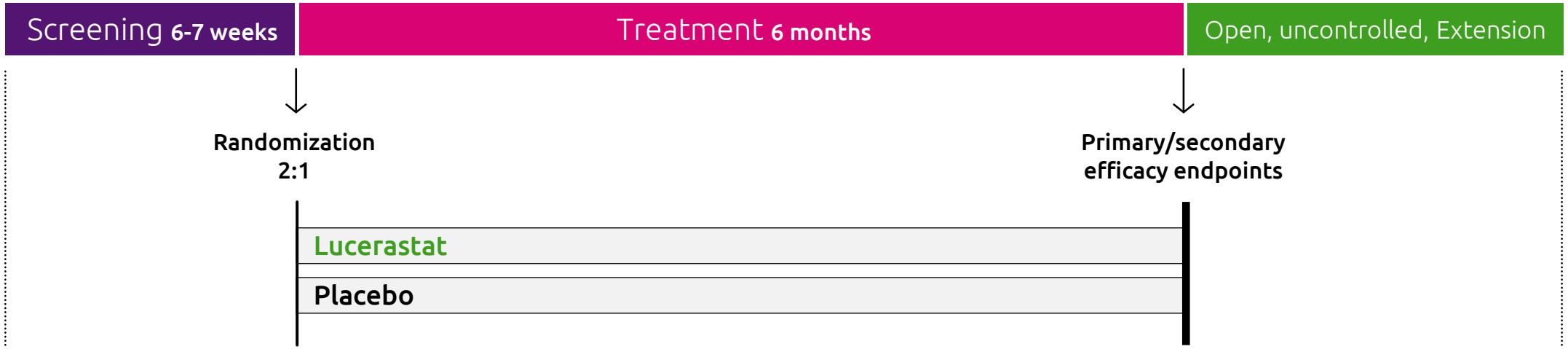
MODIFY: Study design

Phase 3 study
MODIFY



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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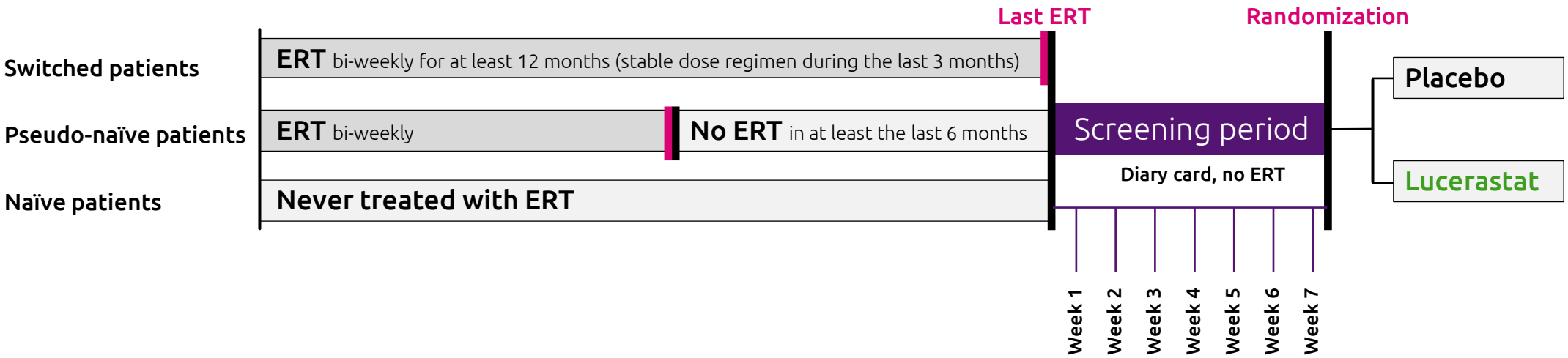
MODIFY: Patient population

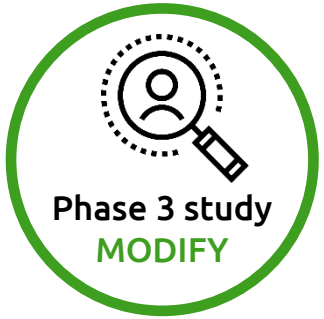
Phase 3 study
MODIFY



- Confirmed Fabry disease – presence of at least 1 mutation in GLA (the gene coding for α-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

