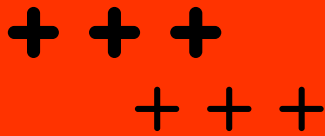


# Business Report



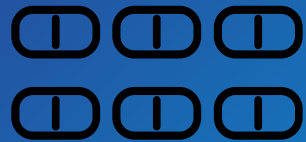
Idorsia –  
Reaching out  
for more



The purpose of Idorsia is to discover, develop, and commercialize innovative medicines to help more patients.

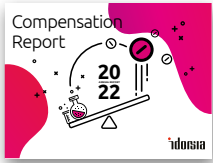
We have more ideas, we see more opportunities, and we want to transform the horizon of therapeutic options.


# More science – For a better future





**Further parts of the  
Idorsia Annual Report 2022**



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+++  
+++



# Global

Commercial operations  
in Europe, Japan, and the US



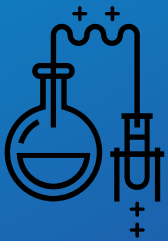
## >10

Compounds in the pipeline,  
with half in late-stage development



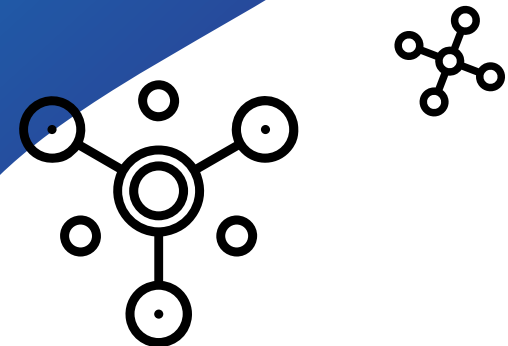
## >1,300

Highly qualified professionals



## >20-year

Heritage of drug discovery



# More science – Bursting with ideas

## **Idorsia is a biopharmaceutical start-up like no other.**

We may be young, but we have a 20-year heritage of drug discovery, a broad portfolio of innovative drugs in the pipeline, an experienced team of over 1,300 professionals covering all disciplines from bench to bedside, and commercial operations in Europe, Japan, and the US – the ideal constellation for bringing innovative medicines to patients.

We began our operations after demerging from Actelion following its acquisition by Johnson & Johnson in 2017. At that time, approximately 650 talented and engaged employees were transferred to Idorsia, together with the discovery pipeline and early-stage clinical assets.

Idorsia is headed by Chief Executive Officer Jean-Paul Clozel; he and Chief Scientific Officer Martine Clozel (who co-founded Actelion) hold more than 25% of Idorsia's shares.

Idorsia is specialized in the discovery, development, and commercialization of innovative medicines, with the aim of transforming the horizon of therapeutic options. We have a broad, diversified, and balanced portfolio, covering multiple therapeutic areas. Our portfolio comprises 2 marketed products and more than 10 assets in clinical development.

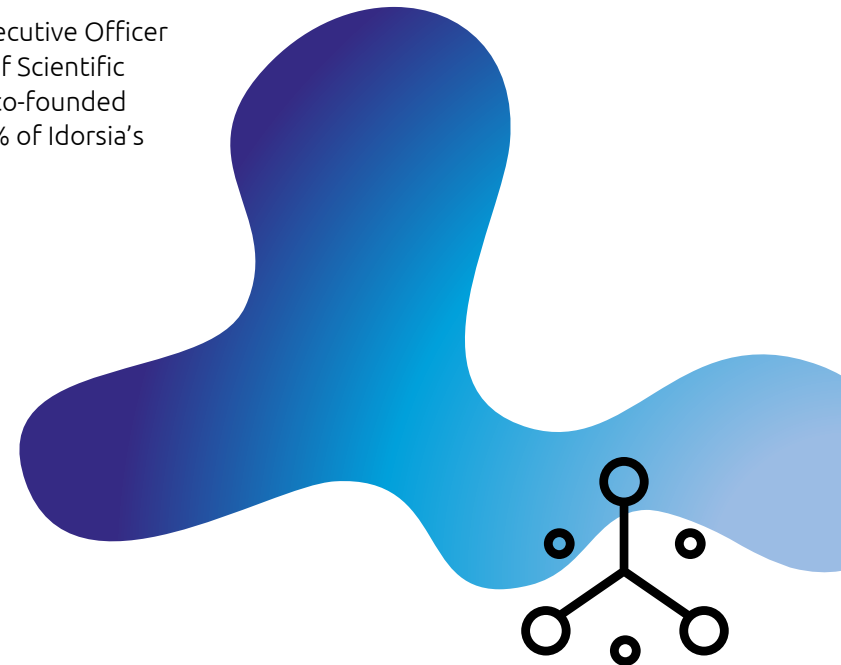
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## Idorsia's key numbers (non-GAAP\* results)

in CHF millions, except EPS (CHF) and number of shares (millions)	2022	2021
Net revenues	97	35
Operating expenses	(854)	(612)
Operating income (loss)	(757)	(576)
Net income (loss)	(782)	(575)
Basic EPS	(4.41)	(3.41)
Basic weighted average number of shares	177.4	168.5
Diluted EPS	(4.41)	(3.41)
Diluted weighted average number of shares	177.4	168.5

\* Idorsia measures, reports and issues guidance on non-GAAP operating performance. Idorsia believes that these non-GAAP financial measurements more accurately reflect the underlying business performance and therefore provide useful supplementary information for investors. These non-GAAP measures are reported in addition to, not as a substitute for, US GAAP financial performance. The full financial statements can be found in the 2022 Financial Report.

## Major shareholders (as of December 31, 2022)

Jean-Paul and Martine Clozel	27.37%*
Cilag Holding AG	5.40%*
Rudolf Maag	5.06%*
The Capital Group Companies, Inc.	3.07%**
Lazard Asset Management LLC	3.00%**

## Key share data (as of December 31, 2022)

Shares outstanding	177.6 million
Closing share price	CHF 13.42
Market capitalization	CHF 2.4 billion
52-week high	CHF 22.16
52-week low	CHF 10.83
YTD price change	CHF -5.22 (-28.00%)
Annual average daily volume	530,651 shares
Free float	110.4 million shares

\* Based on the share capital listed on SIX Swiss Exchange as of December 31, 2022

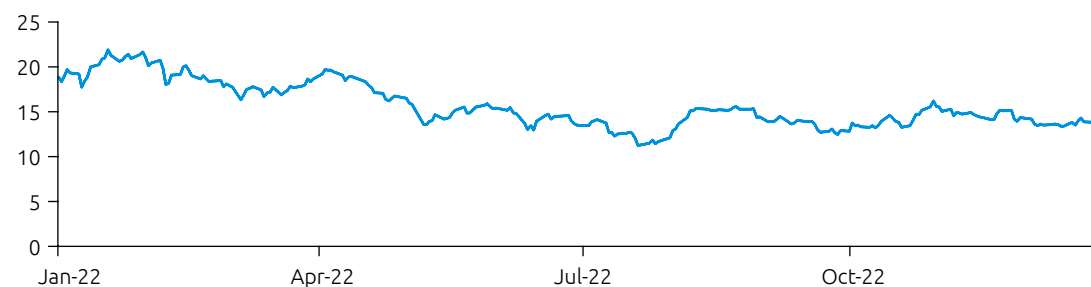
\*\* As per the latest significant shareholder notifications available on the website of the Disclosure Office of SIX Swiss Exchange

Idorsia Ltd is part of the following indices: SPI, SPIEX, SPI ESG, SXSLI, SXI Life Sciences, SXI Bio+Medtech, and SSIRT.

Idorsia is traded under the following symbols: Reuters IDIA.S/Bloomberg IDIA:SW

## Share price development

(in CHF)



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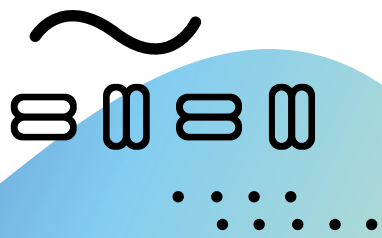
**Financial outlook for 2023**

With PIVLAZ (clazosentan) available in Japan and QUVIVIQ (daridorexant) available in the US, Germany, and Italy, and additional launches anticipated in Switzerland and the UK during 2023, the company expects net revenue in 2023 to be around CHF 230 million. Regulatory applications for aprocitentan have now been filed with the FDA and the EMA, so registration activities will continue throughout 2023. Recruitment into the Phase 3 studies with selatogrel and cenerimod are expected to ramp up in 2023. The company is prioritizing those

projects in drug discovery and early clinical pipeline that are expected to result in the greatest return in the near term, as well as seeking partnership opportunities to share costs where appropriate. The company therefore expects US GAAP operating expenses around CHF 965 million and non-GAAP operating expenses around CHF 880 million – leading to US GAAP operating loss of around CHF 735 million and non-GAAP operating loss of around CHF 650 million – unforeseen events excluded.

“As progress is made with commercial reimbursement of QUVIVIQ in the US, the continued launches in Europe, and the good performance of PIVLAZ in Japan, I expect net revenues to reach around 230 million Swiss francs in 2023. Implementing our current business plan implies that we need to raise cash and we continue to carefully weigh our funding options to do so, including non-equity dilutive opportunities.”

**André Muller**  
Executive Vice President, Chief Financial Officer



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# Milestones in 2022

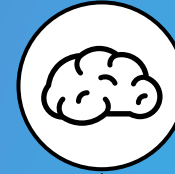


2022 has been a transformative year for Idorsia, with the launch of the company's first two products and further advances in the clinical development pipeline.



## January 2022

*The Lancet Neurology* reports impact of daridorexant on both nighttime symptoms and daytime functioning in adults with insomnia



## April 2022

PIVLAZ (clazosentan) launched in Japan for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aSAH



## January 2022

The US FDA approves QUVIVIQ (daridorexant) for the treatment of adults with insomnia

## January 2022

PIVLAZ (clazosentan) approved in Japan for the prevention of cerebral vasospasm

## April 2022

*Journal of Neurosurgery* reports impact of clazosentan on cerebral vasospasm-related morbidity and all-cause mortality after aneurysmal subarachnoid hemorrhage (aSAH)

## April 2022

Europe's first dual orexin receptor antagonist – QUVIVIQ (daridorexant) – granted approval for the treatment of adults with chronic insomnia disorder

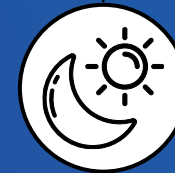
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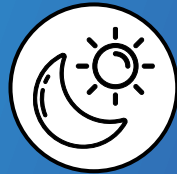
**May 2022**

QUVIVIQ (daridorexant) 25 mg and 50 mg launched in the US for the treatment of adults with insomnia



**October 2022**

Positive results reported for daridorexant in a Phase 3 study of Japanese patients with insomnia



**November 2022**

QUVIVIQ (daridorexant) became Europe's first dual orexin receptor antagonist available for patients with chronic insomnia disorder in Italy and Germany



**November 2022**

Swissmedic approves QUVIVIQ (daridorexant) for the treatment of adults with chronic insomnia disorder



**December 2022**

New Drug Application for aprocitentan submitted to the US FDA for the treatment of patients with difficult-to-control hypertension

**May 2022**

Phase 3 study with aprocitentan demonstrates significant antihypertensive efficacy in patients with resistant hypertension

**November 2022**

*The Lancet* and American Heart Association (AHA) late-breaking science session reports significant and sustained antihypertensive effect of aprocitentan in patients with resistant hypertension

**November 2022**

Licensing agreement with Simcere for daridorexant in China

**December 2022**

Initiation of a Phase 3 registration program with cenerimod for the treatment of patients with systemic lupus erythematosus

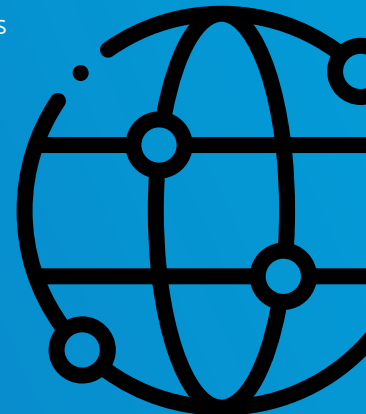
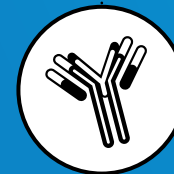
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# The purpose of Idorsia is to discover, develop, and commercialize innovative medicines to help more patients.

**Mathieu Simon**  
Chairman of the Board



## Dear Shareholders,

As the world took tentative steps back to normality following the global pandemic, Idorsia continued to make rapid progress on its strategic priorities. 2022 was an outstanding year for the company, with so many achievements that it's hard to keep track of all the good news. It was the year when the company completed the value chain, taking innovation at the lab bench all the way through to the patient's bedside.

We must remember that Idorsia started out just 5 years ago with an early-stage pipeline comprising four assets in Phase 2 and five in Phase 1. Today, just 5 years later, the company has launched two products in different markets and submitted another product for marketing authorization in the US and EU, while continuing to advance its clinical development and drug discovery

portfolio. The rapid progress made by Idorsia in a relatively short time is a huge achievement; how rare it is in our industry to deliver positive results so consistently on all fronts!

As the company entered this new phase, the Board, together with the management team, has sought to ensure that we have the correct guiding principles, along with appropriate checks and balances, strengthening the compliance function to drive safe and appropriate use of our medicinal products.

While the scientific and commercial milestones keep on coming, we are fully aware that we need to bridge the funding gap and continue to carefully weigh our funding options to do so, including non-equity dilutive opportunities.



“The rapid progress made by Idorsia in a relatively short time is a huge achievement; how rare it is in our industry to deliver positive results so consistently on all fronts!”

**Mathieu Simon**  
Chairman of the Board

Of course, the size of the funding gap depends on how we invest in our innovation and how our products perform on the market. The commercial team is looking to widen prescribing, mainly – in the case of QUVIVIQ – by establishing broad payer reimbursement. In addition, the company is prioritizing projects that are expected to result in the greatest return in the near term, as well as seeking partnership opportunities to share costs where appropriate. As a result, we have reiterated our objective to achieve sustainable profitability in 2025.

We are building Idorsia with a long-term focus and running the company in a responsible and sustainable way. We have reported our performance on numerous non-financial measures in each Annual Report since our founding, and we remain committed to transparency on topics important to our stakeholders. This year we have once again strengthened our

sustainability reporting, and we are now well-positioned to navigate the newly implemented Swiss regulations.

As Chairman of the Board of Directors, I can assure you that the whole Board, with its broad pharmaceutical experience and geographical representation, is closely monitoring Idorsia’s progress and is continually impressed by the teams’ achievements and by the quality of the people who are executing on our strategic priorities. I’m very proud that we can attract and retain the best in the business, on a global basis. To this end, in 2022, we launched “Ambition 2027”, an incentive program aimed at engaging all employees in our efforts, over the next five years, to achieve specific, ambitious performance targets. Our people will thus have an opportunity to share in the company’s prosperity, ensuring that our employees’ efforts are fully aligned with Idorsia’s business strategy and with the long-term interests of you, our shareholders.

On behalf of the Board, I would like to take this opportunity to thank you once again for your confidence in the company. I am absolutely convinced that the commercial team has the right strategy to make both of our marketed products a great success in their respective indications, that aprocitentan has the potential to be the first antihypertensive product with a new mechanism of action for decades, and that the R&D team will continue to innovate and advance the pipeline. With so many achievements behind us and concrete success on the horizon, I am optimistic that it is only a matter of time before you will be rewarded for your trust.

Sincerely,



**Mathieu Simon**  
Chairman of the Board



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# Developing Idorsia into a leading biopharmaceutical company with a strong scientific core.

**Jean-Paul Clozel**  
Chief Executive Officer

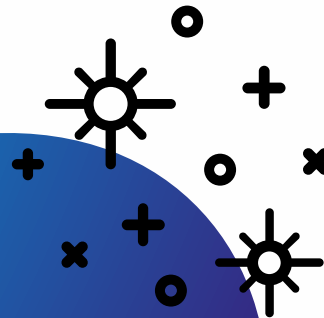



## **Dear Shareholders,**

At the start of 2022, we committed to a year of transformation, and that is exactly what we delivered. We launched our first two products and made significant progress with key late-stage clinical assets, while our drug discovery engine continues to fuel the pipeline, setting a strong trajectory for future growth. Only five years after being founded, Idorsia is already a fully fledged biopharmaceutical company, with drug discovery, clinical development, and commercial capabilities spanning from bench to bedside.

## **QUVIVIQ disrupting the sleep market in the US**

The last year saw our first-ever product approval, with QUVIVIQ (daridorexant) being approved by the FDA for the treatment of insomnia. Since the launch in mid-2022, we have invested significant resources in raising awareness among US healthcare





“2022 was a transformative year for Idorsia –  
and our achievements have laid the foundations  
for success in 2023.”

**Jean-Paul Clozel**  
Chief Executive Officer

providers and consumers about the burden of insomnia for patients, as well as educating them on the wealth of evidence we have generated concerning the impressive benefits and tolerability of QUVIVIQ. This evidence includes a publication in *The Lancet Neurology*, with comprehensive data showing that QUVIVIQ is the first insomnia medication to demonstrate efficacy in improving both nighttime symptoms and daytime functioning in patients with insomnia disorder, as well as confirming the treatment’s safety profile.

Our US-focused activities are disrupting the sleep market through initiatives ranging from celebrity partnerships to harnessing the power of an alliance of sleep experts. These initiatives have built increasing consumer demand, as has prescribers’ initial experience with QUVIVIQ – our surveys show that the drug has reached the highest satisfaction level of all prescription

insomnia treatments among US healthcare providers. All the signs point to strong and growing demand for QUVIVIQ in the US: rising monthly total prescription levels, a steady increase in the writer base, and accelerating refill prescriptions. Lack of reimbursement has, however, been a significant barrier to prescribing, and we are laser-focused on addressing this issue in 2023. In fact, this year, we have already announced a major coverage agreement with the Express Scripts National Preferred Formulary, and we expect to secure further coverage throughout 2023. With broad payer reimbursement, we can enable more patients to access QUVIVIQ, translating the strong demand we have created into commercial success.

### **QUVIVIQ on track to become a global brand**

The QUVIVIQ story is not confined to the US market. The product is well on its way

to becoming a global brand, with approvals also granted in 2022 in the EU, Switzerland, and the UK. In Europe, there has been very little innovation in the sleep space over the last 30 years, and QUVIVIQ – with its innovative dual orexin receptor antagonist (DORA) mechanism of action – is now the first-in-class DORA available to patients in Europe with chronic insomnia. Through our interactions with physicians, we know that they are eager for new safe and effective treatment options for insomnia, and we are engaging with payers to ensure they understand the value that QUVIVIQ brings to insomnia patients in Europe. Our first European launches of QUVIVIQ took place in November 2022 in Germany and Italy, with initial uptake showing a strong start. We plan to launch QUVIVIQ in other key European markets in 2023 and 2024, and we are especially excited to bring QUVIVIQ to Switzerland, our home market, in mid-2023.

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Adding to the great body of evidence showing the differentiated product profile of QUVIVIQ, our team in Japan reported positive results from the Phase 3 study of daridorexant in Japanese patients. We are preparing to file a New Drug Application for daridorexant in Japan in the second half of 2023.

We have also entered into an exclusive licensing agreement for daridorexant in China with Simcere, giving the company the rights to develop and commercialize the drug in the Greater China region.

### **Successful launch of PIVLAZ in Japan**

Meanwhile, less than two weeks after the US approval of QUVIVIQ, the Japanese health authorities granted approval for PIVLAZ (clazosentan) for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction, and cerebral ischemic symptoms after treatment for aneurysmal subarachnoid hemorrhage (aSAH). We

quickly secured reimbursement and launched PIVLAZ in April 2022, with the Idorsia team in Japan delivering a phenomenal launch. Our engagement with Japanese experts in this field – including those who practice at large medical centers specializing in aSAH – has promoted rapid adoption of PIVLAZ for patients with this devastating condition. Already, almost all of the accounts targeted have ordered PIVLAZ, and approximately 25% of aSAH patients were treated with PIVLAZ in the month of December.

### **Positive Phase 3 results and FDA filing for aprocitentan**

For me as a cardiologist, our positive Phase 3 results for aprocitentan in patients with resistant hypertension were one of the year's most satisfying achievements. The expert community is also excited, as demonstrated by our well-received presentation at the American Heart Association conference and – importantly – our publication of clinical data in *The Lancet*. When you consider that most of the patients in our study were already receiving four or more antihypertensive medications as background therapy – and that many of them have additional medical problems on top of their hypertension – the demonstration of a significant, clinically meaningful reduction in blood pressure, sustained over 48 weeks, with a manageable safety profile, is absolutely outstanding.

The New Drug Application for aprocitentan was filed with the FDA in December, and

the market authorization application in Europe was made in January 2023. Under our partnership agreement, Janssen is responsible for the commercialization of aprocitentan, and we are eligible for tiered royalties of up to 35%. I am confident that this treatment holds great promise for patients with resistant hypertension – and also for our company.

### **Strong progress in clinical development**

Our clinical development programs continue to show strong progress. In 2022, we finalized recruitment for REACT, our global Phase 3 study of clazosentan in patients with aSAH. This enabled us to conclude the study late last year, and we are on track to deliver the results in early 2023.

Also progressing well is recruitment for our Phase 3 study with selatogrel for acute myocardial infarction (AMI or heart attack), having now reached more than 3,300 patients. This potent and highly selective P2Y<sub>12</sub> inhibitor, with its rapid onset of action and formulated to be subcutaneously self-administered via an autoinjector, has the potential to be a game-changer for the treatment of AMI. Our trial enables patients at high risk for AMI to self-administer selatogrel via our autoinjector at the onset of symptoms – before first aid arrives and they are transported to a hospital for emergency medical care. Our aim is to show that this early intervention leads to better short- and long-term patient outcomes.

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We have also initiated OPUS, our Phase 3 confirmatory program, investigating cenerimod in patients with systemic lupus erythematosus (SLE). In the Phase 2 study, cenerimod – an S1P<sub>1</sub> receptor modulator which can be taken as an oral therapy – showed clinically meaningful and sustained effects at a dose of 4 mg, particularly in patients with more severe forms of the disease. We have every expectation that OPUS will provide the evidence enabling cenerimod to be approved as the first next-generation oral drug for SLE.

### **Our people continue to be our most important asset**

At Idorsia, our people are crucial to our success. They hold the talent, expertise, and experience needed to feed our pipeline with new discoveries, to develop our compounds through to approval, and to commercialize our innovative products so as to help more patients.

It is thanks to their contributions, supported by the unique culture we have built at Idorsia, that we have been able to achieve so much in 2022. It is not by chance that we consistently deliver excellent results. Many of our scientists have worked together for years, if not decades, and have built the long-term relationships and trust that underpin the highest levels of collaboration. In the commercial space, our people have been recruited from among the best in the industry, and I've been impressed by how quickly this team has adopted Idorsia's entrepreneurial mindset and by their clear focus on execution.

### **Building momentum in 2023**

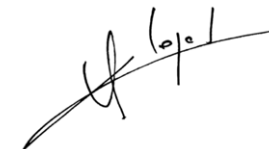
Idorsia's numerous achievements in 2022 have laid the foundations for our success in 2023. We intend to ramp up our commercial launches, particularly with reimbursement for QUVIVIQ in the US, and in Europe where launches are now underway.

We will advance our pipeline, with key milestones including results from the Phase 3 REACT study with clazosentan expected in February, an agreement on the path forward with lucerastat for Fabry disease by the middle of this year, and a decision by the FDA on apocritentan in December.

We also expect to narrow the liquidity gap, bringing the company closer to profitability. Through our global sales of QUVIVIQ, sales of PIVLAZ in Japan, and expected royalties from apocritentan, the company is committed to reaching sustainable profitability in 2025, with global revenues exceeding CHF 1 billion.

Throughout the year ahead, we will build momentum toward reaching these ambitious goals. By the end of 2023, Idorsia should be a very different company, even closer to realizing our vision of becoming a sustainable, mid-sized, innovation-driven biopharmaceutical company.

Best regards,



**Jean-Paul Clozel**  
Chief Executive Officer



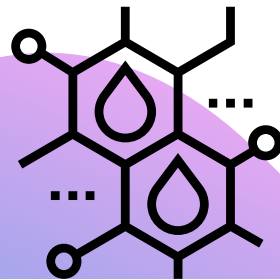
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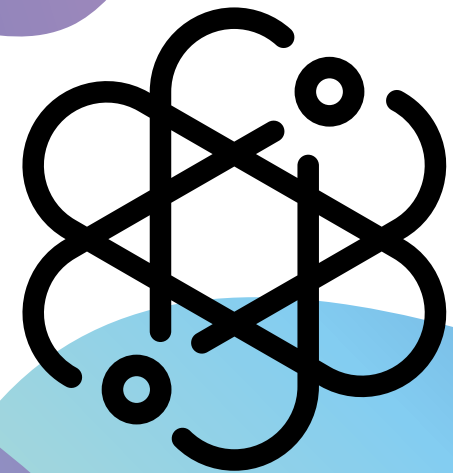
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# Our strategic priorities

We will develop Idorsia into a leading biopharmaceutical company, with a strong scientific core. We have identified five key strategic priorities to ensure the company's success going forward.



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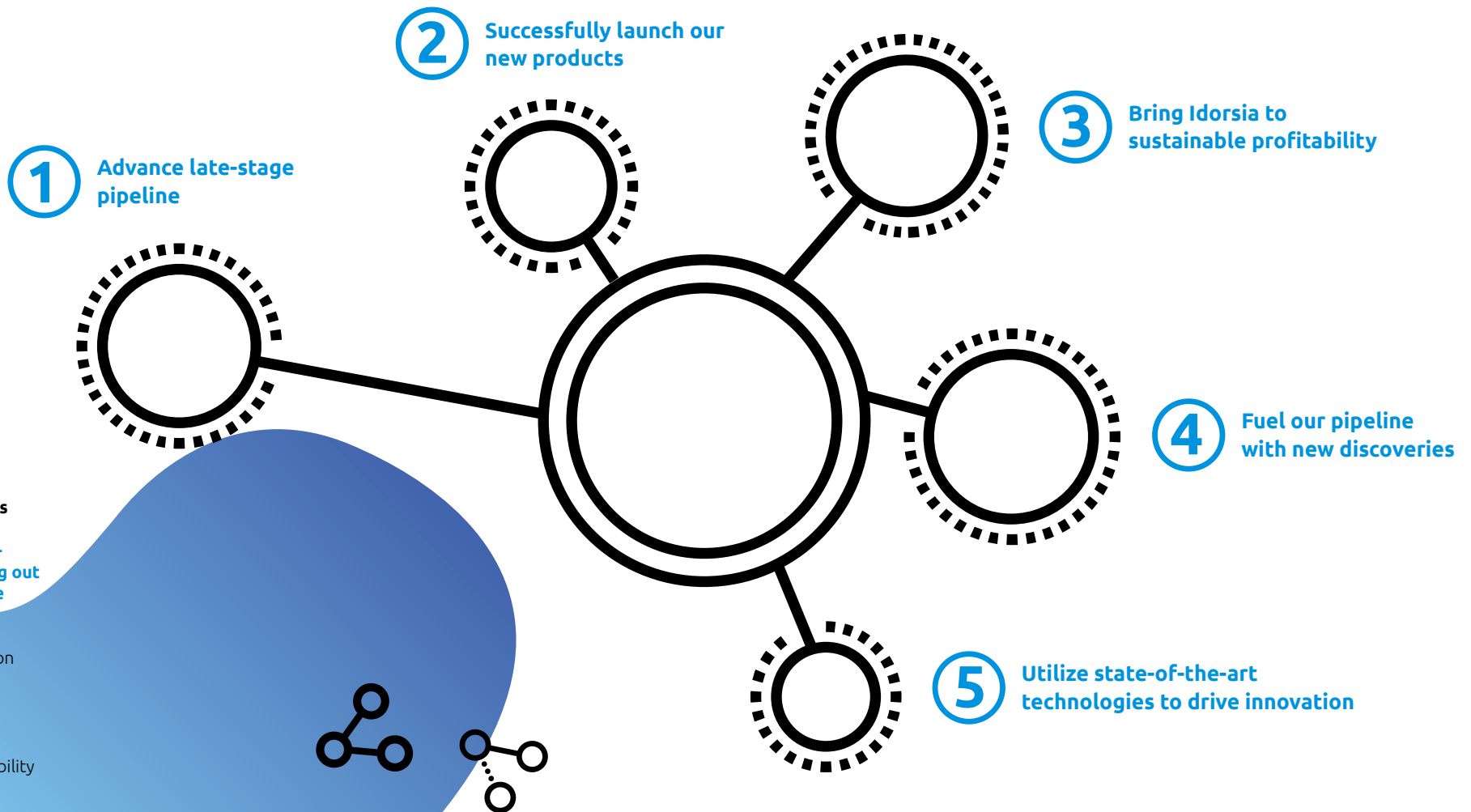
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# More energy – Growing and delivering

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



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# Advance late-stage pipeline

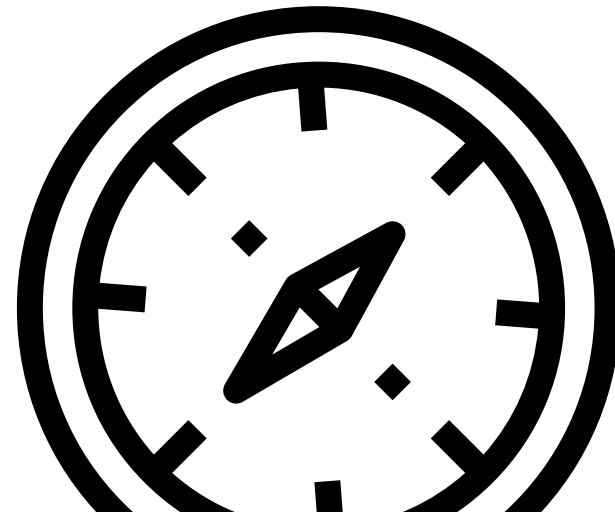
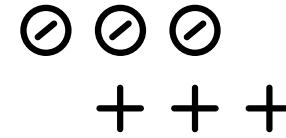
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We believe that our development compounds have the potential to significantly change treatment in their target diseases, resulting in medicines with substantial commercial potential.

We have a diversified and balanced clinical development pipeline, covering multiple therapeutic areas, including CNS, cardiovascular, and immunological disorders, as well as orphan diseases.

The pipeline comprises more than 10 compounds, with half in late-stage development. The development of an innovative compound into a future therapy is a complex undertaking, which inevitably involves an element of risk. With our scientific, data-driven approach helping to mitigate risk at each step, we have already brought two products to the market, QUVIVIQ in the US and Europe and PIVLAZ in Japan, with apocitentan currently undergoing regulatory assessment in the

US and EU. We now aim to broaden the availability of our products by launching QUVIVIQ in additional markets, and seeing the results with clazosentan outside of Japan, and bring additional products from our late-stage development pipeline, such as lucerastat, selatogrel, and cenerimod, to the market in the near term. Our late-stage pipeline is described in detail in the “Our Innovation” section of this report (from page 36).



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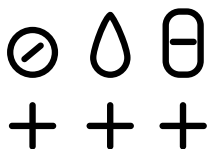




# Successfully launch our new products

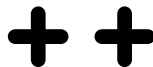
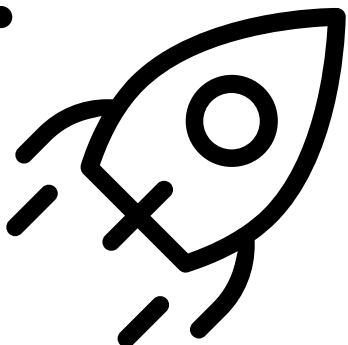
2

In order to successfully bring our pioneering therapies to patients and to maximize the value of our innovations, we will continue to build and strengthen our global commercial organization.



We have taken a simple, efficient approach to our first product launches, utilizing shared, best in class platforms and ways of working that enable fast decision-making and cost effective growth. We will continue to focus on transforming treatment in underserved markets, such as insomnia, and building new markets, such as cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage, using scientific and medical evidence to engage effectively with experts in the field and with payors. We plan to remain flexible and nimble in the way we commercialize our portfolio. We have built the core capabilities required to successfully launch our products, while also entering into partnerships where we need support to reach a primary care market.

We have established commercial operations in the US, Japan, and the major European markets, with experienced leadership teams and strategic locations. We have also established a robust and lean global supply chain function to ensure consistent supplies of our innovative medicines to patients.



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# Bring Idorsia to sustainable profitability

3

We are building Idorsia with a long-term focus and ambitious aspirations. By advancing our development pipeline and successfully launching our first products, we aim to bring Idorsia to sustainable profitability as soon as possible.

We believe that we have the potential to generate significant revenues from our innovative portfolio, which now includes two products on the market, spanning multiple geographies.

To maximize the medical value of our discoveries and to provide a source of liquidity in the short to medium term, we have entered into several collaborative partnerships with pharmaceutical companies. These include development, commercialization, and revenue sharing agreements, under which we are eligible to receive milestone payments based on the progress of the development compound in question.

Furthermore, with several unencumbered assets in clinical development, additional contract revenue from partnerships and/or out-licensing remains an option for us.

# Fuel our pipeline with new discoveries

4

While launching our first marketed products and developing our late-stage clinical pipeline to bring our innovative therapies to patients, we also continue to discover new compounds.

In addition to several drug candidates in the early stages of clinical and preclinical development, we must continue with our discovery efforts, to maintain a steady supply of innovative compounds to our pipeline. We aim to create a pipeline with a sales potential of at least CHF 5 billion.



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# Utilize state-of-the-art technologies to drive innovation

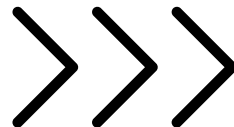
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As we wish to remain at the cutting edge of science, it is vital that we consider innovative approaches and utilize state-of-the-art technologies at each stage of the process, from bench to bedside.



We integrate computational tools and digital technologies at various stages of the drug discovery, development, and commercialization process, so as to maximize our potential and bring breakthrough medicines to patients.

We look for creative ways to harness advances in technology to focus on novel targets and use new drug development methods. All functions involved in drug discovery and in clinical and pharmaceutical development are streamlined to assist in the delivery of tailored, high-quality medicines.



