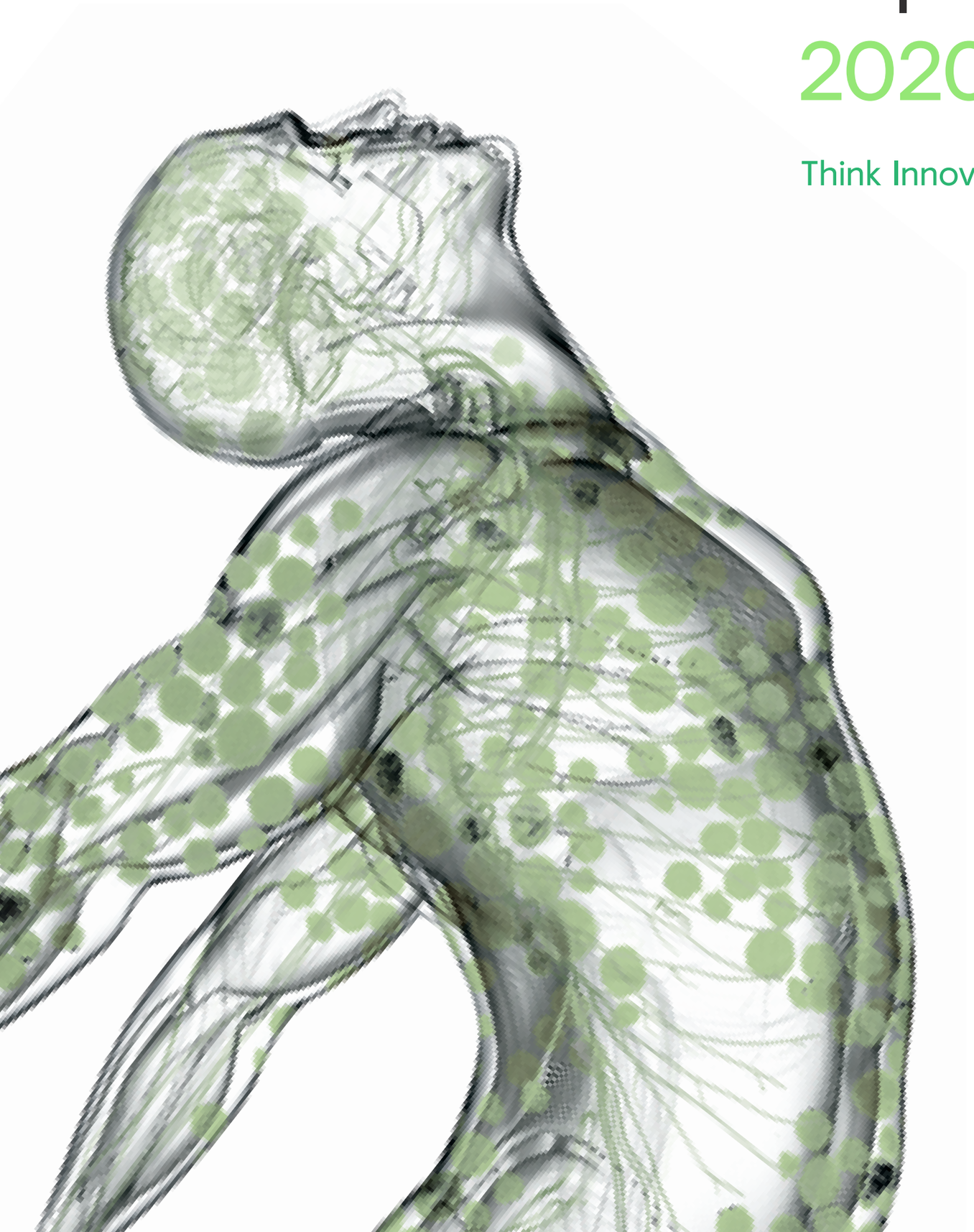
Grünenthal Report 2020/21

Think Innovation. Feel Life.



GRÜNENTHAL

Grünenthal Report 2020/21

Think Innovation. Feel Life.

oud to work for a
rld free of pain.

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Letter from the CEO

2020 was an unprecedented year, with the Covid-19 pandemic disrupting our lives in ways that none of us could have imagined. At all times, our top priority was to protect the well-being of our employees while ensuring an uninterrupted supply of our medicines for patients. I am proud of the agility, solidarity and teamwork that our teams showed to achieve this important goal.

Despite the obvious challenges, 2020 was a successful year for our business. Our revenue for the year was €1,280 million, and we achieved an adjusted EBITDA of €338 million, which is close to our record year in 2019. This excellent result was made possible by our resilient business model and our financial discipline.

Our performance in 2020 is strong proof that our strategy is taking us in the right direction. The brands that we recently acquired – Nexium™, Vimovo™ and Zomig™ – made valuable contributions by generating solid profit. We also took another major step forward by acquiring the European rights (excluding Spain and the UK) to Crestor™ (rosuvastatin) in December of last year. This latest investment expands our portfolio with another established medicine that will boost our EBITDA and enable us to further invest in the transformation of our company and our focused R&D approach.

Developing innovative medicines for diseases with high unmet medical needs is our passion, and we continue to make great progress against that goal. Two investigational medicines entered clinical development.

Our NOP compound became our first proprietary Grünenthal compound to enter clinical development since 2017. It is the frontrunner of our peripheral Nociceptin/orphanin peptide receptor (NOP) agonist programme and is being developed as a potential treatment for chronic neuropathic pain. The investigational medicine's selectivity for the NOP receptor, combined with its peripherally restricted mode of action, may lead to an improved safety profile compared to the currently available standards of care.

In addition, our GRM compound is a new anti-inflammatory agent that has the potential to address various indications with the efficacy of cortisone but without the side effects of long-term corticosteroid use such as reduced bone formation. Preclinical data shows that it has the potential to offer a more favourable benefit-risk ratio compared to current glucocorticoid-based therapies like prednisolone.

We also acquired the company Mestex AG with their Phase III agent MTX-071 (resiniferatoxin). This non-opioid investigational medicine is a transformative opportunity for patients suffering from osteoarthritis of the knee.

Our business in the US reached some fantastic milestones in 2020. The US Food and Drug Administration (FDA) approved our application to expand the label for Qutenza™ to treat neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. This opens up opportunities to deliver relief to millions of patients in the world's largest pharma market. On top of this, our start-up business, Fern Health, has rapidly transformed from a bright idea into a functioning entity. It is now supporting people with musculoskeletal pain by creating personalised care programmes via a mobile app.

Our culture is the backbone of everything we want to achieve – and it is shaped by our Values & Behaviours. We received our highest ever rating in the Great Place to Work® survey in 2020, with 81 percent of participating employees stating that Grünenthal is a great place to work. Our scores improved in all dimensions across all regions with an increase in the overall Engagement by 9 percent compared to 2017. This shows the good progress we have made on our cultural journey.

2021 is a very special year for Grünenthal as we are celebrating our 75th anniversary. Since 1946, our company has been developing breakthrough medicines for patients around the globe. Our anniversary is a great chance to reflect on our history and look forward to our future with excitement about the next generation of innovative treatments that we are going to create for patients worldwide.

Overall, our company is in a solid position in terms of turnover and profit, while we are also continuing to reduce our net debt faster than expected. We have a fantastic platform to maximise our investment in the future. This includes exploring potential acquisitions.

2020 was a testament to our strategy and I am proud of the company's development. We have driven innovation and continued to build our pipeline with three promising Phase III and two Phase I projects. We have also more than doubled our adjusted EBITDA since 2017 from €129 million to €338 million in 2020. We have entered the capital market and received strong credit ratings, which are further external validation of our company's performance and potential.

On behalf of the Corporate Executive Board, I would like to invite you to join us in 2021 as we keep moving closer towards our vision of a world free of pain.

Best regards,

Gabriel Baertschi

"Grünenthal achieved success in 2020 despite the global pandemic. Our great teamwork and our strong focus on patients kept our business moving forward – and opened up exciting opportunities."

Gabriel Baertschi,
Chief Executive Officer

Anniversary note from the Chairman of the Supervisory Board

In 2021, Grünenthal celebrates its 75th anniversary. This significant milestone is an excellent opportunity to look back at the Company's history – and forward to its future. For three-quarters of a century, Grünenthal employees and shareholders have been joining forces based on a passion for innovation and a deep commitment to improving patients' lives. Together, they have built a strong basis for success, and I am excited about the next chapters in this story.

Founded in 1946, Grünenthal became the first enterprise in West-Germany to register penicillin after World War II. Since 1957, the Thalidomide tragedy has been part of Grünenthal's history. The Company withdrew Thalidomide from the market after learning about the teratogenic side effects. This tragedy will never be forgotten, and the Company deeply regrets the consequences for the people affected and their families. While we cannot change the past, Grünenthal focuses on supporting affected people today. The Grünenthal Foundation provides support in the form of benefits such as wheelchairs, hearing devices and modifications of cars that aim to improve living situations. The team of the Grünenthal Foundation is in constant dialogue with those affected in order to adapt and further develop new projects.

1968 marked the beginning of Grünenthal's international expansion when the Company founded its first overseas affiliate in Peru. Almost a decade later, in 1977, the development of Tramadol signaled a shift to become a specialist in pain treatments. The European launch of Transtec™ in 2001 was another key milestone, providing a safe and easy-to-use treatment for chronic pain. In 2007, the launch of Versatis™ in the European Union strengthened Grünenthal's position as a true pain expert.

Most importantly, Grünenthal never stopped bringing innovative therapies to patients. Recent steps in this unique track record include the launch of Palexia™ in 2010, which was the first innovative molecule in the centrally acting analgesic class to be approved for more than 25 years. In July 2020, Grünenthal achieved another major success when it received approval to extend the label for Qutenza™ in the United States to treat neuropathic pain associated with diabetic peripheral neuropathy of the feet.

Since 2017, Grünenthal has invested approximately €1.3 billion in the acquisition of established product brands, including Nexium™, Vimovo™ and Zomig™ as well as Crestor™. And in 2018, the Company created its commercial presence in the US. This was followed by the realignment of the Company's R&D strategy to further strengthen its ability to develop and commercialise cutting-edge pain treatments for patients in need. In April 2021, the Company completed another strategic deal to acquire the Swiss biotech company Mestex AG and its late-stage investigational treatment for osteoarthritis of the knee.

Financially, the Company has managed a turnaround and is now in a very strong position to drive growth by investing in profit-accretive acquisitions and innovative R&D projects. It is actively pursuing an ambitious growth strategy with support from committed shareholders who have made this remarkable transformation possible. As a result of this journey, Grünenthal is now very different from the enterprise that was launched 75 years ago. A small team has grown into a workforce of 4,500 people. A German business has transformed into an international organisation, with products available to patients in around 100 countries. The Company has specialised to become a global leader in pain, with a broad portfolio of life-changing treatments. Its capabilities cover the full value chain, from R&D through to vertically integrated manufacturing, regulatory and commercialisation expertise. This enables Grünenthal to generate commercial and production synergies across its existing portfolio and when acquiring additional brands.

Congratulations to all Grünenthal employees and shareholders for everything they have achieved in the Company's 75-year history. This long tradition creates an excellent launchpad for Grünenthal's strong ambitions for the future. I am convinced that Grünenthal will leverage this anniversary year to generate momentum for continued success.

Prof. Dr. Wilhelm Moll LL.M.
Chairman of the Supervisory Board

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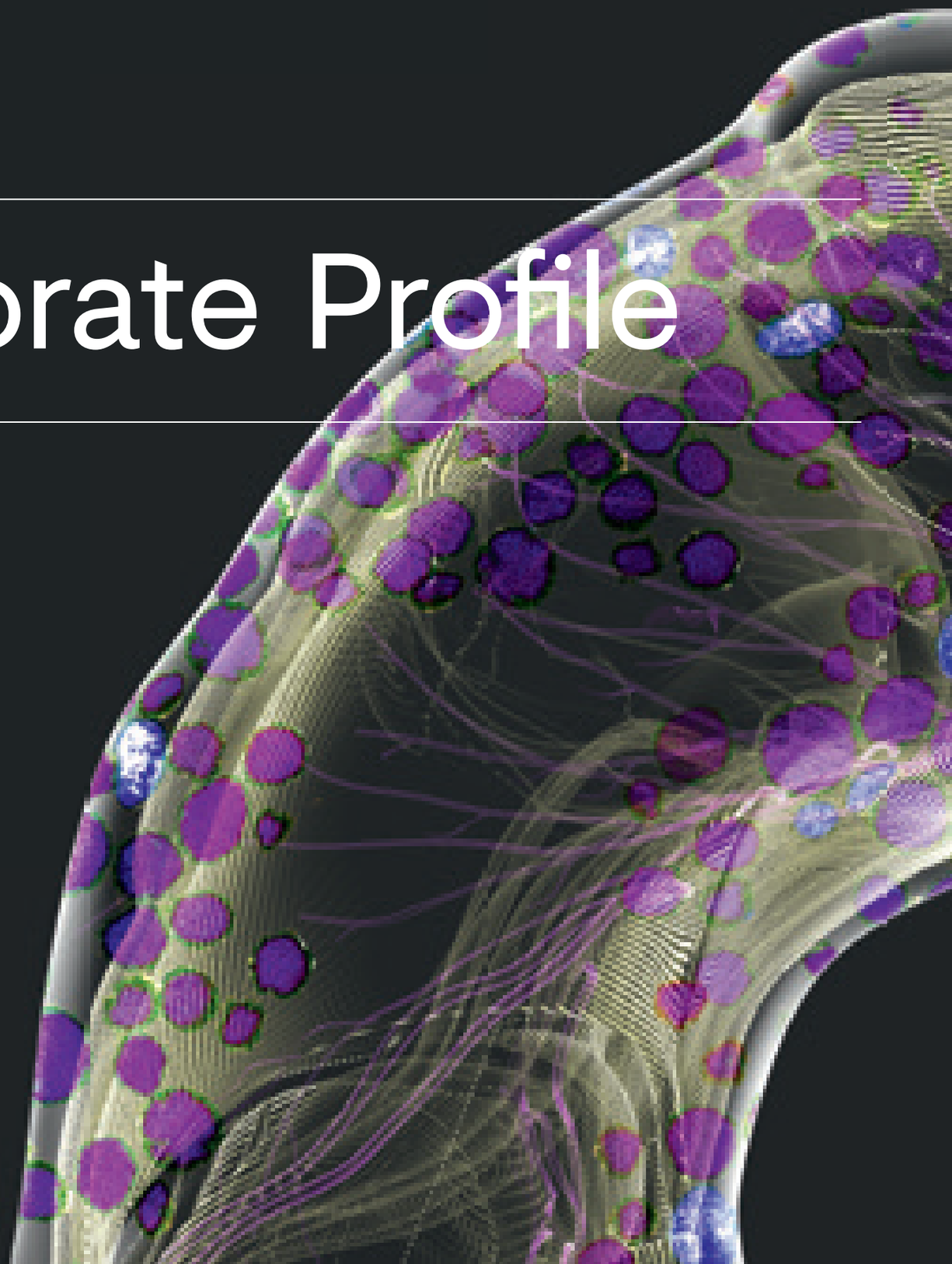
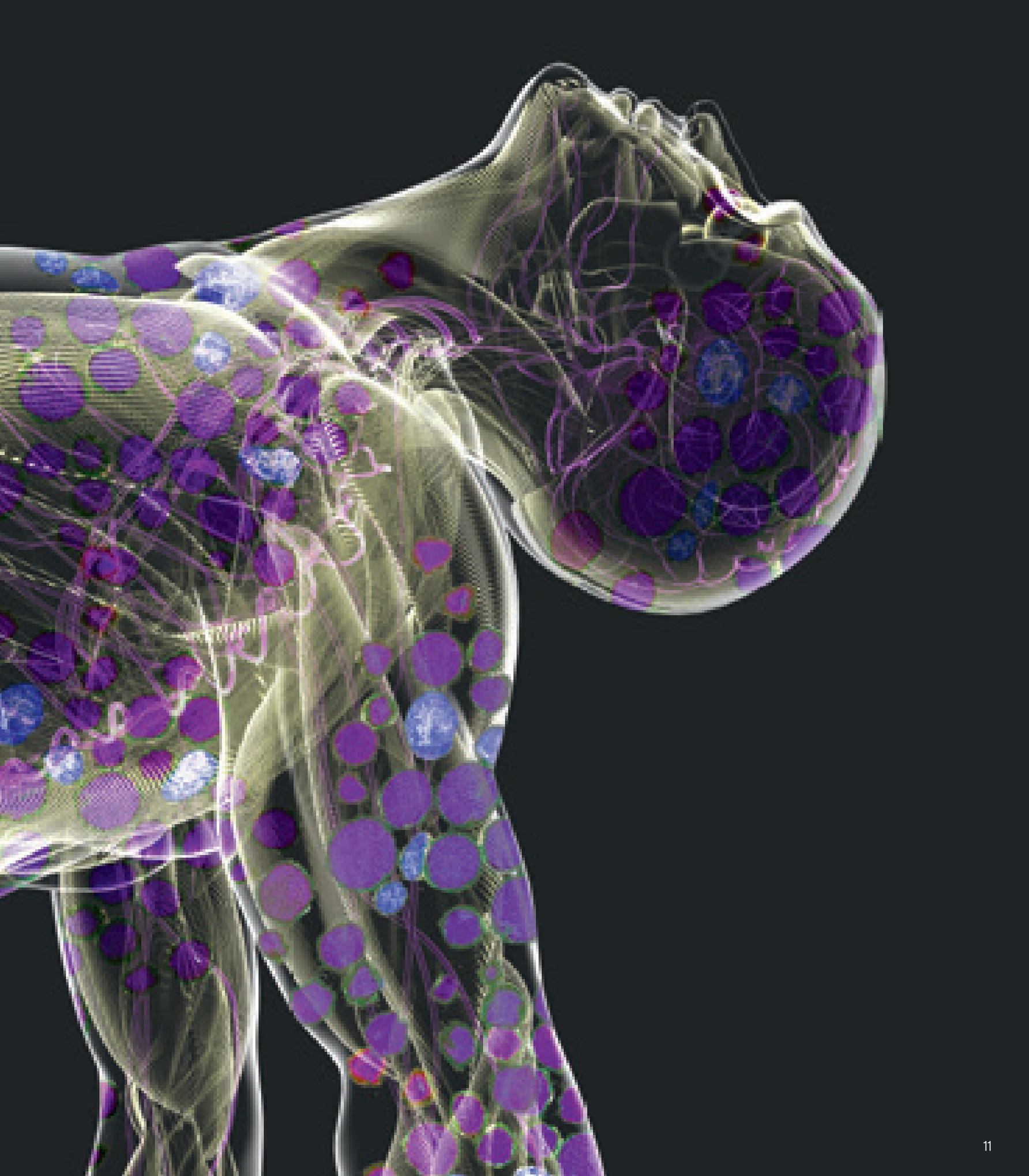
Corporate Profile





1.1 | Corporate Profile

Grünenthal is a leading pharmaceutical company focused on pain therapies with 50 years of experience in developing, manufacturing, and commercialising innovative products. We direct our efforts towards our vision of a world free of pain. This vision is a driving force for our employees, and motivation for their daily work and for the personal commitment it involves.

Pain, especially chronic pain, is a major burden for patients and society. The number of patients with chronic pain is expected to increase further, partly driven by rapidly aging populations in developing countries.

There is an urgent need for pharmaceutical innovation and more effective, better tolerated treatment options in this context. As a science-based pharmaceutical company, we are committed to transforming the future of pain management. We have a long track record of bringing innovative treatments and state-of-the-art technologies to people living with pain. Our R&D efforts aim to further strengthen our disease area leadership in pain by developing new, highly innovative, non-opioid pain therapies for patients in need. Our strong partnerships with leading healthcare and science organisations support this endeavour, and our clear commitment sets us apart from our competitors.

