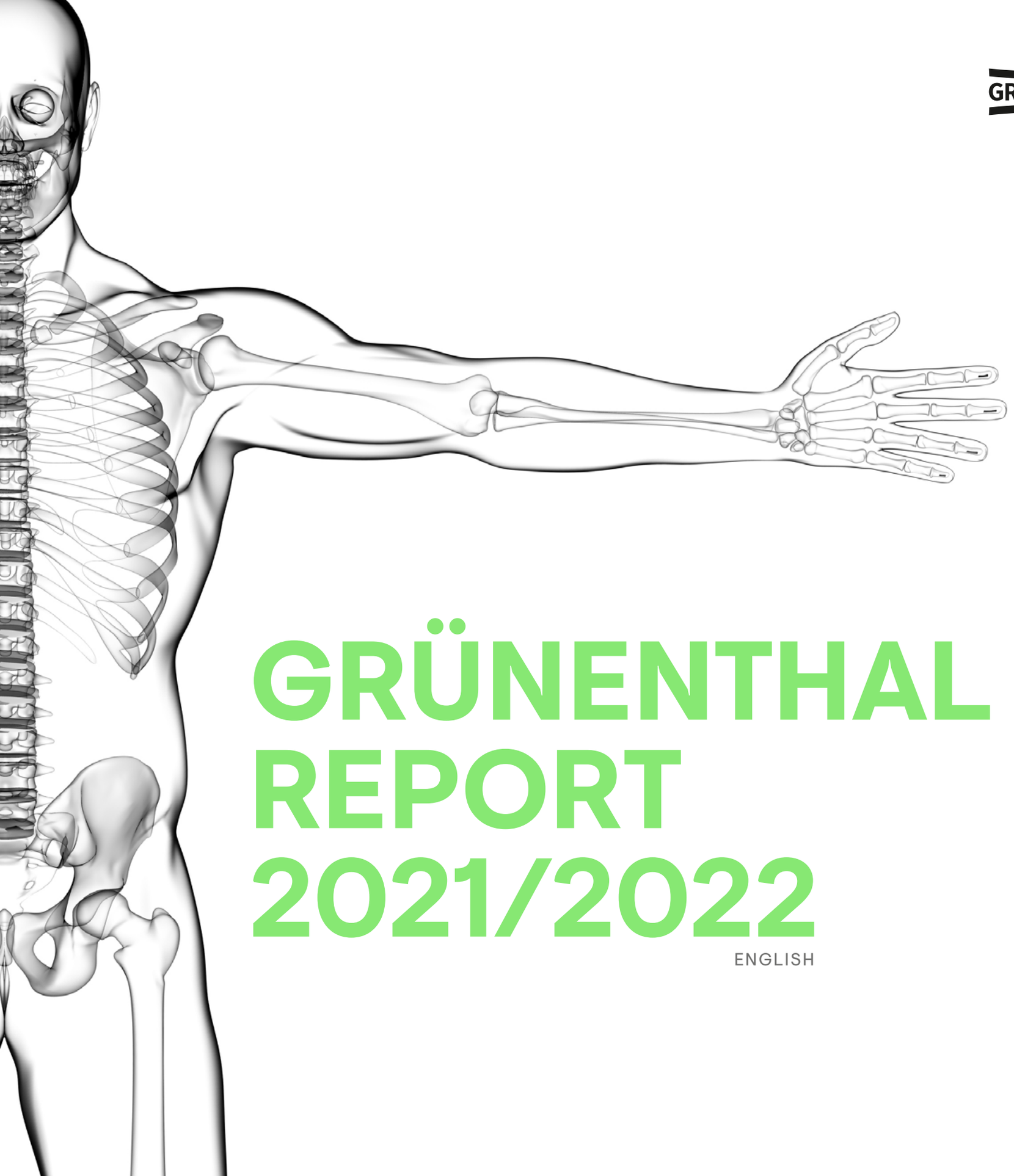
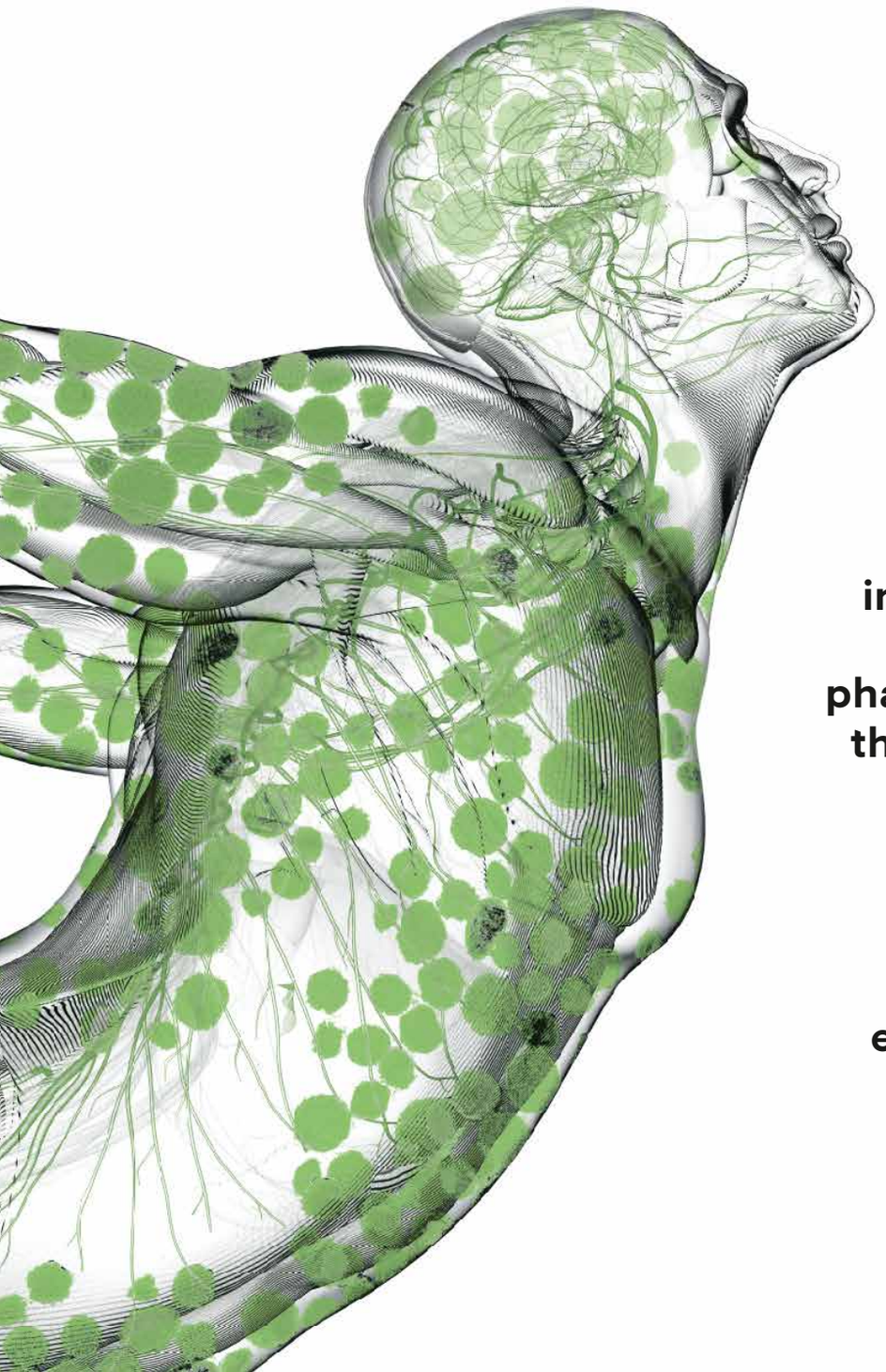