**Achieving our strategic priorities is dependent on a company-wide effort, so we must attract, retain, and develop a talented and engaged workforce. We want our employees to feel proud of their work, and of the company they work for. We provide a supportive and stimulating environment for high-performing teams, recognizing and rewarding their contributions.**

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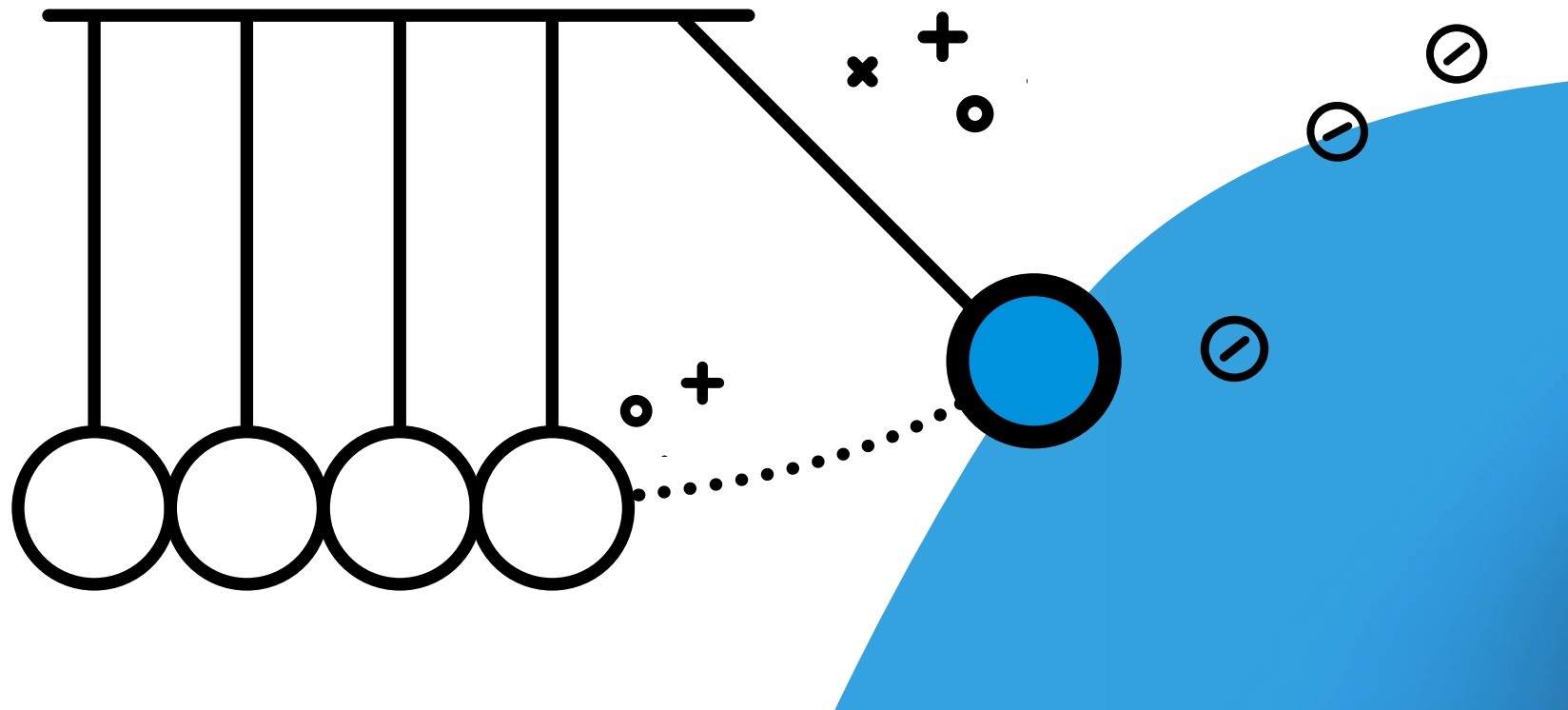
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# More momentum – The year of launch

The success of our launches relies on the strong foundation upon which they are built: having the right products, taking the right commercial approach, led by the right team.



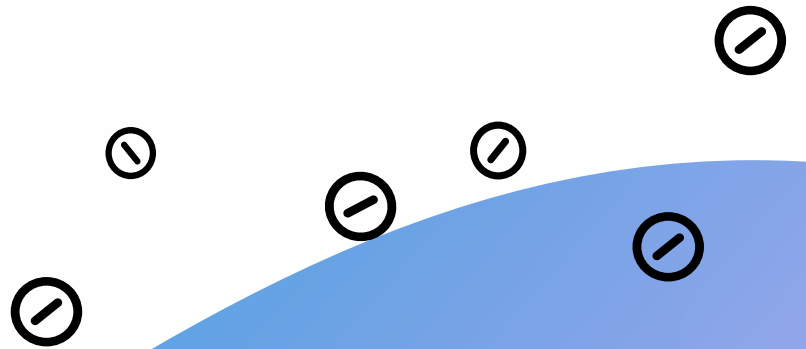
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“During 2020 and 2021, we made strong progress on our goals to build a world-class commercial organization and launch Idorsia’s first products, and 2022 was the transformational year we put our plans into action by launching our first two products.”

**Simon Jose**  
Executive Vice President, Chief Commercial Officer

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# The right products

Idorsia's products reflect our scientific core and our clear focus on research centered around small molecules. Within our first five years, we have launched two products discovered by our own scientists, which have brought much-needed innovation to the conditions they treat.

**QUVIVIQ (daridorexant)** is a dual orexin receptor antagonist (DORA), offering a new treatment option for patients with insomnia. Rather than inducing sleep through broad inhibition of brain activity, QUVIVIQ offers a targeted mechanism of action that decreases overactive wakefulness during the night.

The safety and effectiveness of QUVIVIQ are supported by a wealth of evidence generated during our development program. An important pillar of this evidence is the data from our pivotal Phase 3 studies, published in the February 2022 issue of *The Lancet Neurology*, and the long-term extension study, published in *CNS Drugs* in December 2022, confirming the safety profile of QUVIVIQ for up to 12 months of treatment.

The publication in *The Lancet Neurology*, entitled "Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials", establishes QUVIVIQ as the first insomnia medication to demonstrate efficacy in improving both nighttime symptoms and daytime functioning in patients with insomnia disorder. It also includes data on the safety profile of QUVIVIQ, which was well tolerated at all doses, with no physical dependence and no evidence of withdrawal or rebound insomnia upon treatment discontinuation.

The publication of this data in *The Lancet Neurology* reflects the importance and novelty of QUVIVIQ as a new treatment for patients with chronic insomnia disorder. QUVIVIQ addresses a high unmet need in a therapeutic area ripe for disruption and modernization.

According to one of the largest US surveys of people with trouble sleeping and healthcare providers, conducted by The Alliance for Sleep and Idorsia in partnership with The Harris Poll, there are several key gaps in education, dialogue and solutions for people affected by insomnia. This survey (*Wake Up America: The Night & Day Impact of Insomnia*) showed that 70% of people with trouble sleeping are desperate to improve their sleep, with spending on sleep aids and related products in the US exceeding USD 7 billion annually. The survey – conducted prior to the launch of QUVIVIQ – also revealed that 66% of people with trouble sleeping did not believe that current treatment options were able to help them. The results shine a light on the daytime impact of insomnia as well, with 29% reporting struggles at work and – in an update to the survey conducted in Q3 2022 – 53% reporting that their insomnia caused stress in their relationships.

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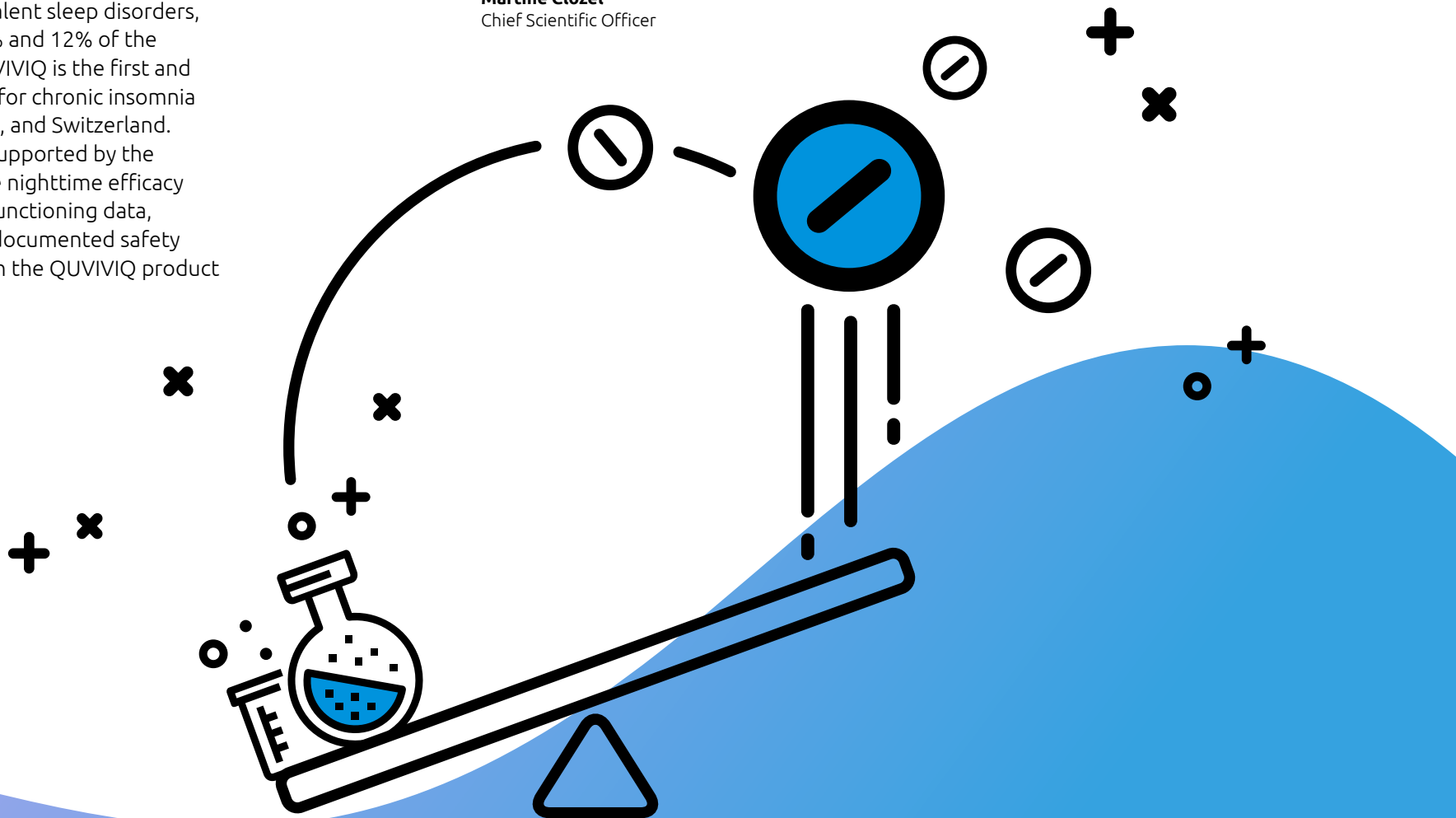
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In Europe, chronic insomnia disorder is one of the most prevalent sleep disorders, affecting between 6% and 12% of the adult population. QUVIVIQ is the first and only DORA approved for chronic insomnia disorder in the EU, UK, and Switzerland. These approvals are supported by the drug's comprehensive nighttime efficacy and unique daytime functioning data, together with a well-documented safety profile, as described in the QUVIVIQ product information.

“Publishing QUVIVIQ/daridorexant clinical data in this prestigious journal, *The Lancet Neurology*, is an impressive achievement for our company and highlights the groundbreaking nature of our work, as well as the outstanding properties of the drug.”

**Martine Clozel**  
Chief Scientific Officer



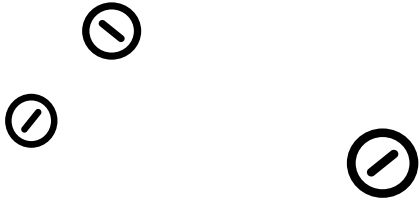
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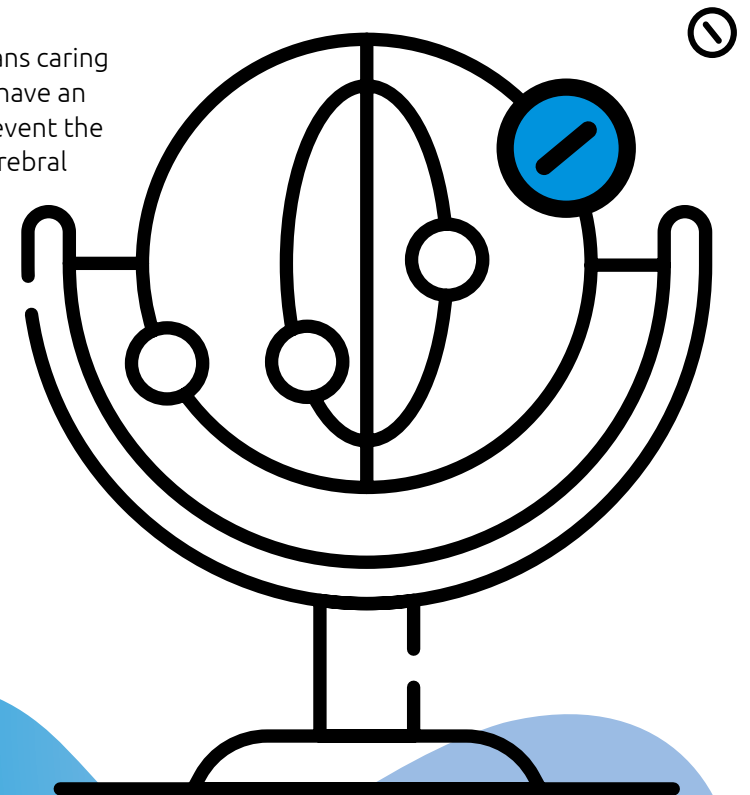
**PIVLAZ (clazosentan)**, our treatment for the prevention of cerebral vasospasm, vasospasm-related new cerebral infarction, and cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage (aSAH) securing, was approved in Japan in January 2022 and launched in April 2022.

The incidence of aSAH in Japan is approximately three times higher than in the rest of the world, and there have been no new treatments for the condition in over 20 years. The inclusion of PIVLAZ as a listed product in Japan's National Health Insurance system shows that the clinical efficacy demonstrated with PIVLAZ fulfills an important medical need for patients facing this life-threatening condition.

Our two Phase 3 studies of PIVLAZ with Japanese patients demonstrated significant reduction of vasospasm related morbidity and all-cause mortality in patients following aSAH, as well as confirming the drug's safety profile.

In April 2022, the results of these studies were reported in a *Journal of Neurosurgery* publication entitled "Effects of clazosentan on cerebral vasospasm-related morbidity and all-cause mortality after aneurysmal subarachnoid hemorrhage: two randomized phase 3 trials in Japanese patients".

With PIVLAZ, the expert physicians caring for aSAH patients in Japan now have an innovative new treatment to prevent the devastating consequences of cerebral vasospasm.



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“Subarachnoid hemorrhage is a relatively common disease in Japanese people. It is a disease that has a profound effect on patients, their families, and workplaces when it occurs in working generations. As a result, there is a great need for new drugs that help with the consequences of this life-changing condition. PIVLAZ is the only drug to demonstrate the prevention of cerebral vasospasm after subarachnoid hemorrhage treatment and the associated new cerebral infarctions and ischemic symptoms. Providing PIVLAZ to Japanese healthcare professionals – the first in the world – is of great significance, and I believe we can change the lives of many patients.”

**Teiji Tominaga**

MD, PhD, Professor & Chairman,  
Department of Neurosurgery, Tohoku University Graduate School of Medicine

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# The right approach

Our innovation does not end with drug discovery and development: it is built into our approach for transforming the insomnia treatment paradigm and commercializing Idorsia's products.

In the US, we have embarked on a comprehensive educational and awareness-raising campaign to help people understand the dual impact of insomnia on both nights and days. Our partnership with Jennifer Aniston – part of the powerful *Seize the Night and Day* campaign – is a unique consumer-focused campaign. Jen, with Idorsia, wants to help the approximately 25 million Americans who aren't getting the quality sleep they deserve to understand that they're not alone when it comes to trouble sleeping, and that they don't have to suffer in silence.

Our educational initiatives also include sponsorship of The Alliance for Sleep – a committee of leading physicians and healthcare experts focused on the critical importance of sleep health. The group shares the mission of advancing research, elevating the standard of care, and improving the health and quality of life of those experiencing insomnia and other sleep

disorders. The Alliance worked with Idorsia to conduct and share the results of the *Wake Up America* survey, designed to reveal and raise awareness of the full burden of insomnia among the general public.

Our documentary "The Quest for Sleep" is another example of the US team's consumer-focused efforts to raise awareness of insomnia. The film, narrated by award-winning actor Octavia Spencer, follows real people on their journey to find sleep, explores their struggles with insomnia through storytelling, and provides viewers with insights into the science of sleep.

Following approval and launch, we are also getting our messages about the unique profile of QUVIVIQ across to consumers through our Patient Ambassador programs, involving world champion skier, philanthropist, and entrepreneur Lindsey Vonn and esteemed actor and author Taye Diggs. Both celebrities are featured in the direct-to-consumer US advertising for QUVIVIQ, as well as our extensive digital and social media campaigns. As long-time insomnia sufferers, after speaking with their doctors, Vonn and Diggs were prescribed QUVIVIQ, and they are now passionate

about sharing their first-hand experience with trouble sleeping and spreading awareness of QUVIVIQ.

Of course, our US educational efforts are not limited to consumers. Using advanced analytics to drive dynamic customer targeting, we are raising awareness of QUVIVIQ among clinicians through our coast-to-coast Medical Science Liaison (MSL) team and dedicated US sales representatives.

US payer engagement to secure coverage and patient access to QUVIVIQ remains central to our approach. While coverage has been limited in 2022, we kicked off 2023 by announcing that QUVIVIQ will be covered at parity to the other branded DORA products for the Express Scripts National Preferred Formulary. We expect to secure further coverage in 2023, enabling more patients to access QUVIVIQ, which in turn will enhance our commercial success in the US.

Meanwhile, our launch of QUVIVIQ in Europe is underway, with the first countries – Germany and Italy – both initiating promotion and generating sales in November. To build awareness about the impact of chronic insomnia on patients'

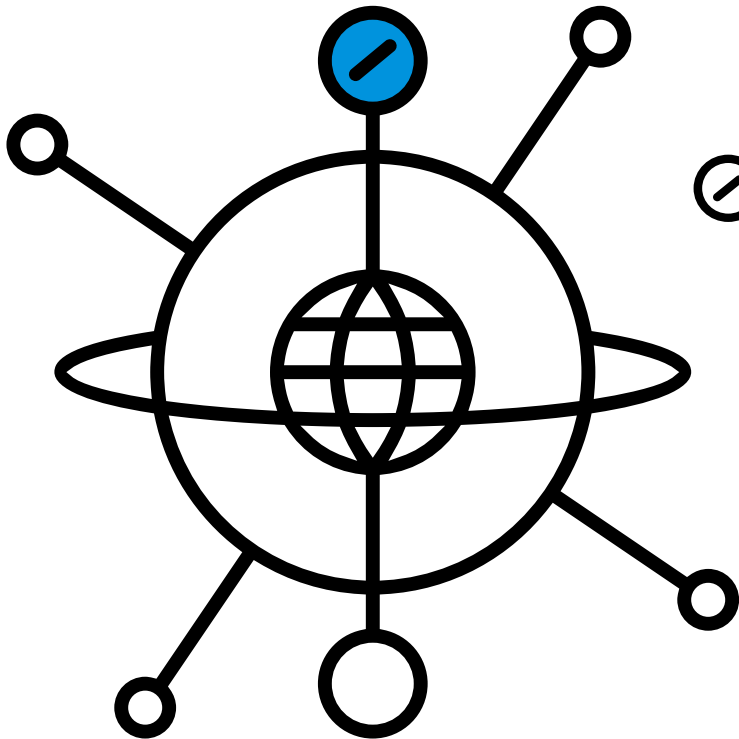
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lives, and the efficacy and safety profile of QUVIVIQ, our team has engaged with scientists and medical experts across the European sleep community.

For example, Idorsia initiated and funded the formation of REST (Redefine Education on Sleep Therapy), a cross border network of sleep experts from Europe and Canada with the vision to challenge the status quo and advance the management of chronic insomnia disorder. One of REST's main initiatives for 2022 was the Sleep Masterclass held in Madrid, Spain. This event, entitled *Chronic insomnia disorder: beyond sleepless nights*, was attended by top European sleep experts and healthcare professionals. Over one-and-a-half days, a faculty of sleep and insomnia experts led engaging and interactive explorations of chronic insomnia as a disease, unmet needs in insomnia treatment, and current research horizons.

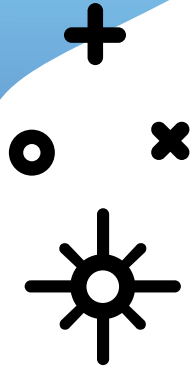
In addition, ahead of our launch of QUVIVIQ in Germany in November, we shared our clinical data for QUVIVIQ at a symposium for sleep specialists held at the annual conference of the German Sleep Society (DGSM).

In January 2023, as part of the launch of QUVIVIQ in Italy, we held a dedicated launch meeting in Venice, attended by over 100 Italian neurologists, with a faculty of 30 sleep experts. Participants experienced the sounds and sights of insomnia through an *in situ* artistic installation inspired by Dante's Divine Comedy, as a metaphor for the distortion of insomnia and the healing power of restorative sleep.

Although the hospital setting in which PIVLAZ is administered is very different from the primary care environment, our team in Japan is taking a similarly patient-centric approach to launch. Our goal is that patients suffering from aSAH in Japan should receive optimal treatment. To achieve this, we are helping to establish aSAH Medical Care Referral Networks in Japan – from Hokkaido to Okinawa – enabling patients to access early diagnosis and be transferred to a hospital with appropriate care.

Through educational efforts for the healthcare community and expert engagement, we have seen more and more hospitals incorporate PIVLAZ in their aSAH treatment protocols – a sign that specialists are recognizing the benefits of our product.

# The right team



The members of our high-caliber commercial team have been hand-picked for their experience and capabilities in launch excellence. They are experts in their fields and know the intricacies of the commercial landscape in their geographic areas.

In the US, the team members focused on QUVIVIQ have collectively executed more than 70 launches between them. It is rare to see a group of people with this level of seniority and experience dedicated to a single product. As commercial leaders recruited from across the industry, they bring a wealth of knowledge to their aim of building Idorsia's US business and successfully launching QUVIVIQ. We have also established lean and agile country-based teams across the EUCAN region, who understand the unique challenges and how to launch new products successfully in each of their markets.

Our team in Japan has forged strong relationships with a broad group of leaders in the healthcare community treating aSAH. These relationships and Idorsia's standing as a scientific leader in this field have been built on the foundation of the Japanese clinical studies of the product, which involved years of collaboration with the specialist community.

## Meet some members of our commercial talent

### Alice Huisman

General Manager, Switzerland and Austria  
Location: Allschwil

### Making the QUVIVIQ launch in Switzerland and Austria successful by...

building a team that supports and informs physicians. When new treatment options become available, it is normal to see a mix of excitement and reluctance. It is my team's responsibility to make sure physicians feel comfortable and well informed about QUVIVIQ.

**I am passionate about...** making new treatments available – ones that help people live and feel better. At Idorsia, I have a chance to do exactly that, and I'm surrounded by people who share this passion.

### Mirjam Korn

Marketing Director, Germany  
Location: Munich

### Making the QUVIVIQ launch in Germany successful by...

conveying the global product strategy and customizing it for our country, with a passion for the product as our driving force.

**I am passionate about...** motivating and inspiring the sales team. They are my first customers. If we train them well, we can be sure that the product's unique profile is conveyed to healthcare professionals and ultimately to patients. Passion is a key driver for successfully marketing a treatment – without it, no real, lasting success can be achieved.



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### Ajay Ahuja

Head of Medical Affairs, US  
Location: Radnor, Pennsylvania

**Making the QUVIVIQ launch in the US successful by...** deploying our medical education plan to communicate the robust clinical data and profile of QUVIVIQ to key US healthcare providers, while also engaging with top experts in the field of sleep medicine to further advance the science.

**I am passionate about...** helping physicians acquire the knowledge and data to make the best decisions for their patients. Much of the feedback we have received about patients who have benefited from QUVIVIQ have been absolutely heartwarming!

### Joanna Stevens

Head of Sales, US  
Location: Radnor, Pennsylvania

**Making the QUVIVIQ launch in the US successful by...** using analytics and insights to adapt in real time to opportunities and to continuously improve our territory management with strong targeting and execution. Our highly trained and motivated sales representatives are deployed across the country, calling on thousands of healthcare providers to help the uptake of QUVIVIQ.

**I am passionate about...** leading our sales team by empowering and enabling them to communicate about the product's safety and efficacy profile to the right healthcare providers – ultimately having a substantial impact on patients and the insomnia treatment paradigm in the US.

### Shuya Takahashi

Head of Medical Affairs, Japan  
Location: Tokyo

**Making the PIVLAZ launch in Japan successful by...** building and deploying a specialized, expert Medical Science Liaison team across Japan. With such a great team, we are confident that we will reach our aim of establishing PIVLAZ as the standard for ICU medical care post-aSAH securing.

**I am passionate about...** helping patients lead a fulfilling life post-aSAH. It's rewarding to work together with the team to bring PIVLAZ – a long-awaited and novel treatment – to patients and physicians in Japan, and hopefully soon also globally.

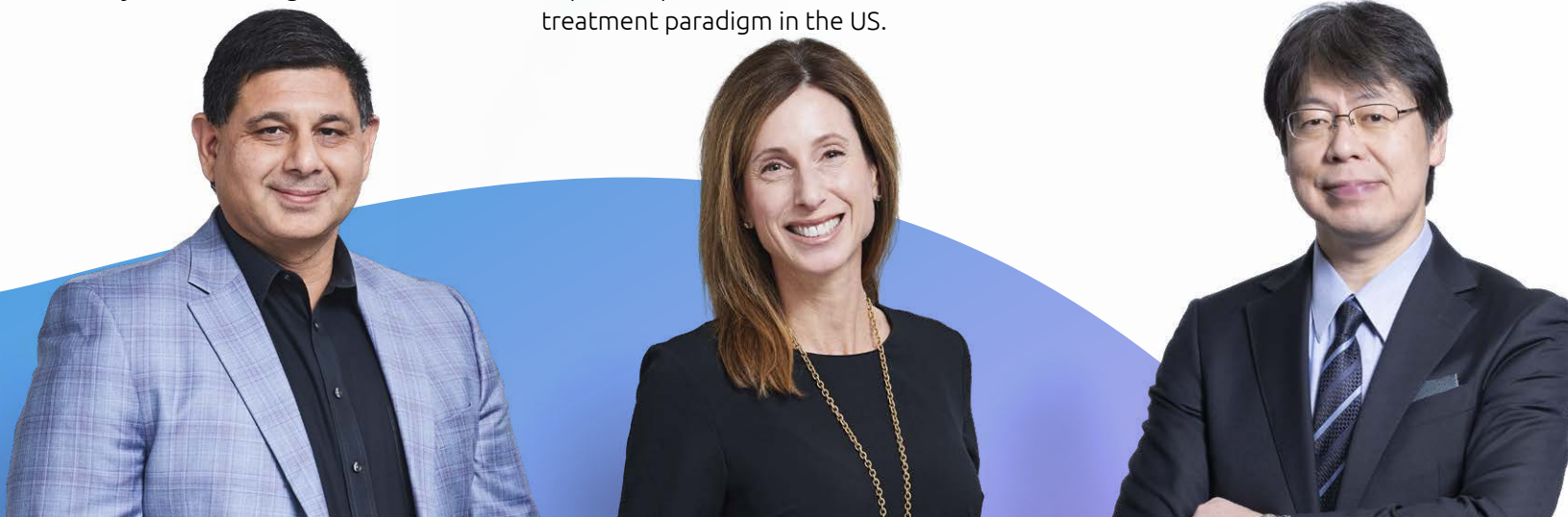
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# More horizons – Expanding globally

## Our commercial organization

- 2017** **Idorsia Pharmaceuticals Ltd**  
Allschwil, Switzerland
- 2018** **Idorsia Pharmaceuticals Japan Ltd**  
Tokyo, Japan
- 2020** **Idorsia Pharmaceuticals US Inc.**  
Radnor, Pennsylvania
- 2021** **Idorsia Pharmaceuticals Germany GmbH**  
Munich, Germany
- Idorsia Pharmaceuticals France SAS**  
Paris, France
- Idorsia Pharmaceuticals UK Ltd**  
London, United Kingdom
- 2022** **Idorsia Pharmaceuticals Korea Co., Ltd**  
Seoul, South Korea
- Idorsia Pharmaceuticals Canada Ltd**  
Montreal, Canada



**Idorsia Pharmaceuticals Italy S.R.L.**  
Milan, Italy

**Idorsia Pharmaceuticals Spain S.L.**  
Madrid, Spain

**Idorsia Pharmaceuticals Nordics AB**  
Stockholm, Sweden

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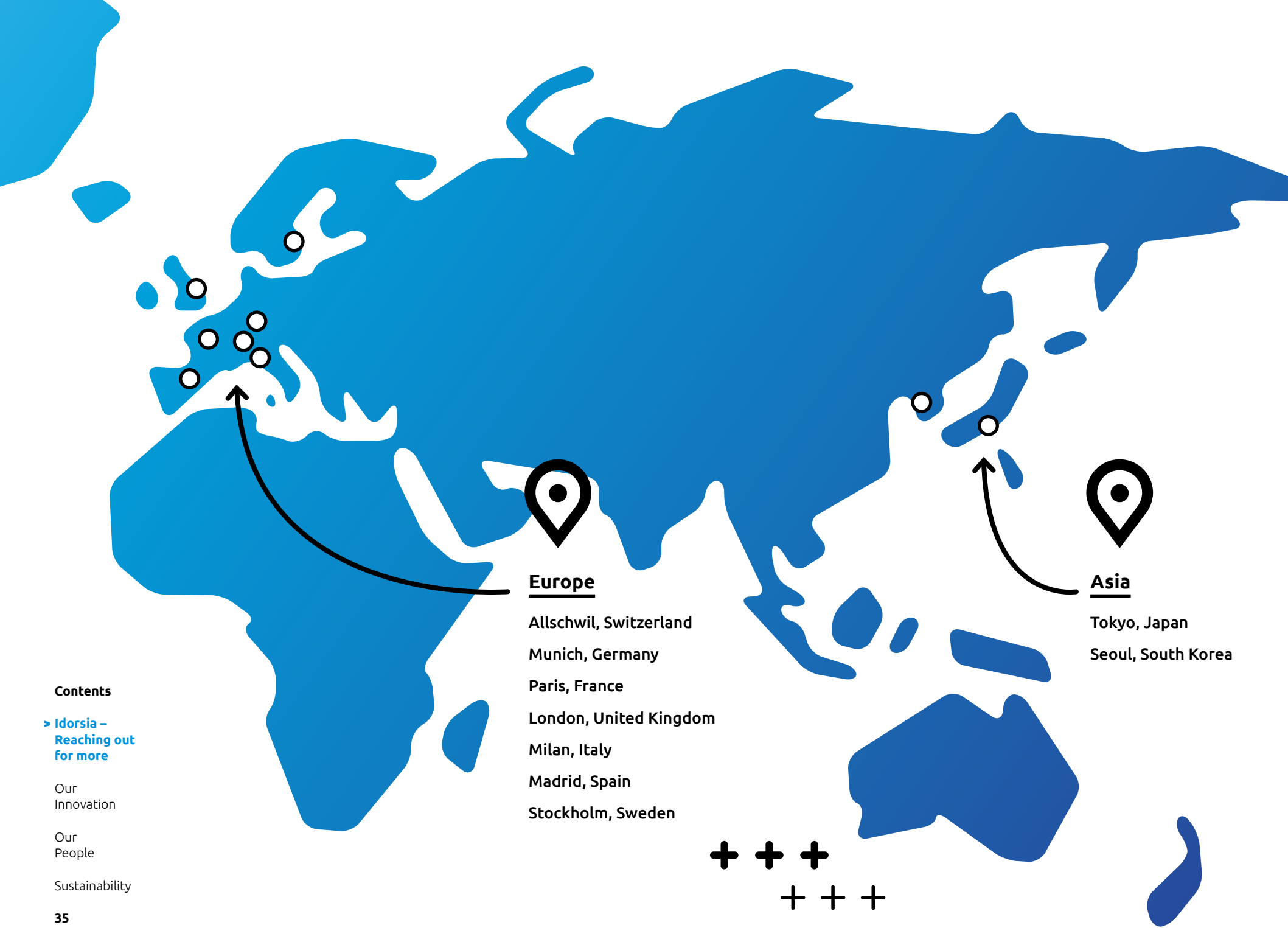
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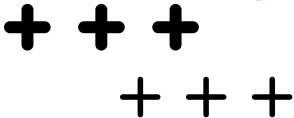


**Europe**

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

**Asia**

- Tokyo, Japan
- Seoul, South Korea



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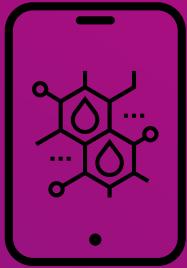
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# Our Innovation



“We need creativity to be innovative, so we need a brilliant idea and a deep understanding of the disease, to translate it into a molecular mechanism, and to try to find a drug to treat that disease.”

**John Gatfield**  
Associate Director, Principal Scientist

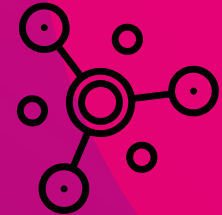
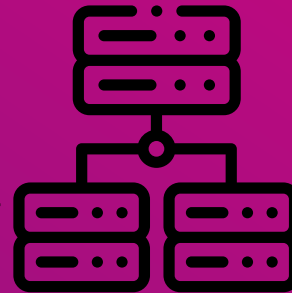
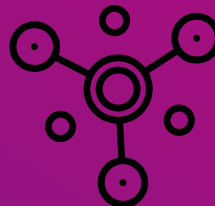
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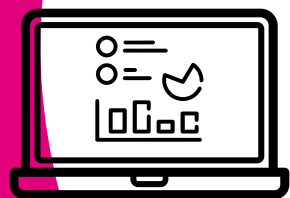
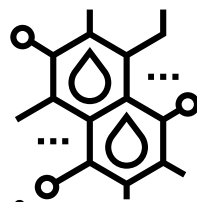
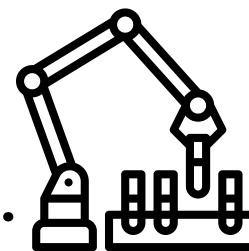
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# More innovation – from bench to bedside



From bench to bedside... from compounds to commercialization... no matter how you put it, Idorsia's ambition is clear: to discover great molecules, build evidence in creative clinical studies, and successfully bring new treatments to patients, creating a sustainable business based on innovation.

Our innovation starts with a brilliant idea and culminates, we hope, in a new drug that can change the treatment paradigm in the target indication.

Idorsia's drug discovery focuses on families of proteins, characterized by the way they work. We pursue innovative programs involving proteins which have not been targeted up to now, so as to develop drugs with novel mechanisms of action. We are also constantly looking for ways to integrate new technologies and approaches to drug design, such as the use of artificial intelligence (AI) tools.

The drug discovery process starts with an idea from our scientists. We scour the literature to see what others have not yet

discovered, to generate ideas and then translate them into a concept which can lead to new treatments for patients.