Grünenthal is a fully integrated pharmaceutical company covering the entire value chain – from compound discovery, research and development through to production and commercialisation. Our company is headquartered in Aachen, Germany, and has affiliates in 29 countries across Europe, Latin America and the US. Our products are available in around 100 countries. In 2020, Grünenthal employed around 4,500 people and achieved sales of €1.3 billion.

Leader in pain management

#1

in Latin America
and Europe
#3 worldwide[1]

Longstanding commitment

50

years in
pain research

[1] IQVIA Midas yearly worldwide Sales of selected CAA molecules by Region, status Q4-2020, fixed EUR
CAA Market includes the main opioids: Strong Opioids: Buprenorphine, Fentanyl, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Pethidine, Tapentadol
Weak Opoids: Codeine, Dextropropoxyphene, Dihydrocodeine, Hydrocodone, Tilidine, Tramadol

Solid revenue base

1.3

billion euro
in 2020

International network

2

R&D Unit in Aachen
and an Innovation
Hub in Boston

Production capacities

5

manufacturing sites
in Europe and
Latin America

Products sold in around

100

countries

Focus on innovation

250

priority patent
applications filed in
the last 10 years

Strong and capable team

4,500

employees
worldwide

Our Executive Board Team

Gabriel Baertschi,
Chief Executive Officer (CEO)

Jan Adams, MD,
Chief Scientific Officer (CSO)

Mark Fladrich,
Chief Commercial Officer (CCO)

Fabian Raschke,
Chief Financial Officer (CFO)

Victor Barbosa,
Head Global Operations

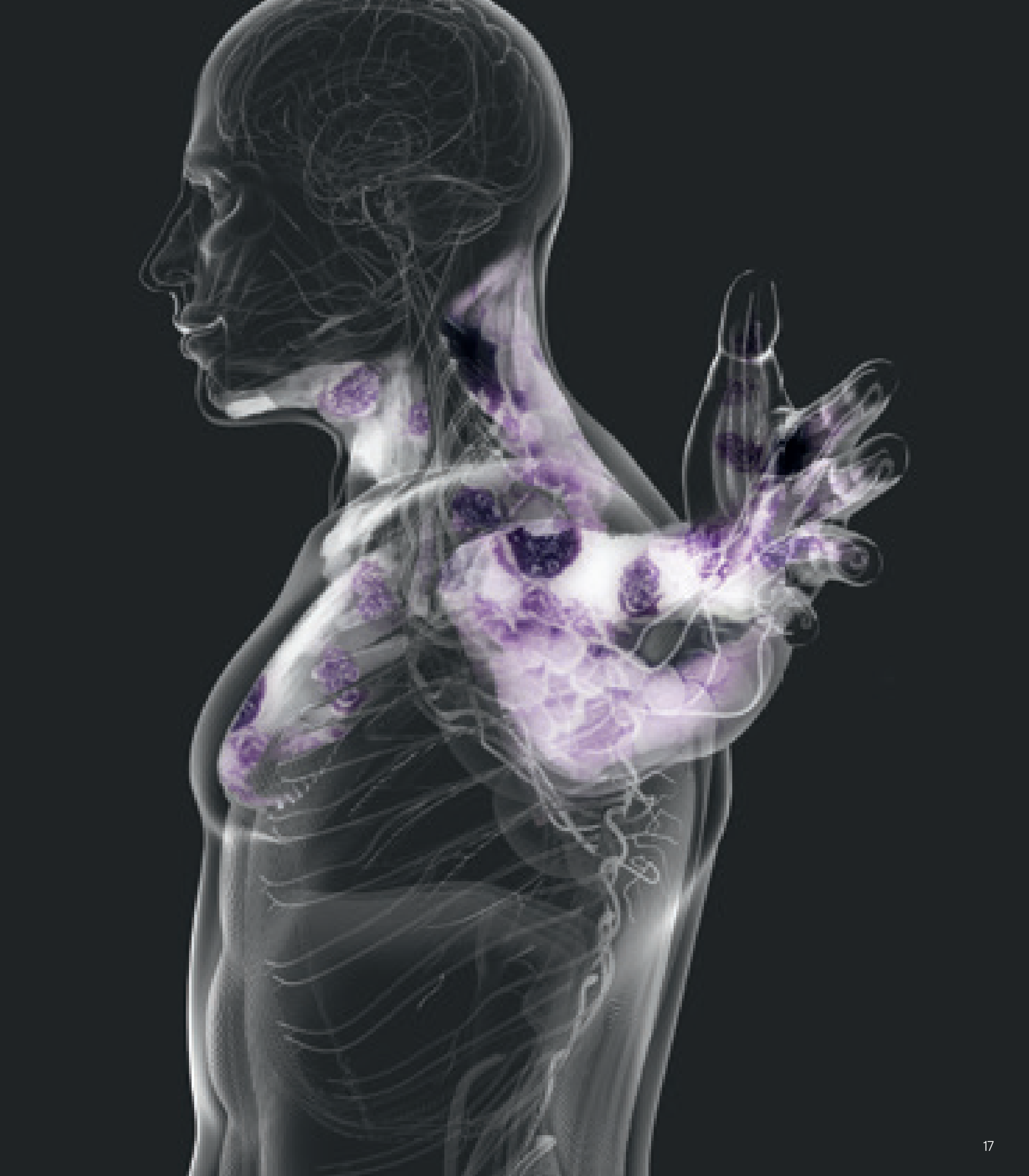
Leen Hofkens,
Head Global Human Resources

Sebastian Köhler,
General Counsel

Quentin Le Masne de Chermont,
Head Global Strategy

2

Corporate Strategy



The five pillars of our corporate strategy

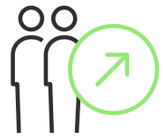
Our journey towards a world free of pain

Be a **leading innovator in pain treatments** to address critical, unmet medical needs, with a focus on non-opioid treatments

Drive the **commercial success of our growth brands,** and evolve our **go-to-market model towards digital and omni-channel**

Drive profitability through **efficiencies across the value chain and manufacture at the best safety, quality and cost**

Complement our portfolio with **established brands deals, irrespective of therapeutic area,** and further maximize profitability of our established brands



Invest in **building capabilities** of our people and operate at the **highest ethical and regulatory standards**

2.1 | Our strategy as the foundation for future-proofing Grünenthal

A world free of pain – that is our vision. Our corporate strategy supports our efforts to bring this vision to life.

In recent years, we have successfully transformed our company. Our results over the last three years showed that our strategy is taking us in the right direction. We will continue to transform our company along our five strategy pillars.

Being a leading innovator in pain treatments

As a science-driven company with a passion for innovation, we focus on developing novel non-opioid treatments for pain therapy. We develop high-value Proof-of-Concept assets, and take a world-leading role in creating pain treatments that address unmet medical needs. Grünenthal focuses on four key pain indications: peripheral neuropathic pain, chronic post-surgical pain, chronic low back pain, and osteoarthritis. You can explore specific examples of our innovative R&D projects on page 36.

We will also continue to selectively source late-stage projects with low technical and commercial risks. For example, we recently acquired the global rights to the Phase III compound RTX (resiniferatoxin), a natural, highly potent, non-opioid substance with a proven and clinically validated mode of action. It targets pain associated with osteoarthritis of the knee, which is a large market with over 50 million affected people across the US and the EU.

Driving the success of our growth brands and evolving our go-to-market model

We are committed to maximising our business and building successful brands now and in the future.

This includes expanding the commercial success of Qutenza™ in the US. The recent label extension for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults represents a unique growth opportunity because up to 20 times more patients in the US can now potentially benefit from this product.

We will continue striving to maximise the value of Palexia™ in Europe. This product is still growing after more than one decade on the market because of its differentiated profile. At the same time, we will prepare for and manage the loss of exclusivity for Palexia™ in Europe in 2025.

Across all brands, we are transforming our go-to-market model towards a digital and omni-channel approach. This has been accelerated by Covid-19 and we substantially and rapidly expanded our use of channels that enable remote interaction, including mail, webinars, and e-detailing.

Improving efficiency and manufacturing with a focus on safety, quality and cost

In line with previous successful programmes, we identified in early 2020, further levers and opportunities to boost efficiency throughout our value chain.

For example, in manufacturing, our expert teams are now working tirelessly to tap into these opportunities – producing our own medicines as well as products as a trusted partner for other pharmaceutical companies. Our key ongoing projects include operational excellence programmes, leveraging digital technologies and automation, and product redevelopment and direct spend optimisation.

At all times, we apply strict measures for controlling costs, and we intend to continue to follow a prudent financial policy supported by the long-term commitment of our shareholders.

Seeking established brand acquisitions, irrespective of therapeutic area

We are striving to keep growing our business through selective acquisitions of established brands based on strict acquisition criteria:

- Well-established brands with high brand loyalty and predictable sales after the loss of exclusivity.
- Synergistic products with significant overlaps and complementarities to our existing infrastructure and regulatory expertise.
- Acquisitions that enhance our portfolio diversification in terms of products, irrespective of therapeutic area and geographies.
- And immediate positive EBITDA and cash flow contributions, with an acquisition at attractive multiples.

So far, these acquisitions and deals have contributed €228 million to Grünenthal's EBITDA. We enforce a disciplined sourcing strategy supported by robust due diligence, and we leverage our experience to ensure fast and effective integration while maintaining an uninterrupted market supply. Our commercial, regulatory and manufacturing expertise and infrastructure will also enable us to achieve valuable synergies. As a result, these acquisitions help to secure our financial stability and support funding for our R&D projects.

Investing in people and operating in line with the highest ethical standards

Our people are the key to our success – and our company's culture is the backbone of everything we want to achieve.

In 2020, we made more good progress on our cultural journey. We received our highest ever rating in the Great Place to Work® survey, with 81 percent of participating employees stating that Grünenthal is a great place to work. Looking ahead, we are going to continue to drive a high-performance culture and a passion for development. This will empower us to achieve outstanding business results and build the capabilities that we need for the future.

We remain committed to maintaining the highest ethical and regulatory standards in our business operations, as well as in our role as an advocate for the responsible use of our products – including medically necessary opioids. In addition to maintaining highly effective control and compliance processes, we have instilled a culture within our organisation to create a highly ethical and engaged workforce. This combination of committed people and our well-defined protocols has helped us to positively impact patients, our partners and all stakeholders involved in pain management. In addition, Grünenthal has achieved a positive ESG-rating in April 2021, putting us in the 5th percentile of the pharmaceutical industry. You can explore more about our responsible business conduct in chapter 8 on page 74.

Quentin Le Masne de Chermont,
Head Corporate Strategy

2.2 | Three questions to Quentin Le Masne de Chermont, Head Corporate Strategy

How do Grünenthal's brands support progress towards its vision of a world free of pain?

Our success builds on our portfolio's complementary mix which is split in two parts – our growth brands and our established brands. The growth brands include our innovative and patent-protected products like Palexia™ and Qutenza™. The established brands bring together all of our mature and off-patent products. This includes Nexium™ and the recently acquired Crestor™ and brands that we have developed over a longer period of time, like Tramal™. Established brands are characterised by high brand awareness, predictable sales, and high profitability. The combination of these two product categories provides a well-balanced and resilient overall business.

Our vision of a world free of pain underscores our commitment to R&D. The profit that we generate with our growth and established brands gives our company financial stability. In turn, that makes it possible for Grünenthal to fund projects that create innovative, urgently needed pain therapies.

How does M&A fit into this picture?

Our M&A activities aim to enrich our portfolio, either through early or late-stage asset R&D deals in the therapeutic area of pain or through the acquisition of established brands, irrespective of therapeutic area. Acquisitions of established brands represent a unique opportunity that matches our strengths and capabilities, and they have a direct impact on our financial stability.

Pharmaceutical products typically experience a steep decline in sales and revenue immediately upon or shortly after losing exclusivity. This is often followed by a phase of stabilisation that is characterised by stable or slowly declining sales and cash flow. We typically acquire established brands that have already reached this sustainable phase and benefit from high brand loyalty. Our recent acquisition of Crestor™ from AstraZeneca is an example of this. We believe more opportunities like this will come along in the future.

As a fully integrated pharmaceutical company with long experience of established brands, we are able to enhance the performance of acquired products to create significant value for Grünenthal. We have dedicated teams to ensure fast and effective integration, and we use our commercial expertise to maximise the market value of established brands while also achieving synergies through our cost-efficient manufacturing.

What are Grünenthal's strengths that help it to pursue its path to success?

We have a unique track record in pain therapies, with nearly 50 years of experience in developing, manufacturing and commercialising innovative products. Our broad geographic presence and diverse product portfolio give us a solid financial profile – and limit our dependence on any specific product or region. On top of this, we have shown that we can adjust our operational costs to external challenges and maintain consistent business performance. Above all, our people have the capabilities, the mindset, and the passion for personal development that empower us to achieve outstanding business results.

We believe that success comes from close collaborations

World free of pain

Acquisitions of well-established brands

We also look for well-established brands with stable sales performance that can support funding for our R&D projects and secure our financial stability.

Partnerships in R&D

We are seeking R&D collaborations that focus on pain indications and have the potential to make a real difference to patients - independent of the modality and their stage of development.

Partnerships in new geographic areas

We seek partners to give patients access to our products in territories where we do not currently have our own presence.

2.3 | Business development and licensing

We believe collaboration is the key to developing life-changing treatments for patients. In this spirit, we actively seek partnerships with organisations that share our vision of a world free of pain. Over many decades, our experts have built strong networks by sharing knowledge and entering into trust-based collaborations – while always maintaining a clear focus on improving patients' lives together.

These partnerships extend beyond R&D. Our exceptional commercial capabilities make us a natural partner for businesses that want to bring projects to market successfully. In particular, we seek partners to give patients access to our products in territories where we do not currently have our own presence. This includes Canada, the Middle East, Africa, and Asia – especially Japan and China.

Alongside these partnerships, inorganic growth also plays a central role in driving progress towards our ambitious plans. We focus on acquiring product rights that are a good fit for our existing commercial footprint, and complement our infrastructure and regulatory expertise. We also look for well-established brands with stable sales performance that can generate an immediate boost for our profitability. We are exploring commercial growth opportunities in our core markets: Europe, Latin America and the US.

Since 2017, we have invested approximately €1.3 billion in acquisitions of established brands. As the latest step in this strategy, we acquired the European rights (excluding Spain and the UK) for Crestor™ and its associated brands from AstraZeneca in December 2020. This deal involves a total consideration of up to US$ 350 million, and gives Grünenthal the exclusive rights to market these brands in more than 30 European countries.

Crestor™ is a lipid-lowering agent. These medicines, commonly known as statins, are used to treat blood-lipid disorders and to prevent cardiovascular events like heart attacks and strokes. People who suffer from these conditions experience a serious negative impact on their life, and this acquisition empowers our company to offer them a truly life-changing solution.

In the coming years, this latest deal is expected to make a significant contribution to our profit. Crestor™ continues to generate impressive revenue, and achieved total sales worth US$ 136 million (€122 million) in 2019 within the countries where Grünenthal has now acquired the rights. On top of this, the deal involves another step towards ensuring optimal capacity utilisation for the long term. As of 2025, the product will be produced and packaged at our own manufacturing sites, adding nearly 12 million packages per year to our current volume and generating substantial cost reductions in production. We are convinced that this acquisition will further support our strategy of concluding deals that strengthen our financial performance and enable further investments into developing innovative treatments for pain patients.

3

Our Commitment to Pain

For 50 years, we have been making progress towards our vision of a world free of pain – with every research project we pursue and every medicine we deliver to patients in need.

3.1 | Our Commitment to Pain

Imagine a disease that affects up to two in five people in the world – which equates up to more than 3 billion individuals – as well as their families and friends. A disease that is one of the most common reasons for people seeking medical help, one of the major causes of people withdrawing from the labour market early, and a significant contributor to disability retirement. A disease that is associated with multiple different conditions, with no standard of care and for which patients frequently experience limited efficacy from the medicines that are available. This would be a significant disease that deserves our attention and that we should fight with all of our strength.

This disease exists. It is called chronic pain.

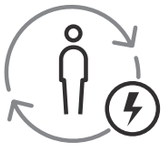
At Grünenthal, we consider pain to be a disease in its own right, rather than just a symptom. For the last 50 years, we have dedicated ourselves to delivering innovative treatment options for people affected by pain. We are now a global leader in pain research and management, after developing six important treatment options for pain patients. This success story began in the 1970s, with Tramadol™, which is now one of the most frequently prescribed central acting analgesics in the world. Another example is Tapentadol™, which was the first innovative molecule in the centrally acting analgesic class to be approved for more than 25 years. As the latest step, the FDA approved Qutenza™ for the treatment of pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults in 2020.

We know that patients are still hugely underserved in this therapeutic area. That is why we are determined to develop the next generation of pain medicines. Our R&D activities focus on four strategic indications that are characterised by a huge unmet medical need in large patient populations: peripheral neuropathic pain, chronic postoperative pain, chronic low back pain, and osteoarthritis. We strive to make a positive impact on patients' lives through our own research, as well as by drawing on external innovation, collaboration and networks.

Why pain matters

1 out of 5

patients suffer from chronic pain[2]



21%

of chronic pain patients in Europe suffer for more than 20 years[3]

78%

of chronic pain patients stated that they were not satisfied with the efficiency of the treatment they received[4]

60%

of permanent work incapacity in Europe is related to muscoskeletal pain alone[5]

560-635

billion US Dollar estimated costs in the United States caused by Pain (acute and chronic) every year[6]

[2] Based on data from 34 countries worldwide. (Elzahaf RA et al. CMRO 2012).
[3] Breivik, H. et al., Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment, European Journal of Pain 10 (2006) 287–333.
[4] Pain Alliance Europe, 2017, Survey on Chronic Pain 2017, Diagnosis, Treatment and Impact of Pain.
[5] Bevan, S. et al., Reducing Temporary Work Absence Through Early Intervention: The case of MSDs in the EU, 2013.
[6] U.S. Department of Health and Human Services (2019, May). Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. Retrieved from U. S. Department of Health and Human Services website: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html).