GRÜNENTHAL REPORT 2021/2022

ENGLISH

CORPORATE PROFILE



Grünenthal is a global leader in pain management and related diseases. We have a long track record of bringing innovative treatments to patients worldwide. As a fully integrated pharmaceutical company we cover the entire value chain – from drug research and development to commercialisation of portfolios with both growth products and established brands. We operate in accordance with the highest ethical and regulatory standards and focus our efforts on our vision of a world free of pain.

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LETTER FROM THE CEO

Gabriel Baertschi, *Chief Executive Officer*

As a science-based pharmaceutical company and a leader in pain therapy, Grünenthal continued to successfully implement its strategy bringing life-changing medicines to patients that address high unmet medical needs. Looking back on 2021, we have much to be proud of.

> Our people have carried Grünenthal to its best-ever financial performance. We have almost tripled our EBITDA over the last five years and significantly advanced our pipeline, creating fantastic momentum to expand our leadership in pain. <

Gabriel Baertschi,
Chief Executive Officer

Dear Readers,

2021 was another record year of double-digit growth for Grünenthal, with €1.5 billion in revenue. This represents an increase of 15 percent over the previous year. Our adjusted EBITDA of €370 million increased by 10 percent over 2020. Our adjusted EBITDA and our company value have almost tripled since 2017.

Drivers of the performance were sales in our core markets in Europe, Latin America and the US. Palexia™ continued its strong growth in Europe, with sales increasing by 11 percent. In Latin America, we saw sales growth of our promoted brands following a strategic focus on differentiated pain products. Qutenza™, our non-opioid cutaneous system in the US, performs above our expectations.

Our strategy is paying off

Acquiring established brands that immediately contribute to our EBITDA is a key part of our strategy. In 2021, we completed the acquisition of the European rights to Crestor™, already showing a substantial sales contribution in its first year. Our revenue from the portfolio of acquired brands, including Nexium™, Vimovo™ and Zomig™, has grown by 20 percent compared to the prior year. COVID-19 had a limited impact on our business operations, and we saw a fast recovery after 2020. The supply of medicines to patients worldwide was uninterrupted.

Gaining further financial flexibility and investing in future growth

Investments included measures to strengthen our business with Qutenza™ in the US. We see significant opportunities for further growth of our innovative non-opioid pain treatment. We more than doubled our customer-facing functions for Qutenza™ , the product that leverages the Nobel Prize-winning discovery of the Transient Receptor Potential Vanilloid 1 (TRPV1).

We also invested in our development pipeline by acquiring the Swiss biotech company Mestex AG with its investigational medicine Resiniferatoxin (RTX) in April 2021. The promising Phase III asset is developed to provide patients suffering from pain associated with osteoarthritis of the knee with a well tolerable, non-opioid therapy option. It leverages an innovative mechanism of action that also targets the TRPV1 receptor. We aim to launch Resiniferatoxin by 2025, which has the potential to address a market with more than 300 million patients worldwide suffering from osteoarthritis.

To create additional financial flexibility to invest in future growth, we entered the debt capital markets with a €950 million bond. The feedback from debt investors was outstanding.