Our work in the lab begins with the target. This may be a particular protein which, when its activity is modulated, can normalize a biological process in the body – with beneficial effects for patients. To see whether we can affect the protein's activity, we first need to be able to measure it.

We produce, or "express", the target in large quantities and measure its natural activity in assays. The assay needs to be sensitive, accurate, and highly reliable. Plus, in order to perform hundreds of thousands of measurements, it needs to be automated, using robotic equipment.

But there are two sides to the discovery process – a target and a compound.

Compounds are substances which, we hope, will modify the activity of a target involved in a pathological process and which can be developed into a drug for patients.

At Idorsia, we maintain a library consisting of hundreds of thousands of different compounds. To begin our hunt for drugs, we test the entire library on the target, in the hope that one of these compounds will modify the activity of the protein. This process is called high-throughput screening; if it's a simple assay, we can test the whole library within a matter of weeks. At this stage, the goal is to identify compounds which exhibit some activity.

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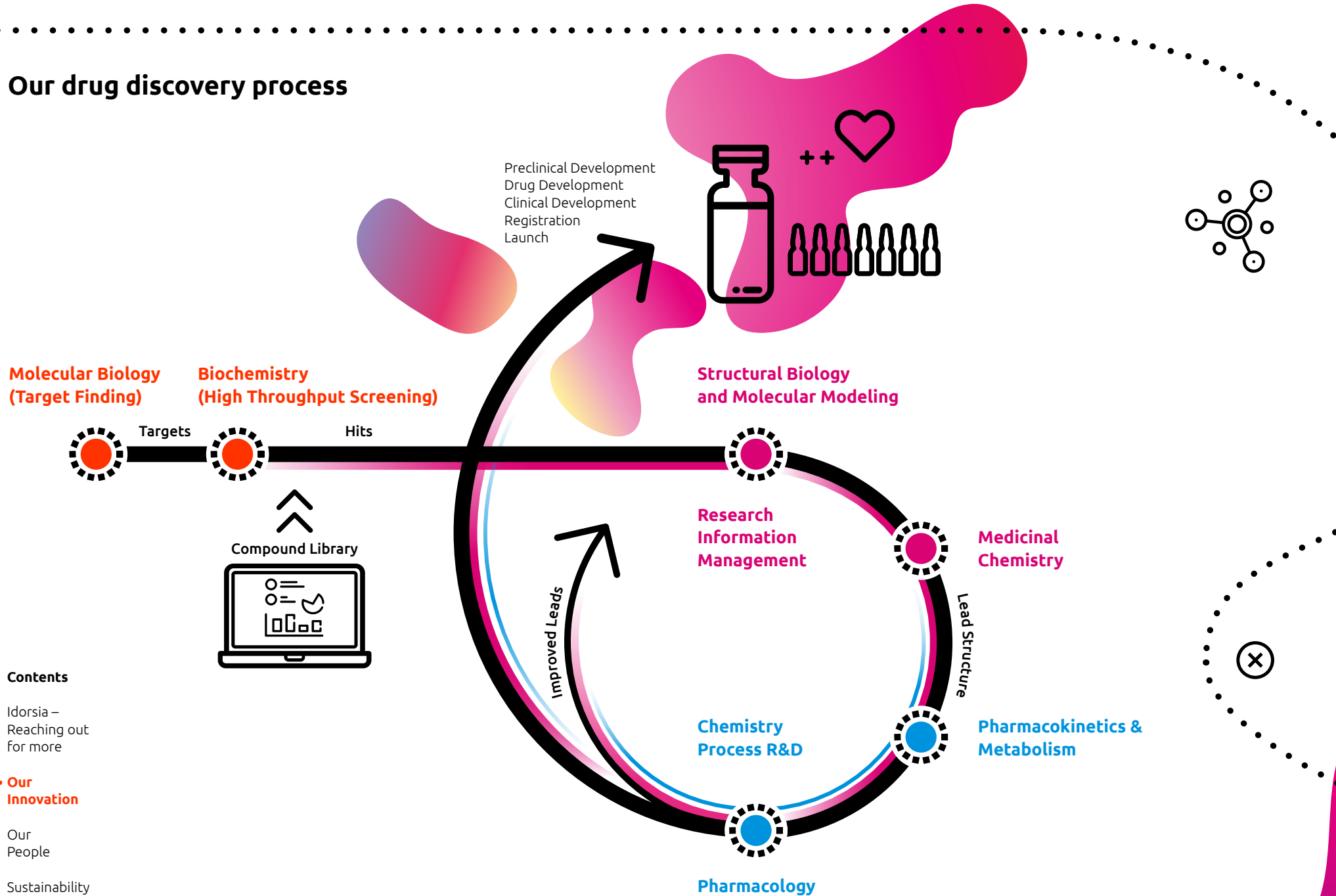
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# Our drug discovery process



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The project team then analyzes these compounds to decide which of them is the most promising starting point for optimization using the art of medicinal chemistry.

Obviously, huge amounts of data are generated, and powerful IT tools are required to extract the knowledge we need. To really understand the data, we visualize it and study the relationship between chemical structures and biological properties.

Target and compound fit together like a lock and a key. The compound can be modified so that it fits better and, ideally, becomes more potent.

Medicinal chemistry involves the use of chemistry's tools to design molecules that are potential drugs. We manipulate the molecular structure and then send the compounds back to our biologists or pharmacologists for testing in an iterative process. With each cycle, the compound is further optimized to finally become a drug.

At first, we seek to enhance the potency of the compound's effects on the target protein, but as we advance, we look at other activities, which may cause side effects. The aim is to ensure that the compound's overall properties allow it to become a drug.

For example, our electrophysiologists screen drugs for side effects by monitoring electrical activity in the heart or brain. Here, electrical communication depends on ion channels in the cell membrane; if a drug blocks some of these ion channels, it can have serious adverse effects.

Small-scale testing for initial assays requires only milligram quantities; for subsequent testing, however, much more material is needed. This is where our process research teams come into the picture. They are responsible for scaling up from milligram to gram quantities, and finally to the kilogram batch which is used for preclinical testing.

It's no good having a potent compound which is destroyed by the body before it has a chance to do its job. Our chemical and drug product specialists take the optimized compound and develop the most robust, safe, and cost-efficient formulation to deliver it to the patient.

Once reproducible processes have been elaborated to produce large quantities of the active compound and the formulated drug product, our technical project teams manage the production of the drug with partner companies. They secure drug supplies for clinical development and, when appropriate, for commercial launch and beyond.

**"For me, invention is making something out of a daring idea. And I really have the feeling that's what we are doing at Idorsia."**

**Corinna Grisostomi**  
Senior Scientist

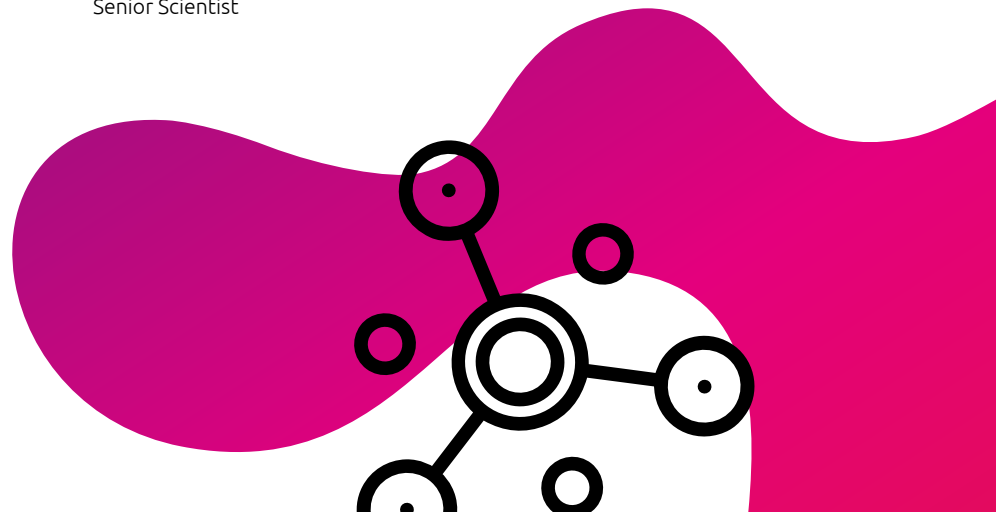
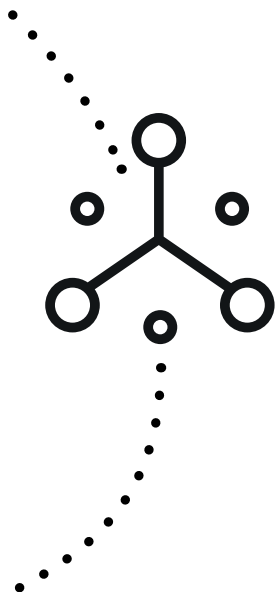
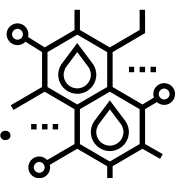
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# More experience – Building the clinical evidence

Following the drug discovery phase, the selected molecule must be comprehensively studied to demonstrate clinical safety and efficacy.

Idorsia aims to deliver new products with the potential to significantly change the treatment options for the target diseases. We want to bring new perspectives to the development of innovative compounds, challenging accepted paradigms to answer the questions that matter most. Our key assets have the potential to transform treatment in the target indications.

“We tailor the target indication to characteristics of the compound. We always try to find the disease, spectrum of diseases, or subset of medical conditions where the molecule will fit best from an efficacy and safety perspective, and where it addresses a medically important need.”

**Guy Braunstein**  
Executive Vice President, Chief Medical Officer

Idorsia’s clinical development function comprises a broad spectrum of expertise clustered within multiple departments: therapy area units, strategic development, clinical pharmacology, biostatistics and data management, drug safety, drug regulatory affairs, clinical operations, and life cycle management. Life cycle cross-functional teams – under the direction of a life cycle leader – bring expertise from preclinical development, clinical development, and technical operations to the efficient development of new medicines. They steer the compounds from entry into human studies through to submission of the dossier to health authorities, approval, and maintenance of the license during the commercialization phase up to the loss of the medicine’s exclusivity in the major markets and beyond. Idorsia’s clinical development function manages clinical programs in accordance with the appropriate ethical, scientific, medical, and operational standards, so as to generate the information required by regulatory health authorities worldwide.

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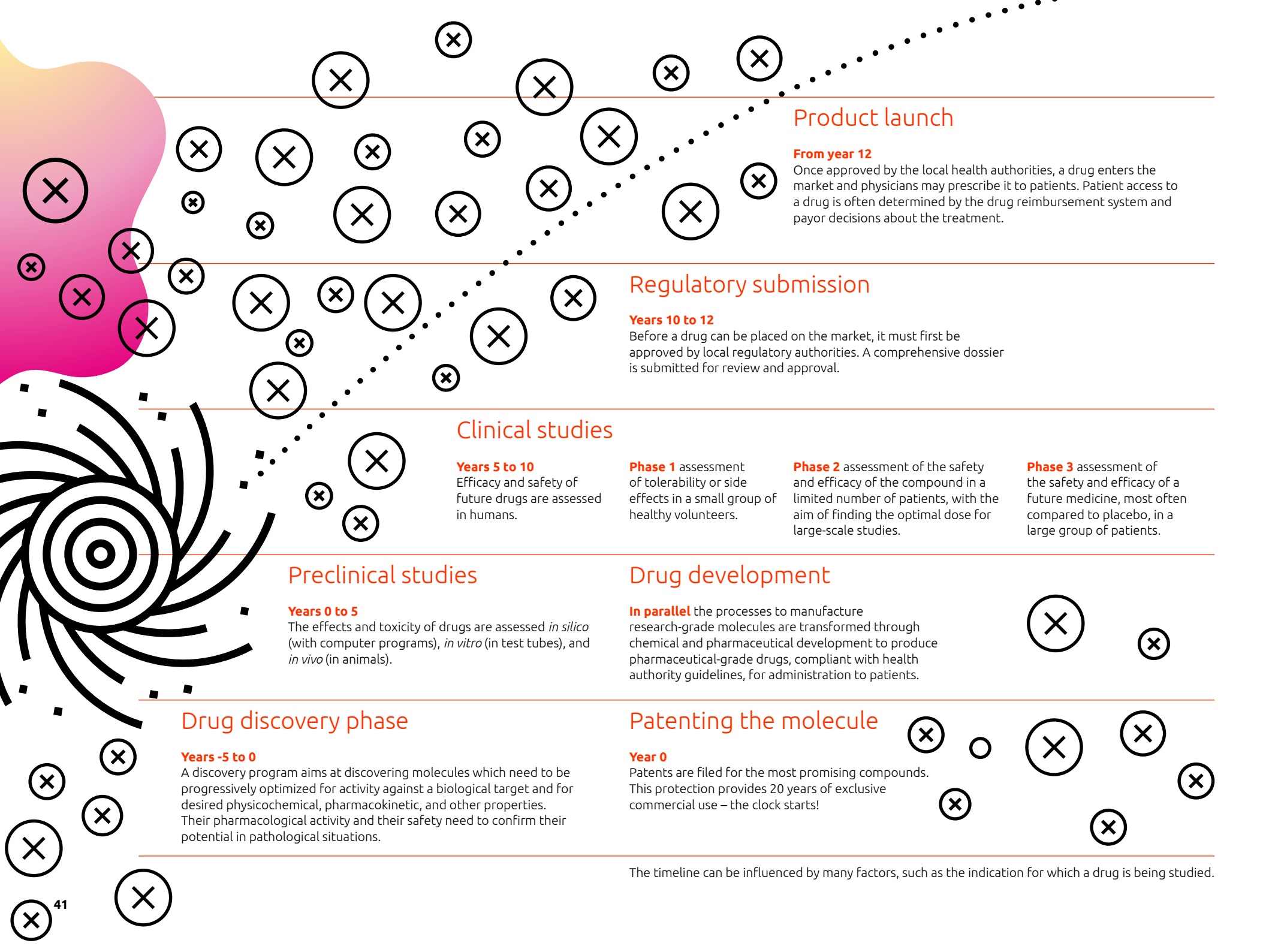
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## Drug discovery phase

### Years -5 to 0

A discovery program aims at discovering molecules which need to be progressively optimized for activity against a biological target and for desired physicochemical, pharmacokinetic, and other properties. Their pharmacological activity and their safety need to confirm their potential in pathological situations.

## Preclinical studies

### Years 0 to 5

The effects and toxicity of drugs are assessed *in silico* (with computer programs), *in vitro* (in test tubes), and *in vivo* (in animals).

## Clinical studies

### Years 5 to 10

Efficacy and safety of future drugs are assessed in humans.

**Phase 1** assessment of tolerability or side effects in a small group of healthy volunteers.

**Phase 2** assessment of the safety and efficacy of the compound in a limited number of patients, with the aim of finding the optimal dose for large-scale studies.

**Phase 3** assessment of the safety and efficacy of a future medicine, most often compared to placebo, in a large group of patients.

## Drug development

**In parallel** the processes to manufacture research-grade molecules are transformed through chemical and pharmaceutical development to produce pharmaceutical-grade drugs, compliant with health authority guidelines, for administration to patients.

## Patenting the molecule

### Year 0

Patents are filed for the most promising compounds. This protection provides 20 years of exclusive commercial use – the clock starts!

## Product launch

### From year 12

Once approved by the local health authorities, a drug enters the market and physicians may prescribe it to patients. Patient access to a drug is often determined by the drug reimbursement system and payor decisions about the treatment.

## Regulatory submission

### Years 10 to 12

Before a drug can be placed on the market, it must first be approved by local regulatory authorities. A comprehensive dossier is submitted for review and approval.

The timeline can be influenced by many factors, such as the indication for which a drug is being studied.

# More potential – Navigating regulatory review

With successful clinical studies demonstrating a compound's safety and efficacy in hand, we must then navigate the regulatory review and approval process.

From the first-in-human study of a drug through market approval and for as long as it remains on the market, we maintain an ongoing dialogue with health authorities in every country where we operate. We ensure that our development plans meet the regulators' expectations and that we generate the types of data that are required to support registration of the product.

Once our products reach the registration phase, we embark on the regulatory review process, shown for the US and EU regulatory bodies on pages 43 and 44. Teams from across Idorsia collaborate to develop a robust and comprehensive dossier for submission to the health authorities. The data included is wide-reaching: preclinical research, such as compound screening, animal models, and all pharmacology, pharmacokinetics, and toxicology data; technical descriptions of the properties and chemical synthesis of the drug substance,

as well as quality controls and procedures for pharmaceutical manufacturing; and complete results and analysis of each of the clinical studies and safety data collected over the course of clinical phases – in other words, the story of each molecule from bench to bedside.

“For each of the dossiers that we submit to health authorities, we highlight the science-based approach that Idorsia has taken to address patients' unmet needs. Our robust data tells an amazing story.”

**Sonja Pumpluen**

Senior Vice President, Head of Global Life Cycle Management & Drug Regulatory Affairs

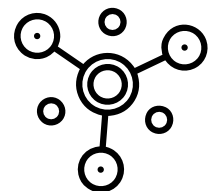
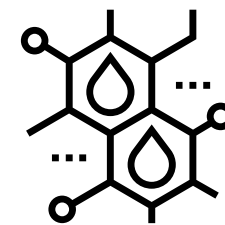
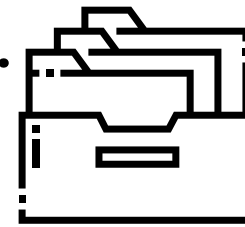
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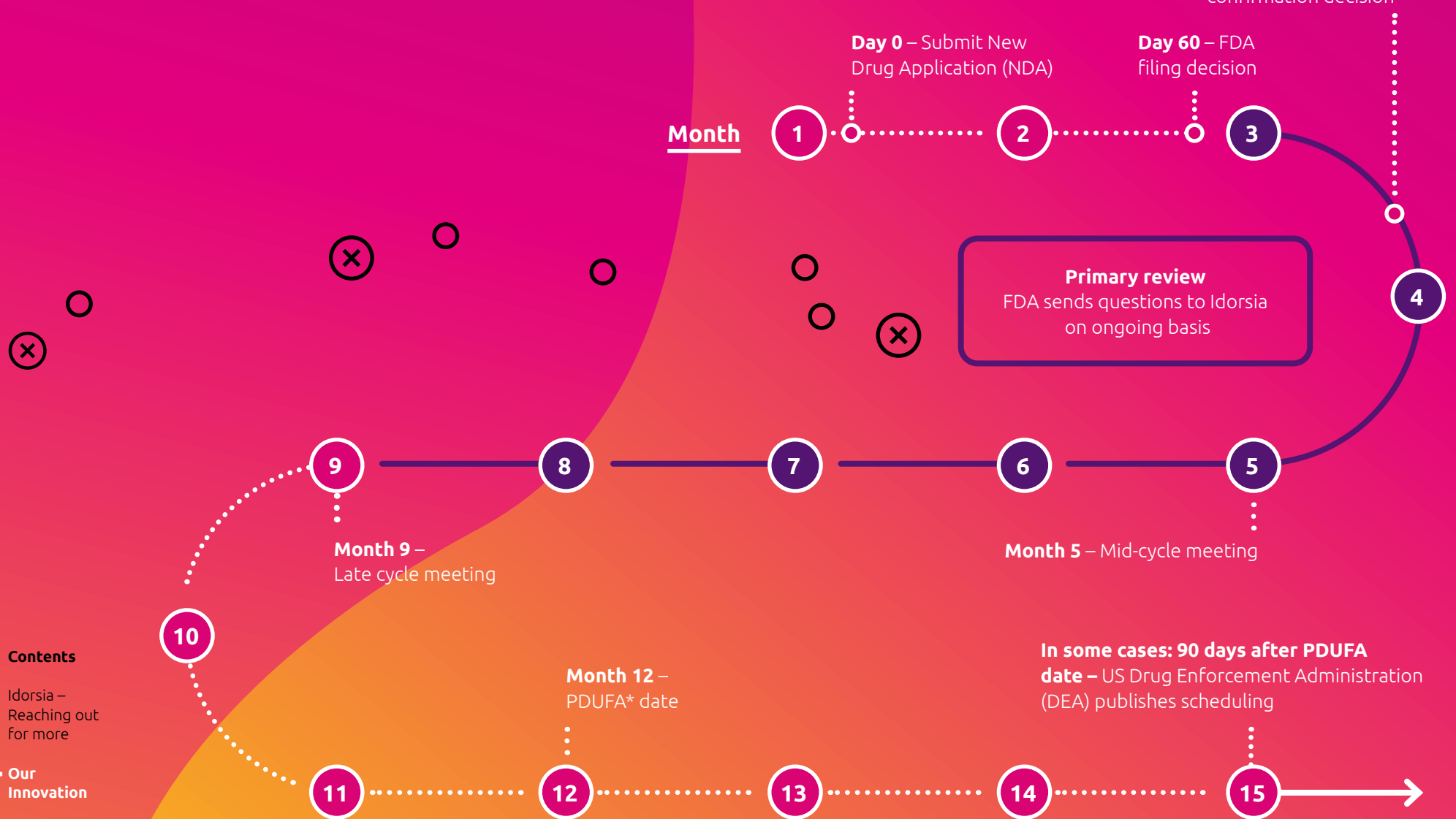
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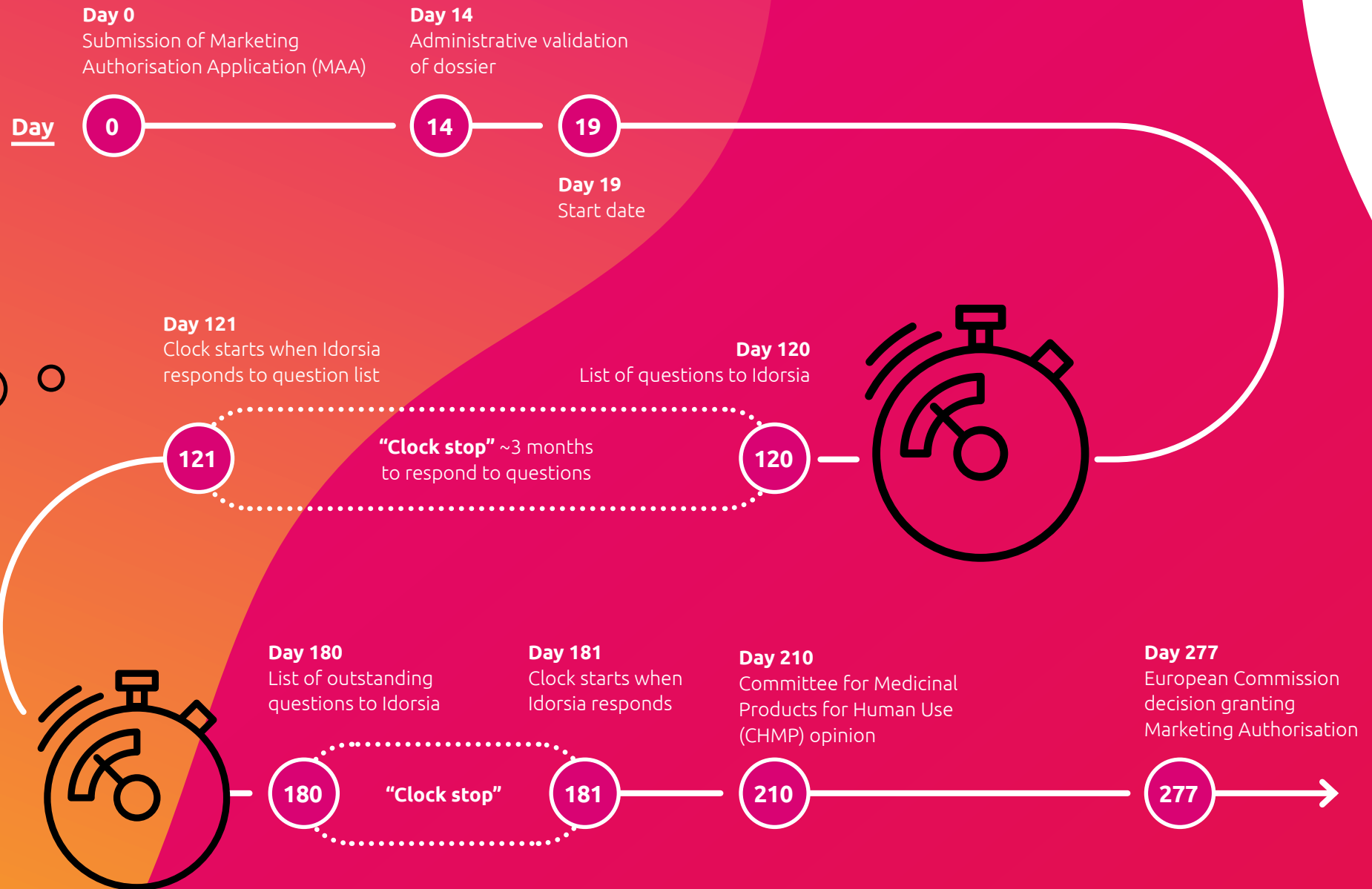
# US regulatory standard review – FDA



\*The date by which the Food and Drug Administration must respond to a New Drug Application under the Prescription Drug User Fee Act.

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# EU regulatory standard review – EMA





# More hope – Changing the treatment paradigm

Regulatory approval is a key milestone, but our treatments can only reach patients if our products are successfully launched by our commercial organization – completing the journey from bench to bedside.

Our approach to launch starts long before approval, with the global product strategy – a roadmap to accelerate our affiliates' efforts to successfully launch our products, while also providing a consistent foundation across the world.

Within our commercial organization, three functions – Marketing, Medical Affairs, and Value & Access – are responsible for the global product strategy, in close collaboration with key country leaders and our discovery and development teams.

Global Marketing generates deep insights from patients and healthcare professionals, which help us to gain a holistic understanding of our customers' needs. This helps us to address unmet needs in the marketplace and to clearly differentiate our brands. We also focus our marketing efforts on raising awareness among patients, healthcare professionals, and other key stakeholders (e.g. policymakers) of the impact of the conditions targeted by our products.

Idorsia's Global Medical Affairs team is responsible for communicating to the healthcare community our science, the data on our products, and the key differences from other treatments. To inform and develop our global strategy, we also seek medical insights regarding how our products' core data resonates with physicians. Our medical and clinical development teams continue to generate new evidence for approved products – with real-world evidence in high demand among payors and physicians alike. Importantly, this team also manages Idorsia's repository of medical information and has developed an intelligent digital platform, providing 24/7 self-service access to scientifically robust, balanced, and easily digestible information.

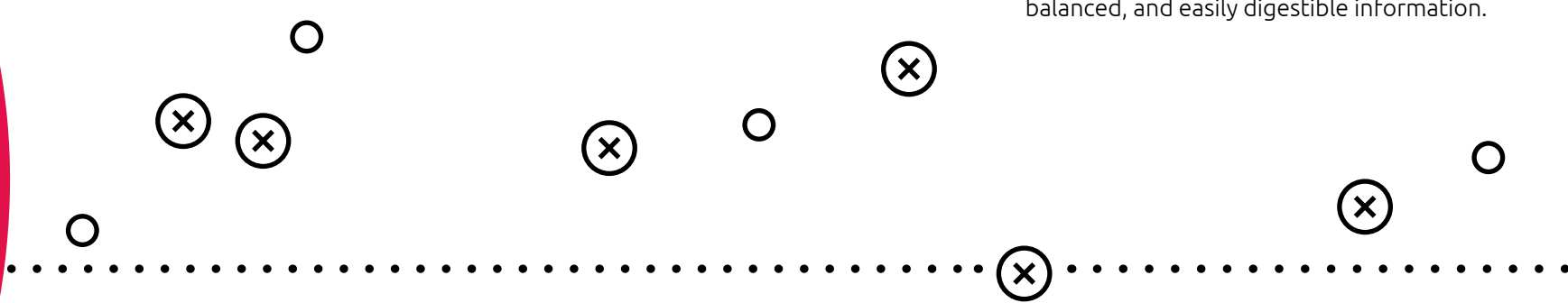
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Value & Access is responsible for demonstrating the value of our products – which is more important than ever, given increasing budgetary constraints in healthcare systems across the world. As an engaged member of the healthcare ecosystem, Idorsia understands its responsibility to help find solutions to the high cost of healthcare, and we are committed to playing our part in supporting patient access to our medicines. The prices of our medicines will reflect the value that our innovations deliver, generating revenues to fuel the discovery and development of future molecules. To demonstrate meaningful innovation, we develop a value proposition, underpinned by our science and clinical data, to help payors determine the value offered by our treatments compared to existing options. Our ultimate goal is to help patients gain access to our treatments through reimbursement or other coverage arrangements.

While our product strategies are global, our country teams own the execution of their local launches and customer relationships, and they tailor the global strategies to their markets. Working closely together, our affiliates and global teams all play a role in ensuring a successful launch and thus maximizing the value of Idorsia's innovation.

**“We ensure that the global product strategy is truly built on scientific evidence and the needs of patients and healthcare professionals.”**

**Antonio Olivieri**  
Senior Vice President, Head of Global Medical Affairs

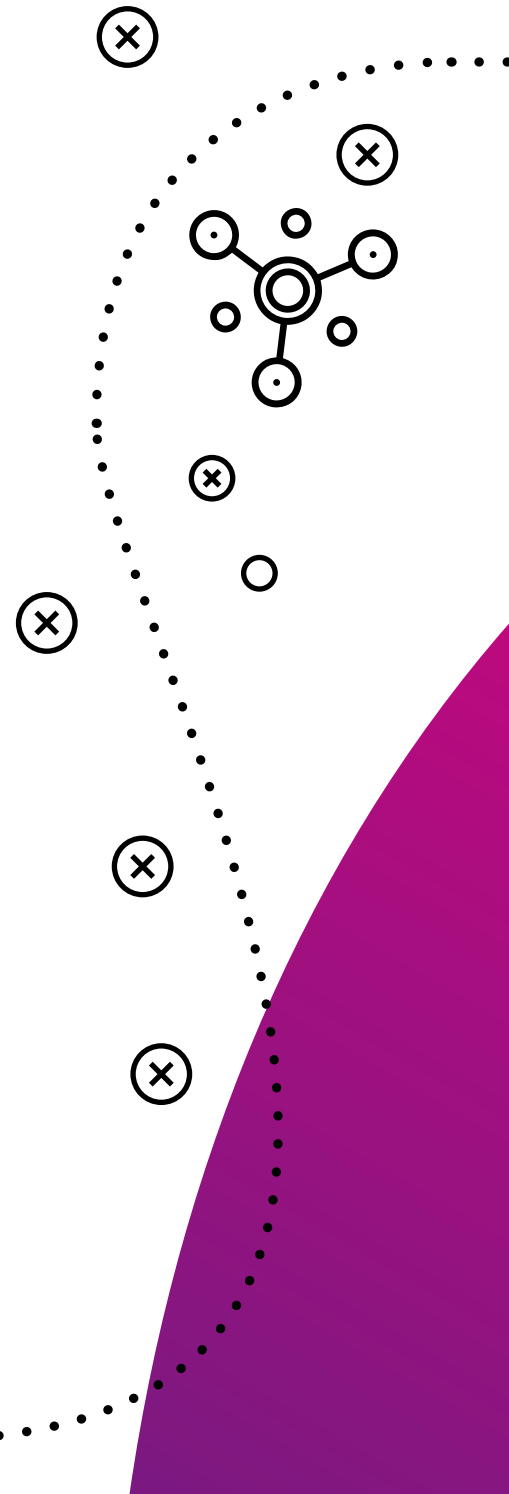
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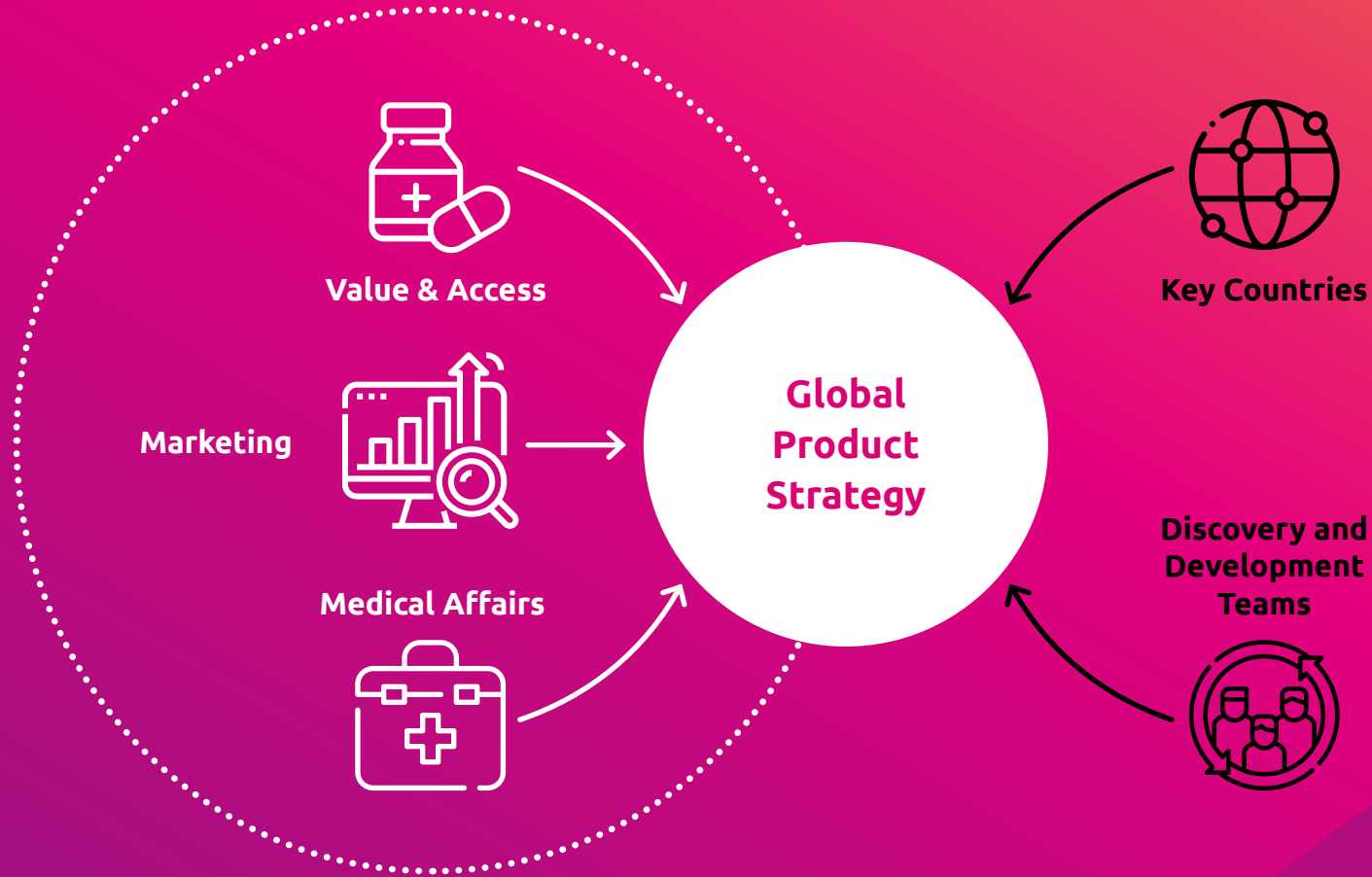
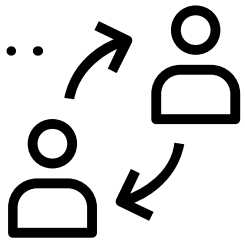
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# More in the pipeline – Promising compounds

We have a diversified and balanced clinical development pipeline covering multiple therapeutic areas, including CNS, cardiovascular, and immunological disorders, as well as orphan diseases.