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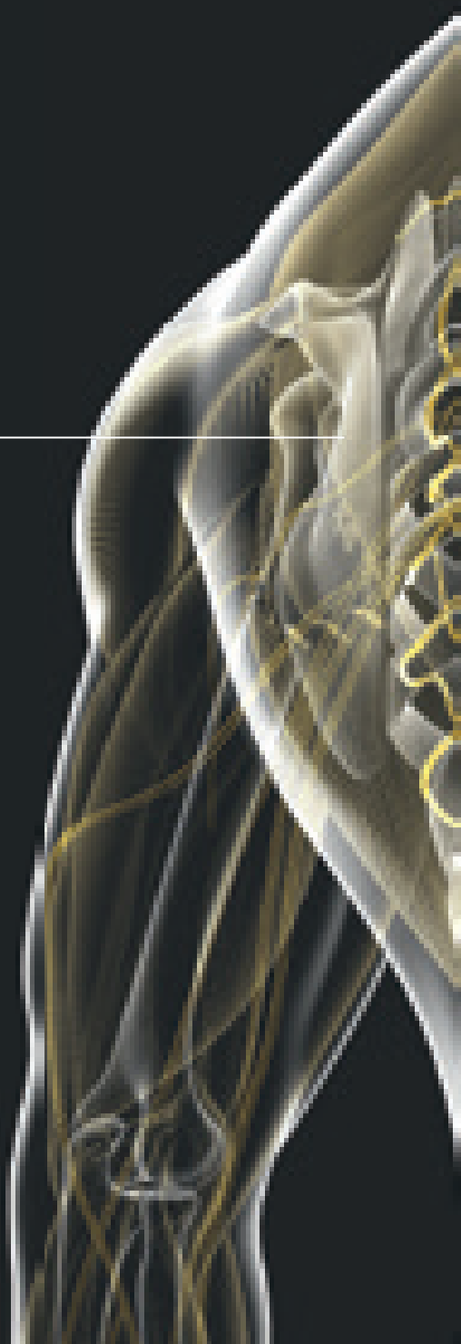
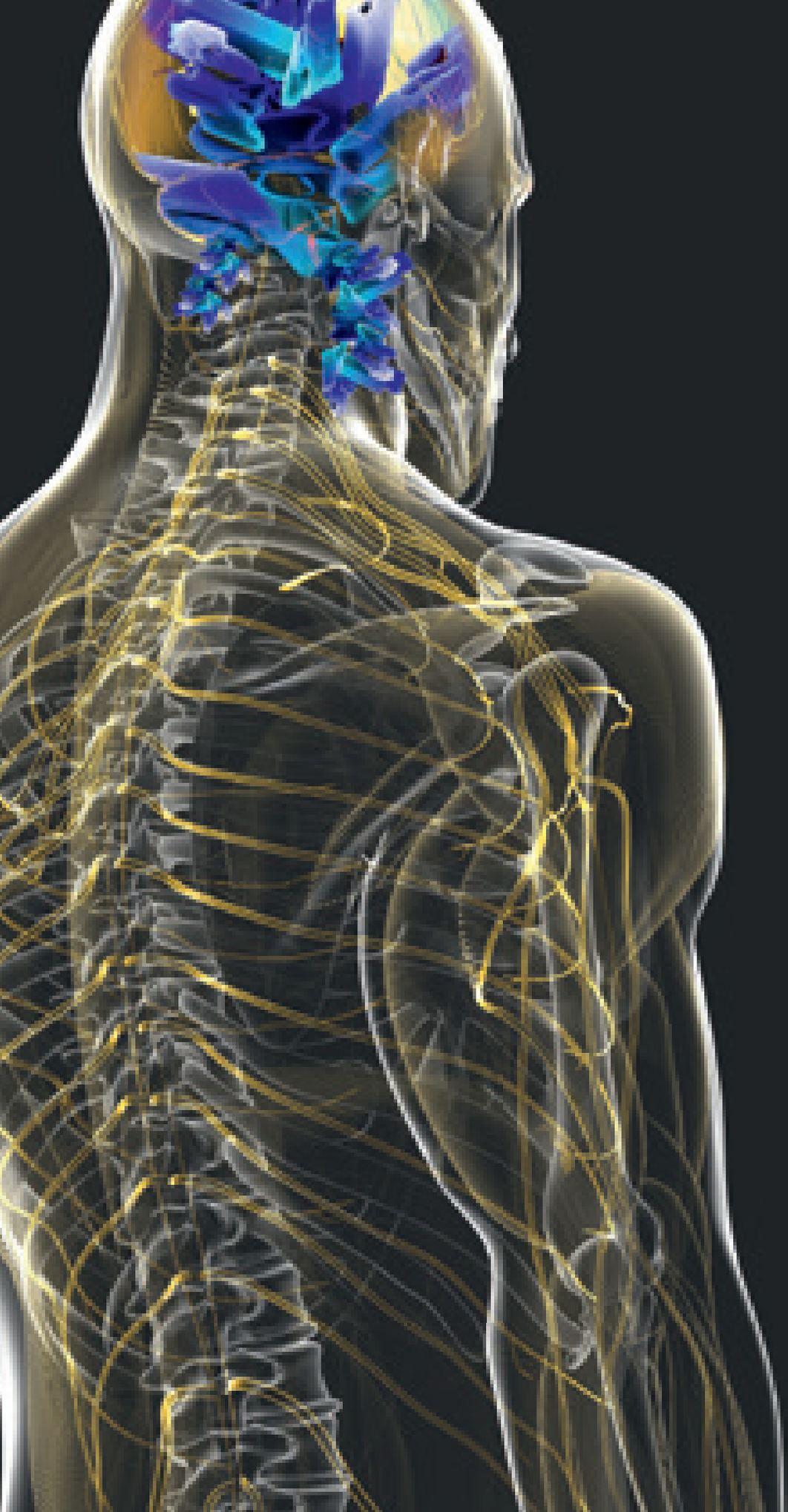
Research and Development





Jan Adams, MD,
Chief Scientific Officer

4.1 | Driving innovation in the therapeutic area of pain

The R&D organisation achieved remarkable milestones and progressed Grünenthal's development pipeline with continued strong momentum. After transforming the organisation in 2019, we started to see the benefits of our new operating model. We were able to make further significant progress in strengthening our pipeline of innovative pain therapies and executing on our priority projects.

The US FDA approval for Qutenza™ for the treatment of pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults marks a major milestone in our efforts to bring this non-systemic, non-opioid treatment to more patients around the world. Painful DPN is a progressive and debilitating complication of diabetes that affected more than 5 million Americans in 2020 and is challenging to diagnose, treat and manage effectively. Building on this achievement, we decided to embark on an additional Phase III programme to study the efficacy, safety and tolerability of Qutenza™ in post-surgical neuropathic pain (PSNP). We have enrolled the the first patients in a pivotal phase III trial in Q3 2021.

In April 2021, we acquired Mestex AG, a Swiss company that has developed the innovative investigational medicine RTX (resiniferatoxin) for the intra-articular treatment of pain associated with osteoarthritis of the knee. This acquisition has the potential to be a transformative step for Grünenthal. It strengthens our late-stage pipeline by adding a promising Phase III asset that has a well validated mechanism of action. It allows us to pursue a truly global development programme covering Europe, the US, Japan and China. And, it opens up a significant business opportunity.

We were also able to progress two proprietary compounds from pre-clinical to clinical development. This marks an important milestone in any development programme. With our peripheral NOP compound we are pursuing the development of a selective, peripherally-restricted oral treatment with a unique mechanism of action for chronic peripheral neuropathic pain. With our GRM compound we are striving for strong anti-inflammatory efficacy but without the treatment-limiting side effects of classical glucocorticoids.

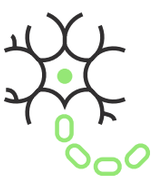
In our Research efforts we invigorated our focus on targets with strong human validation. As a result, we have complemented our Research portfolio with exciting ion channel projects while de-prioritising projects that currently lack sufficient validation.

The results of our partner Mesoblast's clinical Phase III trial MSB-DR003 showed a significant and long-lasting treatment effect of MPC-06-ID on pain relief, however, the trial did not achieve its primary outcome measure between the treatment groups. After having analysed the data obtained through this trial, Mesoblast anticipates to conduct another confirmatory trial in the US, and to design this trial to support potential parallel product approvals in both the US and Europe. With the further development of MPC-06-ID, we hope to bring this unique cell therapy for chronic low back pain to patients.

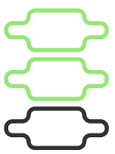
Alongside progressing our pipeline programmes, we continue to invest heavily in external innovation and collaboration activities and stay committed to striving for win-win partnerships with leading institutions around the world. We advance our capabilities across a wide range of scientific domains and deploy cutting edge technologies such as AI-based drug design or innovative translational models.

Looking back at a successful 2020 and 2021 so far, I am very much looking forward to continuing this exciting journey with our team of highly skilled and motivated Grünenthal colleagues as well as our exceptional external partners. Further advancing and adding to our three projects in Phase III and two projects in Phase I, we will continue to expand Grünenthal's disease area leadership in pain therapies and strive towards our vision of a world free of pain.

A Concise Therapeutic Area Strategy



Peripheral neuropathic pain

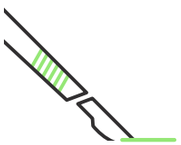


Chronic low back pain

Osteoarthritis

Chronic post-surgical pain

Substantial in-house research including target identification and validation linked to disease understanding. Projects in all phases from research up to clinical development are of potential interest.



Peri-surgical pain

Migraine

Fibromyalgia

CRPS

Focus on identifying and establishing collaborative partnerships for projects undergoing clinical development.

“Our research activities are characterised by a small and well-validated portfolio that we explore to create breakthrough medicines.”

Gillian Burgess,
Head of Research

4.2 | Our approach to pain research – Interview with Gillian Burgess

Gillian joined Grünenthal as Head of Research in April 2020. In this role, she leads our research activities – from target identification to the moment a project enters clinical development. We spoke to her about the challenges and opportunities in pain research, and how Grünenthal is addressing them.

What are your priorities for building Grünenthal’s research portfolio?

I want to make sure that we select the right targets to build a well-validated portfolio of pain targets. A high rate of attrition in clinical Phase II studies is extremely expensive and wastes resources – and, most importantly, does not serve patients. By selecting the right targets, our scientists can lay the foundation for a successful clinical Proof of Concept. Grünenthal’s research model gives us the opportunity to leverage a wide range of modalities to create the right candidates for painful conditions. To be successful it is really important that we build up a comprehensive understanding of the underlying pathological processes responsible for causing pain.

What is Grünenthal’s benchmark for a well-validated target?

Scientists in the pharmaceutical industry – and especially companies like Grünenthal that are dedicated to pain research – have learned that pre-clinical, behavioural models do not have sufficient predictive validity to serve as the basis for initiating a new project. For example, the expression profile of proteins varies between species and therefore their functionality may also be different. That is why we are now adopting models based on human tissues and cells.

In general terms, it is important that we understand the role of a target in pain processing. We also want to know if natural variation, such as genetic differences, in the target has functional consequences. As well for genetic evidence, we can also look for existing clinical evidence that modulating the activity or function of the target has an impact on the condition. A target that combines a real understanding of its function in pain processing with clinical and genetic evidence is obviously really promising. It is also very important that we consider the safety implications of modulating a target before selecting it for a research project.

How does Grünenthal’s Research team find this kind of evidence?

We use our expertise in bioinformatics to tap into the huge amount of omics-data that is now available and, along with our experience in systems biology, we try to turn that data into knowledge to inform our research activities. This is not something we can do alone, so we are building up strong partnerships with academic groups and other experts to mine this data and understand how different cells and tissues communicate with each other in painful conditions.

We are also investigating human cells such as nociceptive neurones, which help carry pain signals. By interrogating these neurones in a dish, alone and in combination with other relevant cell types, we can get close to understanding how they work in the human body. Of course, as I mentioned, collaboration is the key to effective research. We cannot know everything, have everything and do everything by ourselves. That is why we connect with the external scientific community to open up opportunities to move closer to our vision of a world free of pain.

4.3 | Developing tomorrow's therapies

In 2020, Grünenthal made remarkable progress in executing its research and development strategy and progressing its innovation pipeline. The hard work and determination of our teams resulted in a successful transition of two investigational medicines into clinical development. The first is a peripherally restricted Nociceptin/Orphanin FQ Peptide receptor (NOP) agonist, which is an oral investigational medicine with a unique mechanism of action for treating chronic peripheral neuropathic pain. The second is a Glucocorticoid Receptor Modulator (GRM), which is an oral investigational medicine with broad anti-inflammatory efficacy that offers a potential alternative to current glucocorticoid-based therapies like prednisolone because it may have a significantly improved safety profile.

The NOP agonist is a proprietary Grünenthal compound that was discovered as a result of the company's longstanding and extensive research into this G-protein coupled receptor class and is currently the most advanced compound within our broader R&D programme for NOP agonists. The selectivity of the investigational medicine for the NOP receptors, combined with its restriction to the peripheral nervous system, is predicted to confer analgesia with an improved safety profile compared to the current standards of care.

Pain Research at Grünenthal

1

Focused therapeutic area strategy

We focus our R&D efforts on four pain indications characterised by high unmet medical need

2

Comprehensive disease understanding

Deep understanding of the underlying human disease biology enables us to identify well validated, highly promising targets

3

Double down on most promising targets

We pursue targets holistically and leverage a wide range of modalities to minimise compound-specific risks and maximise probability of success

4

Teaming up

We collaborate with leading institutions around the world to tap into the best science and technologies wherever they exist

“The peripherally-restricted NOP agonist offers exciting potential to address significant unmet needs in treatment of chronic neuropathic pain conditions and is a significant step towards achieving our vision of a world free of pain.”

Eric Nisenbaum,
Project Lead

The Phase I trial will involve 76 healthy participants and aims to demonstrate favourable safety and tolerability, while also confirming the pharmacokinetic characteristics of the compound. The results of the study are expected in 2021. We estimate that our NOP agonist has the potential to have a positive impact on the lives of millions of people. One of the most prevalent indications, painful diabetic peripheral neuropathy (DPN), affects more than 10 million people across Europe, the US and Japan.

The clinical Phase I study for Grünenthal’s GRM includes, among others, a head-to-head comparison between the investigational medicine and prednisolone, which is one of the most commonly used glucocorticoids. The trial involves 80 healthy participants and aims to demonstrate favourable safety and tolerability, while also confirming the pharmacokinetic characteristics of the compound. By obtaining data from various biomarkers at an early stage of the clinical development process, our experts will be able to draw initial conclusions about the extent to which our investigational medicine can differentiate itself from prednisolone and if this investigational medicine might offer patients a therapy option that combines high efficacy with a significantly improved safety profile. The results of the study are expected in 2022.

4.4 | Providing medicines to patients in need

In 2020, Grünenthal received approval from the U.S. Food and Drug Administration (FDA) for Qutenza™ to be used for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. Before this landmark achievement, Qutenza™ was only indicated for the treatment of neuropathic pain associated with post-herpetic neuralgia in the United States.

DPN is also known as diabetic nerve pain. It is a progressive and debilitating complication of diabetes that affected more than 5 million Americans in 2020, with this number expected to double by 2030. Patients with this condition typically experience symptoms of numbness or tingling, as well as shooting or stabbing sensations that most often affect the lower extremities. It is extremely challenging to diagnose, treat and manage effectively, and has a significant negative impact on quality of life for many patients because they receive ineffective pain treatment or experience side effects from current treatment options.

I. How we are leveraging biomarkers in our Phase I study for Glucocorticoid Receptor Modulators (GRM)

Our Phase I study for GRM will observe several biomarkers to assess how our investigational medicine influences critical processes. In this way, we will gain insights into its potential to differentiate against typical glucocorticoids at an early stage. We are going to look at bone metabolism and glucose levels. Reduced bone formation may lead to osteoporosis, while increased glucose levels are increasing the risk of diabetes. These are among the most common side-effects of glucocorticoids – and are a key drawback of their long-term use for treatment.

II. About chronic neuropathic pain

Neuropathic pain is defined as pain that arises as a direct consequence of a lesion or disease that affects the somatosensory system, which is a complex system of sensory neurons and pathways that responds to changes at the surface or inside the body. Neuropathic pain can be caused by nerve injury or diseases that affect the peripheral or central nervous system. It is characterised by symptoms including shooting or burning pain, numbness or altered sensation. General population studies that use validated screening instruments have found that 7-10 percent of adults currently suffer from chronic pain with neuropathic characteristics. Despite the availability of various therapeutic options and guidelines, treatment remains a challenge.[7]

III. About the NOP receptor

The Nociceptin/Orphanin FQ (N/FQ) Peptide receptor (NOP), is a G protein-coupled receptor. Its natural ligand is the 17 amino acid neuropeptide known as nociceptin (N/OFQ). NOP agonists have been shown to suppress nocifensive responses in pre-clinical models of hypersensitivity. Although NOP shares high sequence identity (~60%) with classical opioid receptors μ-OP (MOP), κ-OP (KOP), and δ-OP (DOP), it possesses little or no affinity for opioid peptides or morphine-like compounds. Likewise, classical opioid receptors possess little affinity towards NOP's endogenous ligand nociceptin.[8]

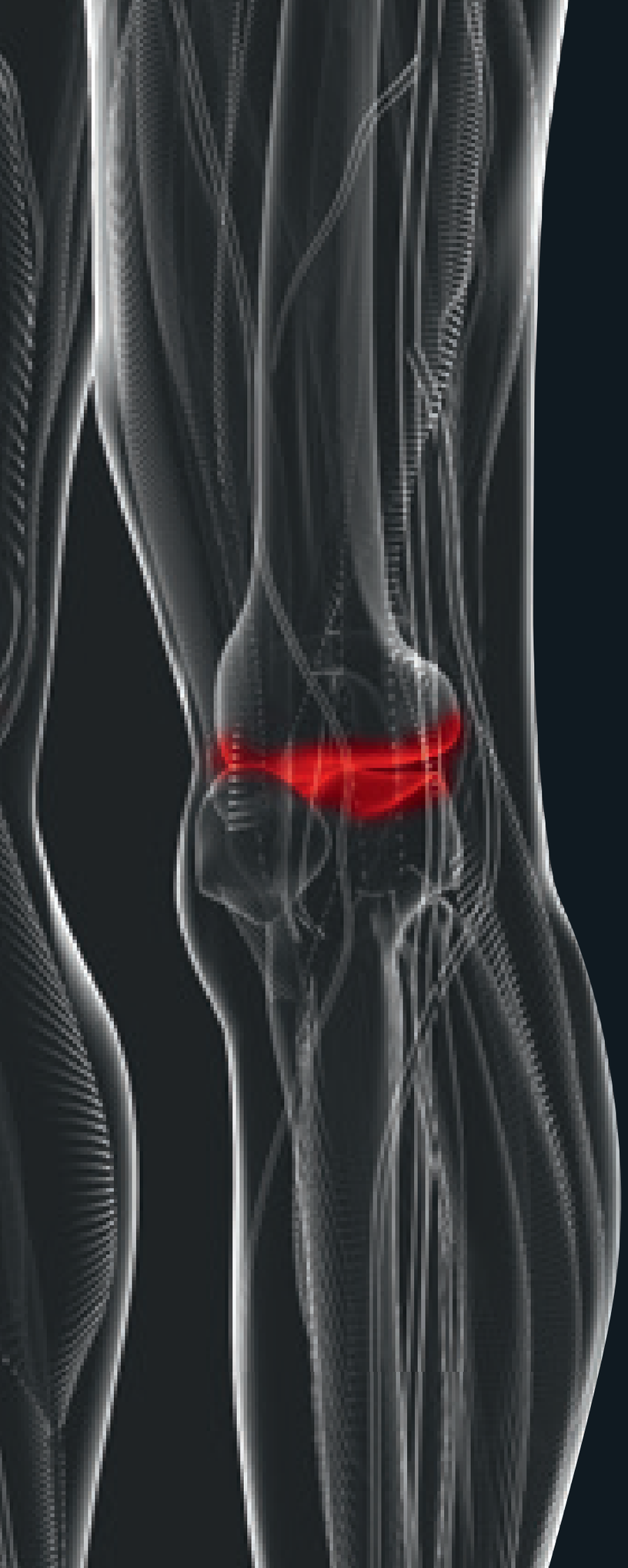
Florian Jakob,
Project Lead

"We are striving to increase patients' quality of life during long-term treatments with glucocorticoid-based therapies by developing a medicine that has the potential to offer high efficacy without the treatment-limiting side effects known of glucosteroids."

With Qutenza™, these patients now have access to a topical, non-systemic, non-opioid pain treatment for DPN. Its active ingredient, capsaicin, is a highly potent Transient Receptor Potential Vanilloid 1 (TRPV1) agonist. Its administration can reversibly defunctionalise TRPV1-expressing cutaneous nociceptors. This results in long lasting pain relief for up to three months.

Of course, our teams continue to work on making Qutenza™ more widely available in the US. Following the successful label extension for DPN, we enrolled the first patients into a Phase III trial to study the efficacy, safety and tolerability of Qutenza™ for post-surgical neuropathic pain (PSNP). The randomised, double-blind trial AV001 will involve up to 500 patients who have been suffering from moderate to severe PSNP for at least six months. It aims to demonstrate a significant reduction in the average pain intensity after 12 weeks and 42 weeks compared to the baseline. We expect to complete the trial in 2024.

[7] Colloca L et al. Nat Rev Dis Primers. 2017 Feb 16.
[8] Butour JL, Moisand C, Mazarguil H, Mollereau C, Meunier JC (February 1997). "Recognition and activation of the opioid receptor-like ORL 1 receptor by nociceptin, nociceptin analogs and opioids". European Journal of Pharmacology. 321 (1): 97–103. doi:10.1016/S0014-2999(96)00919-3. PMID 9083791.