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

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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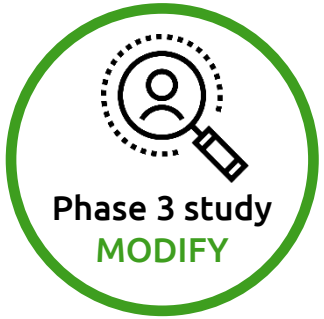
MODIFY: Results



- 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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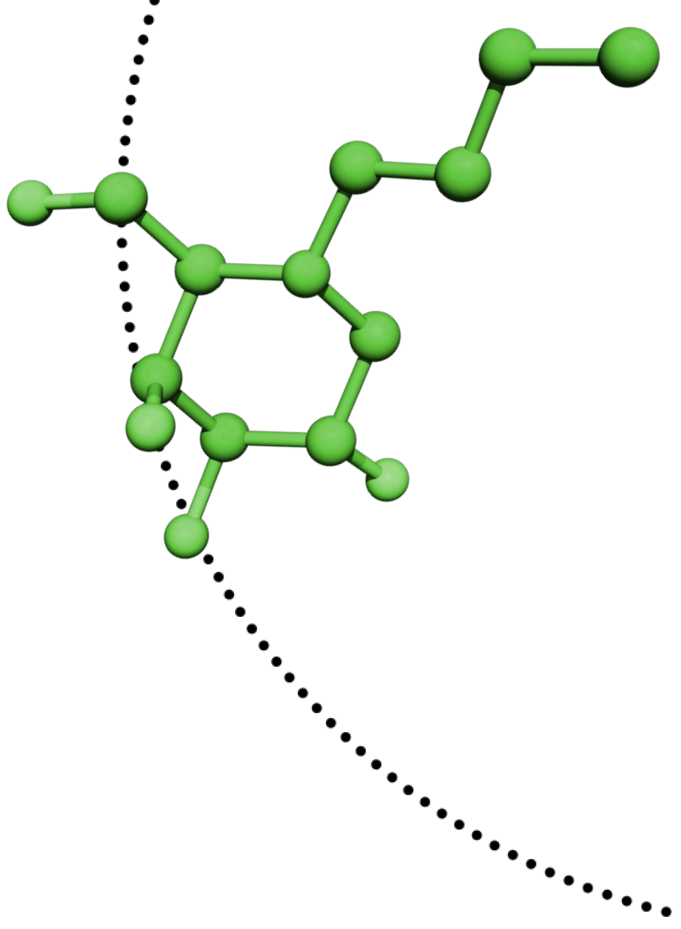
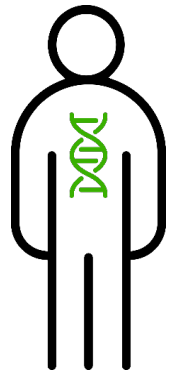
Lucerastat for Fabry disease

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 and cardiac echocardiography 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 substudy within a subset of patients currently participating in the OLE study in order to steer further development in Fabry disease.
- In parallel, Idorsia is working with regulatory authorities to design the next Phase 3 study to evaluate the effect of lucerastat on renal function.





