Business Report

idorsia

Idorsia – Reaching out for more

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

We have more ideas, we see more opportunities and we want to help more patients.

More science –
For a better future

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>750

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10

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

>1 bn

Swiss francs in cash

> 550

State-of-the-art laboratory workspaces

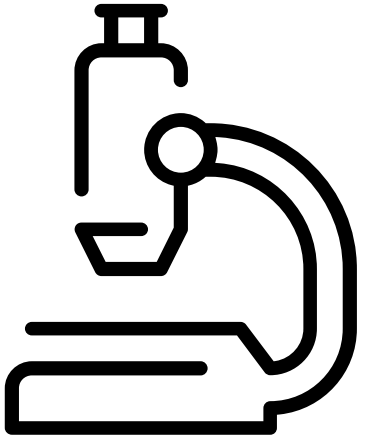
More ambitions – Courageous and energetic

Idorsia effectively started its operations after demerging from Actelion on June 15, 2017, and registered shares of Idorsia Ltd were listed on the SIX Swiss Exchange the next day. Today, Idorsia has an experienced team of highly qualified professionals, a full R&D pipeline, state-of-the-art facilities, and strong liquidity – the ideal constellation for bringing successful medicines to the market.

Idorsia's key numbers	**Full year 2018**	
in CHF million, except EPS (CHF) and number of shares (million)	**US GAAP**	**Non-GAAP**
Revenues	61	61
Operating expenses	(432)	(399)
Operating income (loss)	(371)	(339)
Net income (loss)	(386)	(340)
Basic EPS	(3.10)	(2.72)
Basic weighted average number of shares	124.8	124.8
Diluted EPS	(3.10)	(2.72)
Diluted weighted average number of shares	124.8	124.8

The full financial statements can be found in the Financial Report, which forms part of the Idorsia Annual Report.

Advancing with speed and agility



Dear Shareholders

In 2018, Idorsia saw advances on all fronts:

– We advanced our pipeline, bringing four products into Phase 3 development.
– We completed demerger activities, with all core systems now running independently of Actelion.
– We appointed a leader to build our commercial organization, thus taking another step forward towards financial sustainability.
– We strengthened our cash position so as to be able to run our Phase 3 clinical trials and then take strategic decisions on how best to commercialize our assets.

Late-stage assets leap forward

Our late-stage pipeline advanced significantly in 2018, with four compounds moving into Phase 3 clinical development. All our late-stage trials are now initiated, with data expected to be reported in 2020 and 2021.

Lucerastat is an oral therapy offering a new treatment approach for patients with Fabry disease. Recruitment for the MODIFY trial started in May and the study is expected to report results in the first half of 2020.

ACT-541468 is a dual orexin receptor antagonist for the treatment of insomnia. It has the potential to deliver fast onset of sleep and a duration of action not exceeding a normal night, while preserving natural sleep architecture. Recruitment for the Phase 3 program started in June and we are on track to report results in the first half of 2020.

Aprocitentan – an orally active dual endothelin receptor antagonist – is being investigated in the PRECISION trial for patients whose hypertension is uncontrolled despite the use of at least three antihypertensive drugs. Patients were enrolled at the first site in June, and we are close to having all sites recruiting as patient screening progresses.

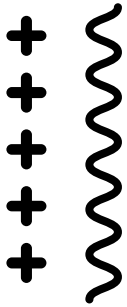
Clazosentan – a selective endothelin (ETA) receptor antagonist – is being developed for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. The global REACT study commenced enrollment at the beginning of February 2019.

Development of clazosentan is further advanced in Japan, where a Phase 3 program was initiated by Actelion in 2016; recruitment continues, and the studies are expected to be completed in the first half of 2020. To pave the way for bringing clazosentan to market, we have established Idorsia Japan. This has the additional advantage of allowing us to tailor our other development programs to include Japan at a very early stage.

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

Jean-Paul Clozel
Chief Executive Officer

Jean-Pierre Garnier
Chairman of the Board



Building the pipeline of the future

We are also making great progress with our early-stage compounds by accumulating information on clinical pharmacology in healthy volunteers or conducting Phase 2 profiling in patients.

Two Phase 2 studies with selatogrel, Idorsia's P2Y12 receptor antagonist, met their pharmacodynamic objectives of significantly inhibiting platelet aggregation and showed the desired profile for future development. We are preparing for the end of Phase 2 meetings with Health Authorities where we will discuss the Phase 3 study.

Another example is cenerimod, our selective $S1P_1$ receptor modulator, which is being investigated for the treatment of adults with systemic lupus erythematosus in a multiple-dose, efficacy and safety study. This is the first time $S1P_1$ receptor modulation has been studied in a large clinical trial for patients with lupus, potentially transforming the treatment landscape for this underserved patient population.

And there's much more to come, as Drug Discovery continues to generate the pipeline of the future.

Operational independence

On the first day after the demerger, Idorsia was operationally fully functional, meaning that our business, research and clinical development could continue without any interruption. However, though Idorsia was launched with a broad pipeline, an established team, and with the necessary laboratories and workspaces, we were still reliant on certain services and systems provided by Actelion.

Over the course of 2018, we cut the umbilical cord and we are now fully independent: all of our core systems – from e-mail and data servers to support environments for research and clinical development – have been decoupled from the old infrastructure, and new, highly scalable state-of-the-art solutions have been implemented in all areas of the business. This, of course, was only possible thanks to the tireless efforts of all our employees.

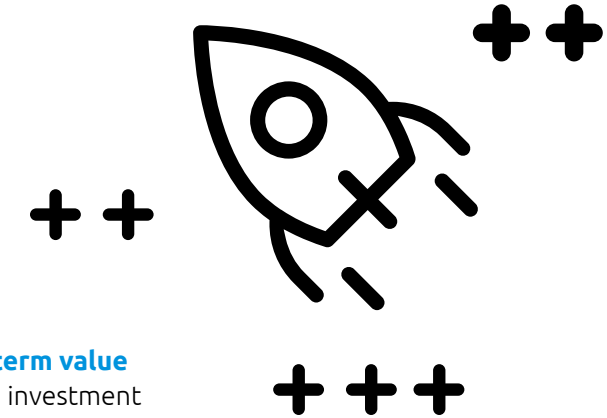
Completing the value chain

In December 2018, Simon Jose joined the Idorsia Executive Committee as Chief Commercial Officer. He is now creating Idorsia's commercial infrastructure and executing on our strategic priority of being able to take our own research and innovation from the lab to patients. The establishment of a fully functional subsidiary in Japan constitutes a major first step in setting up a global commercial infrastructure.

Building a company with its own commercial infrastructure means that we are in control of the planning, development and implementation of commercial strategies for our assets. This in turn will give us financial independence and sustainability, thus maximizing the potential benefits for Idorsia.

"The team at Idorsia has made outstanding progress in 2018. The efforts required to become operationally independent in our highly regulated industry should not be underestimated. To do that in parallel to initiating four Phase 3 studies and progressing the early stage pipeline is an outstanding achievement."

Jean-Pierre Garnier
Chairman of the Board



Financing pipeline development

Rather than focusing all our efforts on a single drug, we have advanced all our late-stage assets into Phase 3 simultaneously. We believe that this approach gives us the best chance of achieving success, building the business, and funding future innovations. However, the level of financing required for a diversified drug pipeline can pose certain challenges for a young company. The CHF 505 million raised in July 2018 should give us the necessary leeway to assess the clinical data for our late-stage pipeline and then make the appropriate strategic decisions regarding commercialization.

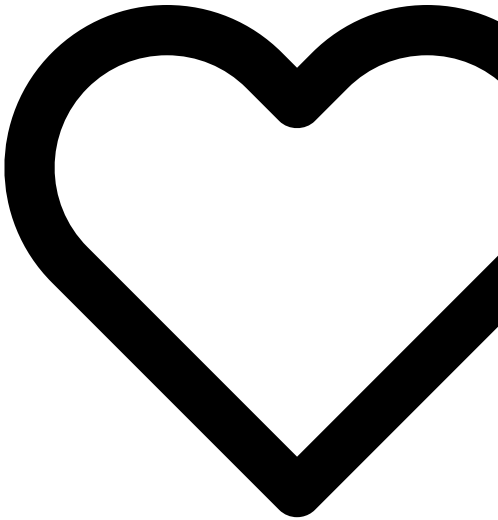
Committed to creating long-term value

Building a company requires an investment of time, effort and money, as well as the confidence of shareholders. We will continue to make these investments to ensure that our innovative medicines can fulfill their potential for the benefit of patients around the world.

Sincerely,

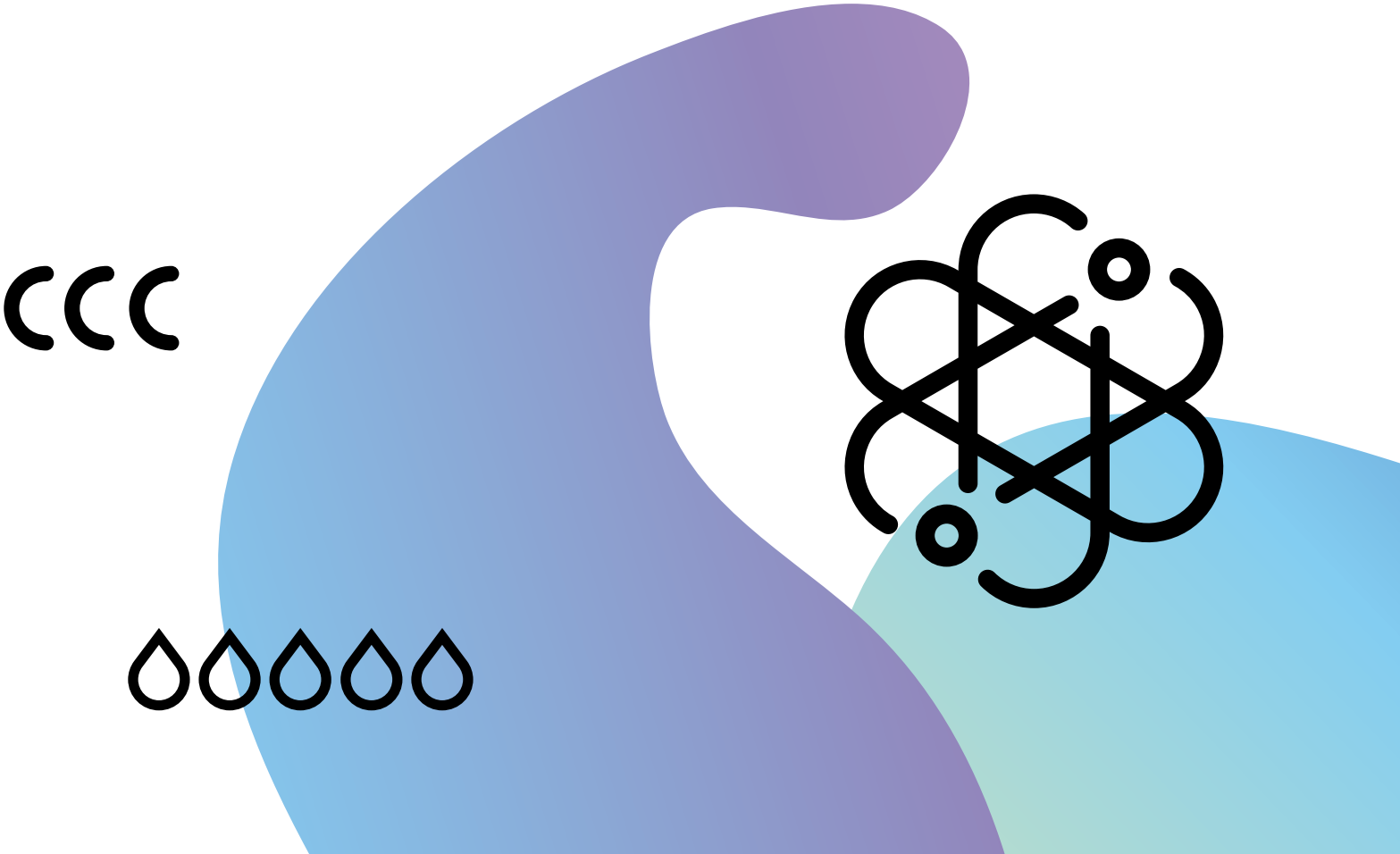
Jean-Paul Clozel
Chief Executive Officer

Jean-Pierre Garnier
Chairman of the Board



Our strategic priorities

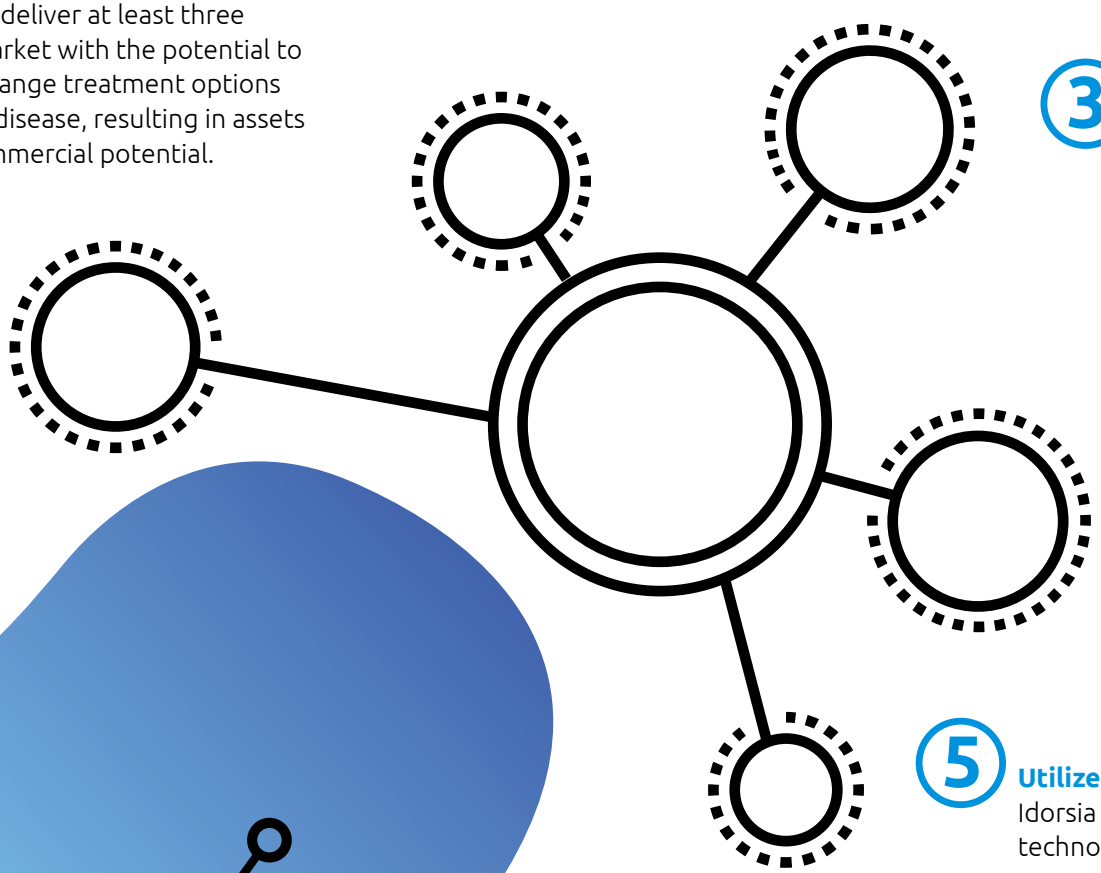
We will develop Idorsia into one of Europe's leading biopharmaceutical companies, with a strong scientific core. We have identified five key strategic priorities to ensure the company's success over the first 5 years.



More energy – Growing and delivering

1 Deliver promising compounds
Idorsia aims to deliver at least three products to market with the potential to significantly change treatment options in their target disease, resulting in assets with major commercial potential.

2 Be there from bench to bedside
Idorsia aims to build a commercial organization to maximize the value of our innovations.



3 Become a sustainable company
Idorsia's highly qualified professionals aim to rapidly advance the development pipeline and commercial readiness, so as to bring Idorsia to profitability within 5 years.