4.5 | Our acquisition of Mestex AG

With Mestex AG and its asset MTX-071 (resiniferatoxin), which we will continue under the name RTX, we were able to add a well de-risked project to our portfolio that is absolutely in line with our therapeutic area strategy and that strengthens our late-stage pipeline with an innovative investigational medicine.

The asset and its development

Resiniferatoxin is a highly potent Transient Receptor Potential Vanilloid 1 (TRPV1) agonist. Its administration can reversibly defunctionalise TRPV1-expressing nociceptors. This can result in long-lasting pain relief. This mechanism of action is well validated by clinical studies with other TRPV1 agonists. It works in a similar way to capsaicin, the active ingredient of Qutenza™, however, resiniferatoxin is significantly more potent.

RTX is currently concluding Phase II of clinical development. Data shows a long-lasting and significant analgesic effect and functional improvements compared to placebo (saline injection), as well as a favourable safety profile. We are now preparing two pivotal Phase III studies to investigate the efficacy, safety and tolerability of RTX in patients with pain associated with osteoarthritis of the knee. The studies will start in 2021 and they are part of a global development programme aimed at meeting the requirements for approval in the EU, the US, Japan and China.

The unmet medical need

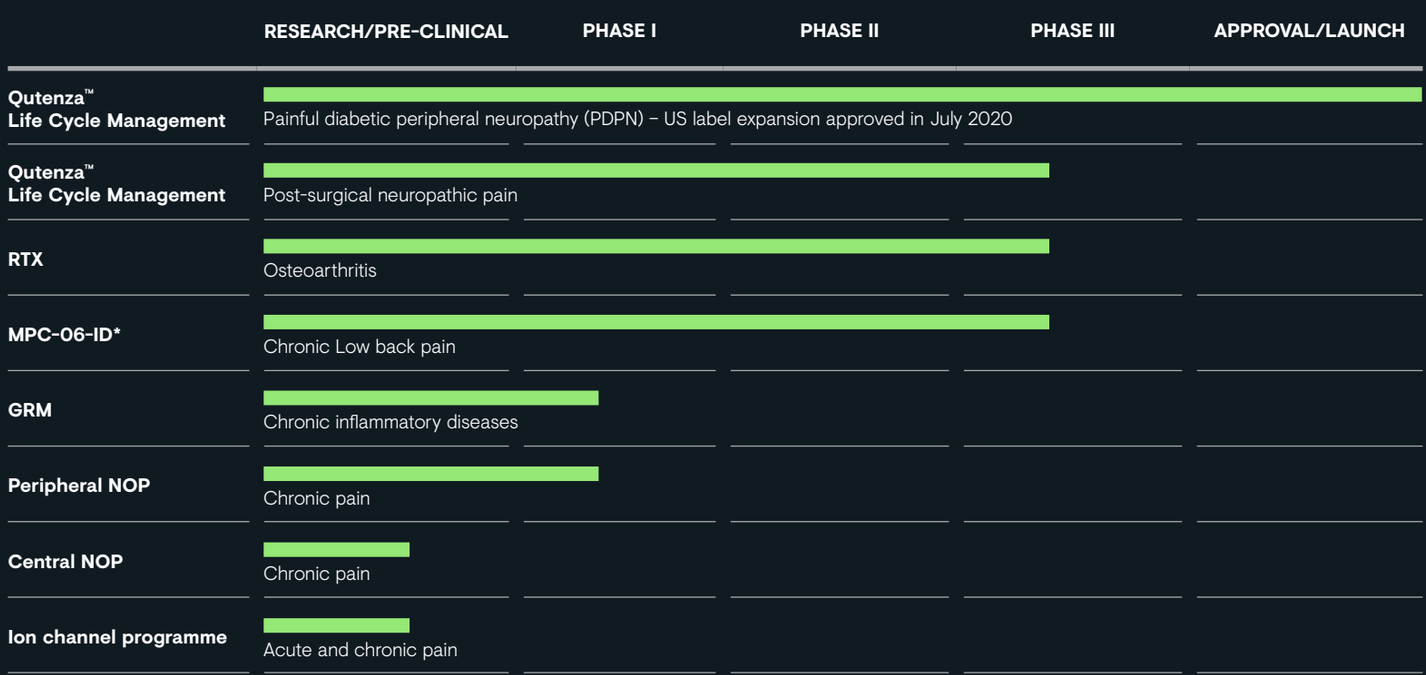
Osteoarthritis is a progressive condition that causes the tissue in the affected joint to break down over time – it mainly affects the hands, knees, hips, neck and lower back. Currently, there is no treatment option available that could slow, stop or reverse the progression of the disease. Today's osteoarthritis therapy focuses on successful and low-risk pain relief as well as improving patients' mobility and quality of life.

In the US and EU alone, over 50 million patients are affected by osteoarthritis of the knee. Many of those patients who experience severe pain associated with this condition receive intra-articular corticosteroids or need to undergo knee replacement surgery as their last remaining treatment option. With RTX, we aim to provide these patients with a well tolerable, non-opioid therapy option that provides long-lasting pain relief and functional improvement of the affected joints to contribute to improving their quality of life.

The business case

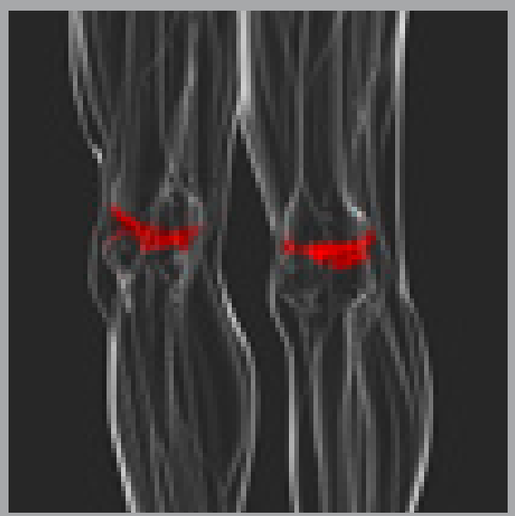
We have secured the global rights for an attractive late-stage osteoarthritis asset with potential global peak sales of more than €2 billion for the treatment of pain associated with knee osteoarthritis. Above and beyond this, RTX also provides significant additional opportunities – we are confident in the mechanism of action and will explore its potential for the treatment of osteoarthritis-related pain in additional joints beyond the knee. Overall, this asset puts us in a strong position to tap into the global osteoarthritis market.

Our R&D portfolio of promising assets with a focus on non-opioid treatments



* In partnership with Mesoblast

Our lead programmes



RTX (resiniferatoxin)

Osteoarthritis (OA) is a progressive condition that currently cannot be cured. The inflamed, swollen and painful joints lead to limitation on mobility of the affected patients and may impact their quality of life significantly. Millions of OA patients currently receive intra-articular corticosteroids or need to undergo knee replacement surgery as last remaining treatment option.

RTX (resiniferatoxin) is an investigational medicine for the intra-articular treatment of pain associated with OA of the knee. The highly potent TRPV1 agonist currently concludes Phase II of clinical development. Its mechanism of action is well validated and initial data shows a long-lasting and significant analgesic effect and functional improvements compared to placebo (saline injection), as well as a favourable safety profile.

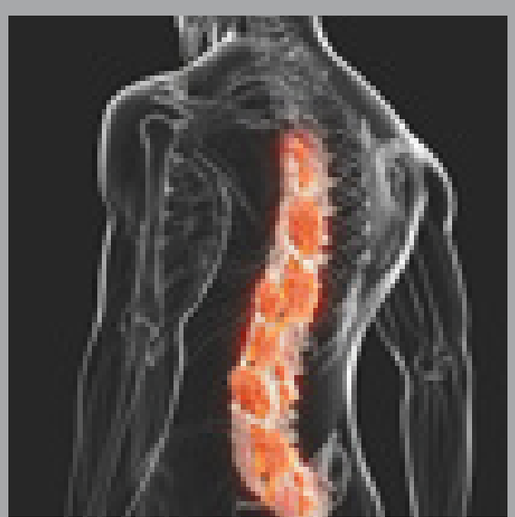
We are currently preparing two pivotal Phase III studies to investigate the efficacy, safety and tolerability of RTX in patients with pain associated with OA of the knee. The studies will start in 2021 and they are part of a global development programme aimed at meeting the requirements for approval in the EU, the US, Japan and China.

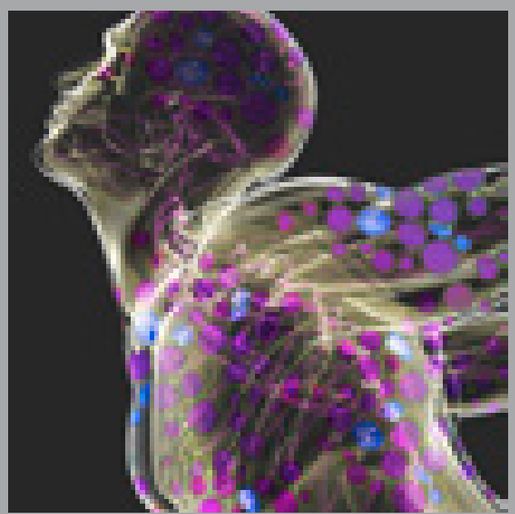
MPC-06-ID

In 2019, we have embarked on a partnership with Mesoblast to develop a highly innovative mesenchymal precursor cell therapy for patients with chronic low back pain associated with degenerative disc disease who have not found effective relief from available treatment options.

Early in 2021, Mesoblast published results from the ongoing Phase III trial MSB-DR003 that was carried out in the US and Australia. The trial provided a number of important findings, including a significant and long-lasting treatment effect on pain relief. However, it did not achieve its primary outcome measure between the treatment groups.

After having analysed the data obtained through this trial, Mesoblast anticipates to conduct another confirmatory trial in the US, and to design this trial to support potential parallel product approvals in both the US and Europe.





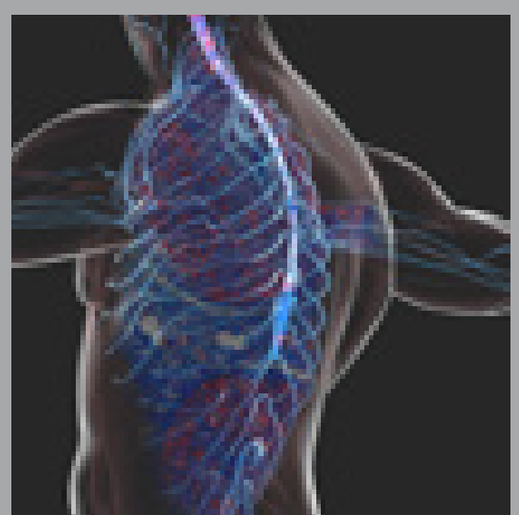
Qutenza™ Life Cycle Management

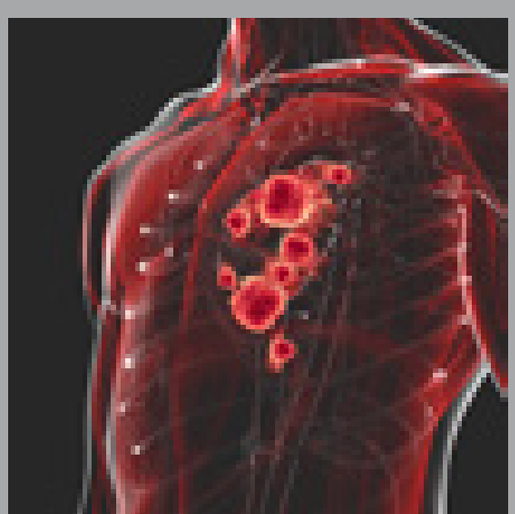
Qutenza™ is a patch containing prescription-strength capsaicin. In Europe, it is approved for the treatment of peripheral neuropathic pain. In the US, it is approved for the treatment of neuropathic pain associated with post-herpetic neuralgia, and in 2020 it also received approval for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults.

Our life-cycle management efforts focus on making Qutenza™ more widely available by expanding the label further, particularly in the United States. Specifically, we have started a pivotal Phase III study in post-surgical neuropathic pain. We are also pursuing selected further exploratory activities in other indications with external partners.

Nociceptin/Orphanin FQ receptor Peptide agonist (NOP)

Although several different treatment options are available, many patients with neuropathic pain still suffer from treatment non-response or insufficient pain relief. With our NOP programme, we are pursuing the development of a selective, peripherally-restricted oral treatment with a unique mechanism of action for chronic peripheral neuropathic pain that offers a more favourable safety profile than current therapies. This programme is based on our many years of intense and ground-breaking research in the field of NOP receptors, and opens up a unique opportunity for a transformative first-in-class treatment. The most advanced compound within our NOP programme entered clinical development in late 2020.





Glucocorticoid Receptor Modulator (GRM)

Glucocorticoids, such as prednisolone, are known to be highly effective anti-inflammatory drugs. However, they come with several significant side effects, including reduced bone formation that may lead to osteoporosis, as well as increased glucose levels, which raises the risk of diabetes. These side effects are a strong limitation for the long-term use of glucocorticoids, despite their efficacy. With our GRM programme, we are pursuing the development of clinical candidates for oral treatment with broad anti-inflammatory efficacy and the potential of significantly reduced side effects when compared to available glucocorticoid-based therapies. The most advanced compound within our GRM programme entered clinical development in early 2021.

5

People and Culture

5.1 | Our vibrant, high-performance culture

At Grünenthal, our company's identity is shaped by a high-performance culture. We grow and transform our business while boosting innovation.

Driving performance is one of our core values. Individual targets are closely aligned with our company strategy and our progress throughout the year is presented transparently. This motivates employees to make a real impact on our shared success.

Our people are guided by Grünenthal's Values & Behaviours. In this spirit, we assess our employees' performance not only in terms of what they have achieved, but also how they made that achievement possible. In addition, we make sure outstanding results are recognised and rewarded. For example, we celebrate exceptional contributions each year with our Grünenthal Global Excellence Award.

As part of our commitment to supporting progress for our company and each individual employee, we are strengthening our emphasis on continuous and actionable feedback. Regular employee surveys help us to gain a clear picture of the progress we have made in evolving our culture. Surveys conducted in 2020 show significant improvements in providing clarity and supporting personal development, appreciation and collaboration.

Employees by function December 2020

305
R&D

1,834
Global Commercial

578
Corporate Functions

1,827
Global Operations

4,553
Total

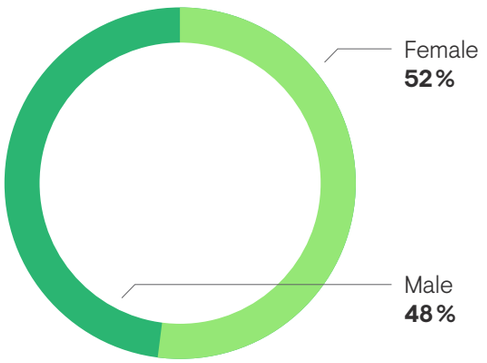
Nationalities and Countries

58
nationalities join forces in

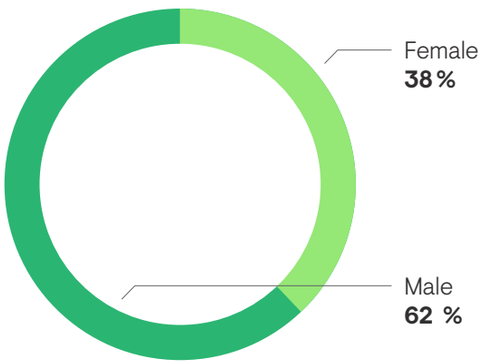
29
different countries.

Percentage of female / male employees

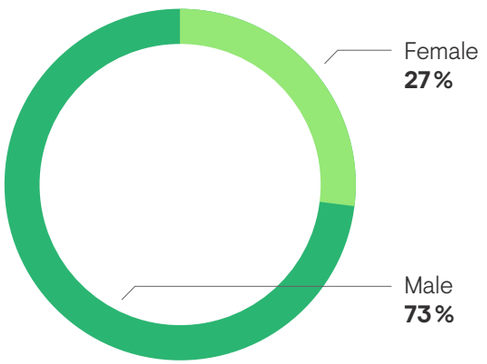
All employees



Employees in leadership roles



Executive level



Highlights from 2020

440

talented people joined our company worldwide in 2020, including 110 new colleagues in Germany.

23

percent of our talents moved into a new role at Grünenthal.

50

percent of our senior leadership vacancies were filled by internal talents and successors.

“At Grünenthal, we create an environment where people can thrive in rich and varied roles, join forces and have a real impact on our shared success.”

Leen Hofkens,
Head Global Human Resources

In 2020, we continued to strengthen our succession pipeline for critical roles at Grünenthal. We achieved a good balance between growing internal talent and attracting external candidates. Looking ahead, we will maintain our focus on providing opportunities for growth, whether within the role, advancing into a new role or taking a lateral move across functions. To fuel our succession pipeline for the long-term, we also bring in young talents and support their personal growth by offering them a broad range of experiences.

Our senior leaders and managers are expected to regularly spend time supporting the development of their employees based on individual development plans. We focus on on-the-job learning, combined with training and learning from others. Our employee surveys indicate that we are making solid progress in this regard.

5.2 | Developing our people and strengthening the diversity of our workforce

Our continuous focus on attracting, developing and retaining a talented and diverse workforce is a key factor in achieving our strategic priorities and building important capabilities for our future.

5.3 | Maintaining high levels of employee engagement

We make sure all of our employees embrace our company’s strategy. Despite the Covid-19 pandemic and the remote working environment, we created frequent touchpoints and gathered direct feedback from our employees – both on

85 %
response rate

Trust Index

Europe	75 %	+1 %
Latin America	78 %	+1 %
Headquarters	70 %	+14 %
Global	**76 %**	Since 2017 **+8 %**

Grünenthal is a great place to work

Europe	82 %	+4 %
Latin America	83 %	+1 %
Headquarters	76 %	+23 %
Global	**81 %**	Since 2017 **+9 %**

a local and on a global level. We offer all employees a range of opportunities to engage in dialogue with our management. We adapted many of these platforms to virtual formats in 2020.

In addition, we use employee satisfaction surveys and leadership feedback surveys to measure employee engagement. These surveys allow us to evaluate the progress we have made on our cultural journey. In 2020, more than 3,600 employees provided feedback during the Great Place to Work® (GPtW) survey, which is a strong indication of their commitment to shaping our company's culture. Furthermore, we conducted our second 180-degree leadership feedback survey.

The results of the Great Place to Work® survey in 2020 were very encouraging. A large majority of participants stated that Grünenthal is a "great place to work", and we achieved our highest ever score since we started conducting these surveys in 2009. The results showed that we have made significant progress since our last survey in 2017. This is reflected in the "Trust Index", which is a key indicator that states how employees evaluate the company's management. Our scores improved in every dimension and every region compared to 2017. The most progress was made at our headquarters.

In recognition of these results, we are now officially certified as a Great Place to Work® in all of the countries where we took part in the certification process. These results also confirmed the encouraging results of the Grünenthal 180° Pulse Checks that we conducted in 2019 and 2020. In these surveys, two-thirds of our employees gave feedback about how leaders are managing performance and development.

We are proud of the progress that our company has made on its cultural journey over the past few years. Moving forward, we will continue to strengthen our activities to maintain a high level of engagement, while also working on several areas for further development. In this spirit, we will join forces to strengthen our unique culture: "We are Grünenthal".