Progress in key R&D projects

2021 also saw significant progress of key pipeline projects. Grünenthal enrolled the first patients in a Phase III trial to prepare for an extension of Qutenza™'s US label to include the treatment of post-surgical neuropathic pain (PSNP). In addition, our teams enrolled the first patients in a Phase I trial with its proprietary Glucocorticoid Receptor Modulator (GRM) and currently conduct a first-in human trial with its Nociceptin/Orphanin FQ peptide receptor (NOP) agonist. If approved, the product has the potential to replace opioids, providing similar efficacy with less side effects.

In terms of our manufacturing capacity, we continued to build the capabilities we need for the future. We advanced GO2025 – our strategic plan in Global Operations for the next few years. On the commercial side, we focused on building our customer-centric go-to-market model leveraging omnichannel and our performance-oriented company culture.

Fostering a high-performance culture paying off

The pandemic has accelerated the move to more flexible working. Throughout, we have maintained high employee engagement. As a testament to this, in 2021, we were certified as a Great Place to Work® in eight countries, including our headquarters in Germany. We have also continued to develop our people through on-the-job learning and other initiatives, to ensure we have the capabilities we need for the future and that we can all perform at a high level in line with our Values & Behaviours.

Conducting our business responsibly

As a global leader in pain management, we aspire to making a positive impact on society – in our core business and beyond. Our goals include driving awareness of pain as a disease and increasing access to pain management tools for patients and HCPs. We have also established a clear roadmap to substantially reduce water consumption at our sites and switch our energy supply to renewables. In 2021, we achieved a significant milestone: Our sites now send zero waste to landfills. At the same time, our stringent ethical framework – for example, bio and data ethics – guides us in how we work. In April 2021, the ESG rating agency Sustainalytics placed us in the top five percent of the global pharmaceuticals subindustry.

On behalf of the Executive Board Team, I invite you to join us in 2022 as we keep working to get closer to our vision of a world free of pain.

Gabriel Baertschi
Chief Executive Officer

Grünenthal Headquarters Campus Aachen, Germany

WHO WE ARE

BY THE NUMBERS

PAIN, ESPECIALLY CHRONIC PAIN, represents a significant burden for people and society. Its alleviation remains a significant unmet medical need. Grünenthal is the leading pharmaceutical company focused on pain therapies and research.

We are committed to transforming the future of pain management within the highest ethical and regulatory standards. A family-owned company, we have been in the business of developing innovative medicines for 75 years. Over the past five decades, we have focussed on developing, manufacturing and commercialising innovative products for the pain market.

From research to distribution, we have capabilities across the full value chain and aim to strengthen our pain leadership by developing highly innovative, non-opioid therapies. In partnership with leading science organisations, we strive to create even more value for patients and healthcare systems. Conducting our business responsibly is at the core of our strategy and culture. Acquisitions of carefully selected established brands have been the key driver of our profitability and growth. This strategy helps secure our financial stability and enables us to reinvest in pain research.

Leader in pain management

#1

in Latin America and Europe[1]

Longstanding commitment

75

years of developing innovative medicines for patients

50

years in pain research

Products sold in more than

100

countries

Solid revenue base

1.5

billion euro in 2021

Focus on innovation

200

priority patent applications filed in the last 10 years

Strong and capable team

4,500

employees worldwide

Production capacities

5

manufacturing sites in Europe and Latin America

International R&D network

2

R&D sites – one R&D Unit in Aachen (Germany) and an Innovation Hub in Boston, MA (USA)

[1] Accumulated evaluation of countries where Grünenthal is present through its own sales force; Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK, US, Brazil, Central America, Chile, Colombia, Ecuador, Dominican Republic, Mexico, Peru. Source: IQVIA MIDAS, Retail+Hospital, Q4/2021, fixed EUR. Corporation based according to IQVIA definition for International Corporation. Defined Pain Market incl.: Strong opioids, weak opioids (Codeine, Dextropropoxyphene, Dihydrocodeine, Hydrocodone, Tilidine, Tramadol), NSAIDs & plain Cox2 Inhibitors, oral solid Rx, Antimigraine Triptans & Anti-CGRPs, Lidocaine & Capsaicin Patches, Anti-epileptics & Anti-depressants with their respective share in Localized Neuropathic Pain acc. Rx information (Pregabalin, Gabapentin, Carbamazepin, Amitriptylin & Duloxetin)

OUR EXECUTIVE BOARD TEAM

Gabriel Baertschi
Chief Executive Officer

Drawing on 20 years of experience in the pharmaceutical industry, Gabriel joined Grünenthal in 2016 as Chairman of the Corporate Executive Board and Chief Executive Officer. Under his leadership, Grünenthal executed a diligent M&A strategy investing approximately €1.3 billion in the acquisition of established product brands, transformed its business model, doubled the pipeline and nearly tripled its adjusted EBITDA.

Jan Adams, MD
Chief Scientific Officer

Jan has more than 15 years of experience in healthcare and biopharmaceuticals and took over the role of CSO in 2020. Under his leadership, Grünenthal transformed its R&D strategy and operating model and significantly strengthened its pipeline of highly innovative non-opioid pain assets. Jan joined Grünenthal in July 2017 as Head of Corporate Strategy and Portfolio Management and was instrumental to many transformational initiatives working at the interface between strategy, business development, research, development and commercial.

Mark Fladrich
Chief Commercial Officer

Mark joined Grünenthal in 2017. With 35 years of experience within the pharmaceutical industry, Mark has worked in various functions, including regulatory, sales and marketing, business development, global marketing, and global commercial excellence. He has held major national, regional and global leadership roles and with this breadth of experience, Mark has transformed Grünenthal's global commercial business into a modern, purpose-driven organisation.