4 Build a bright future
Idorsia aims to create a clinical development pipeline comprising assets with a sales potential of at least CHF 5 billion.

5 Utilize state-of-the-art technologies
Idorsia aims to increasingly utilize state-of-the-art technologies to aid discovery, development and commercialization of our innovative therapies.

Building a state-of-the-art IT environment

Our IT strategies are built on three fundamental concepts – more power, more capability, and more security.

The spin-out of Idorsia offered a unique and exciting opportunity to entirely reshape our IT environment, not just for today, but with an eye towards the future. In our efforts to create a new IT ecosystem, innovation, scalability and speed had to be balanced with simplicity and usability. We needed not only to increase computing power but also to drastically reduce the application portfolio, while addressing the whole range of business processes – from R&D to corporate and business functions. By partnering with select, industry-leading technology companies, we aim to lower costs for the company and reduce complexity for users while at the same time accelerating the adoption of innovative technology. In addition, employees must be able to access critical information from anywhere so that they can collaborate and perform their work efficiently. Underpinning all these objectives is the laser-sharp focus on security and compliance which is required to ensure Idorsia's reputation for excellence in this highly regulated industry.

Lastly, this new, state-of-the-art IT environment needed to be fully operational and independent by the end of 2018.

"In order to maximize our potential to bring breakthrough medicines to patients, we must integrate computational tools and digital technologies at different stages of the drug discovery, development and commercialization process."

Joseph Bejjani
Chief Information Officer

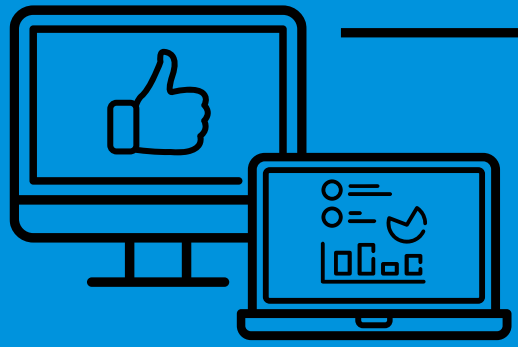
More accomplished – Bold transformations

After 12 months of hard work, the Global Informatics Services (GIS) team can proudly say that the IT challenge has been met. As of the beginning of July – 6 months ahead of schedule – Idorsia was operating with state-of-art, standalone IT systems.

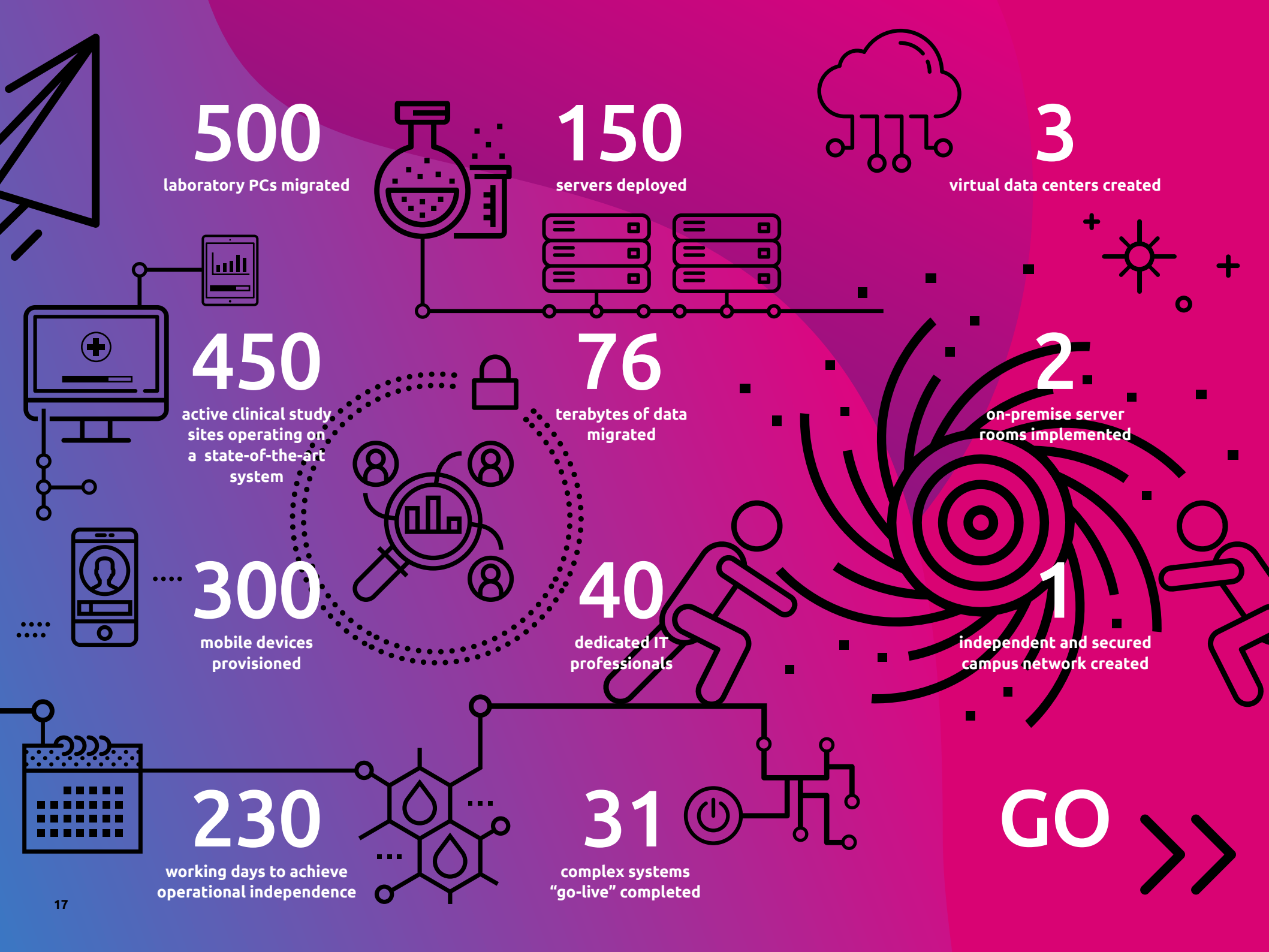
35,000
trial master files migrated

23,000
documents imported

1,300
user accounts setup

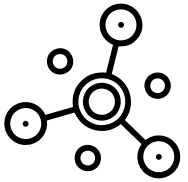


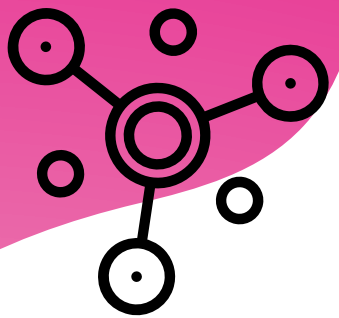
800
laptops/desktops replaced


500
laboratory PCs migrated
150
servers deployed
3
virtual data centers created
450
active clinical study sites operating on a state-of-the-art system
76
terabytes of data migrated
2
on-premise server rooms implemented
300
mobile devices provisioned
40
dedicated IT professionals
1
independent and secured campus network created
230
working days to achieve operational independence
31
complex systems "go-live" completed
GO

Our Research & Development

More knowledge – Powered by science





"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
Principle Scientist, Cardiovascular & Fibrosis Biology

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

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

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

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

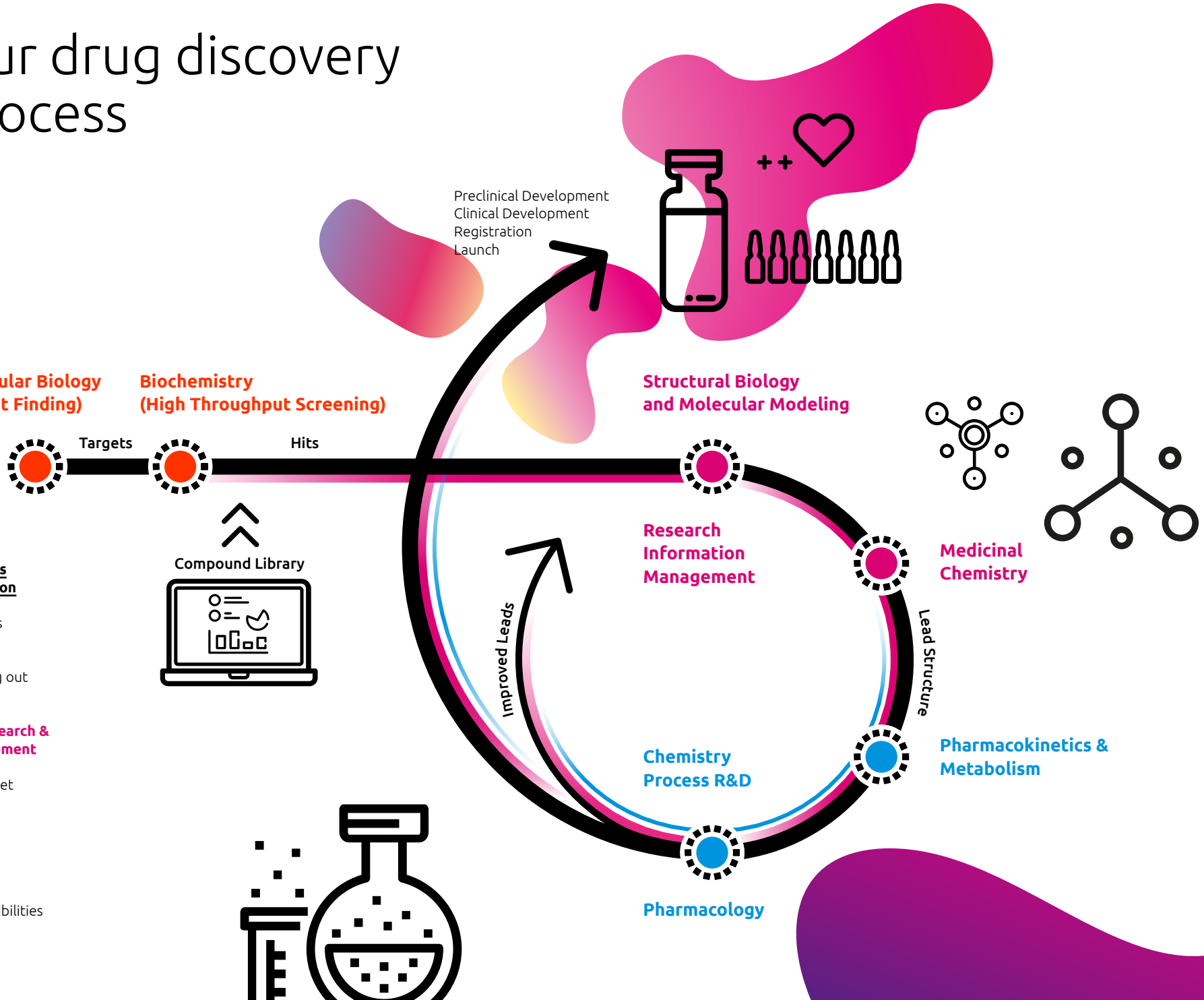
We produce, or "express", the target in large quantities and measure its natural activity in assays. The assay needs to be sensitive, accurate and highly reliable. Plus, in order to perform hundreds of thousands of measurements, it needs to be automated, using robotic equipment.

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

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

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

Our drug discovery process



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

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

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

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

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

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

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

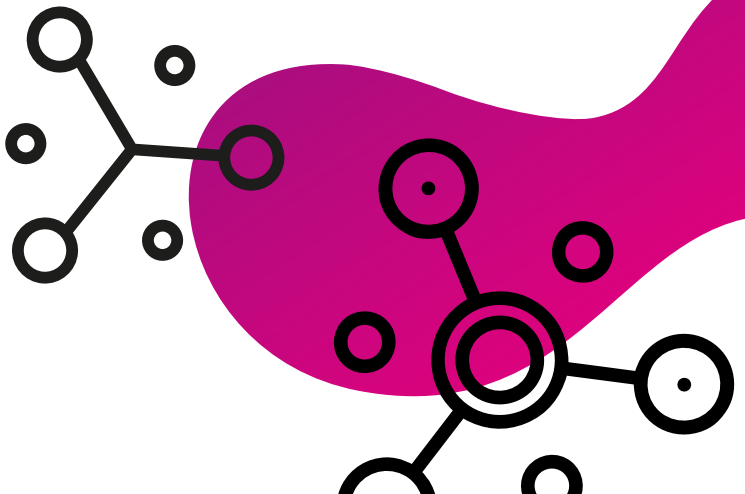
It's no good having a potent compound which gets destroyed by the body before it has a chance to do its job. Our formulation specialists take a compound which has been optimized by the chemists and ask how it can best be delivered to the patient. One way to protect the compound, for example, is to package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

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

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

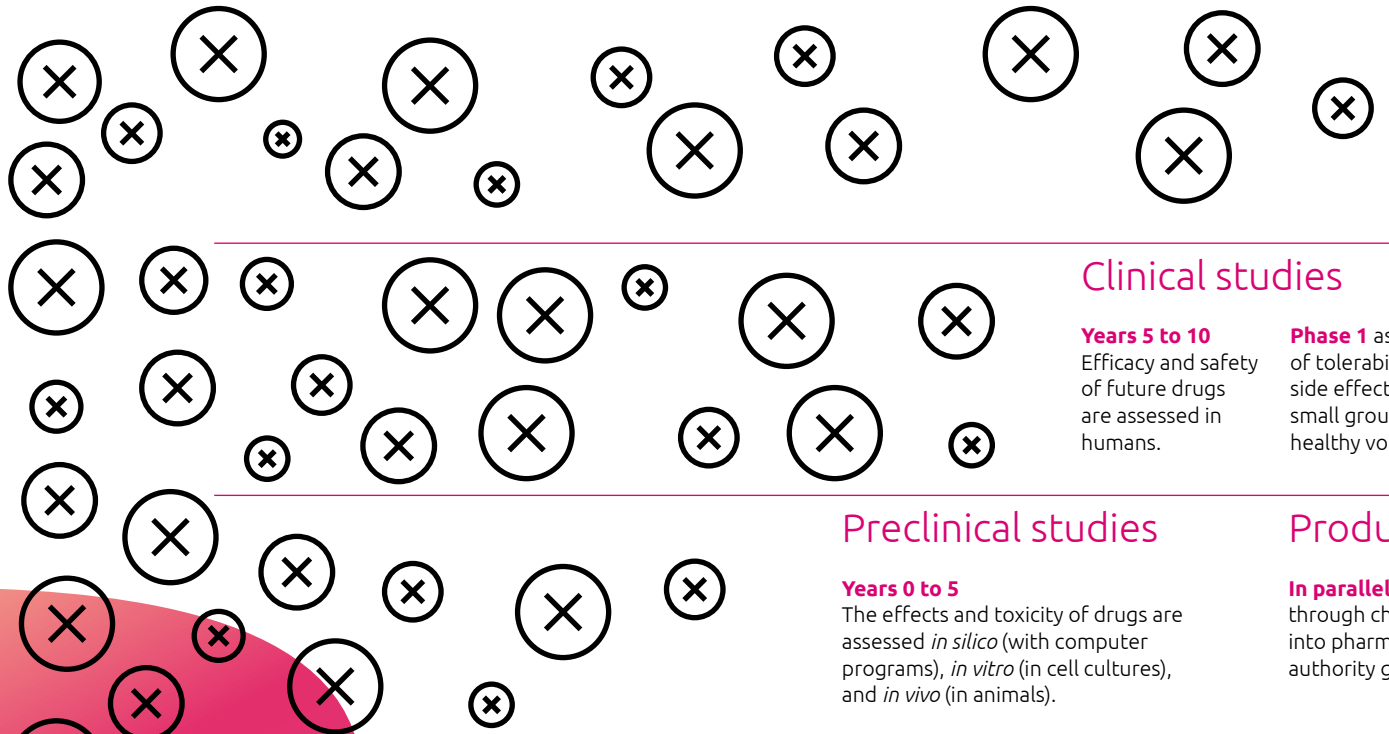
"For me, invention is making something out of a daring idea. And I really have the feeling that's what we are trying to do at Idorsia."