Employees confirmed that the management has a clear view of where the organisation is going and how to get there

GPtW

2020 75 %
(+13 % since 2017)

Grünenthal 180° Pulse Check

The great majority stated that priorities are clear **(92%)** and that their manager keeps the team focused on priorities and results **(88%)**

We have made great progress in supporting personal development

GPtW

2020 65 %
(+16 % since 2017)

Grünenthal 180° Pulse Check

Managers actively support employees in their development and provide helpful feedback **(79%)**

In GPtW, we saw improvements in all aspects related to collaboration compared to 2017

GPtW

2020 78 %
(+8 % since 2017)

Grünenthal 180° Pulse Check

Employees confirm that managers actively encourage cross-functional collaboration **(87%)**

5.4 | Management during Covid-19 outbreak perceived positively

As part of the Great Place to Work® survey, we asked our employees to provide feedback about our management of the Covid-19 outbreak. A large majority of our employees stated that they felt well informed, were able to carry out their work at a high level of quality, and felt supported by their line manager.

91 %

feel **well informed**

84 %

are **able to carry out their work** with a quality and scope comparable to that before this outbreak

85 %

say their **direct supervisor supports the team** and actively maintains contact

5.5 | What makes Grünenthal a great place to work

Working at Grünenthal means working in a mid-sized, science-driven company that is on a journey. Our employees work in rich and varied roles, and they join forces across our teams, functions and international locations. They work hard, challenge and support each other, and seek opportunities to learn while demonstrating integrity in everything they do.

Our company's culture reflects our firm belief that it takes a team to truly change lives for the better. Every employee at Grünenthal plays an important role in helping to achieve our common goals. As a result, people in our teams directly experience the impact they have on the lives of patients and on Grünenthal's overall results.

On top of this, Grünenthal's leaders passionately encourage our employees to innovate in every possible way – whether they are building our pipeline by focusing on our strategic indications and the latest science, challenging the status quo, improving our processes or implementing new ideas to drive performance along the value chain. Our company is a global leader in pain management and we have a long-term outlook, while also seizing new opportunities quickly.

Daily work at Grünenthal is guided by our Values & Behaviours. Our company's vision of a world free of pain gives us a clear focus and differentiates us from other companies. Together, we share a deep sense of pride in what we do.

We are patient-centric
We live entrepreneurship
We join forces
We act with integrity
We drive performance

Join forces. Make an impact.
Innovate for a world free of pain

Proud to work for a world free of pain – People at Grünenthal

Ralf Radermacher

Ralf Radermacher
Head of Corporate Development & Licensing in Aachen, Germany

My career at Grünenthal has been an international adventure – and it stretches back for almost 40 years. I joined the company as an apprentice in 1984. Next, I got a job in market research, which was still very focused on the German market at that time. After a couple of years, I got a new role with a strong focus on Japan. My next role focused on the US. And I have spent a lot of time in Latin America. These experiences earned me a chance to support the internationalisation of our market research department. After a while, I decided to focus my career on Business Development and Licensing.

From the very beginning, Grünenthal was incredibly supportive of my personal and professional growth. From improving my foreign language skills through to attending a variety of specialized training courses, I have always been encouraged to continue to broaden my knowledge base. Grünenthal is an independent company and we are smaller than some of the giants in our industry – and that is what I love most about working here. There is a culture of stepping up, being bold and getting things done. We never back down from a challenge.

João Simões

João Simões
General Manager at our affiliate in Madrid, Spain

Put simply, working at Grünenthal has transformed me as a person. Since 2004, when I got a job as a controller in Portugal, I have had the opportunity to work in different departments, different regions and different cultures. Among other great experiences, I was responsible for the integration of Andromaco, an acquisition that involved joining together two organisations with very different cultures. I also had the task of managing our Spanish business through the Covid-19 pandemic, which required me to think quickly and promote an unbelievable team spirit together with the local leadership team.

My development has been turbo-charged by the diversity of my projects and assignments. Grünenthal has also supported my training and education, whether at top universities or through on-the-job coaching. This is a place where people are empowered to try new things. You can make a real impact on the company – and the company will make an impact on you. Today, I see the world through different eyes. And I cannot wait to see where my career will take me next.

Marion François-Brazier
Global Commercial Lead RTX in Aachen, Germany

After spending six years as a consultant, I wanted to join a mid-sized company with a mission that I could really get passionate about – and where I could make a meaningful impact. Grünenthal fits that description perfectly. Even during my interview, I was so inspired by the people I met. It was clear that the team here was committed to the company's vision and empowered to make things happen. I could not wait to get started. My first role was in the Strategy department, where I started in September 2018. I moved into the Commercial area two years later, first as Regional Sales Manager in our German Sales Division, leading a team of 10 sales representatives, which gave me the opportunity to interact closely with our customers and bring our strategy to life in the field. I then recently became Global Commercial Lead for RTX (resiniferatoxin), our recently acquired late-stage R&D asset. I have learned a lot by collaborating with other teams and interacting directly with our senior leaders. Every day, my job pushes me to get better. And I still feel inspired about the positive impact that I can make on patients' lives.

Marion François-Brazier

Clint Young
Pharmacology, Biology & Translation Expert at our Innovation Hub in Boston, USA

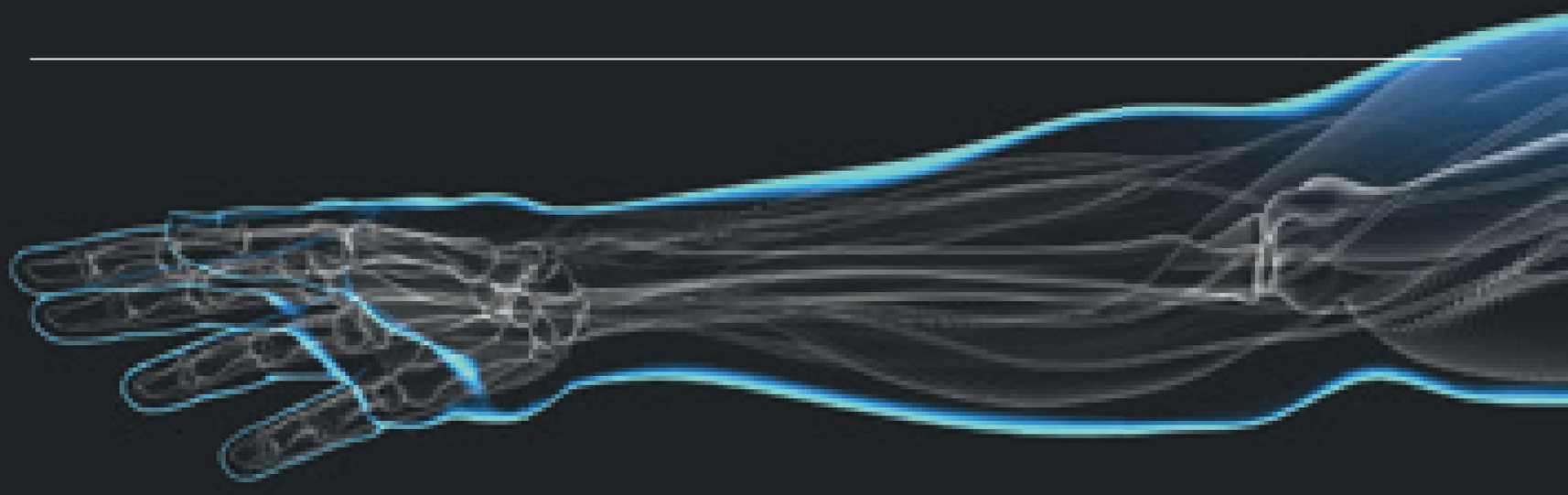
My father suffered debilitating back pain after a workplace accident, and my mother has very painful rheumatoid arthritis in her hands. That is why joining a world leader for pain management was a big emotional decision, as well as an important professional step. Since January 2020, I have been using my 15 years of industry experience to support the development of life-changing treatments at Grünenthal's Innovation Hub in Boston.

As a scientist, I think an R&D company needs two key attributes. First, it needs to create a competitive advantage through innovation. Second, it needs to do it quickly. Grünenthal ticks both of these boxes. In my daily work, I collaborate with leading experts and cutting-edge biotech startups to deepen our understanding of pain. I am encouraged to point out any obstacles – and to find ways of moving past them. There is a true culture of scientific spirit here. I feel free to explore. And I know I have a real chance to make a positive impact on the lives of people living with pain.

Clint Young

6

Markets and Products



"In our 75-year history, Grünenthal has made great strides towards its vision of a world free of pain – by delivering six pain therapy options to patients. We will keep striving to improve pain management and change the lives of patients around the world for the better."

Mark Fladrich,
Chief Commercial Officer

6.1 | Adapting to unprecedented challenges

Our field teams across Europe, Latin America and the US are driven by a commitment to delivering our innovative product portfolio to more patients in need. We serve a diverse customer base of approximately 247,000 customers – including physicians, pharmacies, hospitals, buying groups, wholesalers and institutions. Our products are available in around 100 countries, either directly from our 29 affiliates or indirectly from our strategic partners. In 2020, the pandemic required us to be more flexible and creative than ever. We adapted our ways of working, and continued to expand our market presence and our product portfolio. This included a significant and important shift to engage with our customers via digital channels. We also continued to build our network of commercial partners in countries where we do not have our own local footprint. Guided by our principles of patient-centricity, integrity, transparency and working in line with the highest ethical standards, our people conducted business responsibly and kept striving to further expand our positive impact on patients and society.

Digital tools played a key role in our collaboration with our customers from across the healthcare sector in 2020, and we made significant progress in advancing our digital transformation. We are building a customer-centric, omnichannel model to deliver useful content about our brands to customers through a variety of channels – guided by our focus on ensuring responsible and appropriate use of our products. We also updated and expanded the content on our CHANGE PAIN™ website to support patients and professionals during this difficult time, and published a Digital Pain Toolkit to support independent pain management for the many patients who were unable to get regular access to their physicians during 2020.

In response to the Covid-19 outbreak and the virtualisation of most of our interactions, we prioritised digitalising both how we engage with our customers as well as our internal processes like brand planning. We also supported our teams in building new skills that enable them to achieve their objectives. For our patients and HCPs, we are proud that we provided added value above and beyond brand and pain disease information. For example we

created specific content about the impact that Covid-19 may have on migraine patients to provide additional support during the challenging time of the pandemic, where contact between healthcare professionals and patients was often limited.

In July 2020, our Qutenza™ brand received the FDA approval for a significant label expansion in the USA. The new label now includes an indication for the treatment of adults with neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet, the largest neuropathic pain indication in the US. When we acquired the rights for Qutenza™ in the US from Accorda in 2018, the brand was only approved for post-herpetic neuralgia (PHN), which is a orphan indication, and only one of the many subtypes of neuropathic pain for which a product like Qutenza™ can potentially bring benefits. With the submission and successful approval of our supplemental new drug application, we demonstrated our commitment to reducing pain in the world and increased the number of patients that potentially benefit from this product in the US from 60,000 patients to approximately 1.2 million. Deep cross-functional experience in drug development, registration and market access played a key role in our successful label expansion. A specialist go-to-market model from our subsidiary, Averitas Pharma, played a particularly important role in the launch process that occurred following approval. Our Key Account team also used a customised approach that leveraged digital tools to provide HCPs and patients with information about managing pain and how to navigate insurance coverage in the US. We have received reports from a number of patients who experienced improvements in their painful symptoms of DPN, some after many years of unresolved pain. Due to our ability to bring clinical benefit to patients in pain, sales of Qutenza™ rose significantly in the last quarter of 2020.

Another key milestone in 2020 was our acquisition of the European rights (excluding Spain and the UK) for Crestor™ and its associated brands from AstraZeneca. This is a lipid-lowering agent, commonly known as a statin, that is used to treat blood-lipid disorders and prevent cardiovascular events.

Big plans for the future

Looking ahead, our key focus areas for 2021 include continuing to provide a great customer experience across all channels and using our omnichannel engagement model across all of our brands. This will also cover our established brands, including Nexium™ and Vimovo™, which we are integrating into our portfolio.

The Palexia™ team will continue their efforts to further differentiate the brand for use in patients with severe chronic pain in cases where the patient's doctor has decided that an opioid is necessary. Our commitment to the responsible use of opioid-based medicines is clear – we always ensure adherence to the highest ethical standards and compliance with our Code of Conduct, Opioid Charter and communication guidelines at all times, regardless of the geography or channel used to engage with our customers. For Qutenza™, we will continue to communicate on the benefits of repeated application globally, and continue to expand our presence in the US by leveraging our focused commercial strategy. We will also pilot a new digital health tool for Qutenza™ that will enable the health care professional team providing the treatment to track a patient's response to their treatment, including the possibility to track

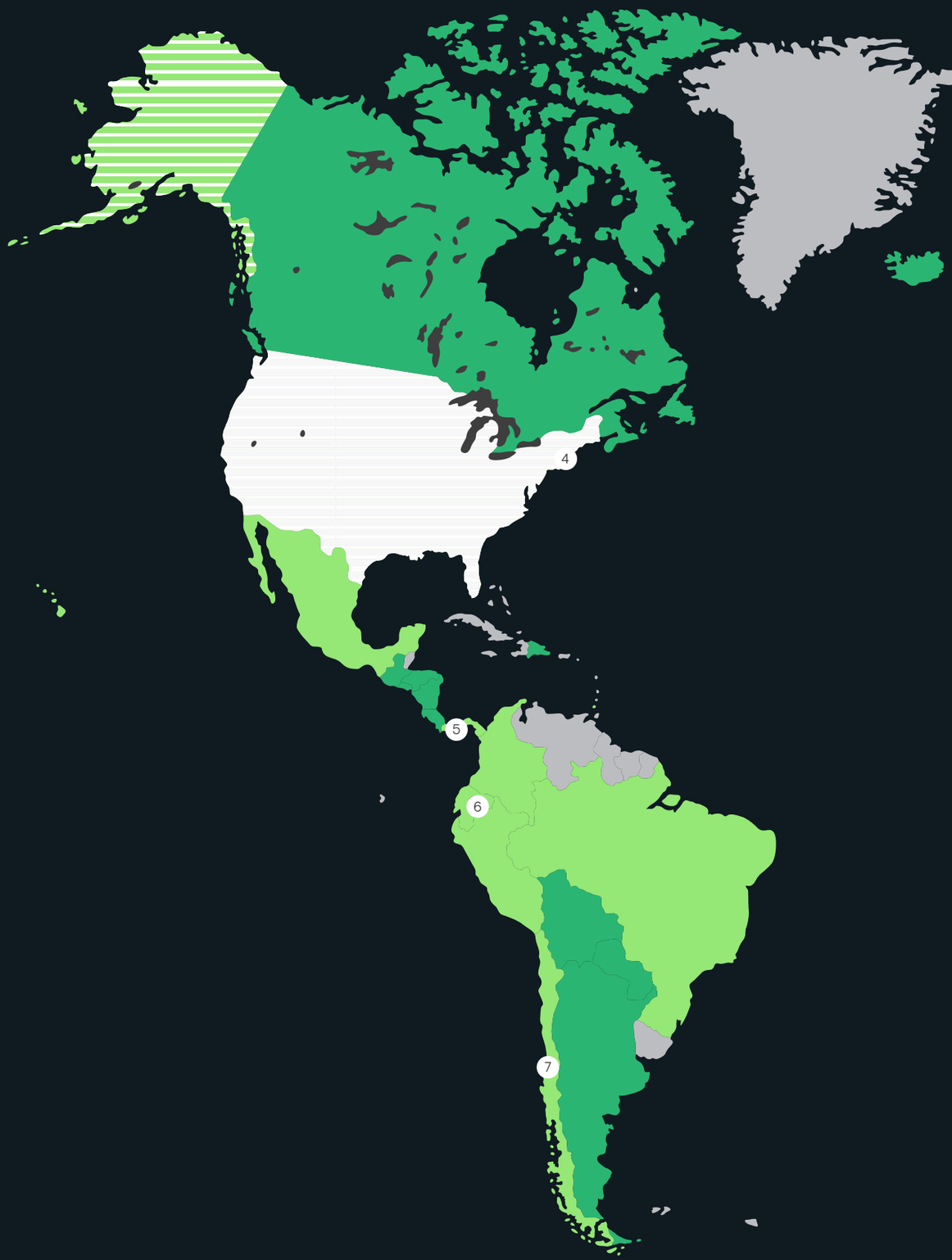
"The acquisition of Crestor™ was a key milestone in our strategy of strengthening and complementing our existing portfolio with well-established brands."

Mark Fladrich,
Chief Commercial Officer

Market Presence – The Grünenthal World

- Grünenthal affiliates
- Grünenthal US Holding
- Partner countries
- Other countries
- R&D unit
- Production
- Regional Office
- Innovation Hub

1. Aachen, DE, Headquarters
2. Mitlödi, CH
3. Milan, IT
4. Boston, US
5. Panama
6. Quito, EC
7. Santiago de Chile, CL

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the size of the painful area and any changes over time. We enrolled the first patients in a Phase III trial for post-surgical neuropathic pain that aims to further expand the label in the US and enable us to offer Qutenza™ to additional patients in need. For Vimovo™, we are striving to communicate the value of gastroprotection with this product for at-risk patients with a new campaign. We are also expanding our full omnichannel approach, especially in priority markets like Germany, Spain, Ireland and Switzerland while also building partnerships in Canada, Central and Eastern Europe, and Asia.

2021 also marks our company's 75-year anniversary. As we celebrate this important milestone, we are proud to reflect on our long track record of improving the lives of patients suffering from pain – and are excited about a future where we are able to develop and deliver new life-changing treatments for even more people around the world.

6.2 | Maintaining our growth momentum

In 2020, Grünenthal made progress on all levels of its portfolio and commercial platform. With regard to acquisitions, Grünenthal continued to execute its strategy of concluding profit-accretive deals that strengthen its financial performance and, coupled with the contribution to growth driven by its commercial teams across Europe, LATAM, in the USA and with our partners, enable continuous investments in research and development. Since 2017, our company has invested approximately €1.3 billion in acquisitions of established brands to strengthen its product portfolio. The latest acquisition was finalised in December 2020, when we agreed to take over the European rights (excluding Spain and the UK) for Crestor™ (rosuvastatin) and its associated brands from AstraZeneca. This deal gives Grünenthal the exclusive rights to market these brands in more than 30 European countries. By acquiring Crestor™, a lipid-lowering agent (commonly known as a statin), our company is now able to offer yet another solution for patients. Crestor™ is used to treat dyslipidaemia and hypercholesterolaemia, as well as to prevent cardiovascular events like heart attacks and strokes.

Alongside expanding our portfolio with additional brands, we also continued to work hard every day to bring the brands within our current portfolio to all patients who can benefit from them, while also supporting our customers to give them the best and most suitable options to treat their patients.

Our portfolio includes nine global brands, three of which are at an early stage in their life cycle, with continued growth in physician demand for these medicines. Palexia™, Qutenza™ and Vimovo™ have dedicated teams to gather deep customer insights and best tailor communication to meet customer needs. For these "growth" brands, we also continue to invest in novel life cycle management opportunities such as patient support programmes, additional strengths or formulations as well as investing in manufacturing infrastructure. We put a special focus on managing our established brands differently. Specifically, we were able to achieve sales of €283 million for Palexia™, which is a 12-percent increase compared to 2019. Qutenza™ has tremendous potential to change the way peripheral neuropathic pain is treated due to its novel mechanism of action, and investments in life cycle management globally are key to long term success, including the label expansion in the USA, the investment in the PSNP study, and the focus on account management as a key to building the specialty pain capability inside Grunenthal. We also launched an award-winning campaign called 'It is a Matter of Perspective' for our Qutenza™ brand and signed a deal with 360Medlink Inc, a pioneer in digital health and digital therapeutics, to collaborate on developing a Qutenza™ digital tool for HCPs to support better patient outcomes.

Our Vimovo™ team launched a new global campaign in our core European markets, and completed the integration and transfer of marketing authorisation in a number of European countries including Austria, Belgium, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Switzerland and the UK. The integration of all remaining markets will follow in 2021.

