Business Report

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ANNUAL REPORT
21

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 2021

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>1,100

Highly qualified professionals

11

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Rapidly expanding commercial footprint, covering the US, Japan and the largest markets in Europe

Strong

balance sheet

>550

State-of-the-art laboratory workspaces

More science – Bursting with ideas

Idorsia is a high-potential biopharmaceutical company, with an experienced team of over 1,100 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 11 assets, 6 of which are in late-stage development, and we expect to see two product launches in two of the largest pharmaceutical markets in the second quarter of 2022. 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) hold more than 25% of Idorsia's shares.

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

in CHF millions, except EPS (CHF) and number of shares (millions)	2021	2020
Revenues	35	72
Operating expenses	(612)	(444)
Operating income (loss)	(576)	(372)
Net income (loss)	(575)	(392)
Basic EPS	(3.41)	(2.75)
Basic weighted average number of shares	168.5	142.8
Diluted EPS	(3.41)	(2.75)
Diluted weighted average number of shares	168.5	142.8

* 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 2021 Financial Report.

"We started 2022 with a strong balance sheet which enables us to fully fund our first product launches. With these activities and the continued investment in our pipeline, I expect net revenue of around CHF 145 million and non-GAAP operating expenses around CHF 920 million leading to non-GAAP operating loss of around CHF 785 million, unforeseen events excluded. While we are not yet funded to break-even, I believe that sustainable profitability is within reach and this puts us in a strong position to close the funding gap."

André Muller
Executive Vice President, Chief Financial Officer

Milestones in 2021

2021 has been another exciting year for Idorsia, with the successful filing of our first new drug applications, the establishment of five affiliates in key European markets, and market preparation for our first products.

2021

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

March 2021
New drug application submitted to the Japanese PMDA for clazosentan for the prevention of cerebral vasospasm

March – August 2021
Marketing authorisation applications for daridorexant submitted to the European Medicines Agency (March), Swissmedic (April), and Health Canada (August)

March/May 2021
The US FDA and the European Commission approve ponesimod for the treatment of adults with relapsing forms of multiple sclerosis*

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

June 2021
Initiation of a Phase 3 registration study with selatogrel for the treatment of acute myocardial infarction

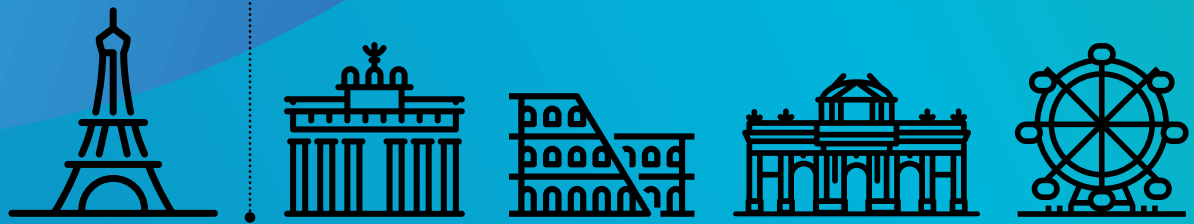
July 2021
Issuance of CHF 600 million of senior unsecured convertible bonds to fund the development of Idorsia into a leading biopharmaceutical company

November 2021
Based on the results from CARE, the Phase 2b study with cenerimod in SLE, Idorsia decided to advance into Phase 3

December 2021
Idorsia decided to further characterize lucerastat for Fabry disease by continuing the open-label extension of the Phase 3 MODIFY study

January 2022
PIVLAZ™ (clazosentan) approved in Japan for the prevention of cerebral vasospasm

September 2021
Five Idorsia affiliates established in key European markets



France Germany Italy Spain UK

January 2022
US FDA approves QUVIVIQ™ (daridorexant) for the treatment of adults with 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,

At the beginning of 2020, the world was facing almost insurmountable challenges. We needed a vaccine against Covid-19, and we needed it fast. The scientific and pharmaceutical communities stepped up in ways we have never seen before. Scientists from all over the planet collaborated to develop vaccines in record time. Now, just two years later, billions of people have been vaccinated and the first effective treatments are available for patients with the awful virus. What an incredible achievement for science and innovation, and what an unprecedented global effort!

I see great parallels to the way in which Idorsia's team has worked collaboratively – in challenging circumstances and with a great sense of urgency – to ensure that patients can benefit from our science and innovation.

This past year saw the company taking further strides to deliver on the ambitious strategic priorities that we defined just a few years ago. As well as continuing to innovate in the lab, Idorsia has advanced the clinical pipeline and prepared the way for introducing its first marketed products. Then, at the beginning of this year, we obtained not only the first approval for daridorexant – our novel insomnia treatment – in the US, but also approval for clazosentan – for the prevention of cerebral vasospasm – in Japan. With these pivotal events behind us, we have tangible evidence of the success of our strategy, and the company's future is more assured than ever.

My role and that of the Board is to provide direction and oversight, as well as governance of the organization. One of my passions is a focus on excellence in all aspects of the business. For this reason, over the past year, the Board has worked very closely with the management team to ensure excellent execution across Idorsia. Great science may deliver great products, but operational excellence is essential to ensure that patients can fully benefit from them.

"Idorsia's team has worked collaboratively – in challenging circumstances and with a great sense of urgency – to ensure that patients can benefit from our science and innovation."

Mathieu Simon
Chairman of the Board

One example of this focus on excellence is the recent creation of a Chief Medical Officer (CMO) role. As we take the final steps to become a fully fledged biopharmaceutical company with products on the market, the Board, together with the CEO, decided to appoint a CMO to unify the company's quality and governance standards. This role will promote an uncompromisingly ethical and scientifically rigorous approach throughout the life cycle of all products in Idorsia's pipeline, ensuring safe and appropriate use of our medicinal products and high ethical standards in engagement with various stakeholders.

Another example can be seen in the appointment of top-quality people with deep expertise and understanding in the various regions where we are establishing our global infrastructure – first in Japan, then in the US, and most recently with our rapid expansion in Europe. Having top-class people to launch our products gives me great confidence in our ability to be successful in the primary care field. We have great products and great people, whose experience has enabled them to develop great strategies, tailored to their markets.

I do, however, recognize that, as we are just entering the launch phase, we have some way to go before success is guaranteed. To advance rapidly, we must therefore maintain our disciplined approach, mitigating risk wherever possible. Our experienced Board members and management continue to carefully weigh our options for closing the liquidity gap until we reach the point of sustainable profitability, which we now see on the horizon in 2025. Having successfully pursued our strategic priorities so far, we are now on the cusp of transformation.

We are building Idorsia with a long-term focus, and we run the company in a responsible and sustainable way. Our progress towards this goal is demonstrated by numerous non-financial measures, and our commitment to transparency on topics important to our stakeholders remains as strong as ever. In this year's report, you will see the progress we have made in 2021 towards meeting internationally recognized standards on non-financial reporting, and how we are pursuing a dialogue with all our stakeholders.

As Chairman, I am extremely proud of what has been achieved in another challenging year. I would like to take this opportunity to thank the Idorsia team around the world and encourage them to maintain their entrepreneurial mentality and their commitment to executional excellence. I also thank you, our shareholders, for your confidence in us and for accompanying us on this extraordinary adventure.

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,
As we approach our fifth anniversary, Idorsia's future is brighter than ever. In 2021, we made great strides toward realizing our vision of creating a sustainable mid-sized biopharmaceutical company based on innovation.

The pandemic continues to affect the way we collaborate with one another – in this company, as in almost every other company around the world. Even so, it has not impacted the productivity of our highly resilient employees, as we have achieved all the ambitious goals we set ourselves for 2021. In January 2022, we saw the culmination of these efforts, with the first approval for QUVIVIQ™ (daridorexant) for adults with insomnia in the US, and the Japanese approval for PIVLAZ™ (clazosentan) for the prevention of cerebral vasospasm and vasospasm-related cerebral infarction and cerebral ischemic symptoms following treatment for aneurysmal subarachnoid hemorrhage (aSAH). I cannot overemphasize the importance of these approvals – both for the patients whose lives can now be transformed by new treatment options and for our company's evolution.

Close followers of Idorsia will remember that, at our inception, we defined five strategic priorities to help us achieve long-term success. Here, I will review the strong progress made on each of these fronts in 2021.

Deliver at least three products to market

With no fewer than six assets in Phase 3 or registration, the strength and depth of our pipeline is unparalleled, thanks to our unique origins and our team's ability to progress these assets at pace. In addition to the approval of QUVIVIQ in the US, daridorexant is well on track to become a global product. It is currently under review for market authorization by health authorities in the EU, Switzerland and Canada, and we anticipate a decision by the European Medicines Agency in the second quarter of 2022. To ensure that daridorexant reaches its full potential, the healthcare community needs to understand the data we have generated and the key differences from other treatments. I was therefore very happy to see the recent publication by our investigators in the prestigious peer-reviewed journal *The Lancet Neurology*, describing in depth the evidence concerning both nighttime symptoms and daytime functioning.

Meanwhile, the excellent data from the clazosentan studies in Japan helped us to achieve a fast-track approval from the Japanese health authorities. The global REACT study of clazosentan is on track to conclude at the end of 2022, and we hope to follow our Japanese team's lead by bringing this much-needed treatment to patients with aSAH around the world.

Our first major clinical read-out of 2021 was the results of the MODIFY study of lucerastat in patients with Fabry disease. While the primary endpoint – an improvement in patient-reported neuropathic pain – was unfortunately not reached, a possible treatment effect on organs was seen, requiring confirmation over the long term. By continuing to collect data in the ongoing open-label extension study, we will determine whether the signals observed so far indicate organ protection in the kidneys and heart, which would then warrant further efforts to progress this compound for the benefit of these patients. Our next step is to confer with the FDA on the regulatory path forward for lucerastat.

Also reported in 2021 were the results of our Phase 2b CARE study of cenerimod in patients with systemic lupus erythematosus – one of the largest studies of its kind. Here, the 4 mg dose of cenerimod demonstrated a very marked clinical effect, and the study has helped us to hone the design for Phase 3, with a clearly defined patient population, optimal dose and endpoints. We will now work with the FDA to ensure that we can move forward rapidly.

2021 also saw the completion of recruitment for the Phase 3 study of aprocitentan, a potential treatment for difficult-to-treat hypertension, and we expect to report results from this exciting study in mid-2022.

Our Phase 3 study of selatogrel for suspected acute myocardial infarction, with its unique autoinjector device, began in 2021 and recruitment is now underway at a growing number of sites around the world.

In parallel with the progress of our late-stage assets, recruitment for the proof-of-concept study of our selective orexin-1 receptor antagonist for binge eating disorder was completed at the end of 2021, and we aim to report results in mid-2022. We also progressed our drug discovery and early-stage clinical pipeline assets, building the evidence for these future growth opportunities.

Build a world-class commercial organization

We have already been running clinical trials on a global scale, but now we are truly going global, with commercial operations now firmly established in the US, Japan, and Europe so that we can bring our products to patients worldwide.

As we gear up for our first launches, we have been focusing on two closely linked sets of activities that are essential to ensure our success: firstly, the establishment of our commercial footprint – the people, infrastructure and processes required for commercial operations; secondly, preparations for the launches of daridorexant and clazosentan in 2022. We have been building the plane as we fly it!

"Our innovations now truly reach from bench to bedside."

Jean-Paul Clozel
Chief Executive Officer

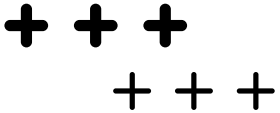
Patty Torr's US team have prepared a launch plan that is as innovative as QUVIVIQ itself. Many people are asking how Idorsia, a relatively new start-up, can be successful at launching a primary care product where others have failed. The answer is quite simple: we have a great product, a great team, and a great approach to go to market. The outstanding qualities of our product have been captured in an excellent label, and we have already kicked off several innovative initiatives to educate the US market about the seriousness of insomnia as a medical condition – including the incredibly exciting ***Seize the Night & Day*** campaign, fronted by Jennifer Aniston. As we approach the launch of QUVIVIQ in May, our medical and sales teams are gearing up to execute our robust launch plans across the country.

Meanwhile, in Japan, Satoshi Tanaka's highly motivated team have spent 2021 ensuring that they are well prepared to launch PIVLAZ – the first innovation for patients suffering from events associated with cerebral vasospasm in more than 30 years. We have developed strong partnerships with the leading experts and key centers across the country responsible for the vast majority of aSAH treatments. I'm confident that our Japanese team are ready to execute a flawless launch of PIVLAZ starting in April 2022.

For our Europe and Canada (EUCAN) region, led by Jean-Yves Chatelan, the past year has been foundational, with five commercial affiliates established across key European markets – Germany, Italy, France, Spain and the UK. The country leadership teams are now rapidly ramping up as we approach the expected EMA decision on daridorexant, with our first European launches to follow later this year.

Bring Idorsia to sustainable profitability

Our strategy to reach profitability relies on dual revenue streams. First, we will generate our own sales income, starting in 2022 with daridorexant and with clazosentan in Japan, to be followed by other products from our pipeline. A second stream will come from partnerships, such as the revenue-sharing agreement for ponesimod, which is marketed by Johnson & Johnson and was approved in the US and Europe in 2021. Johnson & Johnson will likewise market aprocitentan, subject to approval, with Idorsia also benefiting from a revenue-sharing agreement. We have also entered into several other milestone-based partnerships which will supplement our revenues.



Major shareholders	(as of December 31, 2021)
Jean-Paul and Martine Clozel	27.44%*
Cilag Holding AG	5.41%*
Rudolf Maag	5.08%*

* Based on the share capital as of December 31, 2021

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

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

Key share data	(as of December 31, 2021)
Shares outstanding	177.0 million
Closing share price	CHF 18.64
Market capitalization	CHF 3.3 billion
52-week high	CHF 29.76
52-week low	CHF 15.80
YTD price change	CHF -6.88 (-26.96%)
Annual average daily volume	396,726 shares
Free float	119.4 million shares

Based on our current sales forecasts and with our disciplined approach to spending, we now expect to become profitable in 2025. This is quite an impressive feat, given that we started with an early- stage pipeline less than 5 years ago and are advancing so many different assets in parallel. We are confident that, once we reach break-even, our rich pipeline can continue to sustain and fuel growth well into the future.

Fuel our pipeline with new discoveries

At Idorsia, drug discovery based on organic chemistry is a strategic choice. We create small-molecule drugs which are suitable for the treatment of acute and chronic diseases, while also meeting key criteria such as ease of administration, affordability and strong patent protection. Idorsia's clear focus allows for differentiation from peer companies diversifying into large molecules, such as biologics, CAR-T and other cell-based therapies. The design and synthesis of small molecules of increasing complexity relies on expertise in organic chemistry, and we are fortunate enough to have some of the world's best chemists in our ranks.

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

Idorsia continues to invest in leading-edge systems and capabilities, embedding the most advanced technologies into our methods so as to drive innovation across the value chain. These range from computer modelling and artificial intelligence to support our ability to discover new drug candidates, to advanced analytics and digital/social platforms to enhance engagement with our stakeholders in the commercial space.

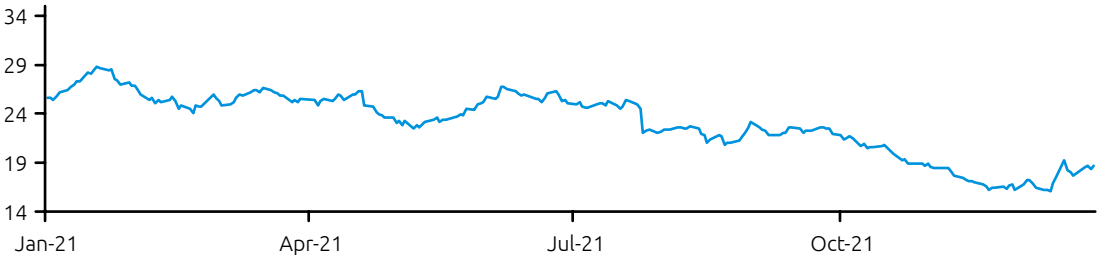
We had high expectations for 2021, and I am proud to report that these have been fully met. We entered the year with a strong balance sheet, and we are starting 2022 with that same level of funding. We achieved all the operational and clinical milestones we set for ourselves, and we are on track for a transformational year in 2022. This is the year in which Idorsia will become a commercial company, simultaneously launching two products in two of the largest pharmaceutical markets. It is also the year we will put sustainable profitability firmly within reach and become a fully fledged biopharmaceutical company – able to bring our innovative therapies to more patients.

Best regards,

Jean-Paul Clozel
Chief Executive Officer

Share price development

(in CHF)



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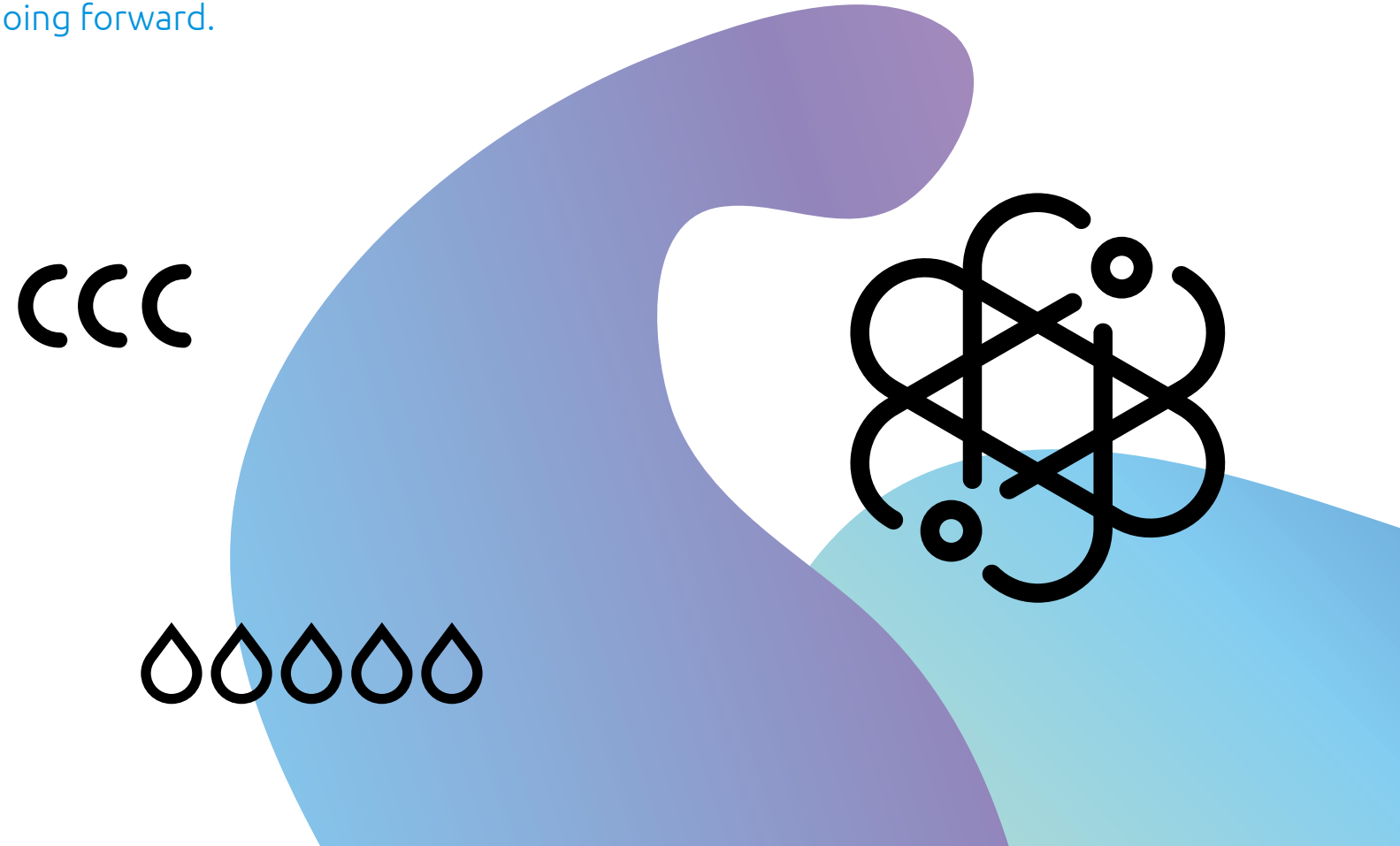
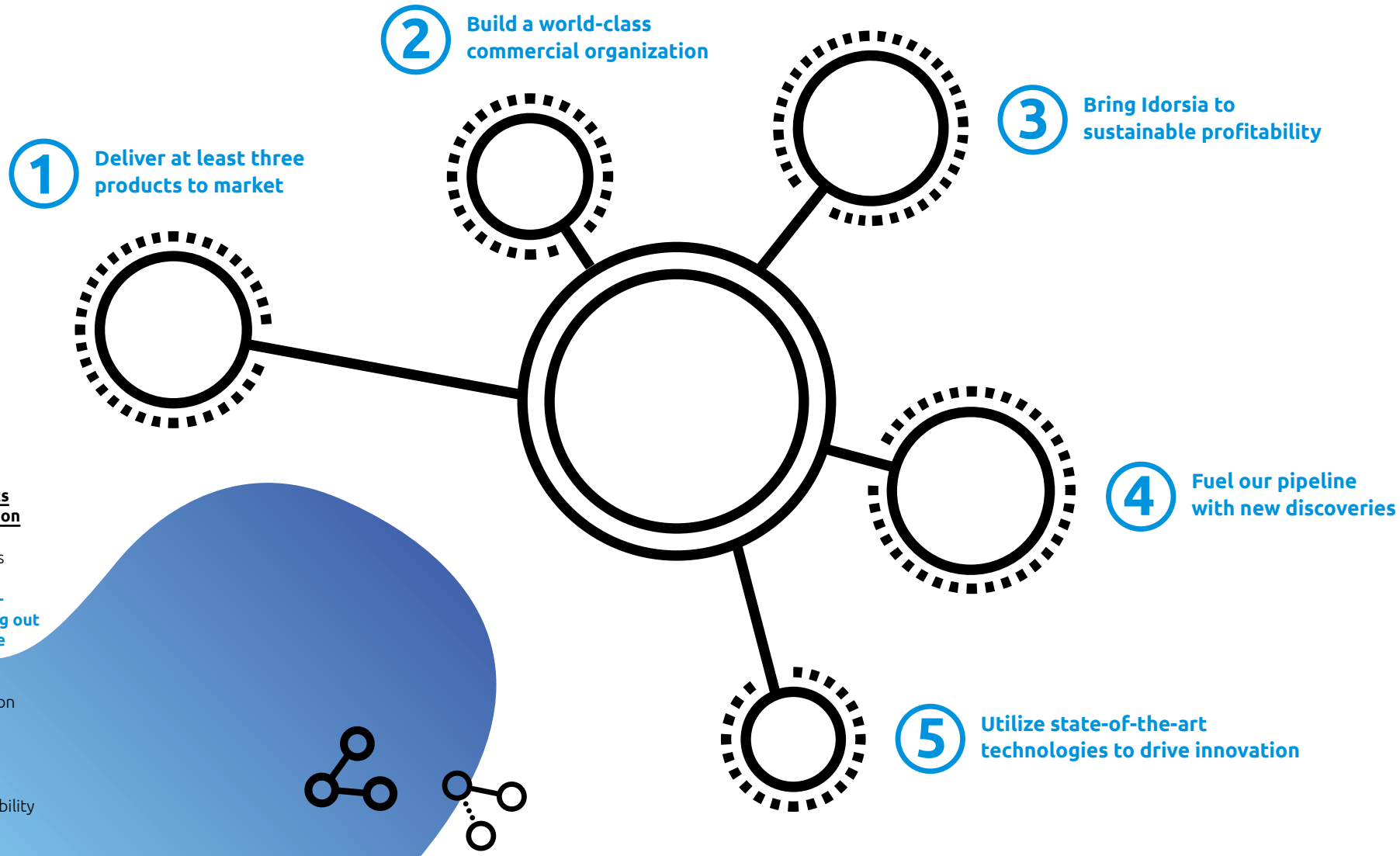
Our strategic priorities

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



More energy – Growing and delivering



Deliver at least three products to market

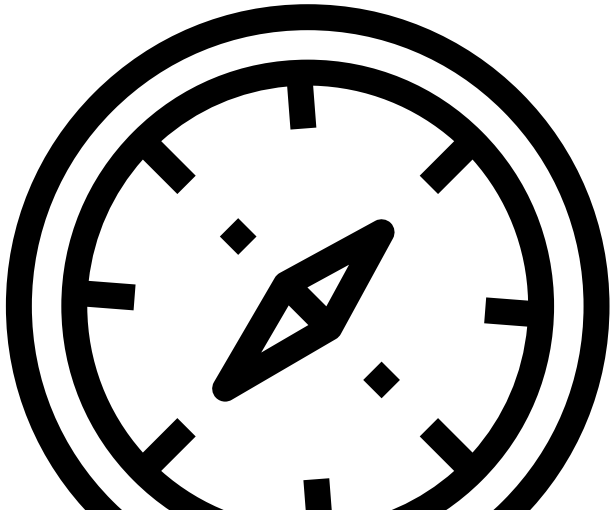
1

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 11 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 near term. Our late-stage pipeline is described in detail in the "Our Innovation" section of this report (from page 32).



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 associated with aneurysmal subarachnoid hemorrhage, using scientific and medical evidence to engage effectively with experts in the field and with payors. We plan to remain flexible and nimble in the way we commercialize our portfolio, 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, Japan, and the major European markets, with experienced leadership teams and strategic locations. We have also established a robust and lean global supply chain function to ensure consistent supplies of our innovative medicines to patients.

Bring Idorsia to sustainable profitability

3

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 our first development compounds reach the market.

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

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

Fuel our pipeline with new discoveries

4

While 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.

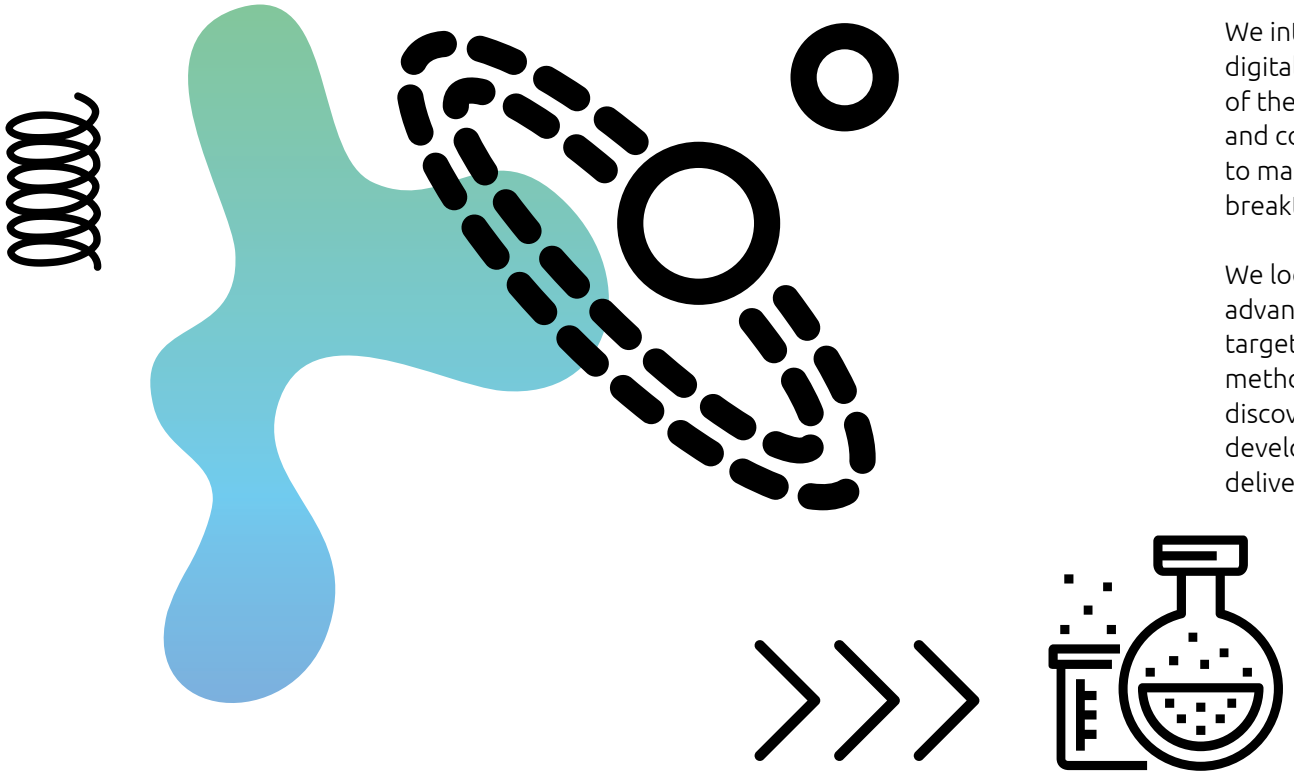
In addition to several drug candidates in the early stages of clinical and preclinical development, we must continue with our discovery efforts, to maintain a steady supply of innovative compounds to our pipeline. We aim to create a pipeline with a sales potential of at least CHF 5 billion.