Corinna Grisostomi
Senior Scientist, Medicinal Chemistry



More molecules – For a better future

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



Regulatory submission

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

Clinical studies

Years 5 to 10
Efficacy and safety of future drugs are assessed in humans.

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

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

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

Preclinical studies

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

Product development

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

Patenting the molecule

Year 0
Patents are filed for the most promising compounds. This protection provides 20 years of exclusive commercial use – the clock starts!

Drug discovery phase

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

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

More in the pipeline – Promising compounds

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

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

Martine Clozel
Executive Vice President, Chief Scientific Officer

Clinical development pipeline

Resistant hypertension management

Aprocitentan
Dual endothelin receptor antagonist
Status: Phase 3
In collaboration with Janssen Biotech, Inc.

Fabry disease

Lucerastat
Glucosylceramide synthase inhibitor
Status: Phase 3

Insomnia

ACT-541468
Dual orexin receptor antagonist
Status: Phase 3

Vasospasm associated with aneurysmal subarachnoid hemorrhage

Clazosentan
Selective endothelin (ETA) receptor antagonist
Status: Phase 3

Acute coronary syndrome

Selatogrel
P2Y12 receptor antagonist
Status: Phase 2

Systemic lupus erythematosus

Cenerimod
$S1P_1$ receptor modulator
Status: Phase 2

Nasal polyposis

ACT-774312
CRTH2 receptor antagonist
Status: Phase 2

Orphan CNS diseases

ACT-519276
GBA2/GCS inhibitor
Status: Phase 1

Anxiety

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

Epilepsy

ACT-709478
T-type calcium channel blocker
Status: Phase 1

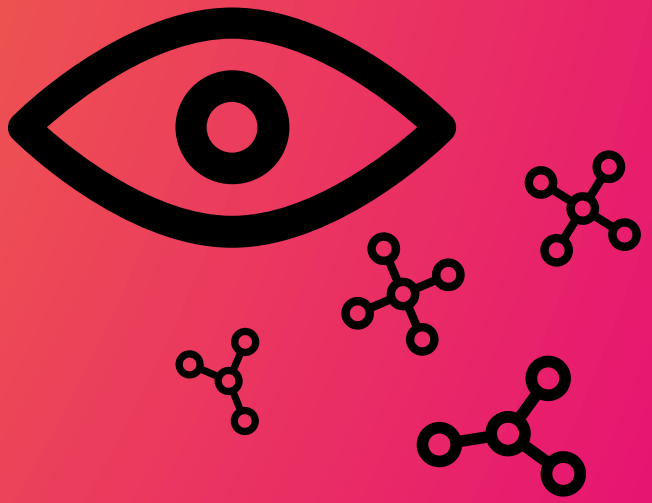
Our Target Diseases

Idorsia aims to deliver new products with the potential to significantly change the treatment options in their target diseases.

We want to bring new perspectives to the development of innovative compounds, challenging accepted paradigms to answer the questions that matter most. Our key assets have the potential to transform treatment in the target indications.

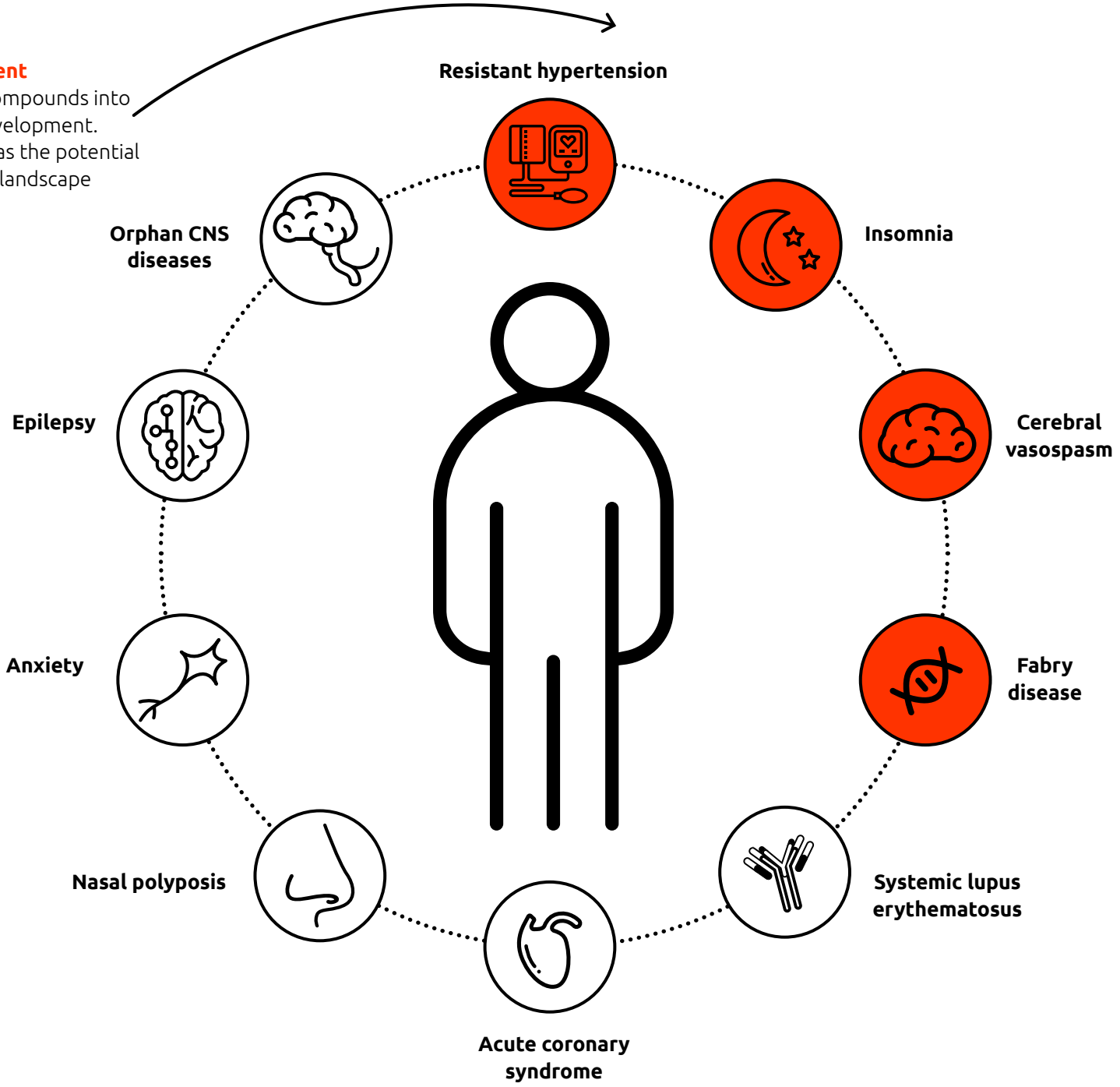
"We tailor the target indication to characteristics of the compound. We always try to find the disease, spectrum of diseases or subset of medical conditions where the molecule will fit best from an efficacy and safety perspective, and where it addresses a medically important need."

Guy Braunstein
Executive Vice President,
Head of Global Clinical Development



Phase 3 clinical development

Idorsia has advanced four compounds into the final stage of clinical development. Each of these compounds has the potential to transform the treatment landscape for patients.



Resistant hypertension

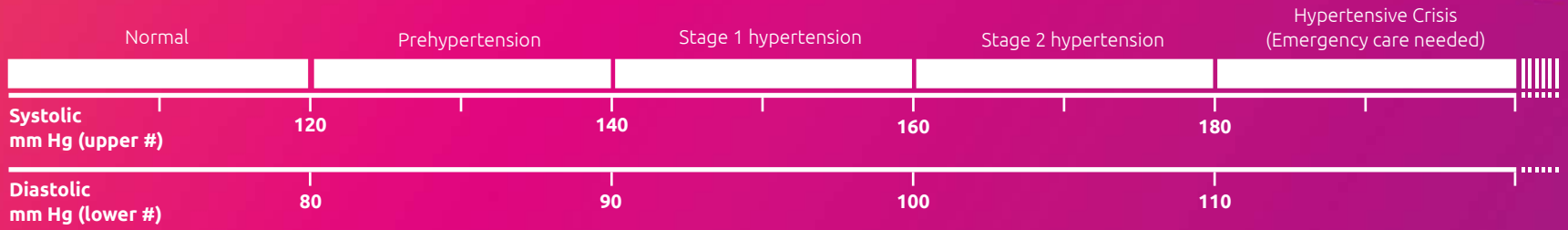
Hypertension (high blood pressure) is one of the most common medical conditions, and its prevalence continues to rise. According to a recent study, there are about 1.13 billion people living with the condition worldwide, a startling number which has almost doubled in the past 40 years. Left untreated, hypertension can lead to life-threatening conditions such as heart failure, stroke, or kidney disease.

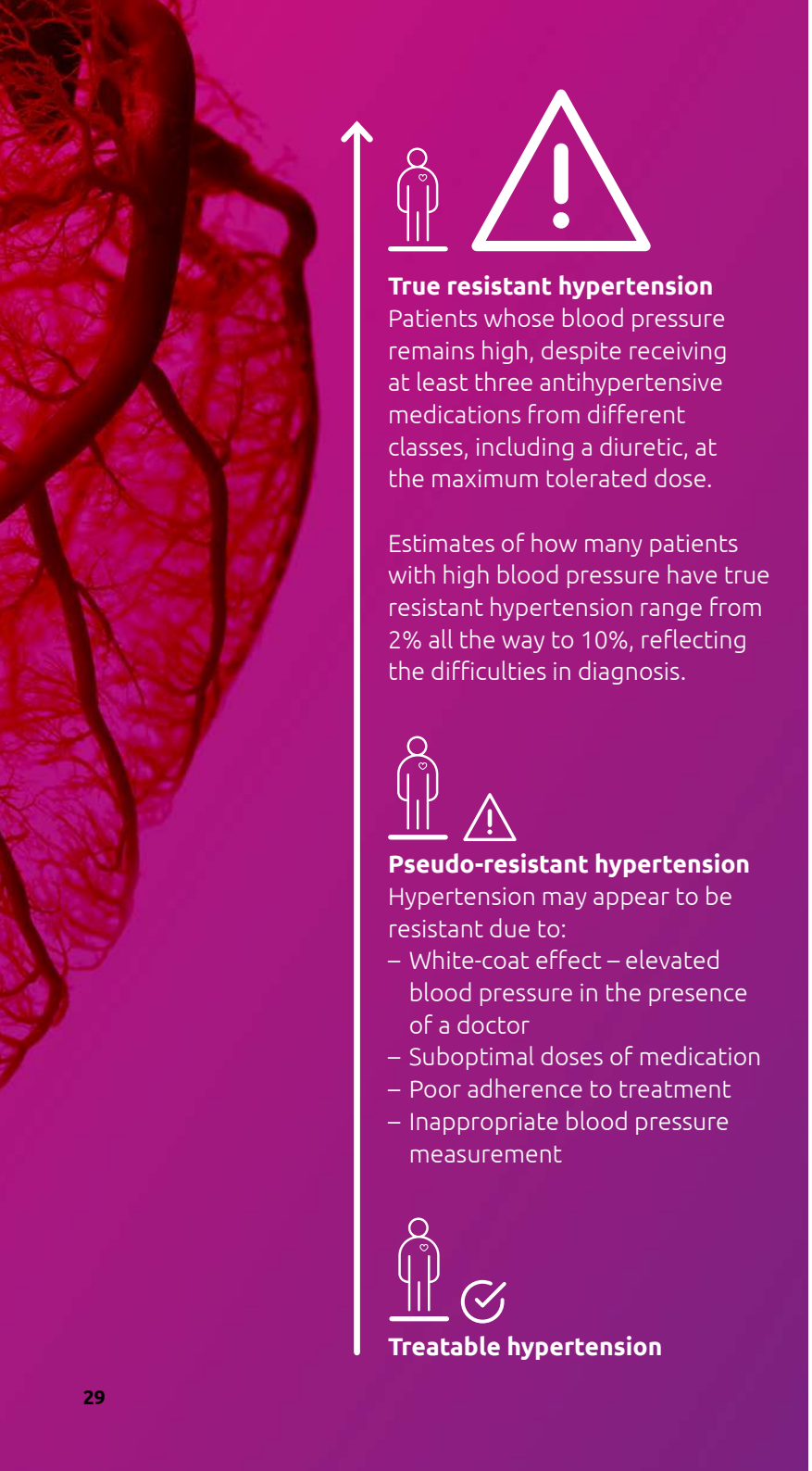
Stages of hypertension

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 be successfully treated by combining a healthier lifestyle with effective medication. However, when high blood pressure is insufficiently controlled by at least three antihypertensive medications from different classes, including a diuretic, it is described as treatment "resistant", and it is this form of hypertension that scientists at Idorsia are trying to find a new way to treat.

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





True resistant hypertension
Patients whose blood pressure remains high, despite receiving at least three antihypertensive medications from different classes, including a diuretic, at the maximum tolerated dose.

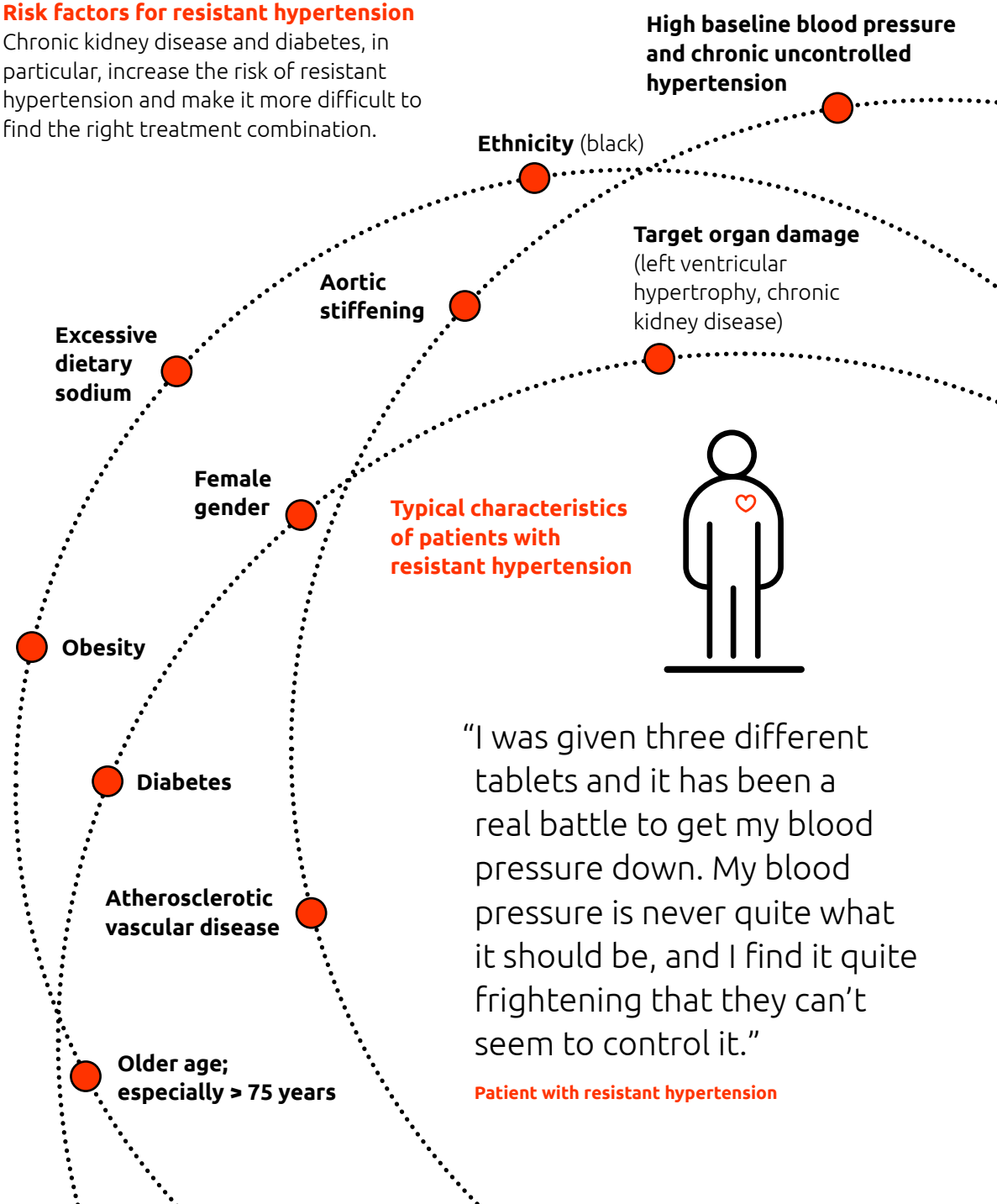
Estimates of how many patients with high blood pressure have true resistant hypertension range from 2% all the way to 10%, reflecting the difficulties in diagnosis.