Grünenthal in the US

The remaining six global brands are what we call “established brands”. These brands are late in the life cycle, and already face generic competition or other market pressures to limit growth in demand. This year, we have updated our approach to these brands by putting in place increased cross-business transparency for the way they are managed, and by ensuring that we can spot selective opportunities to increase demand or reduce costs. For Versatis™, we conducted digital promotion to a select group of physicians in France to communicate the benefits of this product.

The integration of Nexium™ and Zomig™ also reached significant milestones. For Nexium™, the integration into our affiliate markets is complete and the brand’s sales in 2020 exceeded our expectations. For Zomig™, we initiated plans to take over the production of the nasal spray and launch additional formulations in two of our European affiliate countries. We also finalised a digital tool for diagnosing migraine that will support our digital activities and contribute to ensuring better management of migraine patients.

Throughout 2021, we will continue to collaborate across functions, and with our colleagues and partners around the globe, to serve patients in need and change their lives for the better. We are proud of the dedication, customer-centricity and patient-focus that enabled our achievements in 2020. Now, we are in a strong position to seize exciting opportunities and drive further progress towards our vision of a world free of pain.

Jeannie Lloyds,
Vice President Sales and Market Access, Averitas Pharma

“The DPN label expansion gave us an incredible boost and I am proud of how our team has overcome challenges related to Covid-19. Together, we have written the latest chapter in the Qutenza™ success story.”

6.3.1 | Serving patients in need – A strong start for our US business

Jeannie Lloyds, Vice President Sales and Market Access at Averitas Pharma, and Marv Kelly, General Manager Grünenthal US, share their experiences of the impressive growth that our business achieved in the US during 2020.

With its specialty pharmaceutical business called Averitas Pharma, Grünenthal is aiming to establish itself in the US market by serving patients in need by delivering innovative, effective, non-opioid pain management options – and by

“Our team did an outstanding job to enable the label extension in DPN, launch the product and serve patients in need. I look forward to continuing this dynamic growth journey.”

Marv Kelly,
General Manager, Grünenthal US

“Doctors and patients are excited about the opportunities provided by Qutenza™. I am proud of the positive impact that we have on the lives of patients every day.”

Daryl Tan,
Key Account Manager, Averitas Pharma Inc.

seizing opportunities for its Qutenza™ (capsaicin) 8% topical system brand. Initially, Qutenza™ was only indicated for treating neuropathic pain associated with post herpetic neuralgia in the US. In July 2020, the US Food & Drug Administration (FDA) approved Qutenza™ for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. This success marked a key milestone in the implementation of our company’s strategy and opens up powerful potential to drive growth for our US business.

In the first month following the label extension, we effectively ramped-up a field team of 30 specialist key account managers (“KAMs”) over 30 strategically defined US regions and further expanded the specialty distributors network. The label expansion, along with focused commercial efforts, drove the sales up by 328% compared to the final quarter of 2019. Utilisation of Qutenza™ patches among patients increased by approximately 375% since July, exceeding our launch plan despite challenges presented by Covid-19.

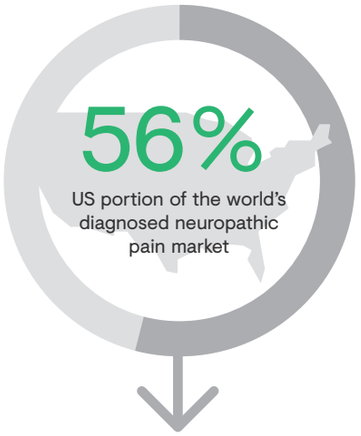
Most importantly, patients now have access to a much-needed non-systemic, non-opioid treatment option. Our team interacts with healthcare providers every day to identify more patients in need. On top of this, patients have given us incredibly valuable feedback about

the efficacy of Qutenza™ and how treatment with this product is changing their lives for the better.

Our US team is now striving to help even more patients with painful diabetic peripheral neuropathy and post herpetic neuralgia by taking advantage of this strong momentum. In addition, we are already preparing the next steps in our ongoing efforts to keep expanding the reach of Qutenza™ and serve even more pain patients. Specifically, we have enrolled the first patients in a Phase III study that aims to support a further label extension. If approved by the FDA, this will enable Qutenza™ to be used for the treatment of post-surgical neuropathic pain, which is a complication of surgery. This condition affects approximately 13 percent of all patients who undergo surgery, which represents 3.3 million patients per year in the US.[9]

The US neuropathic pain market is growing rapidly and there is significant opportunity for differentiated new therapies like Qutenza™

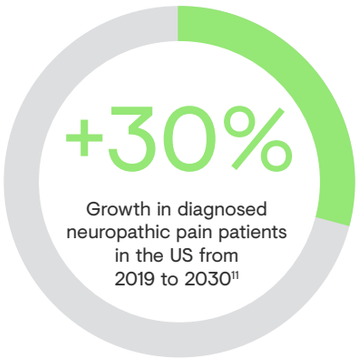
The US represents the majority of the global neuropathic pain market...



$4.5 bn

2016 US Sales in NP therapies[10]

...and is expected to grow substantially

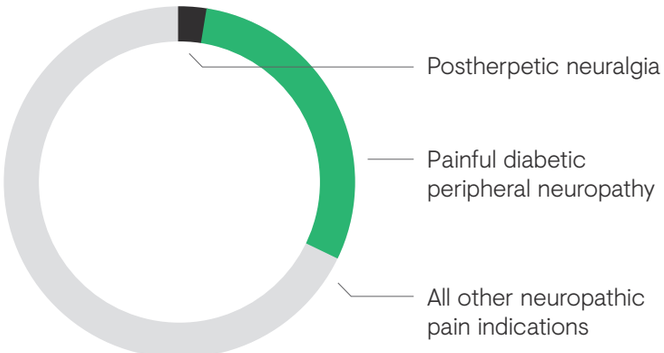


$5.9 bn

Expected US sales of NP therapies by 2026[10]

PDPN will allow us to grow Qutenza™ and the neuropathic pain market

Market Share of neuropathic pain by Indication in US Market



[9] Classifying surgeries were factored against their respective time-bound frequency of PSNP to yield the prevalence based on:
- Carroll, I. R., Hah, J. M., Barelka, P. L., Wang, C. K. M., Wang, B. M., Gillespie, M. J., ... Mackey, S. C. (2015). Pain Duration and Resolution following Surgery: An Inception Cohort Study. Pain Medicine, 16(12), 2386–2396. doi:10.1111/pme.12842.
- Shipton, E. (2008). POST-SURGICAL NEUROPATHIC PAIN. ANZ Journal of Surgery, 78(7), 548–555. doi:10.1111/j.1445-2197.2008.04569.x
- Borsook, D., Kussman, B. D., George, E., Becerra, L. R., & Burke, D. W. (2013). Surgically Induced Neuropathic Pain. Annals of Surgery, 257(3), 403–412. doi:10.1097/sla.0b013e3182701a7b.

[10] 1. Decision Resource Group 2. GRT US Holding Data. The DPN / PSNP markets are expected to grow at 71% and 27% respectively, while the PHN declines by 15%. 3. Qutenza LTP as of July 5, 2019 4. Rehab Management citing University of Michigan study 5. IQVIA.

[11] 1. Cleveland Clinic 2015. 2. International Association for the Study of Pain (IASP) 2014.

David Simpson,
Professor of Neurology at the Icahn School of Medicine at Mount Sinai in New York City

6.3.2 | The unmet medical need for painful diabetic peripheral neuropathy – Interview with Dr. David Simpson

We are proud to have achieved a label extension that allows Qutenza™ (capsaicin) 8% topical system to be used as a treatment for adults with painful diabetic peripheral neuropathy (DPN) of the feet. How does this condition affect people's lives? We invited Dr. David Simpson, Professor of Neurology at the Icahn School of Medicine at Mount Sinai in New York City, to share his experience with us.

Dr. Simpson, can you tell us about diabetic nerve pain and its symptoms?

Diabetes affects 34 million Americans, which is just over one in ten citizens[12]. Neuropathic pain associated with diabetes, which is known as DPN or diabetic nerve pain, is a progressive and debilitating condition that affected more than 5 million Americans in 2020[13] – and the number of people suffering from it is expected to double by 2030[14]. DPN damages the sensory nerves in the body, and patients typically experience symptoms of numbness or tingling, as well as shooting or stabbing sensations that most often affect the lower extremities.[15] It is a difficult condition to diagnose, treat and manage effectively. As a result, many patients receive unsatisfactory or inadequate pain relief.

The disease progresses over time and can impose a significant daily physical, emotional and psychological burden. Patients with persistent DPN are affected by high levels of anxiety or depression, as well as difficulty sleeping because the condition can often be worse at night.

What treatment options are currently available?

As I mentioned, DPN is hard to diagnose, manage and treat. That is because it requires a neurologist or pain specialist to conduct a range of special tests. However, the journey to an accurate diagnosis can be difficult and emotional for many patients. They often have to visit several physicians and seek multiple referrals before they receive an accurate diagnosis and appropriate treatment.

Oral antidepressants, antiepileptic drugs and opioids are the current standards of care for diabetic nerve pain. However, many patients do not respond to treatment and many experience systemic side effects – particularly when the dosage of the treatment escalates.

How does Qutenza™ differ from standard treatments for this condition?

Qutenza™ (capsaicin) 8% topical system is a non-systemic, non-opioid pain treatment that is delivered in the form of a patch. It offers physicians a different way to effectively treat neuropathic pain associated with diabetic peripheral neuropathy.

What is your advice for patients who have diabetes and are experiencing pain?

Patients should always listen to their body and trust what they feel. If a patient suffers from diabetes and experiences symptoms of pain, numbness, tingling or anything similar, they should speak to their doctor and consider contacting a neurologist or pain specialist.

Thank you for these insights, Dr. Simpson

Dr. Simpson has served as a paid consultant and speaker for Grünenthal.

[12] CDC Division of Diabetes Translation, National Diabetes Statistics Report, 2020. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html#:~:text=New%20in%202020%2C%20the%20report,1%20in%203%E2%80%94have%20prediabetes. Accessed July 6, 2020.
[13] LTP 2020-2030: ADDRESSABLE POPULATIONS BY CONDITION (PDPN, PSNP, PHN, CINP). Company data on file. April 30, 2020.
[14] Gore, M., Brandenburg, N. A., Dukes, E., Hoffman, D. L., Tai, K.-S., & Stacey, B. (2005). Pain Severity in Diabetic peripheral neuropathy is Associated with Patient Functioning, Symptom Levels of Anxiety and Depression, and Sleep. Journal of Pain and Symptom Management, 30(4), 374-385. doi:10.1016/j.jpainsymman.2005.04.009.
[15] American Diabetes Association. Peripheral Neuoropathy Overview. https://www.diabetes.org/diabetes/complications/neuropathy/peripheral-neuropathy. Accessed July 17, 2020.

Product portfolio performance

Our product portfolio comprises a complementary mix of innovative, patent-protected growth brands and mature, off-patent established brands with high levels of brand awareness.

Our growth brands comprise Palexia™, Qutenza™ and Vimovo™. Palexia™ accounts for 22 percent of total sales and is our highest-selling product. Qutenza™ has become an even more powerful potential growth driver following a US label extension in July 2020, significantly increasing the patient population that can benefit from its use.

Our established brands include Nexium™, Versatis™, Tramal™, Zaldiar™/Ixprim™, Crestor™, Zomig™/AscoTop™ and Transtec™/Norspan™.

Diversified product mix

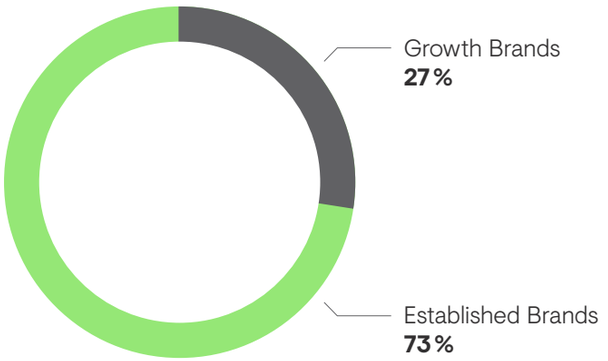
Revenue from sales of pain products accounted for 63 percent of our revenue in 2020.

Through our successful acquisitions of established brands in recent years, we have diversified our product portfolio beyond the pain segment.

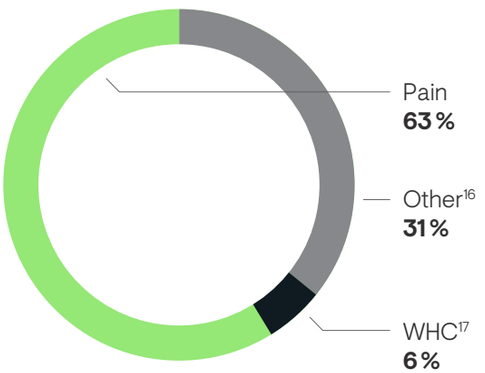
Revenue distribution by geography

The diversification of products and geographies enables us to spread the risks more effectively, making us less dependent on a single market or area.

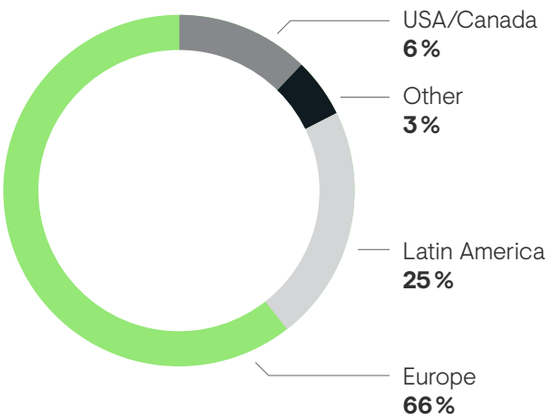
Revenue by product typology 2020



Revenue by therapeutic area 2020



Revenue by geography 2020



[16] Includes Nexium™, Andromaco branded generics, contract manufacturing, partner business in Asia-Pacific region.
[17] Women's Healthcare.

6.4 | Initiatives

CHANGE PAIN™ is an initiative established by Grünenthal in 2009 and endorsed by the European Pain Federation EFIC, Pain Alliance Europe (PAE) and The European Society of Regional Anaesthesia & Pain Therapy (ESRA).

Its mission is to improve patient outcomes through research, communication and education about effective pain management. The CHANGE PAIN™ medical education platform is a global initiative, with country teams using the platform to locally provide translated and tailored educational content about pain to health care professionals and patients. Every year, many customers attend CHANGE PAIN™ educational initiatives like meetings and webinars, and also use the tools that we provide to help educate their staff and their peers, while also supporting patients' self-management. In the last 12-18 months, CHANGE PAIN™ has also increased its digital reach, expanding beyond face to face meetings by organising educational webinars for HCPs and digital tools to support patients.

In order to bring CHANGE PAIN™ to the next level, we launched a new version of the website in June 2020 that offers a wide selection of practical and educational tools for multi-disciplinary pain management teams. On top of this, CHANGE PAIN™ joined forces with patient representatives to build a new section of the website to support pain patients who are facing challenges with managing their pain because of limited access to HCPs during the Covid-19 pandemic.

Since CHANGE PAIN™ was established, a broad range of resources has been developed to support better diagnosis of pain. This includes a series of webinars launched in December 2020 that aim to keep HCPs up-to-date on data related to pain management. The first webinar was attended by more than 200 HCPs and covered the top 10 scientific publications about pain medicine in 2020.
www.changepain.com

CHANGE PAIN®
Taking care of pain

- **June 2020:** CHANGE PAIN™ website re-launch
- **December 2020:** Launch of '30-minute expert talk challenge' webinar series: for HCPs about current pain topics - **already about 700 participants reached!**
- **2021:** new educational resources for HCPs and patients, continued efforts to raise awareness about available resources for HCPs and patients

SIP
Societal Impact of Pain

Grünenthal is one of the main sponsors of Societal Impact of Pain (SIP), a multi-stakeholder partnership led by the European Pain Federation (EFIC) and Pain Alliance Europe (PAE).

It aims to raise awareness about pain and encourage changes to pain policies by providing opportunities for discussion among HCPs, pain advocacy groups, politicians, healthcare insurance providers, representatives from health authorities, regulators and budget holders. SIP is endorsed by more than 300 European and national patient and healthcare organisations, and collaborates with many stakeholder organisations from other disease areas to advocate for improved management of pain (for example in the area of cancer and in rheumatology).
www.sip-platform.eu

EGG
EFIC-GRÜNENTHAL GRANT

6.5 | Grants

Grünenthal and the European Pain Federation (EFIC) offer biennial grants worth a total of €200,000.

These grants support early-career scientists within EFIC member countries to carry out innovative clinical pain research. Since 2004, the EFIC-Grünenthal Grant (E-G-G) has successfully funded 65 innovative research projects, awarding almost €1.6 million to participants in more than 13 countries.

The recipients of the 2021 E-G-G were announced at the 12th Congress of the European Pain Federation EFIC™ in April 2021.
www.e-g-g.info

BMP GRANT Patient Centred Innovation

Grünenthal provides financial support for the Brain, Mind and Pain (BMP) grant, which encourages patient-centred innovation in pain research and pain care. The BMP grant is the first pan-European grant that selects applications based on the impact they have from a patient´s perspective.

The theme for second edition of the BMP grant in 2020/2021 was 'STOP Stigma! Reduce Stigma to Improve Quality of Life for Brain, Mind and Pain Patients'. Three projects have been selected to review the grant:

ASpida: Against Stigma pain intervention development Approach (Vasilis Vasiliou, University College Cork)

StigmApp (Yiannis Koumpouros, University of West Attica)

#RompeConElDolor – Breaking stigma on chronic pain in diabetes and other diseases through shared experiences on social media (Federación Española de Diabetes (FEDE), Spain)
www.bmp-grant.eu

Global brands

Brand Name	Active ingredient / Technology	Indication range[18] Unless otherwise specified, below indications refer to the EU SmPC. Indications and formulations may vary from country to country. Please refer to the respective local product information.	Sales 2020[19] in € m
Qutenza®	Capsaicin 8%/179mg	**EU indication** Treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for the treatment of pain. **US Indication** Treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults.	27.3
Vimovo®	Fixed-dose combination of Esomeprazole and Naproxen	In adults for the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.	29.1
versatis®	Lidocaine	Symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults.	118.4
Zomig® ZOLMITRIPTAN AscoTop®	Zolmitriptan	**Oral formulations:** In adults aged 18 years and older for acute treatment of migraine headache with or without aura. **Nasal spray:** In adults and adolescents aged 12 years and older for the acute treatment of migraine headache with or without aura, and in adults for the treatment of cluster headache.	72.0

[18] Status: April 2021. Please note that indications and formulations may vary from country to country. Please refer to the respective local product information or Summary of Product Characteristics (SmPC).
[19] Including revenues from licenses.
[20] See SmPC for 'Nexium™ 10 mg gastro-resistant granules for oral suspension, sachet' and for 'Nexium™ 40 mg Powder for solution for injection/infusion'.