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

Going global

"We have the enormous challenge – and pleasure – of preparing for the successful launch of not one, but two products in different regions in 2022: QUVIVIQ™ (daridorexant) in the US and Europe, and PIVLAZ™ (clazosentan) in Japan. I'm excited about the unique opportunity we have ahead of us. Building an organization from the ground up, combined with launching two products in major markets, is the type of challenge that energizes me and the people in my team."

Simon Jose
Executive Vice President, Chief Commercial Officer

Simon Jose, Idorsia's Chief Commercial Officer, leads a team which spans global functions in Marketing, Medical Affairs, Value & Access and Supply Chain, as well as commercial operations in our US, Japan and EUCAN (Europe and Canada) region affiliates.

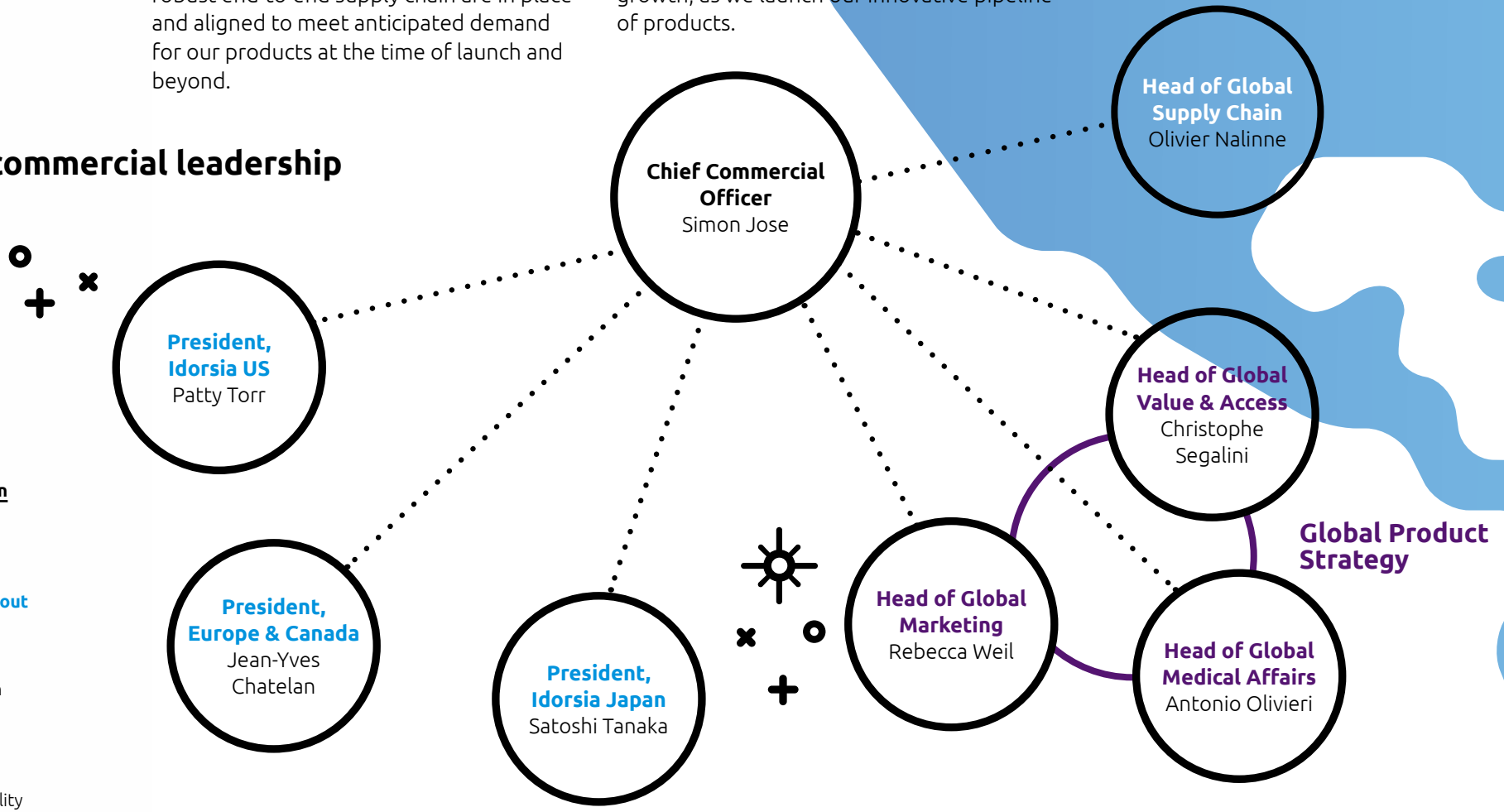
The global product strategies are developed by our Marketing, Medical Affairs and Value & Access functions in close collaboration with the major affiliates and with our research and development teams.

Here, the deep understanding of each asset built up during the discovery and development phases is brought together with the unmet needs of prescribers and patients, along with the opportunities arising in the markets we will enter. The Supply Chain function is also part of the global commercial organization, ensuring that all the components required for a robust end-to-end supply chain are in place and aligned to meet anticipated demand for our products at the time of launch and beyond.

We have made enormous progress building our country affiliates in 2021, in line with our strategy of focusing on those markets where the largest numbers of patients can benefit from our products. The US, Japan and EUCAN major markets will be our commercialization engine, and we are prioritizing our efforts in these countries. They will be the key to generating long-term growth, as we launch our innovative pipeline of products.

Our commercial team, both in our global functions and in our affiliates, is building an organization to last – one that can realize the full potential of today's products and of those to come, well into the future.

Our commercial leadership



More horizons – expanding globally

Our commercial organization

2017 **Idorsia Pharmaceuticals Ltd**
Allschwil, Switzerland

2018 **Idorsia Pharmaceuticals Japan Ltd**
Tokyo, Japan

2020 **Idorsia Pharmaceuticals US Inc.**
Radnor, Pennsylvania

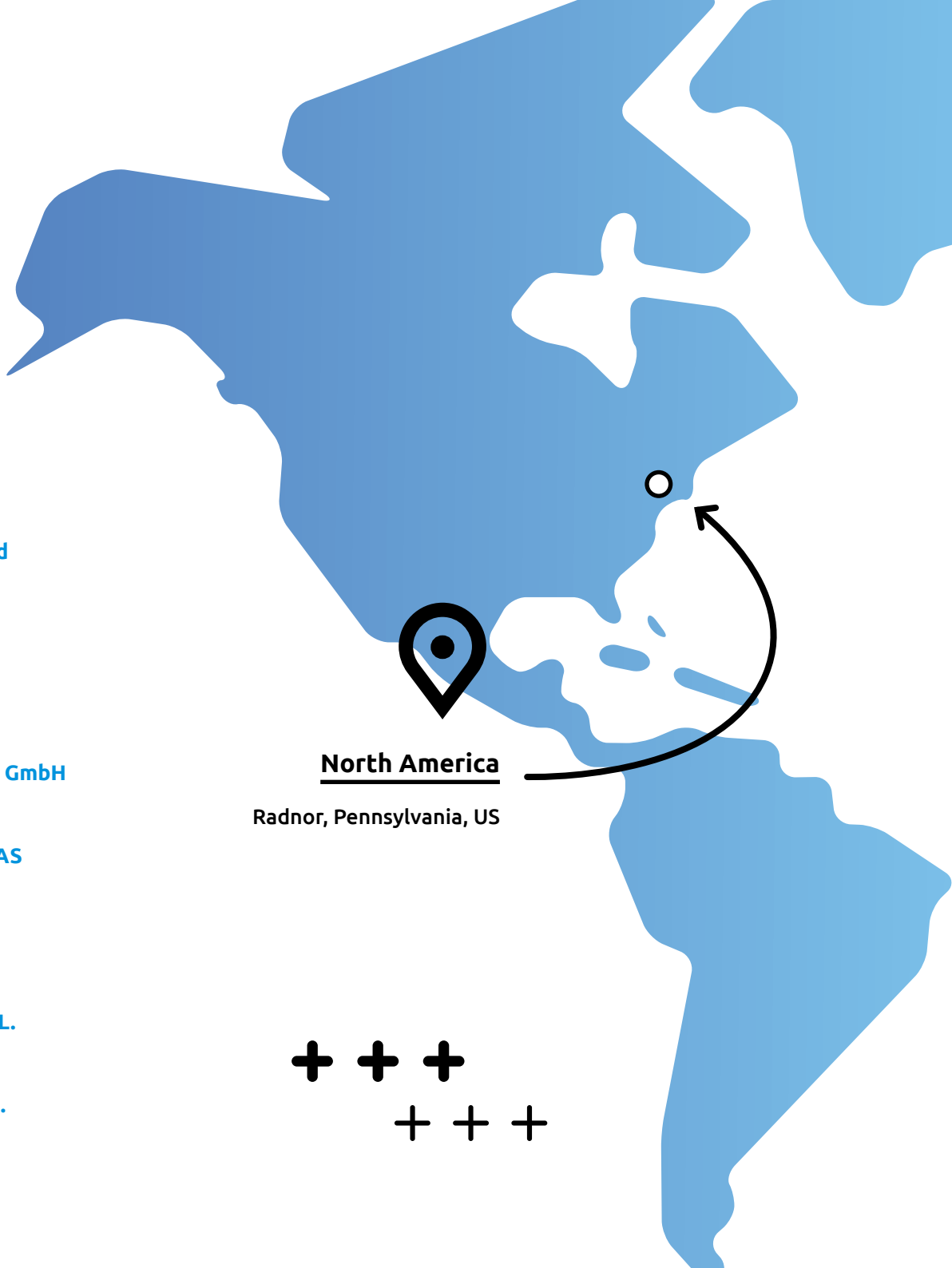
2021 **Idorsia Pharmaceuticals Germany GmbH**
Munich, Germany

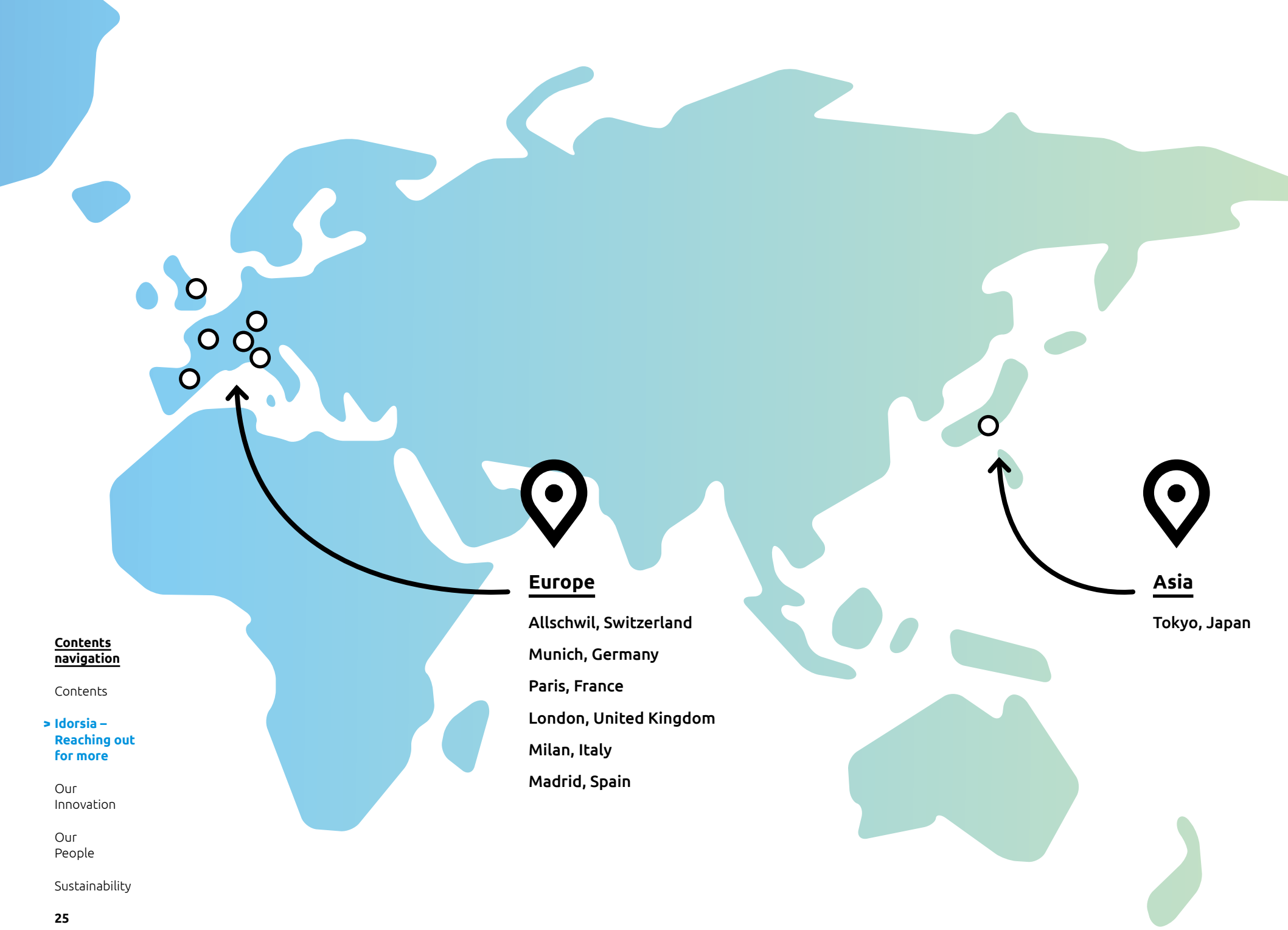
Idorsia Pharmaceuticals France SAS
Paris, France

Idorsia Pharmaceuticals UK Ltd
London, United Kingdom

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

Idorsia Pharmaceuticals Spain S.L.
Madrid, Spain





Europe

Allschwil, Switzerland

Munich, Germany

Paris, France

London, United Kingdom

Milan, Italy

Madrid, Spain

Asia

Tokyo, Japan

More power – delivering for patients

"Our goal is to bring sleep to the forefront of the health conversation, encouraging consumers, healthcare professionals, payors and government to think of sleep, along with diet and exercise, as one of the three pillars of good health. With QUVIVIQ we have a new treatment option that can help adults with insomnia get to sleep faster and stay asleep longer, which we know plays an important role in how they feel the next day."

Patty Torr
President of Idorsia Pharmaceuticals US

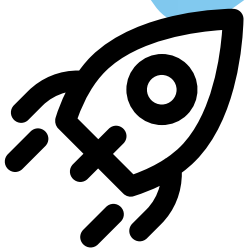
Patty Torr, President and General Manager of Idorsia Pharmaceuticals US, has built a skilled and experienced organization in preparation for the launch of QUVIVIQ™ (daridorexant), Idorsia's first product approved by the US Food and Drug Administration (FDA).

And they have hit the ground running: they have established our US headquarters in the Philadelphia (Pennsylvania) region, recruited a fantastic team, formed strategic partnerships, and put the infrastructure in place to launch QUVIVIQ and subsequent products well into the future.

Building on this strong foundation, the US team has been engaging with key stakeholders, with outreach efforts involving payors and physicians. For example, our US Medical Science Liaisons started meeting with key opinion leaders across the country to introduce Idorsia and discuss insomnia. The feedback to date has been extremely insightful, with many healthcare professionals expressing the need for better treatment options in the sleep space. To help inform our activities, we have also founded "The Alliance for Sleep", a group of some of the foremost medical experts in this field.

Our Market Access experts are meeting with US payors to discuss the high level of unmet need for insomnia sufferers, as well as the depth and breadth of the Idorsia pipeline and what to expect from the company in the coming years. They share data and insights with the goal of demonstrating the high value that our treatment can deliver for patients.

US Marketing efforts include producing a documentary, ***The Quest for Sleep***, highlighting real people suffering with insomnia, set to air in March 2022. The team has also launched a unique awareness-generating and educational campaign, ***Seize the Night & Day***, to shine a light on the impact of insomnia. The campaign's focus is on the current unmet need, the night and day impact of insomnia, and the resulting effects on patients and their families. The importance of sleep as one of the pillars of good health, along with diet and exercise, is amplified through our collaboration with Jennifer Aniston, as well as through a powerful social media campaign.



Meanwhile, our US Sales team is ramping up to engage with physicians, the people who ultimately need to be convinced that QUVIVIQ will help their patients. US sales management has developed a strategic customer target map, infusing advanced analytics into the process, to inform where we deploy our Syneos Health specialty sales representatives.

In less than two years, Idorsia's US team has prepared for a stellar launch of QUVIVIQ – helping to fuel Idorsia's future. We are proud of the immense efforts of our US affiliate, and all those at Idorsia who have worked tirelessly to help the patients who suffer every day from this debilitating medical condition.

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More entrepreneurship – courageous trailblazers

"We have established highly capable leadership teams across Europe. They bring talent and experience, as well as enthusiasm for science and patient care – the perfect set of ingredients to transform the treatment paradigm for patients with insomnia and our other targeted disease areas."

Jean-Yves Chatelan
President of the EUCAN Region

Thorsten Löchle
GM Germany

Manuel Ortega
GM Spain

Francesco Scopesi
GM Italy

Dominique Le Terrier
GM France

Robert Moore
GM UK

In September 2021, Idorsia opened affiliates and announced the appointment of General Managers (GMs) in the five largest European markets: France, Germany, Italy, Spain and the UK. Now the real work begins, as patients – particularly those suffering from insomnia – await our innovation.

Idorsia is expecting a decision on daridorexant from the European Medicines Agency (EMA) in 2022, so we need to be prepared in the major markets. Jean-Yves Chatelan, President of Idorsia's EUCAN region, started laying the groundwork for execution of the global commercial strategy in EUCAN by building strong core capabilities in medical affairs, access, and marketing.

Our initial focus in EUCAN is on highlighting the significant unmet need in insomnia to the healthcare community. One example of these efforts is the satellite symposium hosted by Idorsia at the 2021 ECNP Congress (the largest gathering of European neurologists and psychiatrists), with the goal to highlight the burden of insomnia, the importance of daytime functioning, and how new drugs have been developed to address both sleep and daytime functioning.

A second key priority is to demonstrate the treatment's value to each country's health system. Here, the strong medical and scientific evidence generated by Idorsia in support of daridorexant will play a vital role.

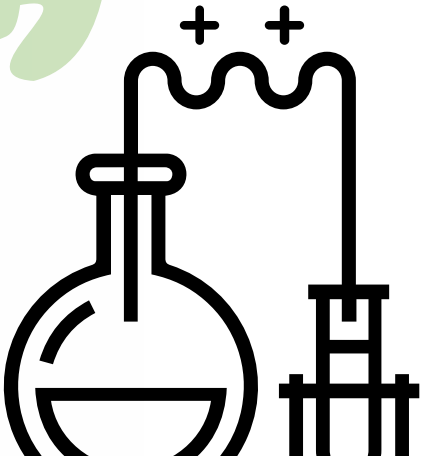
Look out for Idorsia in Munich, Paris, London, Milan or Madrid! Our offices in these cities are home to the newest members of the Idorsia team, joining us in putting science and patients at the heart of our work.

More perseverance – to revolutionize treatment

Satoshi Tanaka
President of Idorsia Japan

PIVLAZ™ (clazosentan) 150 mg was approved for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aneurysmal subarachnoid hemorrhage (aSAH) in Japan on January 20, 2022.

In this interview, Satoshi Tanaka (President, Idorsia Japan) explains how Idorsia's Japanese affiliate has been transformed to include a strong commercial team, and why he is confident that the launch of PIVLAZ will be welcomed by patients and physicians, who are waiting for better treatment options for this debilitating condition.



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Satoshi-san, what has changed in the Idorsia Japan organization as you prepare for a commercial launch?
Since we filed the NDA for PIVLAZ with the Japanese Health Authorities in March 2021, Idorsia Japan's organization has expanded rapidly. It is now comprised of a Medical Affairs team, including specialized Medical Scientific Liaisons (MSLs) who have been deployed since mid-2021, a focused marketing team, and an experienced field-based sales force. These teams have been working in close collaboration to plan for a successful launch of PIVLAZ.

What would you say differentiates your team from other biopharmaceutical companies in Japan? What makes Idorsia unique?
Idorsia Japan was built from scratch with people who have a lot of expertise and experience in the clinical development, registration and commercialization of innovative compounds. I am very proud of the teamwork shown by all our functions in successfully establishing an organization that is ready to launch Idorsia's first compound commercialized in Japan.

What have you learned about current aSAH and vasospasm treatment from your research into the patient journey in Japan?
There is a significant unmet need in this disease area. Vasospasms continue to occur despite the use of existing prevention measures.

There are also disparities in patient management after aSAH across the country. Cerebral vasospasm with serious clinical consequences can occur in 10% to 70% of cases, depending heavily on local care. Patients may not be admitted to a hospital that can provide the specialized care needed, and mild cases are sometimes not admitted at all.

Why is the approval of PIVLAZ particularly good news for patients and healthcare professionals in Japan?
aSAH is a significant problem in Japan, with an incidence approximately three times higher than the rest of the world. It is also on the rise, with an increase of nearly 60% observed over the last three decades.

PIVLAZ is an innovative and effective prophylactic treatment for cerebral vasospasm, cerebral infarction and delayed ischemic neurological deficit (DIND), with clear supporting clinical evidence from two robust double-blind studies.

How are you preparing for the launch of PIVLAZ?
Our goal, together with the global team, is to incorporate PIVLAZ to become the new standard of care for post-aSAH treatment. We start by establishing the high unmet need through education and expert engagement with the healthcare community. Best practices for monitoring and preventing cerebral vasospasm post-aSAH are also being shared with hospitals and ICU physicians.

Our dedicated sales team is focused on 650 centers representing 90% of the aSAH market potential and will be deployed as soon as we receive a reimbursement decision, which is expected in Q2 2022.

How is the launch delivering on Idorsia's purpose of "helping more patients"?
We are taking a patient-centric approach to launch. We want to create an environment where patients can receive aSAH treatment as soon as possible after the initial rupture. One way we will do this, in cooperation with existing hospital groups, is by establishing aSAH Medical Care Referral Networks all over Japan – from Hokkaido to Okinawa – enabling patients to access early diagnosis and be transferred to a hospital with appropriate care. The Networks will also educate providers on the standardization of ICU medical care, including the use of PIVLAZ, and facilitate the sharing of ICU best practices across the regions.

This innovative therapy is truly transforming treatment for aSAH patients – helping them overcome the consequences of this devastating condition.

PIVLAZ
clazosentan

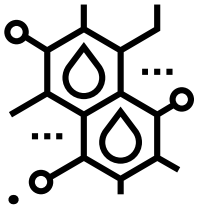
PIVLAZ is expected to be available in April 2022 in Japan

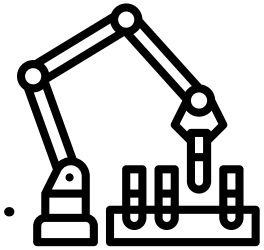
Our Innovation

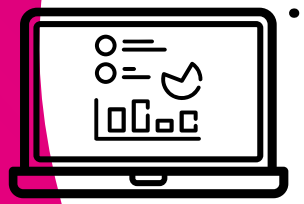
"We need creativity to be innovative, so we need a brilliant idea and a deep understanding of the disease, to translate it into a molecular mechanism, and to try to find a drug to treat that disease."

John Gatfield
Associate Director, Principal Scientist

More innovation – from bench to bedside







From bench to bedside… from compounds to commercialization… no matter how you put it, Idorsia's intention is clear: to become a fully fledged biopharmaceutical company that not only discovers great molecules and builds evidence in creative clinical studies, but also successfully brings them to patients, creating a sustainable business based on innovation.

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

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

The drug discovery process starts with an idea from our scientists. We scour the literature to see what others have not yet discovered, to generate ideas and then translate them into a concept which can lead to new treatments for patients.

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

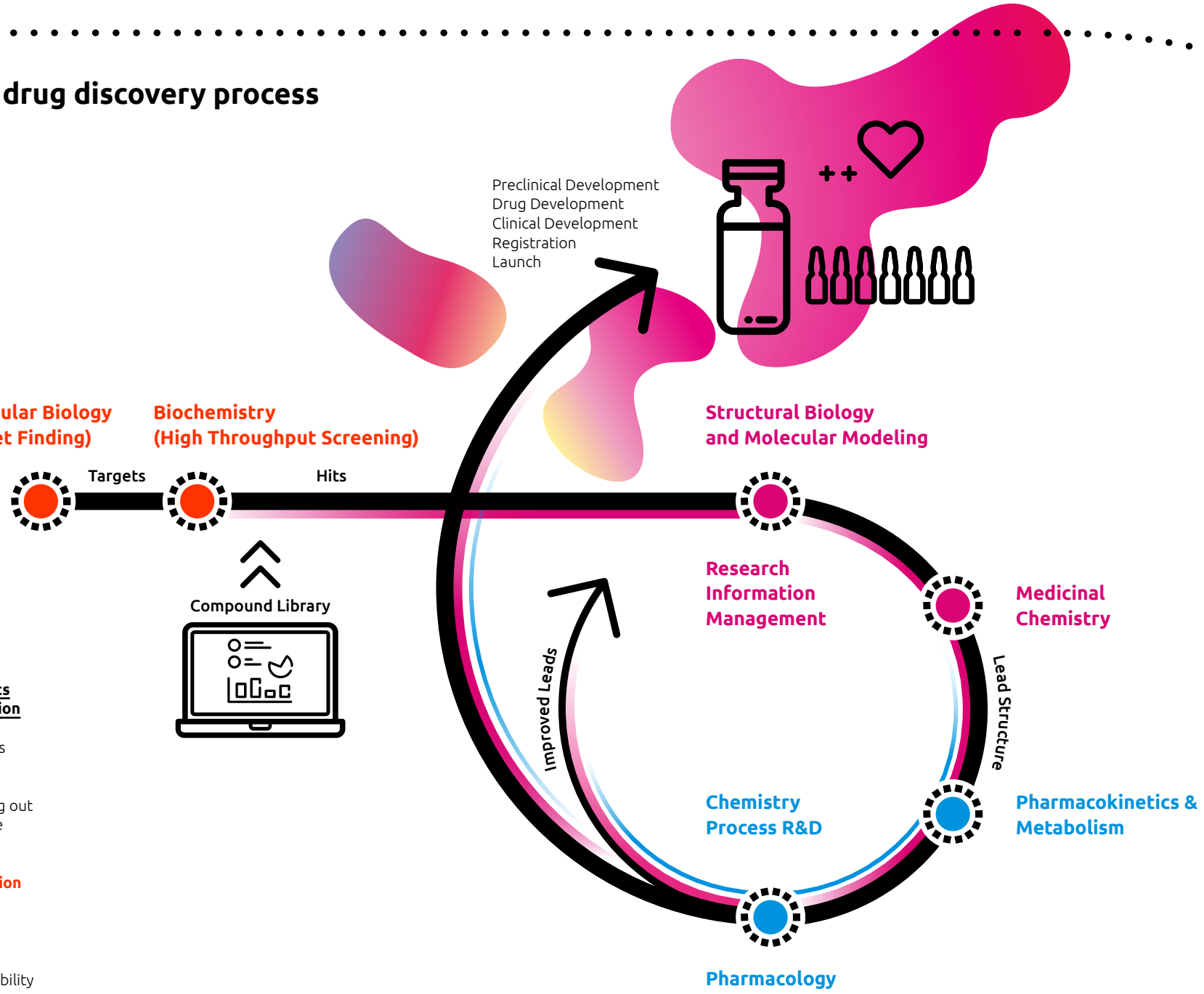
We produce, or "express", the target in large quantities and measure its natural activity in assays. The assay needs to be sensitive, accurate and highly reliable. Plus, in order to perform hundreds of thousands of measurements, it needs to be automated, using robotic equipment.