Pseudo-resistant hypertension
Hypertension may appear to be resistant due to:
- White-coat effect – elevated blood pressure in the presence of a doctor
- Suboptimal doses of medication
- Poor adherence to treatment
- Inappropriate blood pressure measurement

Treatable hypertension

Risk factors for resistant hypertension

Chronic kidney disease and diabetes, in particular, increase the risk of resistant hypertension and make it more difficult to find the right treatment combination.

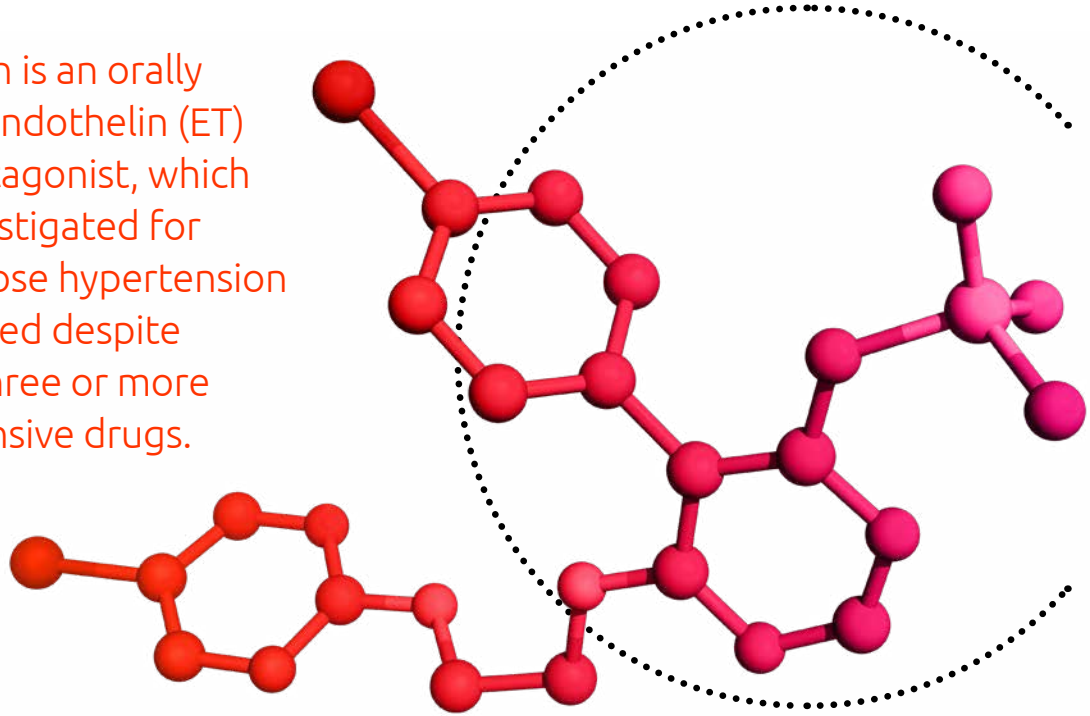


"I was given three different tablets and it has been a real battle to get my blood pressure down. My blood pressure is never quite what it should be, and I find it quite frightening that they can't seem to control it."

Patient with resistant hypertension

Aprocitentan for resistant hypertension

Aprocitentan is an orally active dual endothelin (ET) receptor antagonist, which is being investigated for patients whose hypertension is uncontrolled despite the use of three or more antihypertensive drugs.



Orally active, potent dual endothelin (ETA and ETB) receptor antagonist

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

Demonstrated antihypertensive efficacy, renal and cardiac protection in animal models of salt-dependent hypertension

Demonstrated blood pressure decrease in patients with essential hypertension

Low potential for drug-drug interactions

Developed in partnership with Janssen Biotech, Inc.

"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 NSW Sydney

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

Frédéric Naud
Director, Life Cycle Leader for aprocitentan

Endothelin receptor antagonism

Clinical and preclinical evidence suggests that resistant hypertension may be endothelin-dependent. Indeed, the endothelin system plays an important role in volume- and salt-dependent forms of hypertension, commonly seen in patients with resistant hypertension. Endothelin-1 is a potent vasoconstrictor, which acts through two types of receptors – ETA and ETB. It also induces neurohormonal activation, vascular hypertrophy and remodeling, cardiac hypertrophy and fibrosis, and endothelial dysfunction.

Phase 3 clinical study

PRECISION is a Phase 3 study to demonstrate the antihypertensive effect of aprocitentan when added to standard of care in patients with resistant hypertension. Idorsia, in consultation with regulatory agencies, has designed a single, placebo-controlled Phase 3 study, enrolling 600 patients, which will efficiently address both the short-term efficacy of aprocitentan and the durability of its effects in long-term treatment.

Resistant hypertension management

Compound: Aprocitentan

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

Insomnia

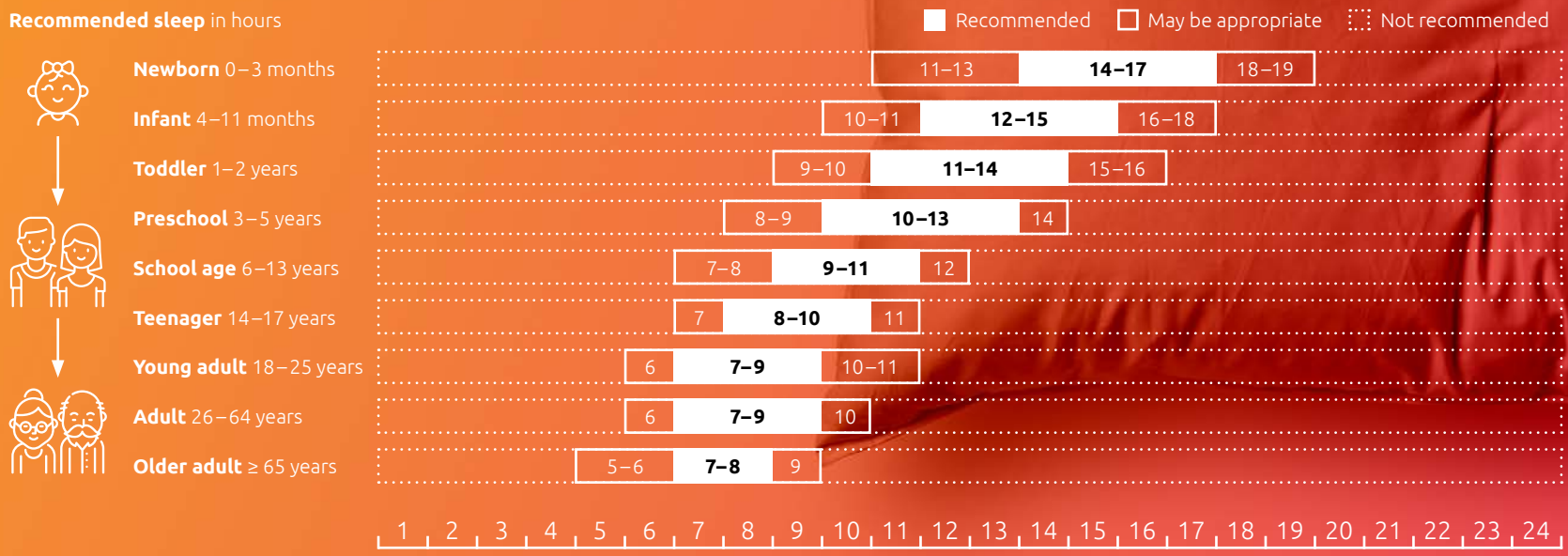
Insomnia – the most commonly reported sleep disorder worldwide – is defined as a combination of dissatisfaction with sleep and a significant negative impact on daytime functioning. Dissatisfaction with sleep refers to difficulty in initiating and/or maintaining sleep on at least three nights per week for at least three months, despite adequate opportunity to sleep.

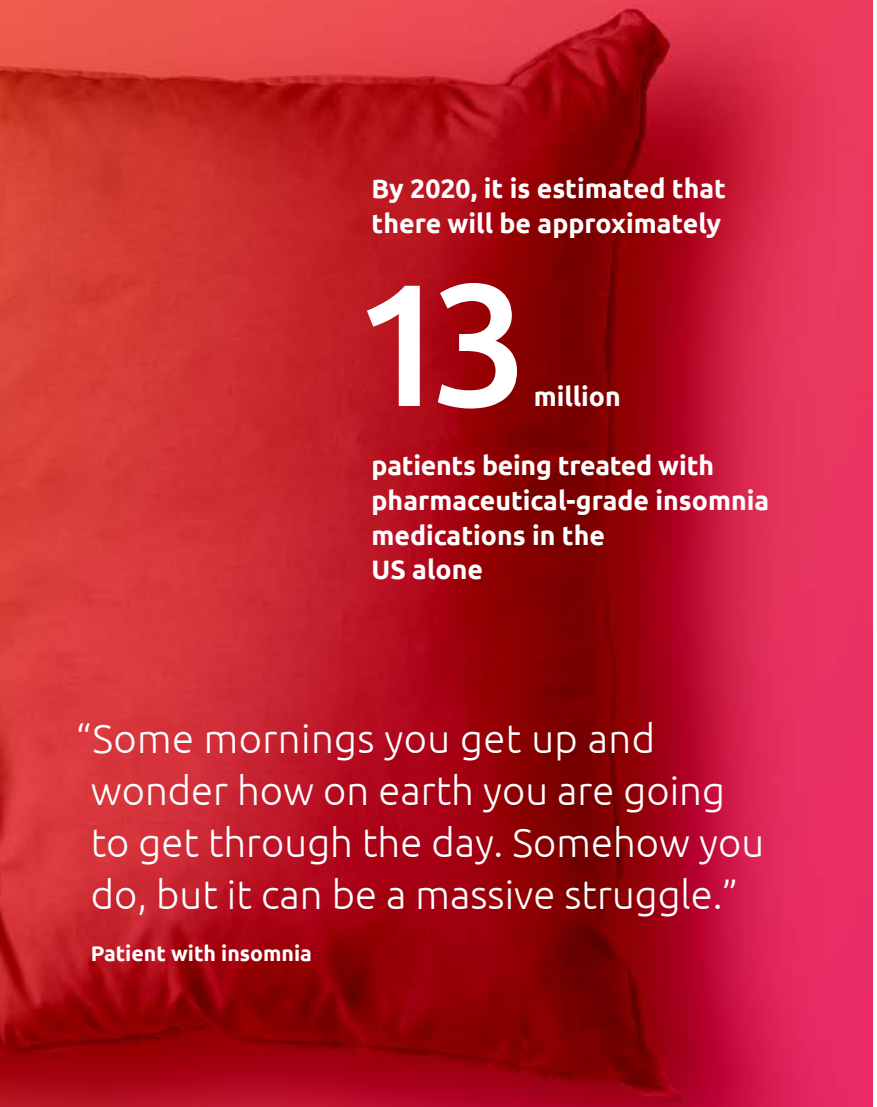
Insomnia is now recognized as a condition that requires clinical attention, regardless of any other medical problems the patient might have. Insomnia is often underdiagnosed and undertreated. It is estimated that around 70% of people with persistent insomnia never seek medical help.

Insomnia is quite different from a brief period of poor sleep and can take its toll on both the physical and mental health. It is a persistent condition with a negative impact on daytime functioning. Poor-quality sleep can affect many aspects of daily life, including the ability to concentrate or work effectively, and driving skills.

How much sleep do you need

There are no set guidelines. Everyone is different, and some people seem to be able to function very well on minimal amounts of sleep. Overall, the quality of sleep is at least as important as the quantity.





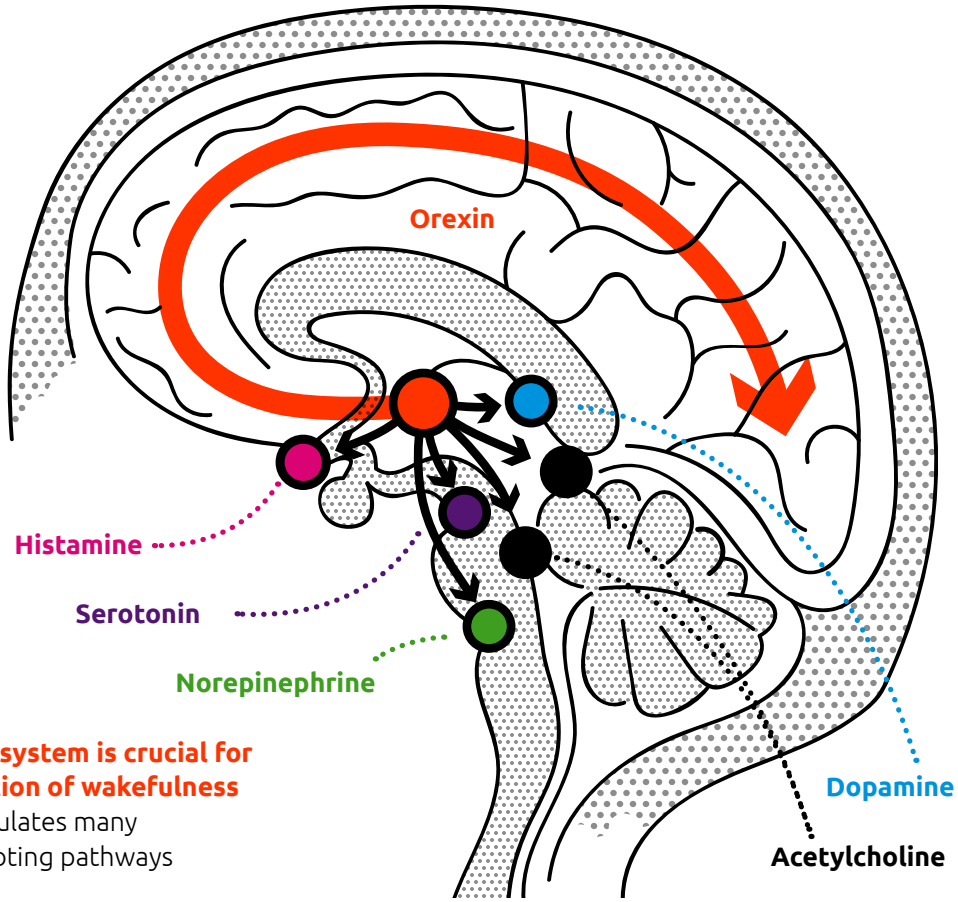
By 2020, it is estimated that there will be approximately

13 million

patients being treated with pharmaceutical-grade insomnia medications in the US alone

"Some mornings you get up and wonder how on earth you are going to get through the day. Somehow you do, but it can be a massive struggle."

Patient with insomnia



The orexin system is crucial for the regulation of wakefulness

Orexin stimulates many wake-promoting pathways

About orexin

Orexins are neuropeptides – small protein-like molecules used by nerve cells (or neurons) to communicate with each other in the brain. Orexins act functionally at the interface of alertness, energy homeostasis and reward/aversion systems, essentially to regulate vigilance and arousal states. Defects of the orexin peptides, or their receptors, are associated with disorders of wakefulness and sleep.

The anatomical distribution of orexin receptors in the brain supports the essential role played by orexin in promoting alertness and maintaining wakefulness under situations of high motivational relevance – e.g. circadian vigilance states, reward opportunities, or exposure to threats.

