Business Report

idorsia

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 2020

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>900

Highly qualified professionals

12

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

Strong

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State-of-the-art laboratory workspaces

More science – Bursting with ideas

Idorsia is a high-potential biopharmaceutical company, with an experienced team of over 900 highly qualified professionals, a full R&D pipeline, state-of-the-art facilities, and a strong balance sheet – the ideal constellation for bringing successful medicines to the market.

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 specialized in the discovery and development of small molecules, with the aim of transforming the horizon of therapeutic options. We have a broad, diversified and balanced development pipeline, covering multiple therapeutic areas. Our clinical pipeline comprises 12 assets, 6 of which are in late-stage development. While we do not yet have any marketed products, we expect to see two product launches in major markets in the first half of 2022, subject to regulatory approval. With this in mind, we have built a commercial organization to bring our products to patients.

Idorsia is headed by Chief Executive Officer Jean-Paul Clozel; he and Chief Scientific Officer Martine Clozel (who co-founded Actelion) now hold almost 30% of Idorsia's shares.

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

in CHF millions, except EPS (CHF) and number of shares (millions)	2020	2019
Revenues	72	24
Operating expenses	(444)	(470)
Operating income (loss)	(372)	(446)
Net income (loss)	(392)	(448)
Basic EPS	(2.75)	(3.41)
Basic weighted average number of shares	142.8	131.2
Diluted EPS	(2.75)	(3.41)
Diluted weighted average number of shares	142.8	131.2

* 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 2020 Financial Report.

"2020 was an outstanding year for Idorsia. We will invest during 2021 to ensure commercial success of daridorexant in the US and clazosentan in Japan, both anticipated to launch in 2022, following market authorization. As a result, our spend will increase in 2021, with US GAAP operating expenses of around CHF 685 million and non-GAAP operating expenses of around CHF 640 million, both measures include an inventory build of around CHF 35 million and exclude unforeseen events."

André Muller
Executive Vice President, Chief Financial Officer

Milestones in 2020

Idorsia started the year with 12 compounds in development – 4 in the final stage before filing for marketing authorization. 2020 has been an incredible year for Idorsia – positive Phase 3 results, preparation of our first new drug application, and market preparation for our first products.

2020

March 2020
Janssen submitted a new drug application to the US FDA and a marketing authorization application to the EMA for ponesimod for the treatment of adults with relapsing multiple sclerosis*

* Idorsia and Janssen have a revenue-sharing agreement in respect of ponesimod

April 2020
Positive results in the first Phase 3 study of daridorexant, demonstrating improved overall sleep and daytime functioning of patients with insomnia

May 2020
Neurocrine Biosciences entered into a license agreement for the development and commercialization of Idorsia's novel T-type calcium channel blocker

May 2020
Successful offering of 11 million new shares secured CHF 330 million of funding to prepare for the launch of daridorexant and to develop our diversified pipeline

July 2020
Positive results of the second Phase 3 study with daridorexant in insomnia, confirming and reinforcing the efficacy and safety profile from the first pivotal study

July 2020
US commercial operations established, with leadership team in place to prepare for the launch of daridorexant

August 2020
Idorsia Japan confirmed daridorexant dose response in Japanese patients with insomnia – preparations for a local registration program underway

August 2020
Daridorexant Phase 3 results in insomnia presented at SLEEP 2020 – the world's largest meeting devoted entirely to clinical sleep medicine, and sleep and circadian research

September 2020
Syneos Health selected as commercialization partner to build the salesforce for the launch of daridorexant in the US

October 2020
Successful capital increase secured CHF 535 million of funding to prepare for the launch of daridorexant and to develop our diversified pipeline

November 2020
Positive results in the Japanese registration program for clazosentan, demonstrating a reduction in vasospasm-related morbidity and all-cause mortality

January 2021
New drug application for daridorexant submitted to the US FDA for the treatment of insomnia

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

Mathieu Simon
Chairman of the Board

Dear Shareholders

It is my great honor to write to you as Chairman of your company for the first time. I am only sorry that we have not yet had the opportunity to interact personally. Our virtual Annual General Meeting was just one of the many disruptions caused by the COVID-19 pandemic – a crisis which has impacted every area of our lives in 2020, bringing misery and hardship to countless millions. In our industry, COVID-19 has upended supply chains and clinical trial timelines, threatening longer waiting times for much-needed treatments.

Despite the devastation all around us, I am very proud and excited to report that Idorsia has not only weathered the storm this year, but gone from strength to strength.

Thanks to the investments made during Idorsia's first few years, our technology platforms are state-of-the-art and scalable. As a result, when the call went out for office-based staff to work from home and for those who need to work on-site to be protected, our workforce was able to transition seamlessly. Our laboratory-based staff willingly turned up every day, motivated to move the company forward.

The resilience and determination of our workforce contributed to an incredibly successful year: the company has delivered on every one of the ambitious goals set by the management and Board at the end of 2019. Jean-Paul Clozel's update on these achievements (see the CEO's letter) makes for very enjoyable reading. As you reflect

"Our workforce's resilience and determination contributed to an incredibly successful year."

Mathieu Simon
Chairman of the Board

on these successes, please bear in mind that it is very unusual for a clinical pipeline to advance so positively. For a young company to have so many innovative compounds – at a late stage of development, and in a wide variety of therapeutic areas – progressing as planned is, in itself, an impressive feat. For two of those compounds to achieve positive results and move towards regulatory submissions, in parallel, is outstanding. Accordingly, as you will see, the Board has recognized this performance through Idorsia's employee reward system.

As Chairman, I am well aware that positive results alone are not enough to ensure sustainable success. With several newcomers to the Board, we have undertaken a critical review of the company to make sure that all the appropriate checks and balances are in place. For me, this is another of the beauties of Idorsia: while the company is only a few years old, it has a rich heritage of over 20 years in pharma. A solid focus on science and quality, together with a strong governance framework, means that the company has sound foundations on which to build its success.

As a Board, we are committed to transparency on the topics that are important to you. This year, we initiated a dialogue to identify and prioritize what matters most to you, and these lines of communication will remain open. I look forward to developing our reporting on these important non-financial measures, in line with the company's development.

One result of the company's willingness to engage is the growth of our analyst base during 2020: 14 analysts are now covering Idorsia, reflecting the great interest in Idorsia's equity story. I personally believe that independent stock research is important in guiding investors and highlighting opportunities for long-term value creation.

Of course, if Idorsia is to become sustainable, we now need to bring our products to market and start generating revenue. The capital market funding we were able to access this year will take us a long way towards this goal. Thank you for your confidence in Idorsia – and stay tuned for the continued success of this dynamic company on the verge of great things!

Sincerely,

Mathieu Simon
Chairman of the Board

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

Jean-Paul Clozel
Chief Executive Officer

Dear Shareholders

I want to begin by recognizing that, while Idorsia has had a very successful year, 2020 was extremely difficult for many people. No doubt some of you will have been seriously affected by the COVID-19 pandemic, and to you I extend my sincere sympathy.

This year, the public has gained a new appreciation of the efforts of all frontline healthcare workers, and also of the mission that drives everyone in the pharma world – finding medicines to prevent or treat illness. Let us hope that the vaccines developed in record time can help the world return to some semblance of normality. I myself am very proud to be a member of this industry, and to see how our efforts in research are helping patients.

In spite of the pandemic, the company has made great strides this year. Our employees achieved every one of the ambitious key goals set for 2020 – and much else besides. Their performance was simply phenomenal. In the development of new medicines, hard work does not always guarantee good results, which makes it all the more rewarding when our efforts are crowned with success.

"I am very proud of all that has been accomplished at Idorsia in 2020."

Jean-Paul Clozel
Chief Executive Officer

Revolutionizing the field of insomnia

Our review of the progress made in 2020 must start with the outstanding results achieved with daridorexant. The Phase 3 registration program demonstrated statistically significant and clinically meaningful improvements in sleep maintenance, sleep onset, total sleep time and daytime functioning, which were sustained over time. Daridorexant was well tolerated, with a favorable safety profile in adult and elderly patients.

Particularly important, as well as efficacy during the night, are the effects seen during the day. While a negative impact on daytime functioning is part of the definition of insomnia, not one of the treatments currently available have rigorously assessed their effect on this key aspect of the condition. Here, in fact, most therapies have a negative impact – especially first thing in the morning, when patients may feel hangover effects of their medication.

For the millions of people suffering from insomnia, daridorexant is an absolute gamechanger, whose excellent benefit and safety profile will encourage patients to seek treatment.

It is important to recognize that these gratifying results were no accident. They are a direct result of our efforts to design a dual orexin receptor antagonist (DORA) with the properties required to deliver all the benefits of a good night's sleep. For more details, I invite you to read the interview with Martine Clozel on page 30.

The team responsible worked tirelessly to evaluate the huge amount of data generated and to present the results appropriately for regulatory agencies. A new drug application was submitted to the FDA in January 2021, and the submission to the European authorities will follow shortly. In anticipation of regulatory approval, the commercial team is now working flat out to prepare for the launch.

Perseverance finally paying off

Our efforts to design the perfect DORA began in our labs as long ago as 1998, but our work with clazosentan goes back even further. This year, the Japanese studies of clazosentan for patients suffering cerebral vasospasm following aneurysmal subarachnoid hemorrhage also demonstrated excellent efficacy results, without any unexpected safety findings (for more information on clazosentan, see pages 52 to 57). I am truly delighted to finally have the evidence that clazosentan can improve outcomes for these patients – often young adults with so much life left to live. These results give the commercial team even more to get their teeth into. The impressive data has renewed the enthusiasm of the whole REACT team to complete the global study of clazosentan as soon as possible, so that patients around the world can benefit.

More to come from the pipeline

Thanks to the development group's speedy response to the COVID-19 pandemic, our ongoing late-stage studies were able to continue, and risk mitigation procedures were agreed with global health authorities.

Recruitment for both the CARE study (cenerimod) and the MODIFY study (lucerastat) was affected, but following some adjustments, in consultation with health authorities, patient enrollment was adapted. Accordingly, we should see the results of CARE and be able to plan for Phase 3 development of cenerimod by the end of 2021, and the results of MODIFY – the Phase 3 registration study for lucerastat – should also be available in the second half of 2021.

In addition, again despite the impact of the pandemic, recruitment for the PRECISION (aprocitentan) study accelerated, with randomization now expected to be completed by mid-2021.

As well as the conclusion of studies, 2021 will also see the initiation of a very exciting study. Under a Special Protocol Assessment (SPA) agreed with the FDA in 2020, a 14,000 patient Phase 3 study will be commenced with selatogrel – a drug-device product for patients with suspected heart attack. The investigation of selatogrel has been designated as a "fast-track" development program, indicating the FDA's interest in this innovative approach. Patients themselves will play a crucial role in the preparations for this study, as they need to be trained to identify symptoms and self-administer treatment. The potential implications for future heart attack patients are enormous, and I look forward to sharing more details in due course.

Taking our innovation to the patient

Work on building our commercial capabilities began in 2019, and we continued to fill key strategic roles on the global team in 2020. We also established our US commercial organization, securing premises and – most importantly – a leadership team. This is a very exciting development for Idorsia, and I am proud to have such an experienced and talented group of professionals on board.

Following the positive results achieved with daridorexant, a tremendous amount of work has been done to prepare for the US launch of this product in 2022 – not least, engaging Syneos Health as the ideal partner to reach the large US primary care market. In addition, after the excellent results with clazosentan, the Japanese team is also gearing up for our first product launch in Japan.

Major shareholders	(as of December 31, 2020)
Jean-Paul and Martine Clozel	29.15%
Rudolf Maag	5.40%
FMR LLC	3.51%
Artisan Partners	3.07%

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

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

Key share data	(as of December 31, 2020)
Shares outstanding	166.5 million
Closing share price	CHF 25.52
Market capitalization	CHF 4.2 billion
52-week high	CHF 33.88
52-week low	CHF 18.69
YTD price change	CHF -4.42 (-14.76%)
Annual average daily volume	603,126 shares
Free float	109.0 million shares

With two product launches in preparation, we have also been building our global supply chain function, to ensure consistent supplies of our innovative medicines to patients. More information on our preparations can be found in the interview with Chief Commercial Officer Simon Jose on page 22.

Ongoing innovation

We have always had a long-term focus for Idorsia, setting ourselves the goal of becoming a fully-fledged biopharmaceutical company, innovating from bench to bedside. As our late-stage pipeline starts to bear fruit, it is essential that we keep the pipeline supplied with fresh innovation for sustainable success. As our Chairman emphasized, work in our laboratories continued unabated in 2020, and there is much to show for it. Progress was made with our early-stage clinical pipeline, and we advanced a new CNS compound into clinical pharmacology studies. On the preclinical front, four compounds were selected as preclinical candidates. These advances in our discovery efforts made during lockdown are a testament to our researchers' commitment and dedication.

Financing our future

Through a series of financing activities in 2020, we have secured additional funding of more than CHF 865 million. Our strengthened balance sheet with CHF 1.2 billion liquidity will take us through to the next inflection points – namely, key clinical data from late-stage assets and the launch of our first product, daridorexant. As you may be aware, Martine and I have participated in each of the capital increases, believing more than ever in Idorsia and in the value that can be created for patients, employees and shareholders alike.

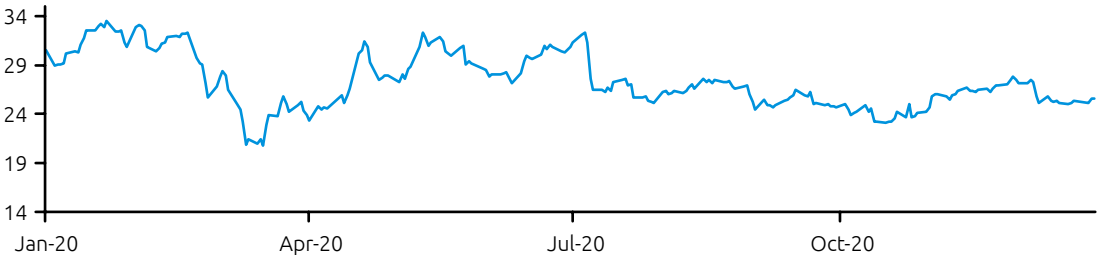
I am very proud of all that has been accomplished at Idorsia in 2020. 2021 will be an extremely exciting year for our growing company, and I look forward to keeping you updated on our progress throughout the year. I would also like to thank you for your confidence in Idorsia.

Warmest regards,

Jean-Paul Clozel
CEO

Share price development

(in CHF)



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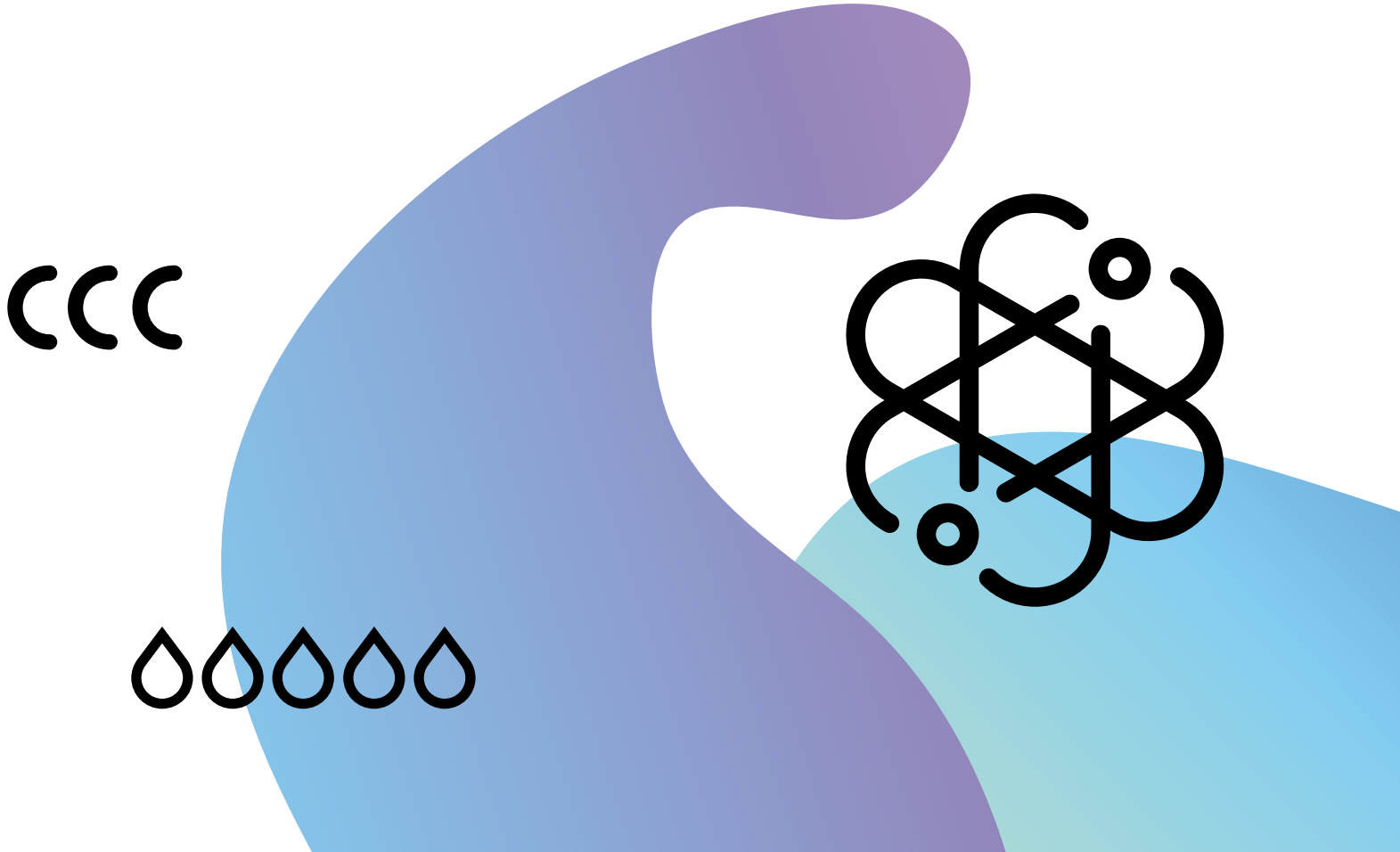
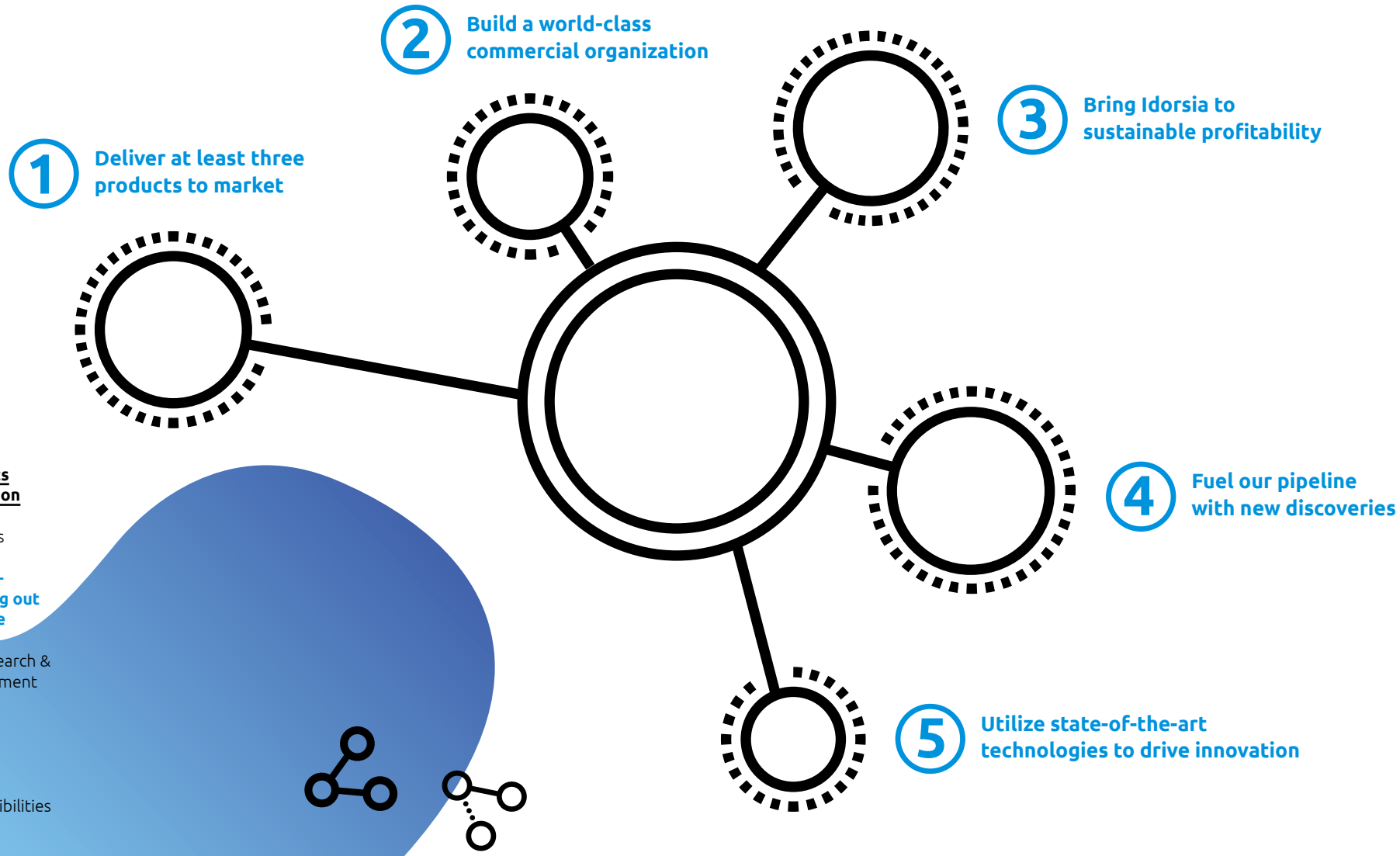
Our strategic priorities

We will develop Idorsia into one of Europe's leading biopharmaceutical companies, with a strong scientific core. We have identified five key strategic priorities to ensure the company's success in the medium term.



More energy – Growing and delivering



Deliver at least three products to market

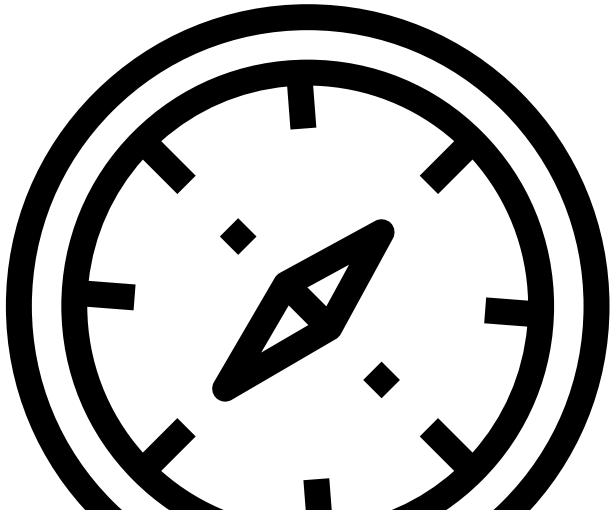
1

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 12 compounds, including 6 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 aim to bring at least three products to the market in the medium term. Our late-stage pipeline is described in detail in the "Research & Development" section of this report (from page 26).



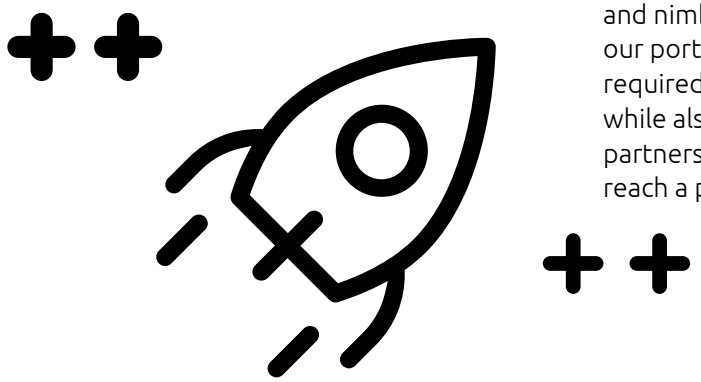
Build a world-class commercial organization

2

In order to bring pioneering therapies to patients and to maximize the value of our innovations, we plan to continue building and integrating our global commercial organization.

We will take a simple, efficient approach to preparing product launches, utilizing shared, best-in-class platforms and ways of working that enable fast decision-making and cost-effective growth. We will focus on transforming treatment in underserved markets, such as insomnia, and building new markets, such as cerebral vasospasm, 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, building the core capabilities required to successfully launch our products, while also being prepared to enter into partnerships where we need support to reach a primary care market.

We have established commercial operations in the US and Japan, 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.



Bring Idorsia to sustainable profitability

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

We believe that we have the potential to generate significant revenues from product sales, once the first of our development compounds has received regulatory approval.

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

While building up our commercial operations and developing our late-stage clinical pipeline so as to bring innovative therapies to patients, we also continue to discover new compounds.

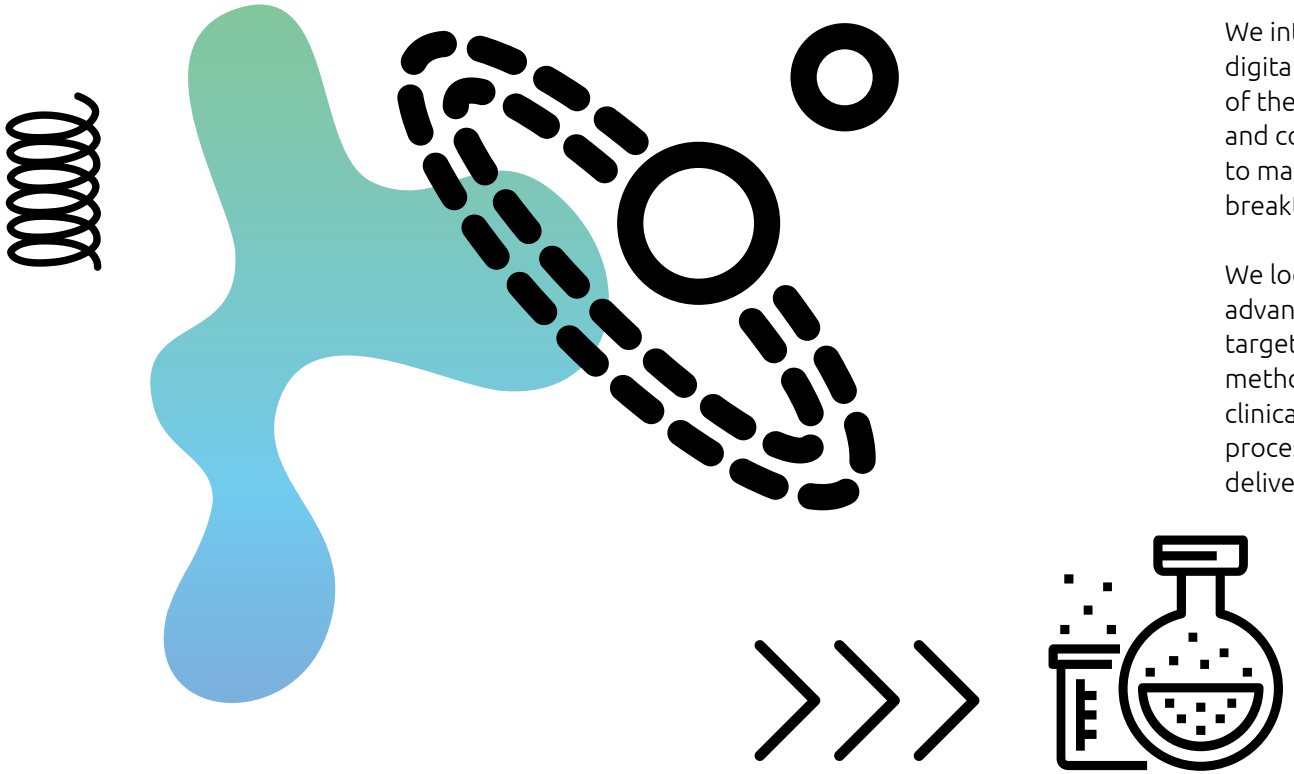
In addition to several drug candidates in the early stages of clinical and preclinical development, we must continue with our discovery efforts, to maintain a steady supply of innovative compounds to our pipeline. We aim to create a pipeline with a sales potential of at least CHF 5 billion.