“The way we work in research is focused on and built around innovation and core competencies. This has led to a diverse pipeline, addressing different diseases where either no treatment is available, or patients have conditions that are resistant to treatment.”

**Martine Clozel**  
Executive Vice President, Chief Scientific Officer



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## Our portfolio

Status: January 2023

Product / compound	Mechanism of action	Target indication / Therapeutic area	Status
<b>PIVLAZ (clazosentan)</b>	Endothelin receptor antagonist	<b>Cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage</b>	Commercially available in Japan; Global Phase 3 complete – results expected Q1 2023
<b>QUVIVIQ (daridorexant)</b>	Dual orexin receptor antagonist	<b>Insomnia</b>	Commercially available in the US and the first countries in Europe; approved in the UK and Switzerland; under review in Canada; Phase 3 in Japan successful – filing expected in H2 2023; Phase 2 in pediatric insomnia – recruiting
<b>Aprocitentan*</b>	Dual endothelin receptor antagonist	<b>Difficult-to-control (resistant) hypertension</b>	NDA submitted in the US, MAA submitted in the EU, other filings in preparation
<b>Lucerastat</b>	Glucosylceramide synthase inhibitor	<b>Fabry disease</b>	Phase 3 primary endpoint not met, open-label extension study ongoing
<b>Selatogrel</b>	P2Y <sub>12</sub> inhibitor	<b>Suspected acute myocardial infarction</b>	Phase 3 recruiting
<b>Cenerimod</b>	S1P <sub>1</sub> receptor modulator	<b>Systemic lupus erythematosus</b>	Phase 3 recruiting
<b>ACT-1004-1239</b>	ACKR3/CXCR7 antagonist	Multiple sclerosis and other demyelinating diseases	Phase 2 in preparation
<b>Sinbaglustat</b>	GBA2/GCS inhibitor	Rare lysosomal storage disorders	Phase 1 complete
<b>ACT-777991</b>	CXCR3 antagonist	Recent-onset Type 1 diabetes	Phase 1
<b>ACT-1014-6470</b>	C5aR1 antagonist	Immune-mediated disorders	Phase 1
<b>IDOR-1117-2520</b>	Undisclosed	Immune-mediated disorders	Phase 1

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\* In collaboration with Janssen Biotech to jointly develop aprocitentan, Janssen Biotech has sole commercialization rights worldwide

Neurocrine Biosciences has a global license to develop and commercialize ACT-709478 (NBI-827104), Idorsia's novel T-type calcium channel blocker. ACT-709478 was investigated in a Phase 2 study for the treatment of a rare form of pediatric epilepsy. The study did not meet the primary endpoint. ACT-709478 was generally well tolerated. Neurocrine continues to analyze the data generated in the study.

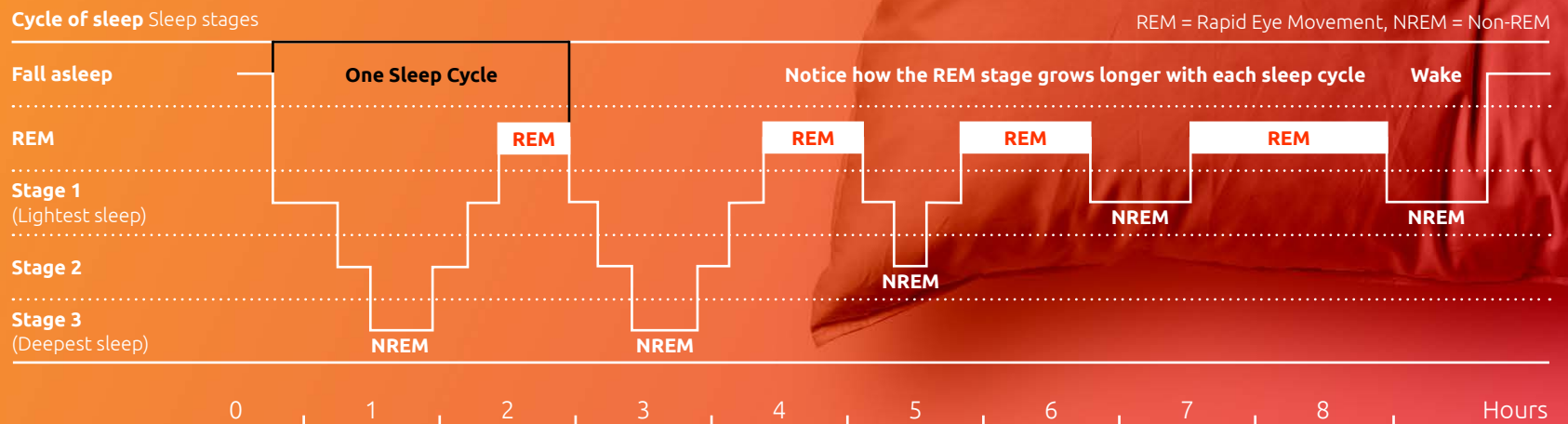
# QUVIVIQ™ (daridorexant) for insomnia disorder

Chronic insomnia disorder is a condition of overactive wake signaling, which can have a profound effect on patients' lives. It can be defined as a combination of dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. It involves difficulty initiating and/or maintaining sleep at least three times a week for a minimum of three months.

Chronic insomnia disorder as a persistent disorder is quite different from a brief period of poor sleep, and it can take its toll on both

physical and mental health. Idorsia's research has shown that poor-quality sleep can affect many aspects of daily life, including the ability to concentrate, mood, and energy levels.

Chronic insomnia disorder is a common problem, with the prevalence being approximately 10%. On this basis, and assuming a US adult population of around 250 million, there are approximately 25 million adults in the US who suffer from chronic insomnia disorder.



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Insomnia is a common problem. The prevalence of insomnia disorder is approximately

10%

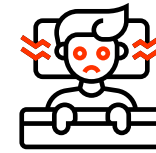
“It really annoys me when people say ‘If you were really tired, you would sleep.’ If only it were that simple! Unless you have suffered from true insomnia, you have absolutely no idea what it’s like.”

Patient with insomnia

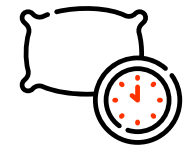
### Sleep architecture

Sleep is vital for repairing and restoring our body and brain. The pattern or structure of sleep is known as “sleep architecture”. Sleep is divided into cycles, lasting around 90 minutes each. On average, we go through four cycles a night.

Sleep is composed of two different types: non-rapid eye movement (NREM) and rapid eye movement (REM).



Studies have shown that lack of slow-wave (stage 3) sleep is associated with cognitive and other health-related issues.



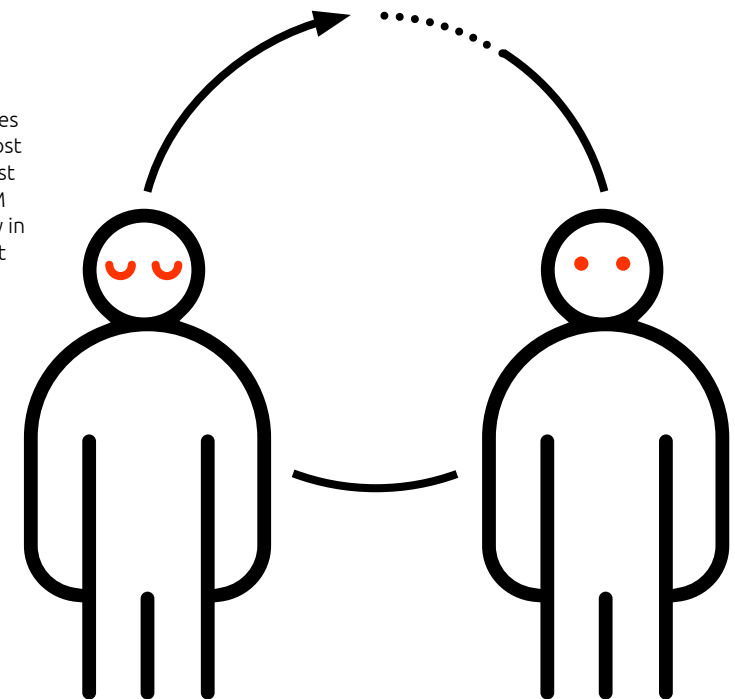
Each night, we wake several times for 1–2 minutes, although we do not usually remember this.



The pattern of sleep changes as the night progresses. Most deep sleep occurs in the first half of the night, while REM sleep tends to occur mostly in the second half of the night



NREM is divided into three further stages (1–3).





### The treatment landscape

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding next-morning residual effects. Current recommended treatment of insomnia includes sleep hygiene recommendations, cognitive behavioral therapy, and pharmacotherapy.

With regard to prescription medications, patients are treated with products indicated for insomnia, as well as off-label treatments. The on-label treatment category primarily comprises drugs that induce sleep by enhancing GABA, the primary inhibitory neurotransmitter in the brain, which works by slowing brain activity in a non-targeted manner. There are two main categories of GABA agonists – benzodiazepines, such as temazepam, and non-benzodiazepines, such as zolpidem, zaleplon, and eszopiclone. In addition, other approved insomnia medications include the melatonin receptor agonist ramelteon and the low-dose tricyclic antidepressant doxepin. The first products in the new class of dual orexin

receptor antagonists were suvorexant and lemborexant, which are available in North America and certain Asia-Pacific markets. These have now been joined by daridorexant, which is available in the US and the first countries in Europe. The most widely used off-label treatment for insomnia in the US is trazodone, a selective serotonin reuptake inhibitor (SSRI) which has an off-target sedation effect.

Overall, before the launch of daridorexant, available agents were perceived to be either effective on certain parameters, but with safety concerns (e.g. next-morning hangover effects, anterograde amnesia, and risk of tolerance and dependence), or safe but with limited efficacy in insomnia. Furthermore, while a negative impact on daytime functioning is part of the definition of insomnia, effects on this key aspect of the condition have not been rigorously assessed for any treatment besides daridorexant. Idorsia's approach to addressing this medical need is explained later.

### The orexin system

Wake and sleep signaling is regulated by intricate neural circuitry in the brain. One key component of this process is the orexin system, which helps promote wakefulness.

Orexin neuropeptides (small protein-like molecules used by nerve cells to communicate with each other in the brain) promote wakefulness through the orexin receptors OX1R and OX2R. Together, these neuropeptides and receptors make up the orexin system. The orexin system stimulates targeted neurons in the wake system, leading to the release of several chemicals (dopamine, serotonin, histamine, acetylcholine, norepinephrine) which promote wakefulness. Under normal circumstances, orexin levels rise throughout the day as wakefulness is promoted and then fall at night. Research suggests that, in chronic insomnia disorder, wake-promoting regions of the brain remain overactive at night (hyperarousal). Orexin therefore provides a specific target for pharmacotherapeutic intervention.

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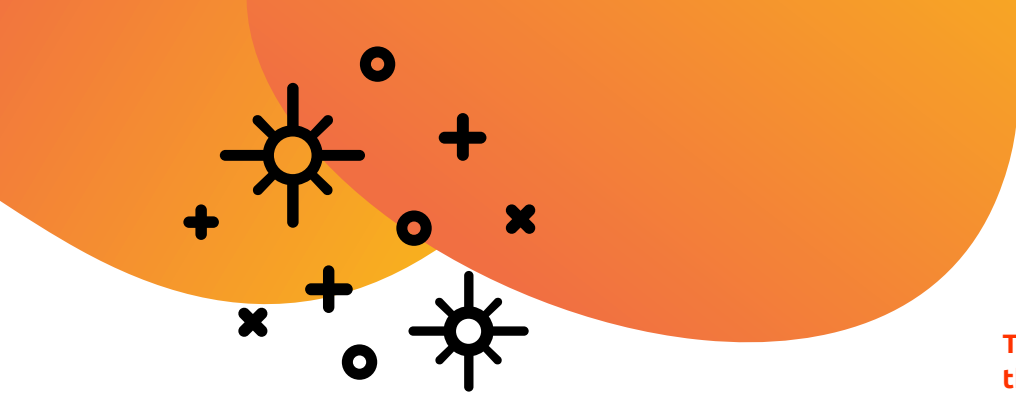
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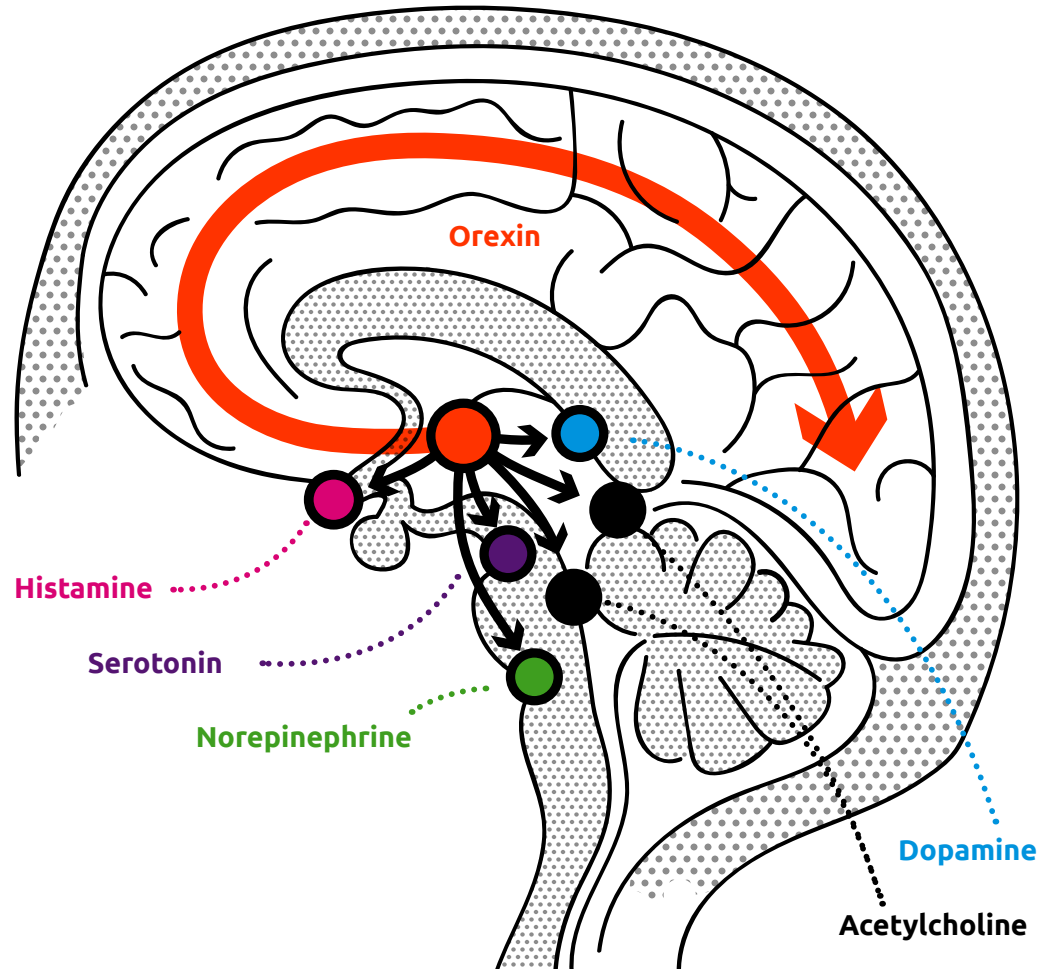




**The orexin system is crucial for the regulation of wakefulness**

Orexin stimulates many wake-promoting pathways

Dual orexin receptor antagonists (DORAs) offer an entirely different approach to treating insomnia than previous drug classes: by selectively blocking the activity of orexin, they turn down overactive wakefulness, in contrast to insomnia treatments which act via general CNS sedation. Blocking orexin receptors reduces the downstream activity of the wake-promoting neurotransmitters that are overactive in insomnia. As a result, orexin receptor antagonism targets the fundamental mechanism of insomnia.



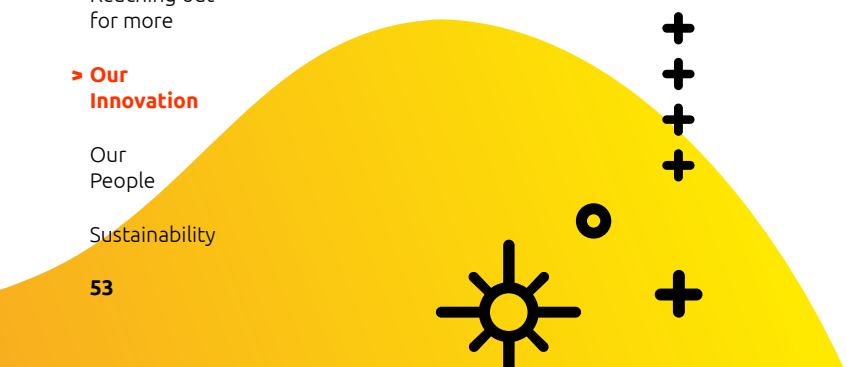
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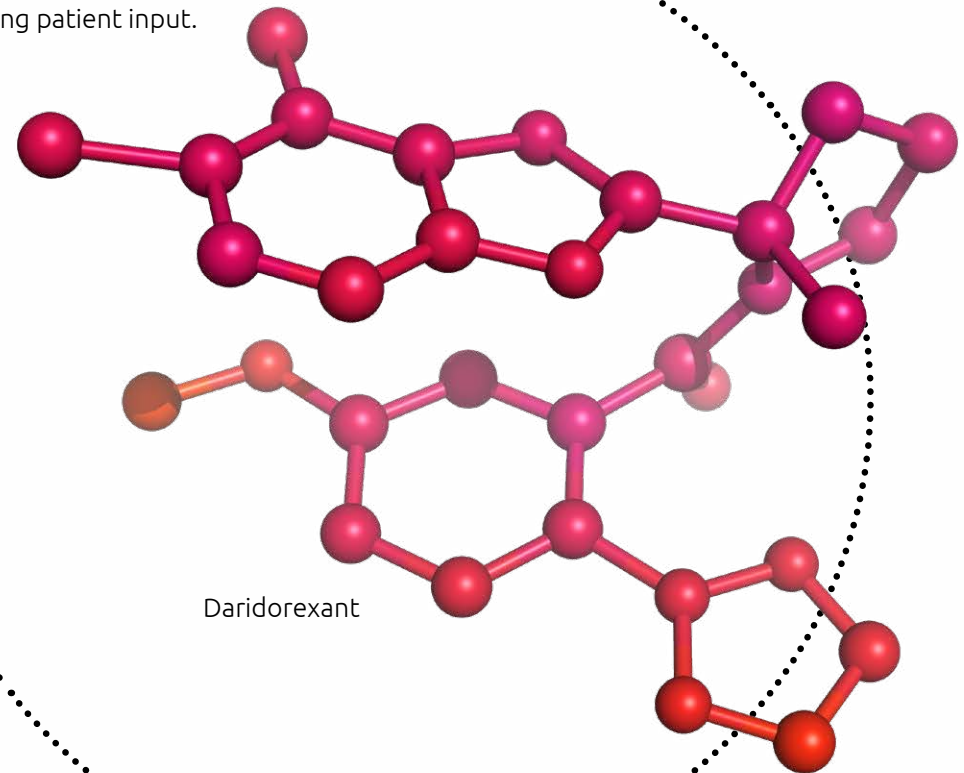


## Idorsia's innovation

Idorsia's research team has been working on the science of orexin and orexin receptors since they were first described in 1998. The team's initial work led to the conclusion that antagonism of the orexin system was the key to preserving a natural sleep architecture for patients with insomnia. With this as the target, the team designed a dual antagonist with the goal of a rapid onset of effect and a duration of action sufficient to cover the night but short enough to avoid any negative next-morning residual activity at optimally effective doses. This task proved to be very challenging, and the team synthesized more than 25,000 compounds to arrive at daridorexant.

The Phase 3 registration program comprised two three-month studies, together with a long term double-blind extension study. The program is now complete, having enrolled around 1,850 patients with insomnia. As insomnia often presents later in life, and elderly patients are more likely to experience fragmented sleep, early awakening, and daytime sleepiness, around 40% of the recruited population was aged 65 years or older.

The placebo-controlled studies investigated the effects of three doses of daridorexant (Study 1: 50 mg and 25 mg; Study 2: 25 mg and 10 mg) on sleep and daytime functioning parameters – objectively in a sleep lab by polysomnography and subjectively with a daily patient diary at home. The impact of insomnia on patients' daytime functioning was measured daily using the sleepiness domain score from the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) – a patient reported outcome (PRO) instrument validated according to the FDA Guidance for Industry, including patient input.



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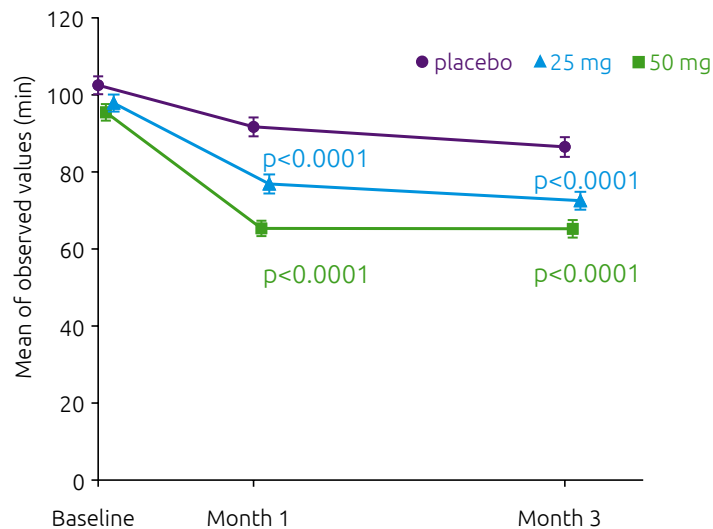
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More than 800 patients continued treatment in the 40-week extension study, which measured the effect of all three doses versus placebo, generating data for long-term treatment of insomnia.

As reported by Mignot E, et al. in the February 2022 issue of *The Lancet Neurology*, the pivotal studies demonstrated that daridorexant significantly improved sleep onset, sleep maintenance

and self-reported total sleep time at months 1 and 3 compared to placebo. The largest effect was observed with the highest dose (50 mg), followed by 25 mg, while the 10 mg dose did not have a significant effect. In all treatment groups, the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.

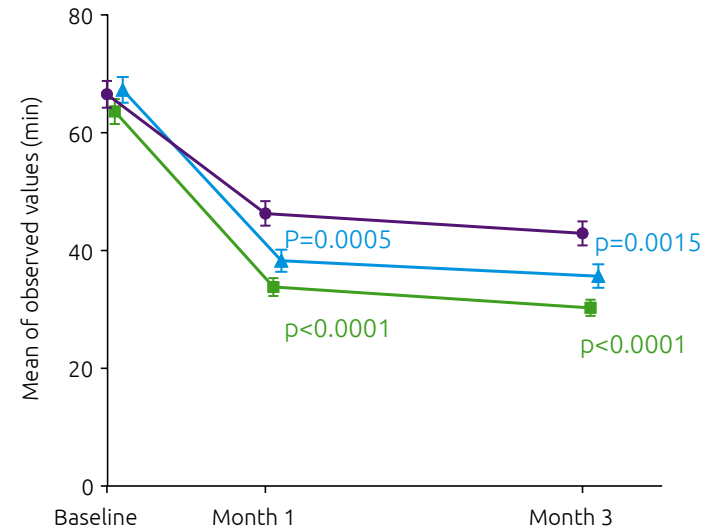
### Wake time after sleep onset



Mean of observed wake time after sleep onset (WASO) values at study timepoints in study 1.

WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

### Latency to persistent sleep



Mean of observed latency to persistent sleep (LPS) values at study timepoints in study 1.

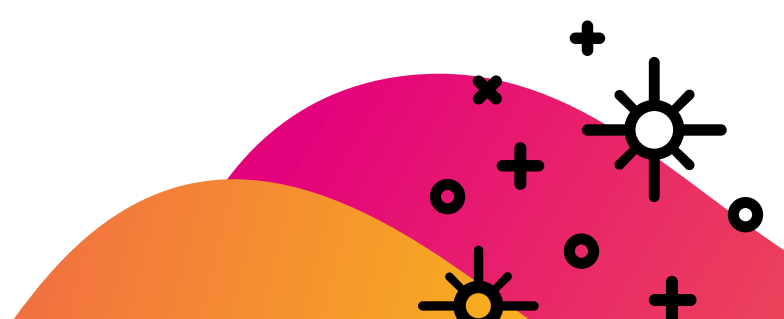
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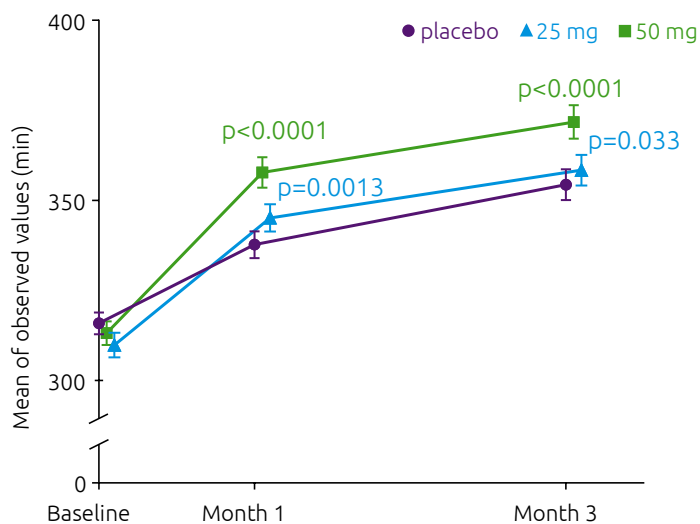
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## Subjective total sleep time



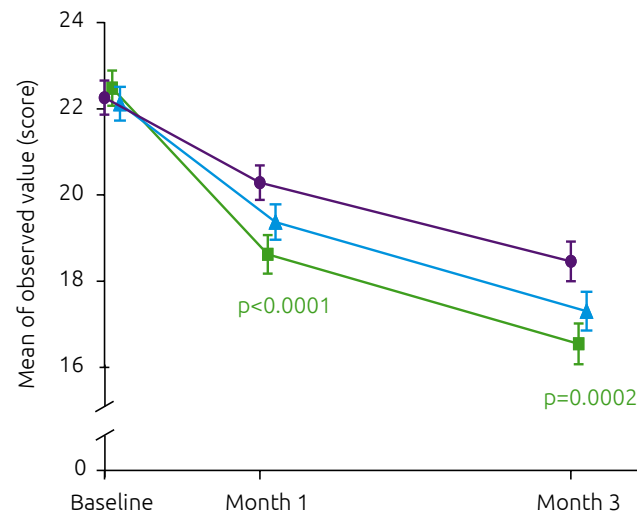
Mean of observed self-reported total sleep time (sTST) values at study timepoints in study 1.

Data for sTST and IDSIQ scores are based on the mean of daily entries in the 7 days before polysomnography nights.

Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia, as assessed by the IDSIQ. The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies, and comparisons to placebo included control for multiplicity. Daridorexant 50 mg demonstrated a highly significant improvement in daytime sleepiness at month 1 and month 3, while the sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint. Daridorexant 50 mg also improved the additional IDSIQ domain scores (alert/cognition, mood) and total score (p values <math><0.0005</math> versus placebo not adjusted for multiplicity). Improvements in daytime functioning with daridorexant 50 mg progressively increased over the three months of the study.

## IDSIQ sleepiness domain



Mean of observed IDSIQ sleepiness domain scores at study timepoints in study 1.

The overall incidence of adverse events was comparable between treatment groups. Adverse events occurring in more than 5% of participants were nasopharyngitis and headache. There were no dose dependent increases in adverse events (including somnolence and falls) across the dosing range. Further, no dependence, rebound insomnia, or withdrawal effects were observed upon abrupt discontinuation of treatment. Across treatment groups, adverse events leading to treatment discontinuation were numerically more frequent with placebo than with daridorexant.

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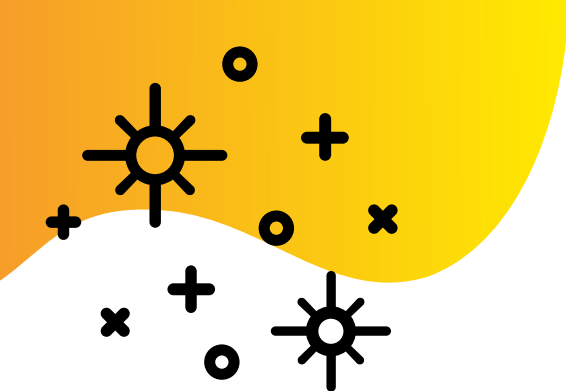
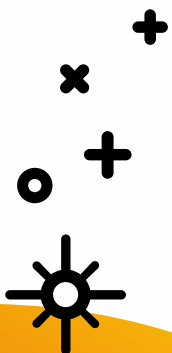
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“It is very exciting to see how truly different the mechanism of dual orexin receptor antagonism is in patients with insomnia. As opposed to being generally sedated, their insomnia is brought under control with nightly administration.”

**Dalma Seboek Kinter**  
Global Medical Director, Insomnia



In addition to the results published in *The Lancet Neurology*, the final results of the 40-week extension study with daridorexant became available in April 2021. This study collected information on the safety of long-term treatment, as well as allowing an exploratory analysis of the maintenance of efficacy. There were no new emerging safety findings. Moreover, efficacy for sleep and daytime functioning appeared to be maintained over the longer treatment duration.

Furthermore, a comprehensive clinical pharmacology program has been conducted, with a total of 18 studies assessing, for example, abuse liability, drug-drug interactions, next morning driving in healthy participants, the effects of daridorexant on respiratory function in patients with chronic obstructive pulmonary disease or obstructive sleep apnea, and the pharmacokinetics of daridorexant in patients with liver and renal impairment.

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### Current status in the US

In January 2022, QUVIVIQ (daridorexant) 25 mg and 50 mg was approved by the US FDA for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. QUVIVIQ was launched in the US in May 2022. For more information about QUVIVIQ in the US, see the **Full Prescribing Information**.



### Current status in the EUCAN region

In April 2022, marketing authorization for QUVIVIQ was granted by the European Commission and subsequently by the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain via the European Commission Decision Reliance Procedure, for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning, making it Europe's first approved dual orexin receptor antagonist. In November 2022, QUVIVIQ was launched in Italy and Germany. Launch preparations are underway in France, Spain, and the UK.

For more information about QUVIVIQ in the EU, see the **Summary of Product Characteristics**. Marketing authorization for QUVIVIQ was granted by Swissmedic in December 2022, and the company aims to make QUVIVIQ available to patients in Switzerland around mid-2023. For more information about QUVIVIQ in Switzerland, see the **Patient Information and Information for Healthcare Professionals**. Daridorexant is under review with Health Canada.



2022

Jan: US FDA approval

Jan: *The Lancet Neurology* publication

Apr: European Commission approval

May: Launched in the US

Oct: Positive Phase 3 in Japan

Nov: Launched in Italy and Germany



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Nov: License agreement with Simcere in China

Nov: Swissmedic approval

### Current status in Japan

In Japan, a Phase 3 study investigating 25 mg and 50 mg doses of daridorexant in 490 randomized adult and elderly patients (30.1%  $\geq 65$  years) with insomnia disorder, reported positive top-line results in October 2022. The study met both primary and secondary efficacy endpoint measures. Daridorexant significantly improved sTST from baseline compared to placebo at 28 days ( $p < 0.001$  for 50 mg,  $p = 0.042$  for 25 mg). Daridorexant also significantly improved sleep onset as measured by a decrease in latency for sleep onset (sLSO) from baseline compared to placebo at 28 days ( $p < 0.001$  for 50 mg,  $p = 0.006$  for 25 mg).

The most frequent treatment-emergent adverse events reported over 3% incidence and higher than placebo were somnolence (6.8% and 3.7% for daridorexant 50 mg and 25 mg groups, respectively, versus 2.4% in the placebo group) and pyrexia (0.6% and 3.7% for daridorexant 50 mg and 25 mg groups, respectively, versus 1.2% in the placebo group). Idorsia Japan expects to file a New Drug Application (NDA) with the Japanese Ministry of Health, Labor and Welfare (MHLW) in the second half of 2023.

### Current status in global clinical development

Idorsia has initiated a Phase 2, double-blind, randomized, placebo-controlled, dose-finding study to assess the efficacy, safety, and pharmacokinetics of multiple-dose oral administration of daridorexant in pediatric patients aged between 10 and  $< 18$  years with insomnia disorder. The primary objective of the study is to characterize the dose-response relationship of daridorexant on objective total sleep time (TST) using polysomnography. The study is expected to enroll around 150 patients, who will be randomized in a 1:1:1:1 ratio to 10 mg, 25 mg, or 50 mg daridorexant, or placebo. The study is part of an agreed Pediatric Study Plan with the US FDA and a Paediatric Investigational Plan with the EU PDCO.

### Insomnia

#### Compound: QUVIVIQ™ (daridorexant)

Mechanism of action:

Dual orexin receptor antagonism

Status: Commercially available

in the US, Germany, and Italy;

approved in the European Union,

UK, and Switzerland;

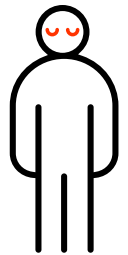
under review in Canada;

Phase 3 in Japan successful –

filing expected in H2 2023;

Phase 2 in pediatric insomnia –

recruiting



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# PIVLAZ™ (clazosentan) for cerebral vasospasm

Aneurysmal subarachnoid hemorrhage (aSAH) involves sudden life-threatening bleeding occurring in the subarachnoid space. It is caused by the rupture of an aneurysm – a weak, bulging spot on the wall of a cerebral artery. An emergency procedure (endovascular coiling or microsurgical clipping) is required to secure the aneurysm to prevent rebleeding.

The worldwide incidence of aSAH is 7.9 per 100,000 patient-years worldwide. Notably, aSAH is a significant problem in Japan, with an incidence three times higher than in the rest of the world.

Bleeding and the release of endothelin-1 – a potent vasoconstrictor produced mainly by the neighboring vascular endothelium – can lead to cerebral vasospasm (constriction of arteries in the brain), which usually starts 3 days after aSAH onset and peaks in intensity between 8 and 11 days. This diminishes blood flow to the brain, and about one third of all aSAH patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability in patients with aSAH.