ACT-541468 for the treatment of insomnia

ACT-541468 is a dual orexin receptor antagonist (DORA) for the treatment of insomnia. It has potential to deliver fast onset of sleep and a duration of action not exceeding a normal night, while preserving natural sleep architecture.

"As shown in the Phase 2 program, ACT-541468 has the potential to offer the combination of fast onset of sleep and sustained efficacy throughout the night, without next-morning residual effects. Our confirmatory Phase 3 program also includes measures to better understand the patient perspective of what matters most to them, during the night and, importantly, during the day."

Beate Sehorz
Director, New Product Strategy

Dual orexin receptor antagonism specifically targets excessive alertness, in contrast to insomnia treatments that act via general CNS sedation

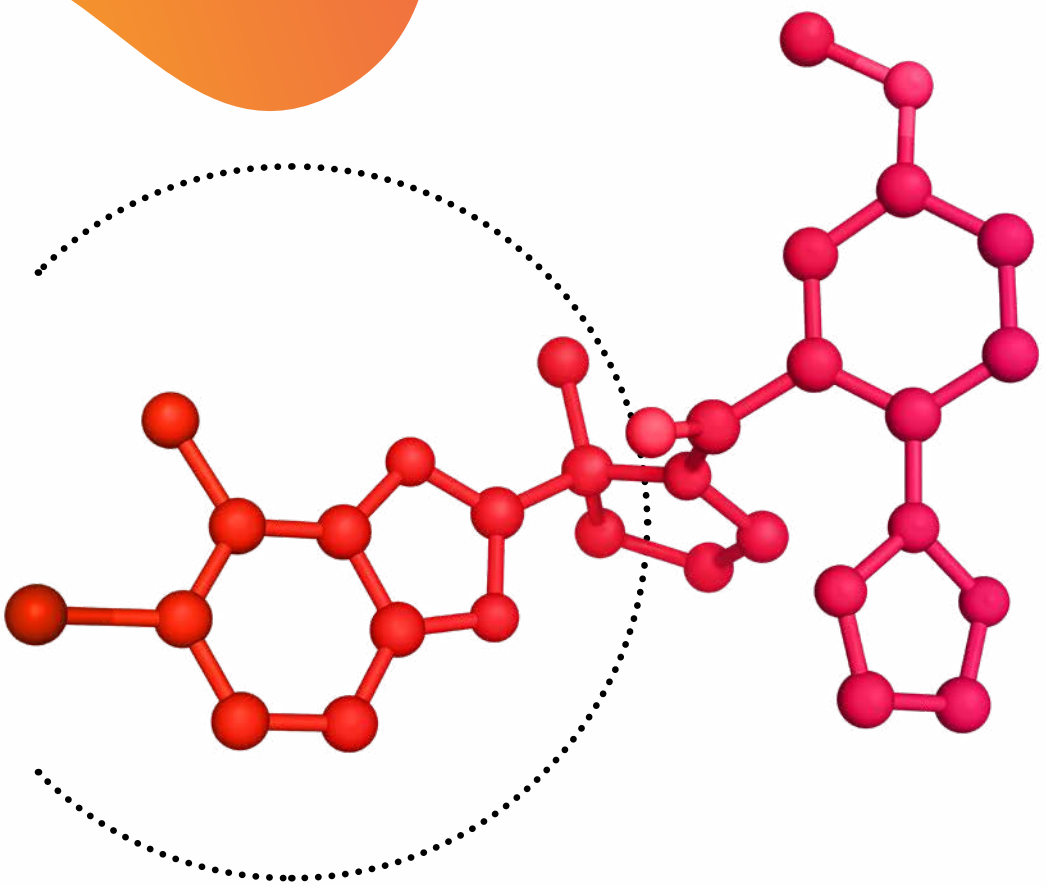
Brain penetrating

Potent dual orexin (OX1 and OX2) receptor antagonist

High *in vitro* potency; *in vivo* efficacy

Quick absorption and appropriate half-life

No next morning residual effect observed



Learning from previous studies

Based on preclinical data, dual orexin receptor antagonism maintains natural sleep architecture. Data from a comprehensive Phase 1 and Phase 2 program indicates that ACT-541468 has a suitable pharmacokinetic and pharmacodynamic profile to deliver fast onset of sleep, a duration of action which is well suited for appropriate sleep maintenance, and low potential for next-day residual effects. These properties are being explored clinically and, if confirmed, will give ACT-541468 the potential to be differentiated from current sleep medications.

Phase 3 clinical program

The registration program comprises two confirmatory studies together with a long-term extension study, which will recruit a total of 1,800 patients with insomnia at over 160 sites across 18 countries. Enrollment commenced in June 2018 and the study is expected to run for around 2 years. As insomnia often presents later in life, around 40% of the recruited population will be aged 65 years or older. The program will investigate three doses (10 mg, 25 mg, and 50 mg), which were all effective and well tolerated in both adult and elderly patients studied in Phase 2. Patients will be treated for three months in the two trials, with the opportunity to continue treatment in a 40-week extension study.

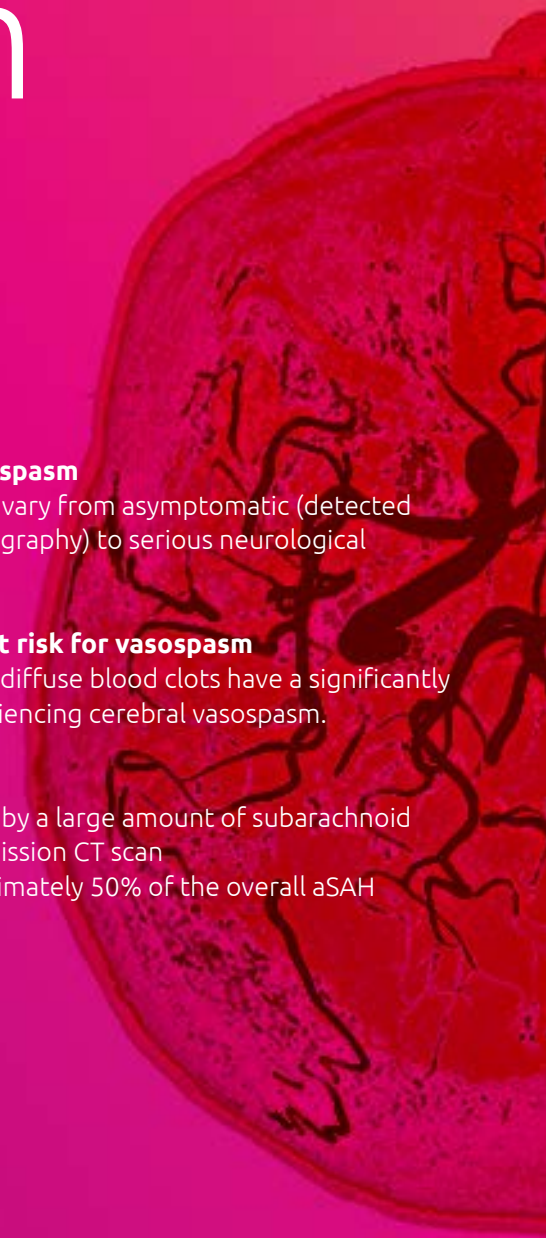
The Phase 3 program aims to confirm the positive results observed in the comprehensive Phase 2 clinical program and was developed in consultation with health authorities. In addition, a comprehensive clinical pharmacology program is to be conducted in parallel.

Insomnia

Compound: ACT-541468

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

Cerebral vasospasm



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

The bleeding and the release of a vasoconstrictor (endothelin) by the neighboring vascular endothelium, contributes to many patients experiencing cerebral vasospasm (constriction of arteries in the brain) between 4 and 14 days after aSAH securing. This diminishes blood flow to the brain, and about one third of patients consequently experience worsening of their neurological condition.

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.

Symptoms of vasospasm
The manifestations vary from asymptomatic (detected by systematic angiography) to serious neurological symptoms.

Patients at highest risk for vasospasm
Patients with thick, diffuse blood clots have a significantly higher risk of experiencing cerebral vasospasm.

These patients:
– are characterized by a large amount of subarachnoid blood on the admission CT scan
– represent approximately 50% of the overall aSAH population.

"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

Worldwide, almost

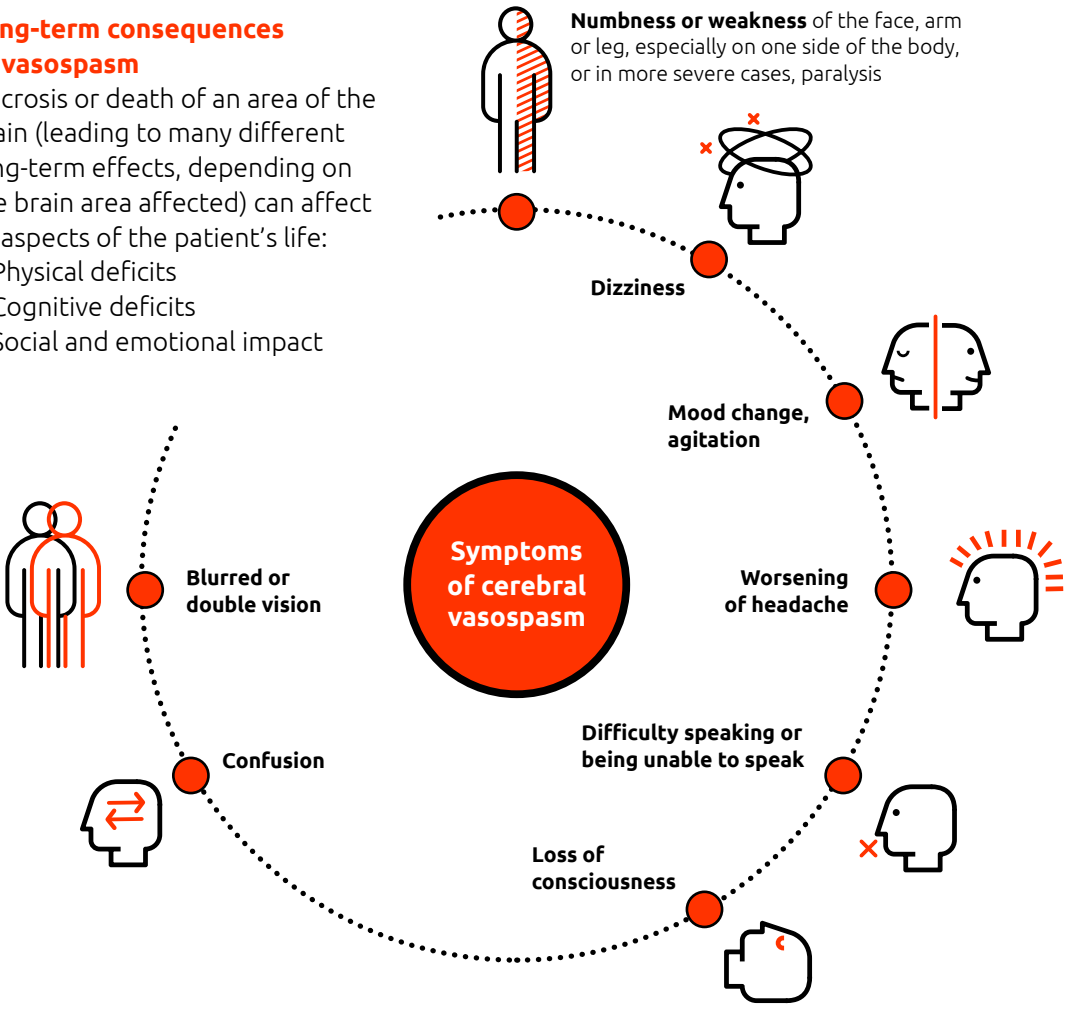
500,000

individuals will suffer from aSAH each year

Long-term consequences of vasospasm

Necrosis or death of an area of the brain (leading to many different long-term effects, depending on the brain area affected) can affect all aspects of the patient's life:

– Physical deficits
– Cognitive deficits
– Social and emotional impact



Role of endothelin in cerebral vasospasm

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

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

Clazosentan for cerebral vasospasm associated with aSAH

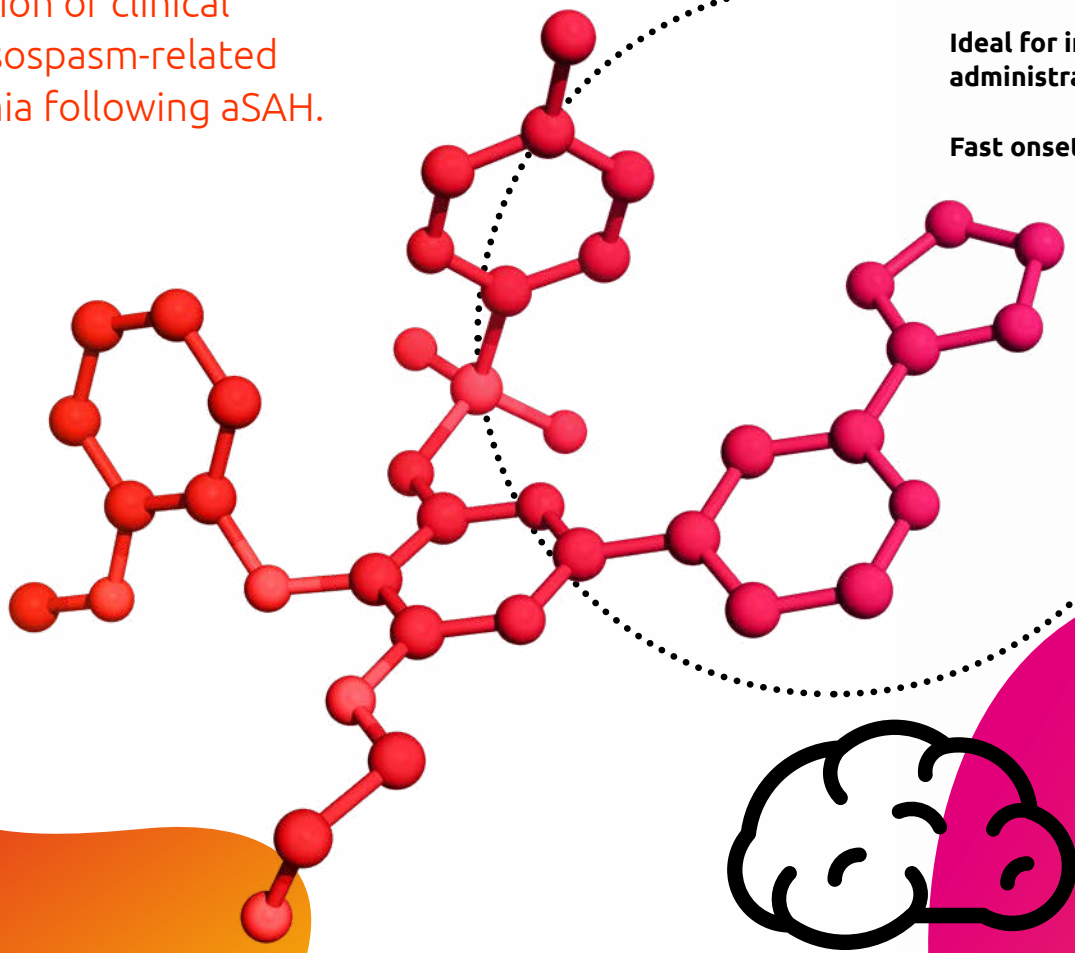
Clazosentan is an endothelin receptor antagonist being developed as an intravenous infusion for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia following aSAH.

Highly soluble

Selective endothelin (ETA) receptor antagonist

Ideal for intravenous administration

Fast onset of action



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

Angelina Marr
Director, Senior Clinical Project Scientist for clazosentan

Learning from previous clazosentan studies

Several studies have built our understanding of the role of clazosentan in preventing or reversing cerebral vasospasm. These studies suggest that clazosentan has the potential to prevent vasospasm-related delayed cerebral ischemia and to reduce the need for invasive neurovascular intervention. In addition, while clazosentan acts on some large brain arteries, the real benefit lies in the effect on smaller arteries not accessible to endovascular therapy. More than 1,800 patients treated with clazosentan provide significant experience in post-aSAH vasospasm and a well-documented safety profile.