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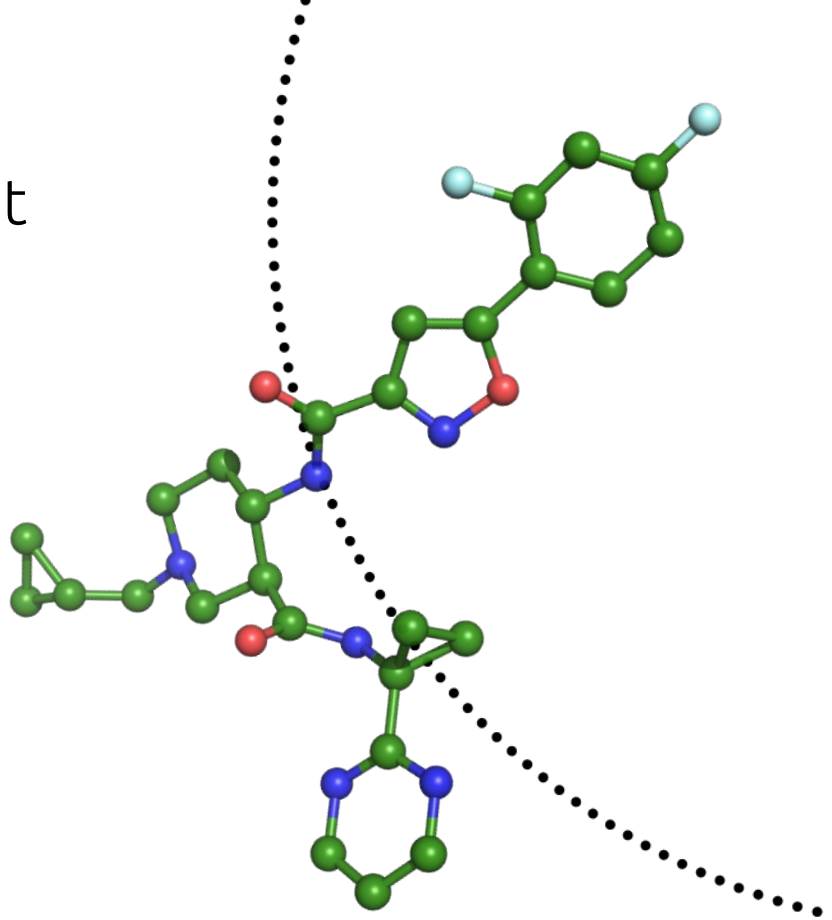
Idorsia-led early stage clinical development assets

ACT-1004-1239

A first-in-class, potent, selective ACKR3/CXCR7 antagonist

- Preclinical data has shown both anti-inflammatory and promyelinating effects
- The Phase 1 SAD and MAD studies have been completed, and following feedback from the US FDA, we are currently preparing the plan for a Phase 2 study in multiple sclerosis

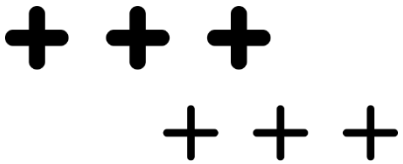


ACT-1004-1239 is investigational, in development and not approved or marketed in any country.

ACT-777991

CXCR3 antagonist

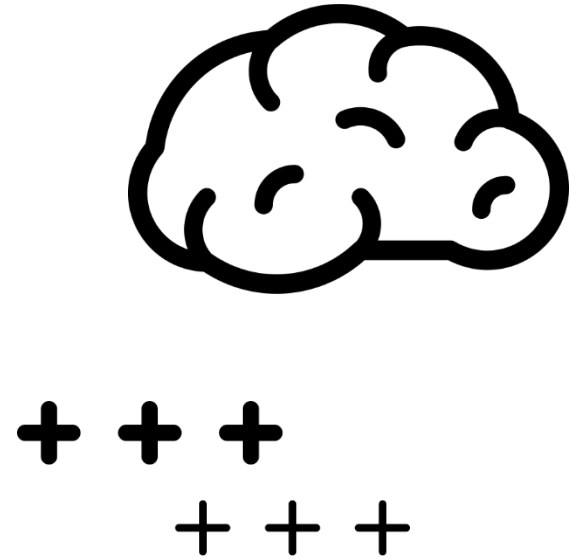
- ACT-777991, a CXCR3 antagonist, has completed initial Phase 1 studies
- A Phase 2 proof-of-concept study in Vitiligo is in preparation



ACT-777991 is investigational, in development and not approved or marketed in any country.