Achieving this 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.

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

5

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 of the drug discovery, clinical and pharmaceutical development processes are streamlined to assist in the delivery of tailored, high-quality medicines.

Gearing up to launch

Simon Jose, Idorsia's Chief Commercial Officer, leads our commercial operations at the region and country levels as well as global product strategy, medical affairs and supply chain. Simon and his team bring deep experience in successfully launching new products across a wide range of therapeutic areas and geographies.

From compounds to commercialization

"We are confident that, with such a wealth of evidence, we can make this unique, non-sedating sleep medication a huge success, and we are excited by the opportunity to lead the transformation and modernization of the sleep market."

Simon Jose
Chief Commercial Officer

Q **As you build Idorsia's commercial organization, what are you most excited about?**

A I'm very excited about the unique opportunity we have at Idorsia to build a commercial organization from the ground up and bring to market multiple innovative products in areas ranging from insomnia to aSAH. Given the remarkable breadth and depth of our late-stage pipeline, we have the potential to transform treatment in multiple disease areas and in doing so create a sustainable mid-sized pharma company based on innovation.

We are now moving full speed ahead to prepare to launch two very different products in the first half of 2022 in two major markets – daridorexant in the US and clazosentan in Japan. It's this type of challenge we're excited about, and we've made huge progress in 2020.

Q **As you focus on successful launches for these products, what are the must-win priorities for your team?**

A There is no doubt that the launch of daridorexant is the number one focus for us – and will remain so over the next few years. Our ambition is to lead the transformation and modernization of the sleep market, and leadership requires a long-term commitment. With over 20 years' experience researching sleep, and orexins in particular, we have built deep scientific expertise in sleep and insomnia, and have developed daridorexant, a product born out of that science. (See the interview with Martine Clozel on page 30.)

We will continue to engage with the medical community and other key stakeholders to advance the science of sleep and raise awareness about the burden of insomnia on patients' daily lives and the need for new safe and effective treatment options.

I'm confident that we have the right ingredients to lead in sleep – a differentiated product profile, strong commitment from our leadership, and deep scientific expertise. For Idorsia, changing sleep will be at the heart of what we do for years to come.

Q **What are you doing now to prepare for a successful US launch of daridorexant?**

A We've made enormous progress in building our US team in 2020. Under the leadership of Patty Torr, President of Idorsia US, we have established our US headquarters in Radnor, a suburb of Philadelphia, and brought on board a talented and experienced leadership team that is already making strides in preparing the US market for the launch of daridorexant.

As announced in August 2020, we have finalized an innovative, revenue-driven agreement with Syneos Health to launch daridorexant in the US and reach the primary care market that accounts for the majority of insomnia prescriptions. In addition, the team is preparing our plans to engage with the medical community, payors and patients, who play a critical role in seeking solutions for their insomnia.

The US team has also prioritized fulfilling governance requirements for US operations, including staffing key enabling functions and forming a Compliance Committee to ensure appropriate oversight of our medical and commercial activities.

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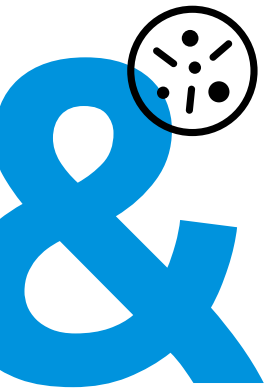


"It is so fulfilling to work on a product which has the potential to prevent the devastating outcomes faced by patients with cerebral vasospasm."

Simon Jose
Chief Commercial Officer

Q Turning to the second launch you're preparing for, how is a Swiss company – with a big US launch in the works – going to be successful in Japan?

A While it's true that these markets are very different, I believe we are well positioned for success. It starts with an innovative asset, clazosentan, and the impressive data from our Japanese registration program, announced in November 2020. Next, we have the strong leadership of Satoshi Tanaka, President of Idorsia Japan, and his established team with deep expertise in aSAH and cerebral vasospasm. The team is already developing a focused launch plan, establishing our local commercial infrastructure and engaging with the neurosurgeons and other intensive care specialists who treat patients with aSAH. The incidence of aSAH in Japan is at least twice as high as in other countries around the world. This well-understood and significant medical need, together with the excellent efficacy and safety data, gives us confidence that we can successfully launch clazosentan in Japan.

It is so fulfilling to work on a product which has the potential to prevent the devastating outcomes faced by patients with cerebral vasospasm. Clazosentan could be a gamechanger for aSAH patients and their treatment teams.

Q Do you have any plans for product launches in Europe?

A Yes, absolutely! We have already appointed Jean-Yves Chatelan to head up Region Europe and Canada, and we plan for daridorexant to be Idorsia's first European launch. As in the US market, Europe also has a high prevalence of insomnia and significant unmet need for new safe and effective treatments. As a result, we believe that there is an exciting opportunity for daridorexant in Europe. What's more, we would be the first company to bring a dual orexin receptor antagonist (DORA) to insomnia patients in Europe. Of course, there is a very different payor environment in Europe, and different approaches to insomnia treatment across countries, so we will need well-thought-out, country-specific strategies. This will be job number one for our new Head of Europe and Canada commercial operations.

Q **With experienced and empowered country-based teams, what role does the global commercial organization play?**

A As a lean and cost-conscious biopharma, we need to keep the right balance between global and market-based resources. The way I see it, the global team leads the development of the overall product strategies, including the medical affairs, marketing, and market access components, by working with our scientists and clinical experts. Together with major markets, particularly the US, they shape the product strategy to align it with the deep scientific understanding we have built during the discovery and development phases.

The global product strategy then gives the countries a head start – which they can then adapt to meet the particular needs of their markets. For example, the global team provides patient insights, global branding, real-world evidence, common systems, and efficient and compliant decision-making processes. The countries are responsible for customer relationships and local execution of the strategy. With my team's extensive experience in launching products at both the global and market levels, we know that this is the optimal set-up to help the countries move quickly without getting in their way.

Q **COVID-19 has highlighted the importance and challenges of ensuring product supply. How are you preparing Idorsia's supply chain to support the up-coming launches?**

A One of our 2020 company goals was to establish a robust global supply chain function and I'm pleased with the progress we have made building this core capability.

Our supply strategy relies on contract manufacturing organizations (CMOs) to manufacture our products, while our internal team leads a range of activities that include Sales & Operations Planning (S&OP), sourcing, logistics, procurement, quality control and systems. Given the long lead times for drug substance production, ramping up our supply chain for commercial launch will require investments in 2021; however, this is critical to ensure that we will be ready to meet the anticipated high demand for daridorexant and clazosentan at the time of launch.

Q **Can you give us a preview of your plans for the commercial organization in 2021?**

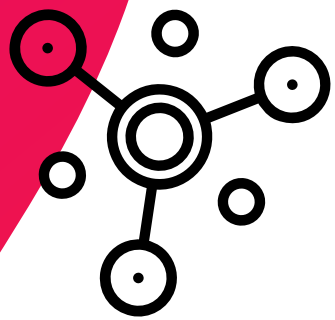
A There is no question of our priorities for 2021. We will be laser-focused on our two important launches expected in the first half of 2022. Given the size and complexity of the US primary care market, preparing for a flawless daridorexant launch will be our number one priority, followed closely by ramping up for the clazosentan launch in Japan.

Not so long ago, Idorsia was founded with the purpose of bringing more innovative medicines to patients, and we are on the cusp of doing just that. There is now so much to be optimistic about as we head into this final pre-launch phase!

Our Research & Development

More knowledge – Powered by science

At Idorsia, our drug discovery focuses on families of proteins, which are characterized by the way they work.



"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

We strive to identify innovative programs involving proteins which have not been targeted up to now, to discover drugs with novel mechanisms of action.

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 a beneficial effect for patients. To see whether we can affect the protein's activity, we first need to be able to measure it.

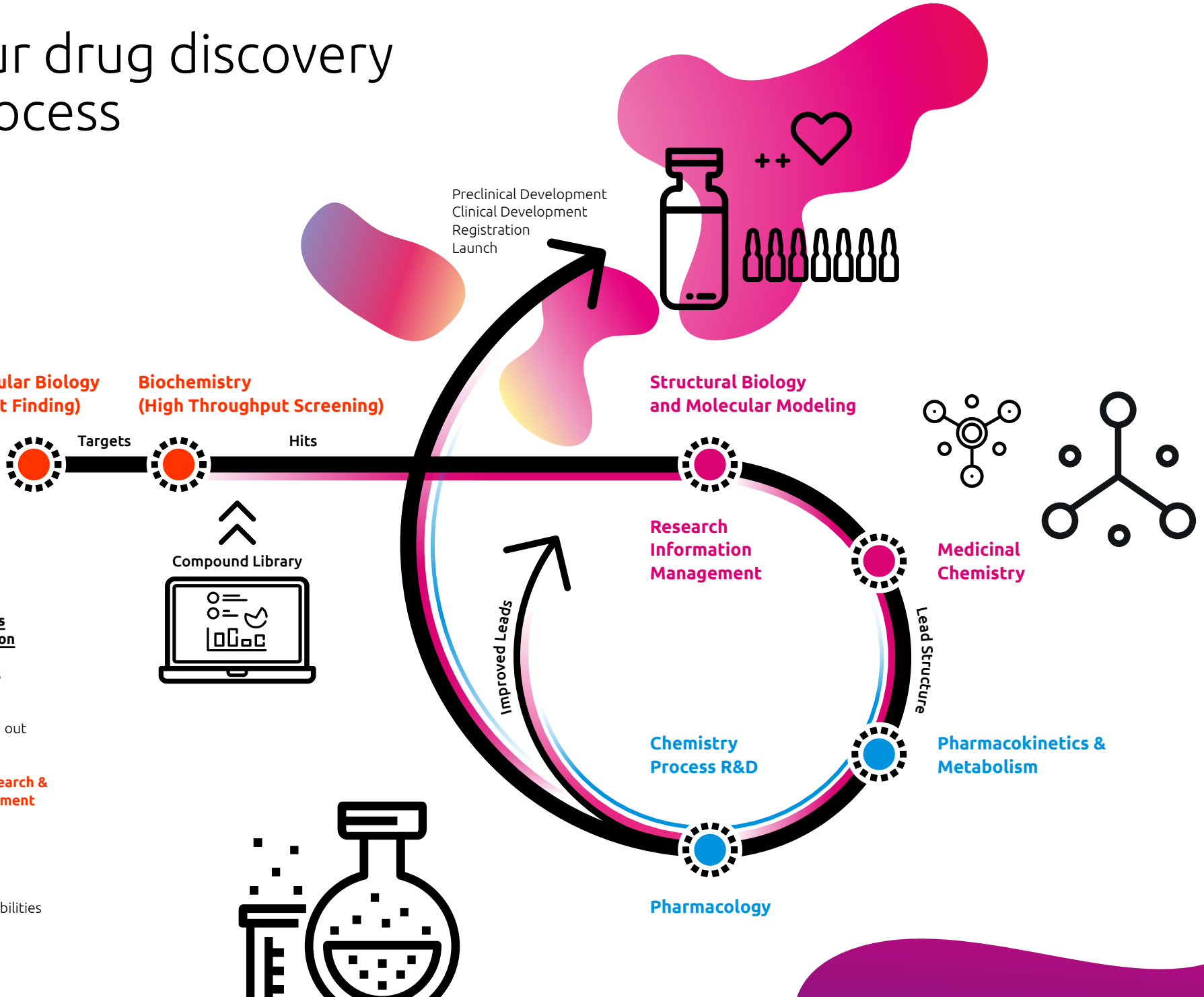
We produce, or "express", the target in large quantities and measure its natural activity in assays. The assay needs to be sensitive, accurate and highly reliable. Plus, in order to perform hundreds of thousands of measurements, it needs to be automated, using robotic equipment.

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 can then 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 of compounds on the target, in the hope that one of them 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.

Our drug discovery process



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.

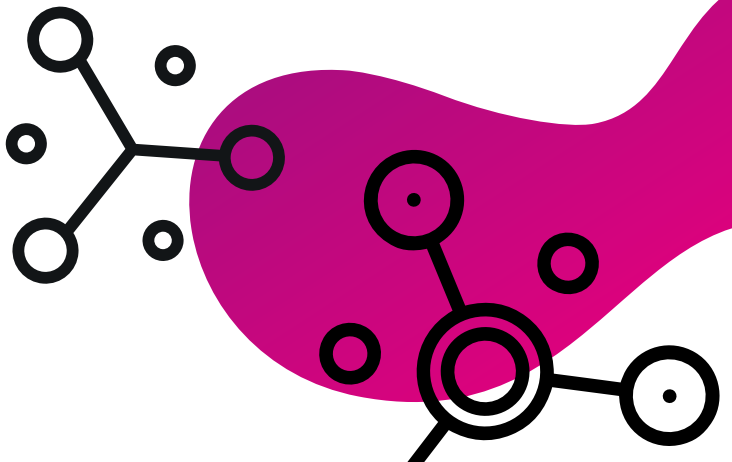
It's no good having a potent compound which gets destroyed by the body before it has a chance to do its job. Our formulation specialists take a compound which has been optimized by the chemists and ask how it can best be delivered to the patient. One way to protect the compound, for example, is to package it in a capsule; alternatively, it may be better to develop an injectable form.

Once reproducible processes to produce large quantities of the active compound and the formulated drug product are elaborated, our technical project teams manage the production of the drug with partner companies. They secure the drug supply for clinical development and beyond.

For Idorsia, the process which begins with drug discovery and preclinical development ends, we hope, with a novel molecule that will help patients in diseases with a high unmet medical need.

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

Corinna Grisostomi
Senior Scientist



Better night, better day – by design!

Martine Clozel
Executive Vice President,
Chief Scientific Officer

As Idorsia's Chief Scientific Officer, Martine Clozel has been a driving force behind the discovery and development of daridorexant, our investigational therapy for the treatment of insomnia (for more details, see page 38). But the story of daridorexant began more than 20 years ago – well before the foundation of Idorsia. Martine and a dedicated research group embarked upon the study of orexins almost as soon as orexin was first identified, and that rapidly led to the science of sleep. This interview reveals how our research and the acquired knowledge of the orexin system enabled Idorsia to find a treatment which, we believe, will transform the lives of patients suffering from insomnia.

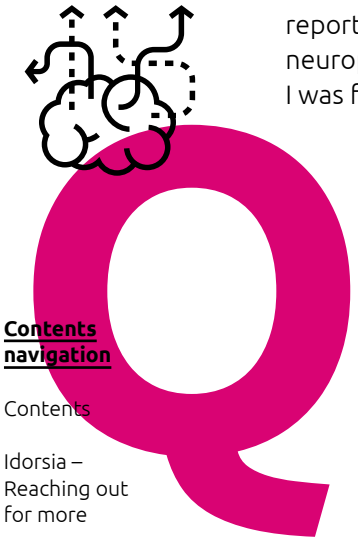
Q **Researchers at Idorsia have a strong track record in rare diseases. What was the trigger for your work on insomnia?**

A The truth is that, at first, we didn't know we were studying sleep! We followed where the science led us, which has always been our approach to drug discovery.

Our journey began when I invited Masashi Yanagisawa – the researcher who first discovered endothelin and a "friendly competitor" in the field of endothelin research – to the labs we were just building at Actelion. He told me about a paper he was about to publish in the journal *Cell*[1], reporting the discovery of a new family of neuropeptides that he was calling orexins. I was fascinated!

The receptors for orexins are so-called G-protein coupled receptors, a preferred family of targets for our drug discovery efforts. We had all the technologies we needed to initiate a drug discovery program focused on orexin receptors, so we hit the ground running.

As soon as we were able to generate antagonists as tools to block the orexin receptors, we discovered that in rats, dual orexin receptor antagonists (DORAs) induced sleep. That changed everything. We were now in the field of sleep and insomnia.



How did that work lead you to daridorexant?

A The team's early work led us to an important conclusion, which remains valid today, more than 20 years later: the orexin system plays a fundamental role in arousal and wakefulness and its blockade by a DORA offers the best hope of inducing a natural sleep for patients with insomnia.

The drug discovery group set about characterizing the effects of DORAs on sleep and selected a compound for clinical development, which would later be known as almorexant. In 2007, we published a paper in *Nature Medicine*[2], which presented the results of this groundbreaking research – "Promotion of sleep by targeting the orexin system in rats, dogs and humans".

Although almorexant trials were stopped because of a particular drug-drug interaction which could not be overcome, it was the first DORA to be studied in humans, and we gained a deep understanding of the orexin system and the science of sleep as a result.

Q **Judging by the results achieved with daridorexant, you obviously did not give up. What drove you to keep going when other, much bigger players had joined the race?**

A You must remember that, until this new class of insomnia medicines was discovered, no significant progress had been made in the treatment of insomnia for many years, and patients have suffered from the side effects of the older classes of insomnia drugs.

Our initial experience and the evidence of efficacy that we had generated convinced us that DORA offered an amazing potential in insomnia and that we needed to pursue our research and discover a next-generation DORA.

1. Cell. 1998, 92(4):573–85
2. Nat Med. 2007, 13(2):150–5

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Idorsia – Reaching out for more

> **Our Research & Development**

Our People

Our Responsibilities

Q What criteria were defined to determine the optimal candidate?

A We needed a compound that would be potent and specific for the two orexin receptors, both to avoid off-target activity and to support the safety profile required for a compound which could be used by many patients. We wanted a molecule which would have a rapid absorption, to help the patient get to sleep quickly, and a duration of action long enough to cover a full night's sleep, but most importantly short enough to avoid negative hangover effects the next morning.

Q How did you design daridorexant to be a better insomnia treatment?

A It has not been easy! We synthesized and tested more than 25,000 compounds in pursuit of the ideal drug. We narrowed down the candidates through a variety of screening and optimization techniques, filtering out any compounds that did not meet our high expectations. In particular, we developed a computer model using animal and human data, including the data for almorexant, to predict the human pharmacokinetic behavior that we could expect from our candidates.

We began the development of daridorexant in 2015 and the results have surpassed even our high expectations! Daridorexant has demonstrated an improvement in objective and subjective sleep measures – almost one hour more sleep, as reported by the patients! – without causing next-morning residual effect, and for the first time daytime functioning is improved. Plus, all this is achieved with an excellent tolerability and safety profile.

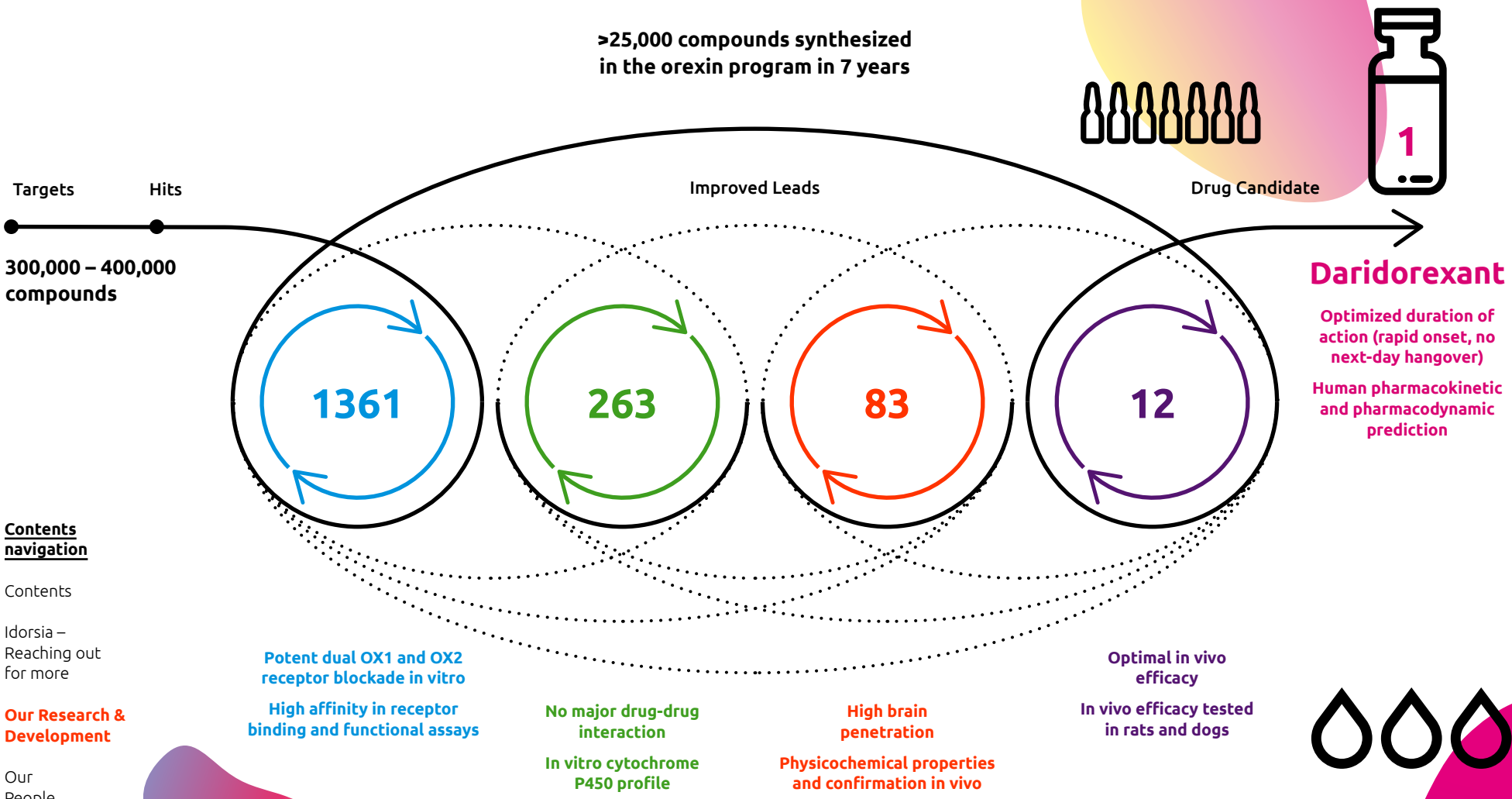
Q The insomnia market is a tough one to crack. Why are you so confident that daridorexant will be a game-changer in insomnia?

A As a research scientist and physician, I believe in evidence-based medicine, and I look at what the data tell us. The results we've seen have rewarded the drug discovery group for the many additional years of work they have put in. Our clinical group designed a development program which placed the needs of patients at the center of the investigation. The team developed and validated tools to establish patient-reported outcomes, particularly for daytime functioning, which is a serious medical need for patients suffering from insomnia.

When we were designing daridorexant, we made assumptions in the lab about what kind of therapy would have meaningful effects for patients. What's so rewarding is that our patients have now confirmed, not only that daridorexant is delivering on the characteristics we designed into the drug, but that those were the qualities which really mattered to them.

With Simon Jose and his growing team of experts, we are handing our baby into safe hands. Science is also at the core of our commercial team's work, making them the ideal steward for the next phase of this exciting journey. They will help both physicians and people suffering from insomnia to understand the benefits that daridorexant brings – better sleep *and* better daytime functioning.