Fabian Raschke
Chief Financial Officer

In his 15-year career, Fabian has a proven track record of success in projects ranging from completely modernising a company's Finance function to increasing efficiency, driving growth and taking advantage of the full range of financing models. Fabian joined Grünenthal in 2016 as Head Group Controlling, before assuming the role of Chief Financial Officer in 2019. He was pivotal in Grünenthal's move to the capital markets with the first bond placement in 2021.

Victor Barbosa
Head Global Operations

Since joining in 2006, Victor has worked across Grünenthal's supply chain and operations teams. With extensive experience in diverse markets, he has been instrumental in redefining the company's organisation for product supply. As Head of Global Operations (GO), Victor is ultimately accountable for Grünenthal's product quality, cost and service to patients and customers worldwide. He leads over 1,800 people in our GO unit, spanning the full value chain of product supply. He is also accountable for Grünenthal's Contract Manufacturing Business.

Leen Hofkens
Head Global Human Resources

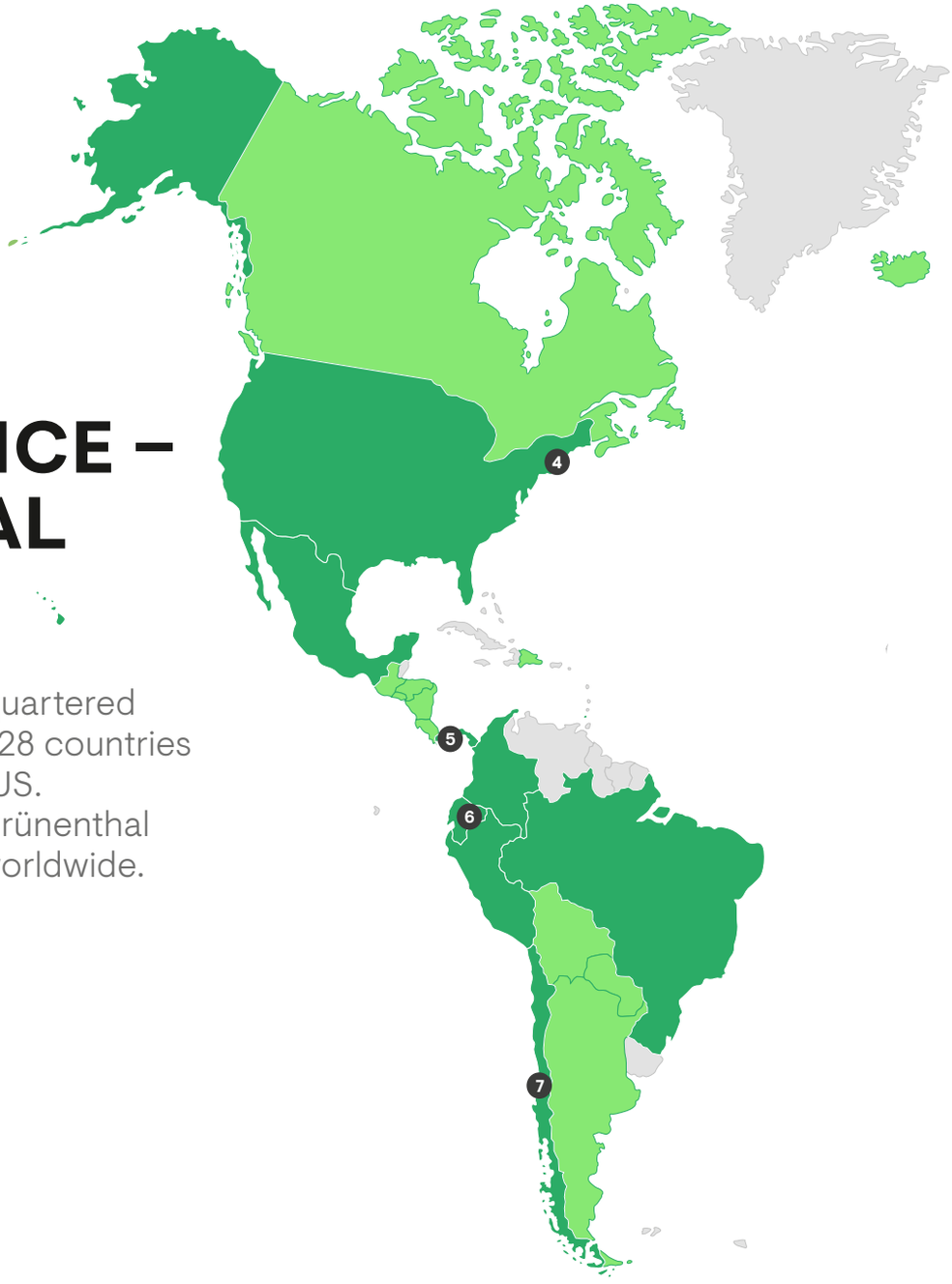
Since joining in 2018, Leen has been committed to driving a high-performance culture where diverse talents thrive in rich and varied roles, join forces and have a real impact on Grünenthal's success. Leen was instrumental in rolling out the company's Values & Behaviours, which guide our decision making and shape our culture. Leen also played a key role in strengthening Grünenthal's Performance & Development Management approach, employee engagement activities and Employer Brand.