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

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

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

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 is destroyed by the body before it has a chance to do its job. Our chemical and drug product specialists take a compound which has been optimized by the chemists and develop the most robust, safe and cost-efficient processes for the drug substance, the formulation, and packaging materials.

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

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

Corinna Grisostomi
Senior Scientist

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More experience – Building the clinical evidence

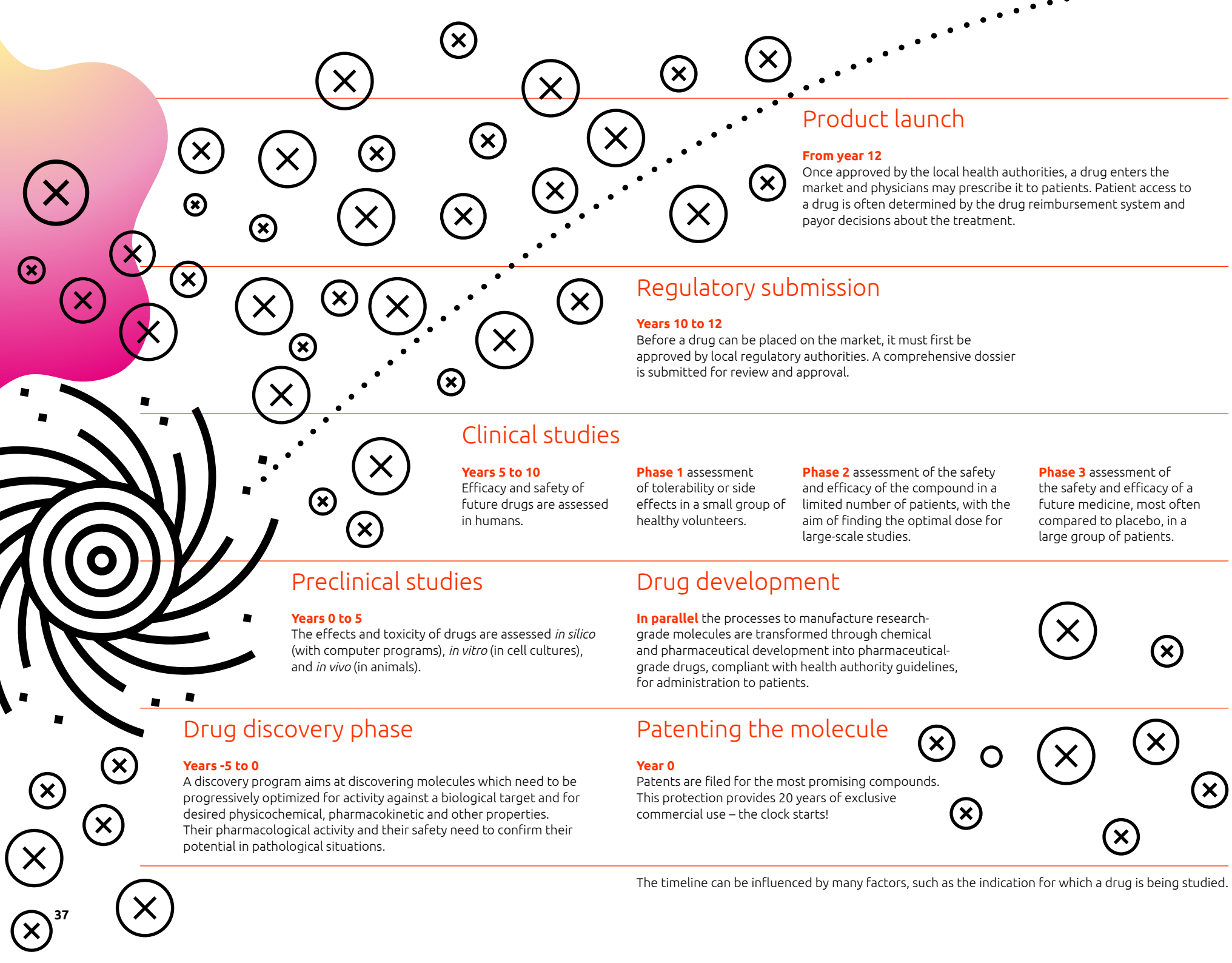
Following the drug discovery phase, the selected molecule must be comprehensively studied to demonstrate clinical safety and efficacy.

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

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

Guy Braunstein
Executive Vice President, Chief Medical Officer

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



Product launch

From year 12
Once approved by the local health authorities, a drug enters the market and physicians may prescribe it to patients. Patient access to a drug is often determined by the drug reimbursement system and payor decisions about the treatment.

Regulatory submission

Years 10 to 12
Before a drug can be placed on the market, it must first be approved by local regulatory authorities. A comprehensive dossier is submitted for review and approval.

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).

Drug development

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

Drug discovery phase

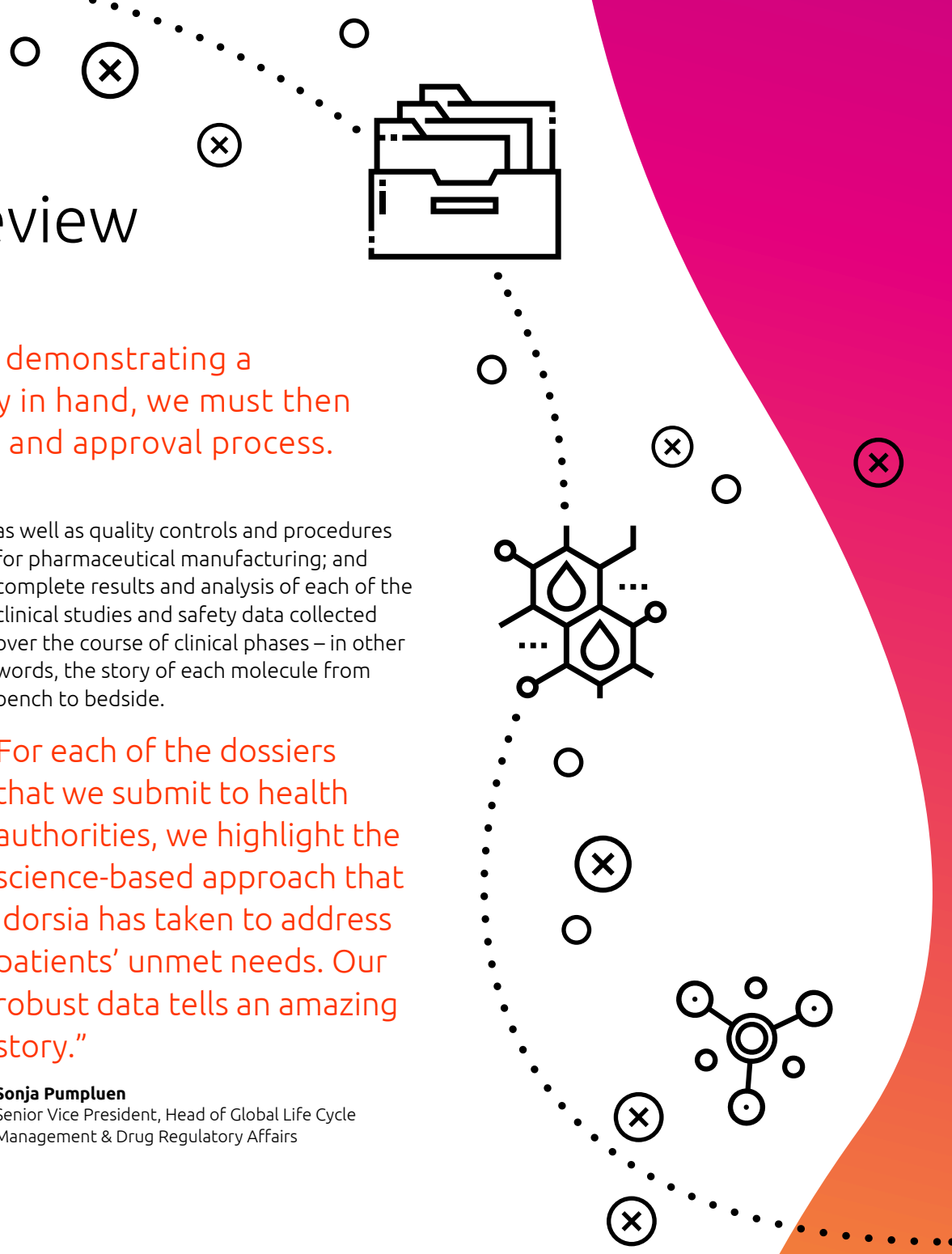
Years -5 to 0
A discovery program aims at discovering molecules which need to be progressively optimized for activity against a biological target and for desired physicochemical, pharmacokinetic and other properties. Their pharmacological activity and their safety need to confirm their potential in pathological situations.

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!

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

More potential – Navigating regulatory review



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

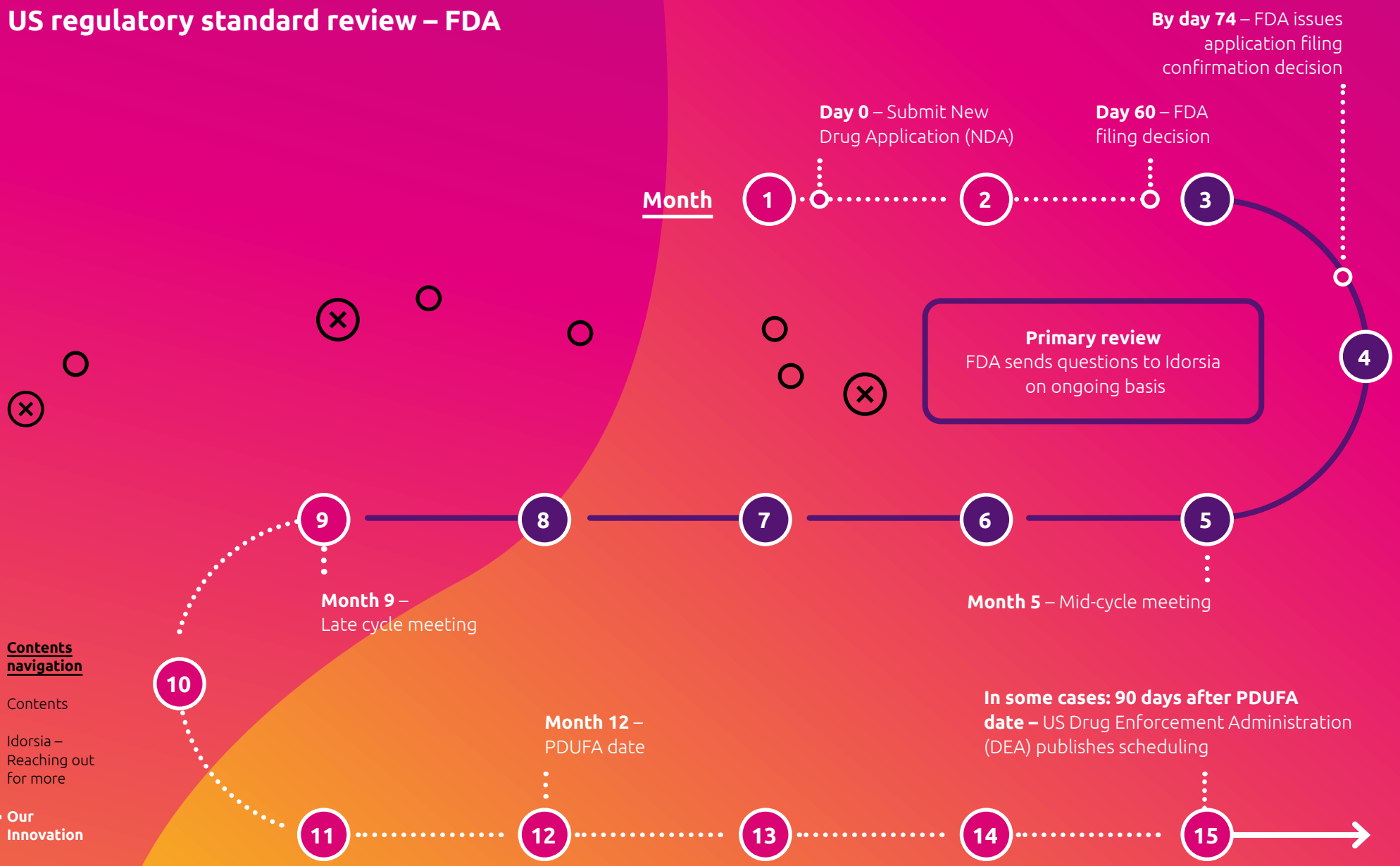
From the first-in-human study of a drug through market approval and for as long as it remains on the market, we maintain an ongoing dialogue with health authorities in every country where we operate. We ensure that our development plans meet the regulators expectations and that we generate the types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

Once our products reach the registration phase we embark on the regulatory review process, shown for the US and EU regulatory bodies on pages 39 and 40. Teams from across Idorsia collaborate to develop a robust and comprehensive dossier for submission to the health authorities. The data included is wide-reaching: preclinical research, such as compound screening, animal models and all pharmacology, pharmacokinetics and toxicology data; technical descriptions of the properties and chemical synthesis of the drug substance, as well as quality controls and procedures for pharmaceutical manufacturing; and complete results and analysis of each of the clinical studies and safety data collected over the course of clinical phases – in other words, the story of each molecule from bench to bedside.

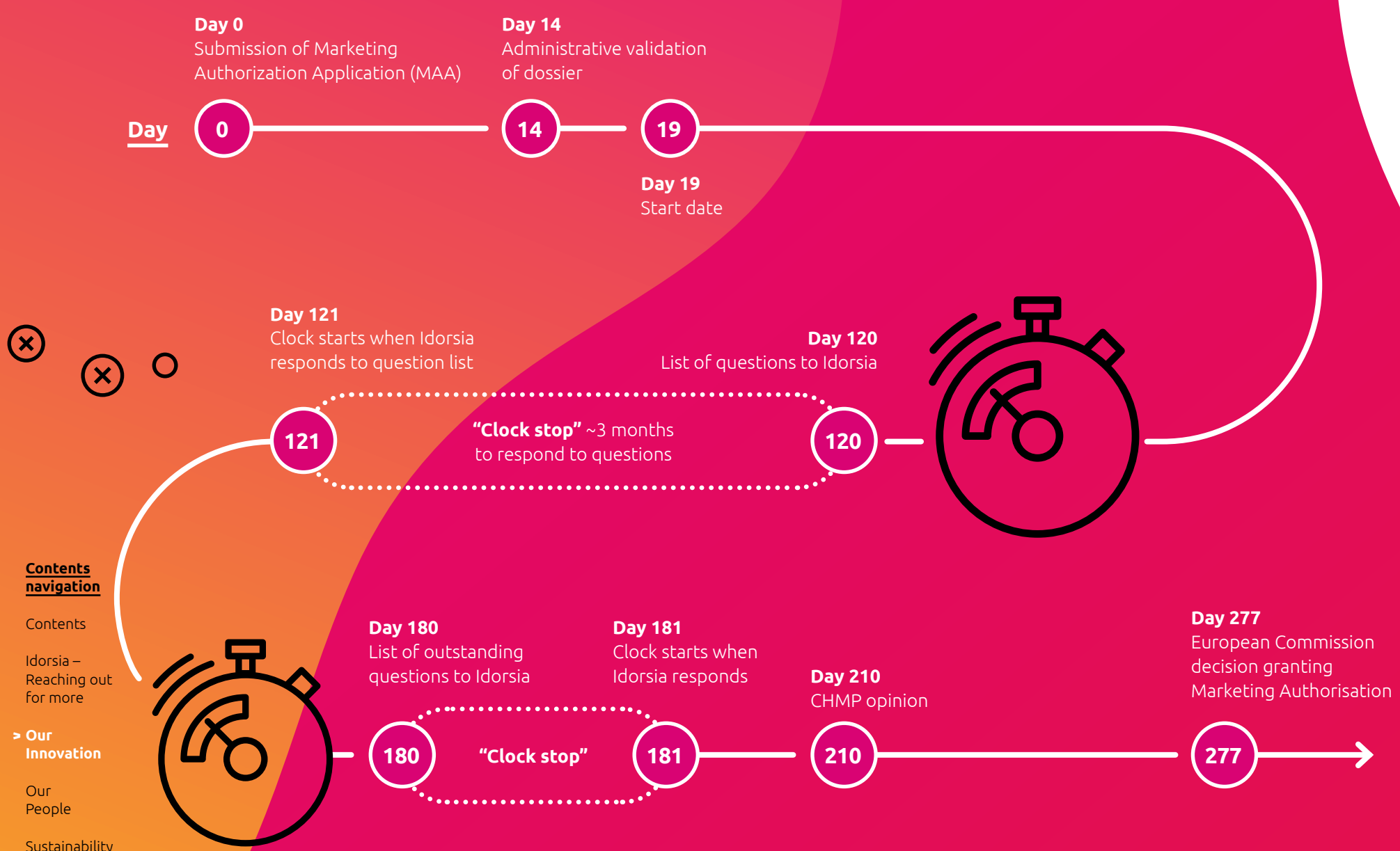
"For each of the dossiers that we submit to health authorities, we highlight the science-based approach that Idorsia has taken to address patients' unmet needs. Our robust data tells an amazing story."

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

US regulatory standard review – FDA



EU regulatory review – EMA



More hope –
Changing the treatment paradigm

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

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

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

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

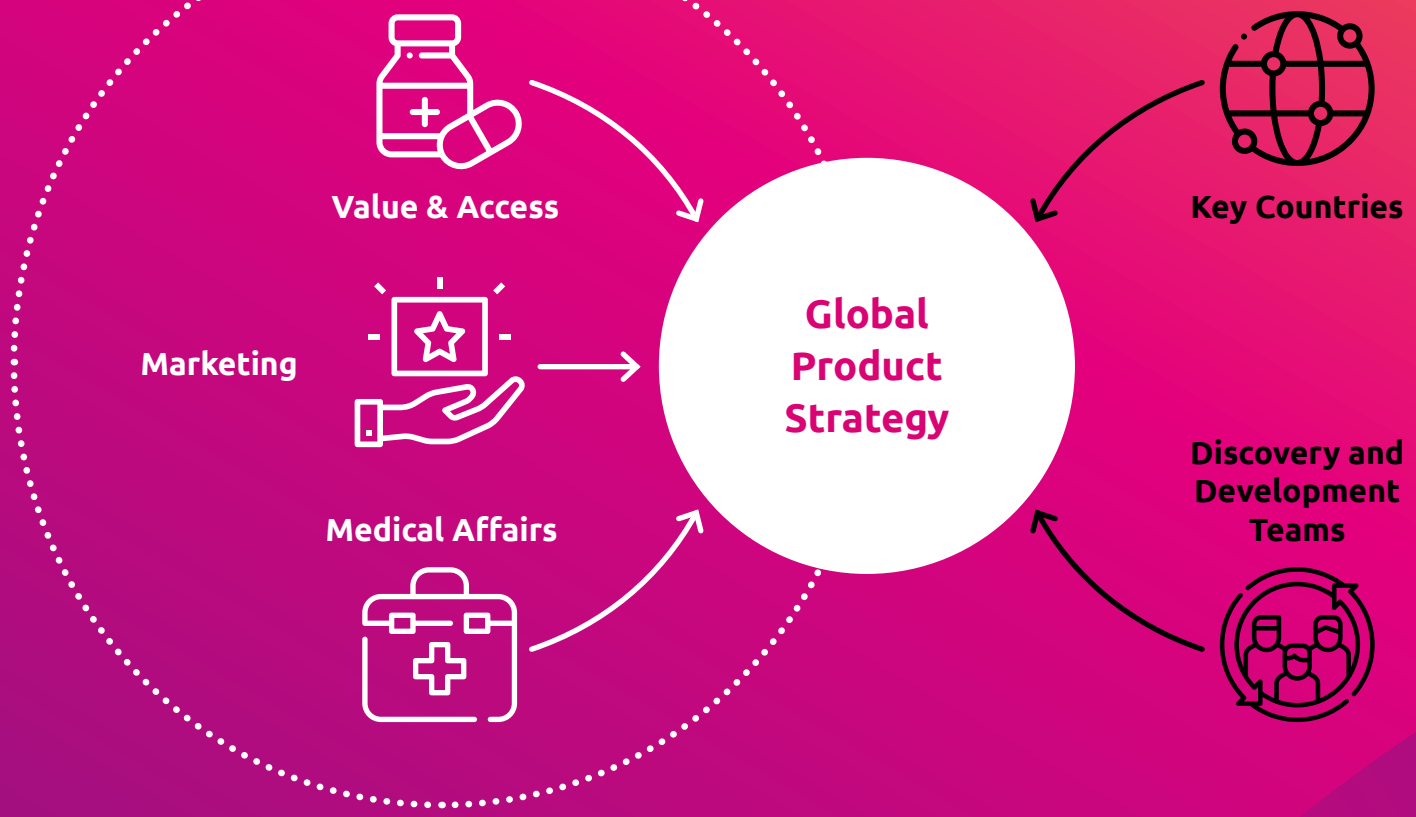
Idorsia's Global Medical Affairs team is responsible for communicating to the healthcare community our science, the data on our products, and the key differences from other treatments. To inform and develop our global strategy, we also seek medical insights regarding how our products' core data resonates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

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

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

"We ensure that the global product strategy is truly built around the science and the needs of patients and healthcare professionals."

Antonio Olivieri
Senior Vice President, Head of Global Medical Affairs

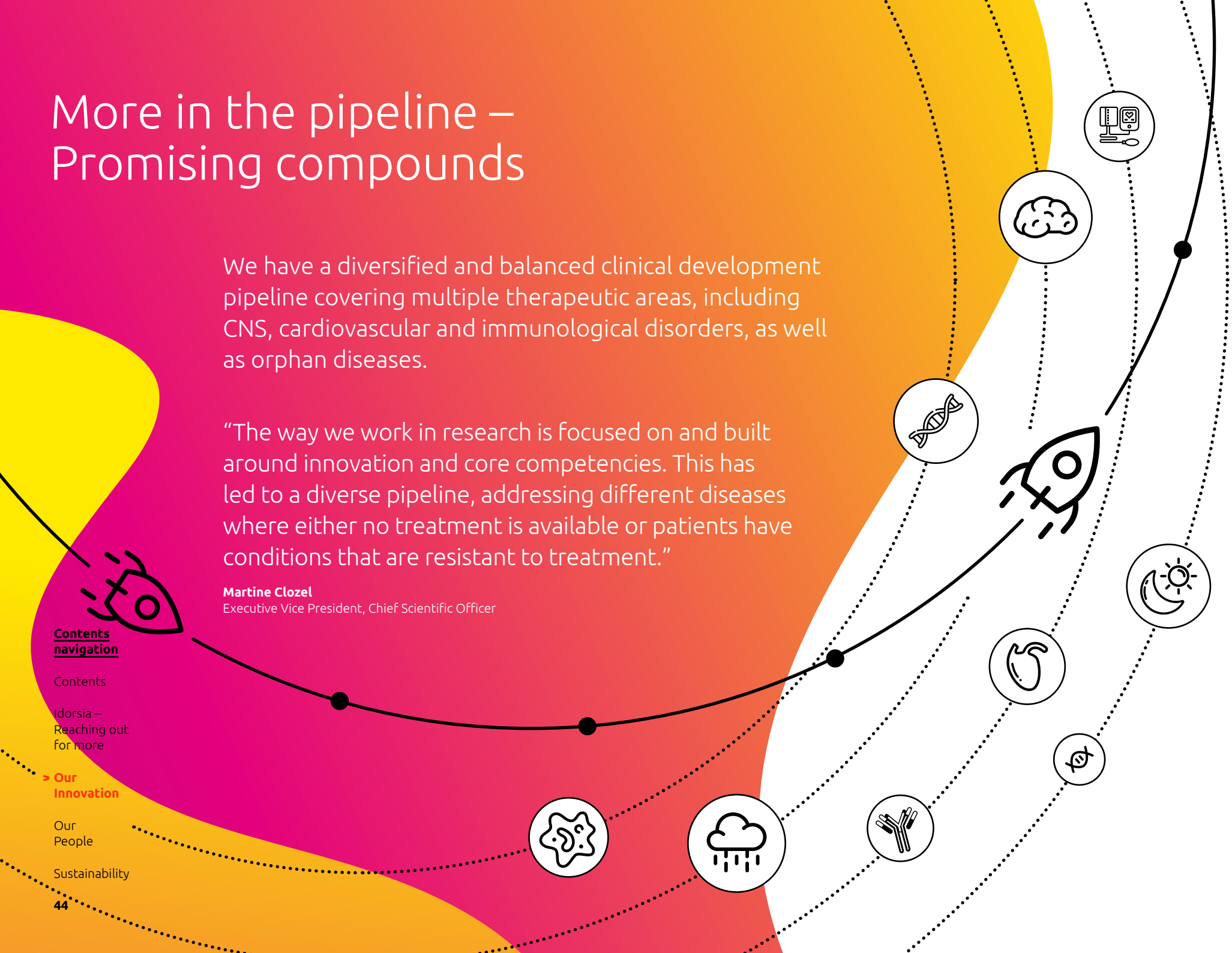


More in the pipeline – Promising compounds

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

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

Martine Clozel
Executive Vice President, Chief Scientific Officer



Our portfolio

Status: January 2022

Compound	Mechanism of Action	Target Indication		Status
Daridorexant	Dual orexin receptor antagonist	**Insomnia**		Approved as QUVIVIQ™ in the US, under review in other countries
Aprocitentan*	Dual endothelin receptor antagonist	**Resistant hypertension management**		Phase 3 recruitment complete
Clazosentan	Selective endothelin (ET_A) receptor antagonist	**Vasospasm associated with aneurysmal subarachnoid hemorrhage**		Status Global: Phase 3 Status Japan: Approved as PIVLAZ™
Lucerastat	Glucosylceramide synthase inhibitor	**Fabry disease**		Phase 3 primary endpoint not met, OLE ongoing**
Selatogrel	$P2Y_{12}$ receptor antagonist	**Suspected acute myocardial infarction**		Phase 3
Cenerimod	$S1P_1$ receptor modulator	**Systemic lupus erythematosus**		Phase 3 in preparation
ACT-539313	Selective orexin 1 receptor antagonist	Binge eating disorder		Phase 2 recruitment complete
Sinbaglustat	GBA2/GCS inhibitor	Rare lysosomal storage disorders		Phase 1 complete
ACT-1004-1239	CXCR7 antagonist	Immunology		Phase 1 complete
ACT-1014-6470	–	Immunology		Phase 1
ACT-777991	–	Immunology		Phase 1

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

** Open-label extension study

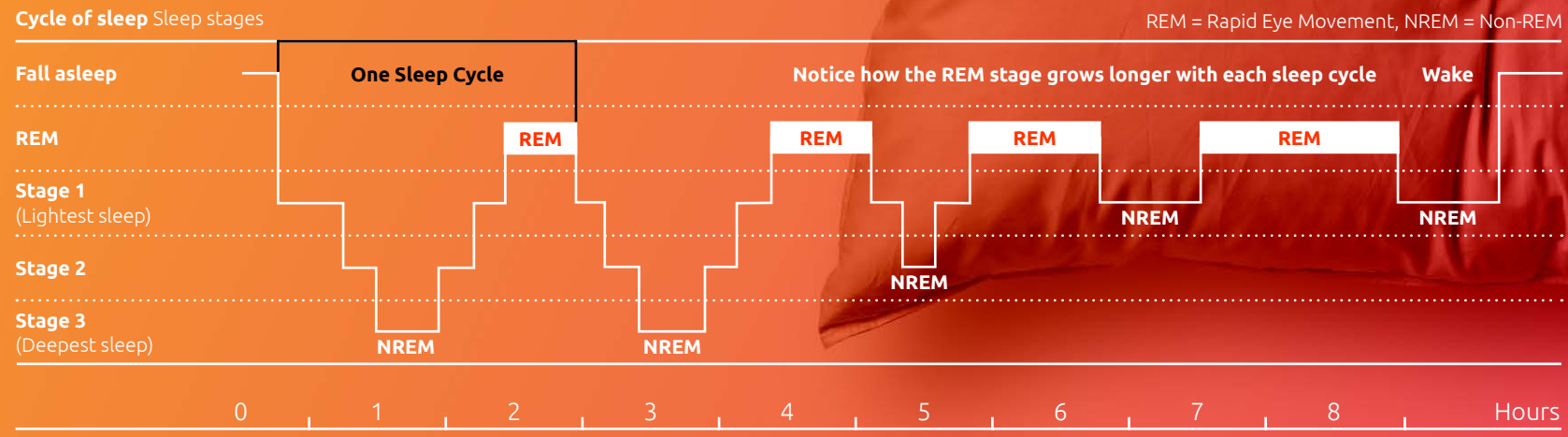
Neurocrine Biosciences has a global license to develop and commercialize ACT-709478 (NBI-827104), Idorsia's novel T-type calcium channel blocker. ACT-709478 is currently investigated in two Phase 2 studies for the treatment of a rare form of pediatric epilepsy and essential tremor.