Daridorexant optimization process



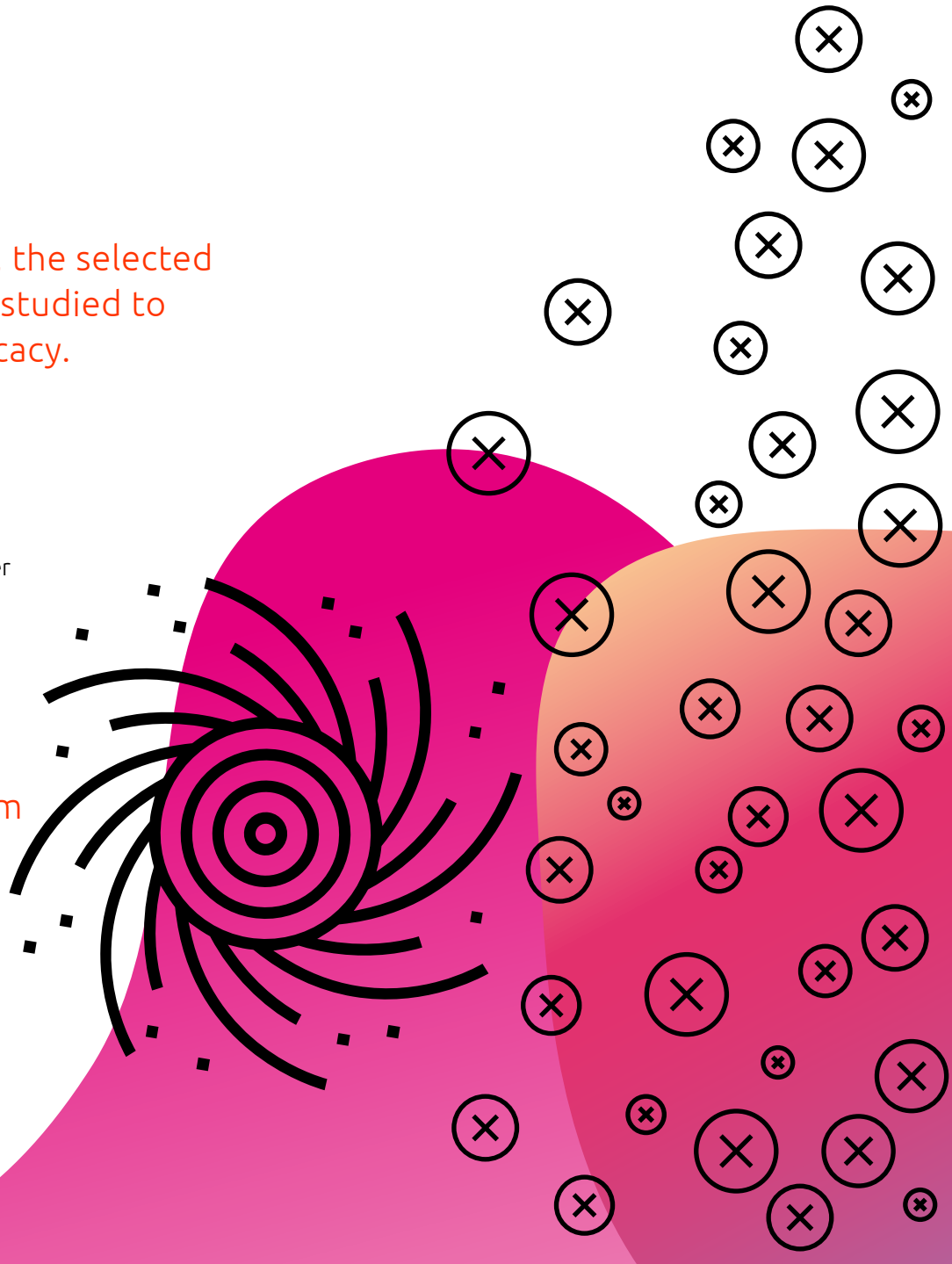
More molecules – For a better future

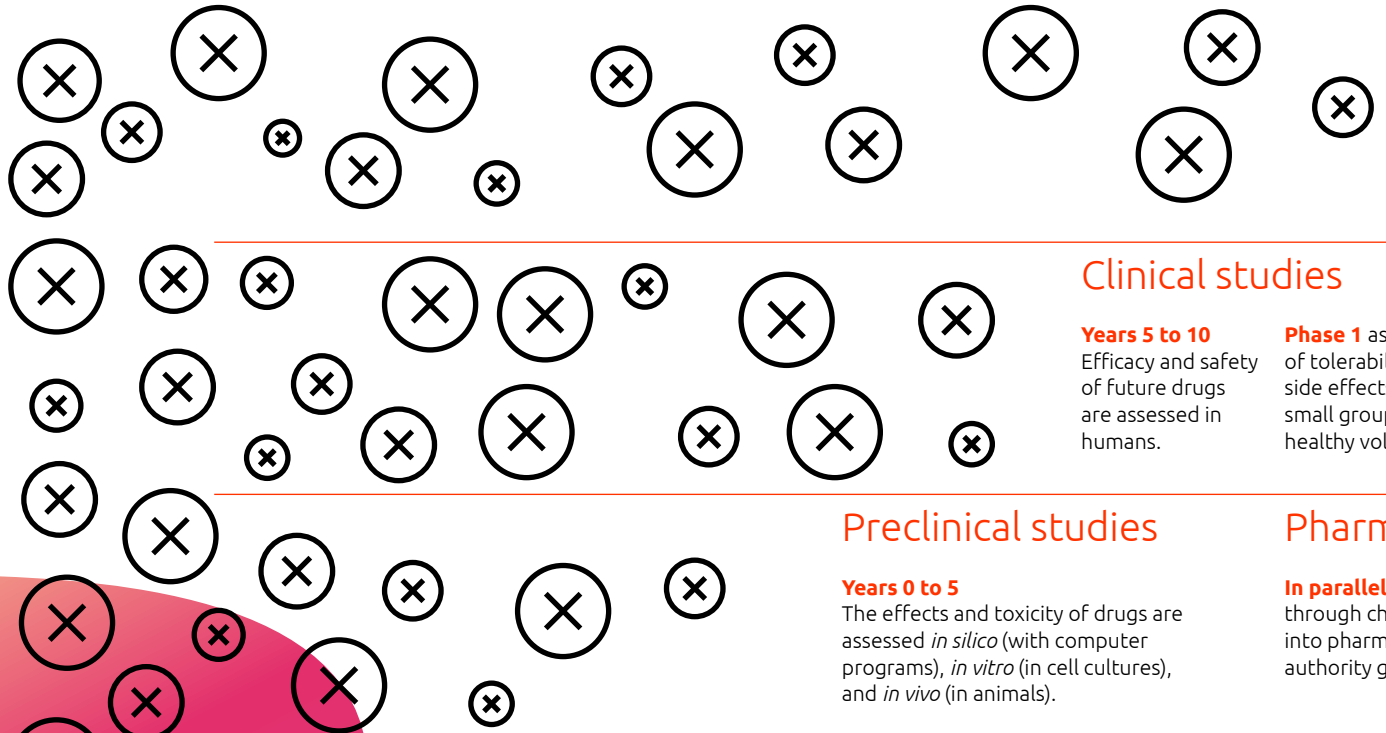
Following the drug discovery phase, the selected molecule must be comprehensively studied to demonstrate clinical safety and efficacy.

Idorsia aims to deliver new products with the potential to significantly change the treatment options in their 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, Head of Global Clinical Development





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 approval.

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.

Preclinical studies

Years 0 to 5
The effects and toxicity of drugs are assessed *in silico* (with computer programs), *in vitro* (in cell cultures), and *in vivo* (in animals).

Pharmaceutical development

In parallel research-grade molecules are transformed through chemical and pharmaceutical development into 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!

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.

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

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 certain patients are resistant to treatment."

Martine Clozel
Executive Vice President, Chief Scientific Officer

Clinical development pipeline

Systemic lupus erythematosus

Cenerimod
$S1P_1$ receptor modulator
Status: Phase 2b

Suspected acute myocardial infarction

Selatogrel
$P2Y_{12}$ receptor antagonist
Status: Phase 3 in preparation

Fabry disease

Lucerastat
Glucosylceramide synthase inhibitor
Status: Phase 3

Resistant hypertension management

Aprocitentan*
Dual endothelin receptor antagonist
Status: Phase 3

Insomnia

Daridorexant
Dual orexin receptor antagonist
Status: NDA submitted, MAA in preparation

Vasospasm associated with aneurysmal subarachnoid hemorrhage

Clazosentan
Selective endothelin (ET_A) receptor antagonist
Status Global: Phase 3
Status Japan: Filing in preparation

Binge eating disorder

ACT-539313
Selective orexin 1 receptor antagonist
Status: Phase 2

Rare lysosomal storage disorders

Sinbaglustat
GBA2/GCS inhibitor
Status: Phase 1 complete

Immunology

ACT-1004-1239
CXCR7 antagonist
Status: Phase 1

Immunology

ACT-1014-6470
Status: Phase 1

CNS

ACT-541478
Status: Phase 1

Immunology

ACT-777991
Status: Phase 1

Rare pediatric epilepsy

ACT-709478
Novel T-type calcium channel blocker
Status: Phase 2

Neurocrine Biosciences has a global license to develop and commercialize Idorsia's ACT-709478

* In collaboration with Janssen Biotech, Inc.

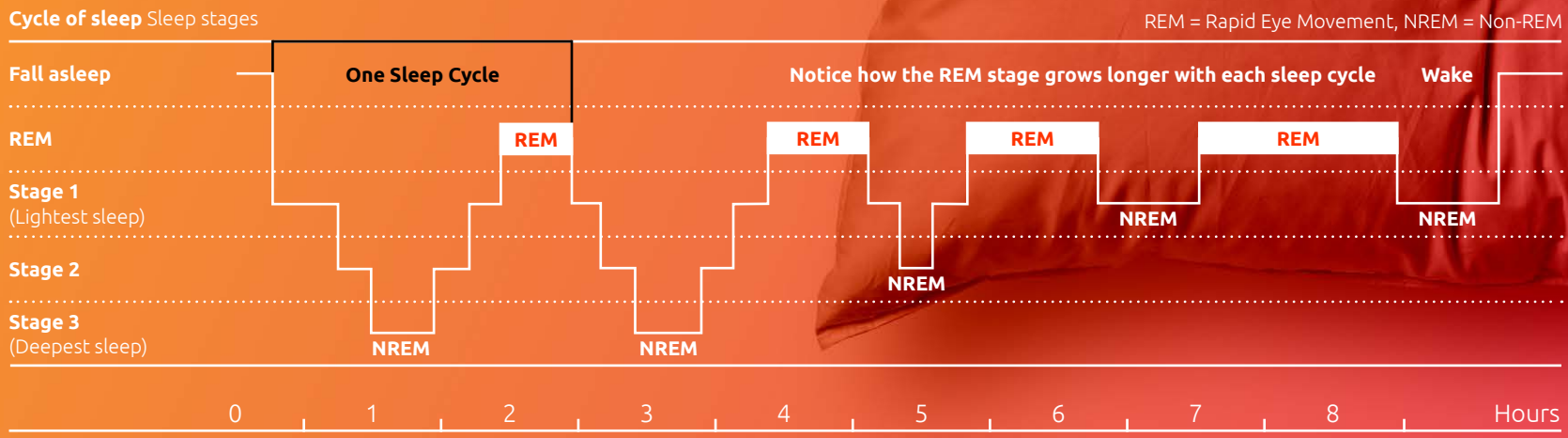
Status: January 2021

Daridorexant for insomnia

Insomnia is a condition of overactive wake signaling which can have a profound effect on the lives of patients. Insomnia can be defined as difficulty falling asleep and/or staying asleep, occurring at least three times a week for a minimum of three months.

Insomnia as a disorder is quite different from a brief period of poor sleep, and it can take its toll on both physical and mental health. It is a persistent condition with a negative impact on daytime functioning. 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.

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



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

10 %

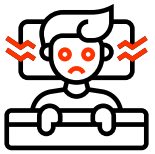
"It really annoys me when people say 'if you were really tired, you would sleep'. If only it were that simple! Unless you have suffered from true insomnia, you have absolutely no idea what it's like."

Patient with insomnia

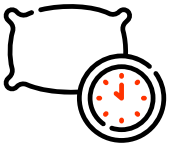
Sleep architecture

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).



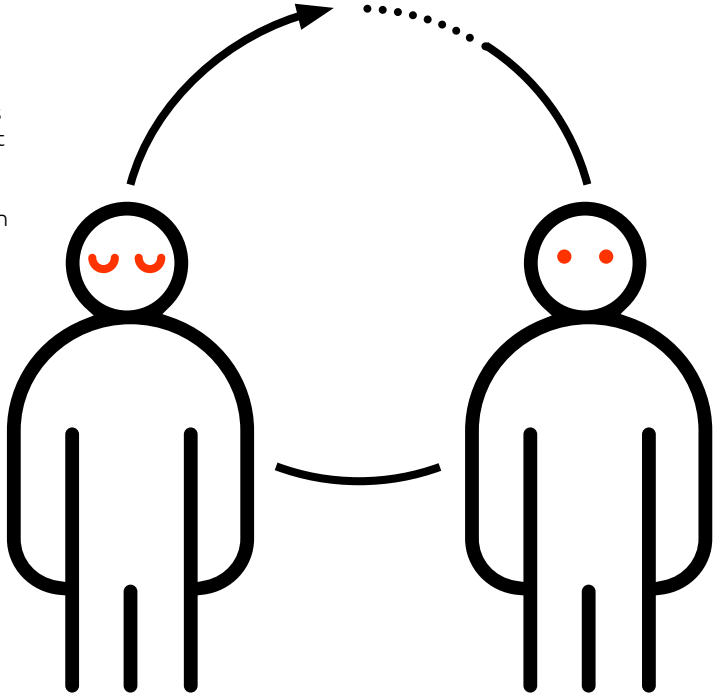
Studies have shown that lack of slow wave (stage 3) sleep is associated with cognitive and other health-related issues.



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 adverse events and 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. 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, current agents are perceived to be either somewhat 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. In addition, most patients suffer from sleep-onset and maintenance problems, and existing sleep agents do not adequately treat both of these problems. Furthermore, while a negative impact on daytime functioning is part of the definition of insomnia, none of the treatments currently available have rigorously assessed their effect on this key aspect of the condition.

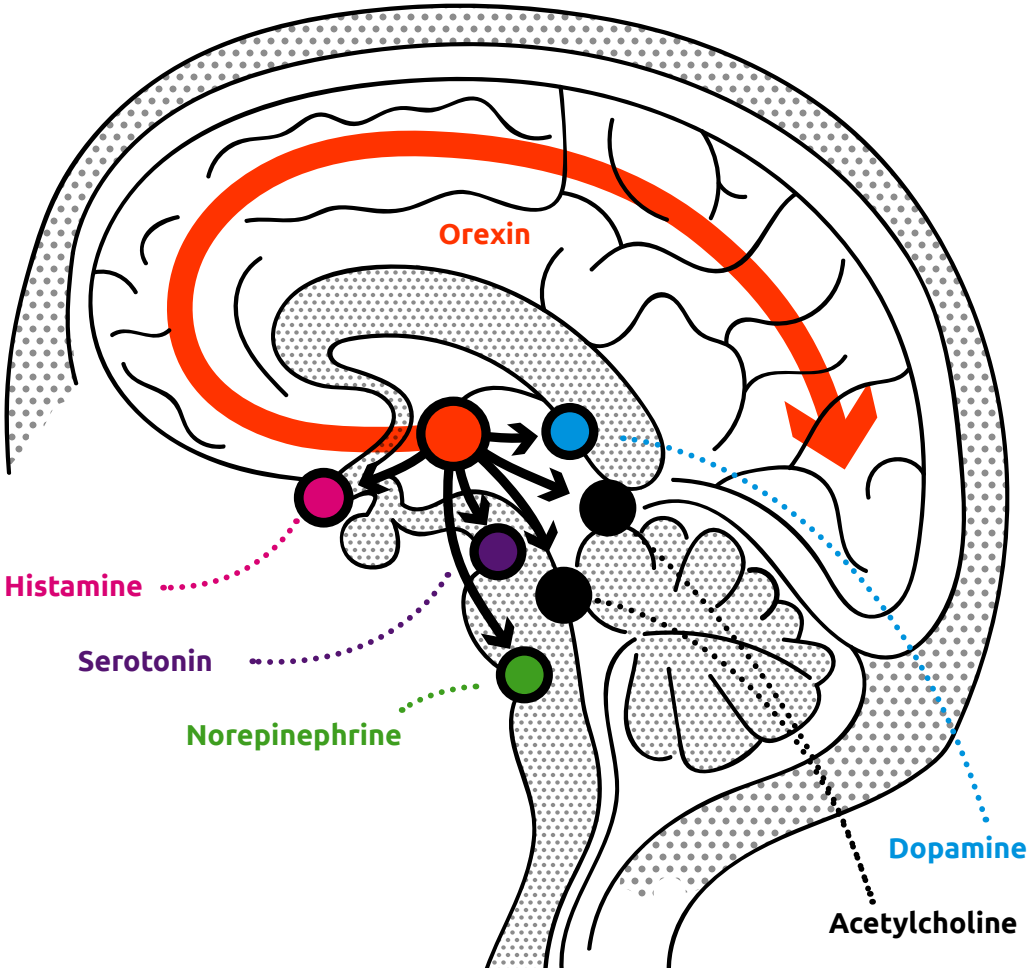
The orexin system

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.

There are two forms of orexin neuropeptides – small protein-like molecules used by nerve cells (neurons) to communicate with each other in the brain – orexin A and orexin B. Orexin promotes wakefulness through its 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. Overactivity of the wake system is an important driver of insomnia.

The orexin system is crucial for the regulation of wakefulness

Orexin stimulates many wake-promoting pathways

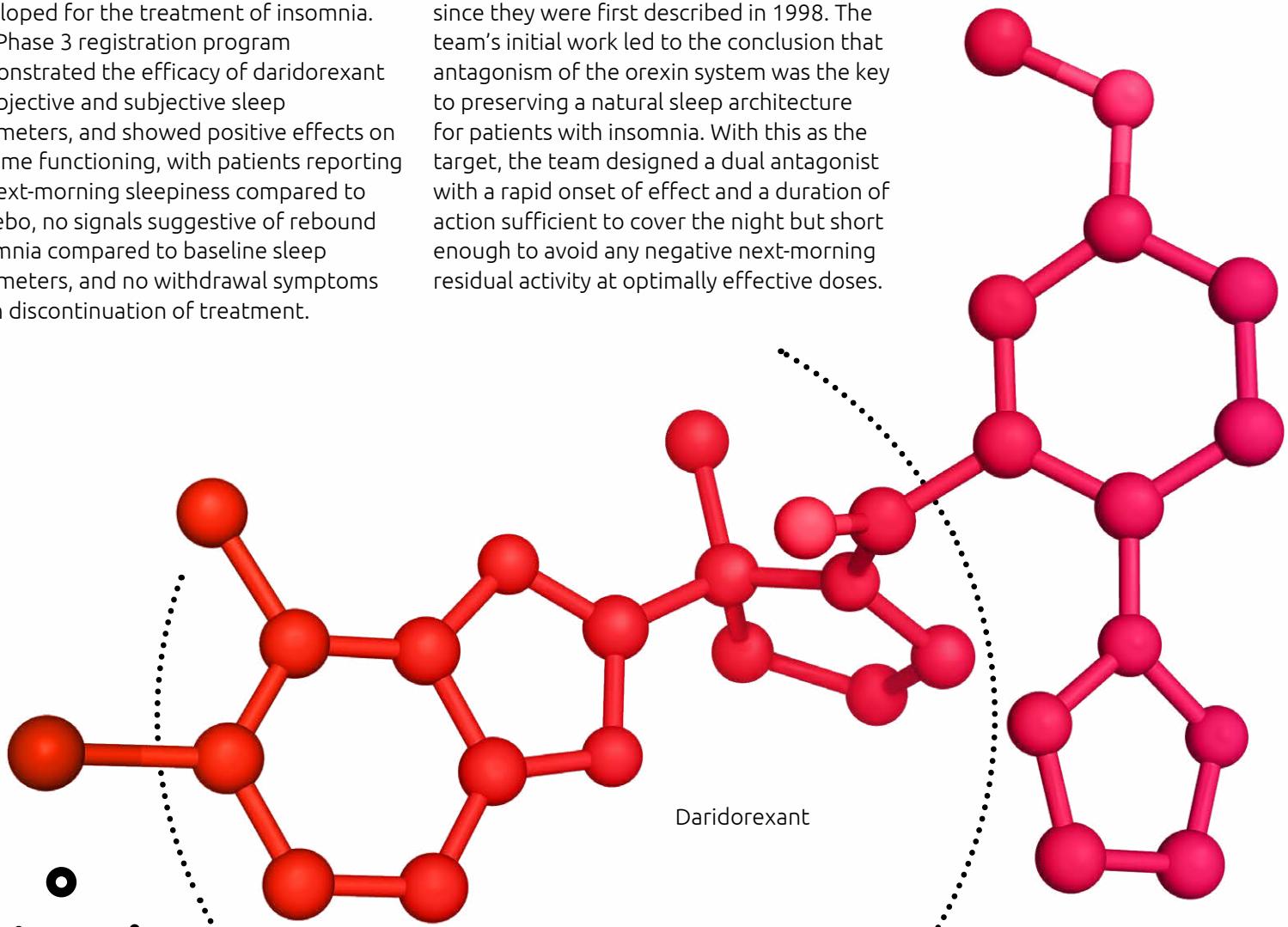


Dual orexin receptor antagonists (DORAs) offer an entirely different approach to treating insomnia than previous drug classes: by blocking the activity of orexin, they turn down overactive wakefulness, in contrast to insomnia treatments which act via general CNS sedation. DORAs specifically target the orexin system by competitively binding with both receptors, thereby reversibly blocking the activity of orexin. 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.

Idorsia's innovation

Daridorexant is a DORA designed and developed for the treatment of insomnia. The Phase 3 registration program demonstrated the efficacy of daridorexant on objective and subjective sleep parameters, and showed positive effects on daytime functioning, with patients reporting no next-morning sleepiness compared to placebo, no signals suggestive of rebound insomnia compared to baseline sleep parameters, and no withdrawal symptoms upon discontinuation of treatment.

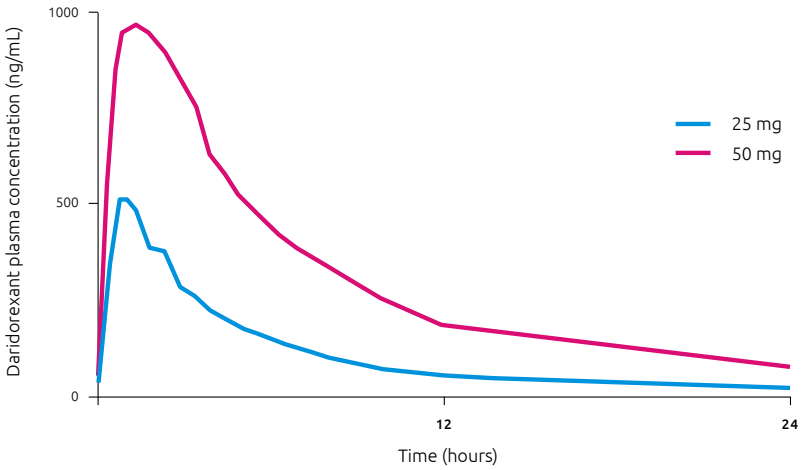
Idorsia's research team has been working on the science of orexin and orexin receptors since they were first described in 1998. The team's initial work led to the conclusion that antagonism of the orexin system was the key to preserving a natural sleep architecture for patients with insomnia. With this as the target, the team designed a dual antagonist with 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.



Daridorexant

Daridorexant has been shown to be quickly absorbed, with a half-life short enough to avoid next-morning carry-over effects and no accumulation over time, as demonstrated by the chart below.

Pharmacokinetic profile showing fast absorption and optimal half-life (8 h)



Mean pharmacokinetic profiles for 25 mg and 50 mg daridorexant, single dose, young adults (n=6 per group)

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study. Both pivotal studies are complete, having enrolled around 1,850 patients with insomnia at over 160 sites across 18 countries. As insomnia often presents later in life, and elderly patients are more susceptible to 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 (10 mg, 25 mg, and 50 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 FDA industry guidance.

More than 800 patients continued treatment in the ongoing 40-week extension study, which will measure the effects of all three doses vs placebo, generating data for long-term treatment of insomnia.

The Phase 3 registration program demonstrated statistically significant and clinically meaningful improvements in sleep and daytime functioning which were sustained over time. The results showed efficacy during the night and the day, in respect of sleep maintenance, sleep onset, total sleep time and daytime functioning. The nighttime symptoms were improved while preserving the proportions of sleep stages. The Phase 3 program provided a deep understanding of the efficacy and tolerability profile of daridorexant.

Summary of the results from the pivotal Phase 3 program

		1st pivotal study				2nd pivotal study			
		Daridorexant 50 mg		Daridorexant 25 mg		Daridorexant 25 mg		Daridorexant 10 mg	
		1 month	3 months	1 month	3 months	1 month	3 months	1 month	3 months
Primary endpoints	WASO	√	√	√	√	√	√	NS*	NS*
	LPS	√	√	√	√	NS*	NS*	NS*	NS*
Secondary endpoints	sTST	√	√	√	√	√	√	NS*	NS*
	IDSIQ	√	√	NS*	NS*	NS*	NS*	NS*	NS*

* Not significant – numerical trend
WASO: wake after sleep onset; LPS: latency to persistent sleep; sTST: subjective total sleep time; IDSIQ: insomnia daytime symptoms and impacts questionnaire

The highest (50 mg) dose was the most effective, followed by 25 mg, while the 10 mg dose had only a marginal effect.

A key consideration in the treatment of insomnia is the reversal of daytime functioning impairment associated with sleep difficulties – altered mood, cognition, and tiredness. To date, no insomnia studies have reported on the effects of pharmacological intervention on daytime functioning using an adequately developed and validated PRO instrument. At 50 mg, daridorexant produced consistent and meaningful improvements in scores for daytime functioning across all IDSIQ domains. Patients on daridorexant felt more energetic and less sleepy, and reported better alertness, cognition and mood.

Daridorexant was well tolerated and had a favorable safety profile in adult and elderly patients. Adverse reactions reported with a frequency of ≥ 2% in daridorexant-treated patients and greater (≥ 1%) than in placebo-treated patients in 3-month efficacy trials were headache, somnolence, fatigue, dizziness, and nausea. There was no excess of morning sleepiness, as assessed by the morning visual analogue scale (VAS), even at 50 mg. The incidence of somnolence was low and did not increase with daridorexant 50 mg compared to placebo. The incidence of adverse events of special interest, considering the potential association of orexin deficiency with narcolepsy, was low, with isolated cases of sleep paralysis or hallucinations in the daridorexant treatment groups.

"I am optimistic that intelligent drug discovery together with our focus on endpoints that matter to patients – not only sleep at night, but also the ability to function during the day – will help us to meet the needs of those who suffer from insomnia."

Eric Luthi
Vice President, Global Marketing Lead Daridorexant

In addition, an interim analysis was conducted on the ongoing 40-week extension study, once all patients had received six months of treatment altogether (during the core and extension study). This study – primarily measuring the safety of long-term treatment with daridorexant and allowing an exploratory analysis of the maintenance of efficacy – did not reveal any new safety findings, either qualitatively or quantitatively, while efficacy (in terms of sleep and daytime functioning) was maintained over the longer treatment duration.

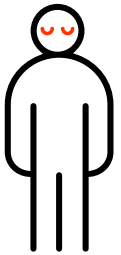
Current status

These results make daridorexant the first non-broadly sedative sleep medication to demonstrate an improvement in sleep and daytime functioning, as measured by a new, specifically developed and validated instrument, while keeping a favorable safety profile.

The new drug application (NDA) was submitted to the US FDA in January 2021. Should market authorization be received on schedule, this would allow for commercialization and launch in the US in the first half of 2022.

Insomnia

Compound: Daridorexant



Mechanism of action:
Dual orexin receptor antagonism
Status: NDA submitted,
MAA in preparation

Aprocitentan for resistant hypertension

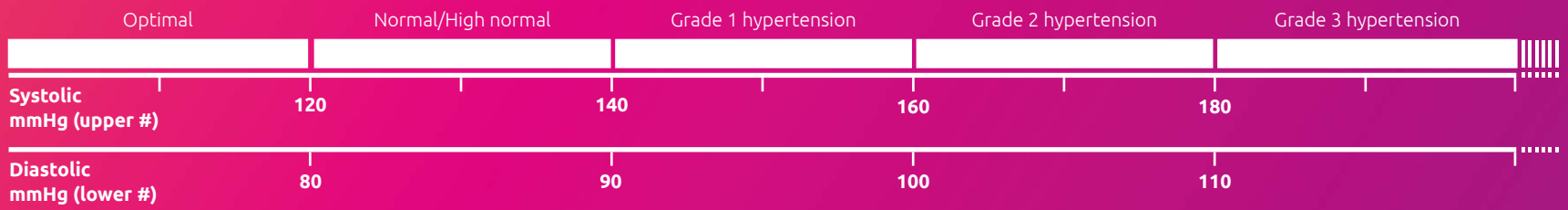
Hypertension (high blood pressure) is one of the most common cardiovascular risk factors, and its prevalence continues to rise. According to a recent study, there are more than a billion people living with hypertension worldwide – a startling number, which has almost doubled in the past 40 years. Left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

The World Health Organization estimates that hypertension causes 7.5 million deaths a year – about 12.8% of all deaths worldwide.