Cerebral vasospasm is challenging to predict and is detected through angiograms in up to 70% of aSAH patients overall. Approximately 50% of the overall aSAH population present with thick, diffuse blood clots characterized by a large amount of subarachnoid blood on the admission CT scan. These patients have an elevated risk of experiencing cerebral vasospasm.

## The treatment landscape

Today, patients with cerebral vasospasm are typically treated with hemodynamic therapy (the administration of fluids and agents to increase blood pressure) or a more invasive neurovascular intervention, such as balloon angioplasty or intra-arterial administration of vasodilators. Fasudil and ozagrel are used to improve cerebral vasospasm for patients in Japan and other Asian countries. Nimodipine is used for patients with aSAH in the US and EU. Until clazosentan was introduced in Japan, there had been no innovation for patients suffering from the events associated with cerebral vasospasm in more than 25 years.

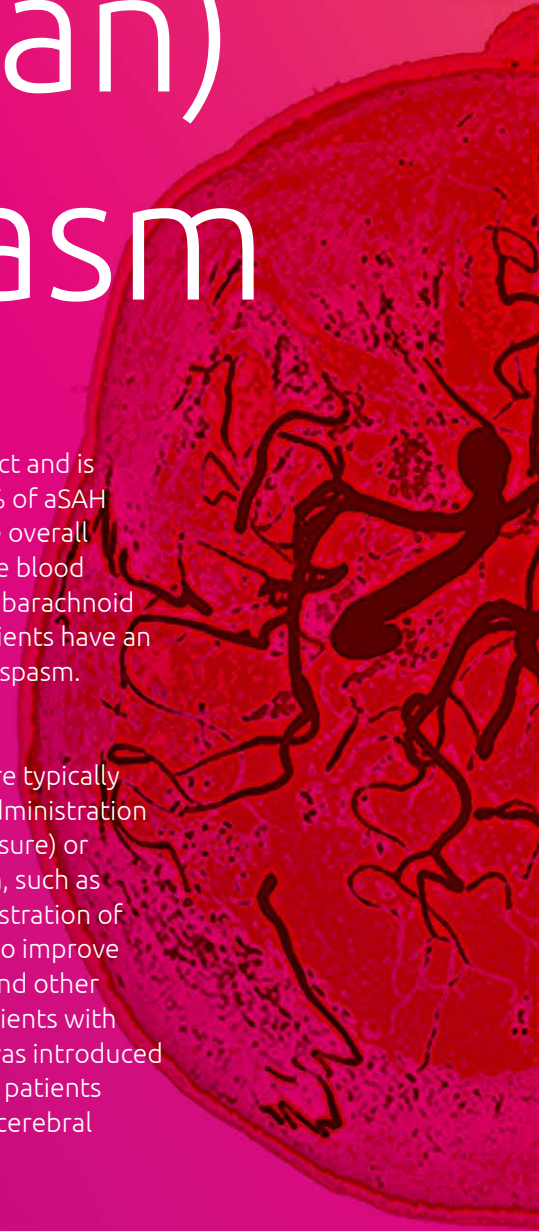
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“It is very frustrating to see our patients survive the initial trauma of the brain hemorrhage and seemingly make a recovery, only for the vasospasm to take hold and cause significant long-term damage.”

**E. Francois Aldrich, MB, ChB**

Professor of Neurosurgery, Director of Cerebrovascular Surgery,  
University of Maryland

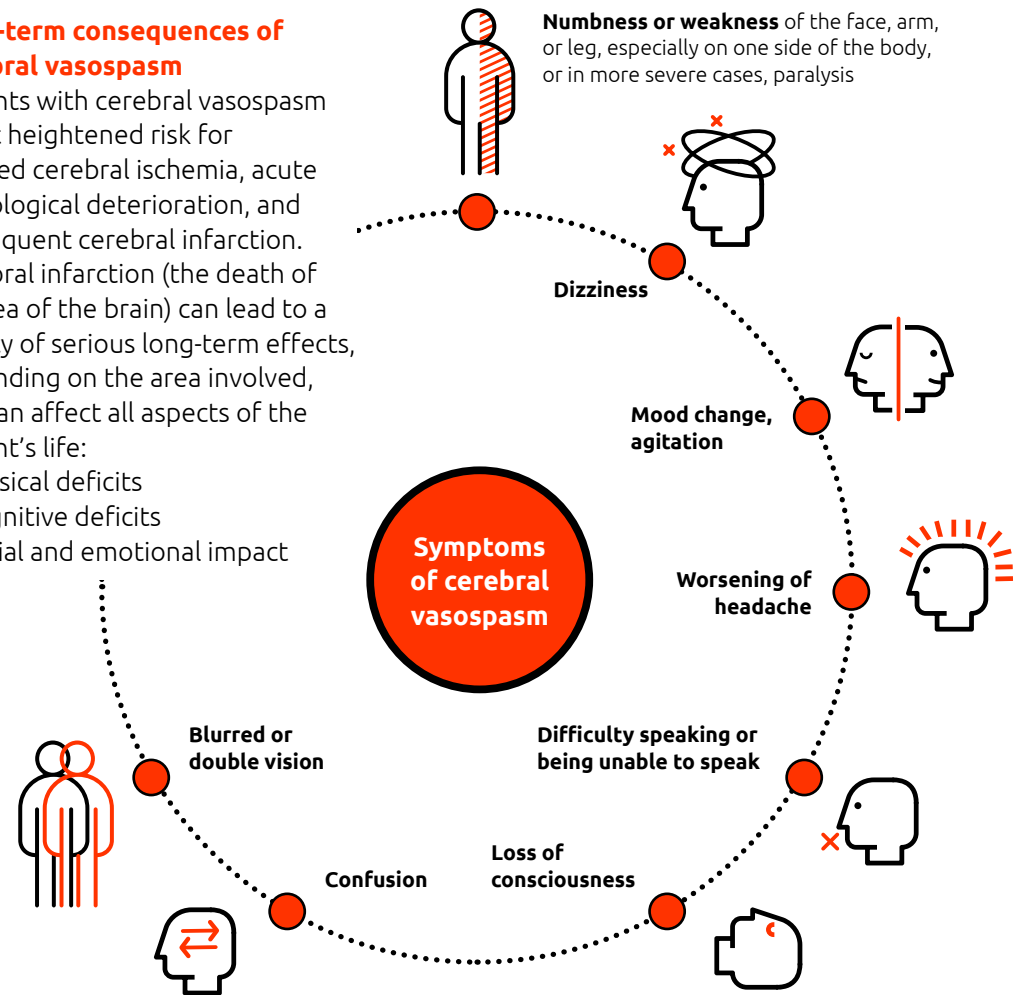
Global incidence of aSAH:

**7.9 per 100,000  
patient-years**

### Long-term consequences of cerebral vasospasm

Patients with cerebral vasospasm are at heightened risk for delayed cerebral ischemia, acute neurological deterioration, and subsequent cerebral infarction. Cerebral infarction (the death of an area of the brain) can lead to a variety of serious long-term effects, depending on the area involved, and can affect all aspects of the patient’s life:

- Physical deficits
- Cognitive deficits
- Social and emotional impact



### The endothelin system in cerebral vasospasm

The release of vasoactive mediators after aSAH causes increased production of endothelin 1, one of the most potent vasoconstrictors known, and an upregulation of its ET<sub>A</sub> receptors. Binding of endothelin-1 to the ET<sub>A</sub> receptor is the key factor leading to cerebral vasospasm after aSAH.

An understanding of the role played by endothelin in cerebral vasospasm prompted our scientists to investigate a compound which blocks the effects of endothelin as a potential way of preventing vasospasm in the future.

### Idorsia's innovation

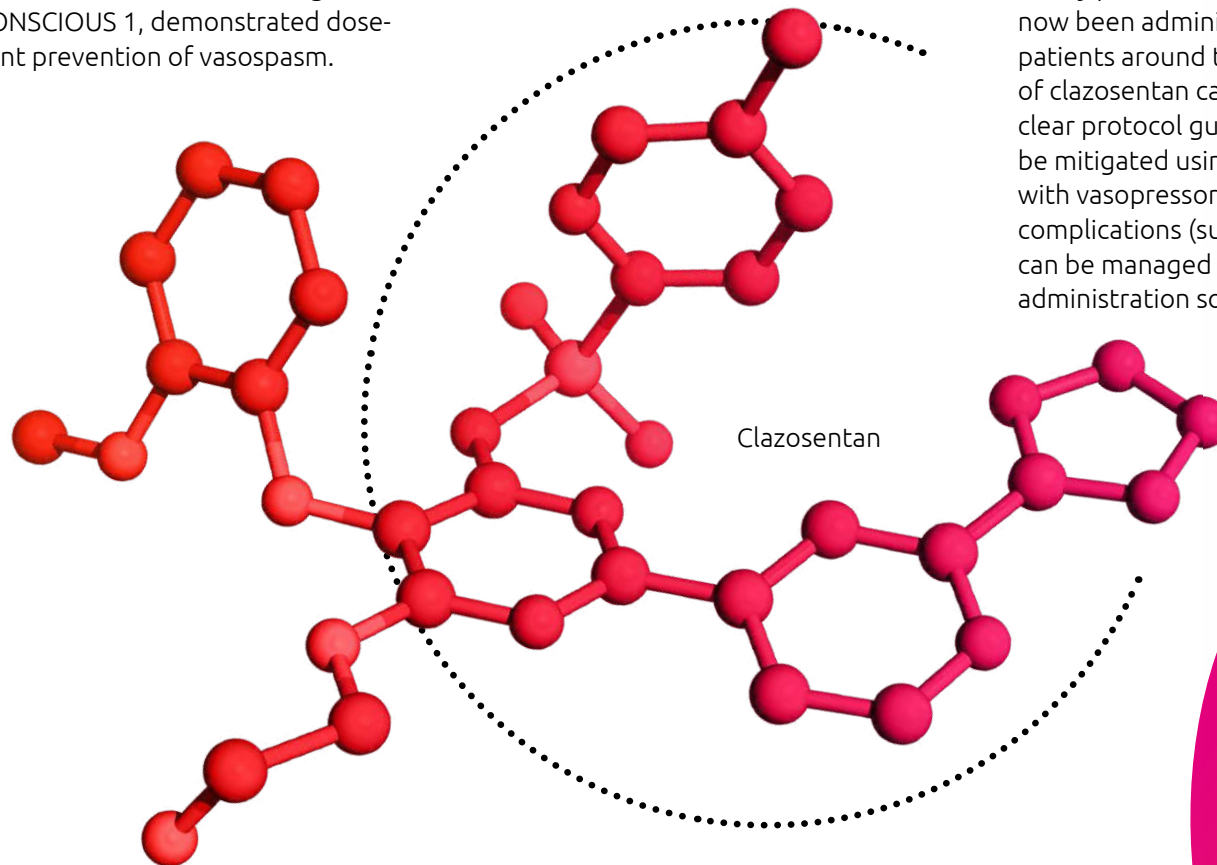
Clazosentan is a fast-acting, selective endothelin A (ET<sub>A</sub>) receptor antagonist, being developed as a continuous intravenous infusion for the prevention of vasospasm-related delayed cerebral ischemia (DCI) in patients following aSAH.

Several studies have built our understanding of the role of clazosentan in preventing cerebral vasospasm. In 2006, results were reported for clazosentan in the prevention of angiographic vasospasm in patients with aSAH. The Phase 2 dose-finding study, CONSCIOUS 1, demonstrated dose-dependent prevention of vasospasm.

This was followed by two Phase 3 studies, CONSCIOUS-2 and CONSCIOUS-3, to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality. In 2010, CONSCIOUS-2 showed that the 5 mg/h dose of clazosentan did not allow a statistically significant treatment effect to be observed, resulting in the premature termination of CONSCIOUS-3. However, an exploratory analysis of the data collected in CONSCIOUS-3 showed that a higher dose of

clazosentan (15 mg/h) significantly reduced cerebral vasospasm-related morbidity and all cause mortality, with a 44% relative risk reduction ( $p=0.0074$ ). The 15 mg/h dose also significantly reduced the incidence of delayed ischemic neurological deficit (DIND), with a 54% relative risk reduction ( $p=0.0038$ ). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not improve long-term clinical outcome.

The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to more than 2000 patients around the world. The side effects of clazosentan can be managed according to clear protocol guidelines: hypotension can be mitigated using blood pressure control with vasopressors in the ICU, while lung complications (such as pulmonary edema) can be managed by avoiding excessive fluid administration so as to maintain euvolemia.



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“Clinical studies have built a deep understanding of the role of clazosentan in preventing cerebral vasospasm. We are confident that we can now show that clazosentan can prevent vasospasm-related clinical deterioration in those patients most at risk of developing cerebral vasospasm.”

**Angelina Marr**  
Senior Director,  
Expert Clinical Project Scientist



All this evidence, together with the registration program in Japan (described later), suggests that clazosentan has the potential to prevent vasospasm-related delayed cerebral ischemia and to reduce the need for invasive neurovascular intervention.



**Current status: Global registration program**

REACT is a Phase 3 study to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in adult patients following aSAH. The Phase 3 study incorporates the learnings from the clazosentan program to identify patients at high risk of vasospasm and delayed cerebral ischemia, the optimal dose, the best measure to demonstrate efficacy, and an optimized patient management guideline to ensure patient safety. The study randomized 409 patients – treated either with microsurgical clipping or endovascular coiling – in a 1:1 ratio to receive placebo or clazosentan 15 mg/h. The study has concluded, and results are expected in the first quarter of 2023.

Clazosentan has been granted orphan drug designation in Europe (2003) and the US (2006), leading to market exclusivity of 10 and 7 years from approval, respectively.



“PIVLAZ is the only drug to demonstrate the prevention of cerebral vasospasm after subarachnoid hemorrhage treatment and the associated new cerebral infarctions and ischemic symptoms. I believe we can change the lives of many patients.”

**Teiji Tominaga, MD, PhD**

Professor & Chairman, Department of Neurosurgery,  
Tohoku University Graduate School of Medicine

### Japanese registration program

A Phase 2 study in Japanese and Korean patients showed that 10 mg/h clazosentan administered by continuous intravenous infusion significantly reduced vasospasm and the overall incidence of vasospasm-related morbidity and all-cause mortality. On that basis, a registration program was initiated with clazosentan in Japan in May 2016.

In November 2020, Idorsia announced positive top-line results from the Japanese registration program investigating clazosentan in adult Japanese patients post-aSAH. The program consisted of two studies assessing the efficacy and safety of clazosentan in reducing vasospasm and vasospasm-related morbidity and all-cause mortality. The two studies followed the same study design, with one enrolling 221 patients whose aneurysm was secured by surgical clipping and the other enrolling 221 patients whose aneurysm was secured by endovascular coiling.

As reported by Endo H, et al. in the April 2022 issue of the *Journal of Neurosurgery*, both studies demonstrated a statistically significant ( $p < 0.01$ ) reduction in the combined incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH.

Clazosentan showed a numerical reduction in the combined incidence of all-cause morbidity and mortality. The effect of clazosentan on this endpoint was significant ( $p < 0.05$ ) in the pre-planned pooled analysis.

There were no unexpected safety findings in these registration studies. Treatment-emergent adverse events occurring in  $>5\%$  of the clazosentan group (with a difference of  $>2\%$  compared to placebo) were vomiting and signs of hemodilution or fluid retention (i.e. hyponatremia, hypoalbuminemia, anemia, pleural effusion, brain and pulmonary edema).

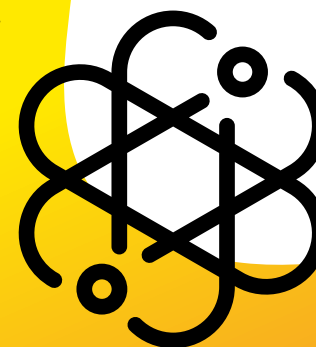
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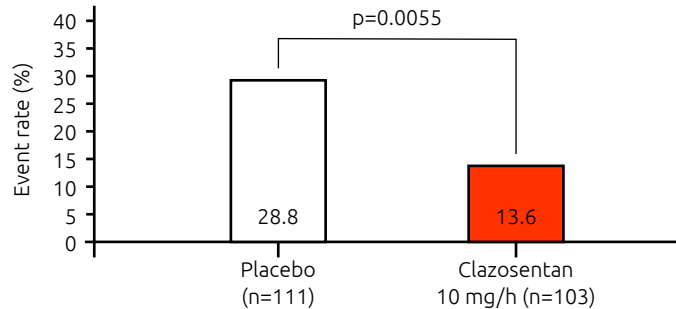


## Top-line results from the Japanese registration program

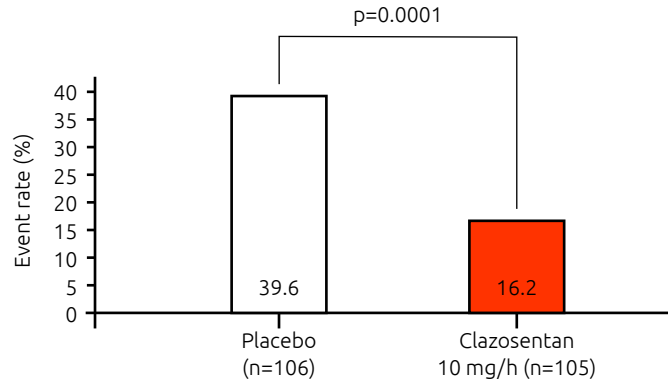
Incidence of vasospasm-related morbidity and all-cause mortality



Coiling



Clipping



Cerebral vasospasm-related morbidity and all-cause mortality was blindly adjudicated by an independent committee and defined by at least one of the following: All death/New cerebral infarction due to cerebral vasospasm/Delayed ischemic neurologic deficit (DIND) due to cerebral vasospasm.

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In January 2022, PIVLAZ (clazosentan) 150 mg was approved in Japan for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction, and cerebral ischemic symptoms after aSAH. PIVLAZ was launched in Japan in April 2022. In Japan, clazosentan has regulatory data protection after approval, leading to eight years of exclusivity.

In addition, during the third quarter of 2022, market registration, based on the Japanese data, was requested in the Republic of Korea.

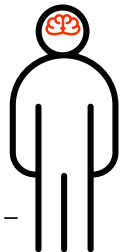
 **PIVLAZ**  
clazosentan

### Cerebral vasospasm associated with aSAH

**Compound: PIVLAZ™  
(clazosentan)**

Mechanism of action:  
Selective endothelin (ET<sub>A</sub>)  
receptor antagonism

Status: Commercially available  
in Japan; Global Phase 3 complete –  
results expected Q1 2023





# Aprocitentan for difficult-to-control hypertension

Hypertension (high blood pressure) is one of the most common cardiovascular risk factors, and its prevalence continues to rise. According to a recent study, there are more than 1.3 billion people living with hypertension worldwide – a startling number, which has almost doubled in the past 40 years. People with uncontrolled hypertension have a greater risk of life-threatening conditions such as stroke, end-stage kidney disease, and heart attack.

Patients with hypertension can often successfully control their blood pressure by combining a healthier lifestyle with effective medication. However, approximately 10% of patients have difficult to-control hypertension, where blood pressure remains uncontrolled despite treatment with at least three antihypertensive medications of different pharmacological classes, including a diuretic, at optimal or best tolerated doses. These patients are also categorized in hypertension guidelines and the medical community as having resistant hypertension.

**1.3** billion people living with hypertension worldwide

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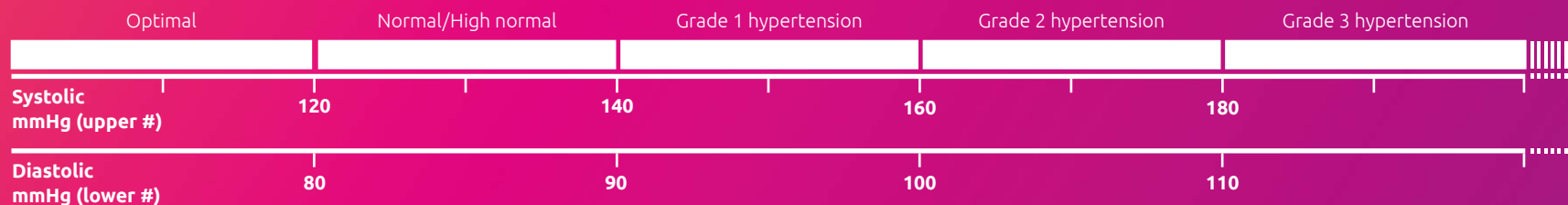
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## Stages of hypertension





### Resistant hypertension

Patients whose blood pressure remains high despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal or best tolerated doses.

It is estimated that 10% of patients treated for hypertension can be classified as having true resistant hypertension.



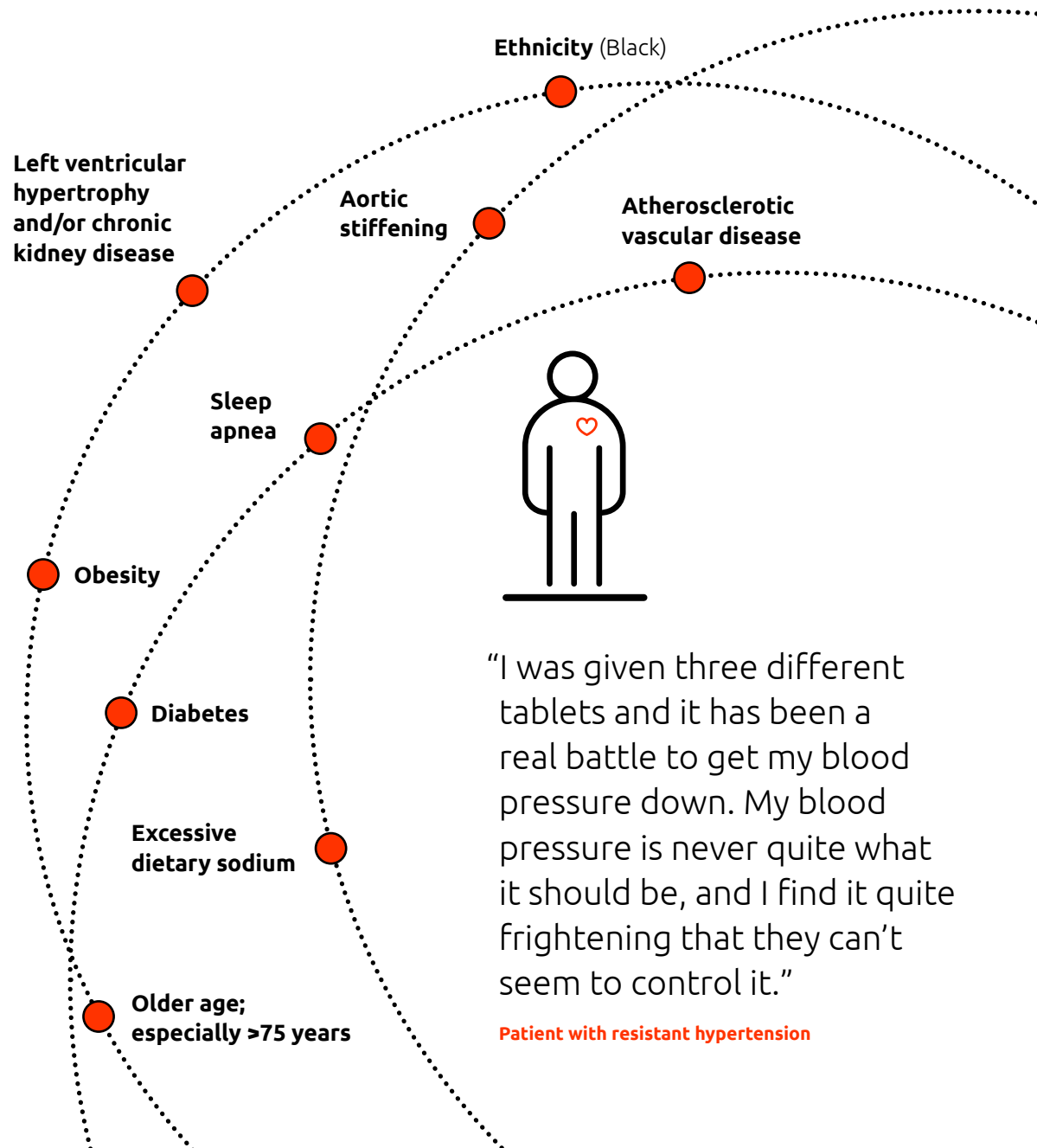
### Not resistant hypertension

Pseudo-resistant hypertension due to:

- White-coat effect (in the presence of medical staff)
- Non-optimal treatment
- Poor adherence to treatment
- Inappropriate measurement

Treatable hypertension

## Typical characteristics of patients with resistant hypertension



“I was given three different tablets and it has been a real battle to get my blood pressure down. My blood pressure is never quite what it should be, and I find it quite frightening that they can’t seem to control it.”

Patient with resistant hypertension

### The treatment landscape

There are more than 260 antihypertensive therapies available (single agents and fixed combinations), acting via 8 different pharmacological pathways. Most of these therapies were introduced decades ago and, although hypertension is a serious and growing problem around the world, it has been over 30 years since an antihypertensive drug working via a new pathway was last brought to the market. To date, no drug has been approved for the treatment of resistant hypertension.

Treatment guidelines and hypertension textbooks consistently emphasize that the use of a diuretic is critically important in the treatment of resistant hypertension, as – from a pathophysiological standpoint – it is considered to be a volume-dependent hypertension. The current pharmacological treatment strategy for patients with resistant hypertension is to add on antihypertensive medications, preferably with a mechanism of action which has not yet been used. To date, there is no consensus on the choice of a fourth agent for patients with resistant hypertension.

### The endothelin system in hypertension

Endothelin-1 (ET-1) is a potent vasoconstrictor that also induces neurohormonal activation, vascular hypertrophy and remodeling, cardiac hypertrophy and fibrosis, and endothelial dysfunction.

The endothelin pathway has been implicated in the pathogenesis of hypertension, especially in volume- and salt-dependent forms, which are a common feature in patients with resistant hypertension, but it is not currently targeted therapeutically, thereby leaving this relevant pathophysiological pathway unopposed with currently available medications. This pathway is activated in patients prone to developing resistant hypertension, such as aging patients, Black or African-American patients, obese patients, or those with obstructive sleep apnea, as well as in comorbid conditions frequently associated with resistant hypertension, such as diabetes and chronic kidney disease.

### Developed in partnership with Janssen Biotech, Inc.

In December 2017, Idorsia entered into a collaboration agreement with Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to jointly develop apocritentan and any of its derivative compounds or products. Both parties have joint development rights over apocritentan. Idorsia conducted the Phase 3 PRECISION study and is overseeing the regulatory review for the treatment of patients with difficult-to-control (resistant) hypertension. The costs are shared equally between both partners. Janssen is responsible for overseeing the Phase 3 development and submission for any additional indications and will have the sole worldwide commercialization rights.



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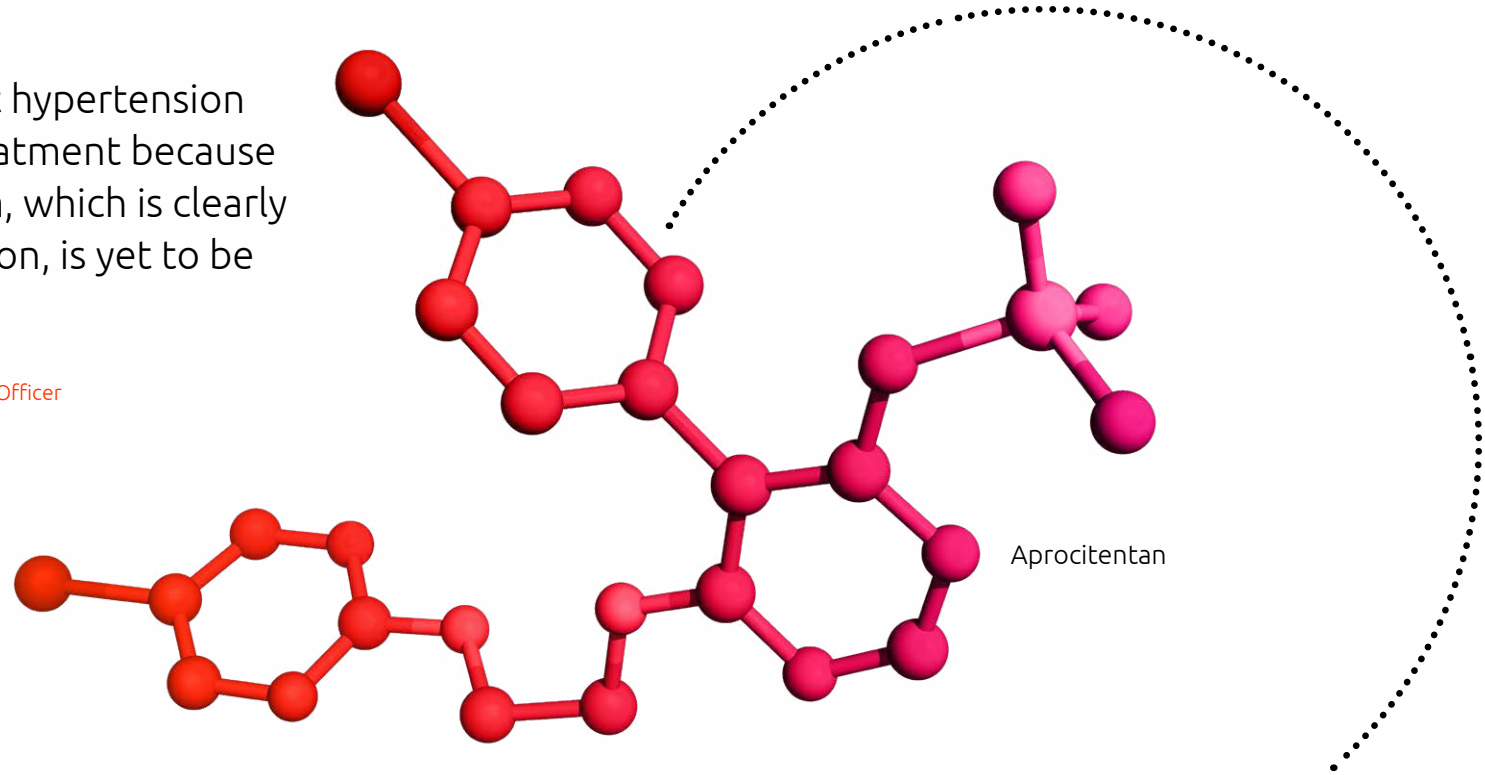
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“I believe that resistant hypertension is only resistant to treatment because the endothelin system, which is clearly involved in hypertension, is yet to be tackled.”

**Martine Clozel**

Executive Vice President, Chief Scientific Officer



### Idorsia's innovation

Aprocitentan is a once-daily, orally active, dual endothelin receptor antagonist, which potently inhibits the binding of ET-1 to ET<sub>A</sub> and ET<sub>B</sub> receptors. Aprocitentan has a half-life of 44 hours and a low drug-drug interaction potential, which is particularly important for patients who are typically being treated for several other problems.

In a Phase 2 dose-response study, patients with hypertension received monotherapy with four doses of aprocitentan or placebo (lisinopril was used as a positive control) for eight weeks, using a randomized, double-blind study design. There was a clear dose response on both diastolic and systolic blood pressure, with clinically relevant effects observed at 10 mg, 25 mg, and 50 mg, with no additional effect at 50 mg. The effect of aprocitentan was shown to cover a 24-hour period. The overall

incidence of adverse events observed in the aprocitentan groups (ranging from 22.0% to 40.2%) was similar to that seen in the placebo group (36.6%). Overall, the most common events were hypertension, headache, and nasopharyngitis.

The data from the preclinical and clinical program gave Idorsia the confidence to embark on a large registration study, PRECISION, in patients with resistant hypertension.

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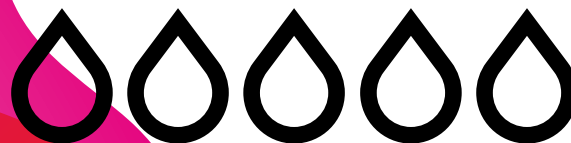
“For decades, healthcare providers have been challenged to help their patients with resistant hypertension achieve better blood pressure control, using treatment options that do not address all of the known mechanisms of the condition.”

**Professor Markus Schlaich, MD, FAHA, FESC, ISHF**  
The University of Western Australia/Royal Perth Hospital

PRECISION was a multicenter, blinded, randomized, parallel-group, Phase 3 study, which was performed in hospitals or research centers in Europe, North America, Asia, and Australia. Patients were eligible for randomization if their sitting systolic blood pressure was 140 mmHg or higher despite taking standardized background therapy consisting of three antihypertensive drugs, including a diuretic. The study consisted of three sequential parts: Part 1 was the 4-week double-blind, randomized, and placebo-controlled part, in which 730 patients were randomized to aprocitentan 12.5 mg (n=243), aprocitentan 25 mg (n=243), or placebo (n=244) in a 1:1:1 ratio; Part 2 was a 32 week single (patient)-blind part, in which all patients received aprocitentan 25 mg (n=704); and Part 3 was a 12-week double-blind, randomized, and placebo-controlled withdrawal part, in which patients were re-randomized to aprocitentan 25 mg (n=307) or placebo (n=307) in a 1:1 ratio. The primary and key secondary endpoints were changes in unattended office systolic blood pressure (SBP) from baseline to week 4 and from withdrawal baseline to week 40, respectively. Secondary endpoints included 24-h ambulatory blood pressure changes.

At baseline, 69.2% of patients were obese or severely obese, 54.1% had diabetes, 22.2% had stage 3–4 chronic kidney disease, and 19.6% had congestive heart failure. At screening, 63% of all patients who were randomly assigned were prescribed four or more antihypertensive drugs.

As reported by Schlaich MP, et al. in the November 2022 issue of *The Lancet*, the least square mean change in office SBP at 4 weeks was –15.3 mmHg for aprocitentan 12.5 mg, –15.2 mmHg for 25 mg, and –11.5 mmHg for placebo, for a difference versus placebo of –3.8 mmHg (p=0.0042) and –3.7 mmHg (p=0.0046), respectively. Office diastolic blood pressure (DBP) also decreased with both aprocitentan doses compared to placebo (–3.9 mmHg for the 12.5 mg dose and –4.5 mmHg for the 25 mg dose). Office SBP and DBP were maintained during Part 2 in patients previously receiving aprocitentan and decreased within the first 2 weeks of Part 2 before stabilizing in those previously receiving placebo. In Part 3, office SBP after 4 weeks of withdrawal (the key secondary endpoint) increased significantly with placebo compared to aprocitentan (5.8 mmHg; p<0.0001). Office DBP also increased with placebo compared to aprocitentan (5.2 mmHg; p<0.001). The difference between the two groups remained up to week 48, confirming the sustained antihypertensive effect of aprocitentan.