Daridorexant for insomnia

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

Insomnia as a persistent disorder is quite different from a brief period of poor sleep, and it can take its toll on both physical and mental health. Idorsia's research has shown that poor-quality sleep can affect many aspects of daily life, including the ability to concentrate, mood, and energy levels.

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 %

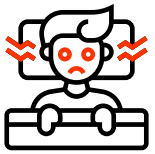
"It really annoys me when people say 'If you were really tired, you would sleep.' If only it were that simple! Unless you have suffered from true insomnia, you have absolutely no idea what it's like."

Patient with insomnia

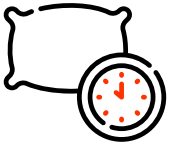
Sleep architecture

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).



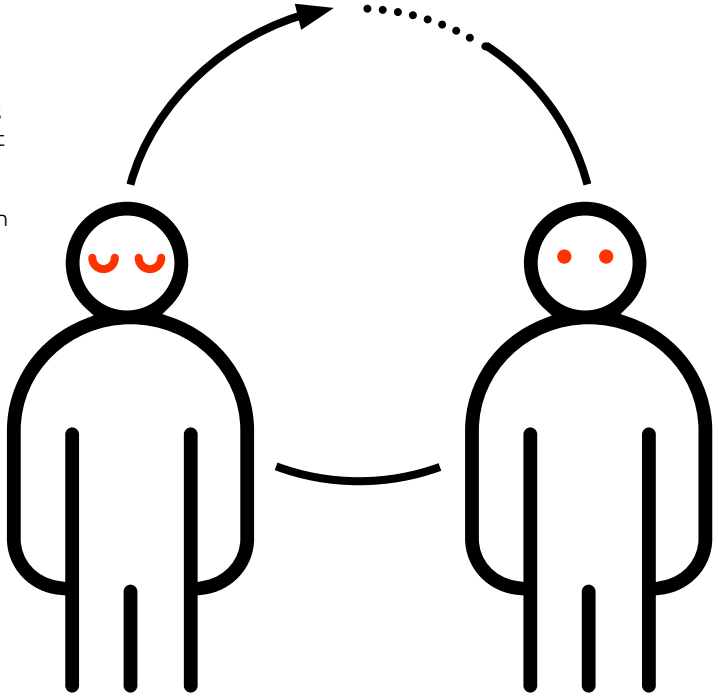
Studies have shown that lack of slow-wave (stage 3) sleep is associated with cognitive and other health-related issues.



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, effects on this key aspect of the condition have not been rigorously assessed for any of the treatments currently available.

The orexin system

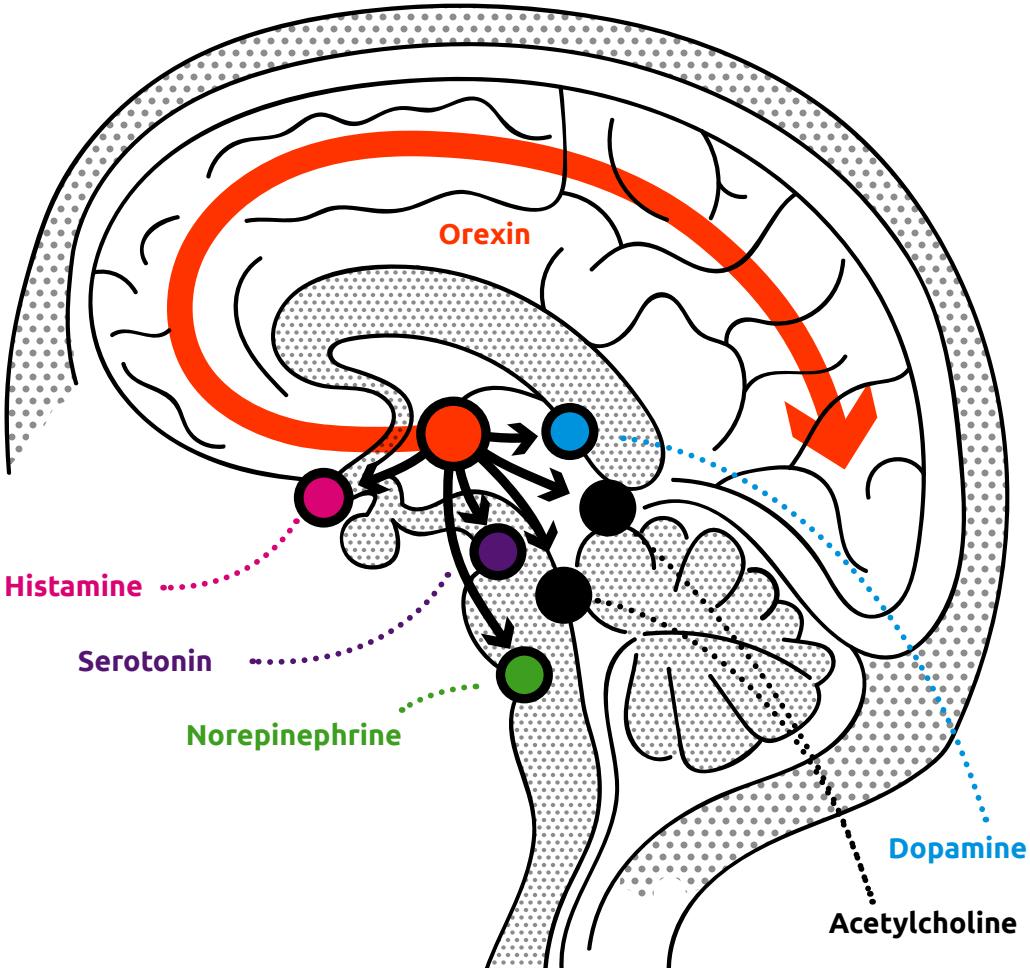
Wake and sleep signaling is regulated by intricate neural circuitry in the brain. One key component of this process is the orexin system, which helps promote wakefulness.

There are two forms of orexin neuropeptides (small protein-like molecules used by nerve cells 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.

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.

The orexin system is crucial for the regulation of wakefulness

Orexin stimulates many wake-promoting pathways

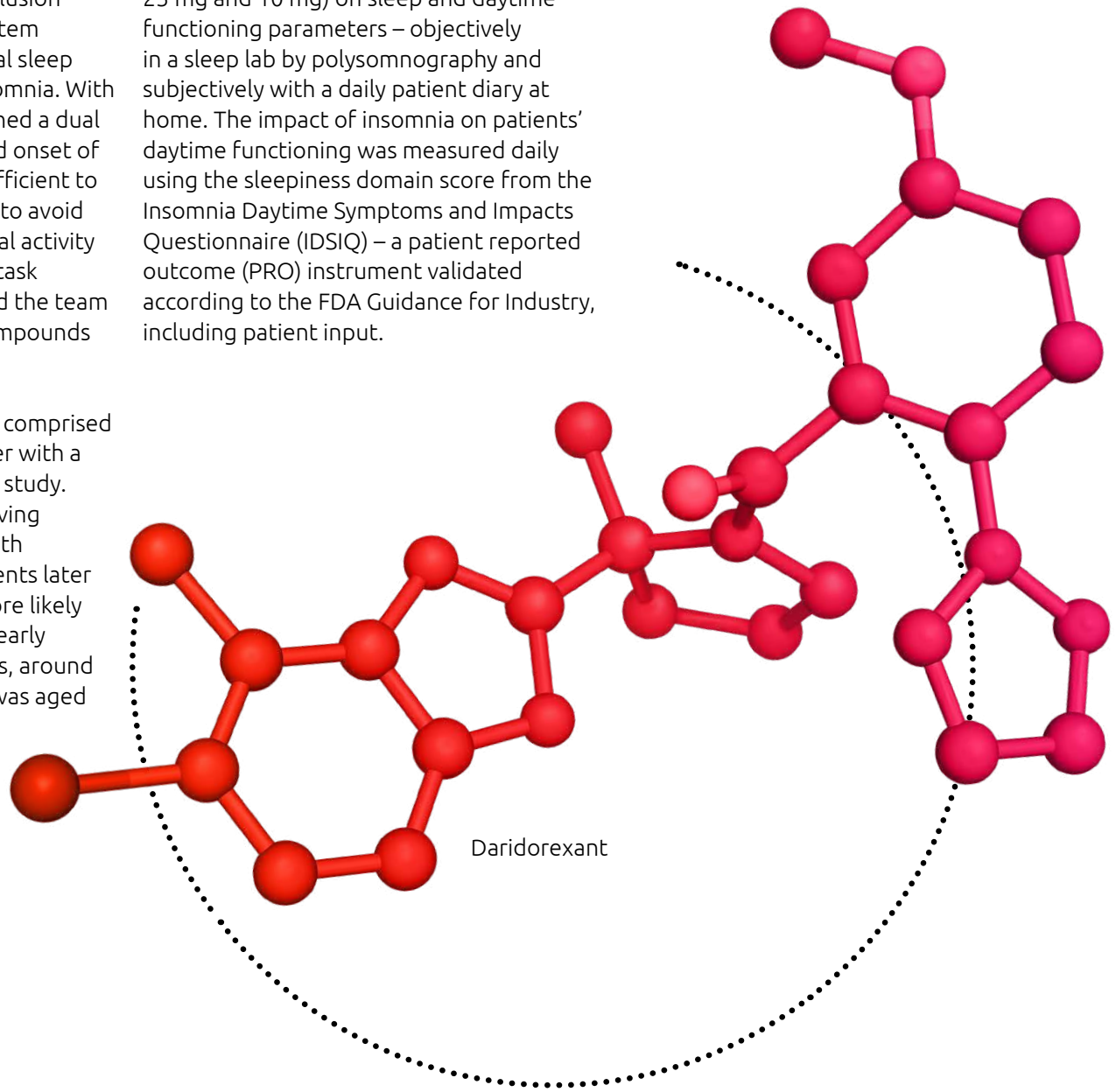


Idorsia's innovation

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

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

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

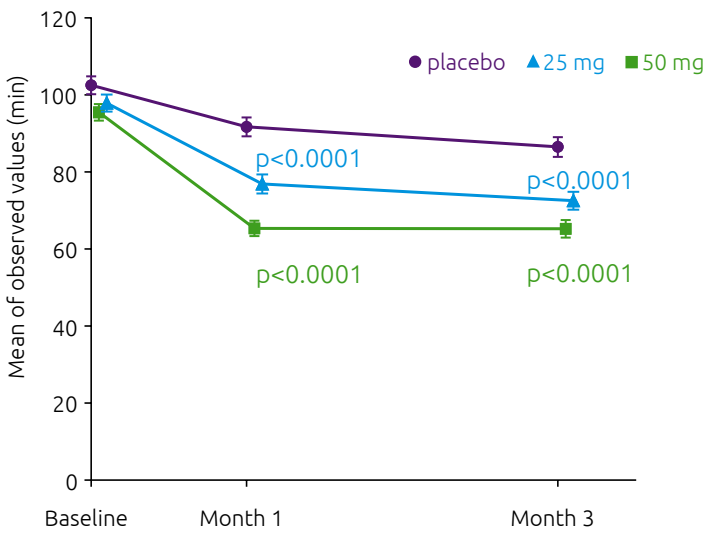


Daridorexant

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

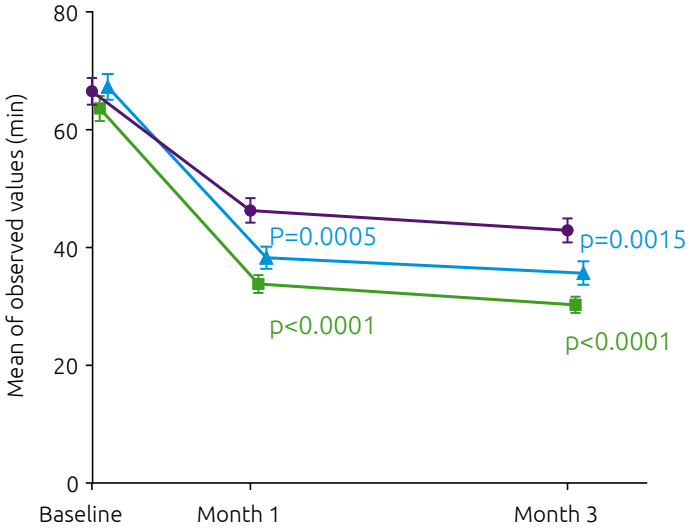
As published by Mignot E, et al. in the February 2022 issue of *The Lancet Neurology*, the pivotal studies demonstrated that daridorexant significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months 1 and 3 compared to placebo. The largest effect was observed with the highest dose (50 mg), followed by 25 mg, while the 10 mg dose did not have a significant effect. In all treatment groups, the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.

Wake time after sleep onset



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

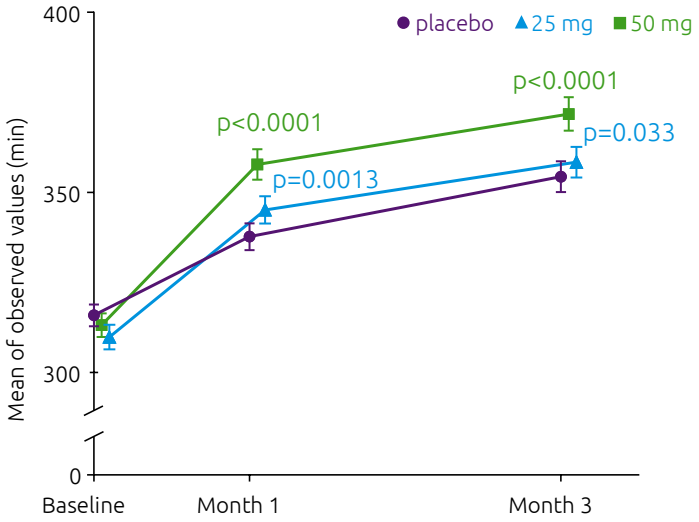
Latency to persistent sleep



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

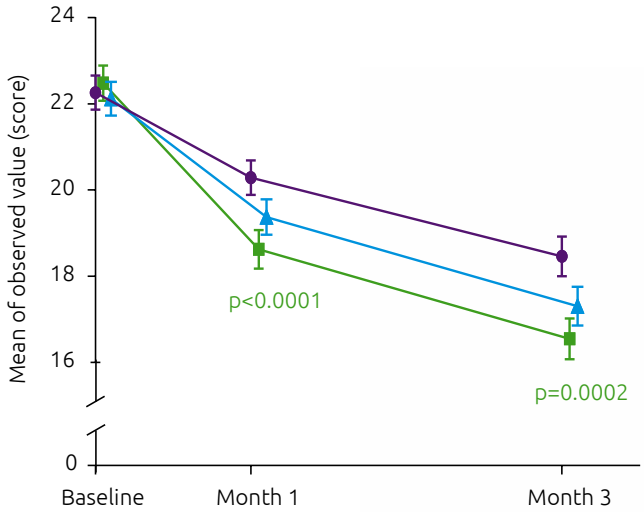
WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

Subjective total sleep time



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

IDSIQ sleepiness domain



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

Data for sTST and IDSIQ scores are based on the mean of daily entries in the 7 days before polysomnography nights.
Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

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

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

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

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

QUVIVIQ™
daridorexant 25mg, 50mg tablets

Current status in the US

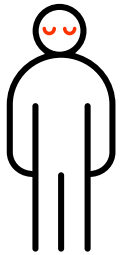
QUVIVIQ™ (daridorexant) – 25 & 50 mg – was approved by the US FDA in January 2022 for the treatment of adults with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. As with other sleep medications, the FDA has recommended that QUVIVIQ be classified as a controlled substance, and it is anticipated that it will be available to patients in May 2022, following scheduling by the US Drug Enforcement Administration. For more information see the Full Prescribing Information (PI and Medication Guide).

Current status outside of the US

Marketing authorisation applications (MAA) were submitted to the European Medicines Agency in March 2021, to Swissmedic in April 2021, and to Health Canada in August 2021. Should approval be received, the company anticipates the first launch in a European country in the second half of 2022, followed by other countries and regions thereafter.

Insomnia

Compound: Daridorexant



Mechanism of action:
Dual orexin receptor antagonism
Status: Approved in the US, MAA under review in other countries

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Aprocitentan for resistant hypertension

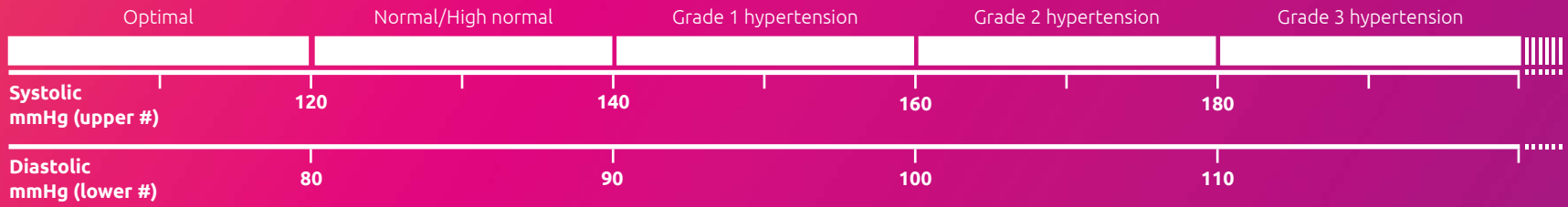
Hypertension (high blood pressure) is one of the most common cardiovascular risk factors, and its prevalence continues to rise. According to a recent study, there are more than a billion people living with hypertension worldwide – a startling number, which has almost doubled in the past 40 years. Left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

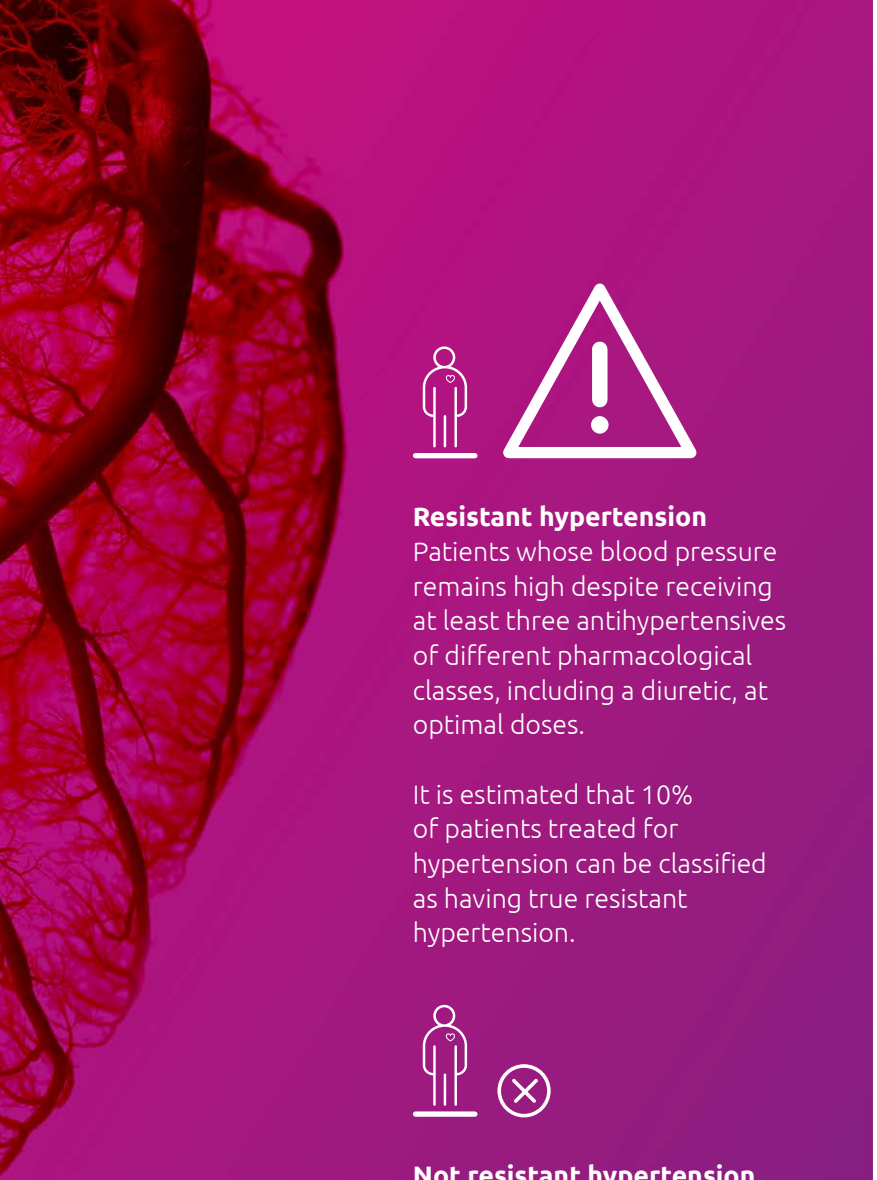
The World Health Organization estimates that hypertension causes 7.5 million deaths a year – about 12.8% of all deaths worldwide.

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





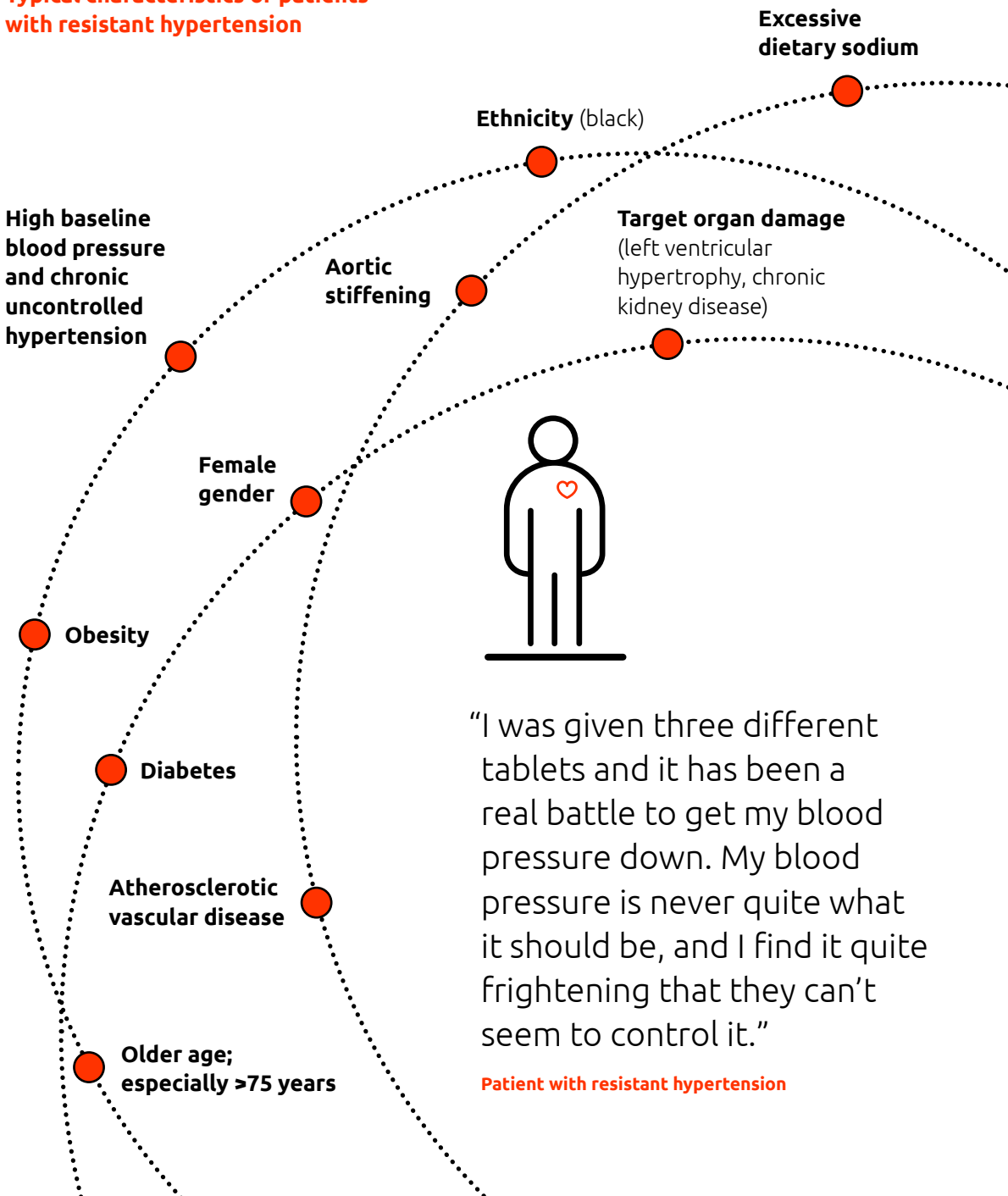
Resistant hypertension
Patients whose blood pressure remains high despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal doses.

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 ET_A and ET_B receptors mediate ET-1-induced harmful effects.