Patients with hypertension can often successfully control their blood pressure by combining a healthier lifestyle with effective medication. However, there are patients whose blood pressure remains high despite receiving at least three antihypertensive medications of different pharmacological classes, including a diuretic, at optimal doses, and they are categorized in hypertension guidelines and the medical community as having resistant hypertension. It is this form of hypertension that scientists at Idorsia are trying to treat.

7.5 **million deaths a year caused by hypertension**

Stages of hypertension

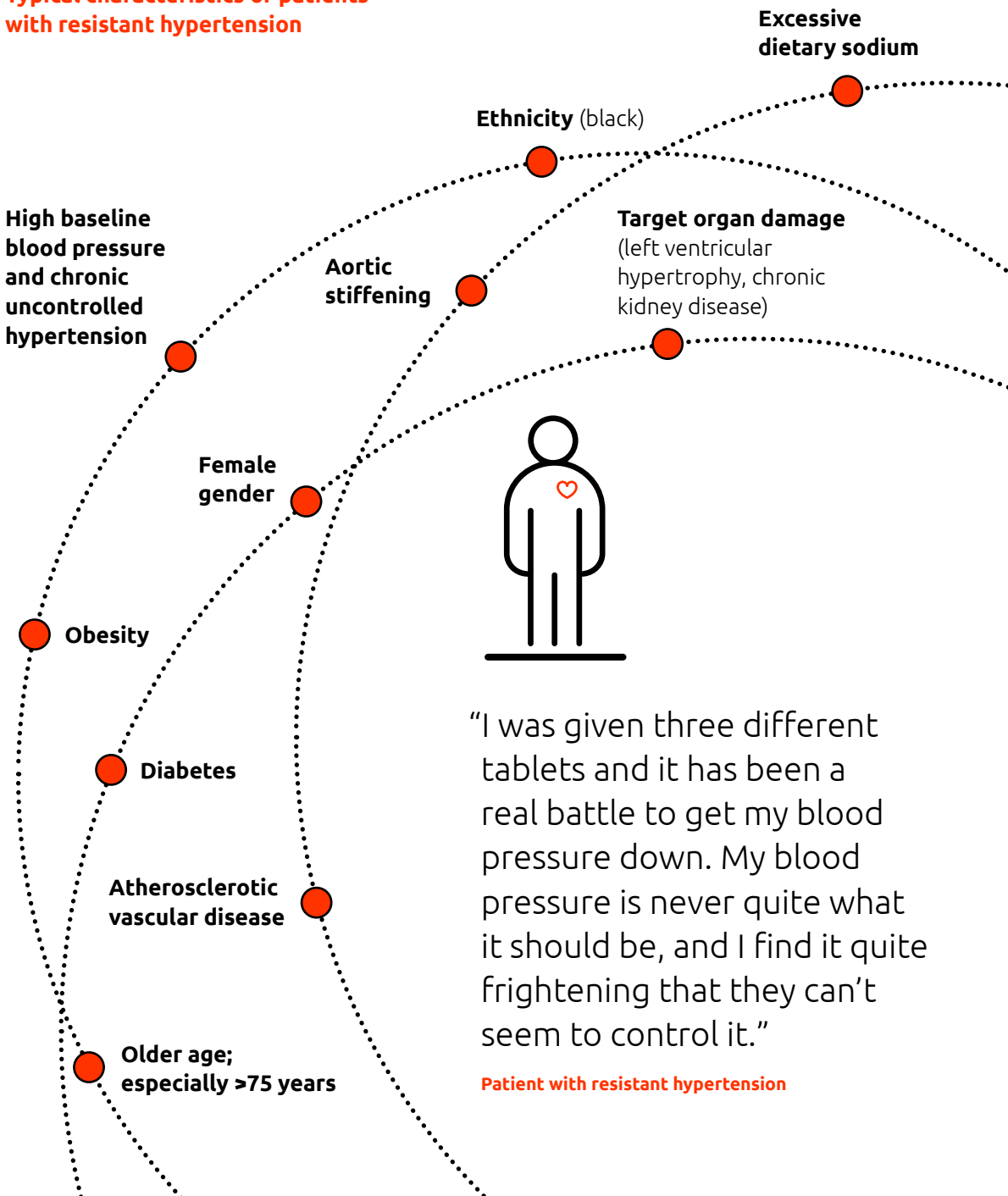


True resistant hypertension
Patients whose blood pressure remains high, despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal doses. It is estimated that 10% of patients treated for hypertension can be classified as having true resistant 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

The current pharmacological treatment strategy for patients with resistant hypertension is to add on antihypertensive medications, preferably with a mechanism of action which is not yet used. 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.

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.

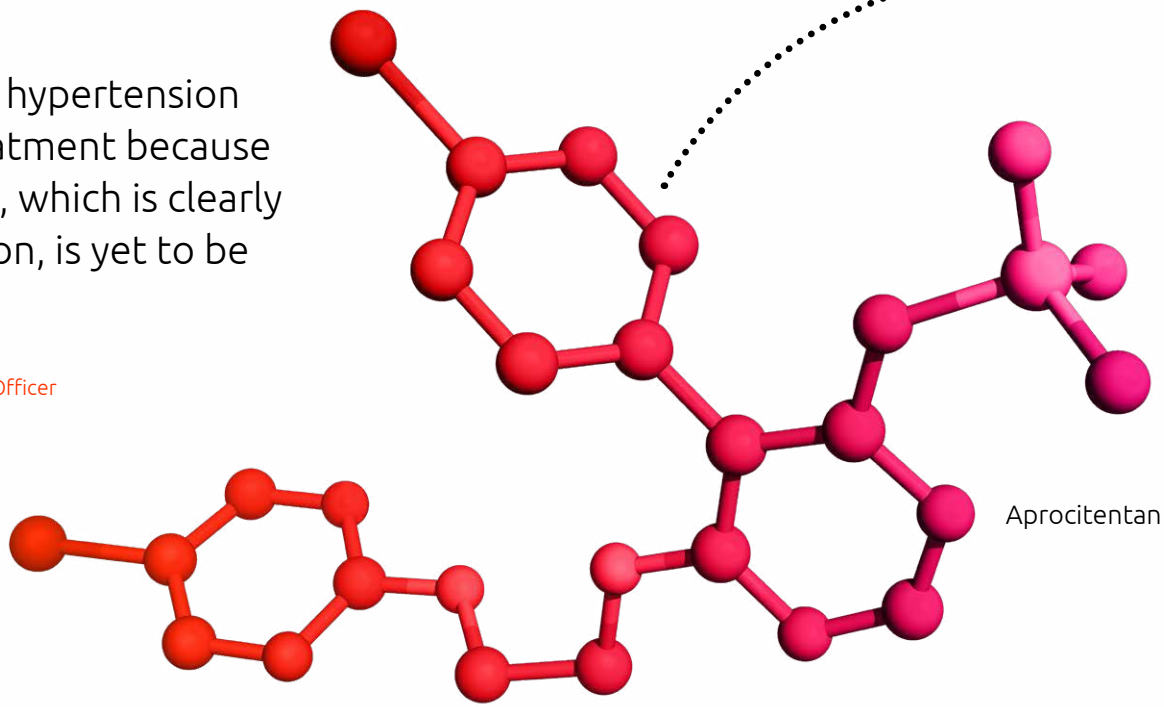
In hypertension, both ETA and ETB receptors mediate ET-1-induced harmful effects. Clinical and preclinical evidence suggests that resistant hypertension may be endothelin dependent. The endothelin system certainly plays an important role in hypertension, especially in volume- and salt-dependent forms, which are a common feature in patients with resistant hypertension. By targeting the endothelin pathway – an as yet untreated pathway in systemic hypertension – Idorsia could provide a new treatment option for difficult-to-treat patients.

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 aprocitentan and any of its derivative compounds or products. Both parties have joint development rights over aprocitentan. Idorsia is overseeing the Phase 3 development and regulatory submission for difficult-to-control hypertension. The costs are shared equally between both partners. Janssen will oversee the Phase 3 development and submission for any additional indications and will have the sole worldwide commercialization rights.

"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



Aprocitentan

Idorsia's innovation

Aprocitentan is a once-a-day, potent dual (ET_A and ET_B) endothelin receptor antagonist, which is being investigated for the treatment of difficult-to-control hypertension.

In animal models of hypertension, aprocitentan has demonstrated a synergistic effect on blood pressure reduction when given with antihypertensive drugs that target the renin–angiotensin–aldosterone system (RAAS). In a second animal model, mimicking resistant hypertension, where rats develop hypertension with low renin levels, RAAS blockers have less antihypertensive effect, while aprocitentan induced a significant blood pressure reduction.
In addition to hypertension, increased endothelin also drives inflammation and fibrosis, and hypertrophy and proliferation in certain vascular and cardiac cells. Particularly in resistant hypertension, this can lead to end-organ damage. Furthermore, increased endothelin also drives aldosterone secretion and salt retention, which also contributes to elevated blood pressure and, again, can lead to end-organ damage.

In the model of resistant hypertension, untreated rats develop hypertension, increased renal vascular resistance and left ventricular hypertrophy. In contrast, treatment with aprocitentan dose-dependently improved renal hemodynamics and decreased cardiac hypertrophy, demonstrating a reduction in end-organ damage – specifically in the kidneys and the heart.

In humans, the clinical pharmacology profile suggests that there is a low propensity for drug–drug interaction, which is particularly important for patients who typically are being treated for several other problems.

"There is an urgent public health need for additional therapies acting on pathways different from those currently used, in line with the underlying disease mechanism."

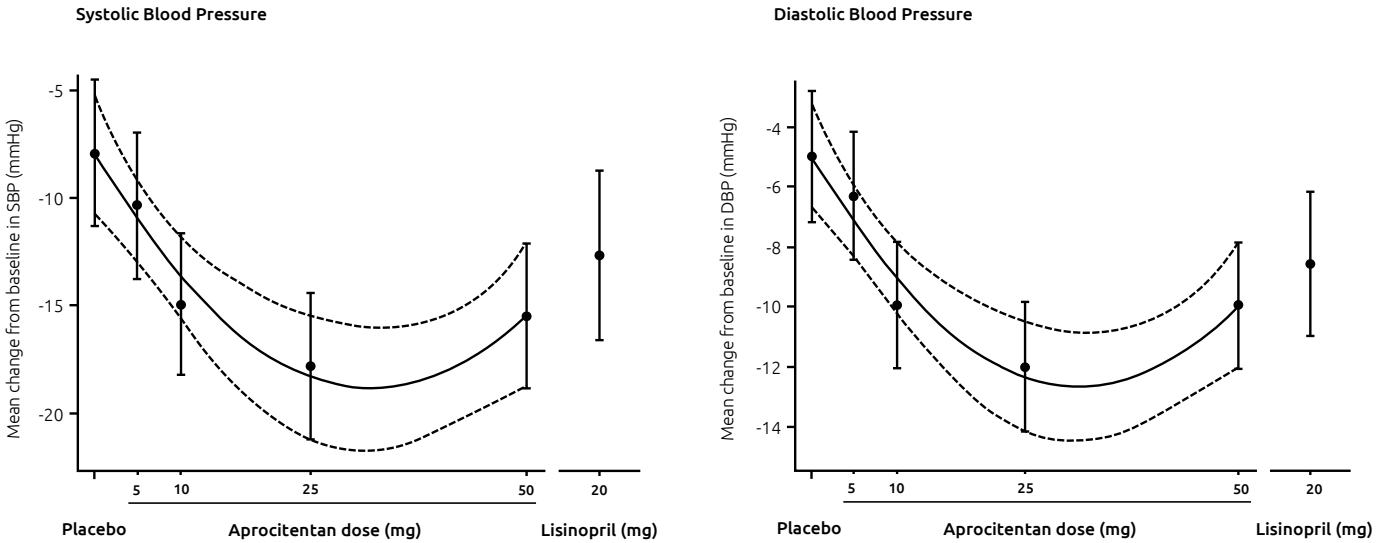
Professor John Chalmers, MD
Senior Director of The George Institute for Global Health
and Professor of Medicine at the University of New South Wales, Sydney

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. A total of 490 eligible patients were randomized, with 430 patients successfully completing the double-blind treatment period. Blood pressure was measured carefully with an unattended automated office blood pressure device. The results are shown in the charts below. No changes in heart rate were observed for any dose of aprocitentan. 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 the large Phase 3 study, PRECISION, in patients with resistant hypertension.

Aprocitentan dose-dependently decreased blood pressure in hypertensive patients



"If successful, the PRECISION study should provide all the information required for filing with regulatory authorities to bring a therapy to patients who have exhausted many other options."

Frédéric Naud
Senior Director, Life Cycle Leader for aprocitentan

Current status

PRECISION is a Phase 3 study to demonstrate the antihypertensive effect of aprocitentan when added to standard care in patients with resistant hypertension. Idorsia, in consultation with regulatory agencies, designed a single, placebo-controlled study which efficiently addresses both the short-term efficacy of aprocitentan and the durability of its effects in long-term treatment. The study aims to randomize 600 patients at approximately 180 sites in around 20 countries, and results are targeted for the first half of 2022.

The evidence built to date gives the company confidence that aprocitentan has the potential to revolutionize the treatment of difficult-to-control hypertension by targeting the endothelin pathway for the first time.

Resistant hypertension management

Compound: Aprocitentan

Mechanism of action:
Dual endothelin receptor antagonism
Status: Phase 3

Clazosentan for cerebral vasospasm

Aneurysmal subarachnoid hemorrhage (aSAH) is a rare condition involving 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. Emergency surgical repair (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage.

The incidence of aSAH is estimated to be between 6 and 9 per 100,000 per year worldwide. Notably, aSAH is a significant problem in Japan, with an incidence at least twice as high as in many other countries of the world.

The bleeding and the release of a vasoconstrictor (endothelin) by the neighboring vascular endothelium can lead to cerebral vasospasm (constriction of arteries in the brain), usually occurring between 4 and 14 days after aneurysm securing. This diminishes blood flow to the brain, and about one third of patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability and death in patients with aSAH.

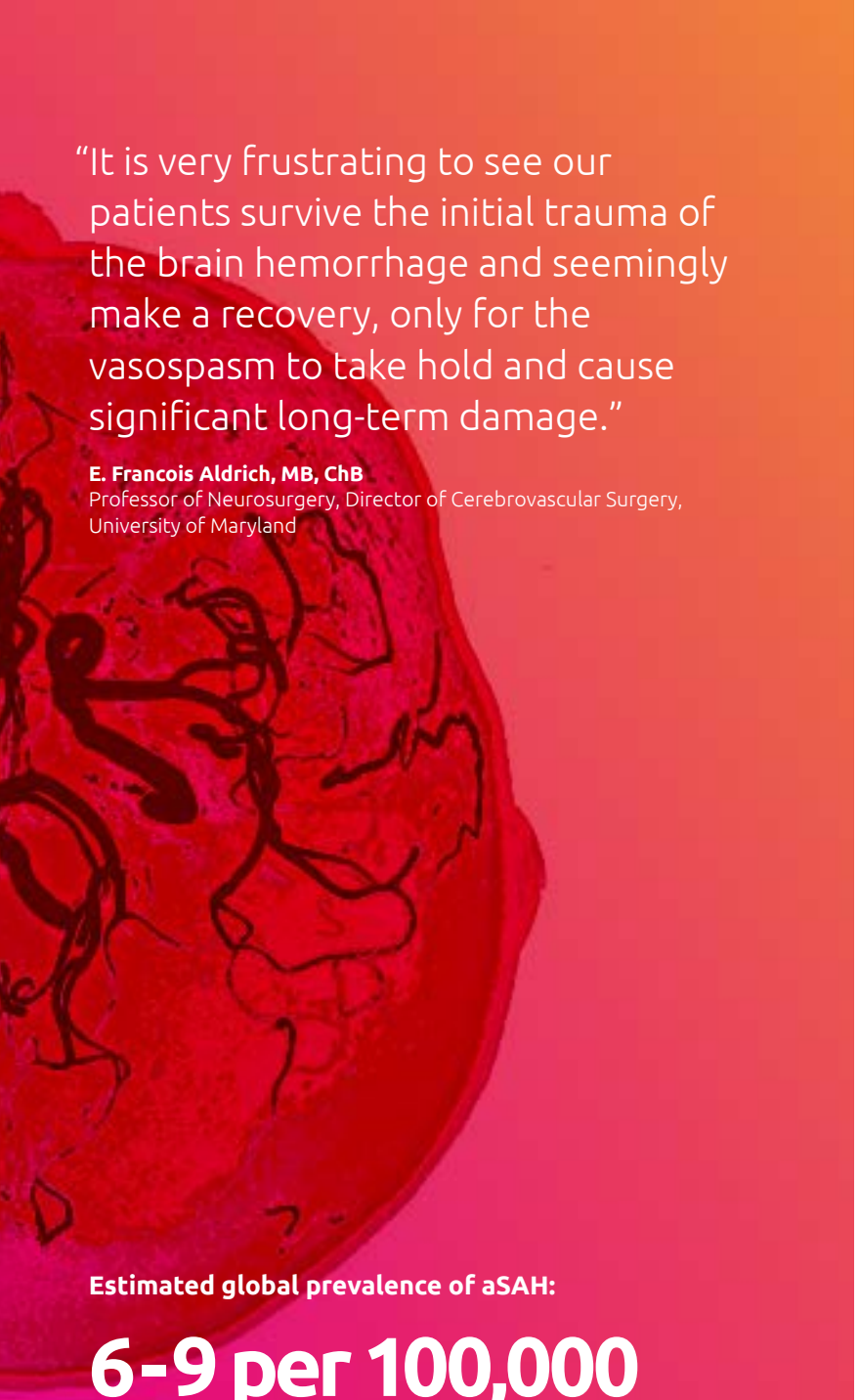
Approximately 50% of the overall aSAH population present with thick, diffuse blood clots characterized by a large amount of subarachnoid blood on the admission CT scan. These patients have a significantly higher risk of experiencing cerebral vasospasm.

The treatment landscape

Today, patients with 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.

"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



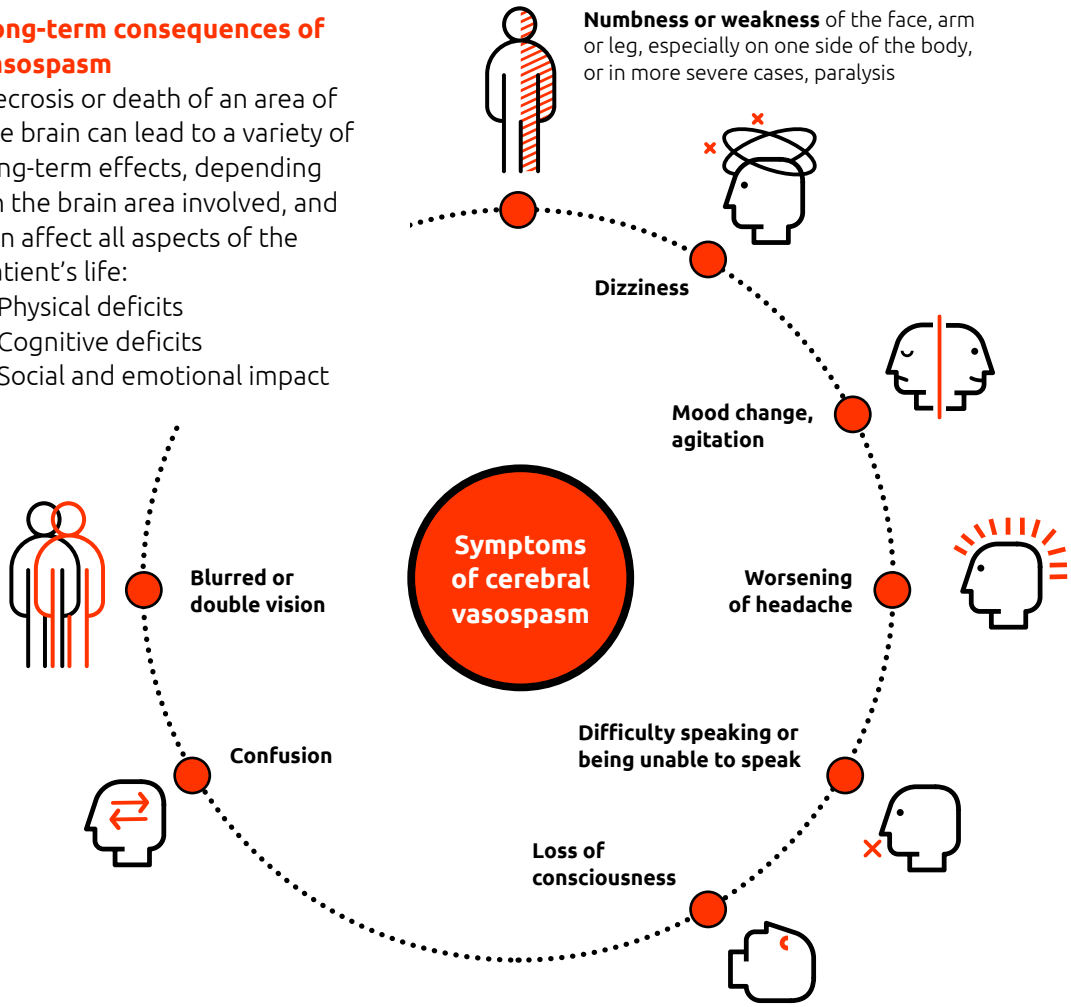
Estimated global prevalence of aSAH:

6-9 per 100,000

Long-term consequences of vasospasm

Necrosis or death of an area of the brain can lead to a variety of long-term effects, depending on the brain 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

Cerebral vasospasm is caused by the release of vasoactive mediators after aSAH. Endothelin is one of the most powerful, long-acting vasoactive mediators, causing constriction of blood vessels. Patients with cerebral vasospasm show high levels of endothelin in the cerebrospinal fluid.

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 or reversing vasospasm in the future.

Idorsia's innovation

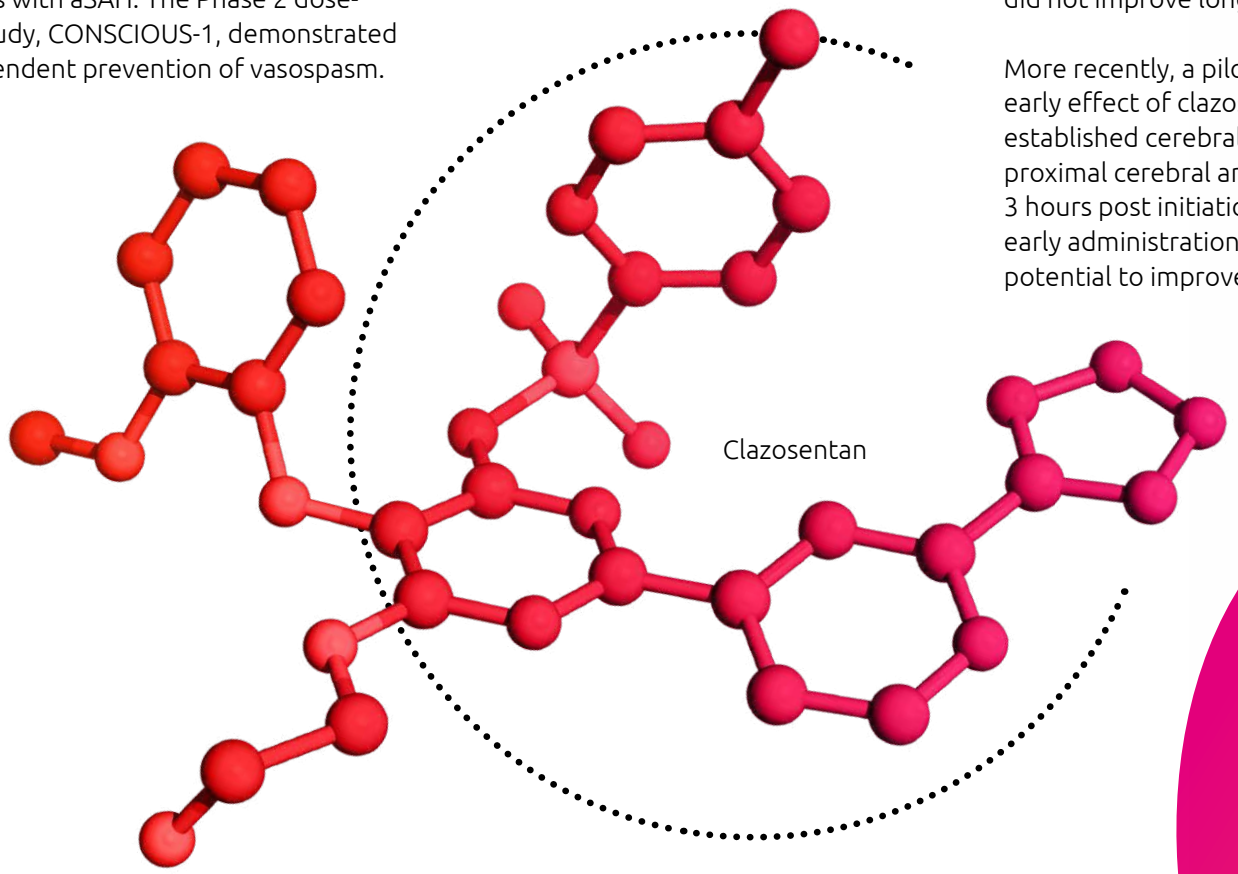
Clazosentan is a fast-acting, selective endothelin A (ET_A) receptor antagonist, being developed as an intravenous infusion for the prevention of vasospasm-related delayed cerebral ischemia in patients following aSAH.

Several studies have built our understanding of the role of clazosentan in preventing or reversing 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, administered by continuous intravenous infusion, 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), administered by continuous intravenous infusion, 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, 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.

More recently, a pilot study evaluating the early effect of clazosentan on reversing established cerebral vasospasm in large proximal cerebral artery segments at 3 hours post initiation suggested that, with early administration, clazosentan has the potential to improve large-vessel vasospasm.



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"Clinical studies have built a deep understanding of the role of clazosentan in preventing or reversing 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
Director, Senior Clinical Project Scientist for clazosentan

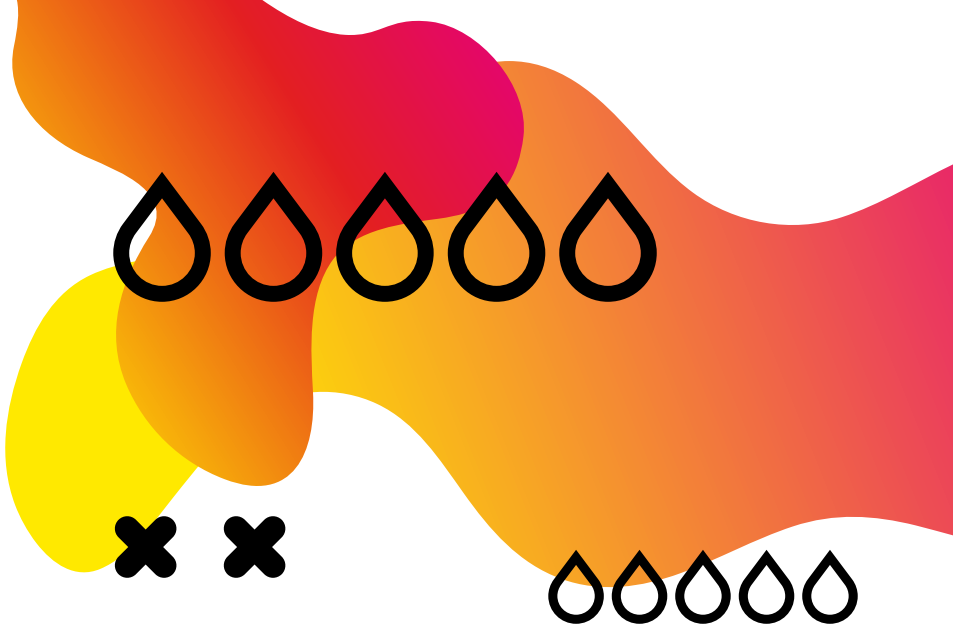
In a post-hoc analysis of the effect of clazosentan on reversing established cerebral vasospasm in the entire cerebral vasculature (including smaller distal vessel segments and the cerebellar arteries), a clearly visible improvement was observed in vessel diameter at 3 and 24 hours.