Sinbaglustat

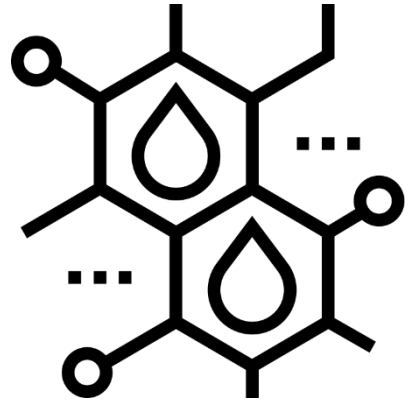
GBA2/GCS inhibitor



- Sinbaglustat, a non-lysosomal glucosylceramidase / glucosylceramide synthase (GBA2/GCS) inhibitor, has potential for the treatment of rare lysosomal storage disorders
- Following a Phase 1 clinical pharmacology program, the company ran a natural history study called “RETRIEVE” which collected disease information from pediatric patients with early onset of rare lysosomal storage disorders (LSDs).
- Based on this information, the company is considering development options for sinbaglustat.

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

Other early-stage pipeline assets



- **IDOR-1117-2520** is currently investigated in a Phase 1 program with the target indication in immune-mediated disorders
- **IDOR-1134-2831** is Idorsia's synthetic glycan vaccine targeting Clostridium difficile infection (CDI). The first study in the Phase 1 clinical pharmacology program has enrolled its first healthy participants to assess the safety, tolerability, and immunogenicity of up to 3 ascending dose levels of the IDOR-1134-2831 vaccine.

These compounds are investigational, in development and not approved or marketed in any country.

More knowledge – Powered by science

Target selection

- High medical need – patient focused
- Therapeutic novelty

Vaccine platform

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

Focus on small molecules

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

State-of-the-art technologies

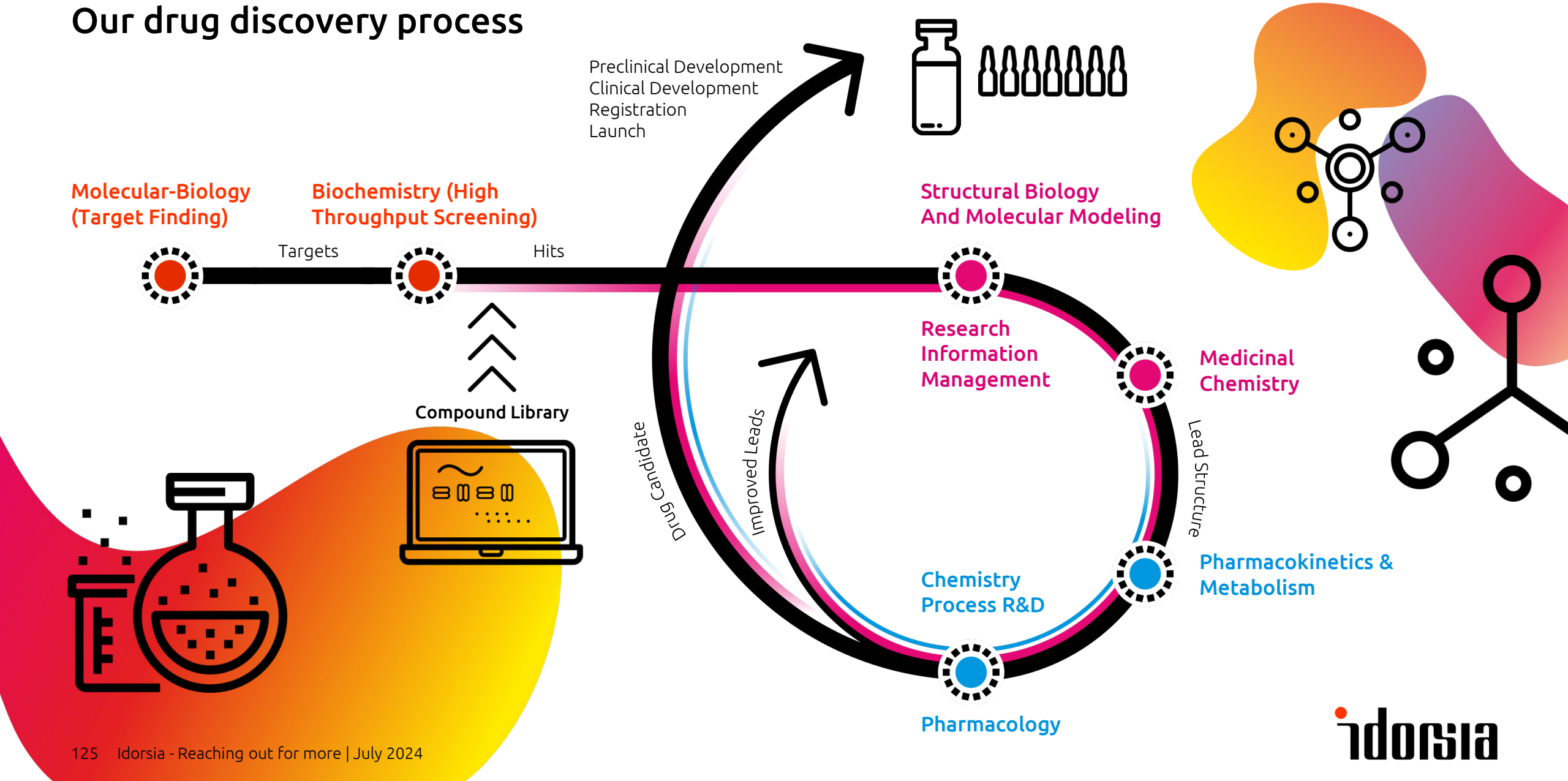
- Artificial intelligence
- Computer modelling
- High throughput screening