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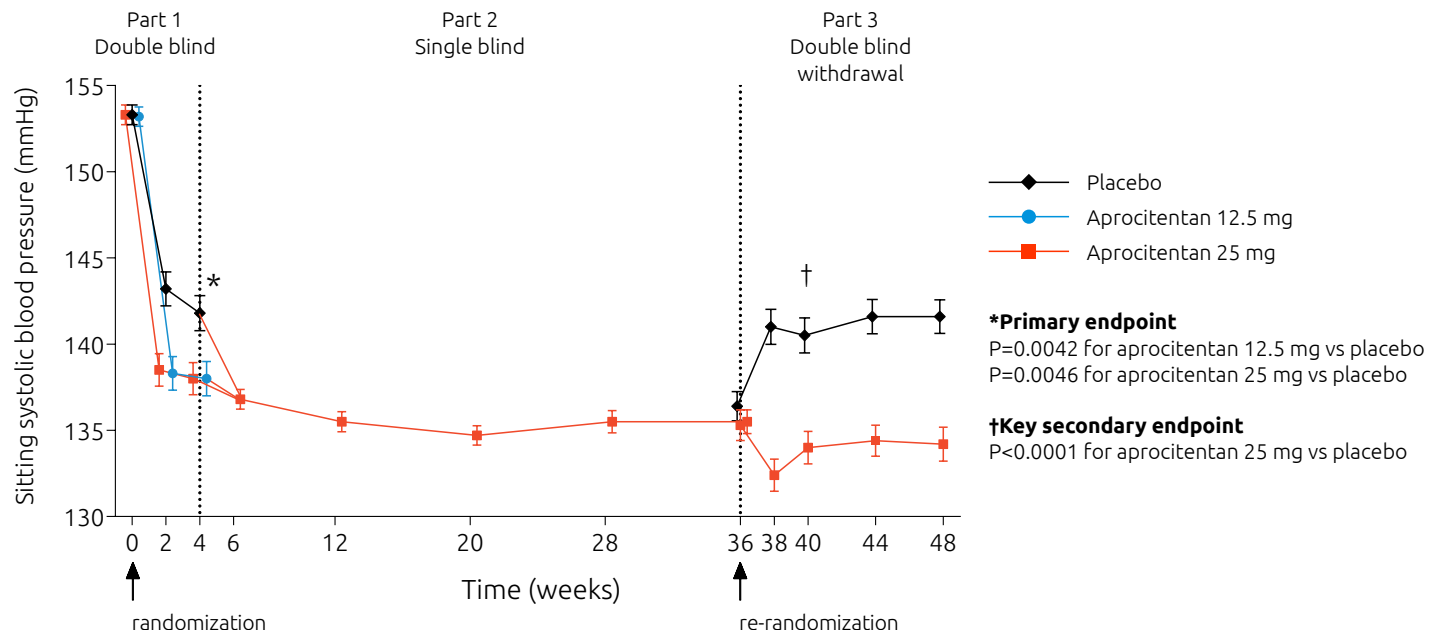
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The results from ambulatory BP monitoring confirmed those derived from office measurements. At the end of Part 1, aprocitentan, after placebo correction, decreased both the 24-hour ambulatory SBP (−4.2 mmHg for the 12.5 mg dose and −5.9 mmHg for the 25 mg dose) and DBP (−4.3 mmHg for the 12.5 mg dose and −5.8 mmHg for the 25 mg dose). The placebo-corrected SBP-lowering effect was −5.1 mmHg and −7.4 mmHg during the

nighttime, and −3.8 mmHg and −5.3 mmHg during the daytime, for the 12.5 mg and 25 mg doses, respectively. In Part 3, after 4 weeks of withdrawal (week 40), both the 24-hour ambulatory SBP and DBP increased with placebo compared with aprocitentan (6.5 mmHg and 6.8 mmHg respectively).

### Aprocitentan has significant and sustained efficacy



Bars are standard error of the mean  
Values are offset from each other for readability

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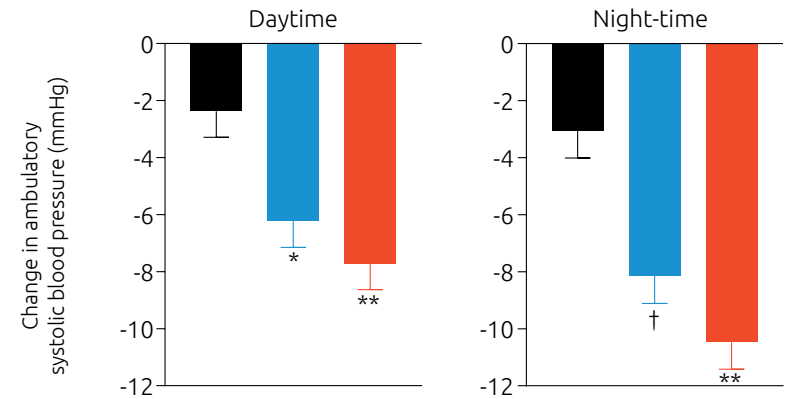
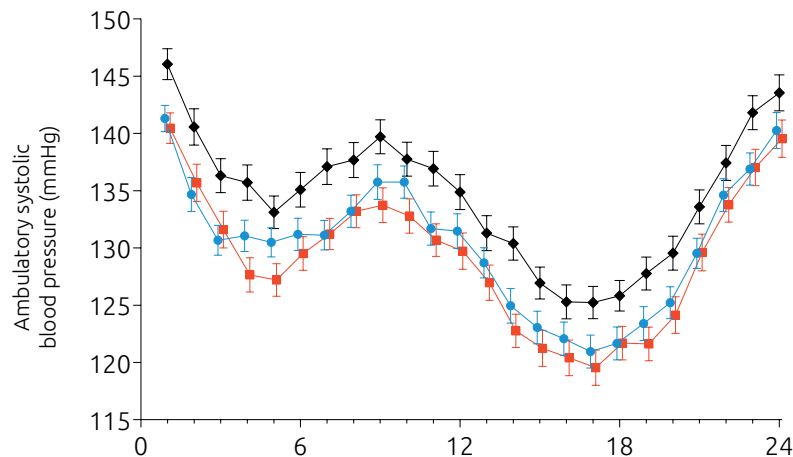
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Treatment-emergent adverse events (TEAEs) during the 4-week double-blind study period (Part 1) were reported in 27.6% and 36.7% of the patients treated with 12.5 mg and 25 mg aprocitentan, respectively, versus 19.4% in the placebo group. The most frequent adverse event with aprocitentan was mild-to-moderate fluid retention, leading to discontinuation in seven patients during the study. Fluid retention was

reported more frequently with aprocitentan than with placebo in a dose dependent fashion (9.1%, 18.4%, and 2.1% for patients receiving aprocitentan 12.5 mg, 25 mg, and placebo during Part 1, respectively; 18.2% for patients receiving aprocitentan 25 mg during Part 2; and 2.6% and 1.3% for patients receiving aprocitentan 25 mg and placebo during Part 3, respectively).

### Efficacy confirmed by Ambulatory BP monitoring at Week 4



—◆— Placebo  
 —●— Aprocitentan 12.5 mg  
 —■— Aprocitentan 25 mg  
 Bars are standard error of the mean  
 Values are offset from each other for readability

No. of patients: 179 (Placebo), 175 (Aprocitentan 12.5 mg), 182 (Aprocitentan 25 mg)  
 178 (Placebo), 174 (Aprocitentan 12.5 mg), 182 (Aprocitentan 25 mg)  
 \*P=0.003, †P=0.0002, \*\*P<0.0001 vs placebo, not corrected for multiplicity

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“The Phase 3 PRECISION study establishes aprocitentan as a promising new therapeutic approach to achieve sustained blood pressure lowering in addition to guideline recommended triple antihypertensive therapy, as measured with both office and ambulatory blood pressure measurements.”

**Frédéric Naud**  
Senior Director, Life Cycle Leader



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#### Current status

In May 2022, Idorsia announced positive top-line results of the Phase 3 PRECISION study with aprocitentan in resistant hypertension. Detailed results were made available in *The Lancet* and as a Late-Breaking Science presentation at the American Heart Association (AHA) Scientific Sessions in November 2022. A new drug application (NDA) for aprocitentan was filed with the US FDA in December 2022, and the market authorisation application (MAA) was submitted to the EMA at the end of January 2023.

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#### Difficult-to-control hypertension

**Compound: Aprocitentan**

Mechanism of action:  
Dual endothelin receptor  
antagonism  
Status: NDA submitted in the US,  
MAA submitted in the EU,  
other filings in preparation



# Lucerastat for Fabry disease



Fabry disease is a rare genetic, lysosomal storage disorder. It is caused by mutations in the GLA gene, leading to a deficiency or dysfunction of alpha-galactosidase A (alpha Gal A), an enzyme that normally breaks down a fatty substance known as globotriaosylceramide (Gb3) in the cells of the body. Over time, this results in an accumulation of Gb3 deposits throughout the body, leading to progressive pathophysiology in the cardiovascular system, the nervous system, and organs including the kidneys, heart, skin, ears, and eyes.

Fabry disease affects a patient's life expectancy and quality of life. Since most symptoms are non-specific, 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.

New therapeutic options are needed to treat the underlying mechanism of the disease and provide symptomatic relief.

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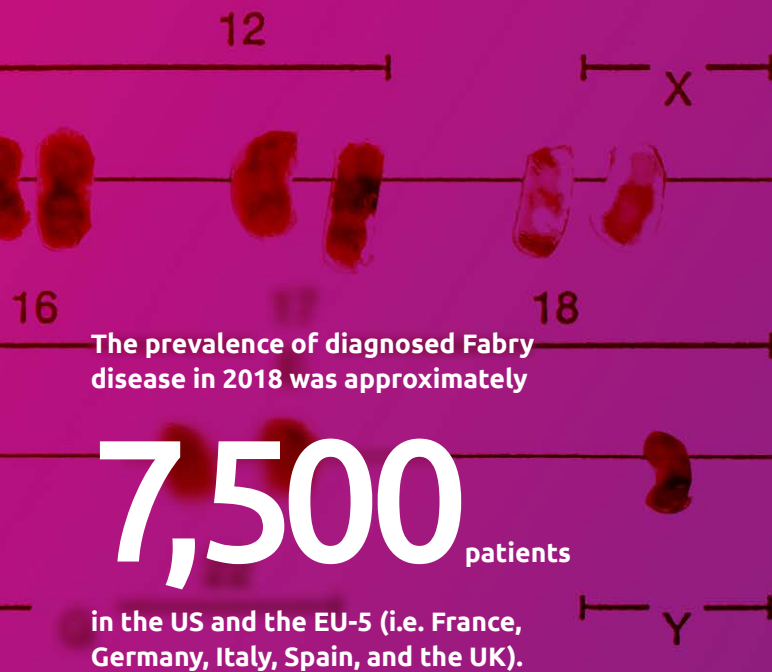
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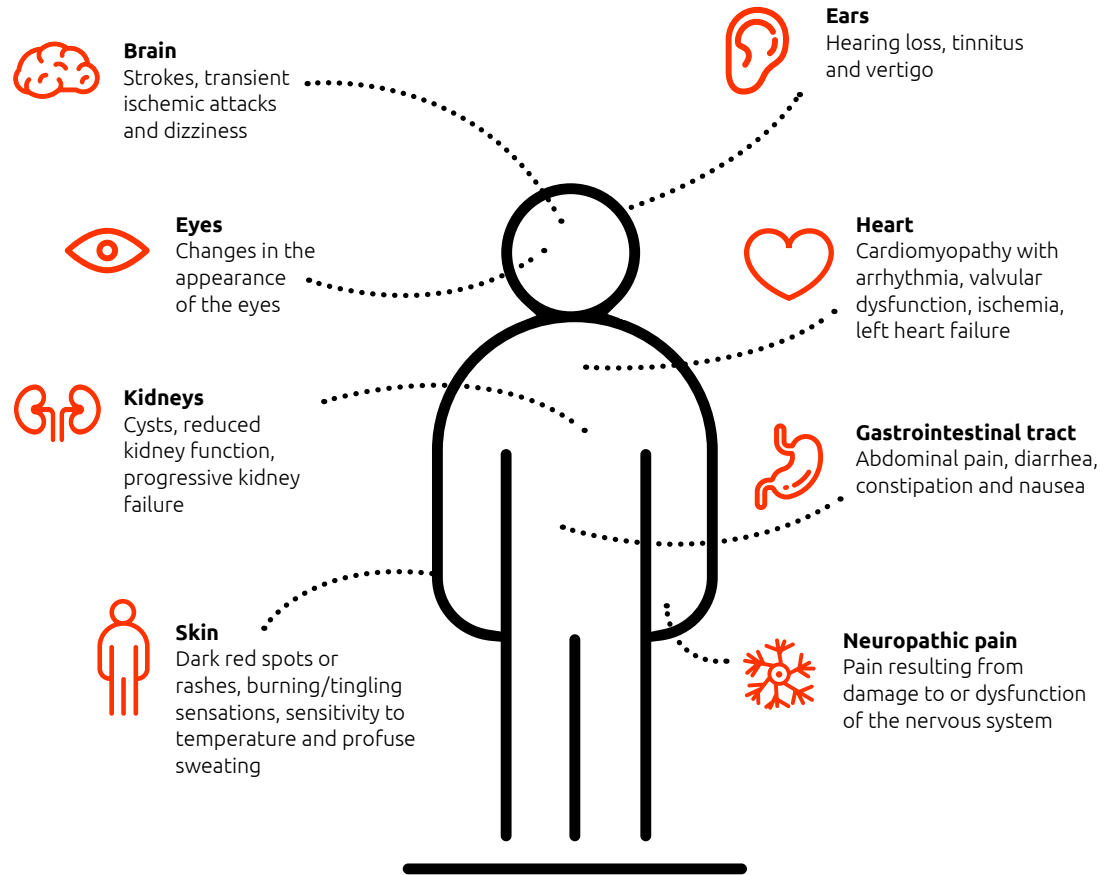
“My doctor called me up, had a chat with us as a family. I felt relief for my son, that at last we knew what was wrong. Then, sort of very scared, once we knew that everyone had got to go for health checks to find out who had got it, and that it could cause lots of other problems with the major organs in your body. It was a scary time.”

Patient and mother of a patient with Fabry disease



### Clinical manifestations of Fabry disease

- Usually more severe in men
- Gradually progressing in severity from childhood to adulthood
- Major impact on quality of life
- Slow progressive damage to vital organs over decades
- Premature death



## The Gb3 cycle and therapeutic approaches

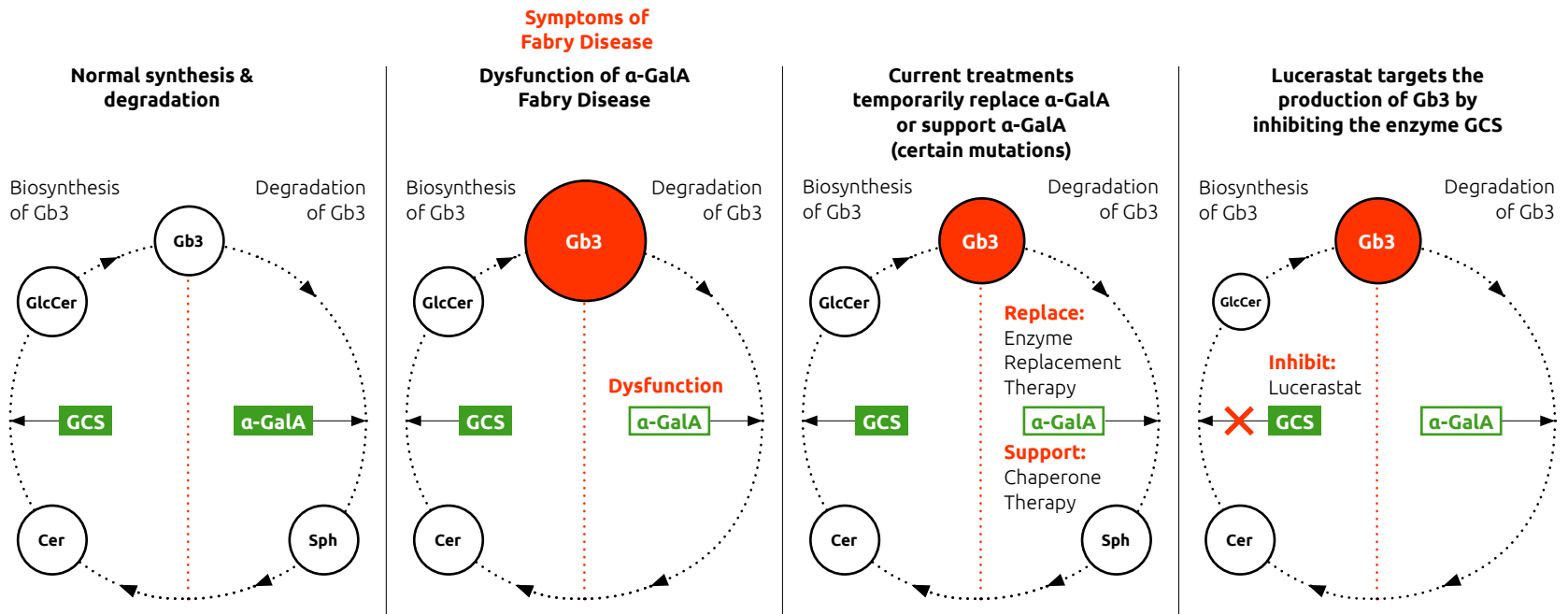
The normal biosynthesis and degradation of Gb3 is shown schematically in the Figure below. In patients with Fabry disease, deficiency or dysfunction of the enzyme alpha-Gal A leads to abnormal accumulation of Gb3, which in turn causes the symptoms of Fabry disease. Current treatments focus on replacing or supporting alpha-Gal A – either through infusion of recombinant enzyme, which temporarily increases

plasma concentrations of alpha-Gal A, or by chaperone therapy, which improves the function of mutated enzymes – but only in patients with amenable mutations.

In contrast, lucerastat, an oral inhibitor of glucosylceramide synthase (GCS), reduces the substrate which forms Gb3. Substrate reduction therapy (SRT) decreases the build-up and is thought to subsequently reduce the Gb3 load in patients with Fabry disease. Since this mechanism is independent of

alpha-Gal A deficiency or dysfunction, it should not be limited to specific mutations of the GLA gene.

## The Gb3 cycle



**Abbreviations:**  $\alpha$ -GalA,  $\alpha$ -galactosidase A; Cer, ceramide; Gb3, globotriaosylceramide; GCS, glucosylceramide synthase; GlcCer, glucosylceramide; Sph, sphingosine

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“We’ve seen a sustained and substantial decrease in plasma Gb3, consistently in almost every patient treated with lucerastat. This shows that substrate reduction therapy with lucerastat has an impact on relevant biomarkers in Fabry disease, which could subsequently translate into beneficial effects on patient’s organs and the course of the disease.”

**Beate Sehorz**  
Senior Director, New Product Strategy



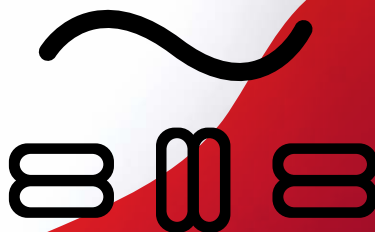
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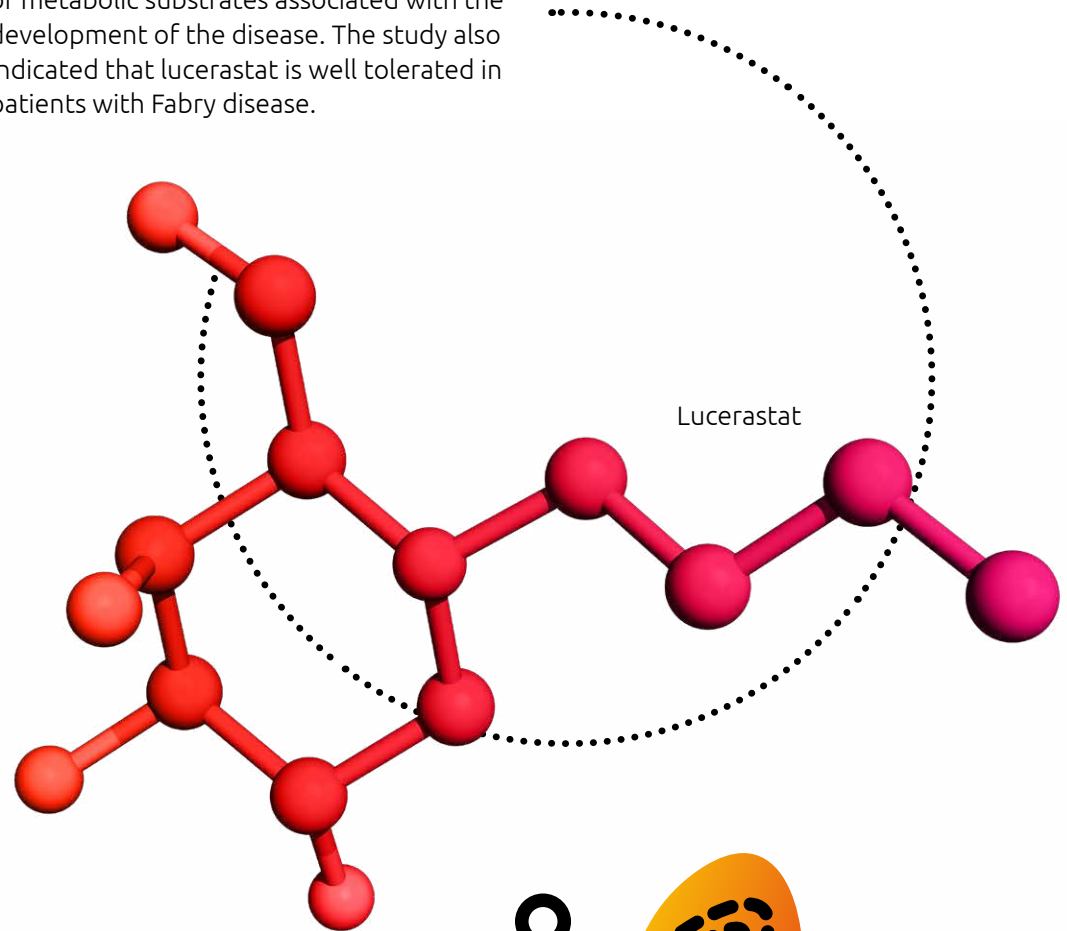
### Idorsia's innovation

Lucerastat is an oral inhibitor of glucosylceramide synthase, offering a potential new treatment approach for all patients living with Fabry disease, irrespective of the mutation type of the GLA gene.

Preclinical studies have shown that lucerastat is an orally available, highly soluble small molecule with rapid and complete absorption. As a small molecule, it is widely distributed to most tissues, including the central nervous system, kidney, and heart.

In an animal model of Fabry disease, treatment with lucerastat reduced Gb3 levels and related biomarkers in dorsal root ganglia, the kidneys, and the heart. This demonstrates that lucerastat has the potential to reduce Gb3 levels in key target organs and, therefore, to show clinical efficacy in Fabry disease.

In an exploratory study in patients with Fabry disease, treatment with lucerastat in addition to enzyme replacement therapy induced a marked decrease in plasma levels of metabolic substrates associated with the development of the disease. The study also indicated that lucerastat is well tolerated in patients with Fabry disease.



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### Current status

MODIFY was a Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. 118 patients were randomized in a 2:1 ratio to receive either lucerastat (80 patients) or placebo (38 patients). At the end of the 6-month double-blind period, 107 patients entered an ongoing open label extension (OLE) study, which aims 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 48 months.

In October 2021, the company reported that lucerastat 1000 mg b.i.d. did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo. However, observations were made 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.

After 6 months of treatment, lucerastat demonstrated a substantial reduction in levels of the Fabry disease biomarker plasma Gb3. A nominally significant ( $p < 0.0001$ ) difference was observed between lucerastat and placebo in the change in plasma Gb3 from baseline to month 6, with a decrease of approximately 50% in plasma Gb3 in the lucerastat treatment group, compared to an increase of 12% in the placebo group.

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. No clinically meaningful changes in vital signs or ECGs or marked laboratory abnormalities were observed. Two patients in each group (lucerastat 2.5%; placebo 5.4%) discontinued treatment due to adverse events. Serious adverse events were reported in 5 patients (6.3%) in the lucerastat group and in 1 patient (2.7%) in the placebo group.

In October 2022, Idorsia conducted an interim analysis of the OLE study, where all patients who are continuing in this 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. The OLE study continues, and the company intends to consult with health authorities in the first half of 2023.

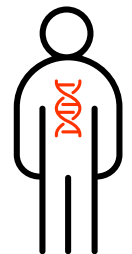


Lucerastat for Fabry disease has received orphan drug designation in the US and the EU and is under review in Japan.

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### Fabry disease Compound: Lucerastat

Mechanism of action:  
Glucosylceramide synthase inhibition  
Status: Phase 3 primary endpoint not met; open-label extension study ongoing



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# Selatogrel for acute myocardial infarction

## About acute myocardial infarction (AMI)

An AMI, or heart attack, is a life-threatening condition that occurs when blood flow to the heart muscle (myocardium) is suddenly decreased or completely cut off. It is usually caused by a blood clot or blockage in one or more of the coronary vessels supplying blood to the heart muscle. An AMI requires immediate treatment and medical attention, as any delay in intervention can result in irreversible damage to the heart muscle. According to the Centers for Disease Control and Prevention, each year more than 800,000 people living in the US will suffer a heart attack.

Although the management of AMI has improved in recent decades, morbidity and mortality associated with AMI remain high, with the majority of early deaths occurring outside the hospital. Early action is crucial for survival and to preserve heart muscle. Besides aspirin, there are no treatment options currently available for the critical time from onset of AMI symptoms to first medical contact. The need for an early intervention has been highlighted by the guidelines of the European Society of Cardiology, which identified the prehospital phase as the most critical for high-risk patients and reiterated that efforts must be made to reduce the delay in initiation of treatment in order to reduce deaths.

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Each year more than

# 800,000

people living in the US  
will suffer a heart attack.

Heart attack can occur in:

**All ages. All ethnicities. All genders.**

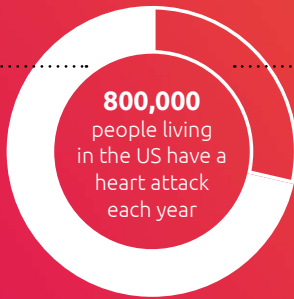


**1/3** of deaths in developed nations can be attributed to heart attack



**80%** of deaths caused by cardiovascular disease are due to heart attack and stroke

**1st heart attack**



**Recurring heart attack**



Average age at first heart attack – risk increases with age



**3.3m** women die of heart attack worldwide every year

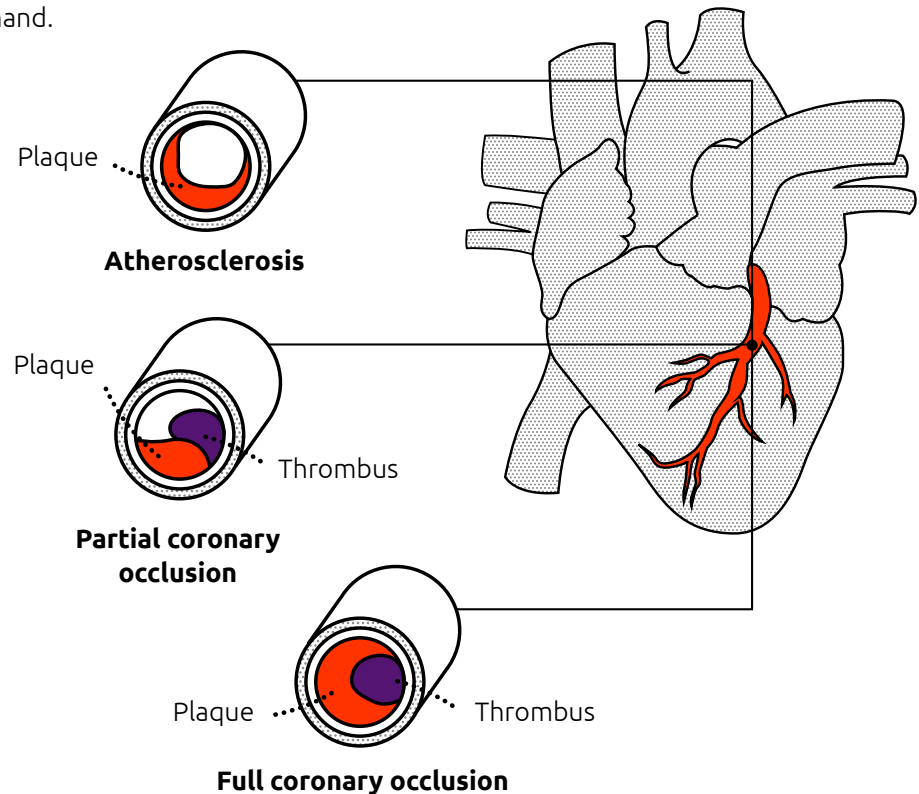
**Women** tend to **underestimate** the risk of heart attacks

### What causes a heart attack?

A heart attack occurs when there is a sudden interruption of the blood supply to some part of the heart muscle.

A heart attack usually occurs in patients with coronary heart disease (CHD), where coronary arteries are narrowed due to the build-up of fat, cholesterol, and other substances (known as plaque or atheroma). This process of build-up is called atherosclerosis. The development of atherosclerosis can progress over decades and often has no symptoms – this explains why around half of the people experiencing a heart attack have no warning signs beforehand.

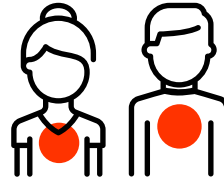
If a plaque ruptures, it triggers the formation of a blood clot at the same site (coronary thrombosis). This can lead to partial – or in extreme cases complete – obstruction of the coronary artery (coronary occlusion). Both coronary thrombosis and coronary occlusion obstruct the blood flow in the coronary arteries, starving the heart muscle of oxygen (a process known as myocardial ischemia).





**Common heart attack symptoms:**

- Chest pain
- Chest discomfort
- Chest pressure
- Chest tightness
- Heaviness in the chest
- Burning in the chest
- A feeling like a band around the chest or a weight on the chest



**Recognizing the symptoms of heart attack**

**Chest pain can radiate to:**



The left arm or both arms



Between the shoulders



The neck or jaws or gums

**The chest symptoms can also be associated with:**

Breaking out in cold sweat



Feeling lightheaded



Feeling the need to take more air, shortness of breath



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### The treatment landscape

Dual antiplatelet therapy – the combination of aspirin and a P2Y<sub>12</sub> inhibitor – is a cornerstone of the treatment of patients with acute coronary syndromes (ACS) and of those undergoing percutaneous coronary intervention (PCI). Oral P2Y<sub>12</sub> inhibitors are indicated for acute treatment as well as long-term secondary prophylaxis of confirmed AMI. An intravenous P2Y<sub>12</sub> inhibitor is intended for specialized use in an acute and hospital setting in patients undergoing PCI who have not been pretreated with an oral P2Y<sub>12</sub> inhibitor.

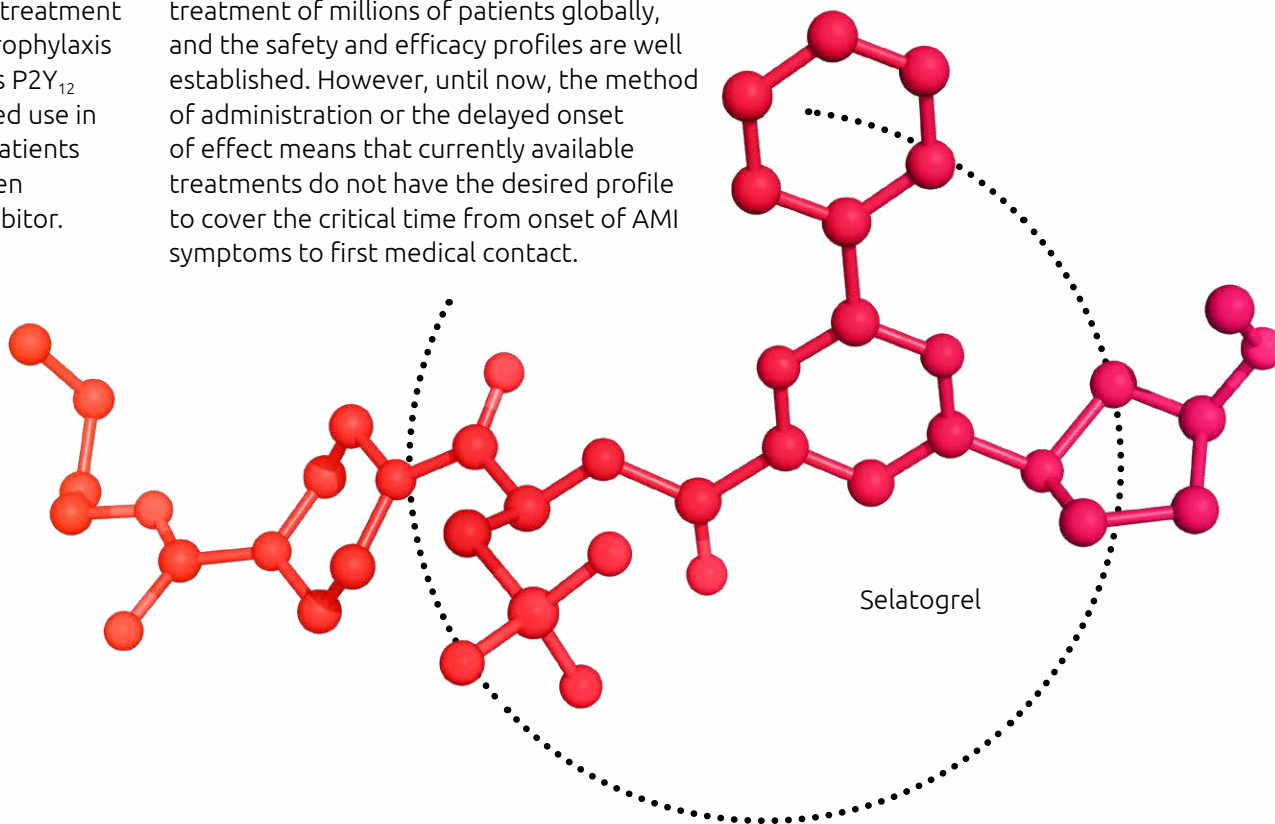
### P2Y<sub>12</sub> inhibition

Platelet adhesion, activation, and aggregation play a pivotal role in atherothrombosis. An essential element in the platelet activation process is the interaction of adenosine diphosphate (ADP) with the platelet P2Y<sub>12</sub> receptor. This platelet activation and aggregation can be inhibited by antagonizing the platelet P2Y<sub>12</sub> receptor. This prevents the binding of ADP to the receptor, which reduces platelet aggregation and the reaction of platelets to stimuli of thrombus aggregation.

P2Y<sub>12</sub> inhibitors have been used in the treatment of millions of patients globally, and the safety and efficacy profiles are well established. However, until now, the method of administration or the delayed onset of effect means that currently available treatments do not have the desired profile to cover the critical time from onset of AMI symptoms to first medical contact.