The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to approx. 2000 patients around the world. The side effects of clazosentan are managed based on 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 aiming to maintain euvolemia by avoiding excessive fluid administration.

All this evidence, together with the registration program in Japan (described below), suggests that clazosentan has the potential to prevent vasospasm-related delayed cerebral ischemia and to reduce the need for invasive neurovascular intervention. As a result, Idorsia has initiated REACT, a Phase 3 study.

"We have worked on the role of endothelin in aSAH for more than 25 years. We had a very clear goal – to help patients following aSAH, who are often young adults and whose lives can be devastated by the terrible consequences of cerebral vasospasm. We are now well on the way to bringing a much-needed therapy to these patients."

Jean-Paul Clozel
Chief Executive Officer



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 set of patient management guidelines to ensure patient safety. The study aims to randomize approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – at around 95 sites across 15 countries, and results are targeted for the second half of 2022.

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

Japanese registration program

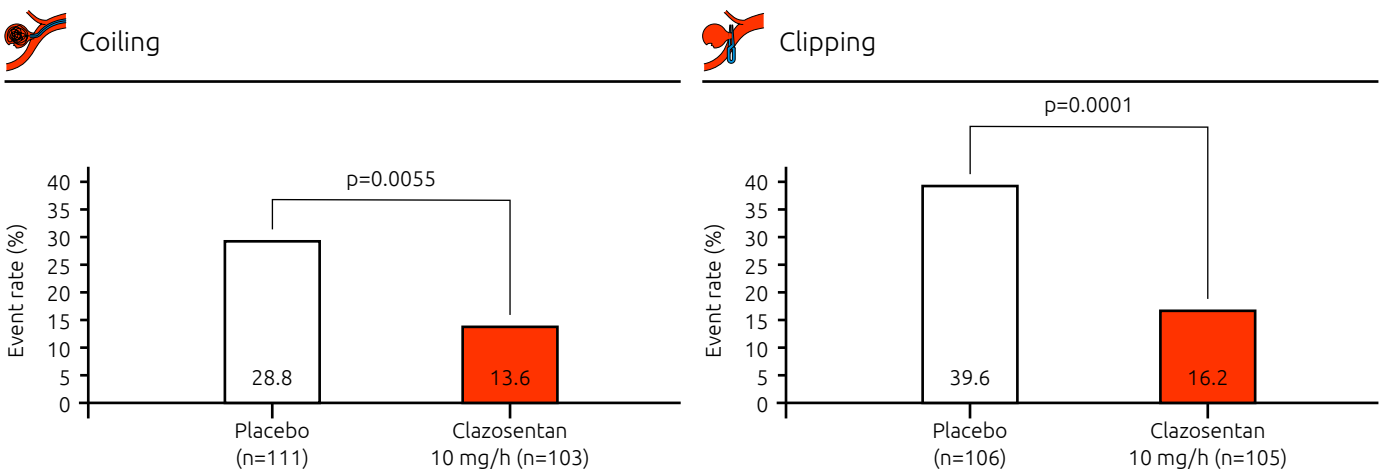
A Phase 2 study in Japanese and Korean patients showed that 10 mg/h clazosentan administered by continuous intravenous infusion significantly reduced vasospasm and vasospasm-related morbidity and mortality events. On that basis, a registration program was initiated with clazosentan in Japan in May 2016.

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-related morbidity and all-cause mortality events. 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.

In Japan, clazosentan has regulatory data protection after approval, leading to eight years' exclusivity.

Top-line results from the Japanese registration program

Incidence of vasospasm-related morbidity and all-cause mortality



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.

Both studies demonstrated a statistically significant ($p<0.01$) reduction in the occurrence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH, as shown in the charts above. Clazosentan showed a numerical reduction of all-cause morbidity and mortality in both studies. The effect of clazosentan on this endpoint was significant ($p<0.05$) in a pre-planned pooled analysis. Further analysis is ongoing, including additional pooled analysis of data from both studies.

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).

Idorsia Japan plans to file a new drug application with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in the coming months. This would in turn allow for commercialization and launch in Japan in the first half of 2022, should marketing authorization be received.

Cerebral vasospasm associated with aSAH

Compound: Clazosentan

Mechanism of action: Selective endothelin (ET_A) receptor antagonism

Status Global: Phase 3

Status Japan: Filing in preparation

Lucerastat for Fabry disease

Fabry disease is a rare, life-threatening, lysosomal storage disorder, 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 may result in a build-up of Gb3 deposits throughout the body, particularly in the kidneys, heart and nervous system.

The symptoms range from neuropathic pain (primarily in the hands and feet) and gastrointestinal, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy and stroke. 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.

"Pain is a genuine and pressing unmet need of the Fabry patient population. Pain remains a significant burden for many patients – even for some of those who are already being treated with enzyme replacement therapy."

Dr Derralynn Hughes
DPhil, FRCP, FRCPath, coordinating investigator of the European studies

"The sensations that I get – it feels like my hands are on fire. It feels like there's a thousand needles poking at my hands and feet… If I was to get out of bed and I was to walk, it would feel like I'm walking on hot coals with needles jabbing into my feet."

Patient with Fabry disease

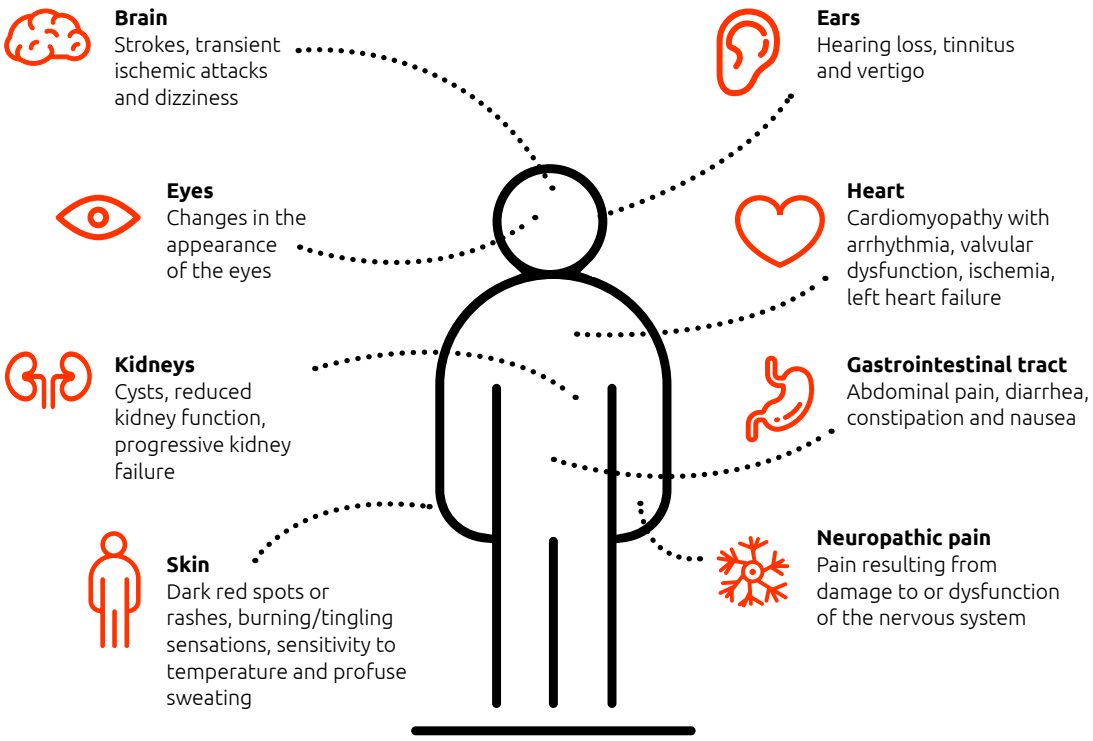
The diagnosed prevalence of Fabry disease in 2018 was approximately

7,500 patients

in the US and the EU-5 (i.e., France, Germany, Italy, Spain and the UK).

Clinical manifestations of Fabry disease

- More frequent/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



Fabry patient survey

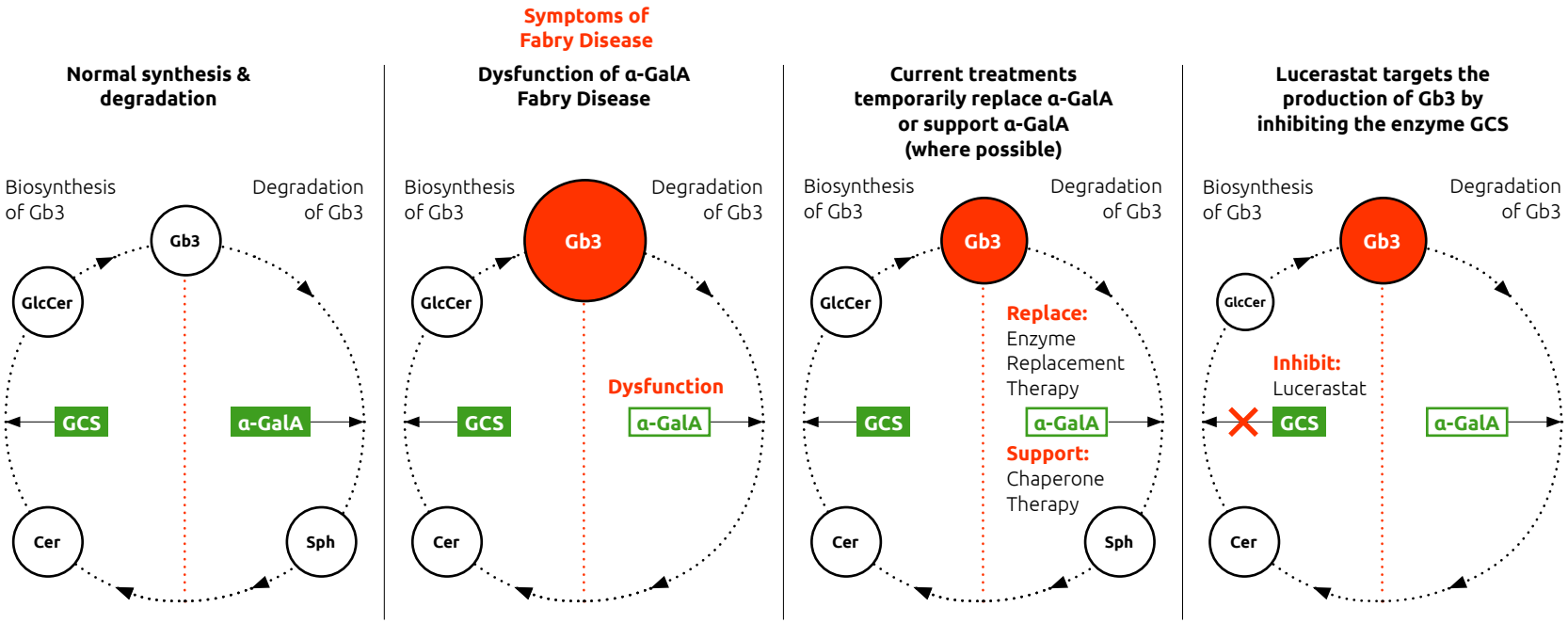
Idorsia conducted an international survey (with 367 patients) to gain a better understanding of the symptoms and needs of patients with Fabry disease, from their own perspective. The findings indicate that Fabry patients experience significant neuropathic pain (in terms of intensity, frequency and location), which has a large impact on their quality of life. Idorsia then conducted a separate study to define neuropathic pain in Fabry patients. The results informed the development of a Fabry-specific pain questionnaire, in which neuropathic pain was defined as a type of pain which feels like burning, shock or shooting, stabbing, tingling and/or pins and needles in the hands and feet.

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 (in patients with amenable mutations). These approaches attempt to reduce the continued accumulation of Gb3.

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 subsequently reduces 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: α-GalA, α-galactosidase A; Cer, ceramide; Gb3, globotriaosylceramide; GCS, glucosylceramide synthase; GlcCer, glucosylceramide; Sph, sphingosine

"By reducing the production of the lipids that cannot be broken down due to Fabry disease, we believe that lucerastat can change the course of the disease for these patients."

Luba Trokan
Director, Clinical Project Physician for lucerastat

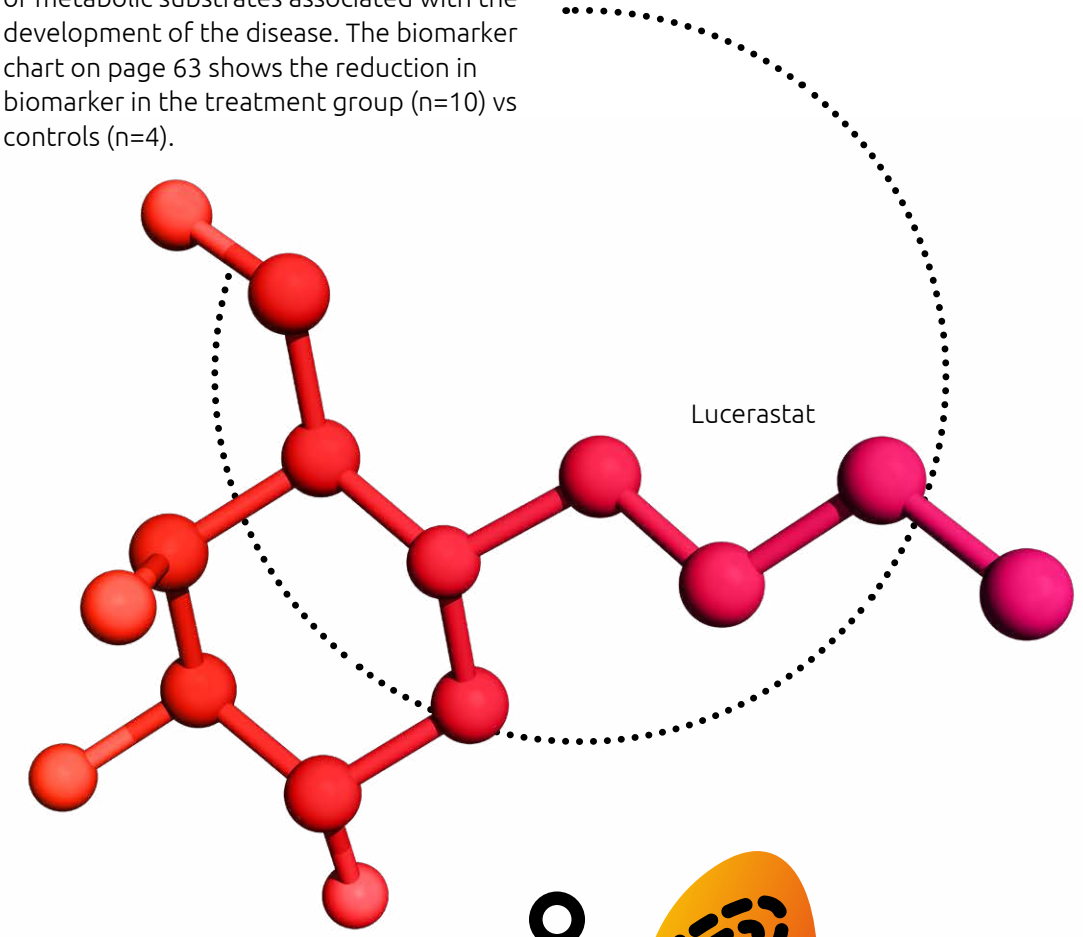
Idorsia's innovation

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

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, as shown by the animal model charts on page 63. 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 biomarker chart on page 63 shows the reduction in biomarker in the treatment group (n=10) vs controls (n=4).



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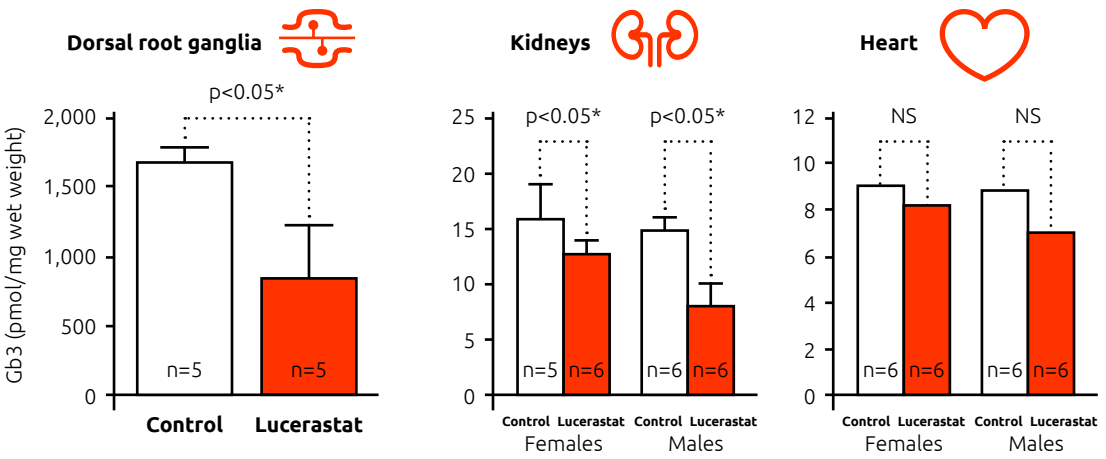
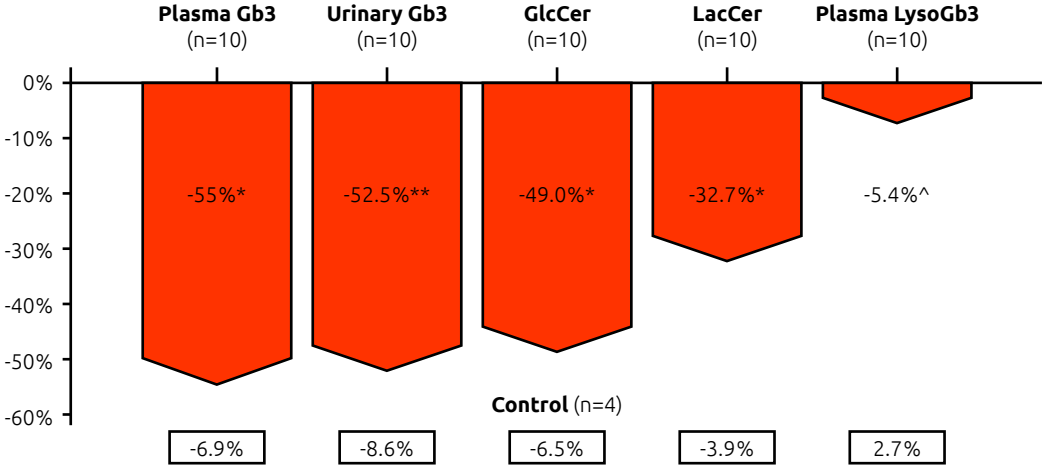
Reduction of Gb3 levels in tissues from an animal model of Fabry disease



* ANOVA with Bonferroni's multiple testing correction

Mean % biomarker reduction from baseline at week 12 in patients with Fabry disease



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

The study also indicated that lucerastat is well tolerated in patients with Fabry disease.

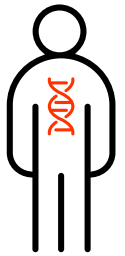
Current status

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

MODIFY is a Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The study aims to determine the effects of treatment on neuropathic pain over a 6-month period, as measured by Idorsia's Fabry disease neuropathic pain instrument (developed in accordance with health authority guidance). At the end of the double-blind period, patients will have the option of entering an open-label extension study to determine long-term safety and to explore long-term efficacy and disease-modifying potential, as measured by estimated glomerular filtration rate (eGFR), left ventricular mass index and biomarkers of Fabry disease. Enrollment in the study concluded at the end of 2020, with more than 100 patients being randomized to lucerastat or placebo in a 2:1 ratio. Results of this study are therefore expected in the second half of 2021.

Fabry disease

Compound: Lucerastat



Mechanism of action:
Glucosylceramide synthase inhibition
Status: Phase 3

Selatogrel for acute myocardial infarction

About 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 persons 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 prior to hospital admission. As a result, early action is crucial for survival; however, there are no treatment options 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 death.

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

800,000 people living in the US have a heart attack each year

Average age at first heart attack – risk increases with age

66

72

3.3m women die of heart attack worldwide every year

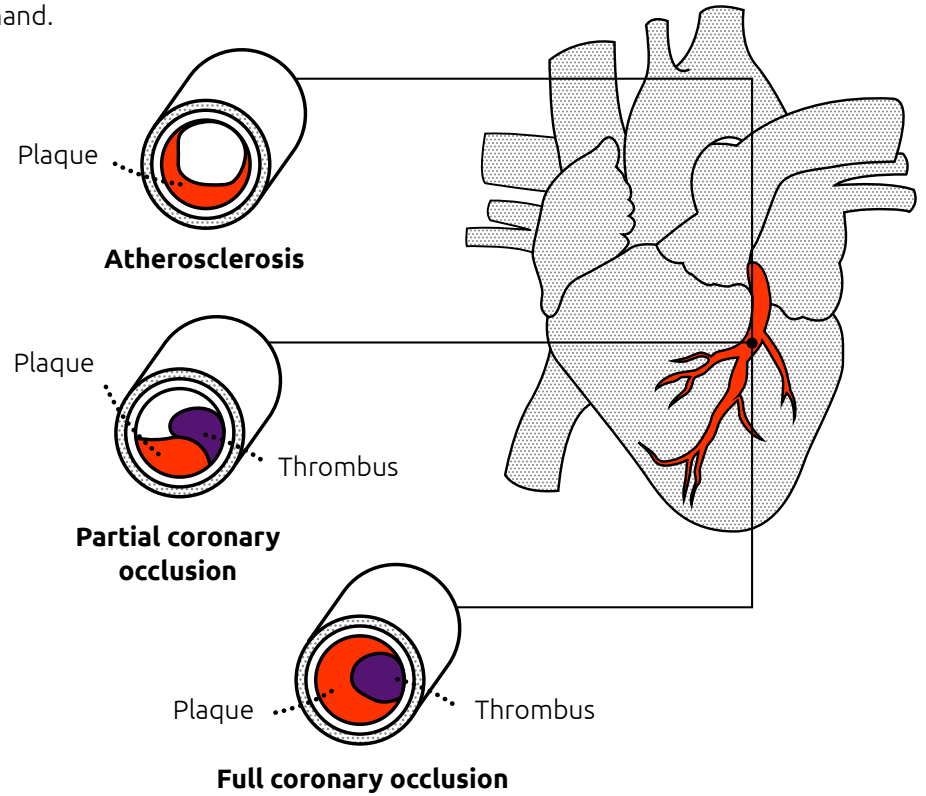
Women tend to **underestimate** the risk of heart attacks

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.

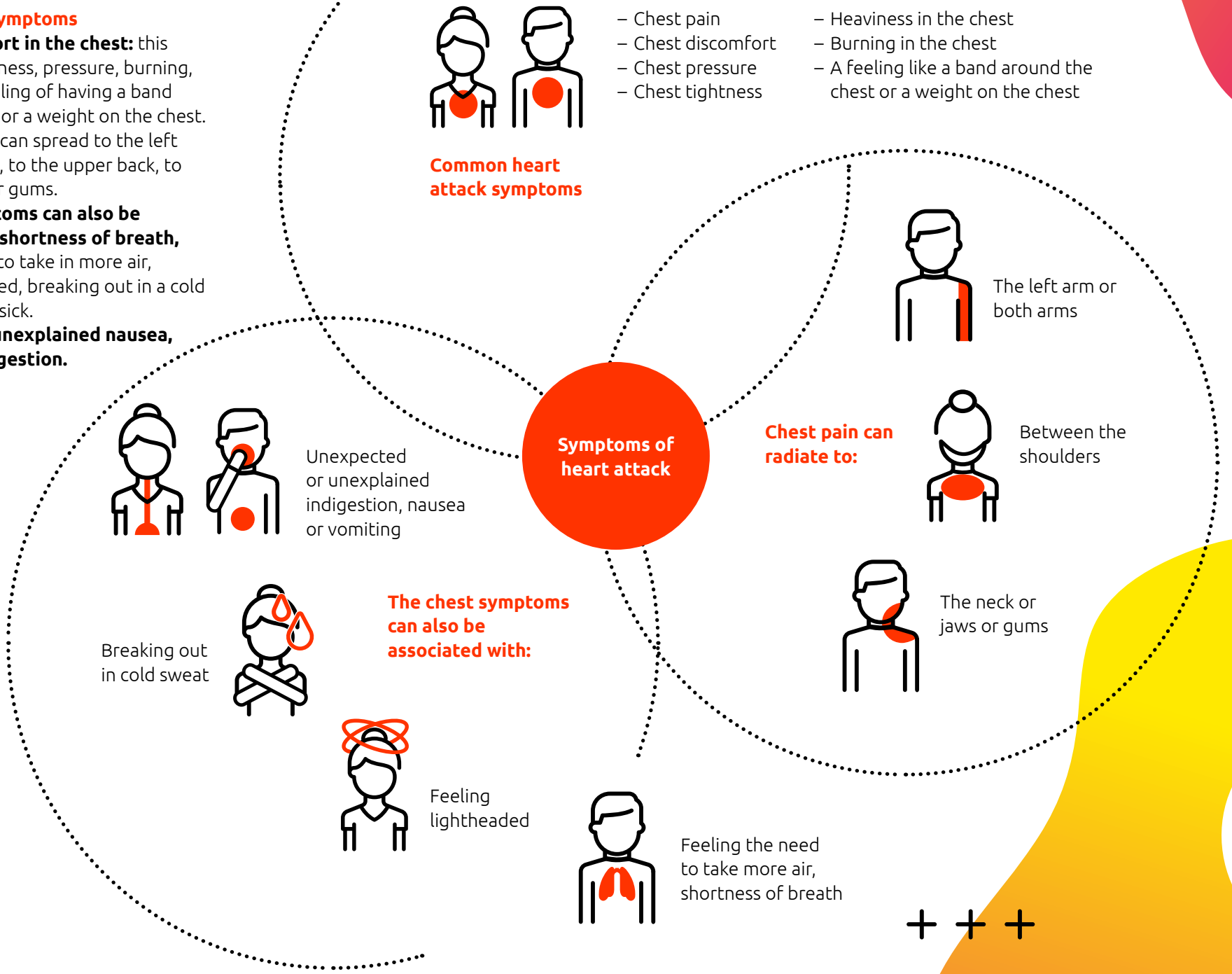
A heart attack usually occurs in patients with coronary heart disease (CHD), where coronary arteries are narrowed due to the build-up of fat, cholesterol and other substances (known as plaque or atheroma). This process of build-up is called atherosclerosis. The development of atherosclerosis can progress 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).