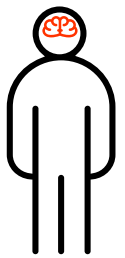
Phase 3 program

REACT is a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study in adult patients with aSAH. Approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – are expected to be enrolled at 100 sites across 15 countries. Patients will be randomized to receive either clazosentan (15 mg/hr) or placebo for a treatment period of up to 14 days. The study commenced enrollment at the beginning of February 2019 and will run for over two years.

REACT will enroll aSAH patients identified as being at high risk of developing delayed ischemic neurological deficit because of high-volume hemorrhage, as assessed by CT scan on hospital admission. Patients experiencing asymptomatic moderate to severe cerebral vasospasm within 14 days of aSAH may also be included.

Cerebral vasospasm

Compound: Clazosentan



Mechanism of action:
Selective endothelin (ETA) receptor antagonism
Status: Phase 3

Fabry disease

Fabry disease is a rare, life-threatening, genetic disorder involving a deficiency or dysfunction of alpha-galactosidase A (alpha-Gal A), an enzyme that normally breaks down a fatty substance known as globotriaosylceramide (Gb3) in the cells of the body. Over time, this may result in a buildup of Gb3 deposits throughout the body, particularly in the kidneys, heart and nervous system.

The symptoms range from neuropathic pain (primarily in the hands and feet) and stomach, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy and stroke. Since the symptoms are non-specific, Fabry disease is often undetected or misdiagnosed. As the disease is progressive, early diagnosis is essential to manage the symptoms as soon as possible and reduce the risk of developing serious complications.

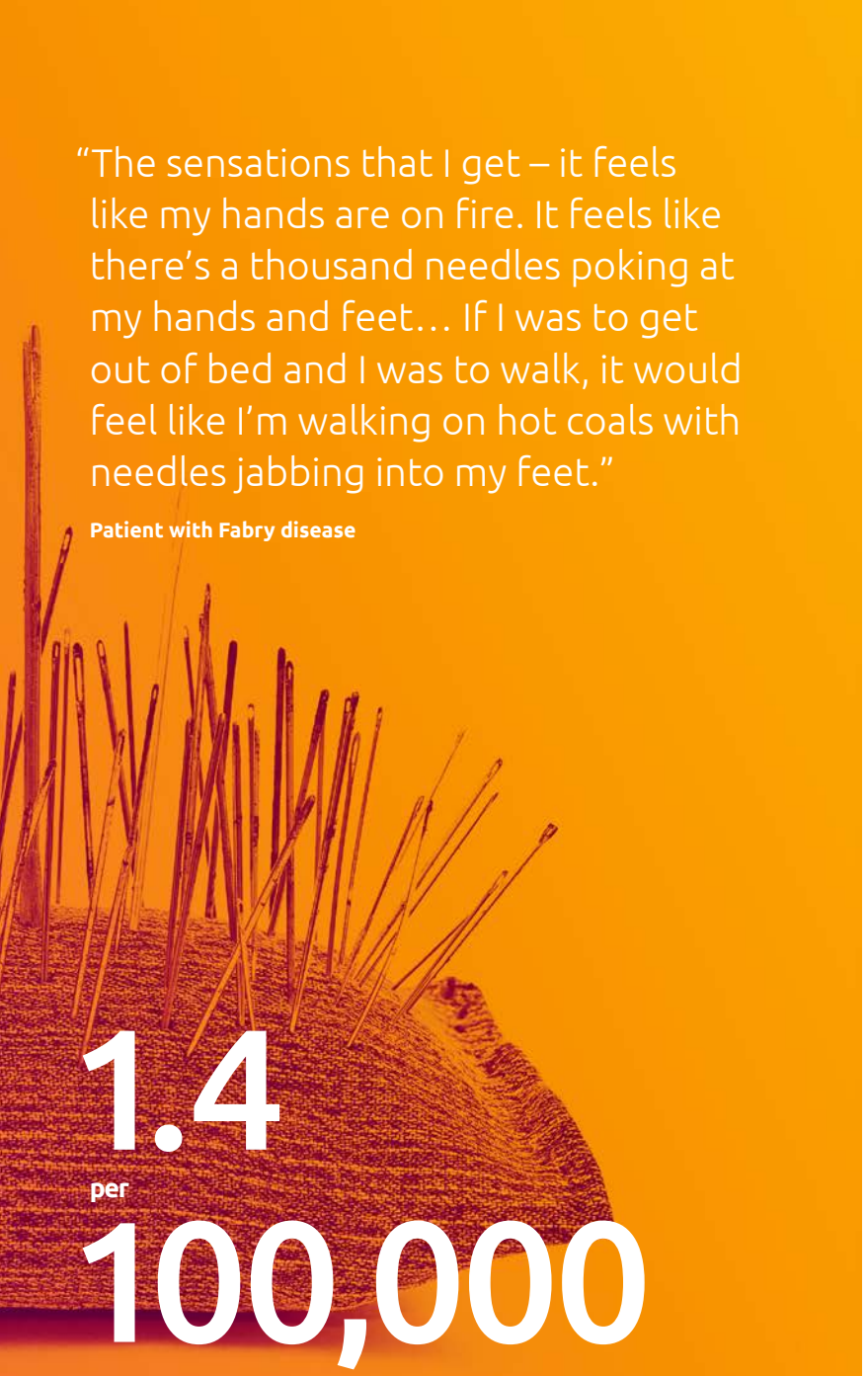
New therapeutic options are needed to treat the underlying mechanism of the disease and provide symptomatic relief.

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

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

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

Patient with Fabry disease

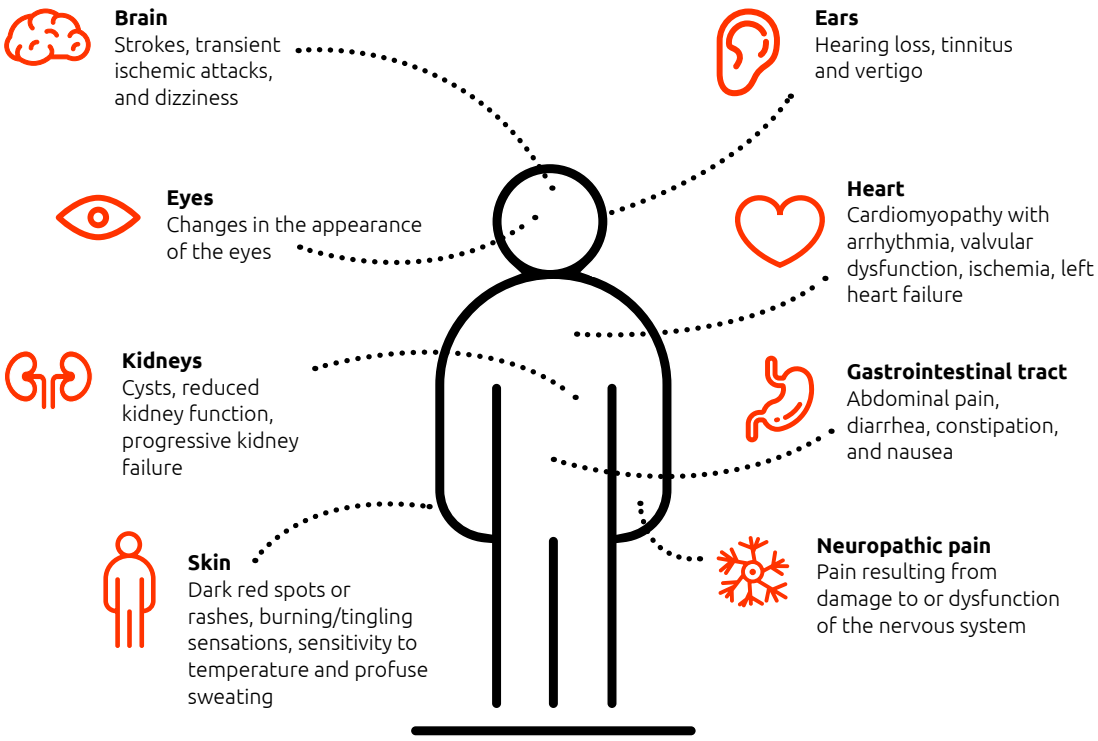


1.4 per 100,000

Estimated prevalence of diagnosed Fabry disease in the general population

Clinical manifestations of Fabry disease

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



Fabry patient survey

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

Lucerastat for Fabry disease

Lucerastat is an oral monotherapy offering a new treatment approach for patients living with Fabry disease.

"By reducing the production of the lipids that cannot be broken down due to Fabry disease, we believe that lucerastat can change the course of the disease for these patients. With neuropathic pain we've found a debilitating symptom of the disease that we can follow in a clinical trial setting to hopefully demonstrate the effect of lucerastat."

Luba Trokan
Director, Clinical Project Physician for lucerastat

Orphan drug status granted in the US and EU

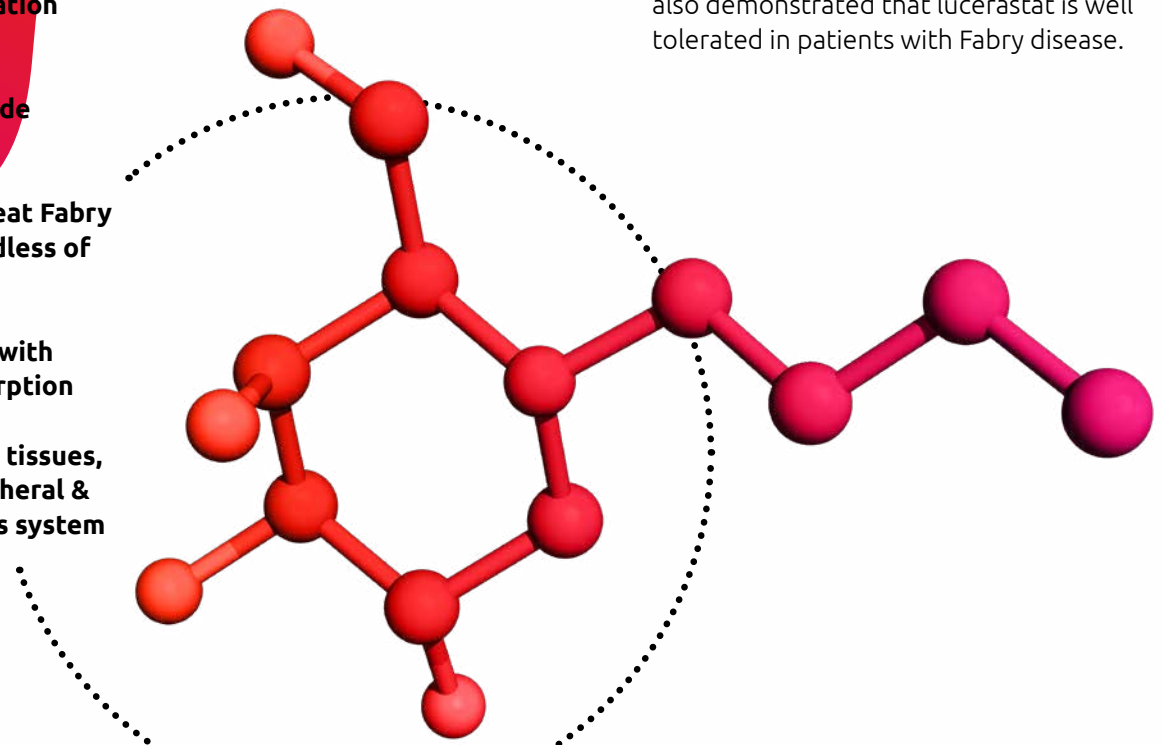
Oral administration

Inhibitor of glucosylceramide synthase

Potential to treat Fabry patients regardless of their mutation

Highly soluble with complete absorption

Access to most tissues, including peripheral & central nervous system



Learning from previous studies

Lucerastat is a small-molecule iminosugar which inhibits glucosylceramide synthase and has the potential to provide substrate reduction therapy for oral treatment of Fabry disease. In an exploratory study in patients with Fabry disease, treatment with lucerastat in addition to enzyme replacement therapy demonstrated a marked decrease in plasma levels of metabolic substrates associated with the development of the disease. The study also demonstrated that lucerastat is well tolerated in patients with Fabry disease.

Phase 3 study

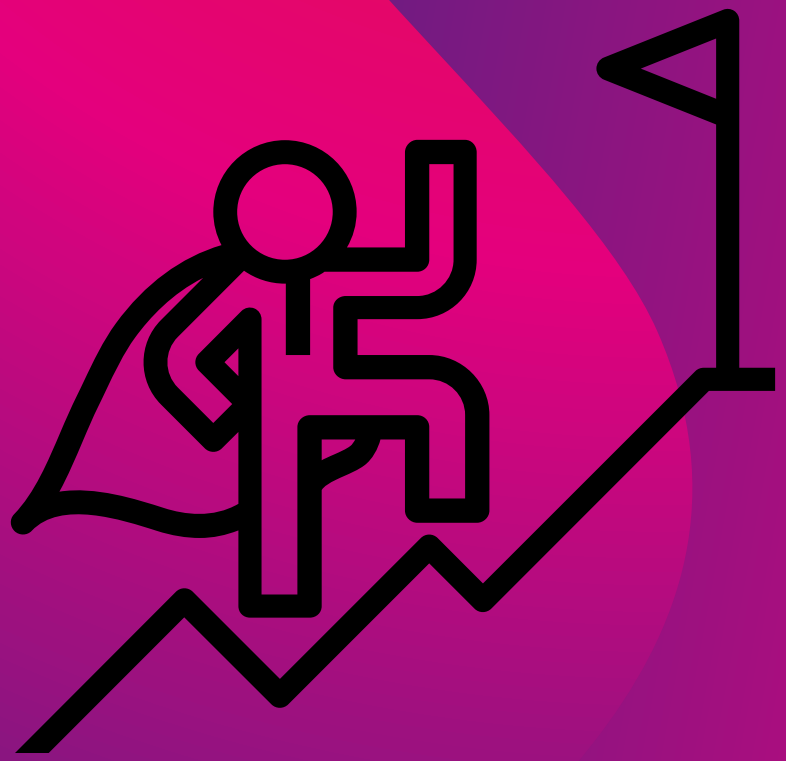
MODIFY is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The study aims to determine the effects of treatment on neuropathic pain over a 6-month period, as measured by Idorsia's Fabry disease neuropathic pain instrument (validated by health authorities). At the end of the double-blind period, patients will have the option of entering in an open-label extension study. Approximately 108 patients are expected to be enrolled and randomized to lucerastat or placebo in a 2:1 ratio. The study is expected to run for around 20 months.

Fabry disease

Compound: Lucerastat

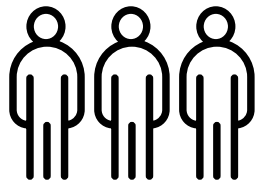
Mechanism of action:
Glucosylceramide synthase inhibition
Status: Phase 3

Our People



More experience – Driving innovation

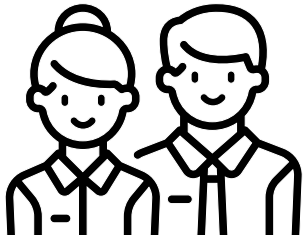
Simply put – our success depends on our people! This is why we want to recruit, engage, and develop talented people who are passionate about working together and applying science to bring benefits to patients.