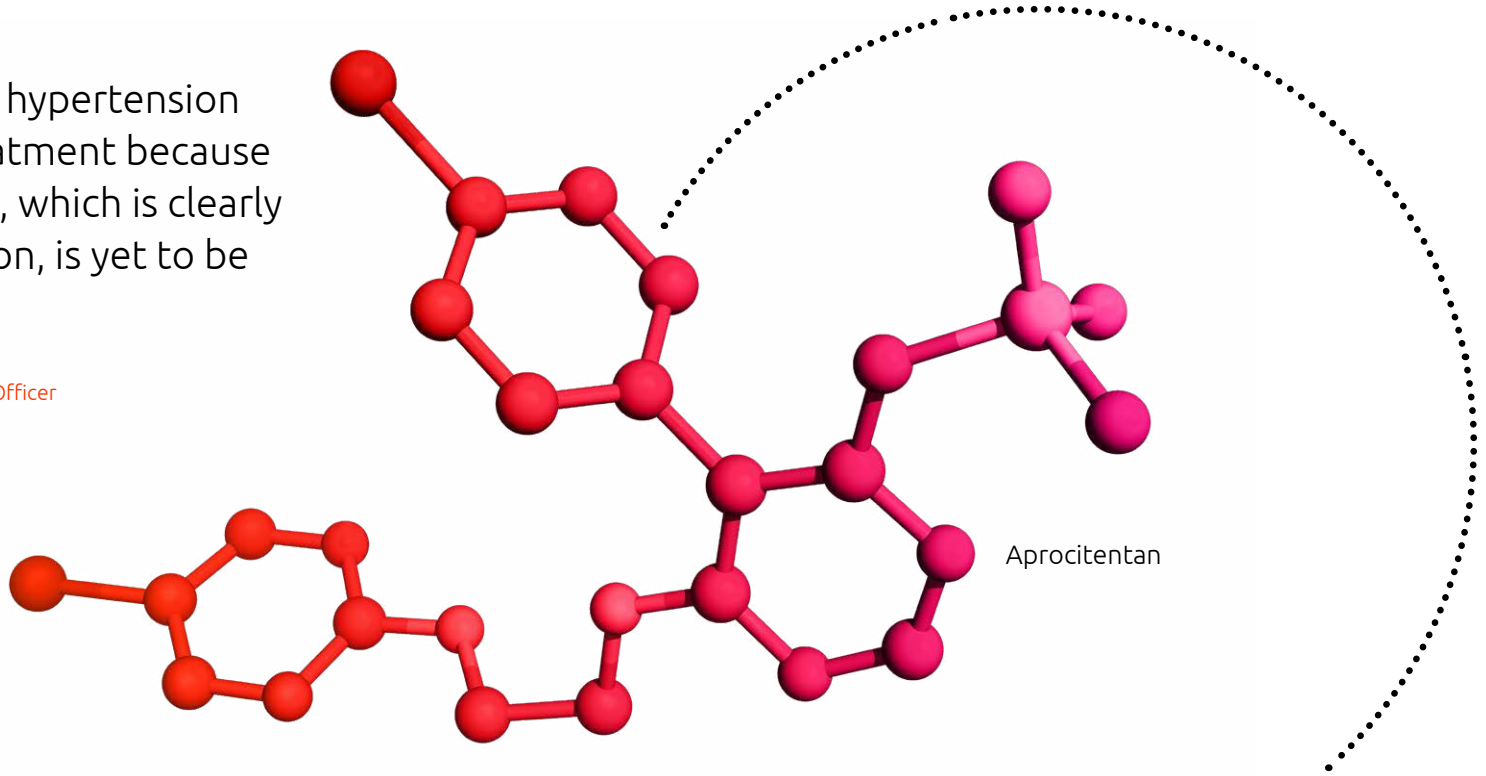
Clinical and preclinical evidence suggests that resistant hypertension may be endothelin dependent. The endothelin system certainly plays an important role in hypertension, especially in volume- and salt-dependent forms, which are a common feature in patients with resistant hypertension. By targeting 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 an oral, once-a-day 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."

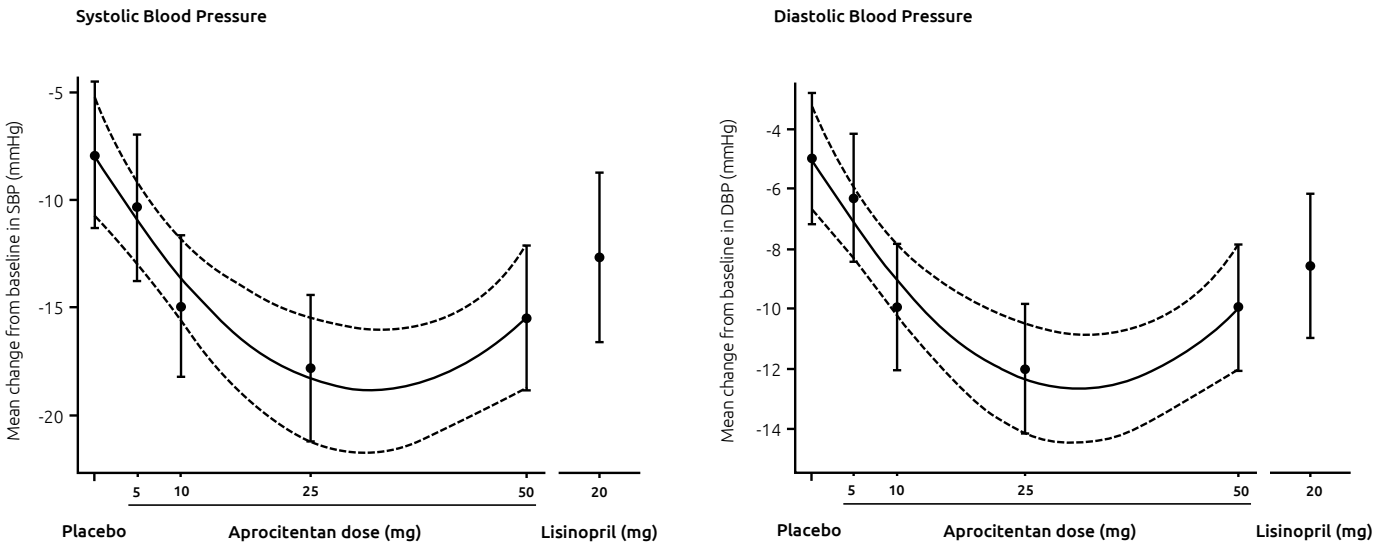
Professor John Chalmers, MD
Senior Director of The George Institute for Global Health and Professor of Medicine at the University of New South Wales, Sydney

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 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

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. Recruitment for the study was completed in April 2021, with 730 patients randomized, and results are expected in mid-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.

Difficult-to-control hypertension

Compound: Aprocitentan

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

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. An emergency procedure (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage.

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

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

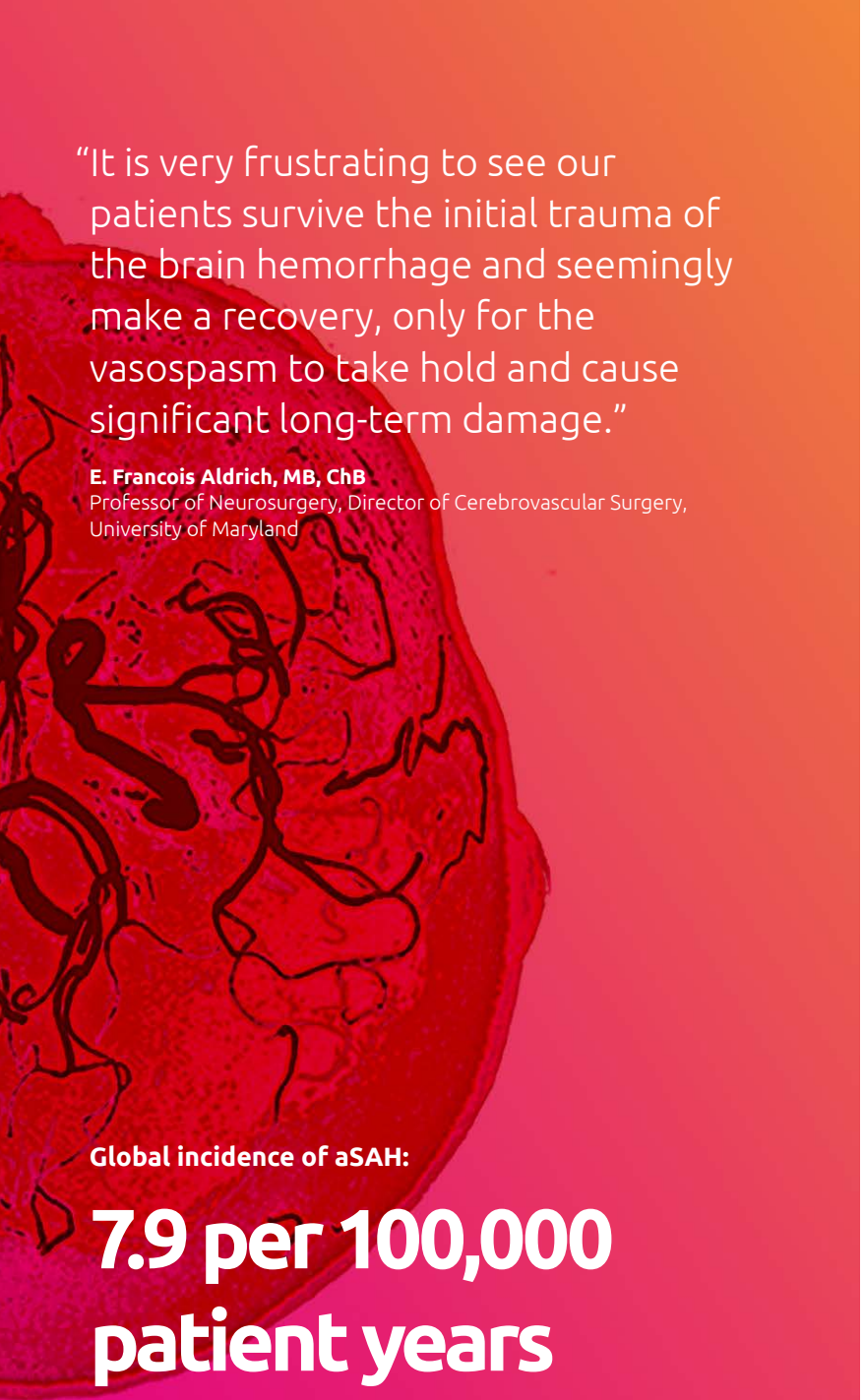
Approximately 50% of the overall aSAH population present with thick, diffuse blood clots characterized by a large amount of subarachnoid blood on the admission CT scan. These patients have a significantly higher risk of experiencing cerebral vasospasm. However, vasospasm is challenging to predict and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

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. Fasudil and ozagrel are used to improve cerebral vasospasm for patients in Japan and other Asian countries. Nimodipine is used for patients with aSAH in the US and EU, although an effect on cerebral vasospasm has not been shown. There has been no innovation for patients suffering from the events associated with cerebral vasospasm in more than 25 years.

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

E. Francois Aldrich, MB, ChB
Professor of Neurosurgery, Director of Cerebrovascular Surgery, University of Maryland



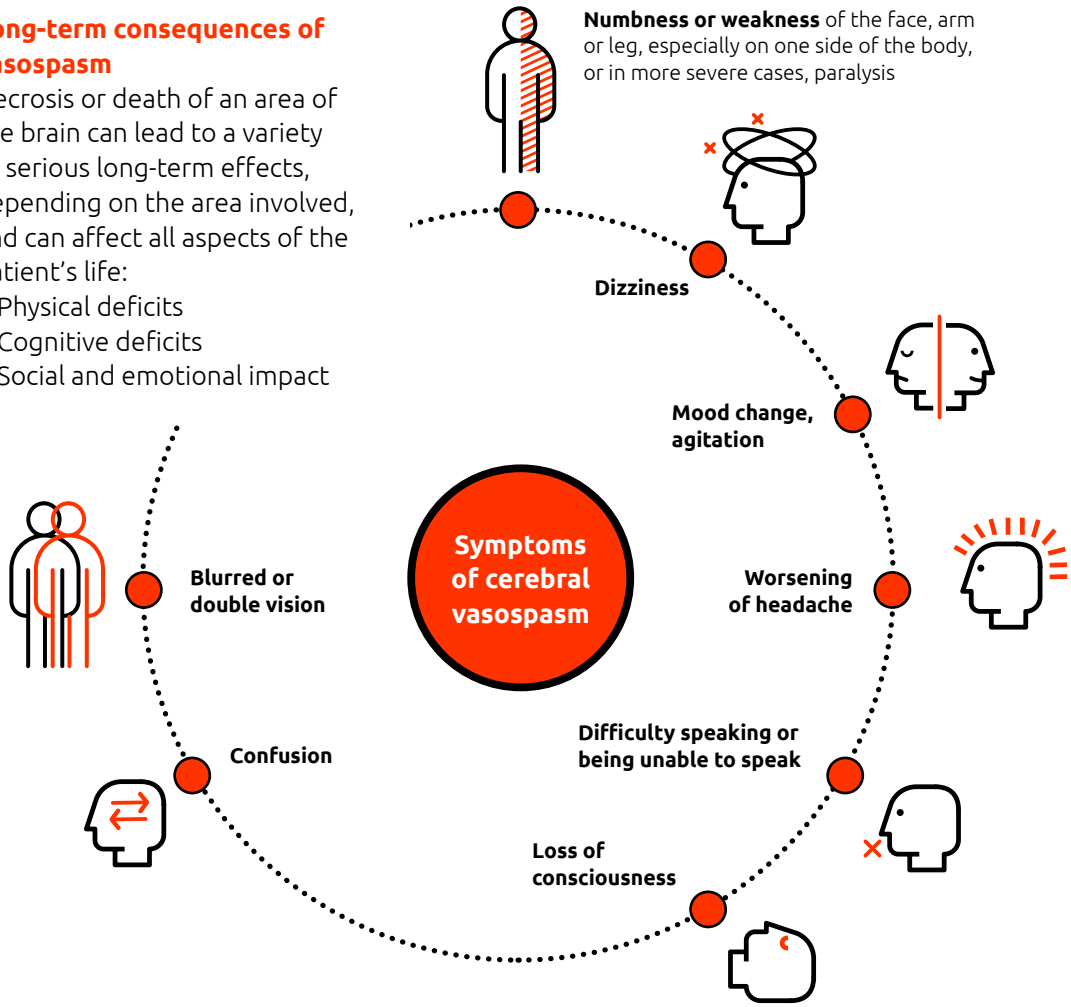
Global incidence of aSAH:

7.9 per 100,000 patient years

Long-term consequences of vasospasm

Necrosis or death of an area of the brain can lead to a variety of serious long-term effects, depending on the area involved, and can affect all aspects of the patient's life:

– Physical deficits
– Cognitive deficits
– Social and emotional impact



The endothelin system in cerebral vasospasm

The release of vasoactive mediators after aSAH cause an increased production of endothelin, one of the most potent vasoconstrictor known, and an upregulation of its ETA receptors. Binding of endothelin-1 to the ETA receptor is the key contributor that leads to cerebral vasospasm after aSAH.

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

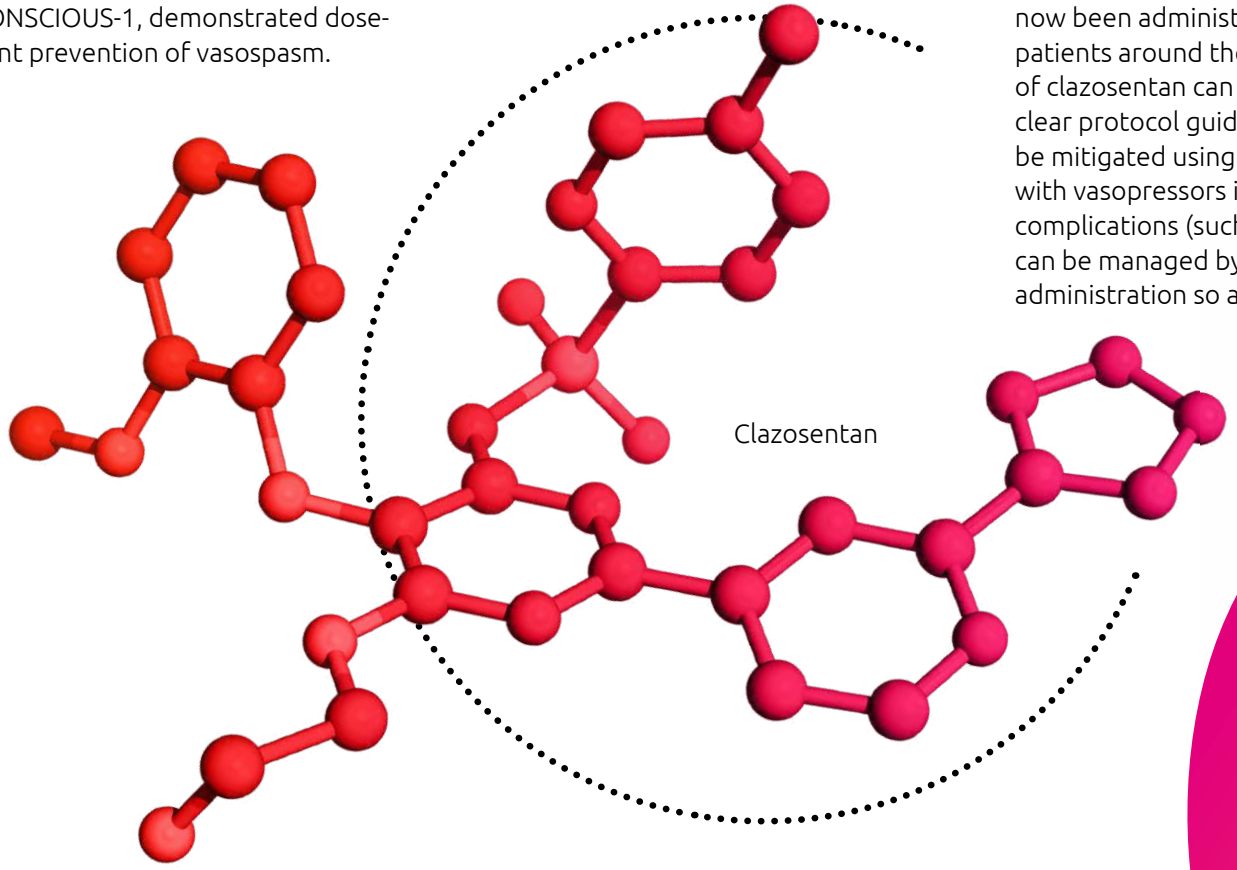
Idorsia's innovation

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

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

This was followed by two Phase 3 studies, CONSCIOUS-2 and CONSCIOUS-3, to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality. In 2010, CONSCIOUS-2 showed that the 5 mg/h dose of clazosentan did not allow a statistically significant treatment effect to be observed, resulting in the premature termination of CONSCIOUS-3. However, an exploratory analysis of the data collected in CONSCIOUS-3 showed that a higher dose of clazosentan (15 mg/h) significantly reduced cerebral vasospasm-related morbidity and all cause mortality, with a 44% relative risk reduction (p=0.0074). The 15 mg/h dose also significantly reduced the incidence of delayed ischemic neurological deficit (DIND), with a 54% relative risk reduction (p=0.0038). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not improve long-term clinical outcome.

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



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

Angelina Marr
Director, Senior Clinical Project Scientist

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.

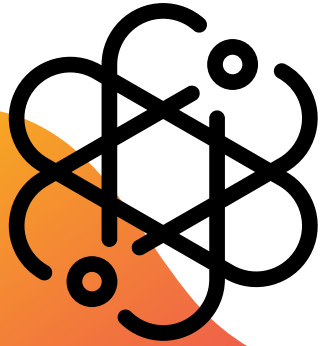
Current status: Global registration program

REACT is a Phase 3 study to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related DCI 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 is expected to conclude around the end of 2022.

Clazosentan has been granted orphan drug designation in Europe (2003) and the US (2006), providing an exclusivity period of 10 and 7 years, respectively, after approval.

"We've long believed that inhibiting the detrimental effects of endothelin after an aneurysmal subarachnoid hemorrhage was the key to helping patients avoid the devastating consequences of cerebral vasospasm, and now we have the evidence from Japanese patients."

Jean-Paul Clozel
Chief Executive Officer



Japanese registration program

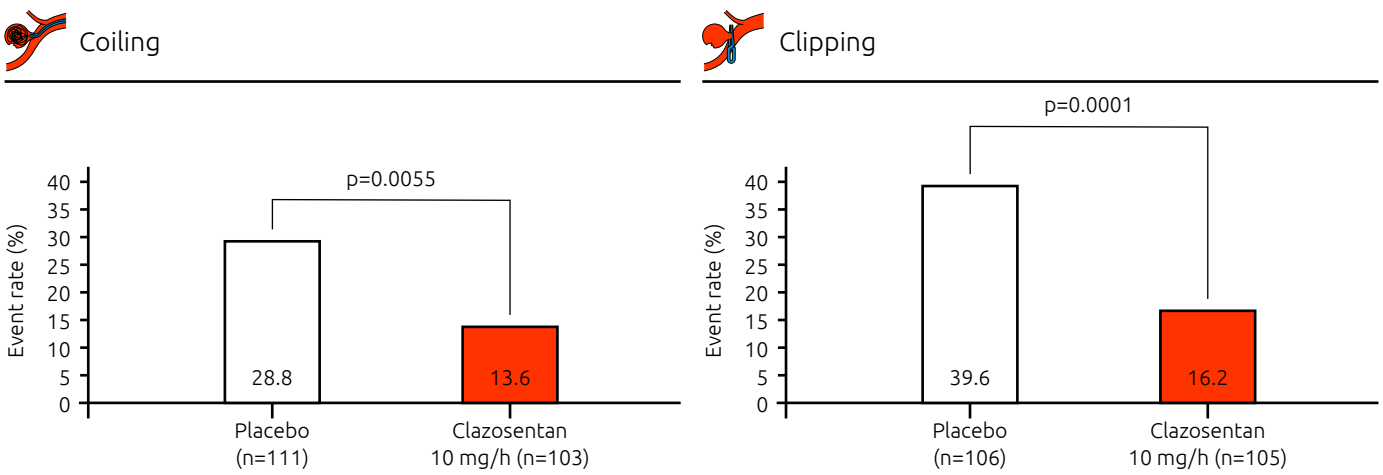
A Phase 2 study in Japanese and Korean patients showed that 10 mg/h clazosentan administered by continuous intravenous infusion significantly reduced vasospasm and the overall incidence of vasospasm-related morbidity and all-cause mortality. On that basis, a registration program was initiated with clazosentan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

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

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.

As shown in the charts above both studies demonstrated a statistically significant ($p<0.01$) reduction in the combined incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH. Clazosentan showed a numerical reduction in the combined incidence of all-cause morbidity and mortality. The effect of clazosentan on this endpoint was significant ($p<0.05$) in the pre-planned pooled analysis.

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

PIVLAZ clazosentan

On January 20, 2022, PIVLAZ™ (clazosentan) 150 mg was approved in Japan for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aSAH. PIVLAZ is expected to be commercially available in April 2022.

Cerebral vasospasm associated with aSAH

Compound: Clazosentan

Mechanism of action: Selective endothelin (ET_A) receptor antagonism

Status Global: Phase 3

Status Japan: Approved as PIVLAZ™

Lucerastat for Fabry disease

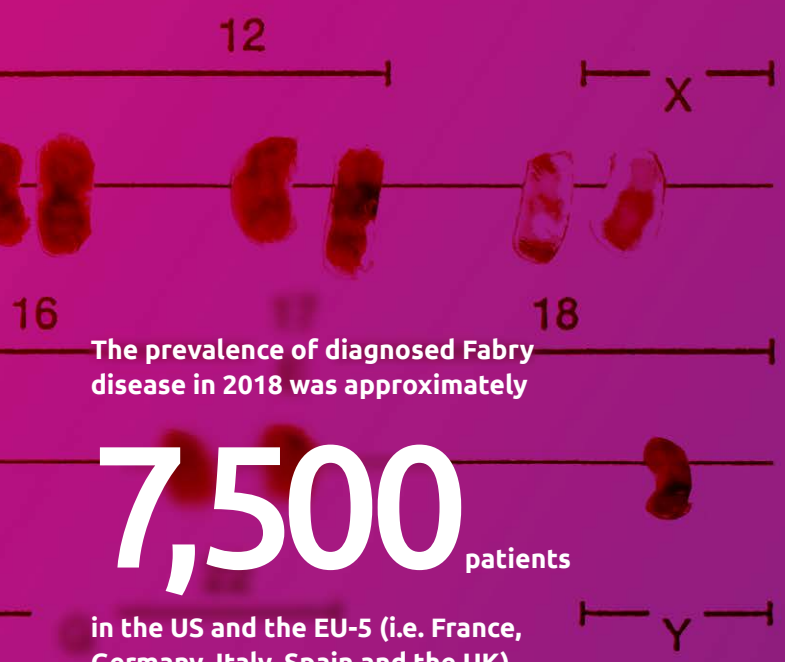
Fabry disease is a rare genetic, lysosomal storage disorder. It is caused by mutations in the GLA gene, leading to a deficiency or dysfunction of alpha-galactosidase A (alpha-Gal A), an enzyme that normally breaks down a fatty substance known as globotriaosylceramide (Gb3) in the cells of the body. Over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

Symptoms of Fabry disease affect a patient's life expectancy and quality of life. Since most symptoms are non-specific, Fabry disease is often undetected or misdiagnosed. As the disease is progressive, early diagnosis is essential to manage the symptoms as soon as possible and reduce the risk of developing serious complications.