Recognizing the symptoms

- **Pain or discomfort in the chest:** this can include heaviness, pressure, burning, tightness or a feeling of having a band around the chest or a weight on the chest.
- These symptoms can spread to the left arm or both arms, to the upper back, to the neck or jaw or gums.
- **The chest symptoms can also be associated with shortness of breath,** feeling the need to take in more air, feeling lightheaded, breaking out in a cold sweat, or feeling sick.
- **Unexpected or unexplained nausea, vomiting or indigestion.**



The treatment landscape

Dual antiplatelet therapy – the combination of aspirin and a $P2Y_{12}$ receptor antagonist – is a cornerstone of the treatment of patients with acute coronary syndromes (ACS) and of those undergoing percutaneous coronary intervention (PCI). Oral $P2Y_{12}$ receptor antagonists are indicated for acute treatment as well as long-term secondary prophylaxis of confirmed AMI. An intravenous $P2Y_{12}$ receptor antagonist is intended for specialized use in an acute and hospital setting in patients undergoing PCI who have not been pretreated with an oral $P2Y_{12}$ receptor antagonist.

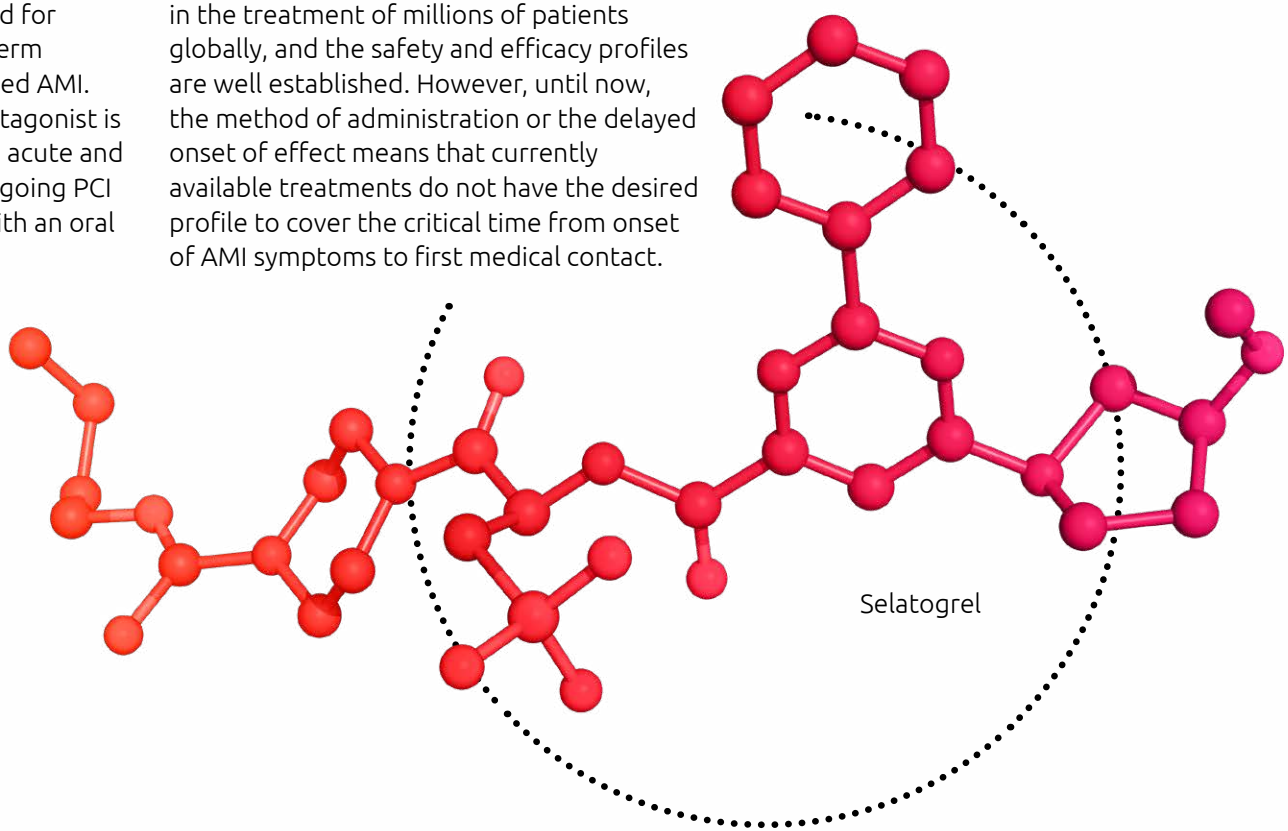
$P2Y_{12}$ receptor antagonism

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 $P2Y_{12}$ receptor. This platelet activation and aggregation can be inhibited by antagonizing the platelet $P2Y_{12}$ receptor. This prevents the binding of ADP to the receptor, which reduces platelet aggregation and the reaction of platelets to stimuli of thrombus aggregation.

$P2Y_{12}$ receptor antagonists 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.

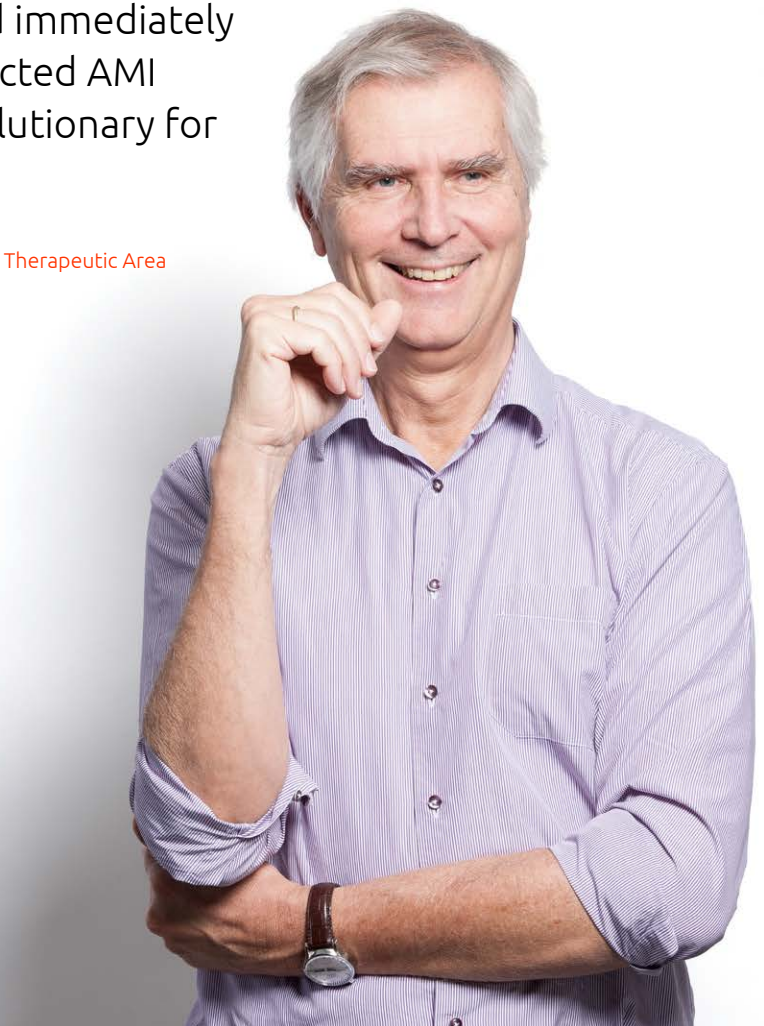
Idorsia's innovation

Selatogrel is a potent, fast-acting, reversible and highly selective $P2Y_{12}$ receptor antagonist, being developed for the treatment of AMI in patients with a history of AMI. It is intended to be self-administered subcutaneously via a drug delivery system (auto-injector). 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 prevent severe clinical outcomes.



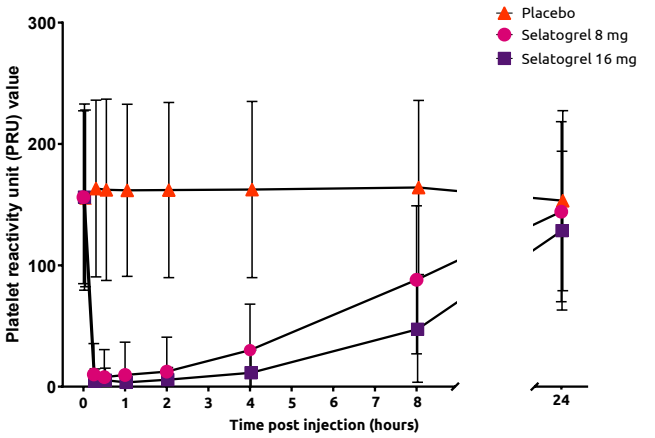
"With our integrated drug delivery device, the potential to self-administer selatogrel in the critical time period immediately following onset of suspected AMI symptoms could be revolutionary for patients."

Sebastien Roux
Senior Director, Medical Expert Cardiovascular Therapeutic Area



Two Phase 2 studies in patients with chronic coronary syndromes and AMI, respectively, have met their pharmacodynamic objectives of significantly inhibiting platelet aggregation. Subcutaneous administration of selatogrel 8 mg and 16 mg has 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 agreement with Antares Pharma, Inc., to develop a novel drug-device product combining selatogrel with the Antares QuickShot® auto-injector for subcutaneous delivery.

"Every patient will play a central role by understanding the symptoms of AMI, taking the decision to self-inject, and calling for emergency medical care."

Corine Bernaud
Director, Clinical Project Physician

Current status

The drug-device product is being tested in usability and reliability studies tailored for emergency use, to ensure safe and effective use can be demonstrated in preparation for a Phase 3 study.

In consultation with health authorities, Idorsia is preparing a large, international Phase 3 study, involving approximately 14,000 patients, to evaluate the efficacy and safety of self-administered subcutaneous injection of selatogrel for the treatment of suspected AMI in patients with a history of AMI. Participating patients will be trained on when and how to self-inject treatment. Initiation of the registration study is targeted for the first half of 2021. A Special Protocol Assessment has been agreed with the FDA. This indicates the FDA's approval of the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints and planned analyses) for a study intended to support a future marketing application.

In December 2020, 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.

Acute Myocardial Infarction
Compound: Selatogrel

Mechanism of action:
Selective $P2Y_{12}$ receptor antagonist
Status: Phase 3 in preparation

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

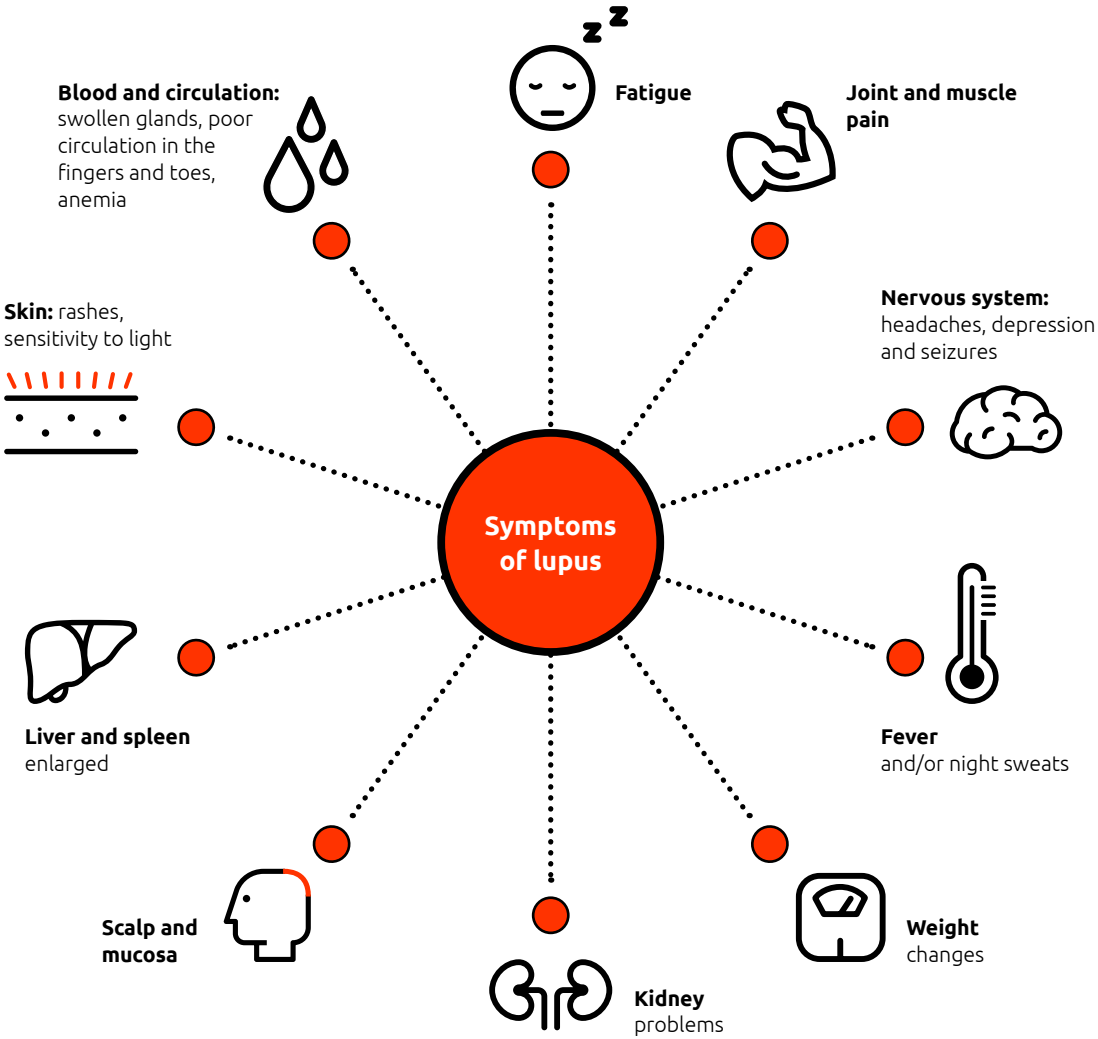
Systemic lupus erythematosus (SLE), the most common form of lupus, is an autoimmune disease, which means that the body's immune system malfunctions and attacks the body's own tissues. Some autoimmune diseases affect just one organ, but in the case of lupus, all parts of the body can be affected.

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 those affected to access 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.

In SLE, the body's immune system malfunctions and attacks the body's own tissues, which can affect the skin, joints, gut, blood cells, lungs 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

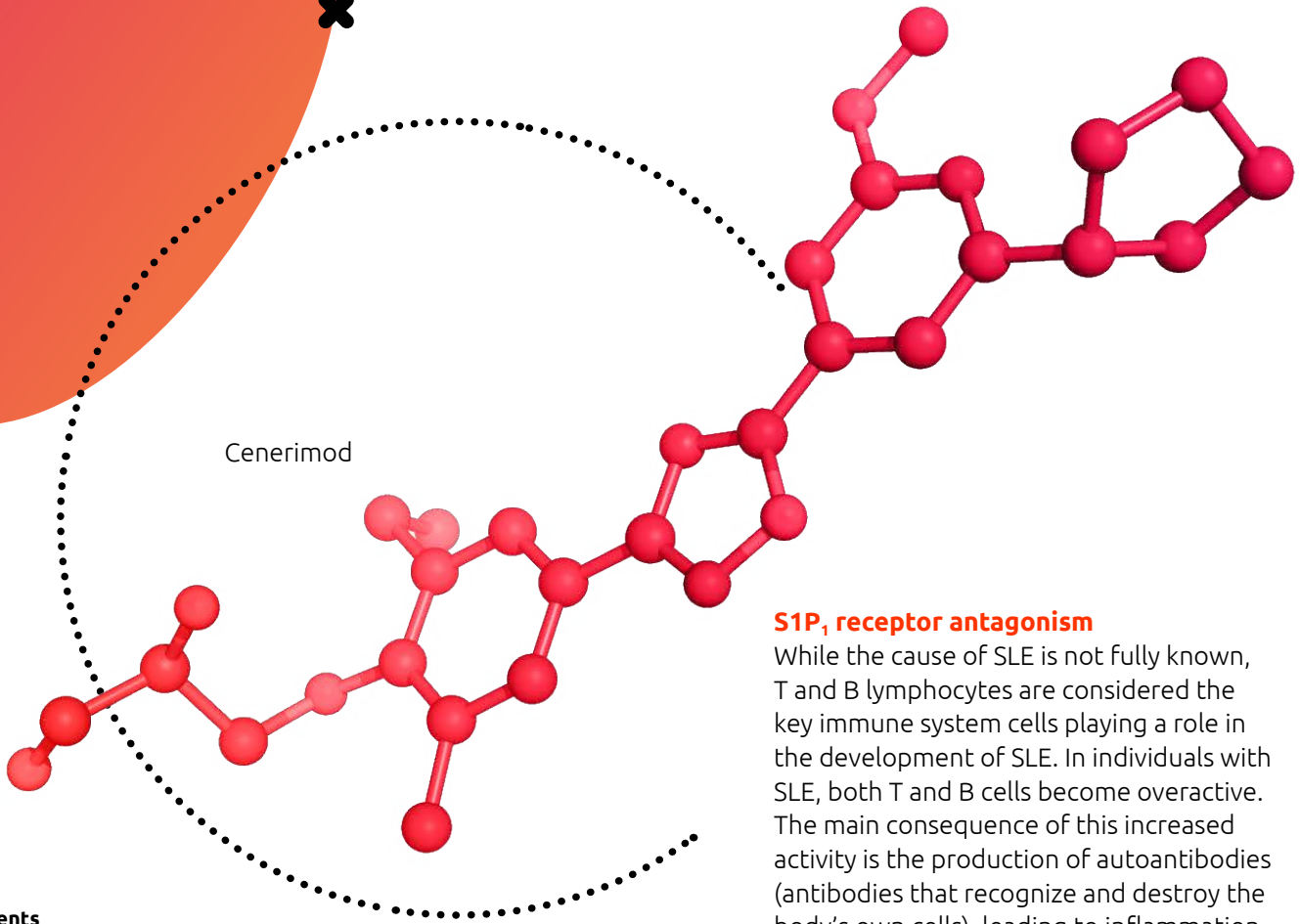
There is no cure for SLE, and a significant need exists for safe and effective therapies. Most people with SLE are prescribed a combination of different medications to manage their symptoms, improve their quality of life and reduce the risk of more serious complications.

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

"The presence of autoreactive T cells and B cells and the subsequent production of autoantibodies is key to the inflammation and organ damage seen in lupus. By acting on both cell types and at a fundamental stage in the autoimmune response, cenerimod has the potential to alter the course of the disease."

Beate Sehorz
Senior Director, New Product Strategy



$S1P_1$ receptor antagonism

While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune system cells playing a role in the development of SLE. In individuals with SLE, both T and B cells become overactive. The main consequence of this increased activity is 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 ($S1P_1$). 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 blood.

By binding to $S1P_1$ 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 circulating autoreactive T and B cells in the blood and thus in the tissues.

As a consequence of this reduction, it is hypothesized that a reduction in autoantibodies and immune cytokines – markers of the underlying disease processes – would also be seen, ultimately reducing inflammation and tissue damage, key contributors to the disease.

Idorsia's innovation

Cenerimod, the result of 20 years of research in Idorsia's labs, is a highly selective $S1P_1$ 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.

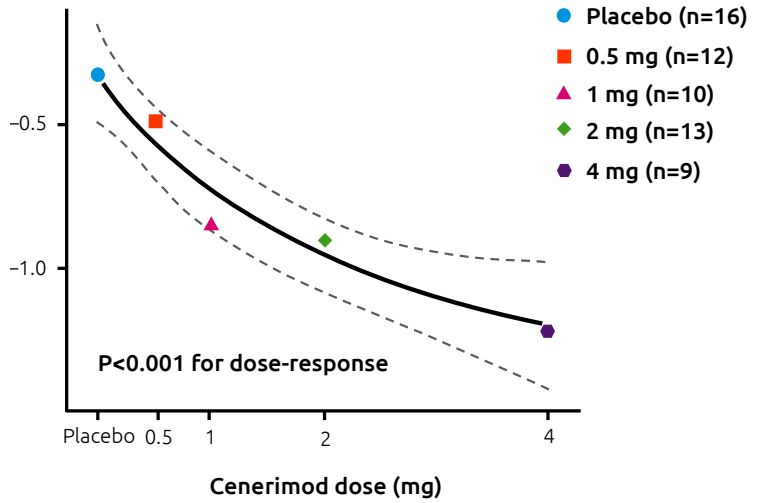
In a mouse model of SLE, mice typically develop an aggressive version of a lupus-like disease, with increased inflammation, autoantibodies and immune cytokines, resulting in damage to the kidney and death. When treated with cenerimod, an increase in survival was observed. This was underpinned by improved kidney structure and function, as well as marked decreases in important key markers of disease.

The effect of cenerimod on lymphocyte trafficking was confirmed in humans when administration of cenerimod induced a dose-dependent, sustained and reversible reduction in circulating lymphocyte counts.

In a Phase 2 proof-of-concept study investigating the effect of cenerimod on circulating lymphocytes, disease activity, safety and pharmacokinetics in SLE patients, cenerimod dose-dependently reduced total lymphocyte count from baseline to end of treatment ($p<0.001$). In addition, the antibody-producing B cells, which are elevated in patients with SLE and critical to the disease process, were markedly reduced by cenerimod.

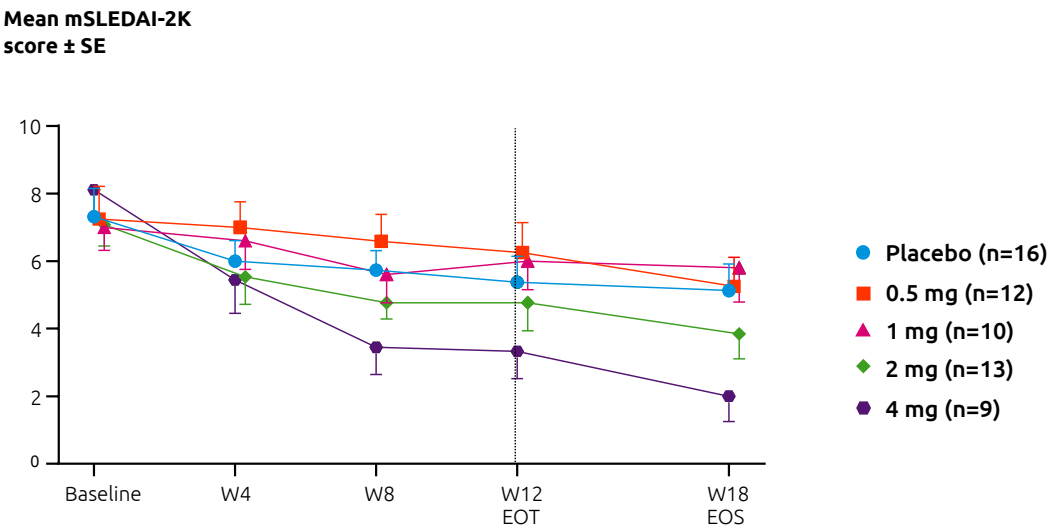
The study provided promising data, with an early indication of efficacy being numerical reductions in mSLEDAI-2K (one of the measures of disease activity) and in anti-double-stranded DNA antibodies. This is very encouraging, especially considering that the result was seen after only 12 weeks of treatment.

Cenerimod induced a dose-dependent reduction of total lymphocyte count in patients with SLE



Dashed line represents the 95% CI
Analysis set: Modified Pharmacodynamic Set
EOT, end of treatment - Week 12

Cenerimod induced numerical reductions in modified SLEDAI-2K in patients with SLE



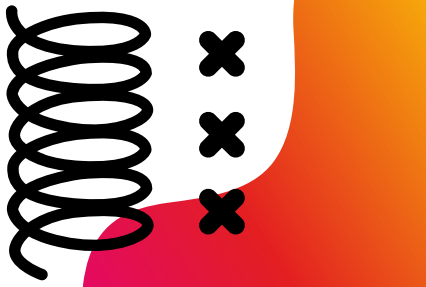
Analysis Set: Modified Pharmacodynamic Set
modified SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000 modified to exclude leukopenia; EOT, end of treatment; EOS, end of study

Cenerimod was well tolerated at all dose levels. The occurrence of adverse events was similar in all five treatment groups.

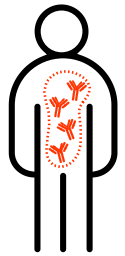
Current status

CARE is a multiple-dose efficacy and safety study with cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The aims of the study are to assess the safety and efficacy of cenerimod treatment at four different dose levels; to determine the appropriate dose, patient population and endpoints for further development in SLE; and to evaluate the effects on quality of life and fatigue, using patient-reported outcome instruments, as well as the effects on SLE biomarkers. Randomization will be completed by the end of February 2021, with at least 350 patients enrolled. The results are targeted for the second half of 2021.

In December 2017, the FDA designated the investigation of cenerimod for the treatment of SLE 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.