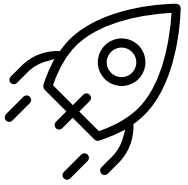
>750
employees

Highly
qualified professionals

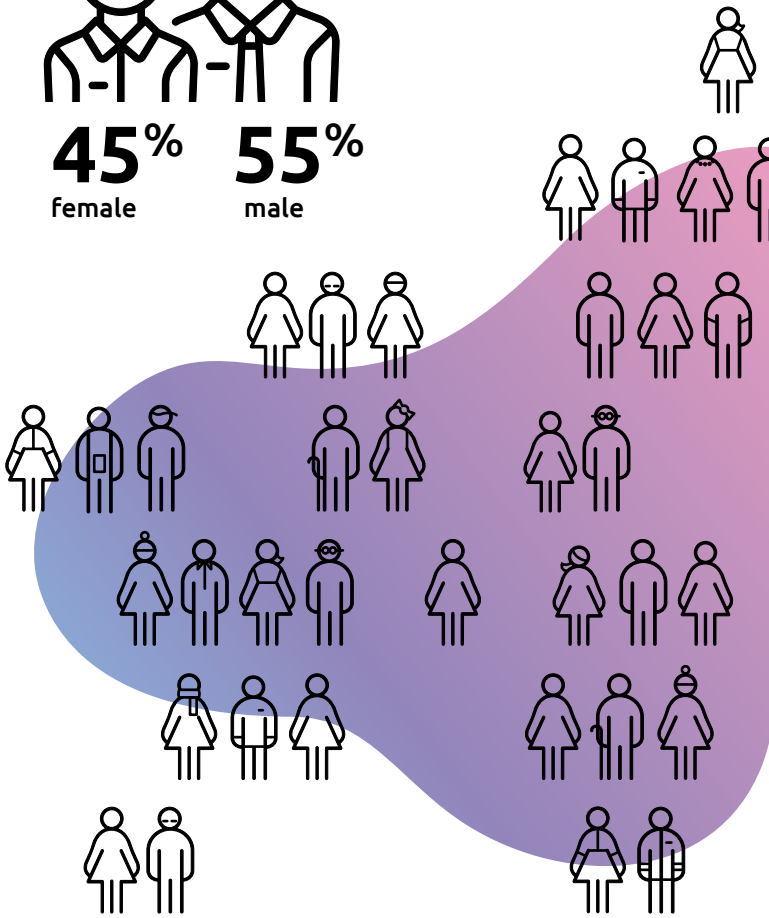
29
nationalities



45% female **55%** male



One
common goal



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Our Research & Development

Our Target Diseases

> **Our People**

Our Responsibilities

More diversity – Expanding the horizon

Advancing our R&D pipeline and preparing for commercialization requires the company to grow its talent base. As a result, we created more than 90 new jobs worldwide in 2018.

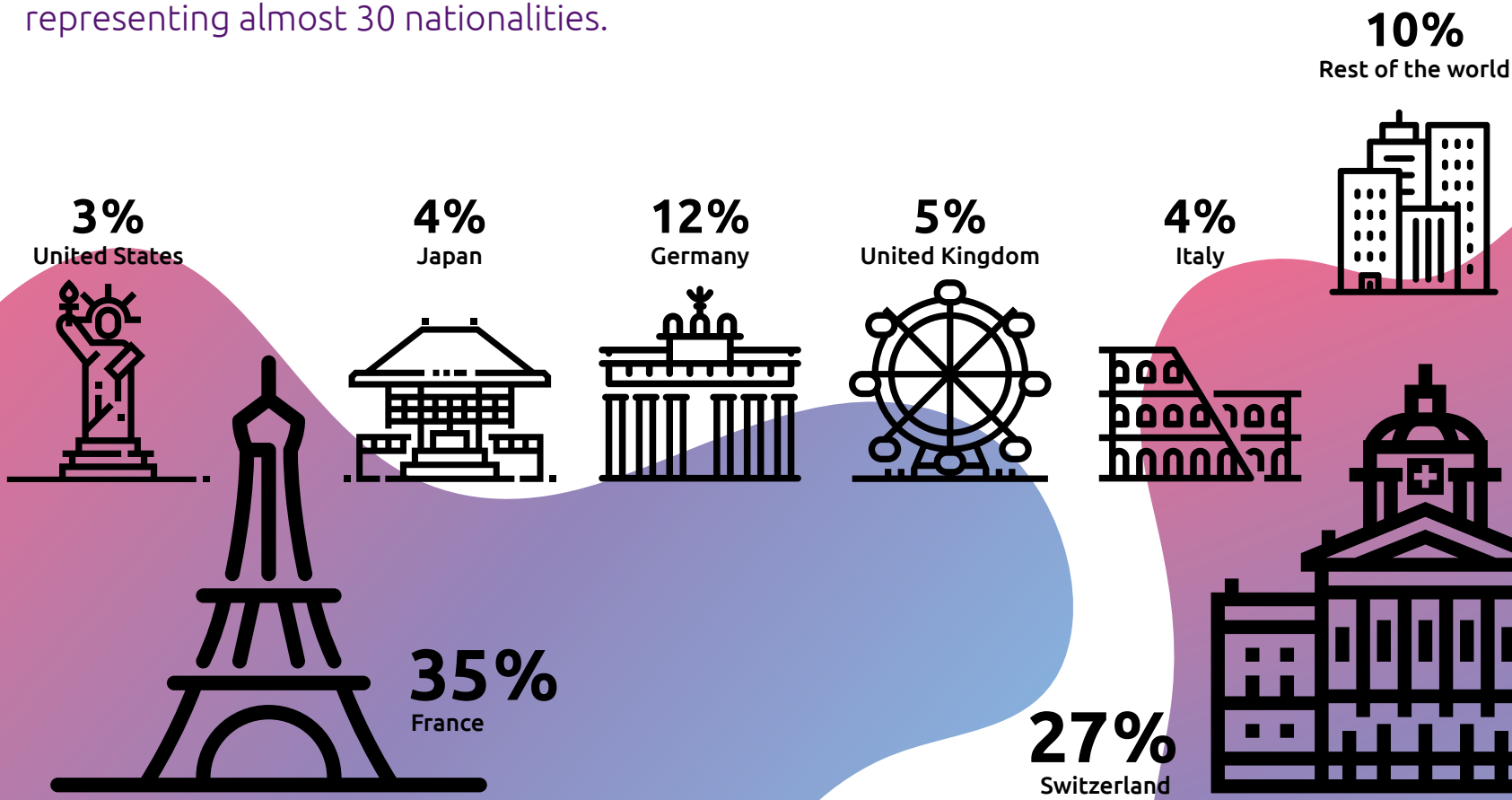
As a growing company, it is important that we attract, retain and advance top talent from all backgrounds and cultures. During the recruitment process, we seek to attract a diverse pool of candidates, focusing on the skill-set they offer and matching their competencies to the behaviors we expect our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

We take an integrated approach to rewards and talent management, designed to build an organization of highly engaged and enthusiastic professionals. Our people are committed to making Idorsia one of Europe's leading biopharmaceutical companies, while at the same time growing both personally and professionally.

"We are doing more with less in a highly productive environment where people enjoy their work – it's a very exciting place to be."

Claire McGeown
Senior Director, Life Cycle Leader

At Idorsia, we harness the power of difference to achieve business success: our employees come from diverse cultural backgrounds, representing almost 30 nationalities.



More ambitious – Courageous and energetic

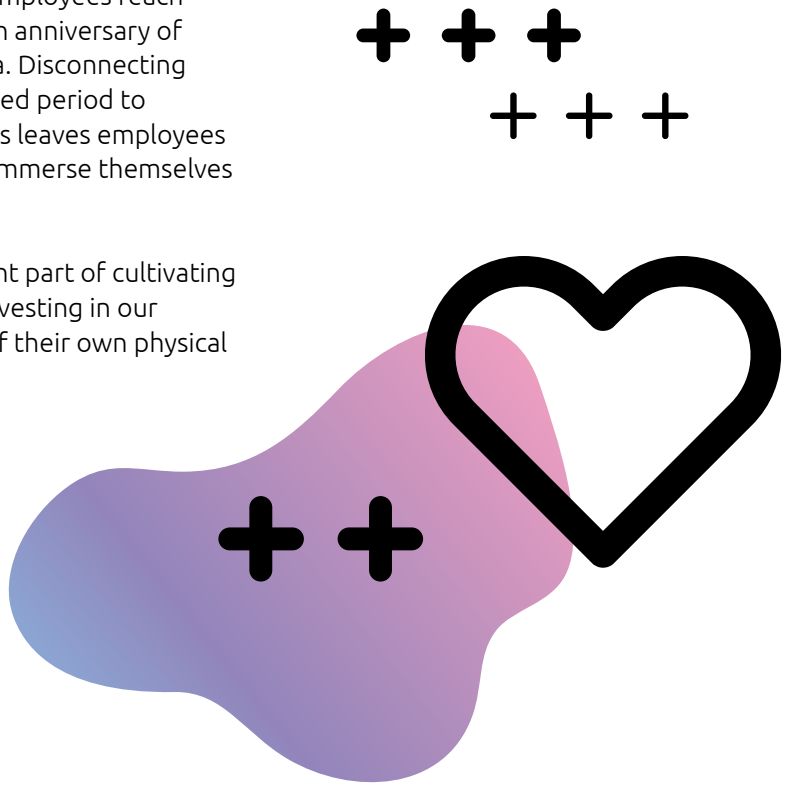
At Idorsia, we have tools in place to recognize extraordinary achievements and emphasize the importance of working in teams.

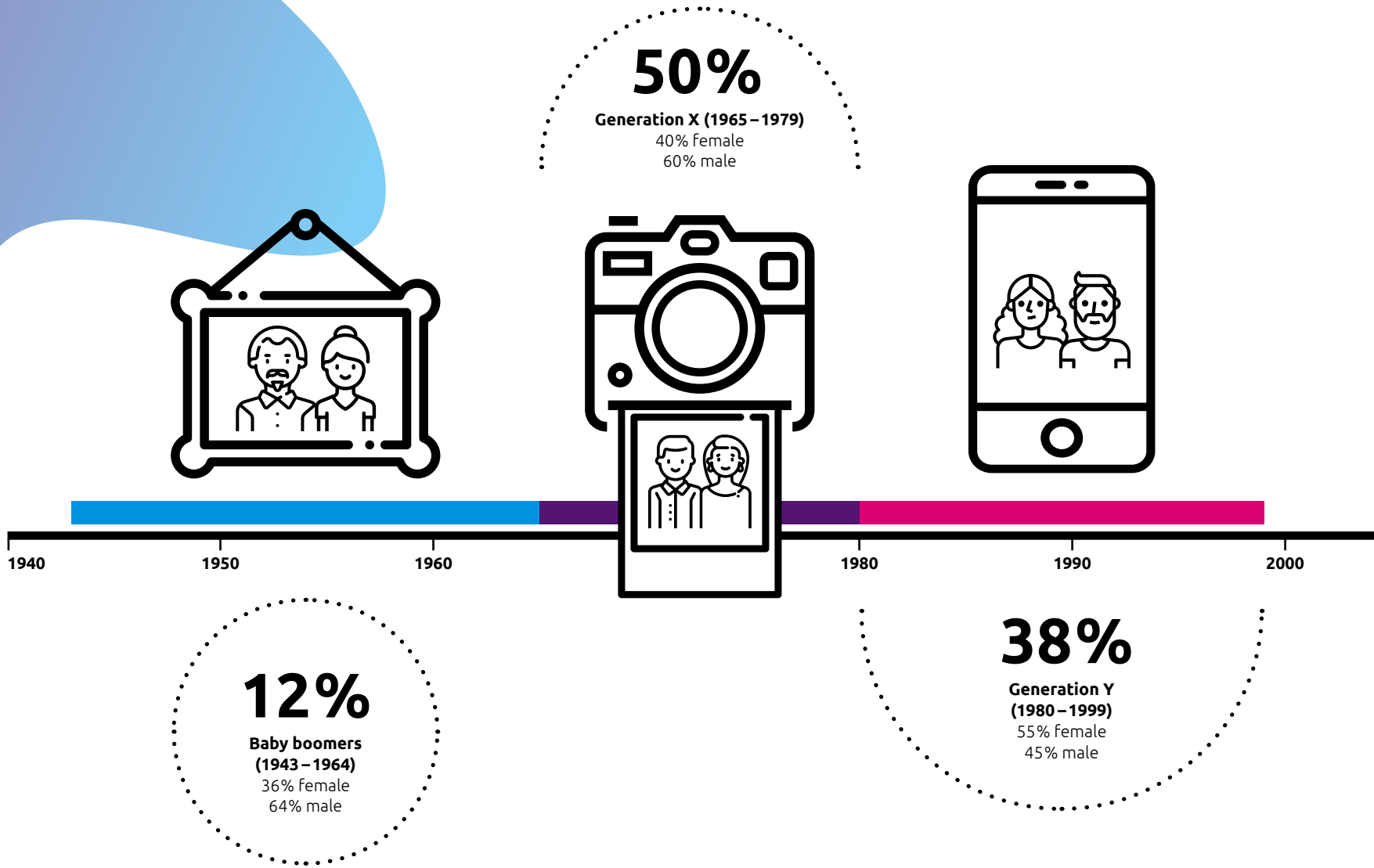
Our simple and transparent reward and recognition philosophy is based on engaging everyone in an entrepreneurial approach to long-term value creation.

We regularly assess our talent to identify high performance and provide support for those who display potential for further growth – e.g. through on-the-job assignments, further education, and leadership trainings.

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

Additionally, an important part of cultivating a healthy workplace is investing in our employees' awareness of their own physical and mental health.

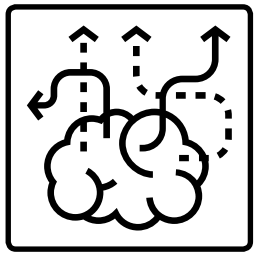




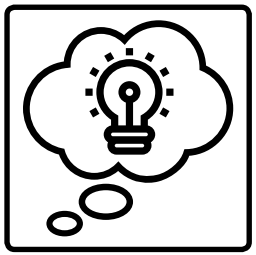
The foundation for our success

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.

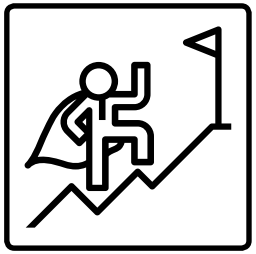
be pragmatic



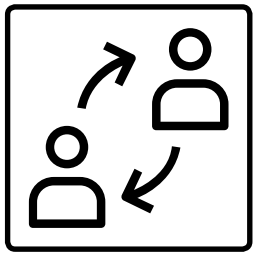
invent



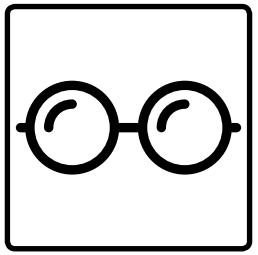
advance

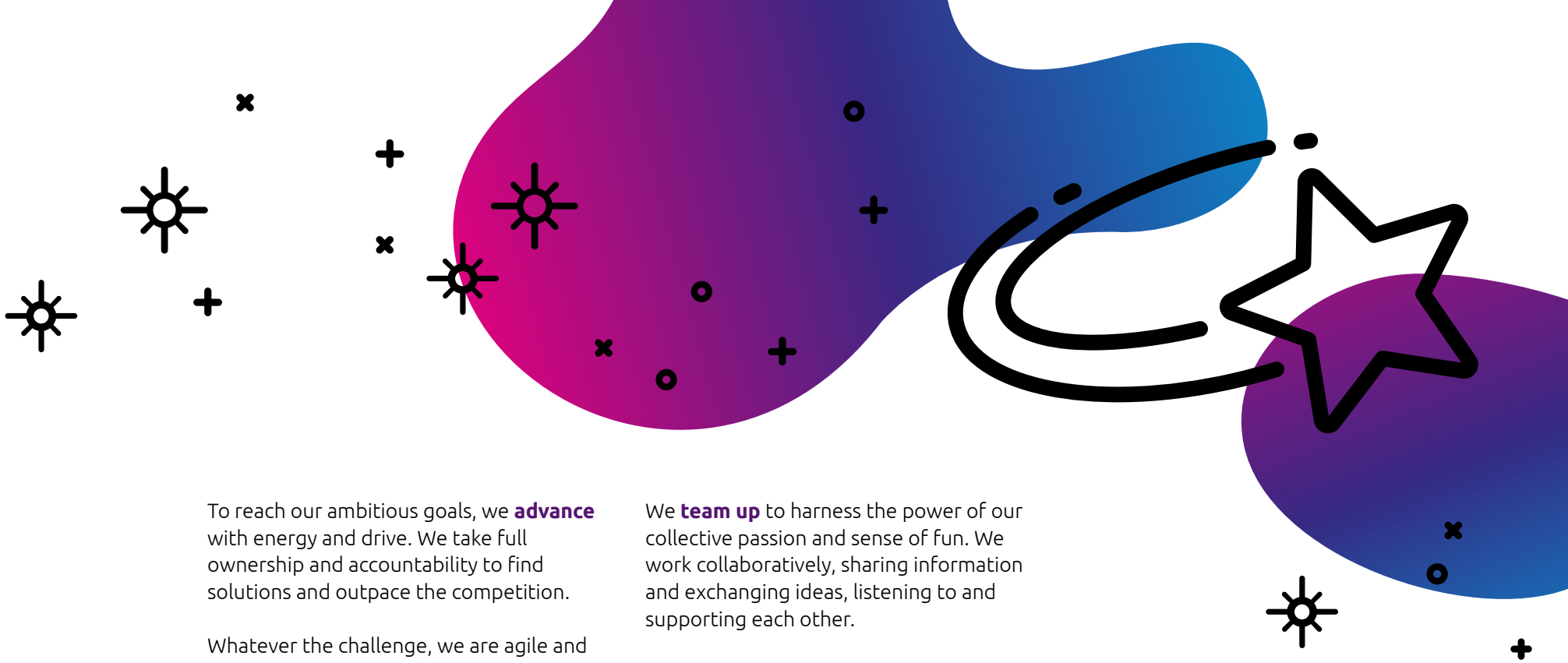


team up



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 Human Resources

The Idorsia Executive Committee

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

In 2018, this management team was further strengthened by the appointment of Simon Jose as Chief Commercial Officer. Simon will be key to realizing the full potential of the company's assets and making strategic decisions on how to commercialize them. Simon brings a wealth of experience and broad expertise, covering both primary care and specialty care markets. He also brings the necessary understanding of the US environment. The whole company is excited by the big step forward, as Simon creates and builds our commercial organization to deliver our innovative therapies to patients.