Sebastian Köhler
General Counsel

Sebastian joined Grünenthal in 2018 to build and lead the General Counsel area comprising Legal, Responsibility, Compliance, Risk, Audit, Patents, Trademarks and Corporate Affairs. In this role, he ensures that our business gets best-in-class in-house advice supporting sustainable implementation and evolution of our strategy. Sebastian brings over ten years of expertise in leadership roles as well as in strategic advice.

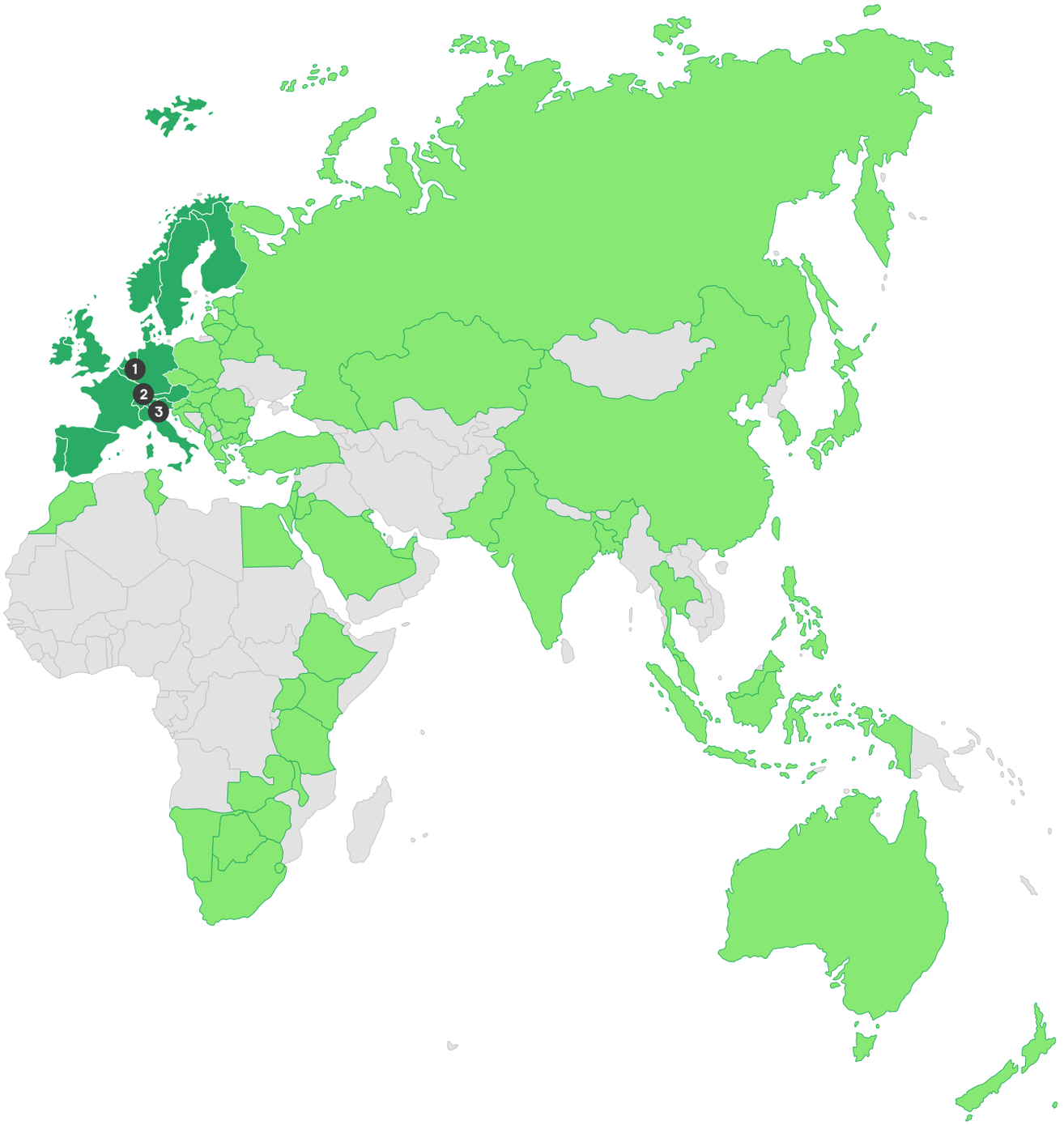
Quentin Le Masne de Chermont
Head Corporate Strategy and Portfolio Management

Before joining Grünenthal in 2019, Quentin, who's career was founded in research, spent eight years consulting companies in the healthcare sector on game-changing business strategies. He drives our business goals at the intersection of Strategy, Commercial, R&D and Operations. Quentin has additional responsibility for deal assessment of established brand acquisitions.



MARKET PRESENCE – THE GRÜNENTHAL WORLD

Grünenthal is a global company headquartered in Aachen, Germany. It has affiliates in 28 countries across Europe, Latin America and the US. Patients and customers benefit from Grünenthal products in more than 100 countries worldwide.



Grünenthal Locations
Grünenthal countries
Partner countries

Headquarters and R&D unit
1 Aachen, DE

Production
1 Aachen, DE
2 Mitlödi, CH
3 Milan, IT
6 Quito, EC
7 Santiago de Chile, CL

Innovation Hub
4 Boston, US

Regional Office
5 Panama

OUR RESPONSE TO THE COVID-19 PANDEMIC

At Grünenthal, we are proud of the solidarity and commitment our employees and partners have shown throughout the Covid-19 pandemic.