Systemic lupus erythematosus
Compound: Cenerimod



Mechanism of action:
$S1P_1$ receptor modulation
Status: Phase 2b

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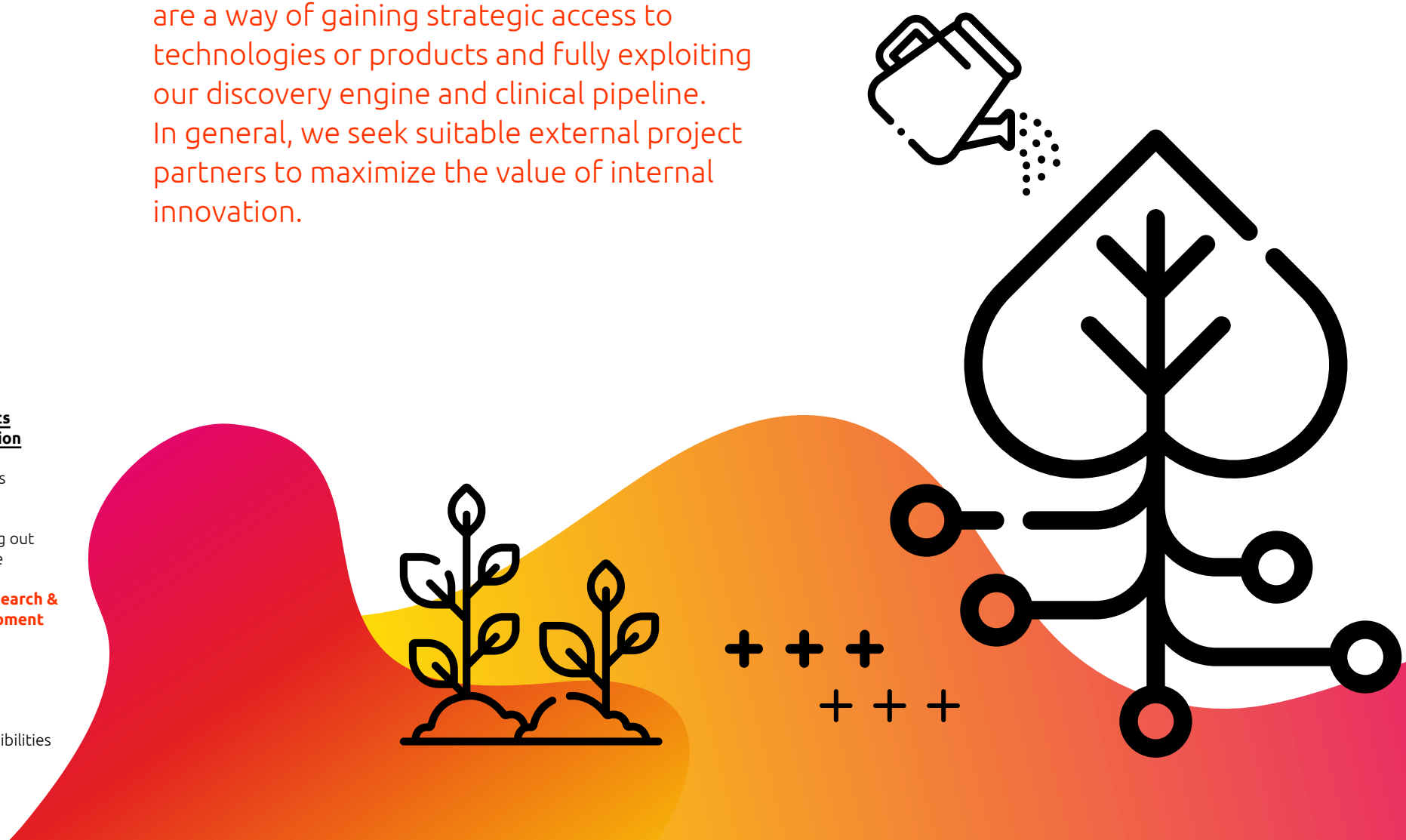
More cooperation – Maximizing the value of innovation

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.



Actelion Pharmaceuticals

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.
www.investor.jnj.com

Antares Pharma

In 2019, Idorsia entered into a global agreement with Antares Pharma to develop a novel drug-device product combining selatogrel – Idorsia's potent, fast-acting, reversible and highly selective $P2Y_{12}$ receptor antagonist – with the Antares subcutaneous QuickShot® auto-injector.
www.antarespharma.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.
www.janssen.com

Mochida

In 2019, Idorsia and Mochida Pharmaceutical entered into an exclusive license agreement for the supply, co-development and co-marketing of daridorexant, Idorsia's dual orexin receptor antagonist (DORA), for insomnia and related disorders in Japan.
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 potent, selective, orally active and brain-penetrating T-type calcium channel blocker, for the treatment of a rare pediatric epilepsy, and a research collaboration to discover, identify and develop additional novel T-type calcium channel blockers.
www.neurocrine.com

Roche

In 2017, Idorsia entered into a research collaboration that provides Roche with an exclusive option right to develop and market first-in-class compounds for a promising new approach in the field of cancer immunotherapy.
www.roche.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.
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 daridorexant, Idorsia's new dual orexin receptor antagonist, being investigated for the treatment of insomnia.
www.syneoshealth.com

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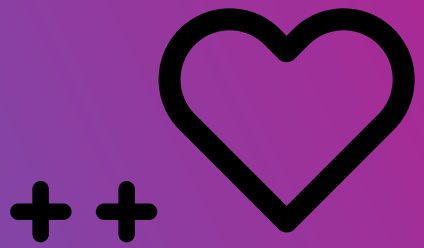
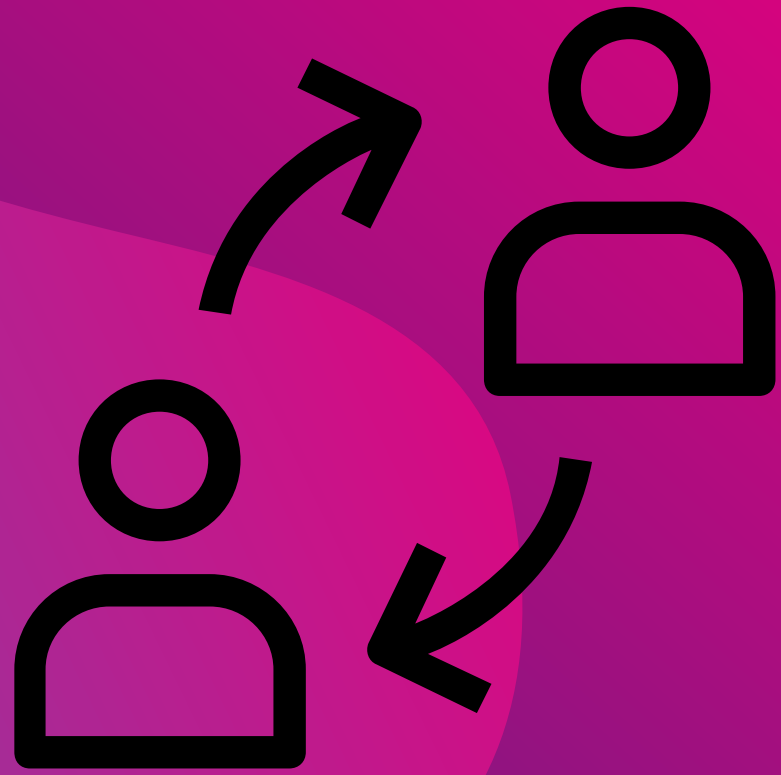
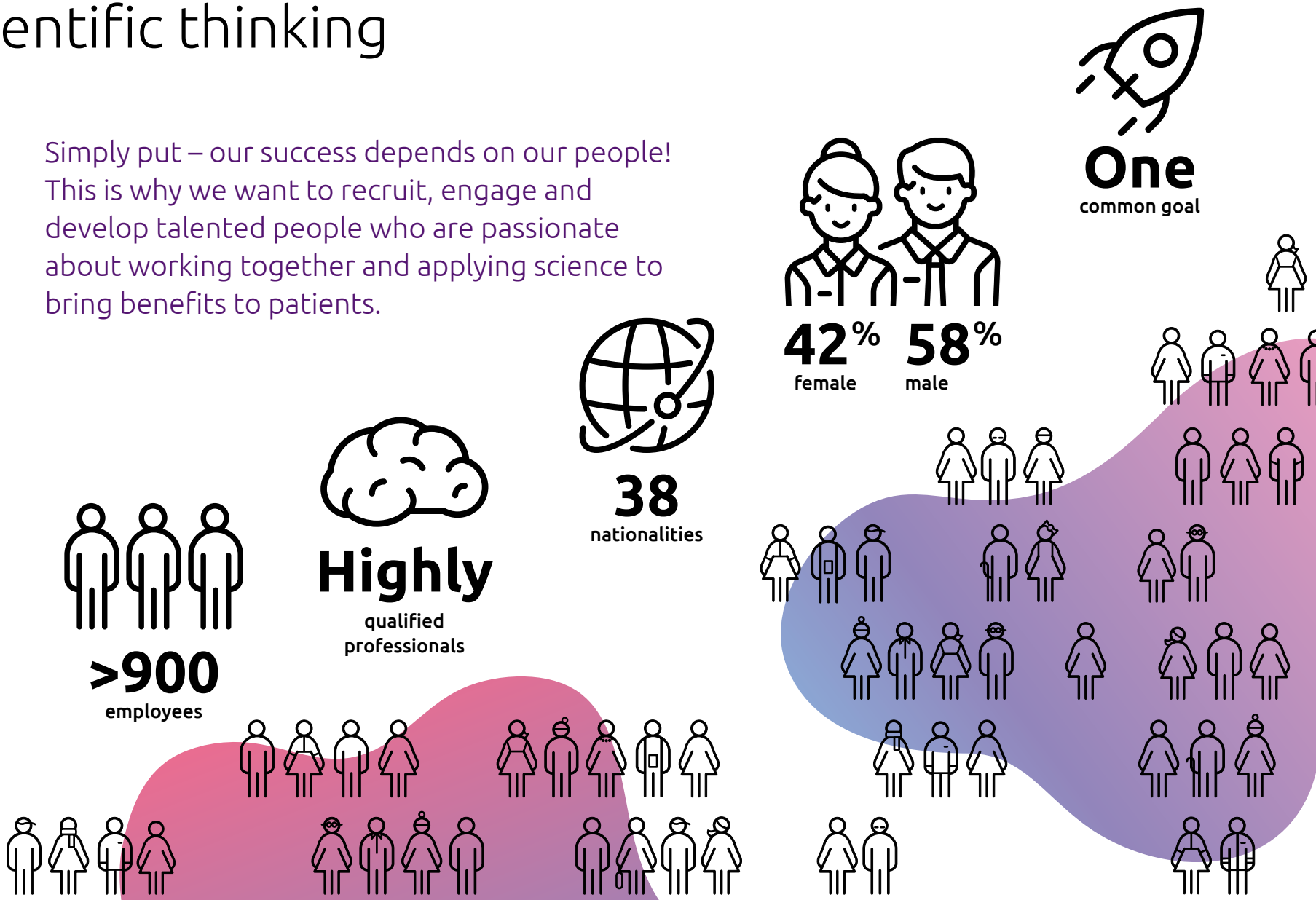




More power –
For scientific thinking

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.



More diversity – Creating opportunities

Advancing our R&D pipeline and preparing for commercialization requires the company to grow its talent base. As a result, we created more than 90 new positions worldwide in 2020.

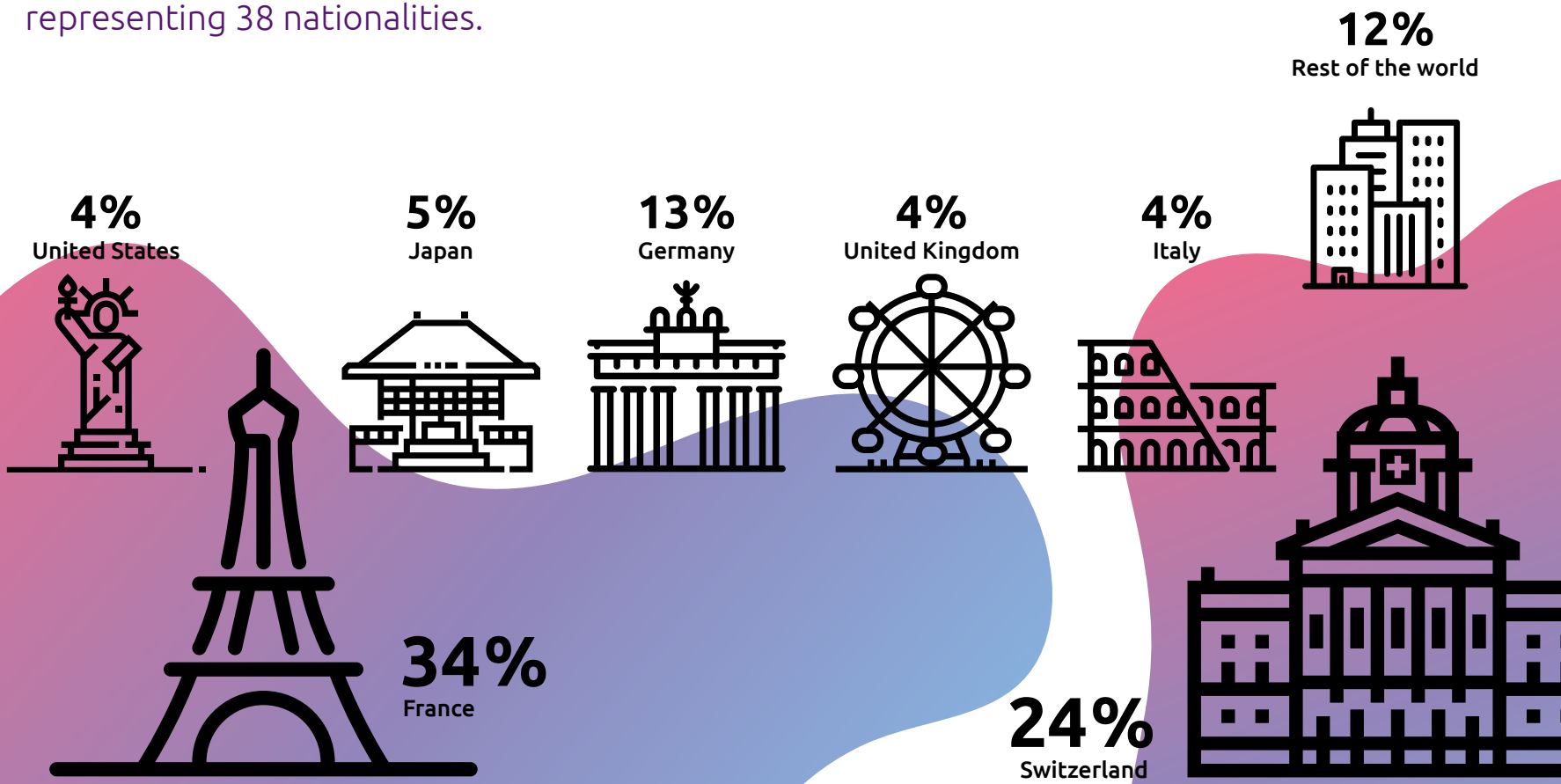
As a growing company, it is important that we attract, retain and advance top talent from all backgrounds and cultures. During the recruitment process, we seek to attract a diverse pool of candidates, focusing on the skill set they offer and matching their competencies to the behaviors we expect our people to live by daily and to the key qualifications required to fulfill the role.

Our people are committed to making Idorsia one of Europe's leading biopharmaceutical companies, while at the same time developing both personally and professionally.

"I'm very glad to have joined Idorsia at this stage of our journey. I've found a highly productive environment where people enjoy their work – it's a very exciting place to be."

Fenna Gloggner
Director, Global Customer Insights

At Idorsia, we harness the power of difference to achieve business success: our employees come from diverse cultural backgrounds, representing 38 nationalities.



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.

In 2020, we conducted a gender equal pay analysis, which encouragingly revealed that there are no relevant differences in pay between men and women at the Swiss Headquarters of Idorsia. The required standard regression analysis – validated by external auditors – of the effect of gender on base salary, and on base salary including annual bonus, showed a non-significant difference of -0.34% and -0.49% in favor of men, respectively, which is well within the 5% tolerance threshold specified by the Federal Office for Gender Equality. For more information please refer to the gender equal pay analysis description in the Compensation Report 2020.

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, offer a variety of training programs, and fully support language learning.

Idorsia also 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 launched a leadership program in 2018 to help managers become great leaders.

This year, we launched 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 experience and discover diseases which we are actively researching, such as lupus and Fabry disease, to help us keep the patient in the center of our daily activities. We also regularly organize internal campaigns to raise awareness of common diseases that could affect our employees, such as breast cancer, testicular cancer and mental health issues.

"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 Integrated Talent Management

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.

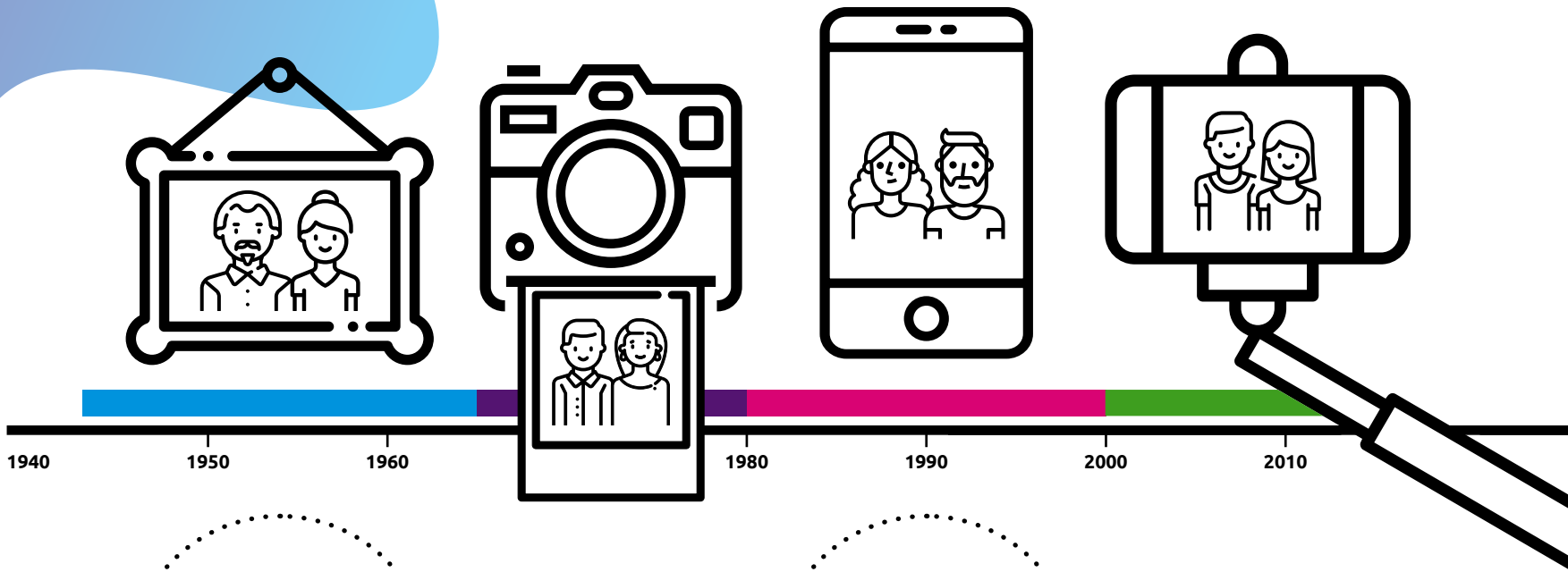
In addition to our stock-based programs, we recognize individual long-term engagement with Idorsia, through a special "Anniversary Vacation" (4 weeks' fully paid sabbatical leave) when employees reach their 10th, 20th and 30th anniversary of employment with Idorsia. Disconnecting from work for an extended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

"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

48%
Generation X
(1965 – 1979)
39% female
61% male

1%
Generation Z
(2000 – 2012)
43% female
57% male



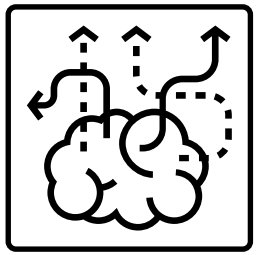
10%
Baby boomers
(1943 – 1964)
30% female
70% male

41%
Generation Y
(1980 – 1999)
49% female
51% male

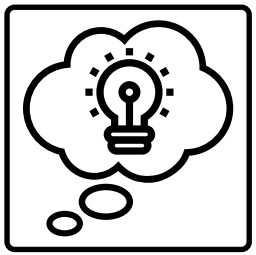
More ambitions – Courageous and energetic

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.

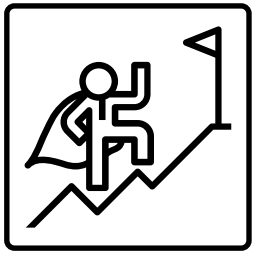
be pragmatic



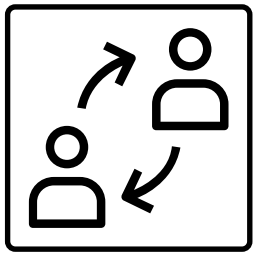
invent



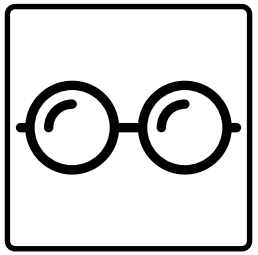
advance

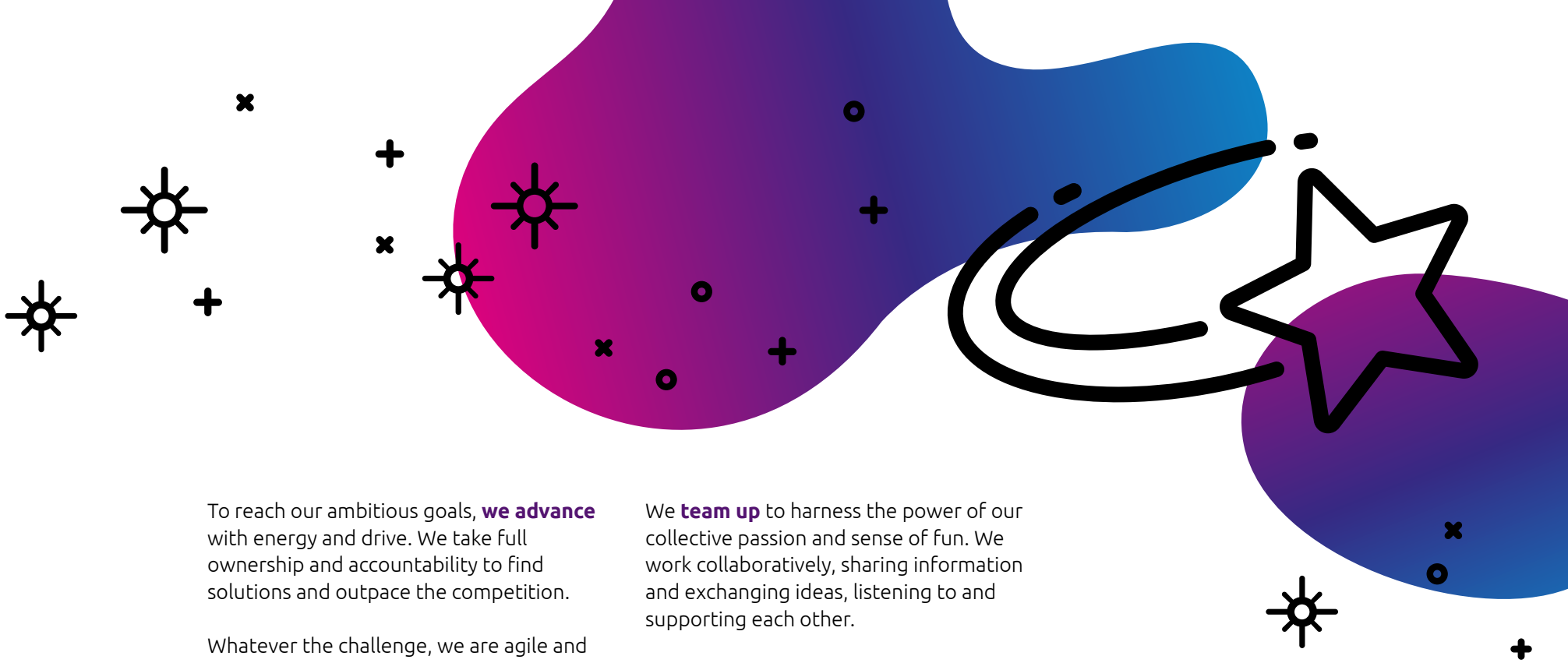


team up



learn





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've 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

More opportunities – Expanding the horizon

Since its foundation, Idorsia has added more than 250 professionals to its ranks. This rapid growth reflects the rapid advancement of our pipeline and ongoing preparations to bring our drugs to patients.

Initially, it was important to bolster the Global Information Services team. As so much of our work depends on smooth-running IT systems, we have made considerable efforts to establish a state-of-the-art environment, supporting all activities. Our proactive efforts towards state-of-the art technology over the past few years proved to be even more important in 2020, when we relied so heavily on technology to allow the company to function throughout the COVID-19 pandemic without missing a beat.

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,
Head of Global Clinical Development

Expansion was also required to ensure the development, manufacturing and control of high-quality drug products, needed first for clinical development and ultimately, of course, for our commercial launches.

We started to build our commercial capabilities in 2019, and this year, our Chief Commercial Officer hired further people to fill key strategic roles, such as the Head of Global Medical Affairs, Antonio Olivieri, Head of Global Supply Chain, Olivier Nalinne, President of Idorsia Europe and Canada, Jean-Yves Chatelan, and the President of our US commercial organization, Patty Torr. Since joining Idorsia in March 2020, Patty has already filled all key positions for her leadership team in the US.

We have formed a talented and diverse leadership team to commercialize and realize the potential of our deep and broad pipeline. The team members each have exceptional experience of the pharma world, in their respective functional areas, as well as a strong entrepreneurial mindset. This combination will be critical to our success as we move a step closer to commercializing our first product in the US.

"This is a very exciting time for Idorsia. I am very proud that such experienced and talented people have decided to join our company."

Jean-Paul Clozel
Chief Executive Officer

The Idorsia Executive Committee

André C. Muller
Executive Vice President, Chief Financial Officer

Jean-Paul Clozel
Chief Executive Officer

Our Responsibilities

More drive – For a better future

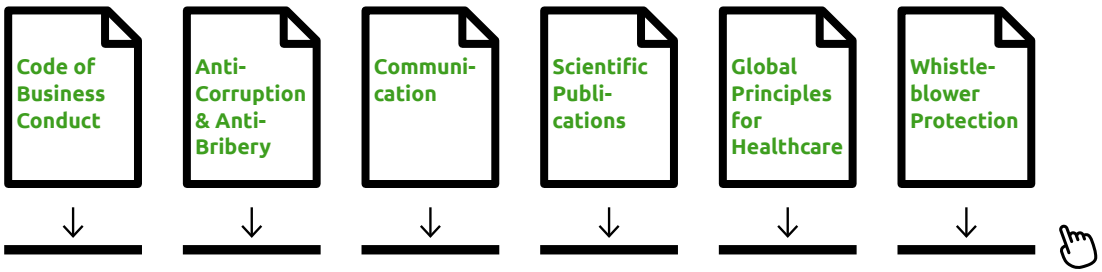
Idorsia's goal is to discover, develop and commercialize innovative medicines to help more patients. We believe that delivering on this mission is our core responsibility to our stakeholders and society in general. We also believe that it is possible to achieve this in an economically, socially and environmentally responsible manner.

Although we are, on paper, a young company, we have already established a robust governance framework, with a broad range of supporting policies, standard operating procedures and guidelines, such as our Code of Business Conduct, driving a culture of integrity.

Idorsia is proud to be working in a highly regulated industry, with codes of conduct, guidelines and regulations designed to protect patients, healthcare professionals and the reputation of the industry. We are a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The EFPIA and Idorsia are fully committed to complying with the highest ethical standards under EFPIA and National Codes.

To ensure that our employees understand how important it is to work in a compliant, ethical and transparent manner, Idorsia has implemented a number of policies and guidelines covering the breadth of its business areas. Access to these documents is ensured for all employees via an electronic quality management system. Policies which are relevant to other stakeholders are available on our corporate website and can be accessed below.