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

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

Patient and mother to a patient with Fabry disease



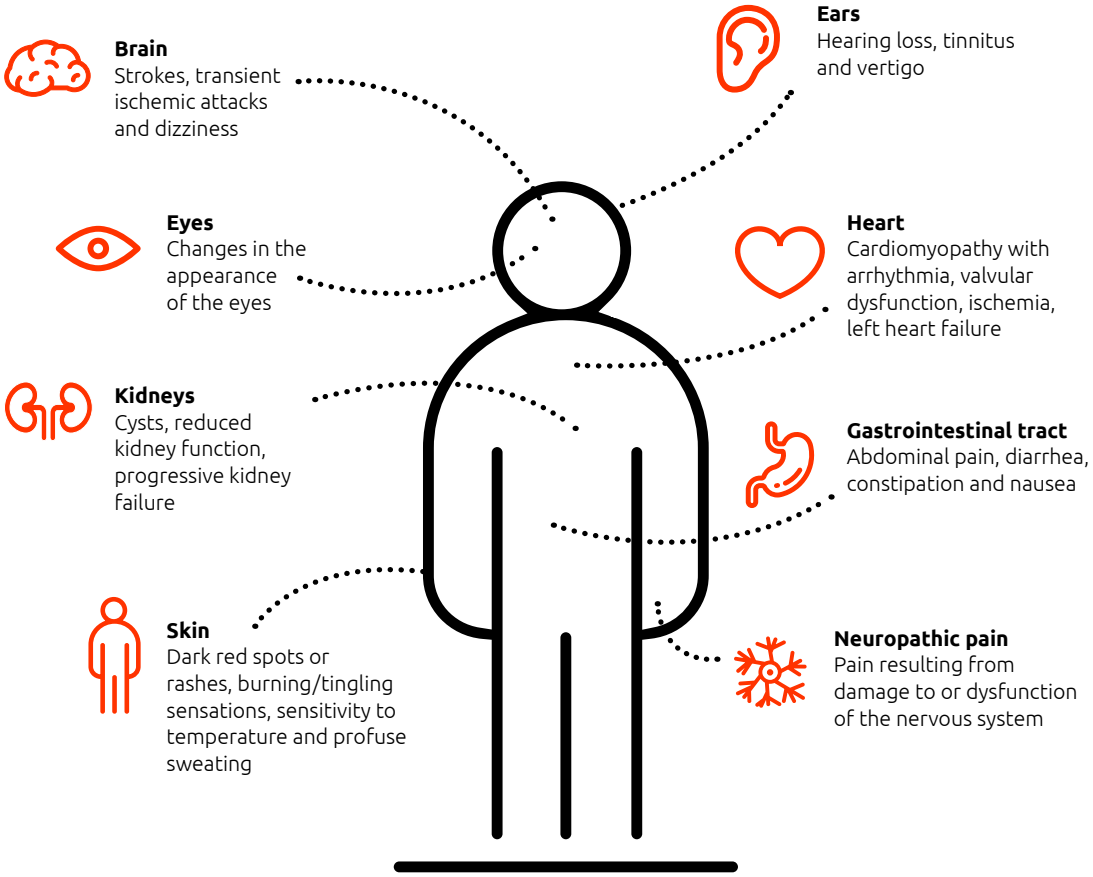
The prevalence of diagnosed Fabry disease in 2018 was approximately

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

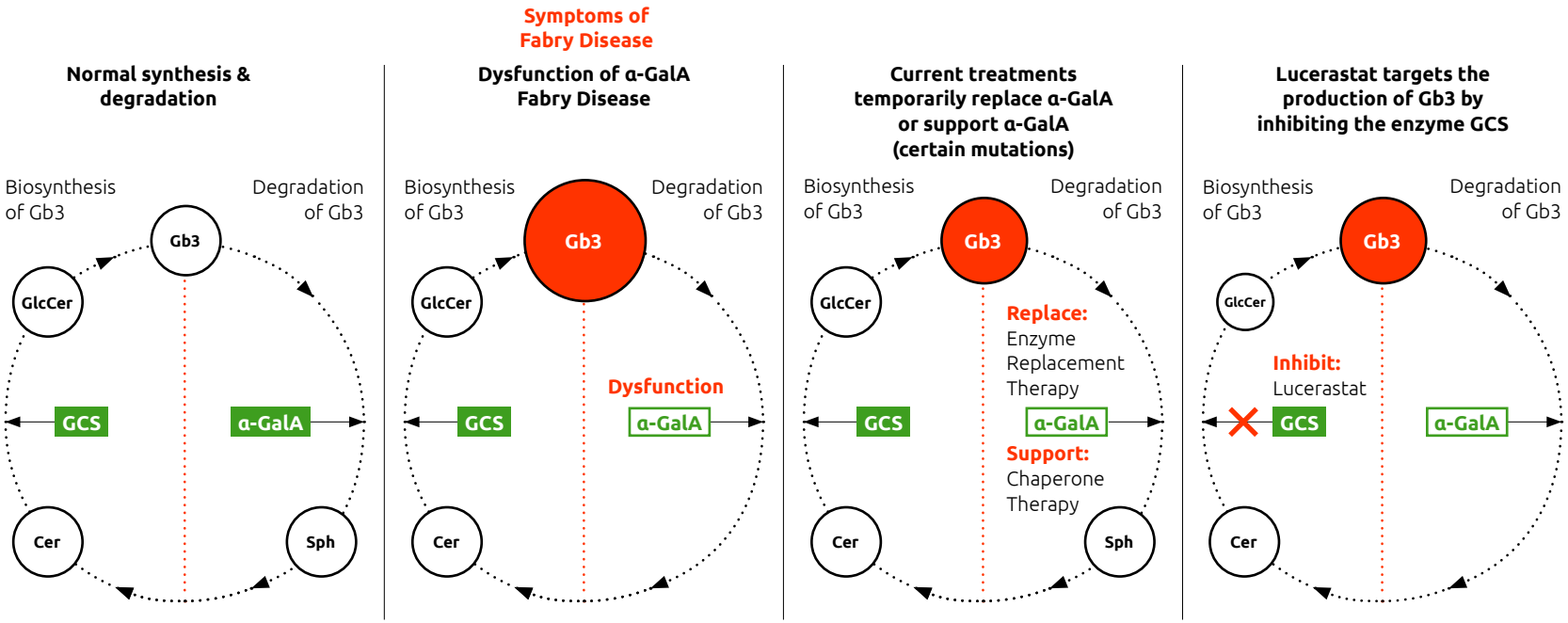


The Gb3 cycle and therapeutic approaches

The normal biosynthesis and degradation of Gb3 is shown schematically in the Figure below. In patients with Fabry disease, deficiency or dysfunction of the enzyme alpha-Gal A leads to abnormal accumulation of Gb3, which in turn causes the symptoms of Fabry disease. Current treatments focus on replacing or supporting alpha-Gal A – either through infusion of recombinant enzyme, which temporarily increases plasma concentrations of alpha-Gal A, or by chaperone therapy, which improves the function of mutated enzymes (in patients with amenable mutations).

In contrast, lucerastat, an oral inhibitor of glucosylceramide synthase (GCS), reduces the substrate which forms Gb3. Substrate reduction therapy (SRT) decreases the build-up and is thought to subsequently reduce the Gb3 load in patients with Fabry disease. Since this mechanism is independent of alpha-Gal A deficiency or dysfunction, it should not be limited to specific mutations of the GLA gene.

The Gb3 cycle



Abbreviations: 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 long-term course of the disease."

Luba Trokan
Director, Clinical Project Physician

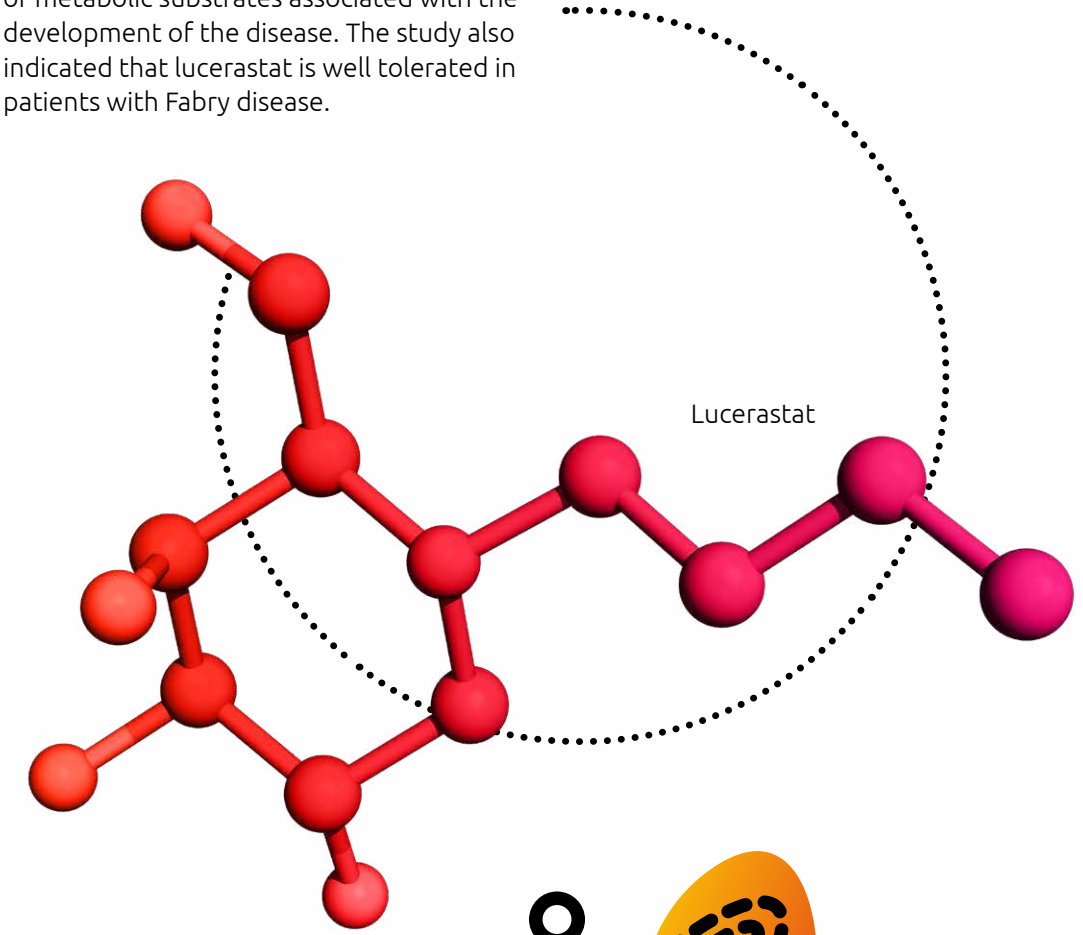
Idorsia's innovation

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 71. This demonstrates that lucerastat has the potential to reduce Gb3 levels in key target organs and, therefore, to show clinical efficacy in Fabry disease.

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



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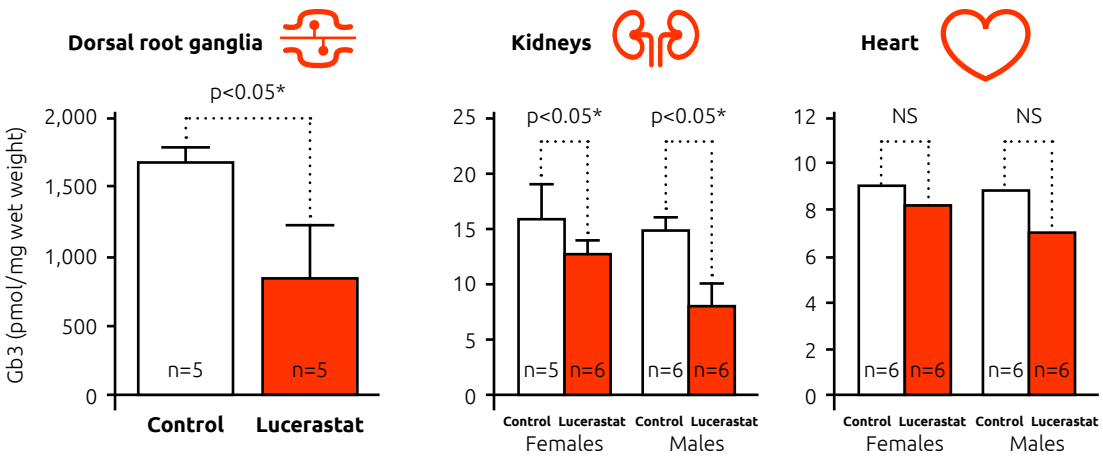
Reduction of Gb3 levels in tissues from an animal model of Fabry disease



* ANOVA with Bonferroni's multiple testing correction

Current status

MODIFY was a Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. 118 patients were randomized in a 2:1 ratio to receive either lucerastat or placebo. At the end of the double-blind period, 107 patients entered an ongoing open-label extension (OLE) study, which aims to determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical effects on renal and cardiac function in adult patients with Fabry disease over an additional period of up to 48 months.

In October 2021, the company reported that lucerastat 1000 mg b.i.d. did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo. However, observations were made on renal function and cardiac echocardiography which, if confirmed with longer-term data, would indicate a treatment effect on the main organs affected by the disease. As a result, the company has decided to further characterize lucerastat for the treatment of Fabry disease by continuing the OLE study. The company will consult with health authorities and share the data collected so far in order to define the regulatory pathway for lucerastat in Fabry disease.

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

Fabry disease

Compound: Lucerastat

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

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Selatogrel for acute myocardial infarction

About AMI

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

Although the management of AMI has improved in recent decades, morbidity and mortality associated with AMI remain high, with the majority of early deaths occurring 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 deaths.

Each year more than

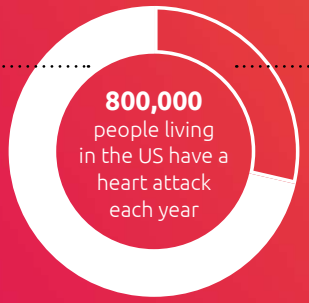
800,000

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



Average age at first heart attack – risk increases with age

3.3m women die of heart attack worldwide every year

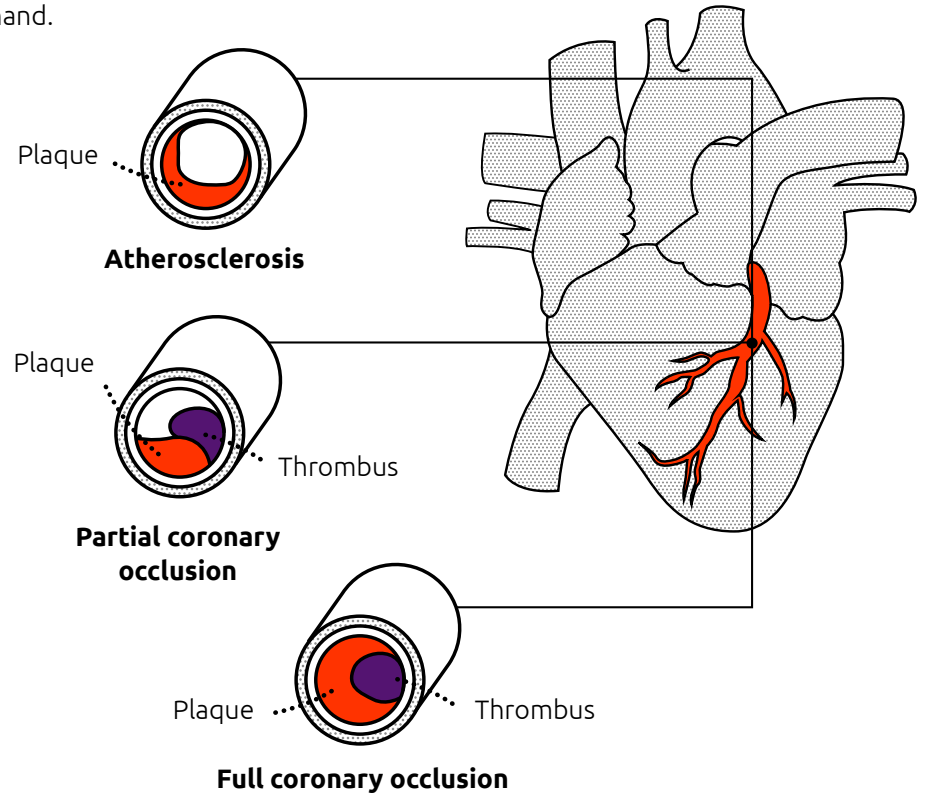
Women tend to **underestimate** the risk of heart attacks

What causes a heart attack?

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

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

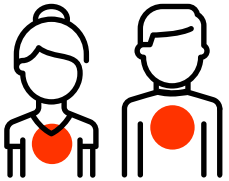
If a plaque ruptures, it triggers the formation of a blood clot at the same site (coronary thrombosis). This can lead to partial – or in extreme cases complete – obstruction of the coronary artery (coronary occlusion). Both coronary thrombosis and coronary occlusion obstruct the blood flow in the coronary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



Recognizing the symptoms of heart attack

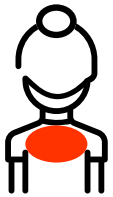
Common heart attack symptoms:

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



Chest pain can radiate to:

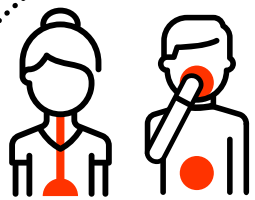
The left arm or both arms



Between the shoulders

The neck or jaws or gums

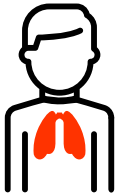
The chest symptoms can also be associated with:



Unexpected or unexplained indigestion, nausea or vomiting

Breaking out in cold sweat

Feeling lightheaded



Feeling the need to take more air, shortness of breath

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.

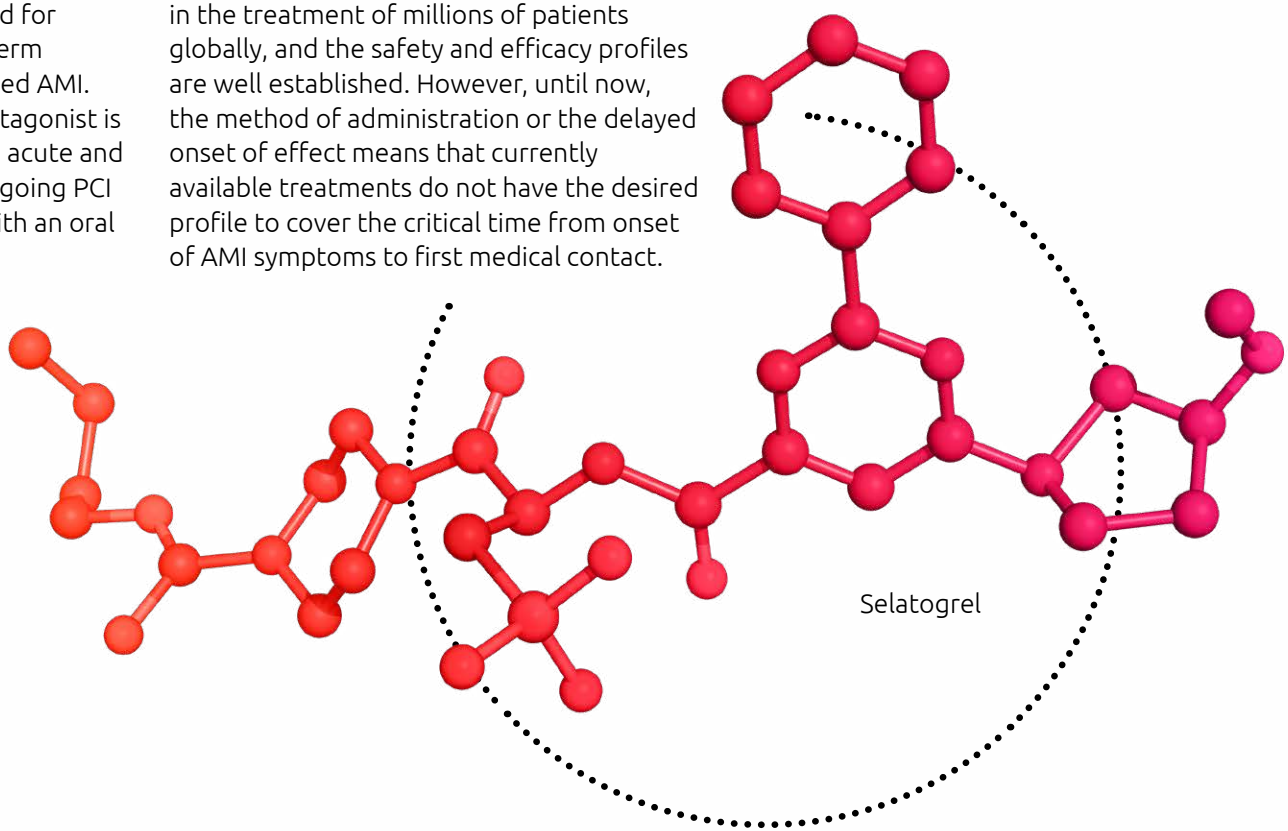
$P2Y_{12}$ receptor antagonism

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.

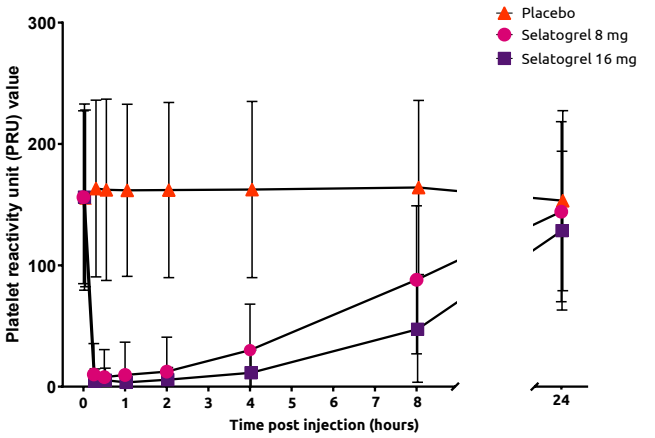


"With our integrated drug delivery device, the potential to self-administer selatogrel in the critical time period immediately following onset of suspected AMI symptoms could be revolutionary for patients."

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.

Current status

In June 2021, Idorsia initiated an international, double-blind, randomized, placebo-controlled Phase 3 study Selatogrel Outcome Study in suspected Acute Myocardial Infarction (SOS-AMI) to assess the clinical efficacy and safety of selatogrel 16 mg when self-administered (on top of standard of care) upon the occurrence of symptoms suggestive of AMI. The primary efficacy endpoint is the occurrence of death from any cause, or non-fatal AMI, after self-administration of the study treatment. The study will enroll approximately 14,000 patients who are at high risk of recurrent AMI, at around 250 sites in about 30 countries.

A Special Protocol Assessment has been agreed with the FDA, indicating its concurrence with the adequacy and acceptability of critical elements of overall protocol design for a study intended to support a future marketing application. In addition, the FDA designated the investigation of selatogrel for the treatment of suspected AMI as a "fast-track" development program. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need.

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

"Every patient 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

Acute myocardial infarction
Compound: Selatogrel

Mechanism of action: selective $P2Y_{12}$ receptor antagonism
Status: Phase 3

Cenerimod for systemic lupus erythematosus

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

Patient with SLE

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

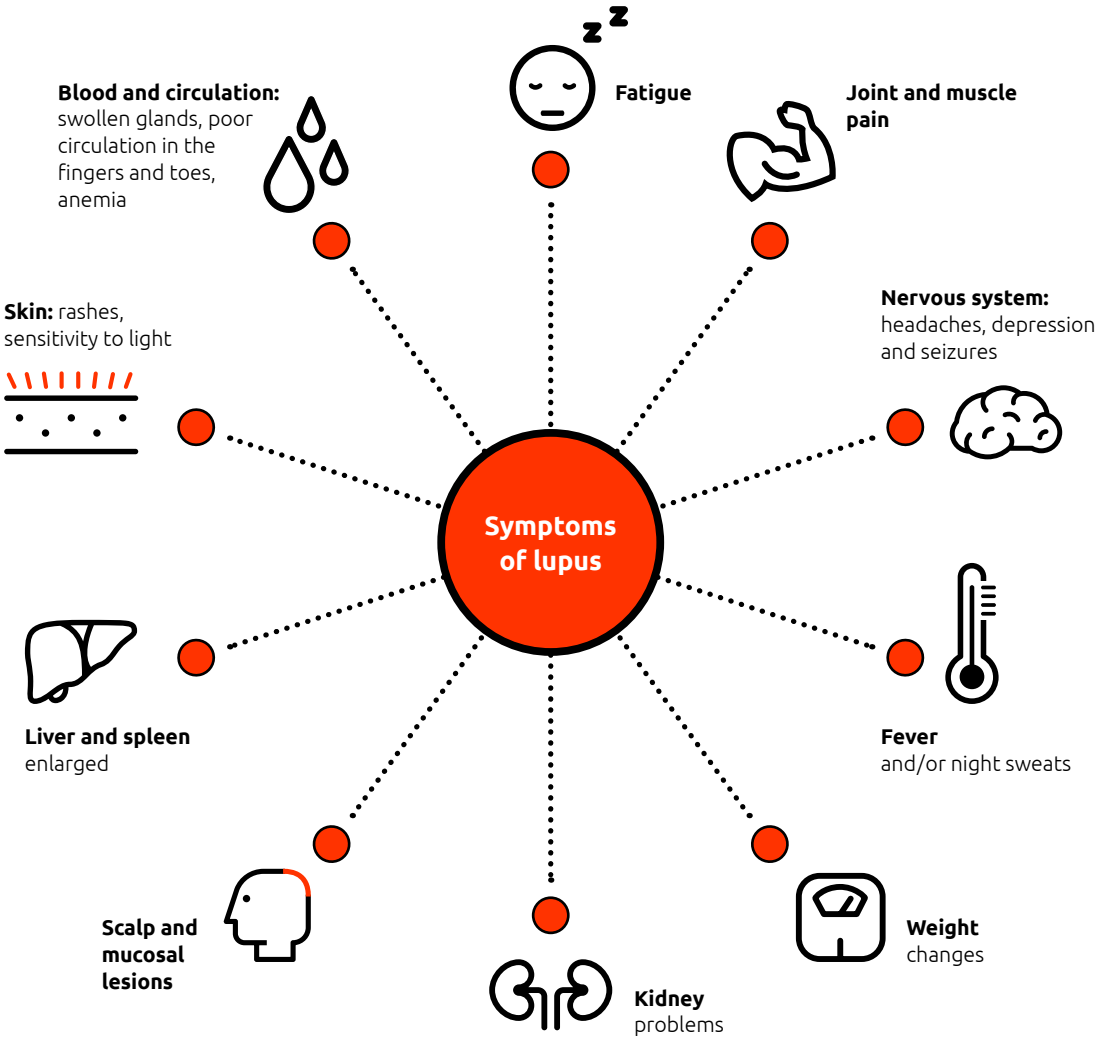
As a result, symptoms vary widely and are often similar to other conditions, which need to be ruled out before a diagnosis can be made. Lupus therefore often goes undetected or misdiagnosed for long periods. Yet early diagnosis is important to manage the symptoms of lupus, initiate treatment to reduce the risk of long-term complications, and enable 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.

Normal immune response	Autoimmune response
Foreign threat invades	Immune system forms antibodies against its own body cells
Antibodies attack and remove invading threat	Antibodies attack the body's own cells
Antibodies continue to protect body	Antibodies remain in the body causing inflamation and tissue damage

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

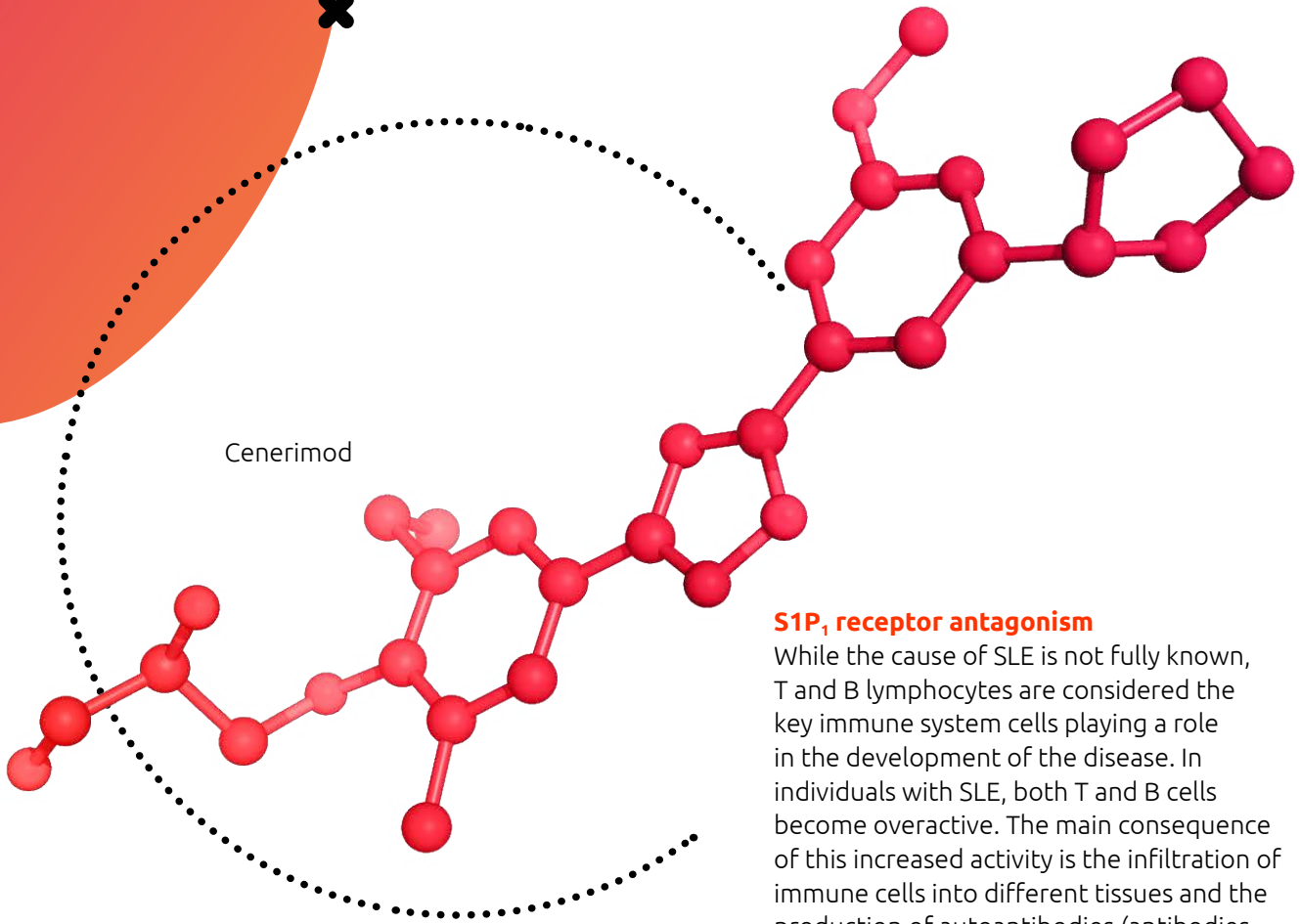
There is no cure for SLE, and a significant need exists for safe and effective therapies. Most people with SLE are prescribed a combination of different medications to manage their symptoms, improve their quality of life and reduce the risk of more serious complications.