In this build-up phase of Idorsia, we all depend on the results that we achieve collectively. Management has therefore put systems in place to recognize contribution, encourage high performance and share the benefits of the results that we achieve individually and collectively.

"I have been struck by the enthusiasm and passion I have experienced at Idorsia and relish the opportunity to build a successful commercial organization from the ground up."

Simon Jose
Executive Vice President, Chief Commercial Officer

Our people show up every day with energy, intellect and creativity.

The Idorsia Executive Committee

Simon Jose
Executive Vice President,
Chief Commercial Officer

Guy Braunstein
Executive Vice President,
Head of Global Clinical
Development

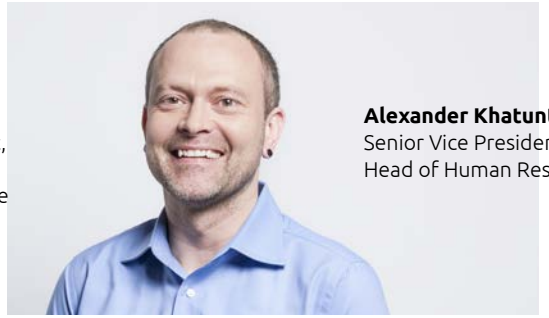
André C. Muller
Executive Vice President,
Chief Financial Officer

Martine Clozel
Executive Vice President,
Chief Scientific Officer

Jean-Paul Clozel
Chief Executive Officer

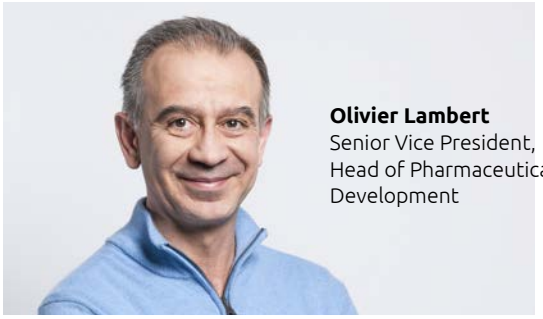
The Idorsia leadership team

Andrew C. Weiss
Senior Vice President,
Head of Investor
Relations & Corporate
Communications



Alexander Khatuntsev
Senior Vice President,
Head of Human Resources

Oliver Peinelt
Senior Vice President,
Group General Counsel



Olivier Lambert
Senior Vice President,
Head of Pharmaceutical
Development

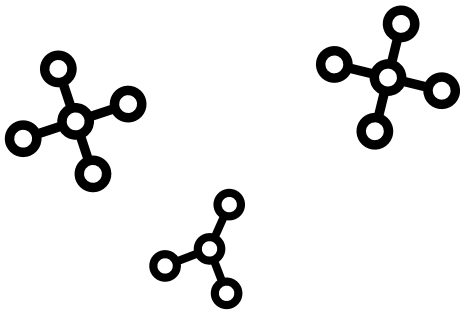
Thomas Weller
Senior Vice President,
Head of Drug Discovery
Chemistry

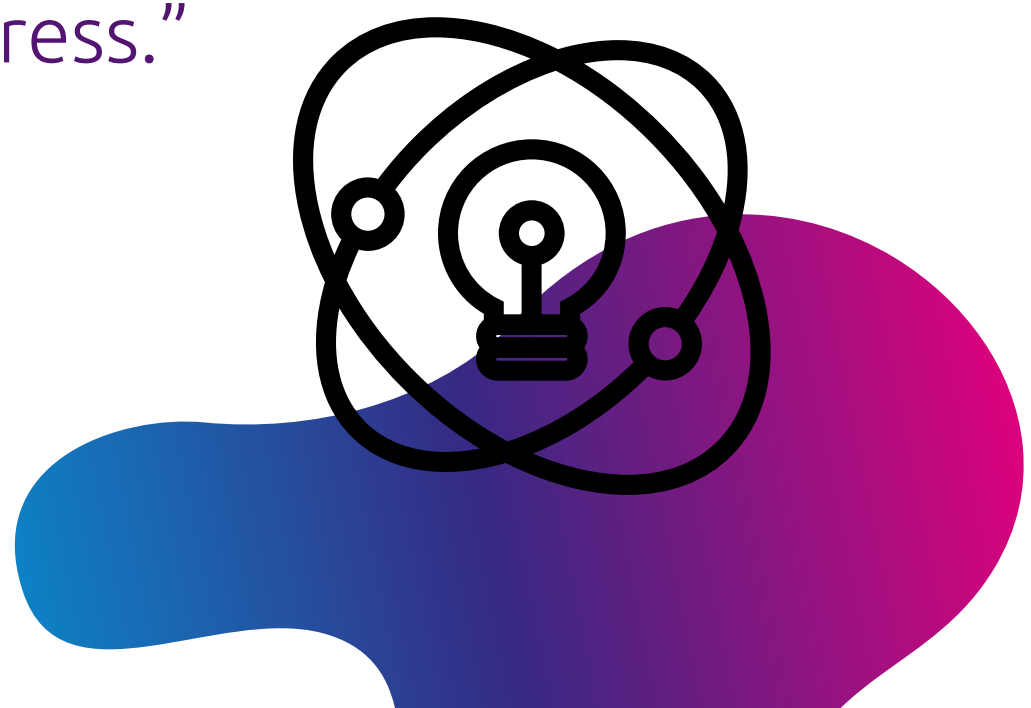
Markus A. Riederer
Senior Vice President,
Head of Drug Discovery
Biology

Ulrich Mentzel
Senior Vice President,
Head of Drug Discovery
Pharmacology &
Preclinical Development

"We have a highly motivated team of people dedicated to delivering high quality in all they do. Together, we are making great progress."

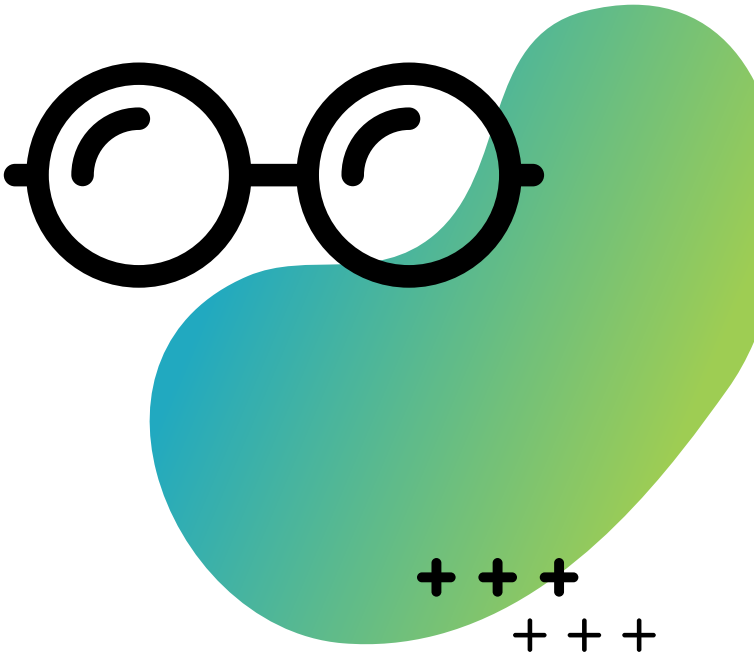
André C. Muller
Executive Vice President, Chief Financial Officer





Our Responsibilities

More drive –
For a better future

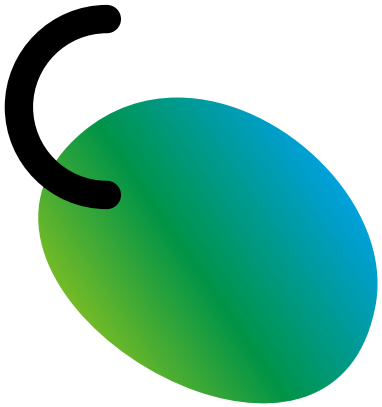


Idorsia's goal is to discover, develop and bring more, innovative medicines to patients. We believe that delivering on this mission is our core responsibility to our stakeholders and society in general. We also believe that it is possible to achieve this in an economically, socially and environmentally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

From the first day of operations, we have had a strong governance framework in place, with a broad range of supporting policies, standard operating procedures and guidelines (such as our Code of Business Conduct), driving a culture of integrity.

As we have become operationally independent, we have taken control of monitoring our performance on topics important to our stakeholders, such as the impact of our efforts on the environment and the communities in which we live. We are in the process of setting up a materiality analysis and associated stakeholder engagement activities to lay the foundations for future sustainability reporting.

For more information on Idorsia's commitment to its stakeholders and our approach to corporate responsibility, please visit our website: www.idorsia.com/our-responsibilities.



Inspiring young minds

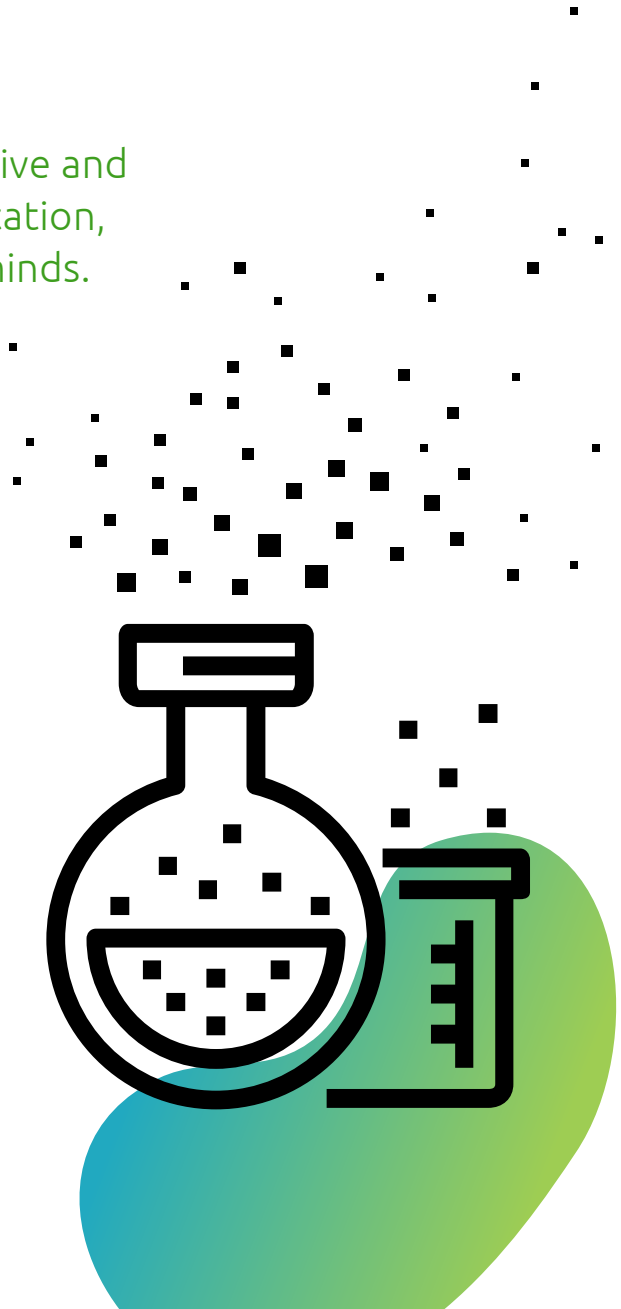
We aim to be good neighbors in the communities where we live and work. Our community efforts focus primarily on science education, with the goal being to ignite a passion for science in young minds.

We have partnered with our neighbor Actelion to invest in children's science education. This year we jointly hosted the annual Elementary School Days, where 180 fourth-year students from Allschwil participated in various science experiments to inspire budding scientists in our community. The students had a great time making goodies for the home (lip balm and bath bombs) and for recreation (slime), as well as setting off (and taking cover from) the Mentos-Coke geyser fountains. We were happy to be able to help make science fun and interesting for potential future recruits!

Shortly afterwards, fifth year students from Allschwil put aside their schoolbags and picked up some new scientific tools to become investigators and solve the mystery of who robbed the bank! The aspiring crime scene investigators had to compare ink samples on paper, take and analyze fingerprints, investigate hair samples, conduct a powder solution test, and check for particles under a laser light to find the criminal. In the end, the bank robber was identified and justice was served!

This year also saw over 220 regional high school students attending our series of summer lectures about life in the pharmaceutical industry. This year's series – entitled "Life in Science" – introduced the students to different areas of our industry, ranging from research capabilities and therapeutic areas of interest, to medical affairs and pharmaceutical branding.

Once again, the feedback was incredibly positive – not only from the students (and teachers) attending, but also from our volunteers, who enjoyed taking time out of their busy days to help inspire the next generation.

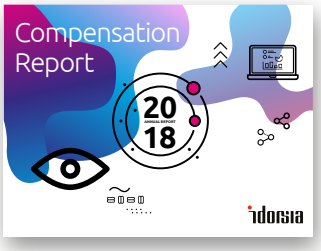


"It was really cool – I especially liked making the slime and the hair gel. I may be a scientist when I grow up, but I still want to be a footballer first."

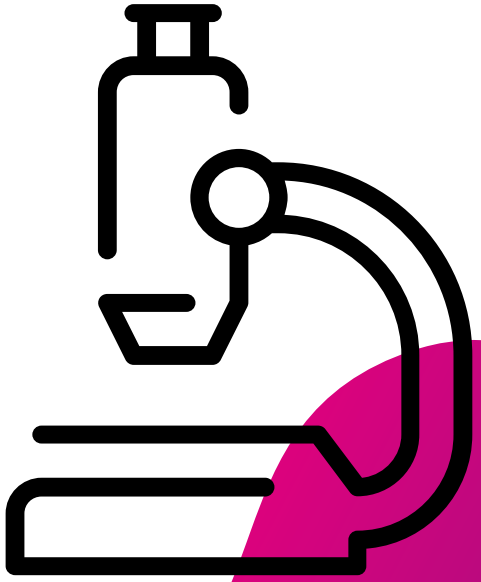
Dylan (10)

Be prepared for more

Further parts of the Idorsia Annual Report 2018



Curious to learn more?
Reach out to us.



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