Industry leading talent

- Experienced team
- Top-quality organic chemists
- Medical expertise in multiple therapeutic areas

More joy – Transforming the horizon

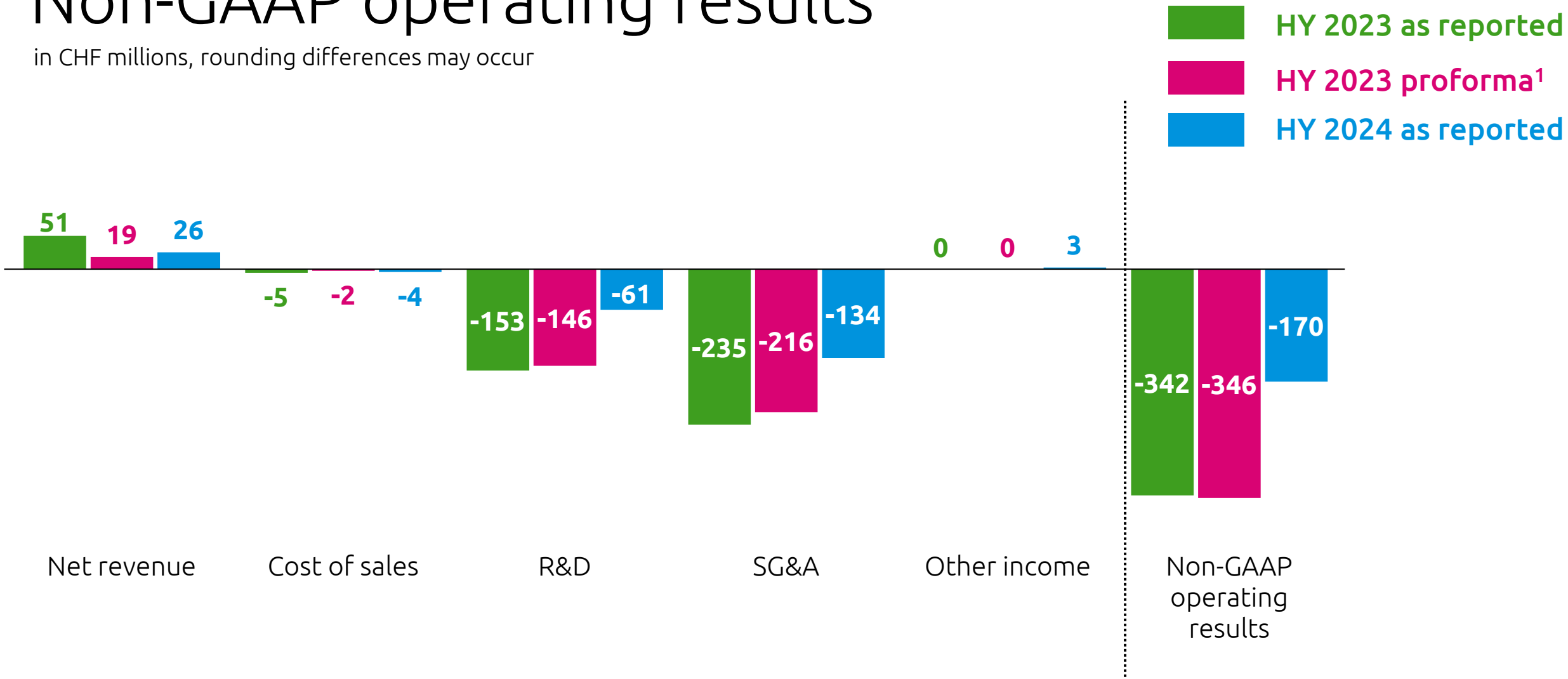
Our drug discovery process



Financial information HY 2024

Non-GAAP operating results

in CHF millions, rounding differences may occur



[1] excluding the business sold as part of the Nxera deal

Financial results as of June 30, 2024

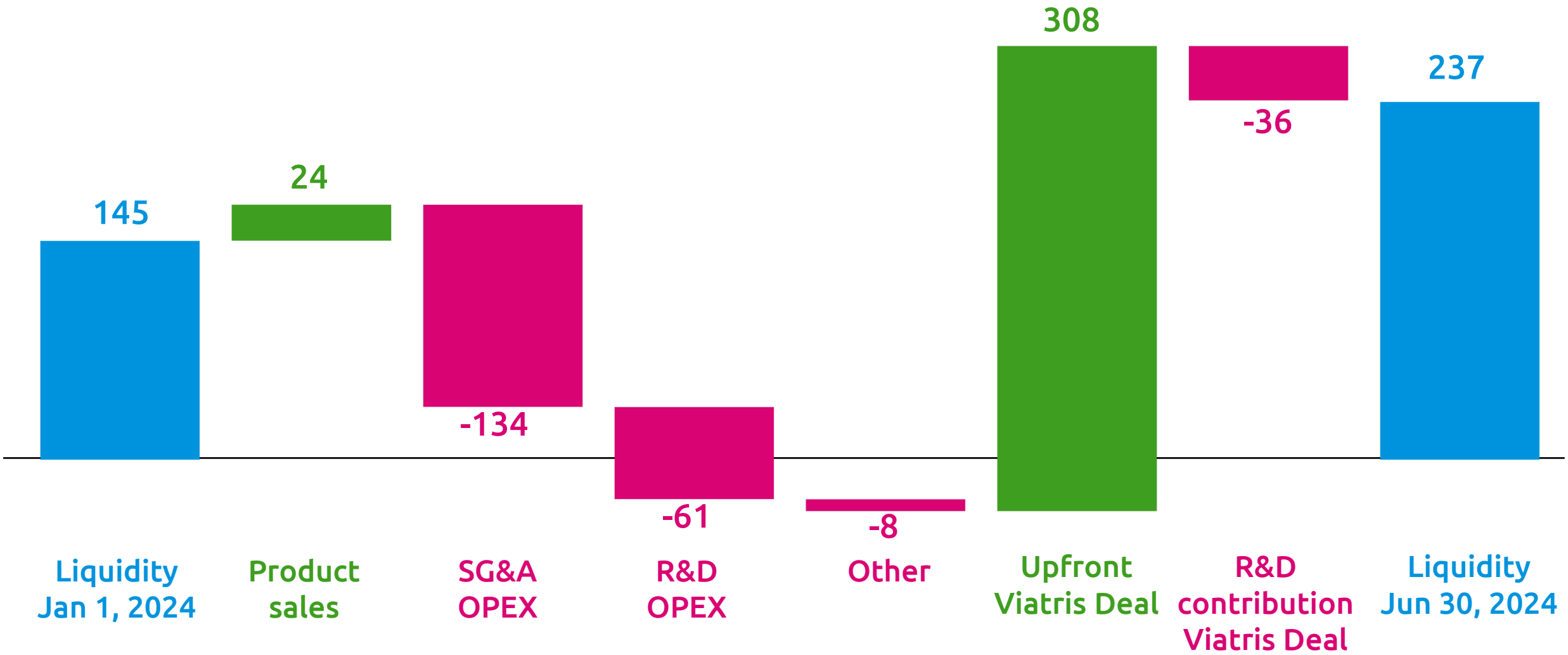
HY 2024 vs 2023 operating performance

CHF million	HY 2024 performance as reported			HY 2023 performance proforma[1]		
	Idorsia business	Partnered business	Global Business	Idorsia business	Partnered business	Global Business
REVENUE	24	3	26	12	6	19
COGS	-4	–	-4	-2	–	-2