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, belimumab, and anifrolumab. 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 the disease. In individuals with SLE, both T and B cells become overactive. The main consequence of this increased activity is the infiltration of immune cells into different tissues and the production of autoantibodies (antibodies that recognize and destroy the body's own cells), leading to inflammation and organ damage.

T and B lymphocytes have a cell surface receptor called sphingosine-1-phosphate receptor 1 ($S1P_1$). 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 circulation.

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 autoreactive T and B cells in the circulation and thus also the tissues.

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

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Idorsia's innovation

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

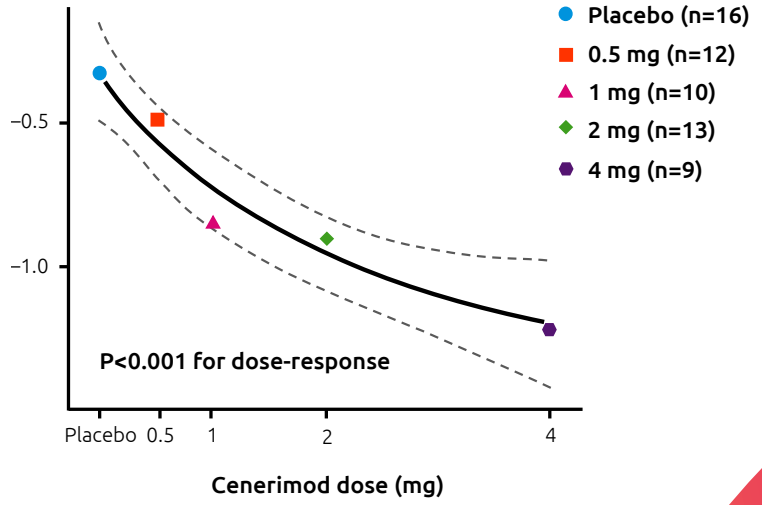
In a mouse model of SLE, mice typically develop an aggressive version of a lupus-like disease, with increased inflammation, autoantibodies and immune cytokines, resulting in damage to the kidney and death. When treated with cenerimod, an increase in survival was observed. This was underpinned by improved kidney structure and function, as well as marked decreases in 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 safety and pharmacokinetics of cenerimod and its effects on circulating lymphocytes and disease activity, cenerimod dose-dependently reduced total lymphocyte count from baseline to end of treatment in patients with SLE ($p<0.001$). In addition, it markedly reduced the antibody-producing B cells, which are elevated in patients with SLE and critical to disease progression.

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

Cenerimod induced a dose-dependent reduction of total lymphocyte count in patients with systemic lupus erythematosus



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

Current status

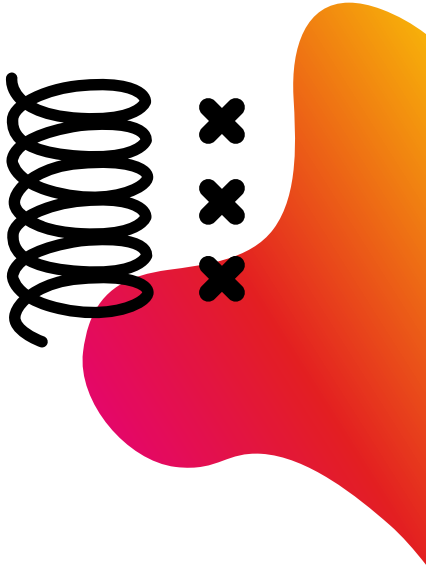
In November 2021, the company reported the results of CARE, a Phase 2b study investigating the efficacy and safety of cenerimod as an oral treatment for adult patients with moderate to severe SLE. In the study, 427 patients with SLE on background therapy were randomized to receive cenerimod (0.5, 1, 2, 4 mg) or placebo. Patients receiving cenerimod 4 mg showed a clinically meaningful improvement in the modified Systemic Lupus Erythematosus Disease Activity Index-2000 (mSLEDAI-2K) score compared to placebo from baseline to month 6 (p=0.029). However, this result did not reach statistical significance in the formal testing strategy when adjusting for the multiplicity of tests for the four doses against placebo. SLEDAI-2K is a recognized index used to assess disease activity in patients with lupus which was modified to exclude leukopenia, maintaining the blinded nature of the study since cenerimod induces a reduction in lymphocyte count as part of its mechanism of action.

The increasing improvement seen with cenerimod 4 mg versus placebo in mSLEDAI-2K over time was further supported by a consistent improvement across several patient subpopulations – particularly in those with more severe disease activity – in the Systemic Lupus Erythematosus Responder Index 4 (SRI-4), and it was associated with an effect on several biological markers of disease activity.

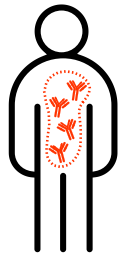
Cenerimod was well tolerated at all doses, with similar rates of adverse events reported across all treatment groups over six months of treatment: 49.4% for 0.5 mg, 64.7% for 1 mg, 59.3% for 2 mg, 58.3% for 4 mg and 54.7% for placebo. The most frequent treatment-emergent adverse events reported with an incidence greater than 5% in any group and higher than placebo over a six-month treatment period were abdominal pain, headache, hypertension, and, as expected from the mechanism of action of cenerimod, lymphopenia. Importantly, objective measurements taken during study visits showed only minimal to no effect on blood pressure.

The results obtained after six months of treatment have provided the information needed to design a Phase 3 development program, including the patient population, the optimal dose and endpoints. The Phase 3 design is to be discussed with health authorities with a view to initiating evaluation before the end of 2022.

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



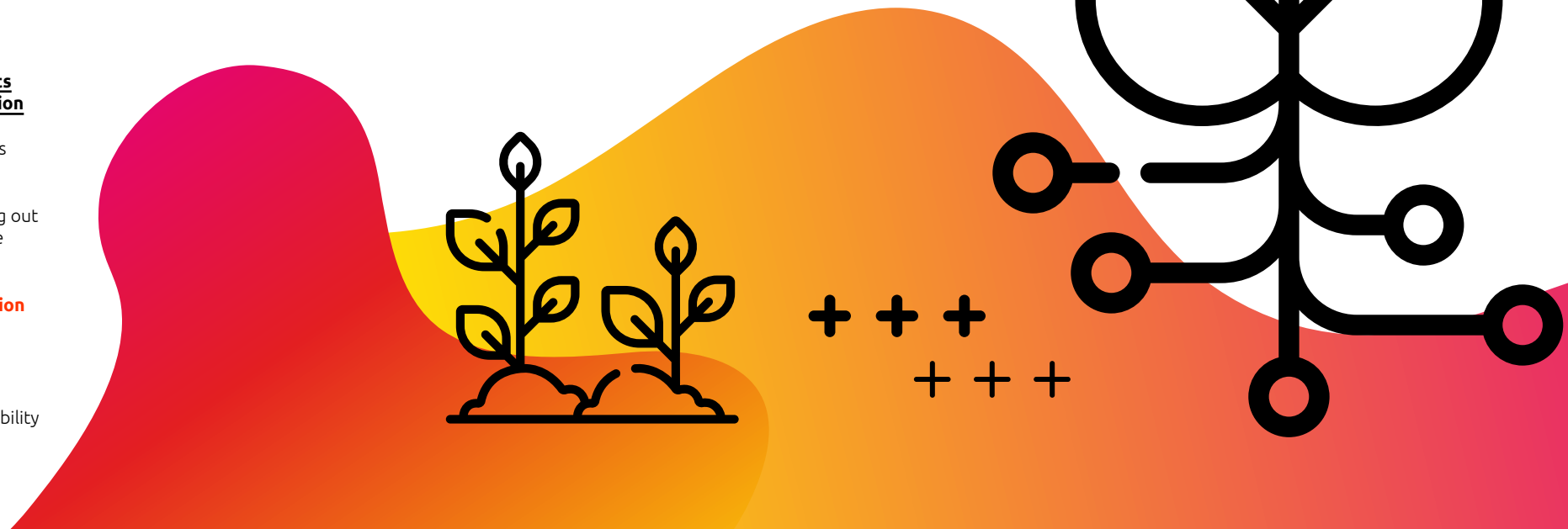
Systemic lupus erythematosus
Compound: Cenerimod



Mechanism of action:
$S1P_1$ receptor modulation
Status: Phase 3 in preparation

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.



Johnson & Johnson

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

www.investor.jnj.com

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. The results of the Phase 3 study of aprocitentan in patients with resistant hypertension are expected in mid-2022.

www.janssen.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. In 2021, Idorsia initiated the Phase 3 study SOS-AMI with the selatogrel drug-device for the treatment of suspected acute myocardial infarction.

www.antarespharma.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, 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 form of pediatric epilepsy; in addition, a research collaboration was established to discover, identify and develop additional novel T-type calcium channel blockers. In 2021, Neurocrine also initiated a Phase 2 study in essential tremor.

www.neurocrine.com

Santhera

In 2020, Idorsia's license, collaborative development and commercialization agreement with ReveraGen BioPharma in respect of vamorolone was transferred in its entirety to Santhera Pharmaceuticals, with the latter replacing Idorsia as a party to the agreement.

www.santhera.com

Syneos Health

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

www.syneoshealth.com

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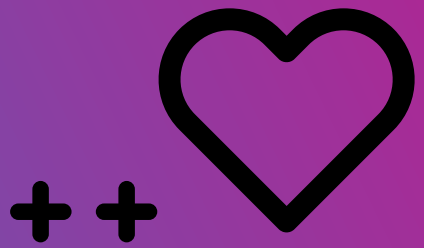
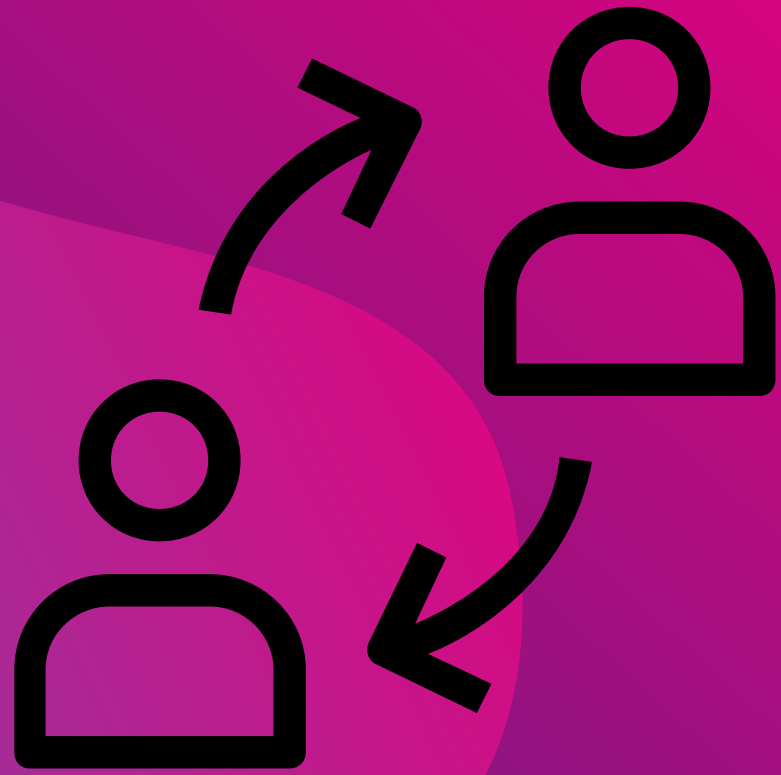
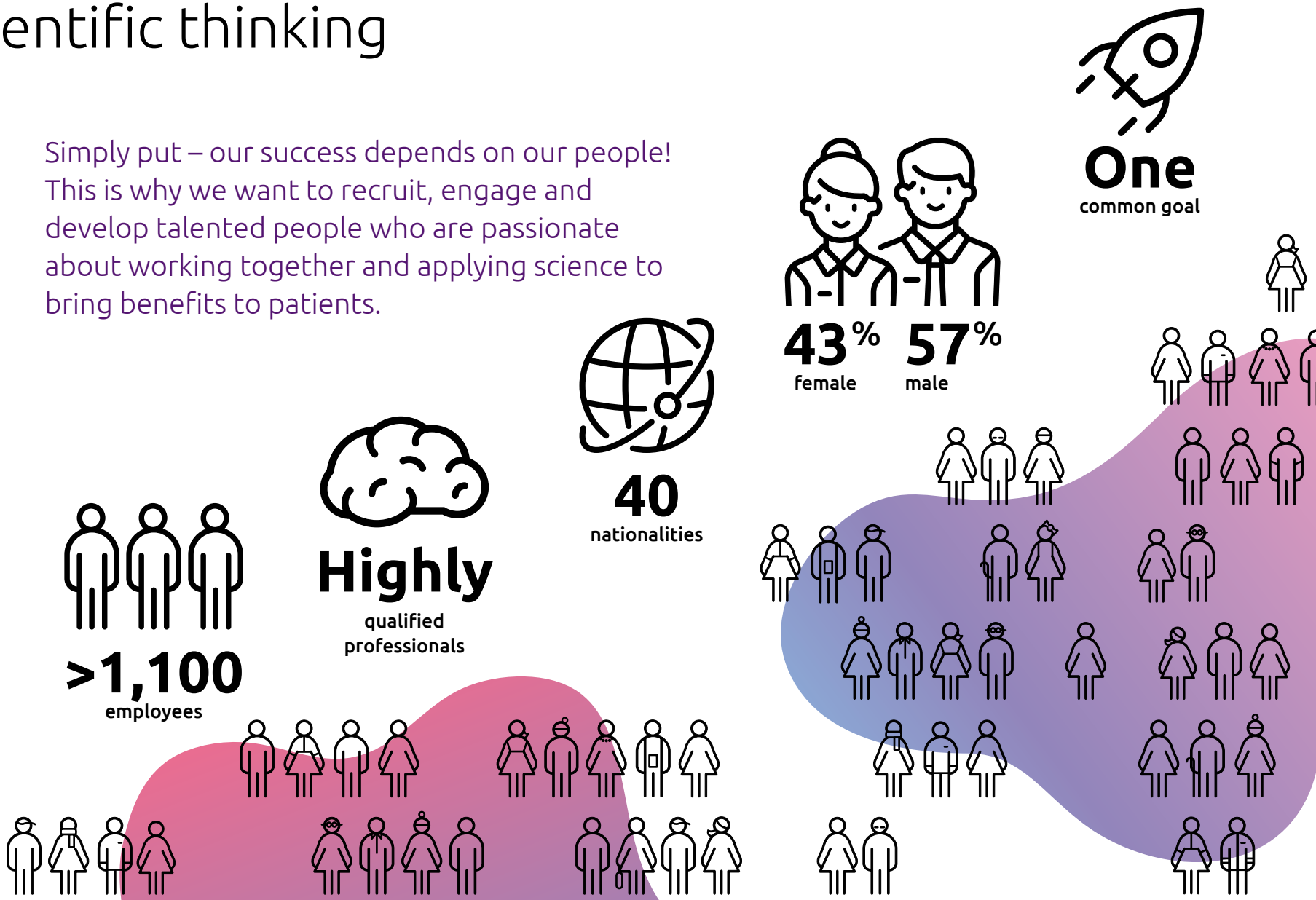




More power –
For scientific thinking

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 250 new positions worldwide in 2021.

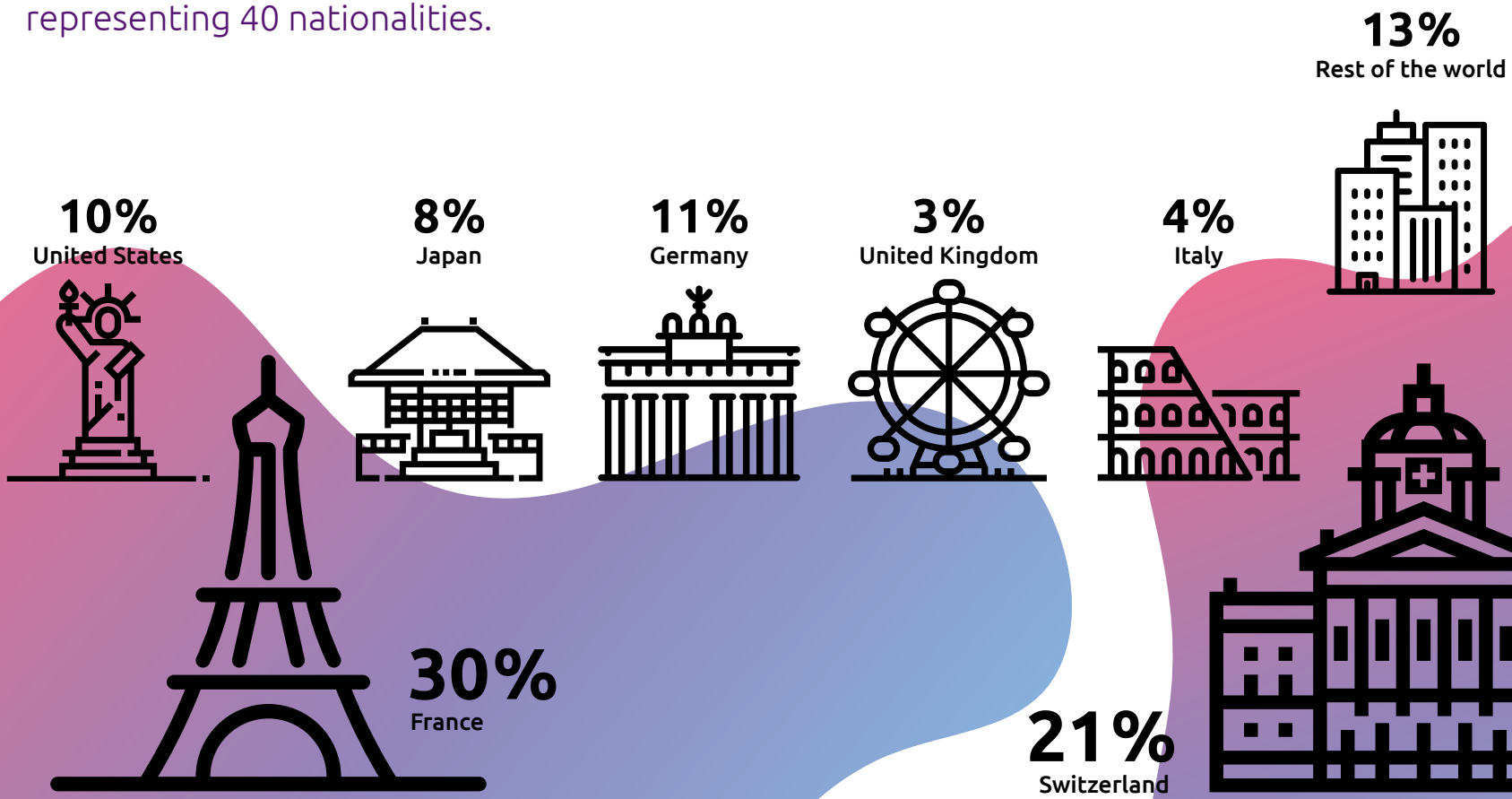
As a growing company, it is important that we attract, retain and advance top talent from all backgrounds and cultures. During the recruitment process, we seek to attract a diverse pool of candidates, focusing on the skill set they offer and matching their competencies to the behaviors we expect our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

Our people are committed to making Idorsia a leading biopharmaceutical company, while at the same time developing both personally and professionally.

"We're going through very exciting times! With product launches just ahead of us, it's all hands on-deck, which is exactly how I like to work."

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 40 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.

Idorsia is committed to ensure full compliance with the gender representation and pay equality required by the Swiss regulations. After our 2020 gender equal pay analysis results in Switzerland (published in the Compensation Report 2020) confirmed our company culture of equal opportunities and equal pay, Idorsia has committed to continue this practice and to monitor this important corporate performance indicator on the global level as the company expands geographically.

Jose Alba Casado
Clinical Operations Manager

Karen Ellis
Director, Drug Safety Compliance Manager

More potential – Expanding opportunities

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

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

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

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

In 2020, 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.

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

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

Pier Paolo Lo Valvo
Director, Integrated Global Talent Management

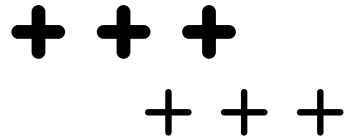
More experience – Driving innovation

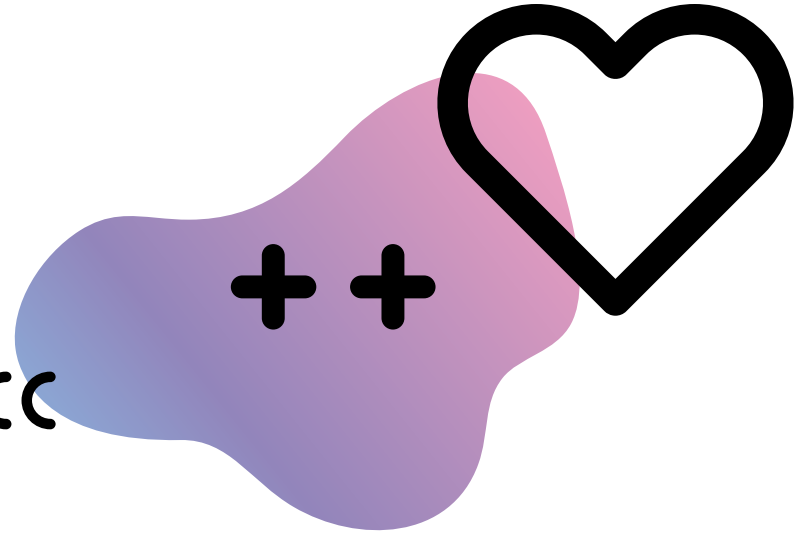
At Idorsia, we have tools in place to recognize extraordinary achievements and emphasize the importance of working in teams.

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" of 4 weeks' fully paid sabbatical leave when employees reach their 10th, 20th and 30th anniversary of employment with Idorsia, and 1 week when reaching the 15th and 25th anniversary. Disconnecting from work for an extended period to pursue personal interests leaves employees energized and ready to immerse themselves when they return.



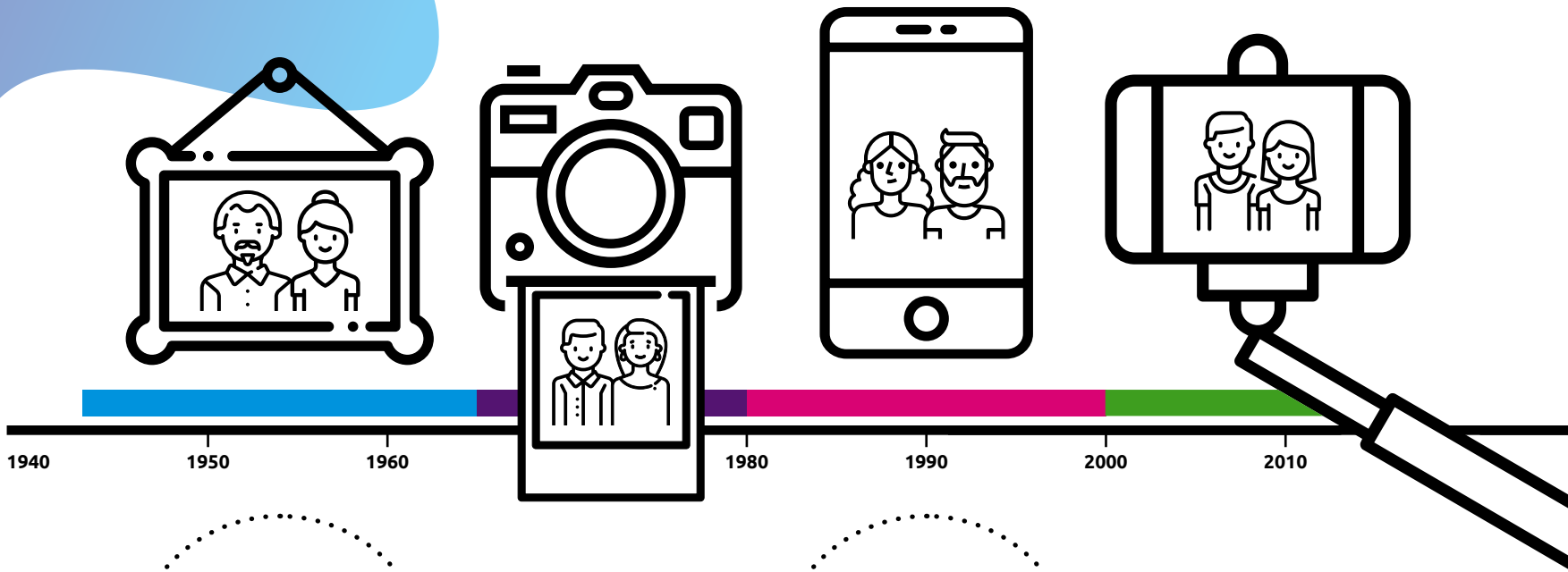


"It's very exciting to be able to discover innovative new treatments and really help patients, while at the same time contributing to the growth and value generation of our company."

Naomi Tidten
Director, Team Leader Computer-Aided Drug Design

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

1%
Generation Z
(2000 – 2012)
56% female
44% male



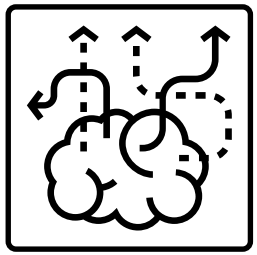
10%
Baby boomers
(1943 – 1964)
28% female
72% male

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

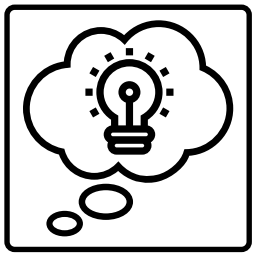
More ambitions – Courageous and energetic

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.