Sound corporate governance and high standards of ethical behavior are essential to the company's success, as well as in maintaining the trust and confidence of our stakeholders. Corporate governance at Idorsia is designed to promote the long-term interests of our shareholders, maintain internal checks and balances, strengthen management accountability and foster responsible decision-making.

Our Legal & Compliance function seeks to drive a culture of integrity, with the following priorities:

- communicate clearly to employees
- focus on key compliance risk areas
- improve compliance behavior through training and support
- ensure that employees can raise concerns and that these are properly addressed
- ensure fair and objective investigations of potential policy breaches

An example of best practice in governance is our Code of Business Conduct, which underpins our commitment to integrity and sets out fundamental rules for interacting with others as we drive our business forward. Supporting policies, standard operating procedures and guidelines provide more detail on how our high-level commitments are to be applied in practice.

All Idorsia employees have undergone mandatory training to ensure compliance with the Code.

The Idorsia Code of Business Conduct is at the foundation of our corporate culture and defines the core principles and ethical standards by which we create value in our company. It is the responsibility of every Idorsia employee to be familiar with and to comply with our Code. We are proactive in establishing policies and practices that support strong corporate governance and transparency. These policies and practices are continually reviewed and enhanced as appropriate.

Employees of Idorsia and its worldwide affiliates are responsible for always demonstrating honesty, integrity and respect in their work activities, obeying applicable laws and regulations, and adhering to Idorsia policies and procedures. Idorsia is committed to a work environment that encourages honest discussion of issues and concerns about legal compliance, company policy, and business conduct. Employees who learn of, or suspect, a legal, ethical or policy violation must raise it with their supervisor, the Corporate Compliance Office, or through the Global Compliance Helpline. Idorsia does not permit sanctions against anyone who, in good faith, raises issues, concerns or allegations of compliance violations or unethical conduct. Idorsia will investigate all allegations of misconduct and, where appropriate, take disciplinary and corrective action, up to and including termination of employment.

Anti-Corruption & Anti-Bribery

Full compliance with applicable laws in all the regions where Idorsia operates is crucial to our success. Idorsia's position is clearly stated in its Anti-Corruption and Anti-Bribery Policy: We take a zero-tolerance approach to bribery and corruption and are committed to acting professionally in all our business dealings and relationships wherever we operate.

We implement and enforce effective systems to counter bribery. We will uphold all laws relevant to countering bribery and corruption in all the jurisdictions in which we operate. All Idorsia employees are required to undergo training on this policy.

Labor & Human Rights

Idorsia respects the rights of its employees as set out in the Universal Declaration of Human Rights, and we fully comply with all relevant laws, rules and regulations governing labor, employment and the employment relationship in all the countries where we operate.

We respect the right of all employees to join a legally recognized employee association, and we comply with all laws relating to employee representation. We strive to maintain an open dialogue with all our employees and their representatives.

Due to the nature of our business and the location of our operations, the risk of child or forced labor is minimal. We do, however, remain vigilant for unexpected issues that may arise – not only in our own operations but also in relation to our procurement practices.

Privacy & Data Security

Idorsia understands the importance of protecting personal information and applying the highest ethical and regulatory standards. We are committed to respecting our stakeholders' privacy and safeguarding their personal information. Idorsia's data protection policy covers all personal data on study participants, healthcare professionals, customers, suppliers and employees.

To ensure the integrity and privacy of personal and health-related information provided to us, we use state-of-the-art information security programs, focusing on protection of sensitive information and detection of unauthorized access.

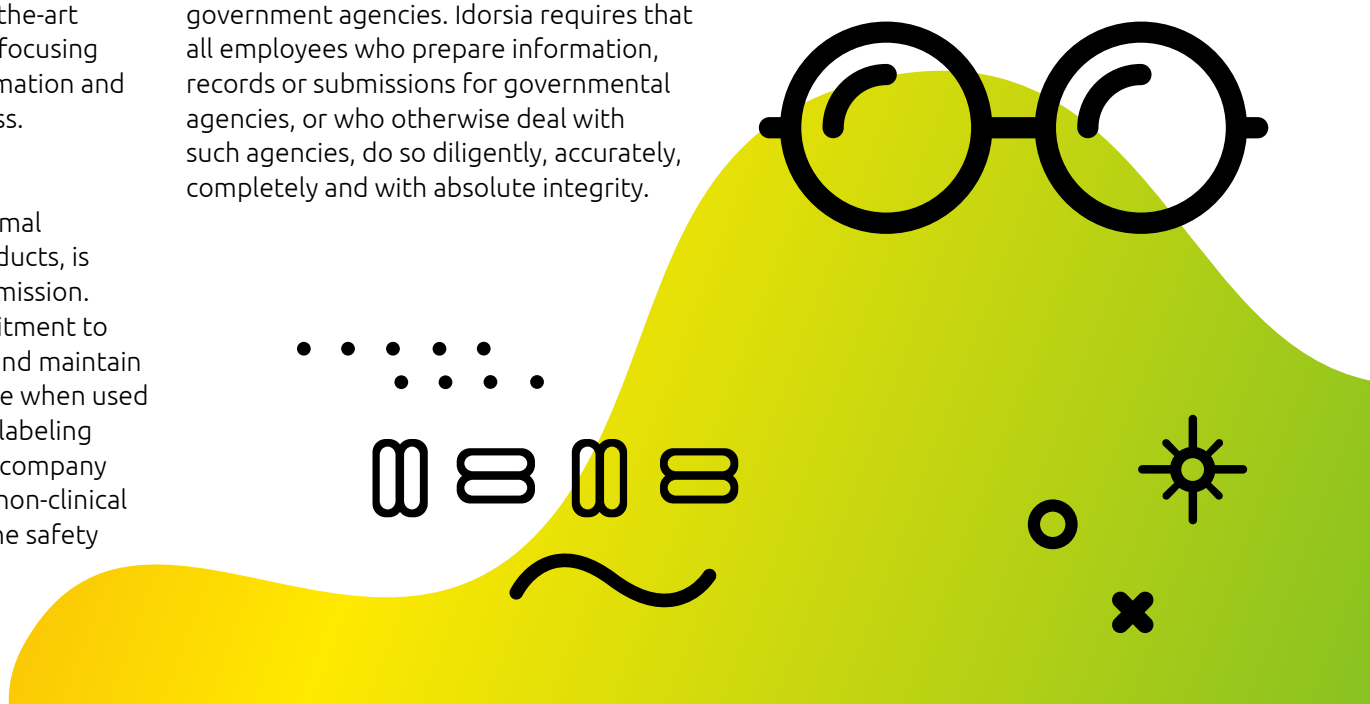
Safety & quality of products

Patient safety, through the optimal performance and quality of products, is fundamental to our company's mission. Idorsia takes seriously its commitment to ensure that our products have and maintain an acceptable risk-benefit profile when used in accordance with the product labeling and good medical practice. The company performs extensive and robust non-clinical and clinical testing to identify the safety and tolerability profile of products and, once approved for use, the products will continuously be monitored through the use of post-marketing surveillance and spontaneous reports from prescribers and patients. It is the responsibility of all Idorsia employees to promptly report any adverse drug experiences that they become aware of that could be associated with an Idorsia product to the company's Global Drug Safety Department.

Idorsia is also committed to quality in the manufacturing, packaging and testing of its products. To ensure patient safety, it strives to meet or exceed applicable regulatory authority requirements for current Good Manufacturing, Clinical and Laboratory Practices (cGXPs). Idorsia is required to compile and maintain numerous records and to file reports and applications with various government agencies. Idorsia requires that all employees who prepare information, records or submissions for governmental agencies, or who otherwise deal with such agencies, do so diligently, accurately, completely and with absolute integrity.

Clinical Trials Transparency

Clinical trials are essential to the development of innovative medicines. We are committed to the highest standards of quality and ethical conduct in all our clinical research. Our trials are performed in accordance with internationally accepted guidelines, and protocols are evaluated by independent review boards and ethics committees prior to study initiation. We are also dedicated to improving public health through responsible clinical trial data transparency which – while complying with applicable regulations – respects our proprietary information and patients' privacy.



With regard to access to medicines outside of a clinical study setting, Idorsia will use a set of criteria to determine whether access to Idorsia's Discretionary Compassionate Use Program can be provided to the patient, including available clinical data supporting an anticipated acceptable risk-benefit profile for the proposed use, as well as any potential implications for the overall clinical development of the medicine and the possible supply of the requested investigational drug.

Research ethics

We strive to maintain the highest ethical, scientific and clinical standards in all our research activities, and to comply with all national and international standards. Idorsia regularly reviews its research policies to align them with its strategic objectives and with the evolving values and goals of stakeholders.

Regulatory authorities around the world require pharmaceutical companies to test all new drugs before they are launched, and there is no alternative to including some animal testing as part of this process. This is essential both for scientific reasons and to safeguard the volunteers and patients who take part in subsequent clinical trials. As a fundamental principle, we support the "**three Rs**" in relation to animal testing:

Refinement – Alleviate or minimize impacts to animals by reducing potentially painful or invasive procedures, whenever possible.
Reduction – Use the absolute minimum number of animals required to obtain valid results in each study.
Replacement – Always look for alternative, non-animal-based research methods where possible.

The number of animals used in drug development has dropped dramatically over the past three decades as a result of industry initiatives of this kind. Idorsia has a strong policy on the care, welfare and treatment of animals, and we conduct regular audits to make sure that our expectations are being met, whether the studies are conducted in-house or outsourced.

In addition, we ensure that the use and care of all laboratory animals meets or exceeds relevant local, national and international regulations. Our programs and facilities are subject to unannounced regulatory review and inspections. For sponsored work at contract research organizations, our animal welfare oversight activities include regular on-site evaluations by our veterinary staff. Idorsia will never use great apes (gorillas, chimpanzees, orangutans and bonobos) in its research.

Health, safety and the environment

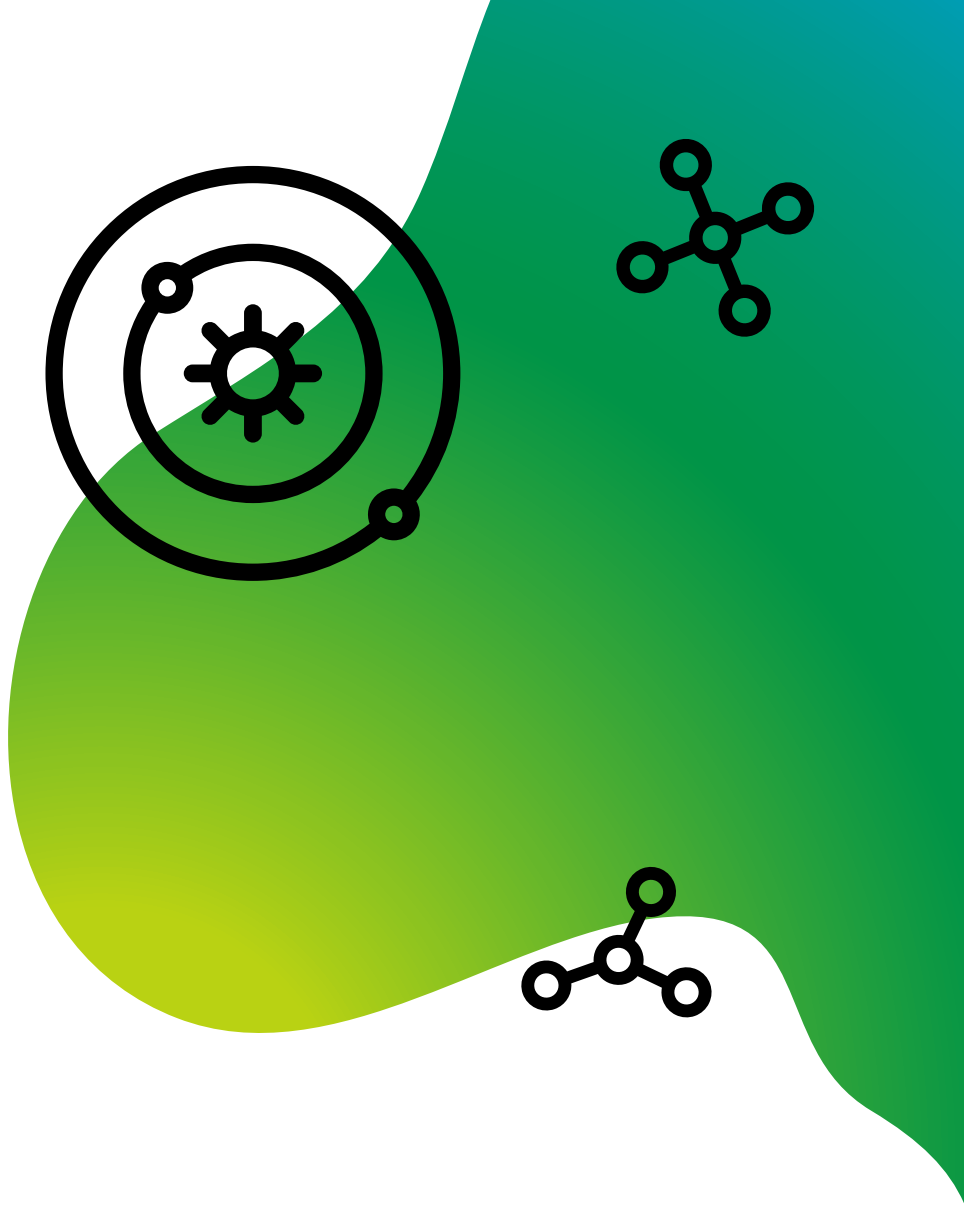
Idorsia recognizes that excellence in health and safety performance is integral to an efficient and successful business, particularly in the field of drug discovery. To this end, we have developed environmental, health and safety policies and procedures which employees are obliged to comply with. Employees must also attend required training and perform their jobs in a manner that promotes a safe and healthy workplace while also preserving and protecting the environment. This has never been more applicable than in 2020, as the company pursued its goals in the context of a global pandemic.

Supply chain management

Idorsia is committed to complying with all applicable laws and regulations in terms of managing our supply chain. In 2020, an internal audit was conducted by an external consultancy to review and assess supplier due diligence, bidding, selection and monitoring, as well as the vendor master data and supplier performance evaluation processes and controls. We are pleased to report that no significant issues were detected.

Transparent communication

Idorsia's goal is to be a company known for its open communication by proactively providing a regular flow of relevant information, thereby avoiding rumors, suspicion and mistrust resulting from concealment of information. Our communication is based on facts from evidence and confirmed data. We provide all information in a timely and consistent fashion and treat all stakeholders equally when considering their information needs. Our goal is to provide simultaneous, targeted dissemination of information and news relating to Idorsia. Moreover, in 2020, we reached out to many representatives of our stakeholder groups to better understand the topics that are important to them. More information on our approach to non-financial, or environmental, social & governance (ESG) reporting follows.



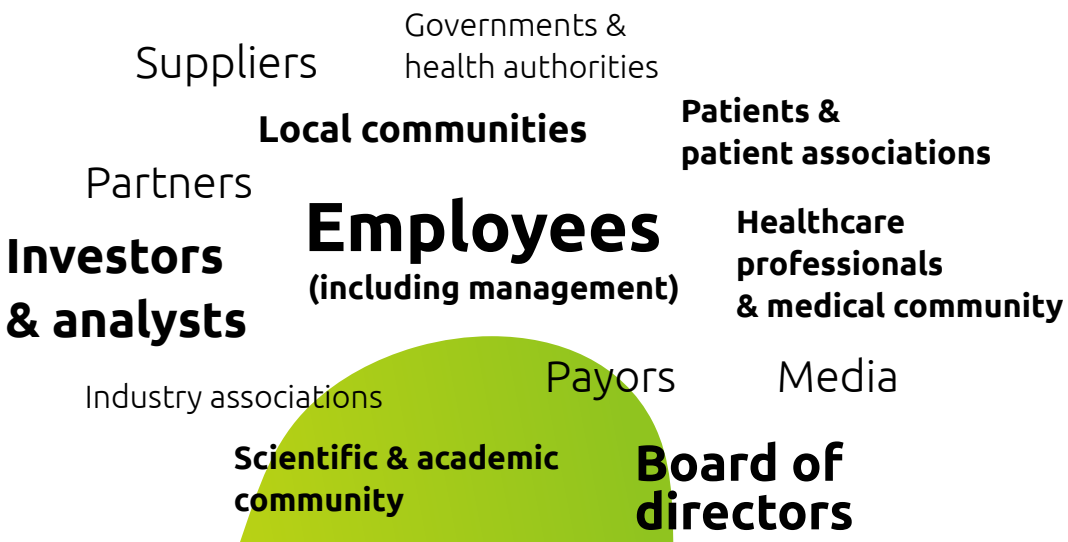
More authentic – Culture of transparency

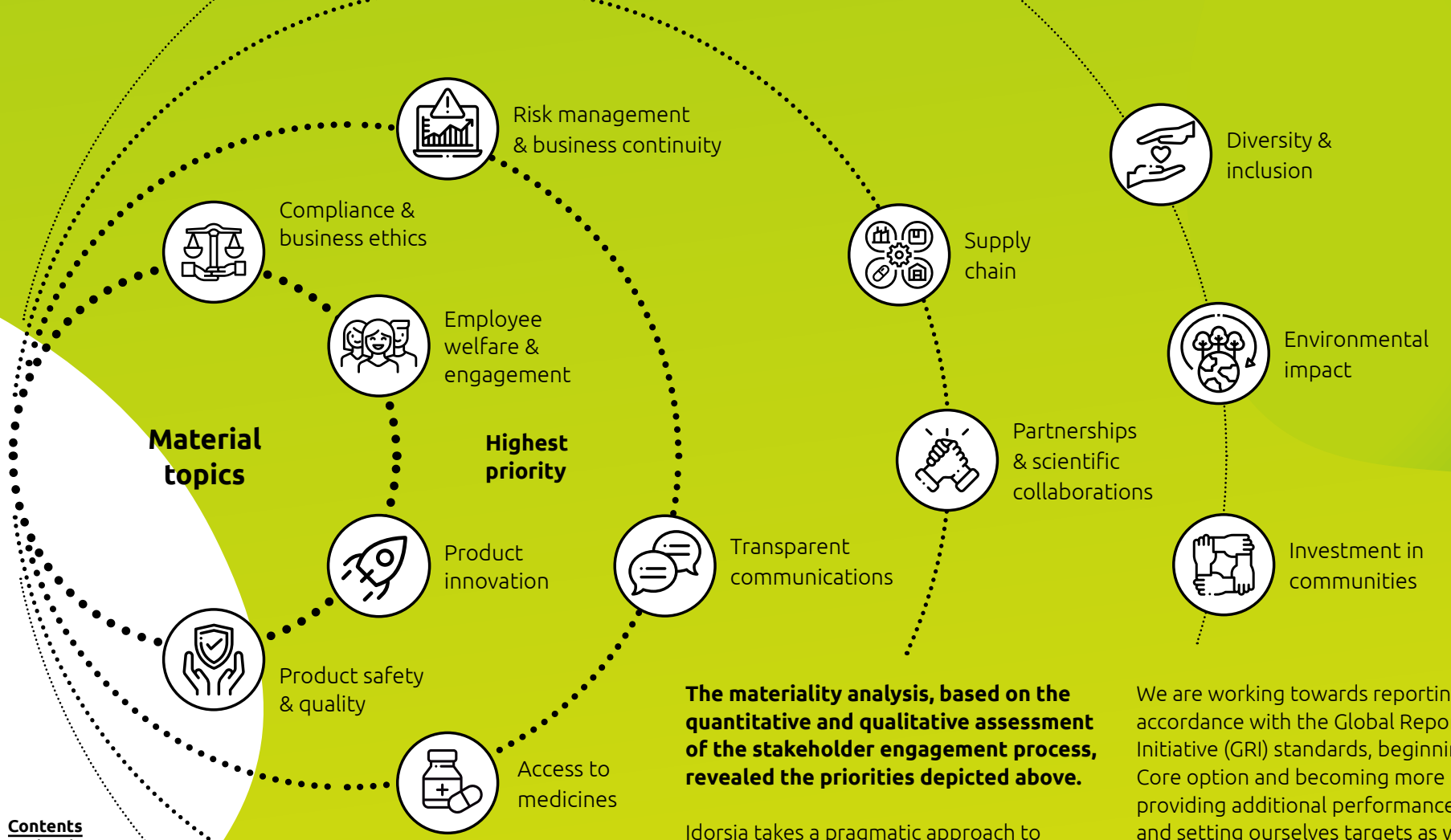
Idorsia aims to be open and transparent on the impact we have as a company on the environment, economy and society in general. We take our responsibility very seriously and seek dialogue with all our stakeholders to find out what really matters to them.

Increasingly, stakeholders are looking beyond the financial performance of a company to its overall impact on the economy, environment and society in general. Idorsia takes a proactive approach in responding to these expectations. In 2020, we set out to develop a tailored sustainability reporting strategy and framework for Idorsia.

To lay the foundations for our sustainability reporting – also known as non-financial or environmental, social & governance (ESG) reporting – we conducted a so-called materiality analysis and associated stakeholder engagement activities.

To begin with, we prepared a comprehensive list of both internal and external stakeholder groups that have an interest in Idorsia becoming a sustainable company, based on our contribution to value creation. We also identified the "material" topics that will be key to our success. We then engaged representatives from seven groups indicated in bold below – chosen because of the high impact they have on our immediate business needs – to validate and prioritize the topics that had been identified.





The materiality analysis, based on the quantitative and qualitative assessment of the stakeholder engagement process, revealed the priorities depicted above.

Idorsia takes a pragmatic approach to sustainability reporting. We will report on all 12 topics that were identified as being key to our sustainable future and of greatest interest to our stakeholders. We want to meet the expectations of our stakeholders, providing the desired information in an engaging format. We will ensure that our efforts and progress with the high-priority topics are described in greater detail, and the present report already provides greater transparency on these topics.

We are working towards reporting in accordance with the Global Reporting Initiative (GRI) standards, beginning with the Core option and becoming more robust, by providing additional performance indicators and setting ourselves targets as we grow. We may use additional standards – such as those of the Sustainability Accounting Standards Board (SASB) – to support the reporting of sector-specific topics.

For more information on Idorsia's commitment to stakeholders, our approach to corporate responsibility, and quantitative data on Idorsia's carbon emissions, water usage and waste management, please visit our website:
www.idorsia.com/our-responsibilities

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More ideas – Changing the world

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

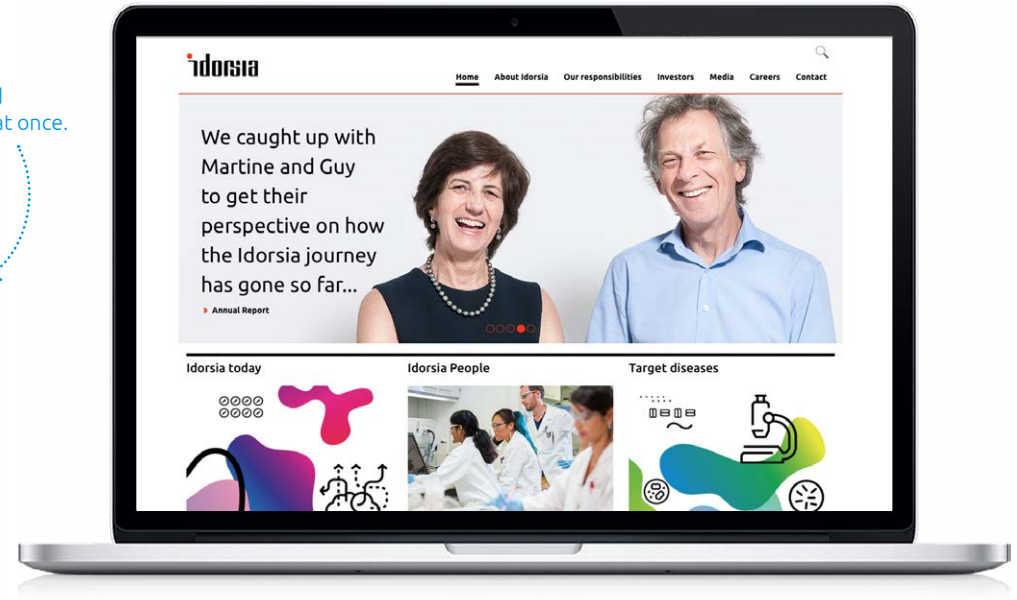
The core idea of the Idorsia brand is “Reaching out for more”. It is perfectly expressed in the energetic, intelligent and creative corporate design, and in the unified key messages.

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

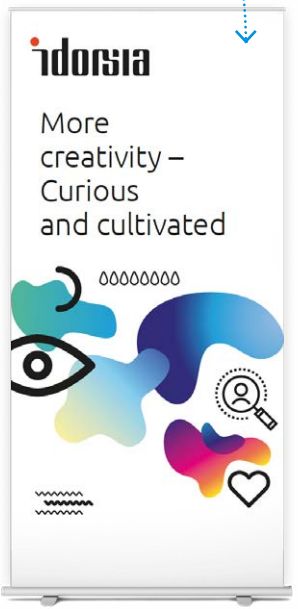
"When Idorsia was founded in 2017, we wanted to create a pharma brand that the world had not yet seen."

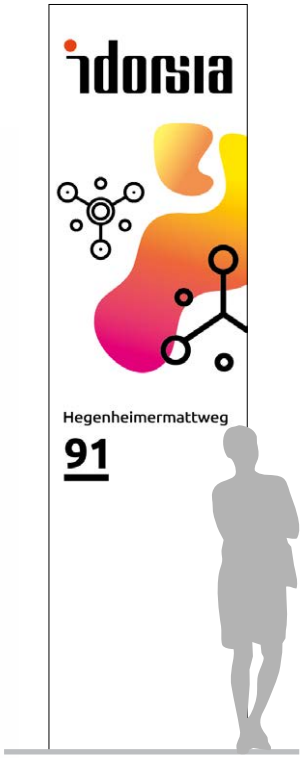
Jean-Paul Clozel
Co-founder and CEO of Idorsia

Joyful and scientific at once.



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

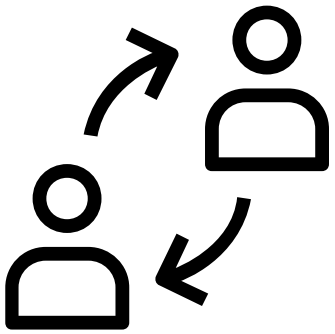


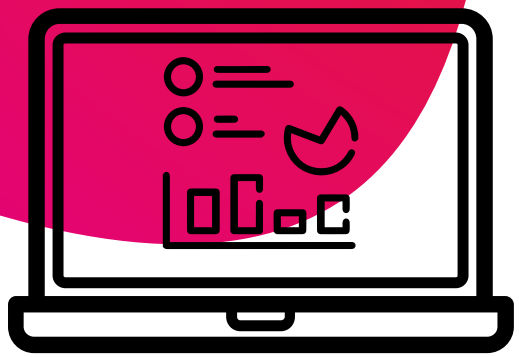


Robust design, born digital.

Enabling both endless variations and high recognition.

Be prepared for more





Curious to learn more?
Reach out to us.

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