### Idorsia's innovation

Selatogrel is a potent, fast-acting, reversible, and highly selective P2Y<sub>12</sub> inhibitor, being developed for the treatment of AMI in patients with a recent history of AMI. It is intended to be self-administered subcutaneously via a drug delivery system (autoinjector). This novel, self-administered emergency agent has the potential to protect heart muscle in the very early phase of an AMI – in the crucial time between symptom onset and first medical attention – so as to treat the ongoing AMI and prevent early death.



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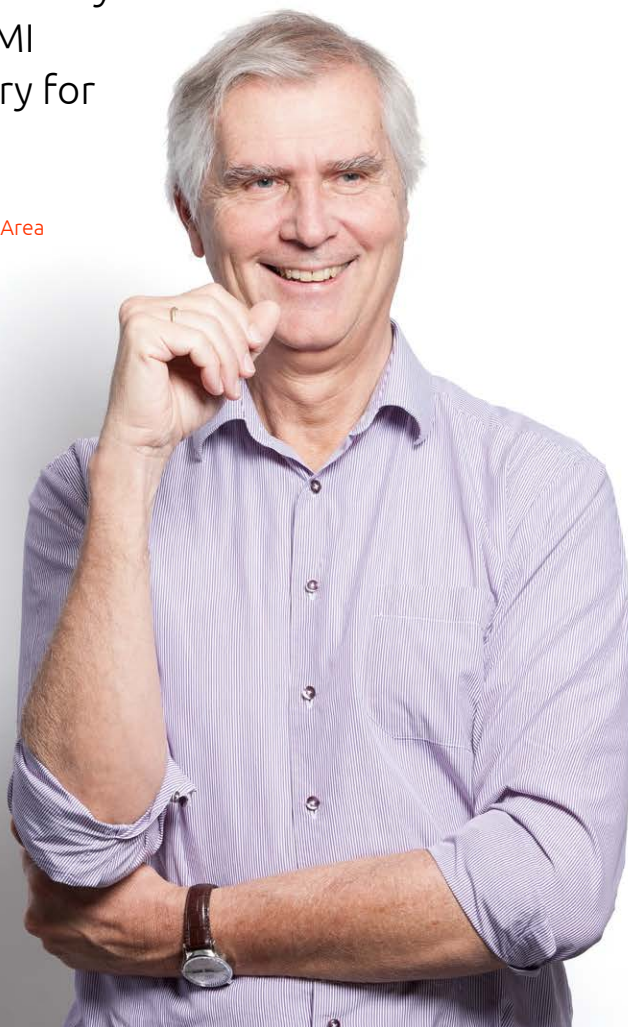




“With our integrated drug delivery device, the potential to self-administer selatogrel in the critical time period immediately following onset of suspected AMI symptoms could be revolutionary for patients.”

**Sebastien Roux, MD**

Senior Director, Medical Expert Cardiovascular Therapeutic Area



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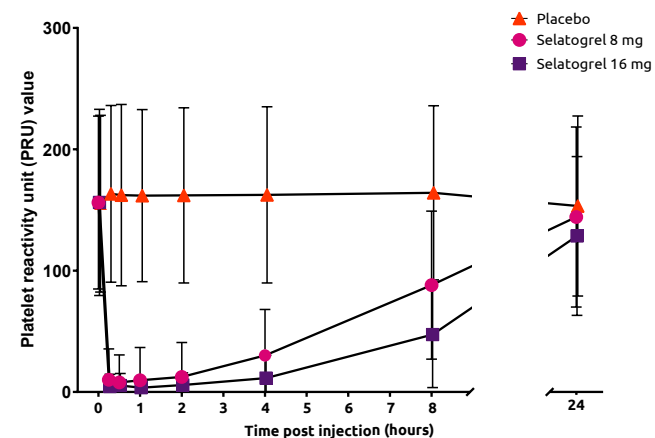
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Two Phase 2 studies in patients with chronic coronary syndromes and AMI, respectively, met their pharmacodynamic objectives of significantly inhibiting platelet aggregation. Subcutaneous administration of selatogrel 8 mg and 16 mg demonstrated a rapid onset of action, within 15 minutes, with the height of its effect extending over four to eight hours, depending on the dose. Selatogrel was safe and well tolerated in both studies, and there were no treatment-emergent serious bleeds. The chart below shows the rapid inhibition of platelet aggregation following subcutaneous injection:

**Selatogrel has a rapid effect following subcutaneous injection**



In late 2019, Idorsia entered into a global development agreement with Halozyme (formerly Antares Pharma, Inc.), to design and customize an autoinjector for subcutaneous delivery of selatogrel. Halozyme’s autoinjector was selected for its robustness, reliability, ease-of-use, and emergency-ready capabilities – key requirements due to the nature of AMI. Idorsia validated the usability of Halozyme’s autoinjector through human factor validation studies prior to initiating Phase 3 investigation.

### Current status

Idorsia is enrolling patients into a large international, double-blind, randomized, placebo-controlled Phase 3 study – Selatogrel Outcome Study in suspected Acute Myocardial Infarction (SOS-AMI) – to assess the clinical efficacy and safety of selatogrel 16 mg when self administered (on top of standard of care) upon the occurrence of symptoms suggestive of AMI. The primary efficacy endpoint is the occurrence of death

from any cause, or non-fatal AMI, after self-administration of the study treatment. The study will enroll approximately 14,000 patients at risk of recurrent AMI, globally.

A Special Protocol Assessment has been agreed with the FDA, indicating its concurrence with the adequacy and acceptability of critical elements of overall protocol design for a study intended to support a future marketing application.

In addition, the FDA designated the investigation of selatogrel for the treatment of suspected AMI as a “fast-track” development program. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need.

SOS-AMI has been designed as a patient-centric study, with patients playing a key role. Patients participating in the study will be trained by qualified professionals, appointed at each study site, on how to recognize AMI symptoms and how and where to self-inject treatment; they will also be instructed to call for emergency medical help immediately. Trainers will use standardized material, mirrored across all countries, which has been developed with the support of education experts, with feedback from post-MI patients, and in compliance with current guidelines.

“Every patient involved in SOS AMI plays a central role by understanding the symptoms of AMI, taking the decision to self-inject, and calling for emergency medical care.”

**Corine Bernaud, MD**

Senior Director, Expert Clinical Project Physician



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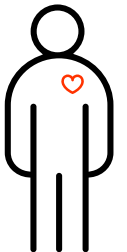
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### Acute myocardial infarction Compound: Selatogrel

Mechanism of action:  
Selective P2Y<sub>12</sub> inhibition  
Status: Phase 3

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# Cenerimod for systemic lupus erythematosus



“There is a stigma attached to lupus. I always talk about my illness and explain it to people first; I tell them it’s an autoimmune disease, but it’s not contagious and I can’t pass it on to them.”

Patient with SLE

Systemic lupus erythematosus (SLE), the most common form of lupus, is an autoimmune disease, which means that the immune system malfunctions and attacks the body’s own tissues. While some autoimmune diseases affect just one organ, in the case of lupus, many parts of the body can be affected.

As a result, symptoms vary widely and are often similar to other conditions, which need to be ruled out before a diagnosis can be made. Lupus therefore often goes undetected or misdiagnosed for long periods.

Yet early diagnosis is important to manage the symptoms of lupus, initiate treatment to reduce the risk of long-term complications, and enable access to wider support (e.g. local patient groups).

It is estimated that 1.5 million Americans, and at least 5 million people worldwide, have a form of lupus, and that 90% of people living with lupus are women, with most developing the disease between the ages of 15 and 44. There is a higher prevalence of lupus among people of Asian and Afro-Caribbean origin than in Caucasians.

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### Normal immune response



Foreign threat invades



Antibodies attack and remove invading threat



Antibodies continue to protect body

### Autoimmune response



Immune system forms antibodies against its own body cells



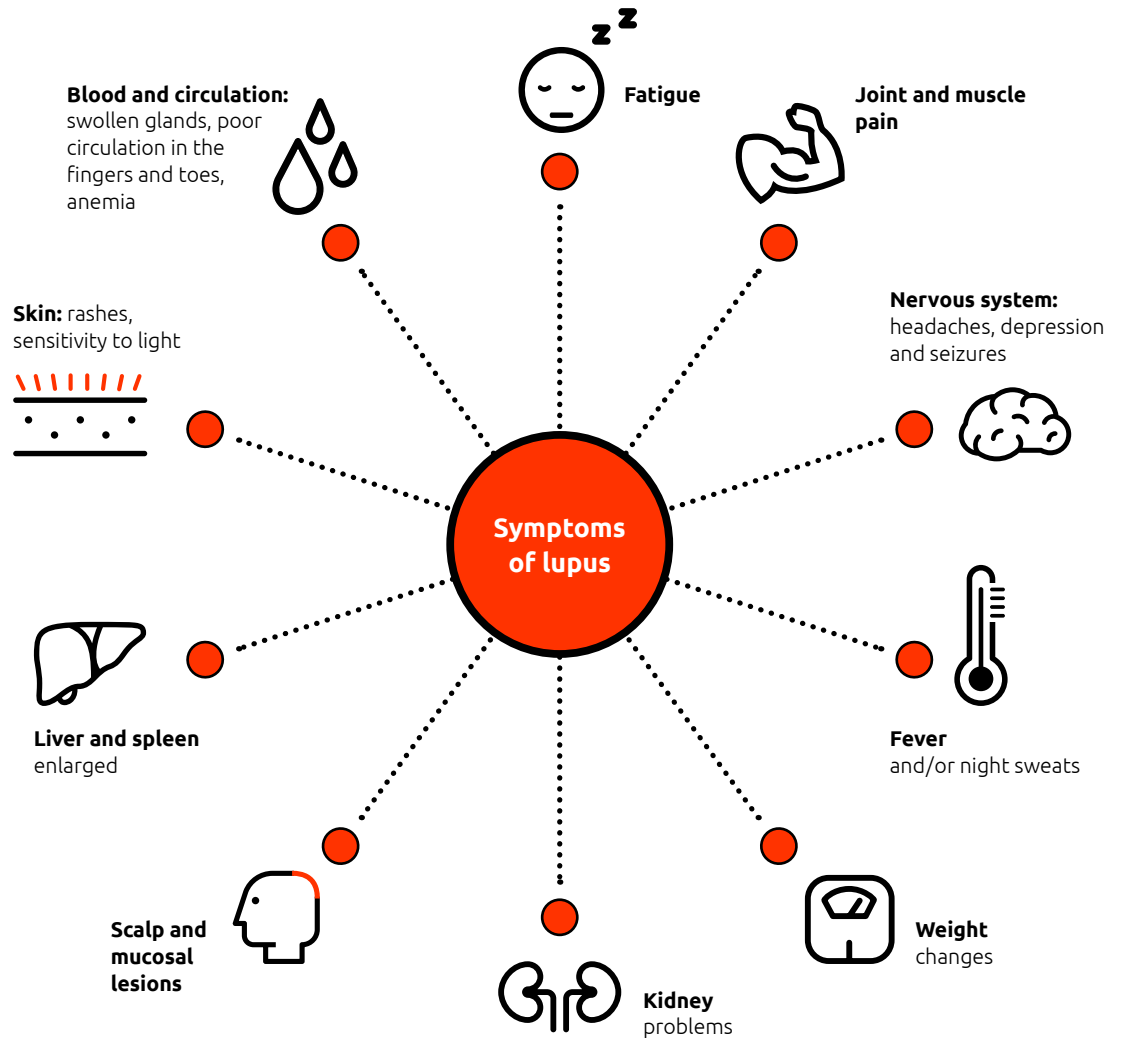
Antibodies attack the body's own cells



Antibodies remain in the body causing inflammation and tissue damage

In SLE, the immune system malfunctions and attacks the body's own tissues, which can affect the skin, joints, kidneys, heart, and other organs.

As any part of the body can be affected by SLE, the condition can manifest itself in a multitude of ways.



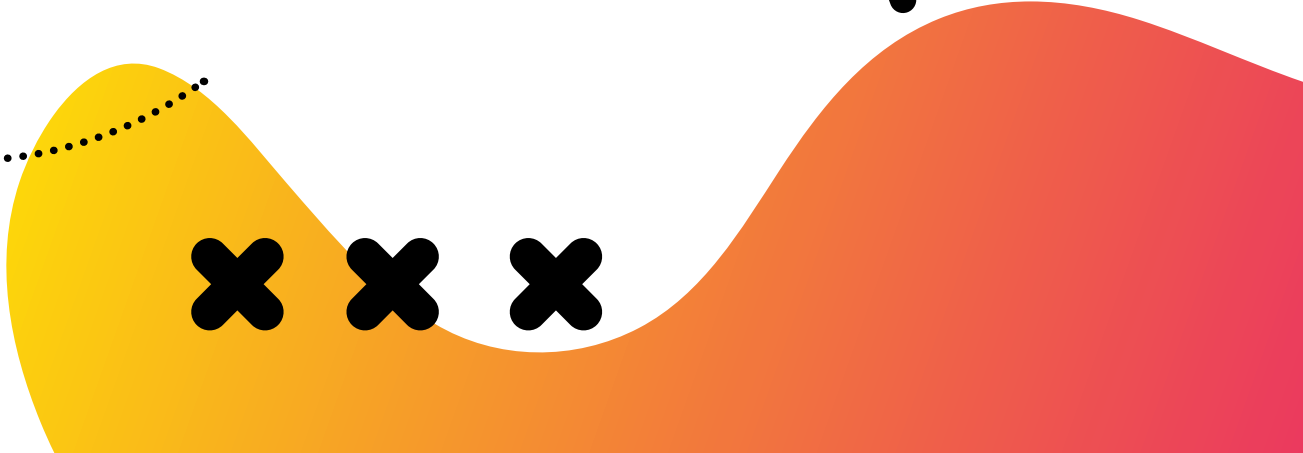
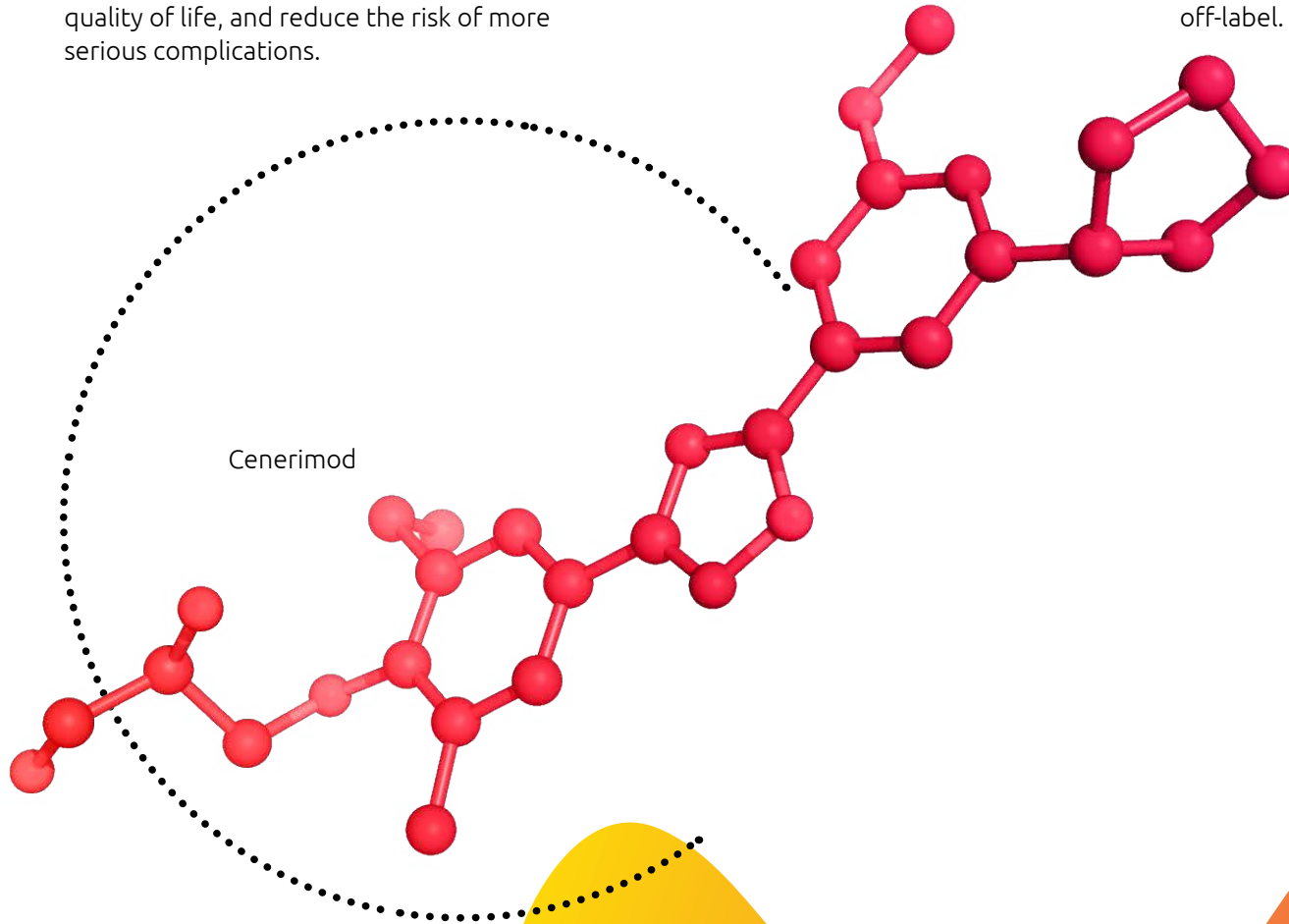


### The treatment landscape

There is no cure for SLE, and a significant need exists for safe and effective therapies. Most people with SLE are prescribed a combination of different medications to manage their symptoms, improve their quality of life, and reduce the risk of more serious complications.

The choice of treatment depends on how the patient with SLE presents – which part of their body is affected and the severity of the condition at the time.

The only approved treatments for SLE are acetylsalicylic acid (aspirin), hydroxychloroquine (an antimalarial), corticosteroids, belimumab, and anifrolumab. Some other immunosuppressive therapies are used off-label.



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“Cenerimod acts on both T cells and B cells and at a fundamental stage in the autoimmune response, meaning it has the potential to alter the course of lupus. Cenerimod showed the potential to modify several inflammatory pathways, demonstrating its broad immune-modulatory pharmacodynamics.”

**Marianne Martinic**

Senior Director, Group Leader Immunology Pharmacology



**S1P<sub>1</sub> receptor antagonism**

While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune cells that play a role in the development of the disease. In individuals with SLE, both T and B cells become overactive. The main consequence of this increased activity is the infiltration of immune cells into different tissues and the production of autoantibodies (antibodies that recognize and destroy the body’s own cells), leading to inflammation and organ damage.

T and B lymphocytes have a cell surface receptor called sphingosine-1-phosphate receptor 1 (S1P<sub>1</sub>). These receptors enable T and B lymphocytes to detect the signaling molecule S1P – sphingosine 1 phosphate – which is responsible for lymphocyte trafficking from the lymph nodes to the circulation.

By binding to S1P<sub>1</sub> receptors, a receptor modulator can trigger the internalization of those receptors. This effectively blinds T and B lymphocytes to the S1P gradient, thereby holding them in the lymph nodes and reducing autoreactive T and B cells in the circulation and, consequently, also in the tissues.

Following the reduction of circulating T and B cells, a reduction in autoantibodies and immune cytokines – markers of the underlying disease processes – is seen. Researchers at Idorsia believe that this will ultimately reduce inflammation and tissue damage – key contributors to the disease.

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## Idorsia's innovation

Cenerimod, the result of 20 years of research in Idorsia's labs, is a highly selective S1P<sub>1</sub> receptor modulator, given as an oral once-daily tablet. Cenerimod potentially offers a novel approach for the treatment of SLE, a disease with a significant impact on patients and limited treatment options. Cenerimod has been tested in several clinical studies, including a Phase 2a proof-of-concept study and the Phase 2b CARE study in patients with SLE, as well as a clinical pharmacology program.

As an S1P<sub>1</sub> receptor modulator, cenerimod inhibits the egress of T and B lymphocytes from lymph nodes. This prevents their migration and infiltration into the various organs, thus affecting the immune response that causes the multiple symptoms of lupus at a fundamental point in the cascade. Based on the results of our Phase 2 studies, we now understand that cenerimod not only decreases the trafficking of T and B lymphocytes but also acts on the other key aspects of SLE. Indeed, cenerimod reduces the transport of autoantigens by professional antigen-presenting cells to the lymph nodes and, consequently, autoantigen presentation and lymphocyte activation. Further, cenerimod reduces pro-inflammatory cytokines and therefore inflammation. As a result, cenerimod will interrupt the vicious circle of SLE pathogenesis. Cenerimod is unique in tackling T cells, B cells, antigen-presenting cells, and inflammation, providing effective

treatment for multiple aspects of lupus pathogenesis.

In November 2021, Idorsia announced the results of CARE, a double-blind Phase 2b study in which 427 adult patients with moderate to severe SLE on stable background therapy were evenly randomized to receive cenerimod (0.5, 1, 2, 4 mg) or placebo. The study duration was 18 months, with two 6-month treatment periods and a 6-month follow-up. After the first 6 months, patients on 0.5, 1, or 2 mg cenerimod and on placebo continued the same blinded treatment, while patients taking cenerimod 4 mg were re-randomized to blinded cenerimod 2 mg or placebo so as to permit assessment of the reversibility of lymphocyte reduction.

The primary endpoint was change from baseline to Month 6 in the modified (to exclude leukopenia) Systemic Lupus Erythematosus Disease Activity Index 2000 (mSLEDAI-2K) score. Secondary endpoints were improvements in the SLE Responder Index 4 (SRI-4) and the British Isles Lupus Assessment Group 2004 index (BILAG-2004). The study did not meet its primary endpoint after type I error control.

However, the reduction in mSLEDAI-2K from baseline to Month 6 with cenerimod 4 mg versus placebo was nominally statistically significant: least squares (LS) mean difference -1.19 (p=0.0291). This effect was greater in patients with greater disease severity and patients with high type 1 interferon gene expression signature status.

The most frequent treatment-emergent adverse events reported with an incidence over 5% in any group and higher than placebo during six months of treatment were abdominal pain, headache, and lymphopenia. A reversible decrease in lymphocyte count is linked to the mechanism of action of cenerimod and, as expected, lymphopenia was seen more often in patients treated with the higher doses (2 mg and 4 mg). Importantly, there was no increased rate of infections compared to placebo: 0.5 mg: 23.5%; 1 mg: 11.8%; 2 mg: 19.8%; 4 mg: 20.2%; placebo: 18.6%.

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At Month 12, the incidence of adverse events reported was between 60% and 80% across all treatment groups, with no dose relationship: 0.5 mg: 63.1%; 1 mg: 81.2%; 2 mg: 77.0%; placebo: 70.9%. For patients in the 4 mg group re-randomized to either 2 mg cenerimod or placebo, the incidence of adverse events was 77.1% and 65.7% respectively. Compared to placebo, as seen during the first 6 months, treatment with cenerimod was not associated with an increased risk of infections.

These results provided the information needed to design a Phase 3 development program, including the patient population, optimal dose, and endpoints.

### Current status

In December 2022, Idorsia initiated the OPUS program (Oral S1P<sub>1</sub> Receptor ModUlation in SLE), which consists of two multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies to evaluate the efficacy, safety, and tolerability of cenerimod in adult patients with moderate to severe SLE on top of background therapy.

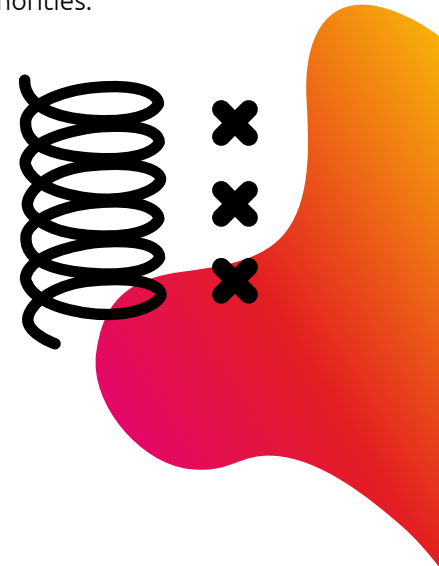
The main objectives of the program are to evaluate the effectiveness of cenerimod 4 mg in reducing disease activity, as well as controlling the disease, compared to placebo. The primary endpoint is change in the mSLEDAI-2K score from baseline to Month 12. Secondary endpoints include SRI-4 at Month 12 and – for the

first time in a lupus registration study – measures of sustained disease control: time to first confirmed 4-month sustained mSLEDAI-2K response and time to first confirmed 4-month sustained response in mucocutaneous manifestations (i.e. rash, alopecia, mucosal ulcers).

The study design was informed by the Phase 2a study with cenerimod showing a dose-dependent reduction in plasma interferon-alpha, feedback from the lupus community, and data from the Phase 2b CARE study suggesting that the treatment effect of cenerimod was greater in patients with higher disease activity and persistent inflammation. The study includes eligibility criteria, and a screening period of up to 60 days, to ensure that only patients with true moderate to severe SLE are enrolled. Those who complete the 12-month double-blind treatment period will have the option to enroll in an open-label extension study, where all patients will receive cenerimod for at least one year.

The Phase 3 program with cenerimod is currently recruiting patients, with a target enrollment of 840 adult patients with moderate to severe SLE from around 25 countries, including Japan.

The investigation of cenerimod for the treatment of SLE has been designated as a “fast-track” development program by the FDA. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need. The Phase 3 program has been discussed with health authorities.



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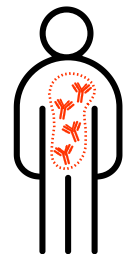
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### Systemic lupus erythematosus Compound: Cenerimod

Mechanism of action:  
S1P<sub>1</sub> receptor modulation  
Status: Phase 3 recruiting

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# Partnerships

For Idorsia, sophisticated partnerships are a way of gaining strategic access to technologies or products and fully exploiting our discovery engine and clinical pipeline. In general, we seek suitable external project partners to maximize the value of internal innovation.

## Johnson & Johnson

In 2017, Idorsia and Actelion Pharmaceuticals, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, entered into a revenue-sharing agreement in respect of ponesimod. In 2021, ponesimod was approved and subsequently launched in the US, Europe, and Canada to treat patients with relapsing forms of multiple sclerosis.

[www.investor.jnj.com](http://www.investor.jnj.com)

## Janssen Biotech

In 2017, Idorsia entered into a collaboration agreement with Janssen Biotech, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to jointly develop aprocitentan and any of its derivative compounds or products. Janssen Biotech has sole commercialization rights worldwide. In May 2022, Idorsia announced positive results of the Phase 3 PRECISION study investigating aprocitentan. In December 2022, the new drug application was submitted to the US FDA for the treatment of patients with difficult-to-control hypertension. In January 2023, the marketing authorisation application was submitted to the EMA for the treatment of patients with resistant hypertension.

[www.janssen.com](http://www.janssen.com)



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### **Halozyme**

In 2019, Idorsia entered into a global agreement with Halozyme (formerly Antares Pharma) to develop a novel drug-device product combining selatogrel – Idorsia’s potent, fast-acting, reversible, and highly selective P2Y<sub>12</sub> inhibitor – with Halozyme’s subcutaneous QuickShot® auto-injector. In 2021, Idorsia initiated the Phase 3 study SOS-AMI with the selatogrel drug-device for the treatment of suspected acute myocardial infarction.

[www.halozyme.com](http://www.halozyme.com)

### **Mochida**

In 2019, Idorsia and Mochida Pharmaceutical entered into an exclusive license agreement for the supply, co-development, and co-marketing of Idorsia’s daridorexant for insomnia and related disorders in Japan.

[www.mochida.co.jp](http://www.mochida.co.jp)

### **Neurocrine**

In 2020, Idorsia entered into a global license agreement with Neurocrine Biosciences for the development and commercialization of ACT-709478, Idorsia’s novel T-type calcium channel blocker. ACT-709478 was investigated in a Phase 2 study for the treatment of a rare form of pediatric epilepsy. The study did not meet the primary endpoint. ACT-709478 was generally well tolerated. Neurocrine continues to analyze the data generated in the study. In addition, a research collaboration was established to discover, identify, and develop additional novel T-type calcium channel blockers.

[www.neurocrine.com](http://www.neurocrine.com)

### **Santhera**

In 2020, Idorsia’s license, collaborative development, and commercialization agreement with ReveraGen BioPharma in respect of vamorolone was transferred in its entirety to Santhera Pharmaceuticals, with the latter replacing Idorsia as a party to the agreement. Idorsia will be entitled to development and sales milestones, as well as low single-digit percentage payments on net sales of vamorolone.

[www.santhera.com](http://www.santhera.com)

### **Syneos Health**

In 2020, Idorsia and Syneos Health entered into an innovative commercial partnership to build the salesforce for the US launch of QUVIVIQ (daridorexant). In January 2022, Idorsia expanded this commercialization partnership to support the launch of QUVIVIQ and effectively reach the primary care market in Europe and Canada.

[www.syneoshealth.com](http://www.syneoshealth.com)

### **Simcere**

In 2022, Idorsia and Simcere entered into an exclusive licensing agreement for Idorsia’s daridorexant in China. Under the agreement, Simcere has an exclusive right to develop and commercialize daridorexant in the Greater China region.

[en.simcere.com](http://en.simcere.com)

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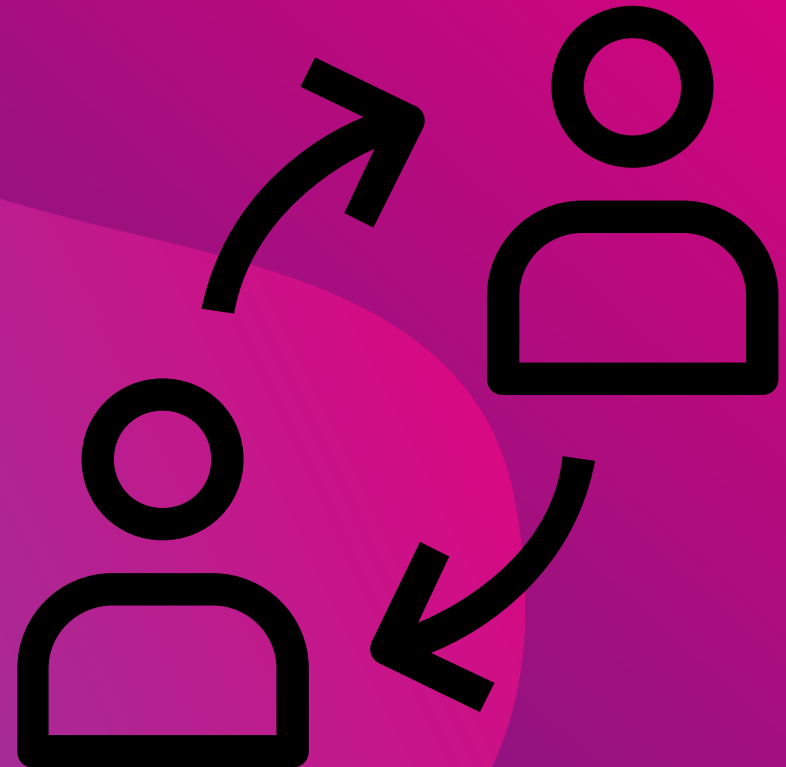
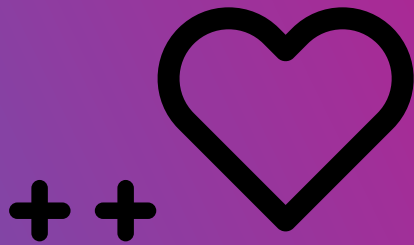
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# Our People



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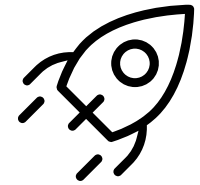
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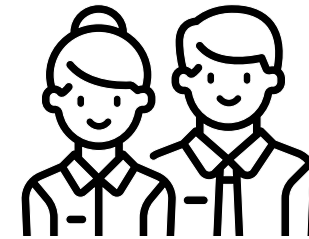
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# More power – For scientific thinking

Simply put – our success depends on our people!  
This is why we want to recruit, engage, and  
develop talented people who are passionate  
about working together and applying science to  
bring benefits to patients.



**One**  
common goal



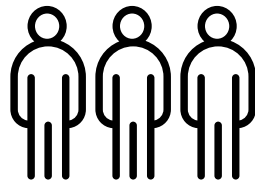
**45%** female  
**55%** male



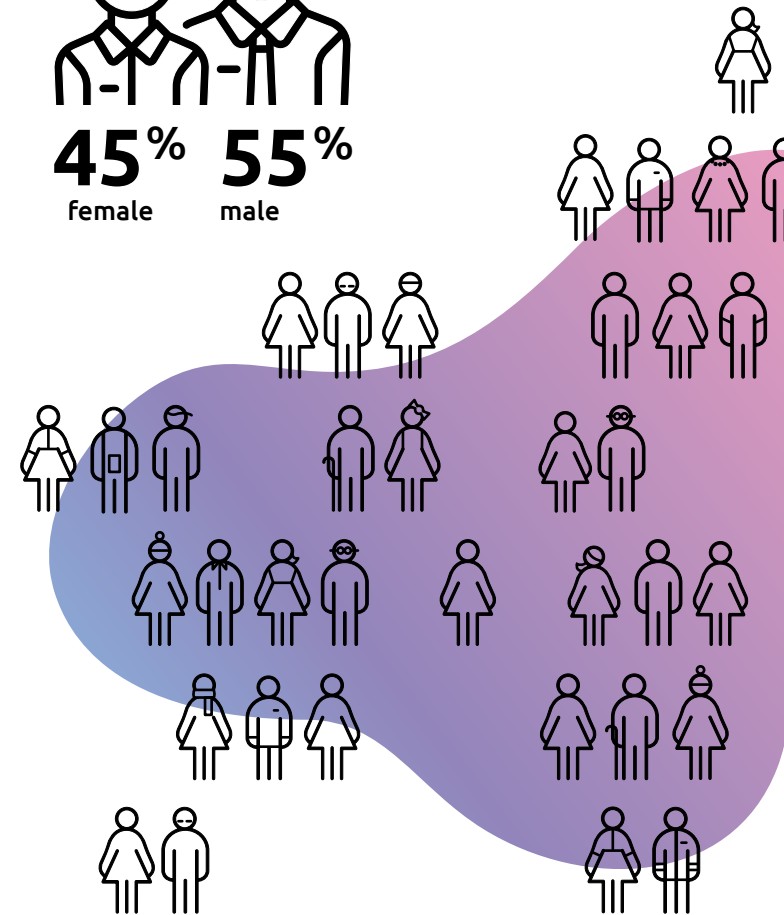
**43**  
nationalities



**Highly**  
qualified  
professionals



**>1,300**  
employees



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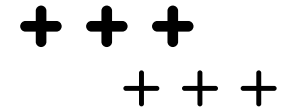
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# More diversity – Creating opportunities

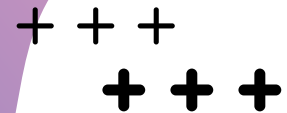


In the first 5 years as Idorsia, we advanced our R&D pipeline while preparing to launch our first products. To achieve this, we expanded our geographic reach and grew our talent base. Today, with over 1,300 employees, we are now well positioned to maximize the value of our innovation.