Brand Name	Active ingredient / Technology	Indication range[18] Unless otherwise specified, below indications refer to the EU SmPC. Indications and formulations may vary from country to country. Please refer to the respective local product information.	Sales 2020[19] in € m
Nexium®	Esomeprazole	**20 mg; 40 mg gastro-resistant tablets: Indicated in adolescents from the age of 12 years and in adults for:** Gastroesophageal reflux disease (GERD) o treatment of erosive reflux esophagitis o long-term management of patients with healed esophagitis to prevent relapse o symptomatic treatment of GERD **Indicated in adults for:** In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and: o healing of Helicobacter pylori associated duodenal ulcer and o prevention of relapse of peptic ulcers in patients with Helicobacter pylori-associated ulcers **Patients requiring continued NSAID therapy:** o healing of gastric ulcers associated with NSAID therapy o prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk Prolonged treatment after intravenous-induced prevention of rebleeding of peptic ulcers. Treatment of Zollinger Ellison Syndrome. **Indicated in adolescents from the age of 12 years** In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori. Nexium™ is also available in other dosage forms with slightly varying indications.[20]	160.4
CRESTOR®	Rosuvastatin	**Treatment of hypercholesterolaemia** Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Adults, adolescents and children aged 6 years or older with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate. **Prevention of Cardiovascular Events** Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.	Acquisition completed in 2021

Global brands with opioid mechanism of action

Brand Name	Active ingredient / Technology	Indication range[19] Unless otherwise specified, below indications refer to the EU SmPC. Indications and formulations may vary from country to country. Please refer to the respective local product information.	Sales 2020[20] in € m
PALEXIA®	Tapentadol	**Film-coated IR tablet:** Relief of moderate to severe acute pain in adults which can be adequately managed only with opioid analgesics. **Oral solution:** Relief of moderate to severe acute pain in children[21] from 2 years of age and in adults, which can be adequately managed only with opioid analgesics. **Prolonged-release tablet:** Management of severe chronic pain in adults which can be adequately managed only with opioid analgesics.	Palexia™ 308.7 + Partner sales of Nucynta™ in the US: 159.5
Tramal	Tramadol	**EU and LATAM Indication** Treatment of moderate to severe pain.	89.1
ZALDIAR®	Fixed-dose combination of Tramadol and Paracetamol	Symptomatic treatment of moderate to severe pain; use should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.	61.5
Transtec®	Buprenorphine	Treatment of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics. Transtec is not suitable for the treatment of acute pain.	54.7

[21] In children restricted to hospital use where appropriate equipment to enable respiratory support is available and for a maximum treatment duration of 3 days.

Scan here to find our global brands online.

Statement regarding the responsible use of opioid-based medicines

General considerations for the management of pain with any medication that contains an opioid mechanism of action.
The following general aspects should be considered:

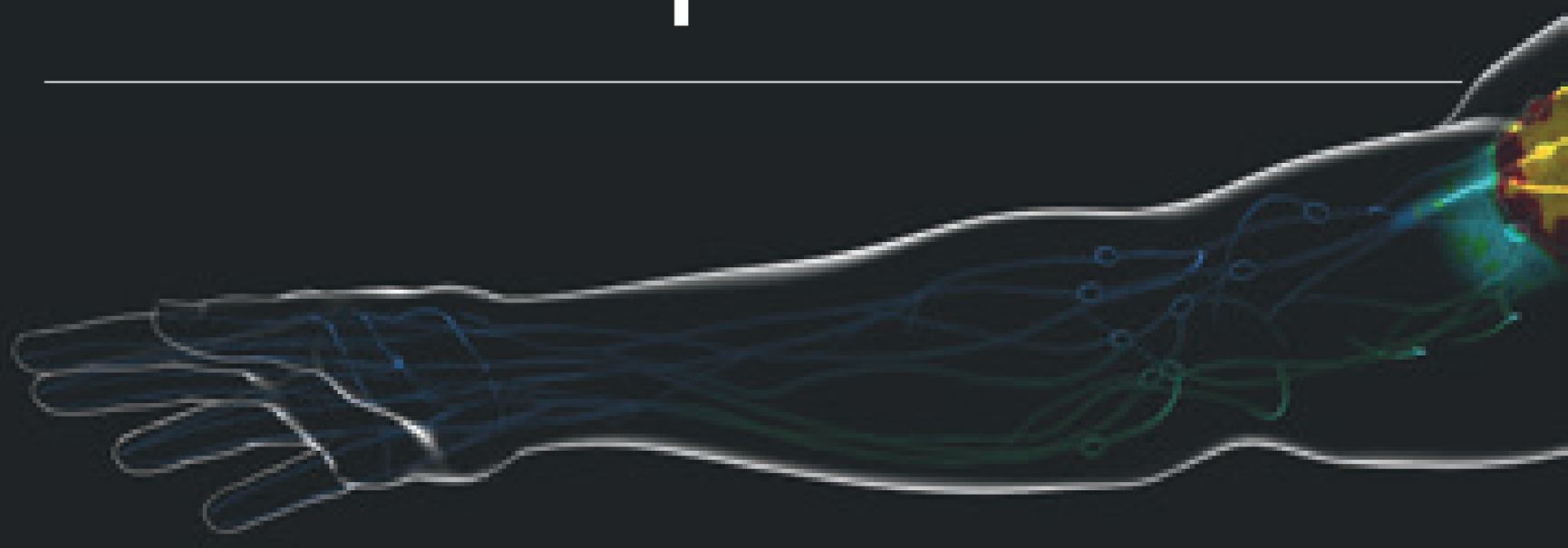
- An individualised, patient-centred approach for the diagnosis and treatment of pain is essential to establish a therapeutic alliance between patient and clinician.
- Consider patient variables that may affect opioid dose for each patient prior to opioid use.[22]
- In patients with acute pain e.g. post-surgery pain, the use of medication should be for the shortest necessary time.[22] All patients should be carefully selected, abuse risk factors evaluated and regular monitoring and follow-up implemented to ensure that opioids are used appropriately[23-24] and in alignment with treatment goals (pain intensity and functionality) as agreed with the patient.[23-24]
- Patients should be made aware of the potential side effects of opioids and the potential for developing tolerance, dependence and addiction.[23-24]
- It is important to optimally use multimodal, non-opioid approaches in acute and chronic pain before escalating to opioids or in conjunction with opioid therapy.[22]
- Addiction is possible even when opioids are taken as directed. The exact prevalence of abuse in patients treated with opioids for chronic pain is difficult to determine.[25]
- Regular clinical reviews are required for long-term opioid treatment to assess pain control, impact on lifestyle, physical and psychological well-being, side effects and continued need for treatment.[26]
- Any long-term treatment with opioids should be monitored and re-evaluated regularly incl. tapering down the dose or discontinuing treatment.[23-24]
- Signs of opioid use disorder should be monitored and addressed.[23-24]
- Patients and the general public can benefit from clear educational materials and awareness interventions to support the responsible use of opioids.[27]

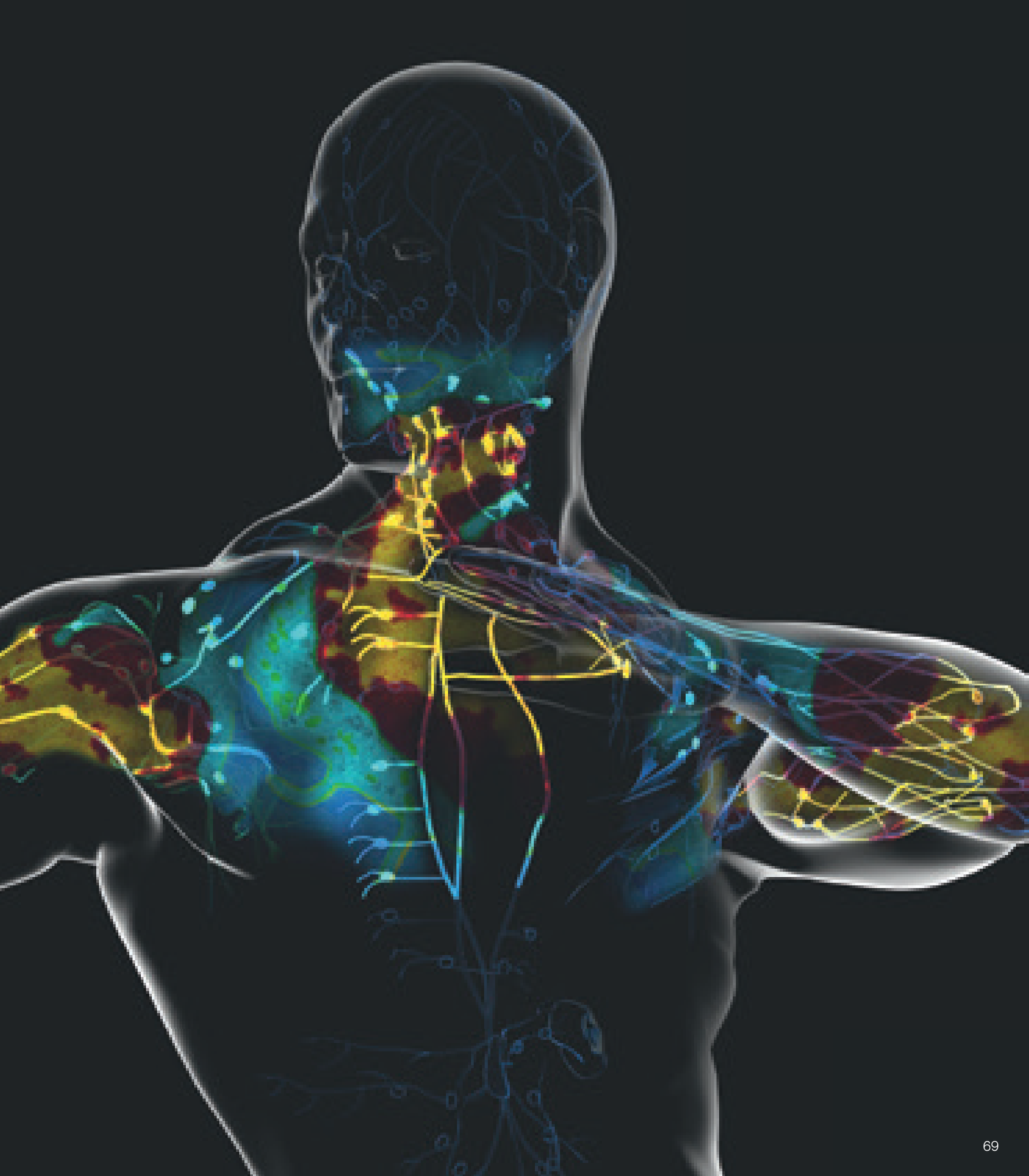
[22] DHHS Pain Management Best Practices Inter-Agency Taskforce Report May 2019.
[23] Faculty of Pain Medicine, Opioids Aware https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware Accessed September 2019.
[24] Kosten TR et al, Scie Pract. Perspect 2002;1:13-20.
[25] Rosenblum A et al Exp. Clin. Psychopharmacol. 2008;16(5):405-416.
[26] O'Brien T et al. Eur J Pain 2017;21:3-192.
[27] OECD Health Policy. Addressing Problematic opioid use in OECD Countries May 2019 http://www.oecd.org/health/addressing-problematic-opioid-use-in-oecd-countries-a18286f0-en.htm.

Scan here to see the Grünenthal statement on the responsible use of opioids.

7

Manufacturing and Global Operations





7.1 | Lean manufacturing and excellence along the entire value chain

Our Manufacturing and Global Operations team ensures a safe, efficient and reliable product supply to patients. The experts in this area constantly strive to ensure excellence at every stage of our value chain. This applies to our own medicines, as well as the medicines we produce as a trusted partner for other pharmaceutical companies.

Grünenthal operates five specialised production sites in Chile, Ecuador, Germany, Italy and Switzerland. These sites manufacture our products and support our external customers, who account for around 50 percent of our overall production capacity. We have around 2,000 people involved in the full end-to-end value chain management of our product supply. They are passionate about satisfying our customers by offering a high service level.

7.2 | #WeBeatTheVirus – Making sure patients get the medicines they need

Covid-19 has disrupted our daily life – but it has not disrupted our production and supply activities. Our Global Manufacturing and Operations team has successfully kept our business running despite the pandemic. Of course, the safety of our people and the patients we serve is always our top priority. For this reason, employees have been advised to adhere to very strict hygiene rules.

We are incredibly proud of the resilience and solidarity that our people and partners showed in 2020 to make sure patients received an uninterrupted supply of our medicines. This was made possible by a coordinated effort across our five production sites, as well as our supply and distribution hubs. At all times, we ensured a constant flow of information about how to anticipate, mitigate and respond to challenges. The team at our site in Origgio, near Milan, developed an approach that became a best practice example for other sites around the world – because Italy was one of the first and most severely-hit countries. This approach is built on solid risk analysis and flexible planning, and covers everything from guaranteeing our supply of raw materials through to finding ways to secure trucks, air and sea freight to bring our medicines to hospitals and pharmacies.

We closely monitor the developments throughout our supply chain, while constantly assessing the situation as it evolves. This is particularly important because we purchase raw materials and finished products directly and indirectly around the globe. Even before the Covid-19 pandemic, we had a strict policy for inventory management and safety stock in place to mitigate potential short-term supply shortages. With this process, and with our relentless focus on ensuring safety, we have been able to supply medicines – and fulfil our obligation to society as a pharmaceutical company.

7.3 | Expanding our Contract Manufacturing Business

Our Contract Manufacturing Business, which is called Grünenthal PRO, offers high-quality products and services for customers worldwide. We are a trusted partner, and we constantly optimise our capabilities and capacities to expand

Grünenthal PRO – our Contract Manufacturing Business

50+
partners

100+
countries supplied worldwide

2,000
people involved end-to-end

Operational excellence
guaranteeing quality, reliable delivery and improvement

GMP & EHS certifications
endorsing our high-quality standards and commitment to health & safety

Our manufacturing sites
Chile, Ecuador, Switzerland, Italy and Germany

the range of support that we provide from our five production sites. Together with partners at every stage in our supply chain, we make sure our customers are satisfied in every way.

In 2020, seven of our existing customers extended our agreements by between three and five years. This includes four key European providers of generics, who source products containing Tramadol, Betahistine and Naproxen from us. This is a fantastic confirmation of the trust that we have built among our customers – including small, medium-sized and large companies from the pharma industry. This trust is based on our strong record of reliable high quality, competitive costs and outstanding service.

Alongside extending existing contracts, we have also been able to expand our Contract Manufacturing Business with longstanding and new customers.

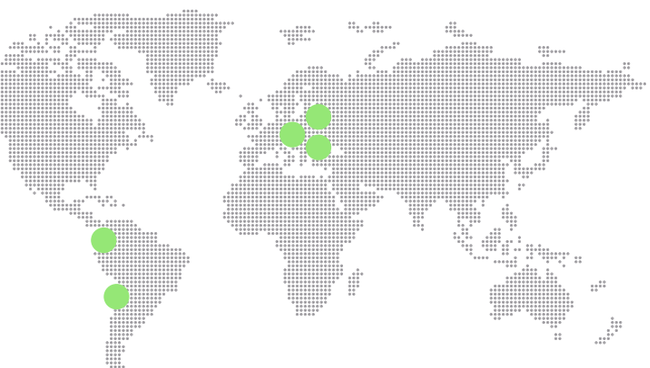
- Our **biopharma business** has substantial potential for further growth. We currently deliver labelled and packaged syringes and vials to approximately 20 countries. In 2020, we expanded the capacities and capabilities at our site near Milan, and we now operate more than seven assembly and packaging lines for pre-filled syringes, pre-filled pens and vials. Our capabilities also include cold storage capacity and quality testing.

- Our **supply to Japan** is also developing well. In 2020, we attracted a second partner with our high-quality small molecule solids production, and a third partner is expected to follow soon.

- We are also close to finalising another new customer for our proprietary **hot-melt extrusion technology**, which allows time-controlled, modified, extended or immediate release, and targeted drug delivery for poorly soluble drugs or those that need taste-masking.

- The **hormone products** from our site in Chile are now being prepared for out-licensing. We have a strong portfolio of these solutions that we are offering to partners.

Our five production sites are modern and well maintained, which enables us to deliver affordable drugs to the countries and partners with whom we operate with. We are always ready to embrace fresh opportunities to support new partners around the globe. In this spirit, we expect 2021 to be another exciting year for Grünenthal PRO.



www.grunenthal-pro.com

Our expertise spans a wide range of cutting-edge technologies:

Standard Technologies Ability to support a variety of formulations:	**Oral Solids** (Tablets, Capsules)	**Semi-Solids and Liquids** (Creams, Suspensions)	**Packaging Solutions** (Bottles, Sachets, Blisters)
Special Technologies An extensive service offering including:	**Biopharma Services** (Assembly, Labelling, Cold-chain Logistics, Handling Light-Sensitive Products)	**Hormone Products** (Oral Solid Dosage Forms, Topical Gels, Isolated Development/ Transfer Area)	**Innovations** (Hot-Melt Extrusion, Bi-/Tri-Layer Tablets)

“We are constantly striving for excellence – in quality, efficiency, safety and service. That is why we are a trusted partner for patients and companies around the globe.”

Victor Barbosa,
Head Global Operations

7.4 | Victor Barbosa, Head Global Operations, takes you on the journey to excellence

What is the main focus for Global Operations in the future?

We strive to support our company’s vision of a world free of pain. Alongside our mission to deliver a safe, effective and reliable supply of medicines to patients, we also aim to drive growth and fund our company’s future by ensuring excellence in what we do, and by embracing innovation and digitalisation in how we operate. We have a clear strategic plan for the next five years, which is called GO2025. This was launched in 2020 and will guide our efforts to boost Grünenthal’s profitability by ensuring the highest levels of safety, quality and cost-efficiency in our manufacturing activities – and at every stage in our value chain.

The first initiatives for GO2025 are already underway. This includes embracing digital technologies to react to changing market conditions and to make our manufacturing processes more resilient. For example, we are now using smart innovations like data capture, advanced analytics and assembly line robotics. We will also implement a Business System across our main end-to-end processes based on lean and Six Sigma principles. One fundamental aspect always remains important: safety first. We are continuously developing preventative measures to improve the level of occupational safety. With every step, however small, in the direction of education, we have the clear ambition of reaching zero accidents. This requires safe framework conditions and safe behaviour. Every accident is one too many. We actively search for unsafe situations and behaviour. We analyse each accident and share it with the other sites worldwide. Prevention is a worthwhile investment.

How do you ensure progress?

We are on our way towards becoming a data-driven organisation. We have created a common set of ambitious Key Performance Indicators (KPIs) for every area of our end-to-end operations to increase transparency and strengthen our performance culture. For manufacturing, these KPIs measure quality, service, costs and Environment, Health and Safety (EHS) factors. In this way, we can see how each site is performing and can compare progress against previous months and years. Performance is measured in the same way at every site because global standards are in place. This means the data creates a solid basis for planning, strategic decision-making and running

our operational business – and it is available to everyone in our company, so we are all looking at the same numbers.

How does Global Operations contribute to Grünenthal's overall growth strategy?

Acquisitions are a key factor in our company's growth strategy – and successful acquisitions depend on integrating new brands into our supply chain quickly and effectively. We have a strong track record of enabling external growth. In addition, companies in the pharma industry recognise our excellent in-house manufacturing capabilities. We have full control over supplies and this generates reliable supply security. This is another key factor in large asset divestments in our industry.

Our dedicated team for integrating acquisitions makes sure that we get full value for our investments, and we are often able to achieve substantial cost reductions in production. The acquisitions of the European rights for Nexium™ and the global rights for Vimovo™ (excluding the US and Japan) are the most recent examples. We have invested €11.8 million in state-of-the-art packaging equipment to create the required capacity in our Aachen site. In 2020, we began production of these brands in line with our plan. Following the takeover of packaging activities from AstraZeneca, we expect cost savings of up to €11.7 million per annum from 2022. We intend to follow a similar model for the integration of Crestor™. As part of the agreed deal, we expect to take over the production and packaging in the relevant markets starting in 2025. We currently expect to achieve substantial synergies through in-house bulk and packaging.

8

Responsible Business

“The long-term success of companies can no longer be measured by financial success alone. As a science-based company, Grünenthal strives to make a net-positive impact on society.”

Sebastian Köhler,
General Counsel

8.1 | Responsibility

At Grünenthal, conducting our business responsibly is a core part of our company’s strategy and culture. As a global leader in pain management, Grünenthal aspires to create a positive impact for society – in our core business and beyond. We are guided by integrity, transparency and the highest ethical standards.