SG&A OPEX	-134	–	-134	-216	–	-216
R&D OPEX	-61	–	-61	-146	–	-146
Other	3	–	3	–	–	–
Non-GAAP EBIT	**-173**	**3**	**-170**	**-350**	**6**	**-346**
D&A	-8	–	-8	-7	–	-7
SBC	-10	–	-10	-24	–	-24
Other	-1	125	124	–	–	–
US-GAAP EBIT	**-192**	**128**	**-64**	**-381**	**6**	**-376**

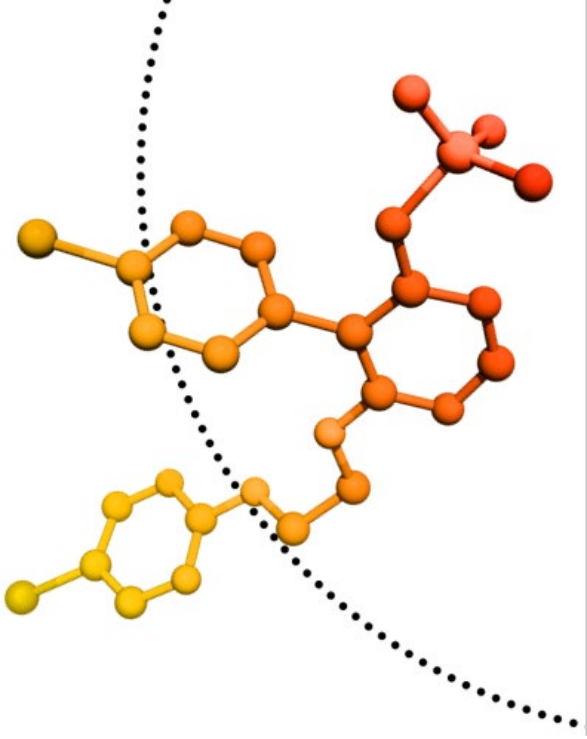
[1] excluding the business sold as part of the Nxera deal

HY 2024 cash development

in CHF millions, rounding differences may occur



Reacquisition of aprocitentan rights



- Idorsia reacquired all worldwide rights to aprocitentan
- Johnson & Johnson entitled up to CHF 306 million
  - If aprocitentan is approved in the US (90%)
  - If aprocitentan is approved in EU (10%)
- Idorsia to pay J&J
  - 30% on aprocitentan out-license deal
  - 10% on other out-license deals
  - Tiered royalties on annual net sales

Financial outlook

Status: July 2024

CHF million	Guidance for 2024 Idorsia business	Partnered business	Global Business
REVENUE	55	15	70
COGS	-10	-10	-20
SG&A OPEX	-300	–	-300
R&D OPEX	-145	0	-145
Non-GAAP EBIT	**-400**	**5**	**-395**
D&A	-15	–	-15
SBC	-35	–	-35
Other	–	125	125
US-GAAP EBIT	**-450**	**130**	**-320**

Excluding unforeseen events

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

Kerstin Niggemann
Head Pharmacological Sciences

Olivier Lambert
Head of Technical Operations

Markus Riederer
Head Translational Sciences

Alex Khatuntsev
Head of Global Human Resources

Eva Caroff
Head Chemical Sciences

Andrew C. Weiss
Head of Investor Relations & Corporate Communications

Be prepared for more