Maintaining the supply of our medicines – ensuring supply chain resilience

The Covid-19 pandemic has put an unprecedented strain on supply chains with port congestion, backlogs and truck driver shortages, to name just a few of the challenges. However, thanks to their entrepreneurial thinking, flexibility and ability to find solutions fast, our Procurement and Supply Chain colleagues have been able to guarantee production and ensure an uninterrupted supply of our medicines to patients worldwide.

The pandemic has shown us how vitally important resilient supply chains are – for us as a company and for patients who need our products. We have detected areas where we can further increase transparency in our multi-tier supply chains. We will continue to monitor and upgrade our supplier networks. Based on our experience gained through the pandemic we will further strengthen our supply chain resilience and our ability to ensure expeditious supply.

Ensuring the health and safety of our employees

Beyond complying with the regulations and laws, we also

- encourage and support remote working wherever possible;
- provide employees with protective materials including masks;
- ensure strict safety rules are maintained on site;
- assist with childcare needs;
- provide support on mental wellbeing.

We are stronger together

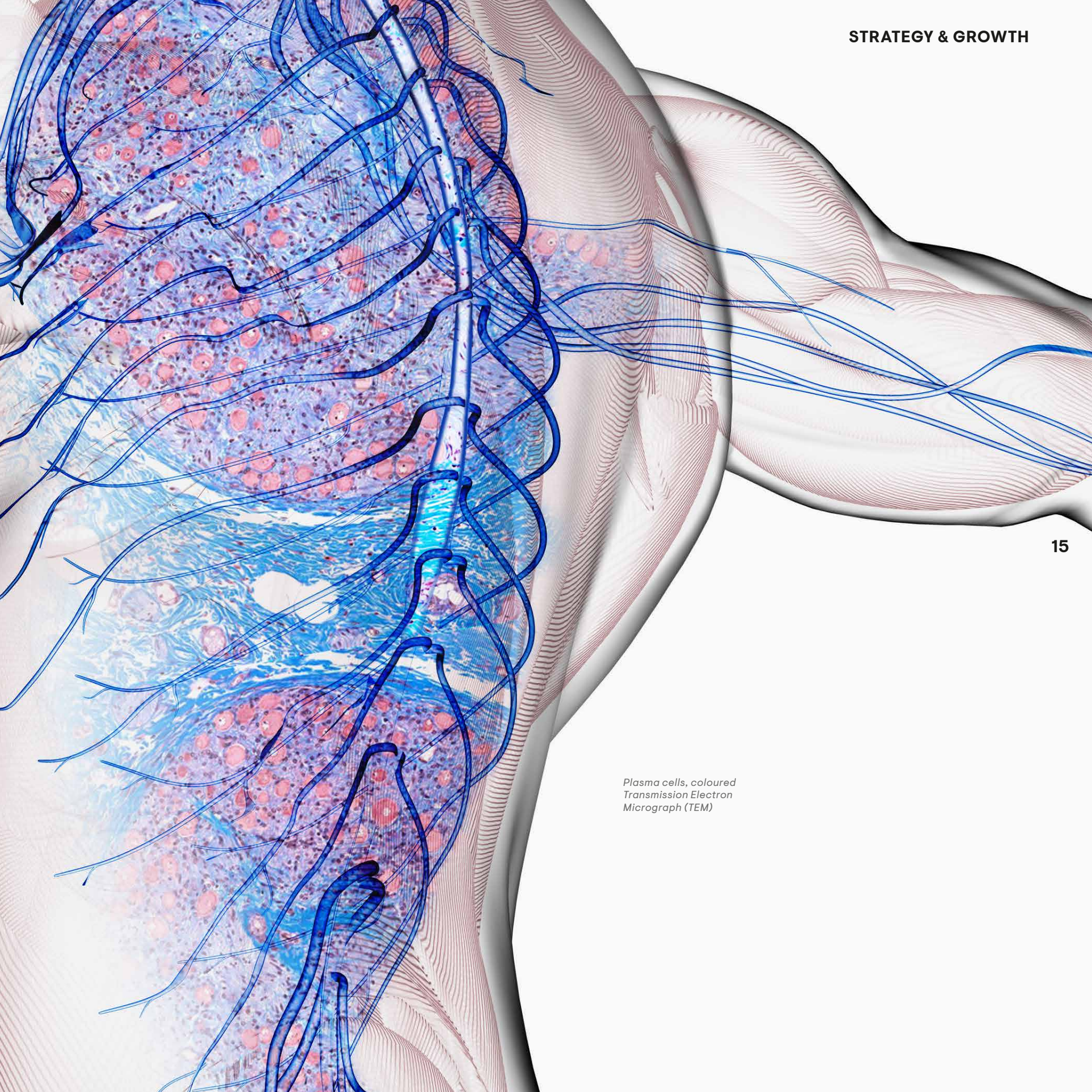
The dedication of our production, supply and distribution hubs, together with an incredible spirit of solidarity and teamwork, have supported multiple countries as they navigate the pandemic.

Our Grünenthal Foundations have donated more than €125,000. Recipients included a fund in Portugal that provides protection equipment related to Covid-19, a hospital in Colombia, and a children's charity in Germany. In France we continued sponsoring the Coalition Innovation Santé, which helps patients with chronic illness – a critical task during the pandemic. In Spain our employees donated to the Red Cross and Spanish Federation of Food Banks, helping some of those who were affected by the sudden lockdown of the economy. In Peru, students at the University of San Marco received tablet computers from our Grünenthal Foundation for Palliative Care and were able to continue their medical education despite the restrictions.