Innovating and raising awareness

As pain specialists, we consider pain to be a disease in its own right rather than just a symptom. This view is based on the prevalence and impact of pain around the globe. It is estimated that up to 2 in 5 people worldwide are affected by chronic pain.[28]

We make a positive impact on society by developing innovative treatments to address this unmet need. A large portion of our revenue is reinvested into R&D each year, which is well-above the industry average. On top of this, we leverage modern technologies to improve outcomes for patients. Our Pain Toolkit, for instance, offers handy tips about how to prevent and manage pain in the form of infographics and videos. Grünenthal also strives to raise awareness about pain as a disease. Our engagement as a main sponsor of Societal Impact of Pain (SIP) is one example. This multi-stakeholder partnership led by the European Pain Federation (EFIC) and Pain Alliance Europe (PAE) promotes discussion about pain and encourages changes to pain-related government policies.

Preserving dignity at the end of life

Our longstanding efforts to promote research into palliative medicine and improve the standard of care is another important area where we create a positive impact for society. Around 40 million people need palliative care each year – but only 14 percent receive it. In 2019, a study by the World Health Organization (WHO) found that funding for palliative care was only available in 68 percent of the 194 countries surveyed.

By creating the Grünenthal Foundation for Palliative Care in 1998, we underscored our deep commitment to preserving dignity and quality of life at the end stage of people’s lives. The foundation provided a donation to establish the Chair of Palliative Medicine at the RWTH Aachen University, while also supporting education about palliative care through activities including scholarships for medical students. To promote awareness and scientific exchange within Latin America, the foundation organised two international congresses on palliative care in Santiago de Chile in 2005 and in Lima, Peru in 2018.

Expanding our positive impact on society

Throughout the 75-year history of our company, we have created a solid foundation as a responsible business. At the moment, we are developing a strategic programme that will further strengthen our positive impact. This includes, in particular, a Sustainability strategy, under the overarching theme PLANET, as well as developing dedicated flagship initiatives under the overarching themes of PEOPLE and PATIENT to increase the social value of our activities. Looking to the future, we are determined to maximise our potential to create sustainable value for society.

Supporting social progress during the pandemic

We have a long track record of supporting projects that have a positive impact on people and communities around the globe. In 2020, our employees stepped up their support for healthcare systems, communities and individuals – from raising funds through to donating medicines, masks and medical expertise.

Read more here.

[28] Based on data from 34 countries. (Elzahaf RA et al. CMRO 2012).

8.2 | Key Topics

Responsible pain treatment and use of opioids

Our portfolio includes opioid pain treatments because we believe opioids should be one of the treatment options available for managing severe pain. We are absolutely committed to ensuring all of our employees, customers, patients and partners have a comprehensive understanding of the responsible use of these medicines.

"Grünenthal is driving a corporate responsibility program rooted in our core business. It is built around our key pillars Patient, People and Planet and is anchored in our commitment to patient centricity."

Prof. Dr. Cordula Meckenstock,
Chief Responsibility Officer

Ethics, Compliance and Transparency

We act in line with strict codes, standards and management systems that ensure transparent and ethical behaviour, as well as compliance with all applicable laws and regulations worldwide. This approach is built around our Code of Conduct, which we relaunched in 2018.

The Grünenthal Foundation for Thalidomide-affected People

The Thalidomide tragedy will always be part of our history and part of who we are today. We cannot change what happened in the past. This is why we place the highest importance on improving the living situations of people affected by Thalidomide. The Grünenthal Foundation for Thalidomide-affected People plays a central role in this commitment by providing assistance in pragmatic ways to give people greater freedom in their day-to-day lives.

Environmental sustainability

The world's limited resources are becoming increasingly depleted and the environmental footprint of humankind is already more than the planet can sustain. That is why we are committed to driving progress towards environmental responsibility and sustainable development.

Occupational safety

Every day, we strive to improve safety awareness among our entire workforce and to avoid unsafe situations. In this way, we aim to keep moving closer towards achieving our goal of zero accidents at work.

You can find more information about these topics here.

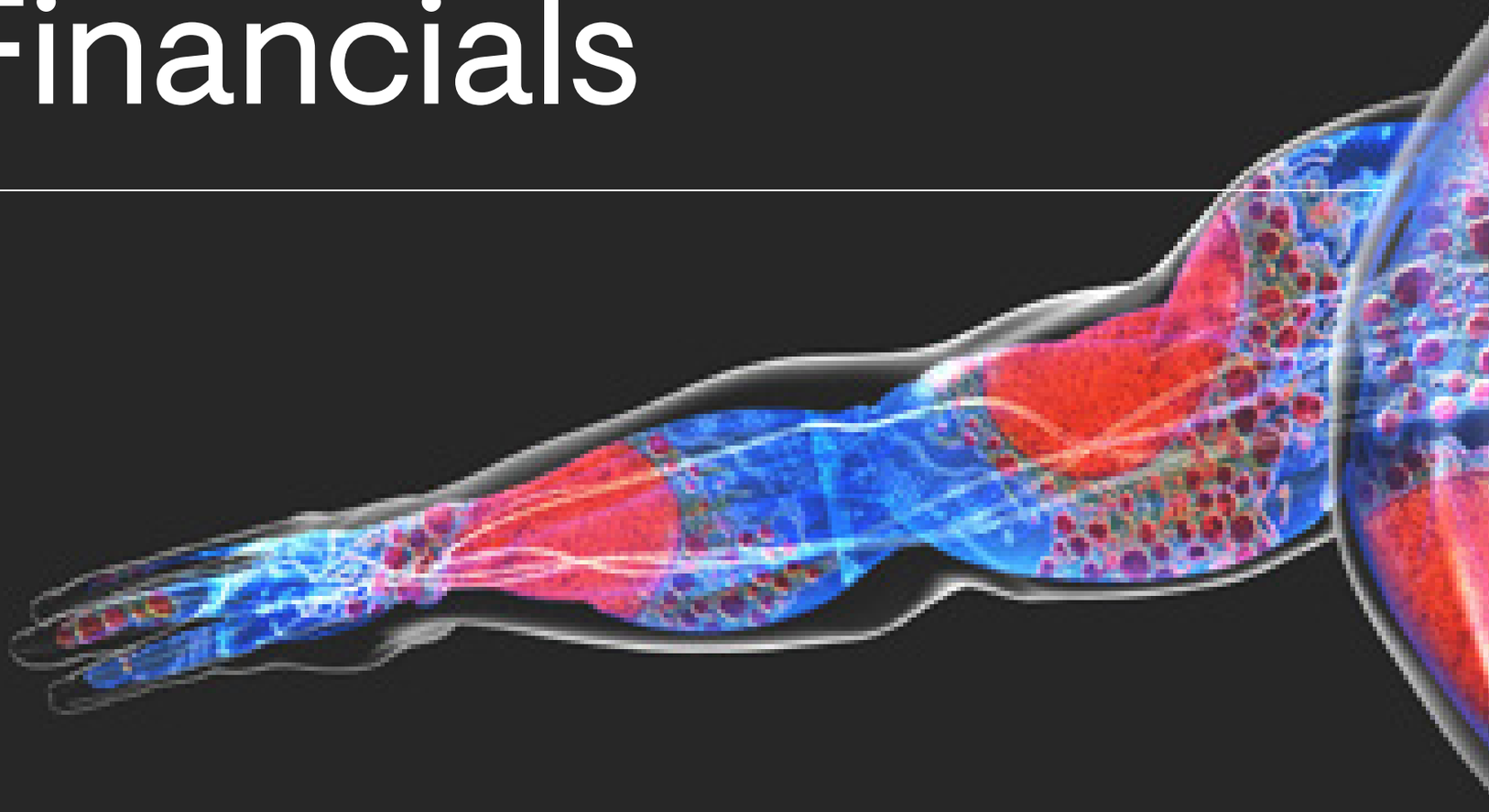
ESG Rating

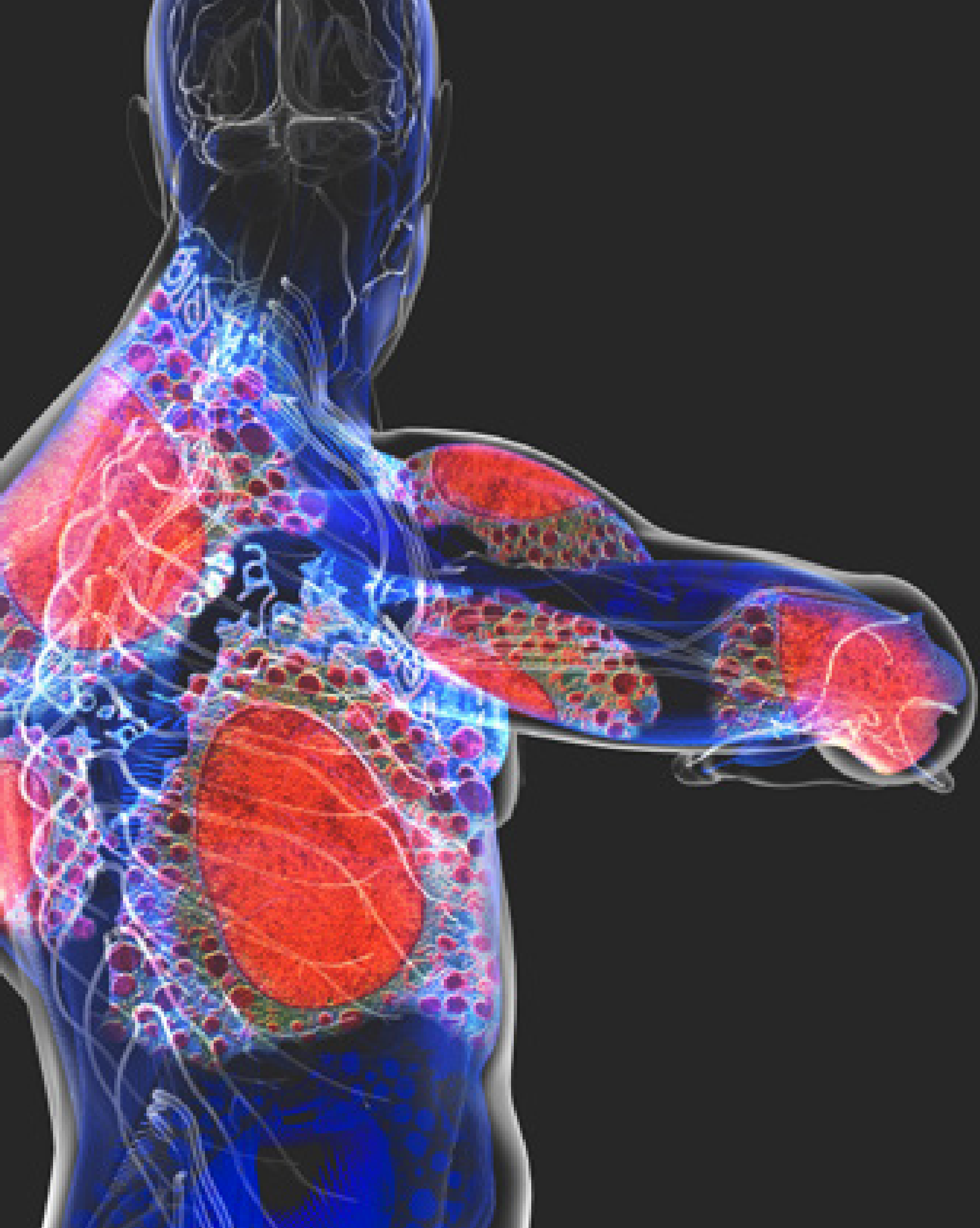
Our performance against environmental, social and governance (ESG) criteria has been recognised in an external rating that placed Grünenthal in April 2021 in the top five percent of the global pharmaceuticals subindustry. The rating agency Sustainalytics attributed a medium ESG risk to Grünenthal and acknowledged the company's strong management of its ESG risks.

Grünenthal was evaluated by Sustainalytics based on its ESG Risk Ratings framework, which focuses on exposure and management of a company's material ESG issues. "Exposure" reflects the degree to which a company's enterprise value is exposed to material ESG issues including ethical marketing, clinical trial transparency, whistleblowing, corruption and bribery. "Management" measures a company's preparedness and track record in managing its exposure to material ESG issues through its policies, programmes, trainings and management systems.

9

Financials





“Despite the impact of Covid-19 in 2020, we were able to finish the year with yet another strong financial performance, positioning us well for a successful 2021.”

Fabian Raschke,
Chief Financial Officer

9.1 | CFO in dialogue

How did the Covid-19 outbreak impact Grünenthal financially?

“As expected, Covid-19 had an impact on our business results and operations. However, Grünenthal showed remarkable resilience, particularly from a financial point of view. We finished the year with revenues[29] of €1,280 million, which is very close to the target that we set ourselves before the Covid-19 outbreak. The biggest Covid-related impact on our financial performance was caused by the devaluations of currencies, especially in Latin America.

Our Sales team delivered positive growth for our Nexium™, Palexia™ and Zomig™ brands despite a challenging market environment. That is a fantastic achievement during a year when our access to physicians and other key stakeholders was restricted. Additionally, we implemented several measures to safeguard our profitability at an early stage. Operating costs[30] were reduced by over 15 percent to €582 million. The actions we took – including a hiring freeze, travel ban, and a reduction in promotional and project spending – as well as the recovery of our business in the second half of the year, enabled us to reduce our net debt[31] faster than expected. Overall, we were able to achieve an adjusted EBITDA[32] of €338 million. That is only €3 million below the figure achieved in 2019, which was our record financial year. This excellent result shows that we have navigated our company through this difficult year very successfully.”

How does the strategy of acquiring established brands support the company’s sustainable growth plans?

“Acquisitions of established brands have been the key driver of our growth in recent years. Since 2017, we have invested approximately €1.3 billion in acquisitions including Zomig™, Nexium™ and Vimovo™, as well as Crestor™ in February 2021. By actively managing the product lifecycle of our acquired brands and reducing costs throughout the value chain, we have been able to generate additional value from these brands, for example by insourcing packaging for Nexium™ at our Aachen site. Driven by our recent acquisitions, our adjusted EBITDA increased from €129 million in 2017 to

[29] (Net) Revenue = Sales. Revenue primarily comprises sales of products and revenue from licensing, as well as milestone payments. It also includes service income from our contract manufacturing business, such as customer refunds for the purchase of machines required to produce a certain product or for customisation of product formulations.
[30] Operating costs = operational costs of a company, including marketing and sales force costs, as well as general and administrative costs. Costs of goods sold and depreciation are excluded due to their level of influenceability.
[31] Net debt indicates the overall debt situation of a company by deducting the value of cash from the value of debt. It is a measure of a company’s ability to repay all debt if it were called immediately.
[32] Adjusted EBITDA, short for Earnings Before Interest, Taxes, Depreciation and Amortisation before special items, is a key driver of free cash flow and has been defined as our most important performance indicator.
[33] Standard & Poor’s assigned Grünenthal and the bond ‘B+’ ratings with a positive outlook. Fitch Ratings assigned a rating of ‘BB’ to Grünenthal (stable outlook) and a rating of ‘BB+’ to the bond. Moody’s Investors Service assigned a ‘B1’ rating to both the company and the bond, with a stable outlook.

€338 million in 2020. Our strategy enables us to reinvest in pain research and fund further targeted acquisitions to enable sustainable and profitable growth."

What are your financial plans for the next three to five years?

"We aim to keep implementing our strategy, as we have in the past. That means striving for strong and sustained organic growth from our growth brands, for example through the extension of our Qutenza™ business in the US. We will also continue to optimise our established brands.

Additionally, we aim to execute further build-muscle deals. This involves acquiring established brands and leveraging substantial synergies with our existing infrastructure to generate an immediate contribution to our profit and cash flow.

Our financial policy is unchanged. We target a low leverage while using external financing for our build-muscle deals. In the last few years, we have expanded our financing instruments. In February 2021, we improved our maturity profile by extending our existing bank facilities. In April 2021, we successfully placed our first bond of €650 million, with a five-and-a-half-year tranche and a seven-year tranche. In July 2021, we successfully increased our existing bond financing by €300 million to a total sum of €950 million.

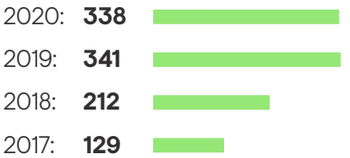
In preparation for the bond, Grünenthal was assessed by three major independent credit rating agencies, all of whom confirmed our company's solid financial position[33]. Accordingly, we are well placed to capitalise on promising acquisition opportunities."

9.2 | Financials

Profit and loss statement[34]

In € million	Actual 2019	Actual 2020
Revenue[35]	**1,394**	**1,280**
Cost of sales[36]	-419	-413
Gross profit[37]	**975**	**867**
Marketing, Sales & Medical costs[38]	-439	-384
Core Research & Development costs	-184	-137
Other costs	-290	-250
Depreciation Fixed Assets[39]	207	191
EBITDA	**270**	**288**
Adj. EBITDA	**341**	**338**
Earnings before taxes	**27**	**63**

Adjusted EBITDA in € million



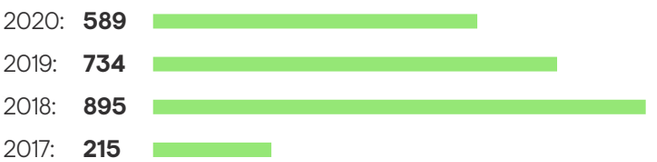
Cash flow and leverage management

We have been able to finance our growth through strong internal cash flow, and with the use of external funding. It is important to us that we reduce the net debt incurred in making these acquisitions in a timely manner. Our conservative shareholders take a long-term view and are strongly committed to deleveraging as rapidly as possible.

We have a strong track record of acquisitions with attractive multiples that meet or exceed our business cases.

Overall, despite investing in large acquisitions, we have been able to significantly reduce our net debt in recent years and are ahead of our plans.

Net debt in € million



[34] Management view. Profit and loss statements (P&L) can be displayed in Accounting and Management view. Both P&Ls include the same information, but are designed to serve different needs. The Accounting P&L is used for reporting according to German Commercial Code (HGB) while the Management P&L is used for internal steering and tracking. Both views are similar for Revenue, Cost of sales and thus gross profit. But they differ in terms of the recognition of depreciation on acquired product rights and medical affairs costs. Depreciation of acquired products rights are recognised in Management view as part of "other costs" whereas Accounting view shows it as part of "selling expenses". Medical commercial R&D costs comprise post approval product costs, e.g. for the maintenance of registration, for clinical studies for phase IIIb/IV and the support of investigator initiated studies as well as structural costs. These costs are part of "Marketing, Sales & Medical costs" in Management view whereas shown as "Research & Development costs" in Accounting view.

[35] Revenue or Sales is Grünenthal's income from its commercial effort to market pharmaceuticals either directly to wholesalers, pharmacies and hospitals or in cooperation with a partner.

[36] Cost of sales or Cost of goods sold are any costs that can be directly associated with products sales.

[37] Gross profit reveals how much money a company earns taking into consideration the costs that it incurs for producing its products and/or services.

[38] Marketing, Sales & Medical costs consists of all costs to promote, sell and distribute our products to the customer. This excludes depreciation an acquired products which is part of "other costs".

[39] Depreciation of machines, IT equipment and several other items is an incremental part of CoGs, Marketing, Sales and Medical costs, R&D costs. In order to derive the Earnings before interest, taxes, depreciation and amortisation (EBITDA), it needs to be added back.

9.3 | Outlook

For the future, we expect the underlying trends seen in 2020 to continue. Our established brands will continue to benefit from our targeted commercial initiatives and optimisations across the value chain. For example, we expect to reap the full financial benefit of taking over the packaging for Nexium™.

Our most recent transaction, the acquisition of the European rights for Crestor™ (excluding Spain and the UK), which closed in February 2021, will also contribute to our revenue and profit. Our growth brands are expected to continue to grow. We expect the strongest growth from Qutenza™ in the USA.

We are going to continue evaluating further established brand deals that strengthen our established brand portfolio with products that offer stable revenue and strong brand equity, and that immediately improve our financial performance. In addition, we will continue to place a strong strategic focus on maximising our existing R&D pipeline and expanding it with further innovative assets in selected therapeutic areas.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