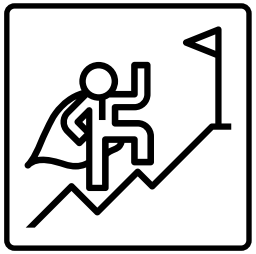
be pragmatic



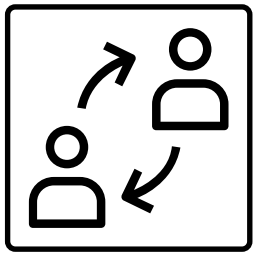
invent



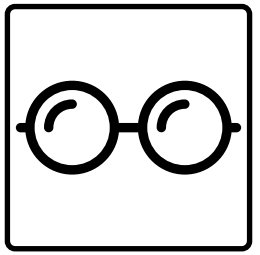
advance

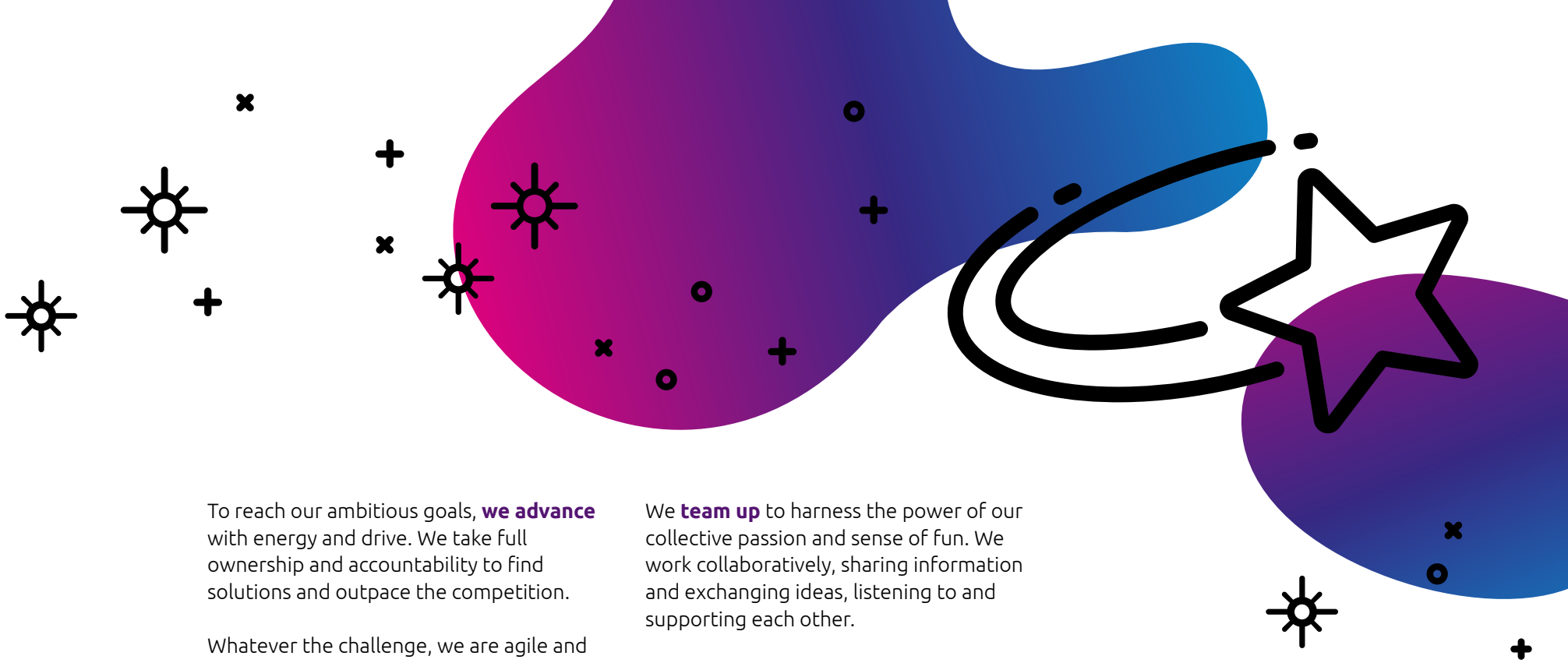


team up



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

In 2021, Idorsia has added more than 250 professionals to its ranks. This growth reflects the rapid advancement of our pipeline and ongoing preparations to bring our drugs to patients.

Having already established our commercial teams in the US and Japan during the course of 2019 and 2020, this year, we started establishing our Europe and Canada business unit. Led by Jean-Yves Chatelan, President of the EUCAN Region, we opened five Idorsia affiliates in key European markets (France, Germany, Italy, Spain, UK), and appointed a General Manager and most leadership team members for each of these countries.

The Idorsia Executive Committee

Simon Jose
Executive Vice President, Chief Commercial Officer

Martine Clozel
Executive Vice President, Chief Scientific Officer

Guy Braunstein
Executive Vice President, Chief Medical Officer (since January 2022)

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 products.

As Idorsia enters this new phase with marketed products, we can benefit from a dedicated focus on medical governance. As a result, the role of Chief Medical Officer (CMO) has been created to ensure that Idorsia's approach to medical governance and its policies and procedures are globally aligned and consistent across the company. With his wealth of experience and his deep knowledge of the Idorsia pipeline, Guy Braunstein was perfectly positioned to take on the role of CMO in January 2022.

Guy was succeeded by Alberto Gimona, as Head of Global Clinical Development and new member of the Idorsia Executive Committee (IEC). Alberto's broad clinical and medical expertise, intimate knowledge of our pipeline and therapeutic areas, as well as his mentorship management style will ensure our clinical development function will continue to thrive, and our pipeline will rapidly advance.

"This is a very exciting time for Idorsia. I am very proud to have built such an experienced and talented team to deliver innovation from bench to bedside."

Jean-Paul Clozel
Chief Executive Officer

André C. Muller
Executive Vice President,
Chief Financial Officer

Jean-Paul Clozel
Chief Executive Officer

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

Sustainability

More drive – For a better future

Our purpose

The purpose of Idorsia is to discover, develop and commercialize innovative medicines to help more patients. We have more ideas, we see more opportunities, and we want to transform the horizon of therapeutic options.

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

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

As Idorsia grows, our commitment to sustainability remains as important as ever.

Our approach to sustainability

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

This has been our approach from the outset: the company was founded with a strong governance framework in place, including a broad range of policies, standard operating procedures and guidelines to drive a culture of integrity. Our commitment to sustainability has been reinforced over the years. For example, we have strengthened the monitoring and disclosure of our performance on a wide variety of environmental, social and governance (ESG) topics important to our stakeholders, including our environmental footprint and the company's impact on the communities in which we operate. Today, ESG reporting is already one of the four topics included in our company goals for the year, affecting every employee's short-term incentive.

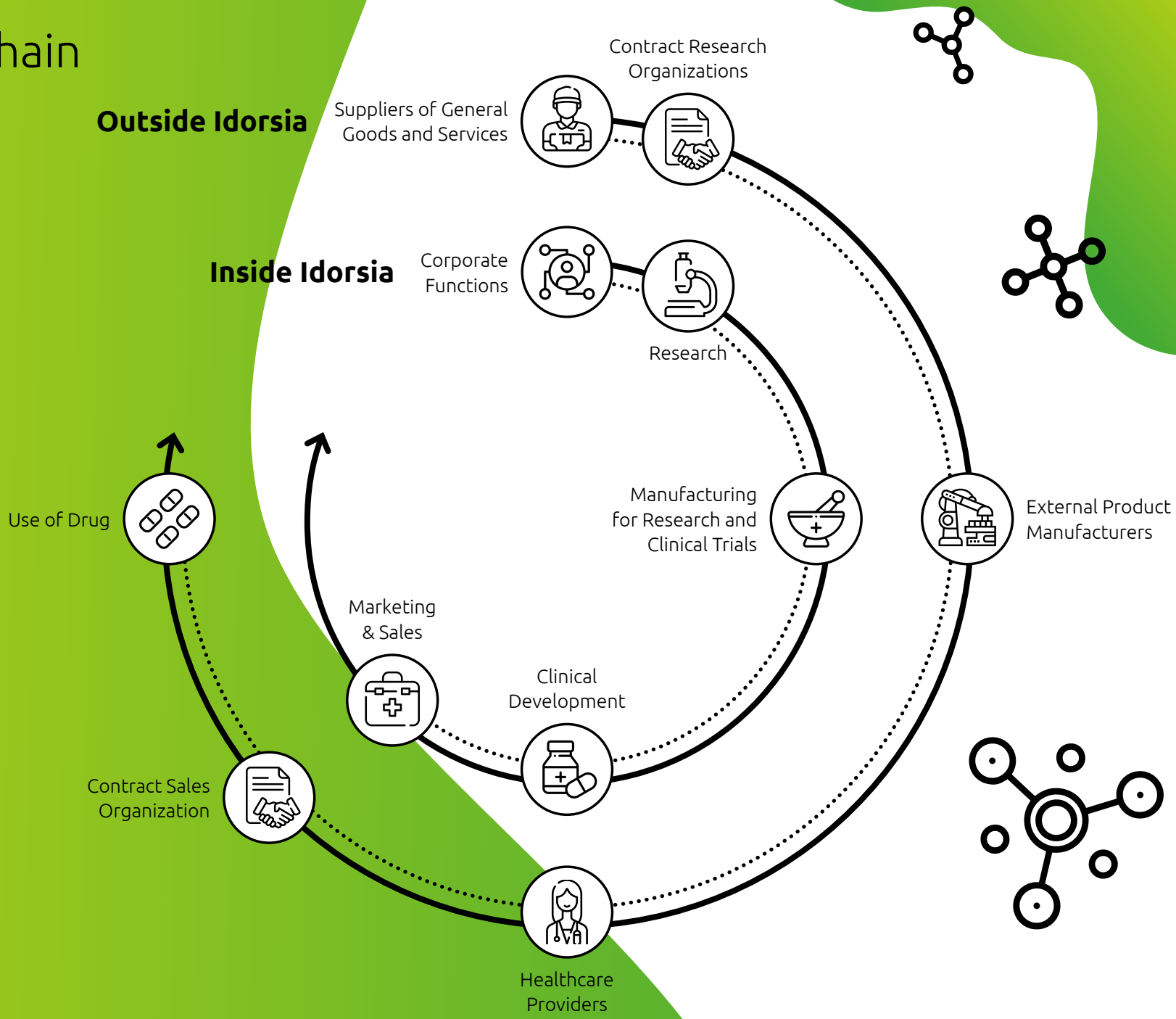
As we look forward to a strong growth trajectory, we aim to be open and transparent, and to continue engaging with our stakeholders as our approach to sustainability evolves.

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

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

Jean-Paul Clozel
Idorsia's CEO, on the establishment of the company

Our value chain



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

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

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

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

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

The results of our stakeholder engagement activities, and in particular the in-depth outreach program, were fed into a materiality assessment which will help Idorsia to prioritize areas of our business that are most important to ensure a sustainable future for our company. The materiality assessment provided key insights on each topic, and the priorities identified are shown in the infographic on page 102.

To build on the learnings from our materiality assessment, we launched an online sustainability survey in 2021. All stakeholders are invited to participate in this survey, which probes the material themes uncovered in the 2020 assessment phase. The survey will be pursued throughout 2022 to inform our efforts on each of the material topics that our stakeholders have helped us identify. Take our survey at: www.idorsia.com/survey

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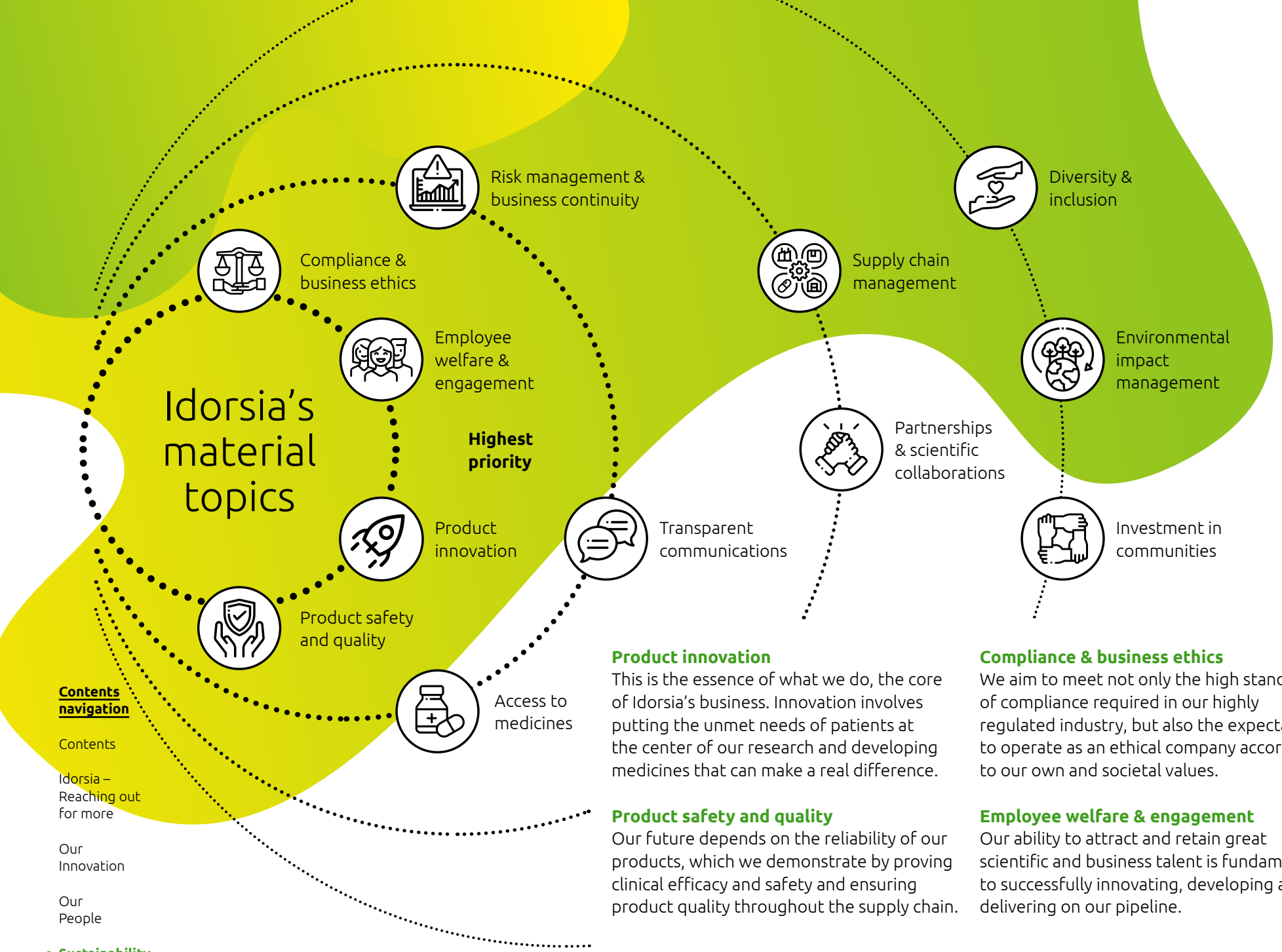


Product innovation
This is the essence of what we do, the core of Idorsia's business. Innovation involves putting the unmet needs of patients at the center of our research and developing medicines that can make a real difference.

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

Compliance & business ethics
We aim to meet not only the high standards of compliance required in our highly regulated industry, but also the expectation to operate as an ethical company according to our own and societal values.

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

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

Access to medicines
As an engaged member of the healthcare ecosystem, Idorsia understands its role to help find solutions to the high cost of healthcare and is committed to doing our part in supporting patient access to our medicines.

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

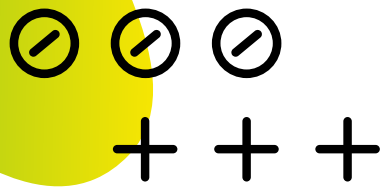
Supply chain management
We will maintain a reliable supply chain to ensure the delivery of safe, high-quality products to patients.

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

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

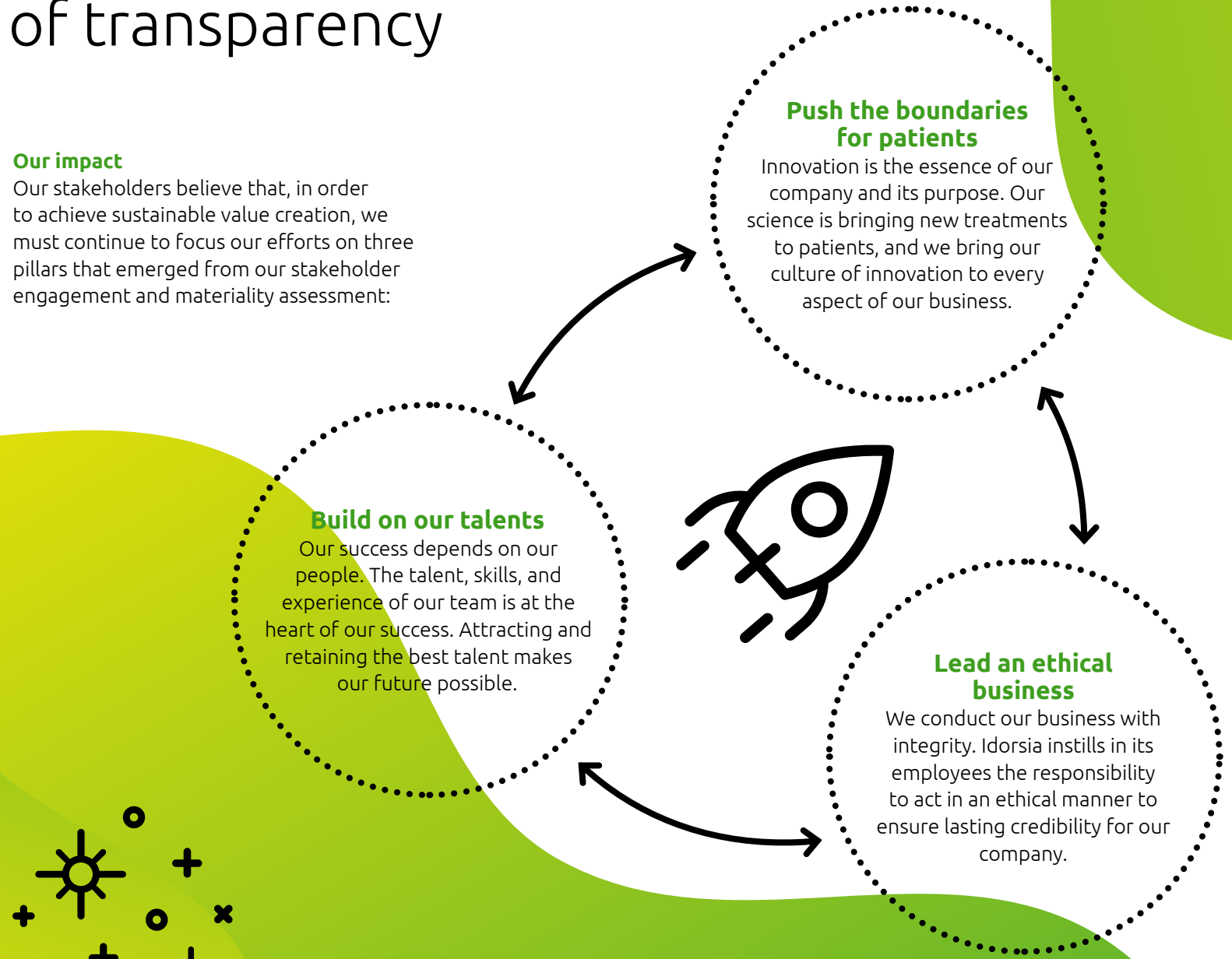
Environmental impact management
Climate change is a challenge that companies are increasingly prioritizing, and we will keep a strong focus on our impact as we grow.

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



More authentic – Culture of transparency

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



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

Push the boundaries for patients

Each of our employees knows that science is at the core of our company. Our scientific expertise in multiple therapeutic areas helps us to find innovative ways to help patients.

Nothing demonstrates our innovation better than our diversified and balanced pipeline. Our projects are a mix of new ideas alongside activities where we have deep knowledge and experience. We have a healthy number of early and late-stage compounds in development, spanning a range of therapeutic areas – CNS, cardiovascular, immunological disorders, and orphan diseases.

In 2021, we achieved a number of milestones demonstrating our progress in pushing the boundaries for the benefit of patients. We filed regulatory submissions for daridorexant, our investigational treatment for insomnia, with the FDA in the US, the EMA in Europe, Swissmedic in Switzerland, and Health Canada. We also filed a New Drug Application in Japan for clazosentan, our investigational treatment for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. These treatments are in areas of high unmet need for patients, and in fact, our first two products were approved in January 2022 as a result of two of these filings. Clazosentan is the first new treatment for the events associated with cerebral vasospasm in Japan in more than 25 years, giving new hope to neurointensivists for patients who have suffered an aneurysmal subarachnoid hemorrhage.

We advanced our clinical pipeline by initiating a Phase 3 study of selatogrel for the treatment of suspected acute myocardial infarction. An autoinjector combined with selatogrel may help close an important medical gap in the treatment of heart attack. The drug is self-injected by the patient at the onset of symptoms to immediately treat the thrombus formation blocking blood flow to the heart during the crucial period until medical help is available.

Build on our talents

Our success depends on our people. Our talented and diverse team is passionate about science, and we are committed to working collaboratively to bring new medicines to patients.

As a growing company, it is important that we attract, retain and advance top talent from all backgrounds and cultures. We harness the power of difference to achieve business success: our employees come from diverse cultural backgrounds, representing 40 nationalities. 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. We will extend this analysis to all our geographic locations as we grow.

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.

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 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.

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.

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

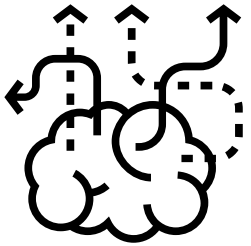
Lead an ethical business

Although we are, on paper, a young company, we have already established a robust governance framework to build compliance and ethical conduct into our company from the ground up. We have implemented a broad range of supporting policies, standard operating procedures and guidelines, such as our Code of Business Conduct, driving a culture of integrity.

The Code of Business Conduct 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 the code is to be applied in practice. All Idorsia employees have undergone mandatory training on the Code of Business Conduct, and the relevant employees are trained in the policies applicable to their role.

Idorsia is proud to be part of the biopharmaceutical industry, living up to the expectations and meeting the requirements for companies operating in this highly regulated industry. We are a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA). Idorsia and EFPIA are fully committed to complying with the highest ethical standards under EFPIA and national codes.

We aim to limit the environmental impact of our company so as to help ensure a safe and healthy environment for future generations. As part of the global community, we take our responsibility to curb the pace of climate change very seriously and are continuously working to find ways to build environmental sustainability into our operations. For example, since 2018, the increased use of a wood chip burner and the continuous optimization of the heat consumption in our buildings, has led to a substantial reduction of 74% of our carbon emissions at headquarters in Switzerland.



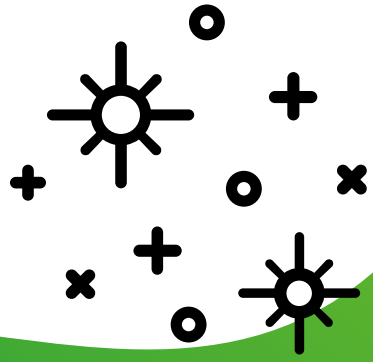
Sustainability performance

As we approach our fifth anniversary, we are proud of our sustainability performance. This topic has been covered in each of our Annual Reports since we were founded in 2017, and we continue to strengthen our performance disclosures.

Idorsia takes a pragmatic approach to sustainability reporting. We are working towards aligning our reporting with the Global Reporting Initiative (GRI), a leading standard in the Environment, Social and Governance (ESG) field. As a first step, we will report in accordance with the Core option of the GRI Standards. We may use additional standards – such as those of the Sustainability Accounting Standards Board (SASB) – to support the reporting of sector-specific topics. As we grow and our reporting system becomes increasingly robust, we will provide additional performance data, set targets and continue to expand our disclosures.

Our website serves as our performance reporting hub, where our sustainability content index is published. The index is based on our 12 material topics, providing links to sustainability content across our corporate publications. See more at: www.idorsia.com/sustainability

We know that transparency – with a focus on our material topics – is key to a sustainable future and is of great interest to our stakeholders. We have every intention of meeting their high expectations.



More ideas – Changing the world

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

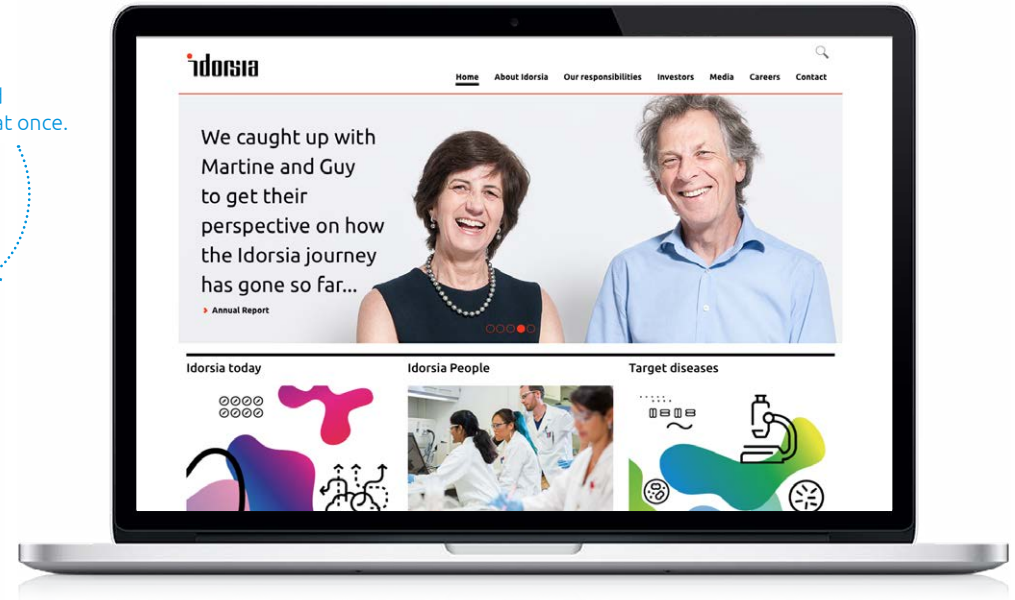
The core idea of the Idorsia brand is “Reaching out for more”. It is perfectly expressed in the energetic, intelligent and creative corporate design, and in the unified key messages.

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

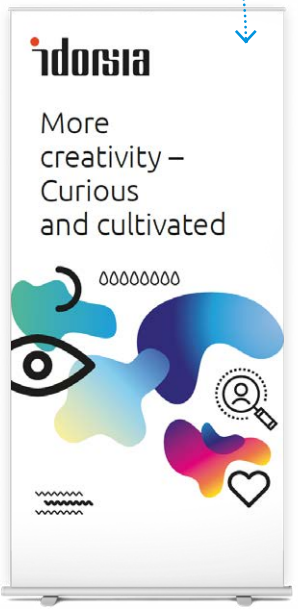
“When Idorsia was founded in 2017, we wanted to create a pharma brand that the world had not yet seen.”

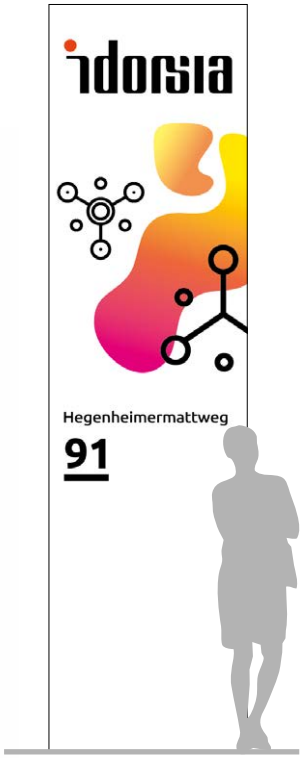
Jean-Paul Clozel
Co-founder and CEO of Idorsia

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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