Building supply chain resilience. ***Andres Marin Gonzalez*** *and* ***Tayfun Arabacioglu****, Distribution Center Aachen, Germany*

STRATEGY & GROWTH

We have a strong corporate strategy to build and transform our company. Our results give us confidence that it is taking us in the right direction.



Plasma cells, coloured Transmission Electron Micrograph (TEM)

1. Innovation *2. Growth* *3. Acquisitions* *4. Efficiency* *5. People*

The 5 pillars of our corporate strategy

1. Innovation

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

2. Growth

Drive the commercial success of our growth brands and evolve our go-to-market model towards digital and omnichannel.

3. Acquisitions

Complement our portfolio with established brands deals, irrespective of therapeutic area.

4. Efficiency

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

5. People

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

OUR STRATEGY FOR ACHIEVING OUR VISION OF A WORLD FREE OF PAIN

As a company committed to developing and commercialising innovative pain products, we are committed to a vision of a world free of pain. Our corporate strategy is designed to bring this vision to life.

OUR CORPORATE STRATEGY IS BUILT ON FIVE PILLARS: innovation, growth, acquisitions, efficiency and people. Our results over the last few years show that our strategy is transforming our company and moving us in the right direction.

Innovation

As a science-driven company, we focus on developing novel non-opioid treatments for pain therapy. We develop promising candidates through proof of concept and beyond, 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 in the chapter A World Free of Pain.

We will also continue to selectively source early and late-stage projects to complement Grünenthal's R&D pipeline. For example, we recently acquired the compound RTX (resiniferatoxin), a highly potent, non-opioid substance with a proven and clinically validated mode of action. It targets pain associated with osteoarthritis of the knee, a huge burden with over 50 million affected people across the US and Europe. Phase III studies will start in 2022 to meet requirements for approval in Europe, the US, and Japan.

Sharing the costs and risks of late-stage development with partners is a vital part of our R&D strategy. In March 2022, Grünenthal entered an agreement with NovaQuest Capital Management for the global clinical Phase III programme of RTX. With NovaQuest, we were able to realise this principle for the first time, as the agreement significantly contributes to securing the development costs of RTX and at the same time opens headroom for Grünenthal to advance promising pipeline assets into the clinic.

Growth

Grünenthal is well positioned to maximise business opportunities and build successful brands now and in the future. This includes expanding the commercial success of Qutenza™ in the US. The label extension for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults represents a unique growth opportunity, potentially allowing us to help more patients in the US than under the original label.

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

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

Acquisitions

We 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 to our existing infrastructure and regulatory expertise;
- acquisitions that enhance our portfolio diversification in terms of products, irrespective of therapeutic area and geographies;
- immediate positive EBITDA and cash flow contributions, with an acquisition at attractive multiples, which guarantee short payback periods and fast deleveraging.

We enforce a disciplined sourcing strategy supported by robust due diligence. Leveraging our many years of experience, we ensure fast and effective integration while maintaining an uninterrupted market supply. Partners benefit from our commercial, regulatory and manufacturing expertise to achieve valuable synergies.

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™. In 2021, these brands contributed €267 million to Grünenthal's adjusted EBITDA, representing more than 70 percent of our adjusted EBITDA for 2021, which is €370 million. Manufacturing synergies reached around €7.5 million in 2021 for Nexium™, Vimovo™ and Zomig™ classic.

Efficiency

We continuously identify levers to boost efficiency throughout our value chain. Key ongoing projects include operational excellence programmes, leveraging digital technologies and automation, product redevelopment and direct spend optimisation. These improvements are integrated end-to-end, producing our own medicines and products for other pharmaceutical companies as a trusted partner.

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

Kseniia Levina, *Global Customer Experience Lead,* ***Héctor Herrera Seittiffe,*** *Global Head of Commercial Performance*

> Looking ahead, we will maintain our drive toward a high-performance culture and our passion for development. <

People

Our people are the key to our success – and our company's culture is the backbone of everything we achieve. We continued to make substantial progress on our cultural journey. In 2021, we were certified as a Great Place to Work® in eight countries, including our headquarters in Germany, and won three Best Workplaces™ certificates.

Looking ahead, we will maintain our drive toward a high-performance culture and our passion for development.

We believe strongly that diversity is the foundation for an innovative business. We are setting up a Diversity & Engagement Council to foster a culture of trust among our employees. 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 order to maintain highly effective compliance processes, we have instilled a culture to create a workforce that is ethically minded and fully engaged. In addition, Grünenthal achieved a positive ESG-rating in April 2021, putting us in the top five percent of the global pharmaceutical subindustry. You can explore more about our approach in the chapter People and Culture.

STRONG BRANDS THAT CREATE VALUE AND FUND FUTURE DRUG DEVELOPMENT

We have the expertise and strategy to maximise value in our brands, whether developed or acquired, to drive growth and fund innovation.

OUR SUCCESS BUILDS on our portfolio's complementary mix of established brands and growth brands. The established brands bring together all mature and off-patent products. They are characterised by high brand awareness, predictable sales, and high profitability. These include Nexium™, Crestor™ and brands that we have developed over a longer period, like Tramal™. The growth brands comprise our innovative and patent-protected products like Qutenza™, and our brands that continue to have valuable growth potential like Palexia™ and Vimovo™. The combination of these two product categories provides us with a well-balanced and resilient business.

But there is more to it – the profit that we generate with our established brands and growth brands gives our company financial stability. In turn, this enables us to fund the development of urgently needed innovative pain therapies.