The company has transformed from a clinical-stage company into a fully fledged biopharmaceutical company with commercial capabilities.

We work in a fast-paced environment, where ambitions and expectations are high. As such, it is important that we attract, retain, and advance top talent from all backgrounds and cultures. During the recruitment process, we seek to attract a diverse pool of candidates, focusing on the skill set they offer and matching their competencies to the behaviors we expect our people to live by daily and to the key qualifications required to fulfill the role.

We have certainly come a long way in 5 years. Today, with a strong pipeline and products on major pharmaceutical markets, our people are as committed as ever to making Idorsia a leading biopharmaceutical company, while at the same time developing both personally and professionally.



“We’re going through very exciting times! With an advancing pipeline and product launches, it’s all hands on deck, which is exactly how I like to work.”

**Fenna Gloggner**  
Director, Global Customer Insights

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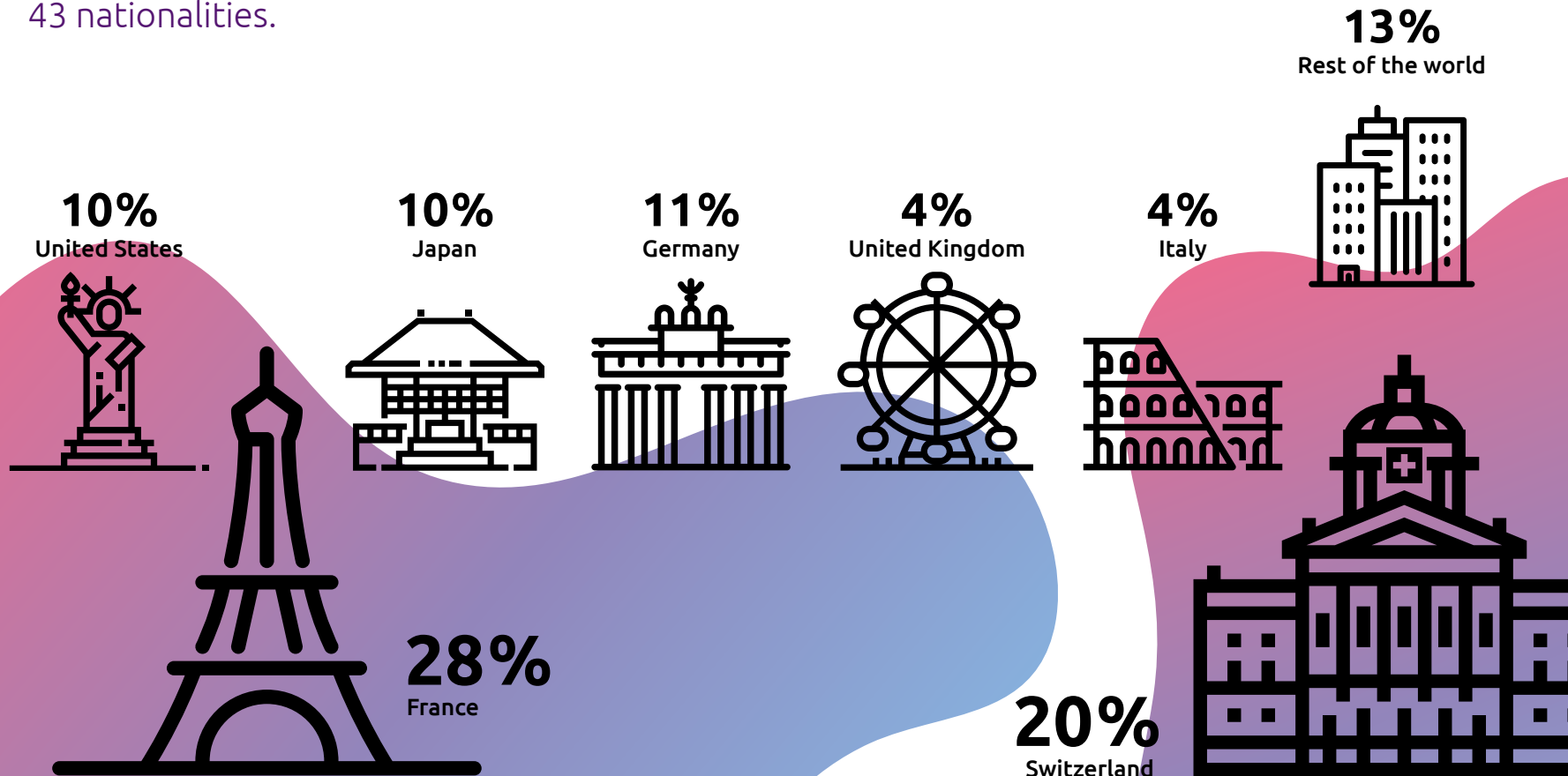
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At Idorsia, we harness the power of difference to achieve business success: our employees come from diverse cultural backgrounds, representing 43 nationalities.



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# More science – Bursting with ideas



Our people work every day with creativity and passion to find new treatments and make them available to patients with serious diseases – from bench to bedside.

We aim to create an inspiring working environment and provide equal opportunities for all our employees. We do not tolerate discrimination of any kind.

Idorsia is committed to ensure full compliance with the gender representation and pay equality required by the Swiss regulations. The results of the 2020 gender pay equity analysis in Switzerland (published in the Compensation Report 2020) confirmed our company culture of equal opportunities and equal pay. Idorsia is committed to monitoring gender pay equity on an ongoing basis. In 2022, we repeated the gender pay equity analysis for Switzerland, which again confirmed our equal pay practice. As we are growing our operations internationally, we are extending our pay equity reviews to new geographies.



**Jose Alba Casado**  
Clinical Operations Manager

**Karen Ellis**  
Director, Drug Safety Compliance Manager /  
Deputy EU QPPV

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# More potential – Expanding opportunities

Our future as a company depends on a workplace that enables employees to achieve their full potential – both at work and outside the office. We believe that a culture fostering employees' development and growth is essential to our success. We take an integrated approach to rewards and talent management, designed to build an organization of highly engaged and enthusiastic professionals.

To support our people in achieving their full potential, we provide a range of internal and external learning and development programs. We emphasize results-oriented coaching, encourage internal mentorship, and offer a variety of training programs, including best practices in project management, presentation skills, applied financial excellence, persuading and influencing, cross-cultural and constructive communication. We also fully support language learning.

Idorsia provides financial assistance to employees who wish to advance their education through an accredited university or business school.

We regularly assess our talent to identify high performance and provide support for those who display potential for further growth. For employees taking on additional responsibilities, we have a leadership

program designed to help managers become great leaders.

Since 2020, we have been running a global virtual program that offers employees a possibility to learn from other colleagues. The main purpose of this program is to encourage cross-functional learning for all employees worldwide – for example, an expert in IT learning about the drug discovery process.

We also run disease awareness campaigns for our employees. Since Idorsia's foundation in 2017, we have hosted several on-site events where employees could explore and discover diseases which we are actively researching, such as lupus, Fabry disease, and acute myocardial infarction, to help us keep the patient at the center of our daily activities.

In 2021, we launched "Mental Health Matters", a campaign to support our employees with training, tools, and further resources for better mental health. As the effects of the global pandemic continue to impact lives, Idorsia wants to ensure that our employees continue to thrive. This campaign supplements existing counseling and coaching services, which are offered, for example, to all permanent, temporary, and hourly-paid employees at Idorsia's headquarters in Switzerland, with support services in other countries varying.

**"Idorsia offers a unique possibility of personal and professional growth as we work together to develop and transform the company."**

**Pier Paolo Lo Valvo**  
Director, Global Human Resources

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# More experience – Driving innovation

At Idorsia, we have tools in place to recognize extraordinary achievements and emphasize the importance of working in teams.

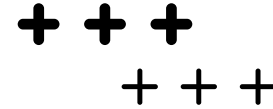
Our simple and transparent reward and recognition philosophy is based on engaging everyone in an entrepreneurial approach to long-term value creation.

Idorsia's approach to performance and recognition provides a simple and effective way to align individual and team efforts with Idorsia's strategic priorities, as well as encouraging excellent performance and sharing the results that we achieve together.

In 2022, we launched "Ambition 2027", a one-time equity program to reward employees for what has been achieved since Idorsia's inception in 2017 and to focus on creating long-term value together.

"It's very exciting to be able to discover innovative new treatments and really help patients, while at the same time contributing to the growth and value generation of our company."

**Naomi Tidten**  
Director, Team Leader Computer-Aided Drug Design



Through the program, every permanent employee globally (excluding all members of the Idorsia Executive Committee), as well as each new hire through 2023, receives a grant of restricted stock units (RSUs) that vest progressively over five years. They are also awarded an equivalent number of matching shares, underpinned with four ambitious strategic goals. Depending on the number of objectives met by the end of 2027, participants can up to double their initial grant of RSUs. With this unique plan, we aim not only to retain our talented employees worldwide, but also to share future successes with all.

In addition to our stock-based programs, we recognize individual long-term engagement with Idorsia through a special "Anniversary Vacation" of 4 weeks' fully paid sabbatical leave when employees reach their 10th, 20th, and 30th anniversary of employment with Idorsia, and 1 week when reaching the 15th and 25th anniversary. Disconnecting from work for an extended period to pursue personal interests leaves employees energized and ready to immerse themselves when they return.



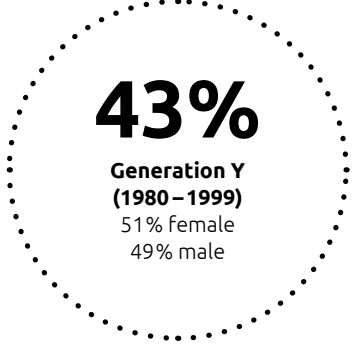
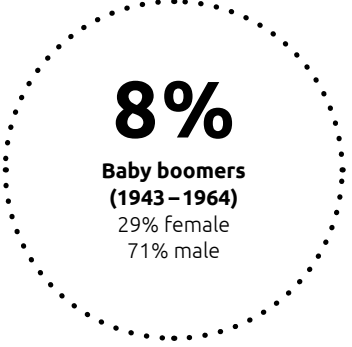
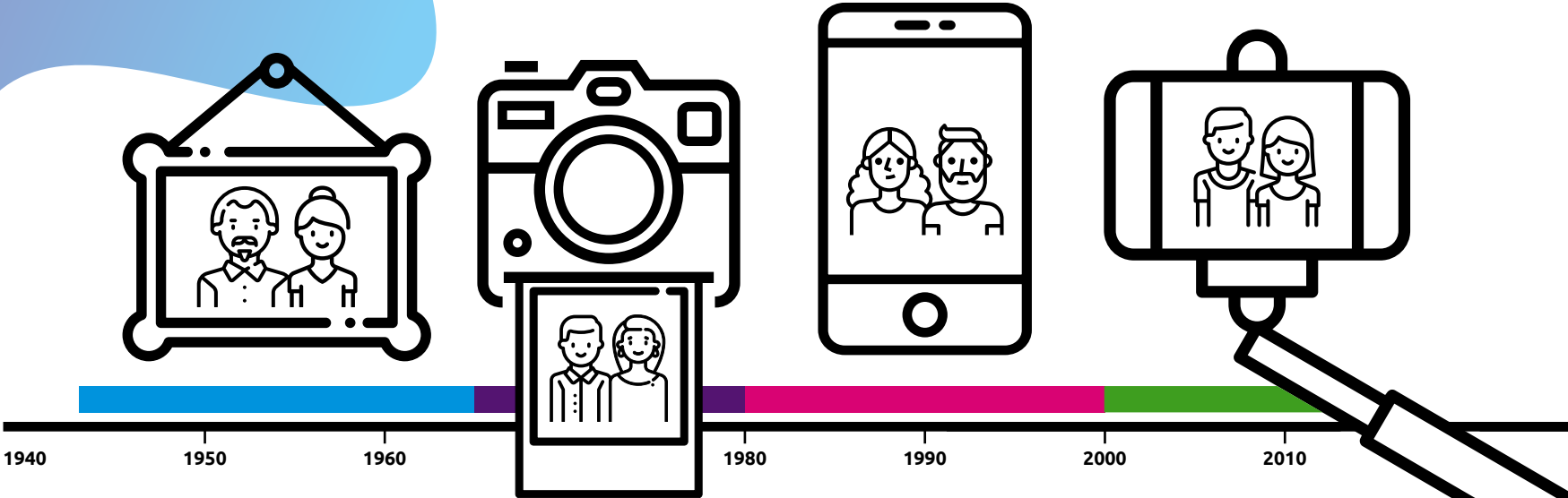
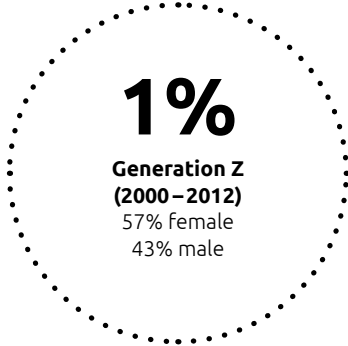
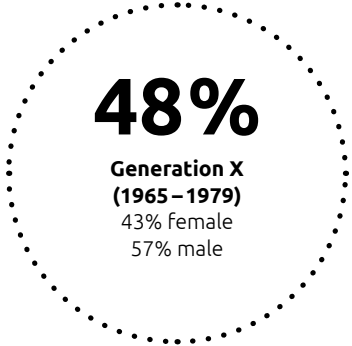
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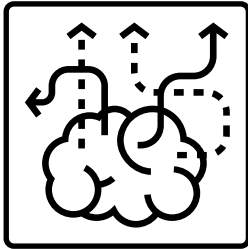
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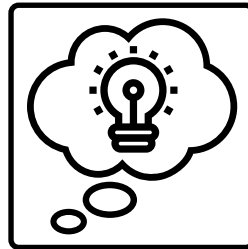
# More ambitions – Courageous and energetic

It is not just what we achieve, but how we get there. To support this, management has identified model behaviors which will help us to implement our strategy, shaping Idorsia's corporate culture.

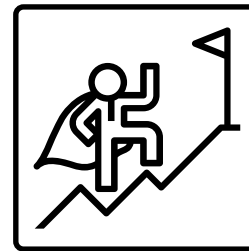
**be pragmatic**



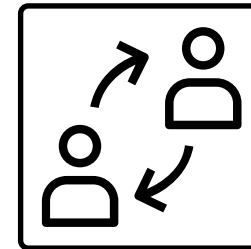
**invent**



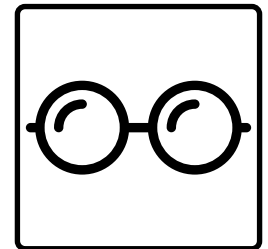
**advance**



**team up**



**learn**



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To reach our ambitious goals, we **advance** with energy and drive. We take full ownership and accountability to find solutions and outpace the competition.

Whatever the challenge, we are agile and **pragmatic** in implementing initiatives without compromising the quality of our work.

To seize more opportunities, we **invent** with creativity and imagination. Our work is science- and data-driven, and we remain open to new approaches in all aspects of what we do.

We **team up** to harness the power of our collective passion and sense of fun. We work collaboratively, sharing information and exchanging ideas, listening to and supporting each other.

We are curious, open-minded, and we **learn** continuously. We are encouraged to expand our knowledge, skills, and self-awareness, while looking for ways to apply what we have learned.

“We create a meaningful and enjoyable environment for people to do their best work.”

**Alex Khatuntsev**  
Senior Vice President, Head of Global Human Resources

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# More opportunities – Expanding the horizon



This year has been a year of transformation for Idorsia, as we launched our first products and became a fully fledged biopharmaceutical company. With the shift to delivering our products to patients, we also take on additional obligations to ensure high quality and ethical behavior.

We are operating in a highly regulated and scrutinized industry, and navigating the applicable laws and regulations becomes more challenging with every step we take towards delivering our medicines to the market. Our good reputation as a company is invaluable, and the management team ensures that all employees are empowered and feel accountable to safeguard and build on it.



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### The Idorsia Executive Committee

**Simon Jose**  
Executive Vice President,  
Chief Commercial Officer

**Martine Clozel**  
Executive Vice President,  
Chief Scientific Officer

**Guy Braunstein**  
Executive Vice President,  
Chief Medical Officer  
(new position created in January 2022)



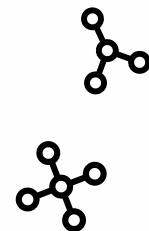


To reinforce this and to ensure that Idorsia’s approach to medical governance and its policies and procedures are globally aligned and consistent across the company, at the beginning of 2022, the role of Chief Medical Officer was created. Guy Braunstein was appointed to this new position, making way for Alberto Gimona, as Head of Global Clinical Development and new member of the Idorsia Executive Committee (IEC).

We have always said that, while what we are trying to achieve is important, how we achieve it should be considered equally important. As we stay focused on bringing our medicines quickly to the patients who need them, we must also be mindful about how we achieve this. Compliance with legal and regulatory requirements is not only a prerequisite for our license to operate but, most importantly, protects the patients we serve. The whole management team is committed to ensuring that our employees have clear quality documentation to guide them in their everyday work and lead by example.

“Acting with honesty, integrity, and respect is the foundation upon which Idorsia is built and how we conduct business.”

**Jean-Paul Clozel**  
Chief Executive Officer



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**André C. Muller**  
Executive Vice President,  
Chief Financial Officer

**Jean-Paul Clozel**  
Chief Executive Officer

**Alberto Gimona**  
Executive Vice President,  
Head of Global Clinical Development  
(since January 2022)

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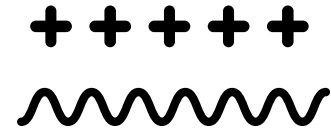
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“We are building Idorsia with a long-term focus and ambitious aspirations. We will run the company in a responsible and sustainable way.”

**Jean-Paul Clozel**

Idorsia's CEO, on the establishment of the company

# More drive – For a better future



## Our purpose

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.

Delivering on our purpose is our core responsibility to our stakeholders and to society. We are committed to achieving this in an economically, socially, and environmentally responsible manner.

We take our responsibility seriously and seek dialogue with all our stakeholders to find out what really matters to them, through efforts such as our materiality assessment, our sustainability survey, and stakeholder-specific engagement activities.

As Idorsia expands its geographical reach, adding complexity to our organization and impact, our commitment to sustainability remains as important as ever.

## Our approach to sustainability

From the beginning, Idorsia's leadership has emphasized that sustainability is central to how we define our success. Sustainability is at the heart of our leaders' decision-making on how to grow our company, and it is part of the ethos instilled in our employees from their first day at work. We are building a company to last, and as we expand – with new affiliates in countries across the world – we integrate sustainability into our global operations.

This has been our approach from the outset: the company was founded with a strong governance framework in place, including a broad range of policies, standard operating procedures, and guidelines to drive a culture of integrity. Our commitment to sustainability has been reinforced over the years. For example, we have strengthened the monitoring and disclosure of our performance on a wide variety of environmental, social, and governance (ESG) topics important to our

stakeholders, particularly our environmental footprint. Furthermore, with our growth and transformation into a commercial company, we have expanded oversight, employee training, and other measures to ensure our business is conducted ethically and in line with relevant legal and regulatory requirements in all the markets in which we operate. Today, ESG reporting is already one of the four topics included in our company goals for the year, affecting every employee's short-term incentive.

As we look forward to a strong growth trajectory, we will continue to be open and transparent, engaging with our stakeholders as our approach to sustainability evolves.

At Idorsia, we follow the science – which often leads us to seek input from a variety of perspectives. We value collaboration with academia, industry partners, governments, NGOs, and others, to help us find solutions to scientific challenges.

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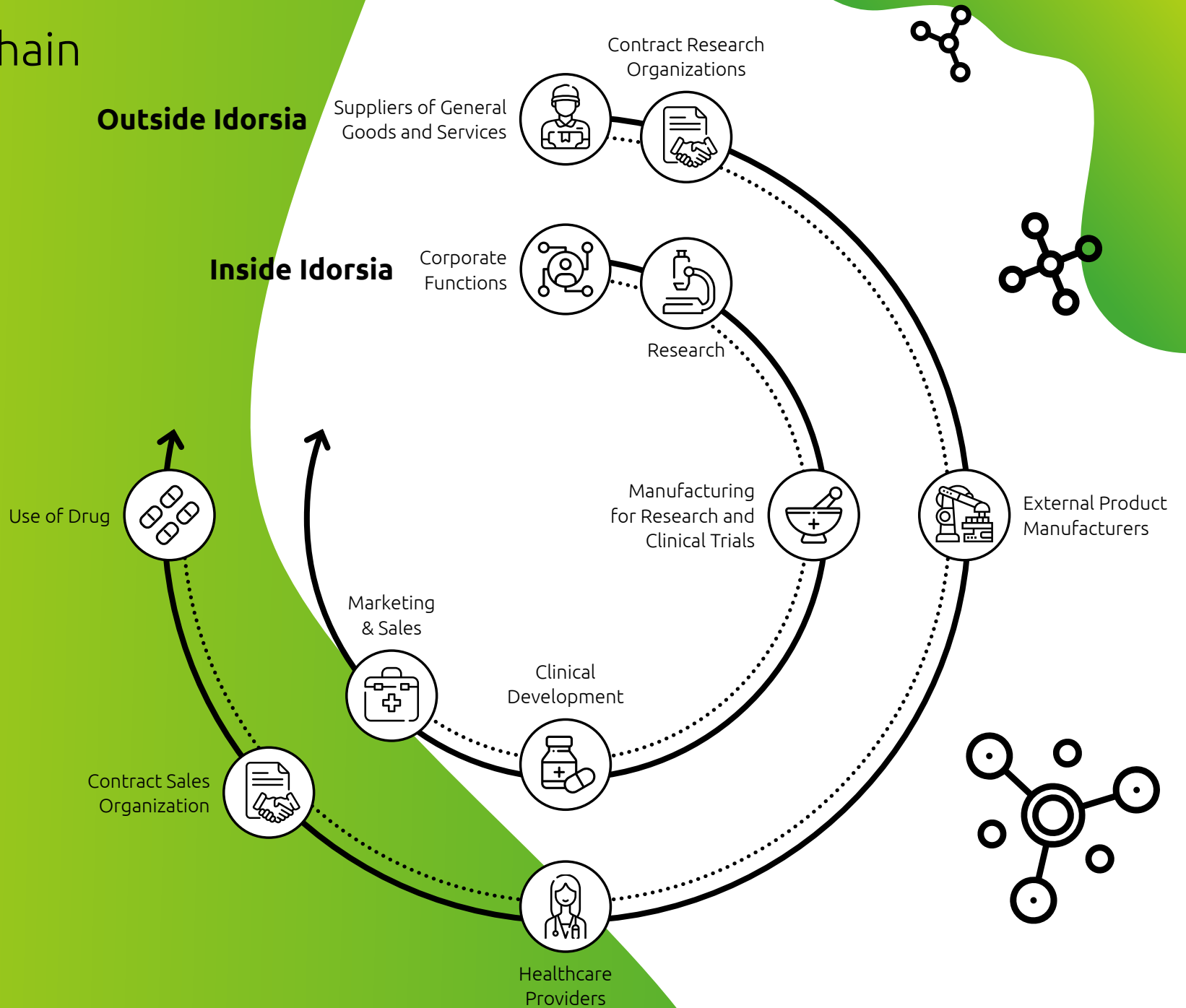
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# Our value chain



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We take this same approach – seeking input from and partnering with stakeholders – to ensure the sustainability of our business. We understand that the best solutions are often found through dialogue with diverse voices from across our value chain.

To achieve this, we regularly reach out to our stakeholders to discover how they rate our performance as we strive to deliver on our purpose. We use their input to shape our company’s approach, manage risk in our operations, and inform our sustainability framework.

Even though Idorsia is a young and relatively small company, we also seek to adhere to industry best practices in our approach to sustainability. In 2020, we therefore conducted a comprehensive stakeholder outreach program to inform our materiality analysis. This involved engaging with seven priority stakeholder groups with an interest in Idorsia’s future as a sustainable company.

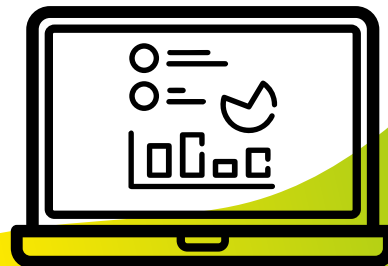
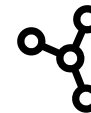
These groups were:

- Patients and patient associations
- Healthcare professionals and the medical community
- Scientific and academic community
- Local communities
- Idorsia employees across all levels of the organization
- Investors and analysts
- Idorsia’s Board of Directors

We asked these key stakeholders to help us explore their expectations on topics that will be key to our future success, and to validate and prioritize the major areas identified in the outreach program. The results of our stakeholder engagement activities, and in

particular the in-depth outreach program, were fed into a materiality assessment, which helps Idorsia to prioritize areas of our business that are most important to ensure a sustainable future for our company. The materiality assessment provided key insights on each topic, and the priorities identified are shown in the infographic on page 110.

To build on these learnings, we continue to engage with our stakeholders to refine our materiality assessment. Part of this engagement is an online survey, first launched in 2021, which we continue to use to gather feedback from our stakeholders. The survey probes the themes uncovered in our initial materiality assessment, looking in particular at how it should evolve as our company develops. All our stakeholders are invited to participate in this survey at: [www.idorsia.com/survey](http://www.idorsia.com/survey).



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# Idorsia's material topics

Risk management & business continuity

Compliance & business ethics

Employee welfare & engagement

Product innovation

Product safety and quality

Access to medicines

Transparent communications

Supply chain management

Partnerships & scientific collaborations

Diversity, equity & inclusion

Environmental impact management

Investment in communities

**Highest priority**

## Product innovation

This is the essence of what we do, the core of Idorsia's business. Innovation involves putting the unmet needs of patients at the center of our research and developing medicines that can make a real difference.

## Product safety and quality

Our future depends on the reliability of our products, which we demonstrate by proving clinical efficacy and safety and ensuring product quality throughout the supply chain.

## Compliance & business ethics

We aim to meet not only the high standards of compliance required in our highly regulated industry, but also the expectation that we operate as an ethical company.

## Employee welfare & engagement

Our ability to attract and retain great scientific and business talent is fundamental to successfully innovating, developing, and delivering on our pipeline.

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### **Risk management & business continuity**

We aim to guarantee our business continuity by achieving financial sustainability. Good governance processes also help us to manage risk throughout our operations.

### **Access to medicines**

As an engaged member of the healthcare ecosystem, Idorsia understands its responsibility to help find solutions to the high cost of healthcare, and we are committed to playing our part in supporting patient access to our medicines.

### **Transparent communications**

We regularly engage with our stakeholders and offer proactive, fact-based, and honest communication to facilitate open dialogue.

### **Supply chain management**

We will maintain a reliable supply chain to ensure the delivery of safe, high-quality products to patients.

### **Partnerships & scientific collaborations**

The success of our pipeline relies on exchanges and partnership with scientists, healthcare professionals, and patient organizations to drive innovation.

### **Diversity, equity & inclusion**

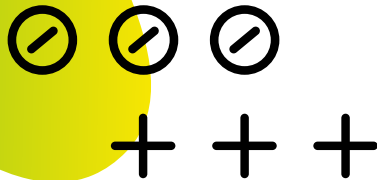
We are dedicated to fostering respect, fairness, and equal opportunities for all our employees, as we believe it is vital to create and support a diverse, equitable and inclusive workplace.

### **Environmental impact management**

Climate change is a challenge that companies are increasingly prioritizing, and we will keep a strong focus on our impact as we grow.

### **Investment in communities**

We have close ties with our local communities and want to bring our passion for science to those, especially young people, who live nearby.



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# More authentic – Culture of transparency

## Our impact

As emerged from our stakeholder engagement and materiality assessment, our stakeholders believe that, in order to achieve sustainable value creation, we must continue to focus our efforts on three pillars:

### Push the boundaries for patients

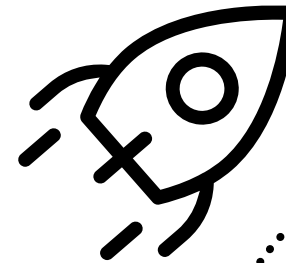
Innovation is the essence of our company and its purpose. Our science is bringing new treatments to patients, and we bring our culture of innovation to every aspect of our business.

### Build on our talents

Our success depends on our people. The talent, skills, and experience of our team is at the heart of our success. Attracting and retaining the best talent makes our future possible.

### Lead an ethical business

We conduct our business with integrity. Idorsia instills in its employees the responsibility to act in an ethical manner.



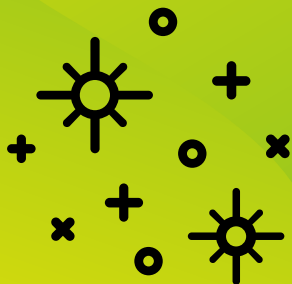
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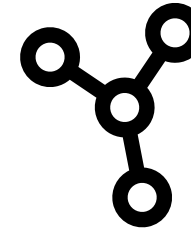
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We understand that to deliver a sustainable future for our company, these three pillars need to be equally strong. Each pillar is dependent on the others – for example, our ability to build talent rests on successful innovation and responsible business practices. Only by succeeding in all three of these areas can we guarantee our future.

### Sustainability performance

In 2022, we celebrated the fifth anniversary of Idorsia’s foundation. Despite being a young company, we are proud of our sustainability performance. ESG topics have been covered in each of our Annual Reports since we were founded in 2017, and we continue to strengthen our performance disclosures.

Idorsia takes a pragmatic approach to sustainability reporting. In 2022, our reporting for the first time included references to the standards issued by the Global Reporting Initiative (GRI), which is recognized as an international authority in this field. We use additional standards – such as those of the Sustainability Accounting Standards Board (SASB) – to supplement GRI on the reporting of sector-specific topics.

Idorsia’s sustainability content index is published on our website. The index is structured according to the 12 topics identified in our materiality assessment. For each material topic, we have published an info sheet summarizing key qualitative and quantitative disclosures and guided by GRI standards for the relevant area. Each info sheet includes a management approach for the material topic, providing a description of our governance model for that area, as well as roles and responsibilities. As well as the info sheets, the content index includes links to sustainability content for our material topics across our corporate publications.

See more at [www.idorsia.com/sustainability](http://www.idorsia.com/sustainability)

As we grow and our reporting becomes increasingly robust, we will provide additional performance data, set targets and continue to expand our disclosures. The info sheets will serve as a basis for future development and reporting according to the evolving GRI standards and newly enacted Swiss regulations. We know that transparency – with a focus on our material topics – is key to a sustainable future and is of great interest to our stakeholders. We have every intention of meeting their high expectations.

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# Our brand strategy

## More ideas – Changing the world

**Joyful colors, science-driven icons and bold messages: this is the brand world of Idorsia.**

The core idea of the Idorsia brand is “Reaching out for more”. It is perfectly expressed in the energetic, intelligent and creative corporate design, and in the unified key messages.

The unique brand identity helped Idorsia from day one to create impact in the market, attract gifted talents, and save costs in brand management.

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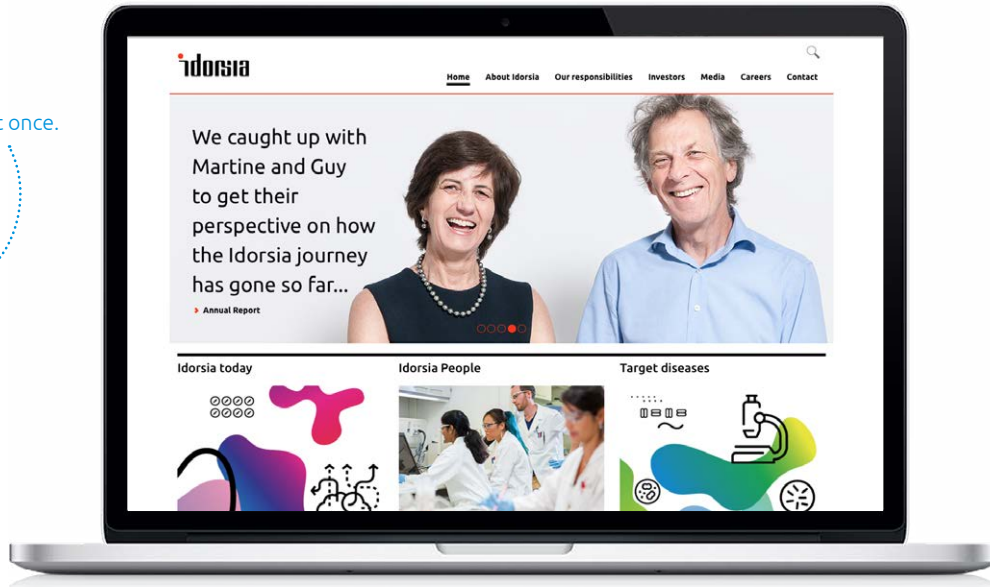
Sustainability



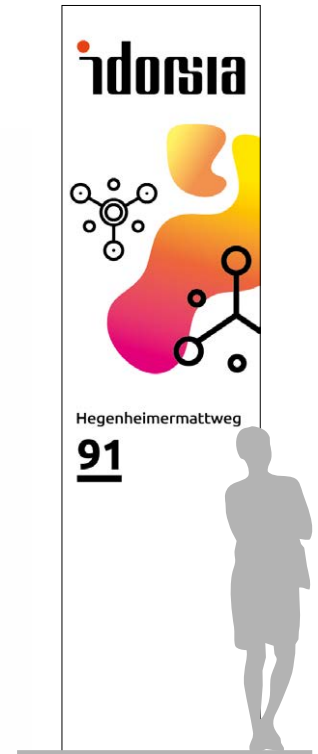
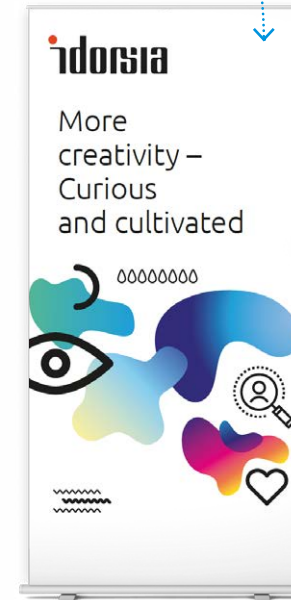
“When Idorsia was founded in 2017, we wanted to create a pharma brand that the world had not yet seen.”

**Jean-Paul Clozel**  
Co-founder and CEO of Idorsia

Joyful and scientific at once.



Intelligent principle: all visuals are derived from one super-visual.



Robust design, born digital.



Enabling both endless variations and high recognition.



# Be prepared for more

**Curious to learn more?  
Reach out to us.**

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