> Combining both established and growth brands in our portfolio provides us with a well-balanced and resilient business. The profits we generate give us the financial stability to fund the development of new pain therapies that patients urgently need. <

Quentin Le Masne de Chermont,
Head Corporate Strategy and Portfolio Management

€2bn

invested in successful acquisitions since 2013.

Enriching our portfolio

Our M&A strategy is designed to enrich our portfolio of brands. We achieve this through early or late-stage asset R&D deals in the therapeutic area of pain and through the acquisition of established brands irrespective of therapeutic area.

Acquisition of early and late-stage development assets in pain

We will continue to selectively source early and late-stage projects in pain to complement Grünenthal's R&D pipeline. With our latest acquisition of Mestex AG, Grünenthal secured global rights for RTX (resiniferatoxin), an attractive late-stage asset that could offer an innovative therapy option for millions of patients affected by pain associated with osteoarthritis of the knee.

Acquisitions of well-established brands

We also seek well-established brands with stable sales performance, irrespective of the therapeutic area and geography, that can support funding for our R&D projects and secure our financial stability.

As a fully integrated pharmaceutical company with extensive experience in established brands, we can enhance the performance of acquired products to create significant value for Grünenthal and its partners. Dedicated teams ensure fast and effective integration, and we use our commercial expertise to maximise market performance while also achieving synergies through our cost-efficient manufacturing.

Acquisitions of established brands represent a unique opportunity that matches our strengths and capabilities, directly impacting 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 stabilisation phase characterised by steady 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 acquisition of Crestor™ from AstraZeneca is an example. We believe there will be more opportunities like this in the future.

Backed by the trust of our shareholders, we are a proven and reliable partner with the ability to execute such acquisitions in a fast and pragmatic way.

Further acquisitions

Besides investing in R&D assets and established brands, we are also open to acquiring selected growth brands as we did with Qutenza™, as well as companies. Since 2013 we have invested close to €2.0 billion in such successful acquisitions.

The power of partnerships

Working with partners is the best way to achieve our vision of a world free of pain.

R&D partnerships in pain management
At Grünenthal, we never stop searching for new partnerships with organisations and individuals that share our vision of a world free of pain. We believe collaboration is the key to developing life-changing treatments for patients. In this spirit, we actively seek R&D collaborations for non-opioid treatments that focus on our core pain indications: peripheral neuropathic pain, chronic post-surgical pain, chronic low back pain and osteoarthritis, and have the potential to make a real difference for patients – independent of the modality and their stage of development.

Over many decades, our experts have built strong networks by sharing knowledge and collaborating – while always maintaining a clear focus on improving patients' lives together.

Commercial out-licensing partnerships in new geographic areas
Through our commercial partner business, we give patients access to our products in territories where we do not have our own presence. This includes Canada, Central Eastern Europe, the Middle East, Asia, Australia and Africa.

Commercial in-licensing partnerships
Our exceptional commercial capabilities and regulatory expertise make us a natural partner for businesses that want to bring projects to the market successfully. We are proud of our robust in-market capabilities to commercialise brands. We do this by using both in-person promotion as well as through multiple, synchronised digital channels.

PRODUCT PORTFOLIO PERFOR-MANCE

Our product portfolio comprises a complementary mix of innovative growth brands and established brands with high levels of brand awareness.

OUR GROWTH BRANDS comprise Palexia™, Qutenza™ and Vimovo™. Palexia™ accounts for 21.5 percent of net revenues (without revenues from licensing) 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™.

Our products help patients around the world.

Diversified product mix

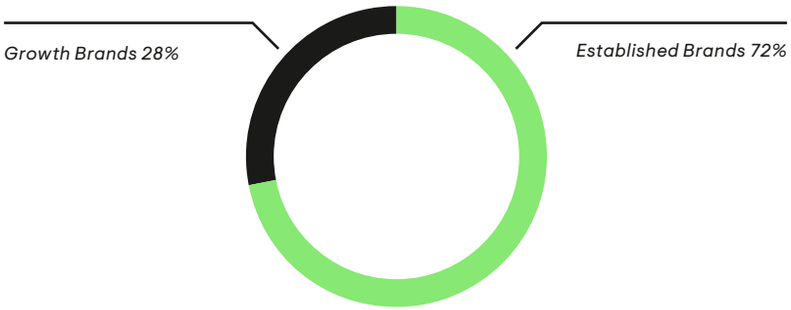
Revenue from sales of pain products accounted for 61 percent of our revenue in 2021. In recent years, we have diversified our product portfolio beyond the pain segment through successful acquisitions of established brands.

Revenue distribution by geography

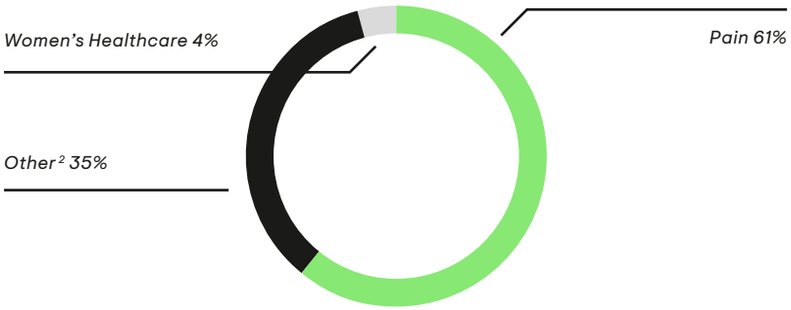
Diversifying products and geographies enables us to manage our business risks more effectively, making us less dependent on a single product or market.

Revenue split as of December 31, 2021

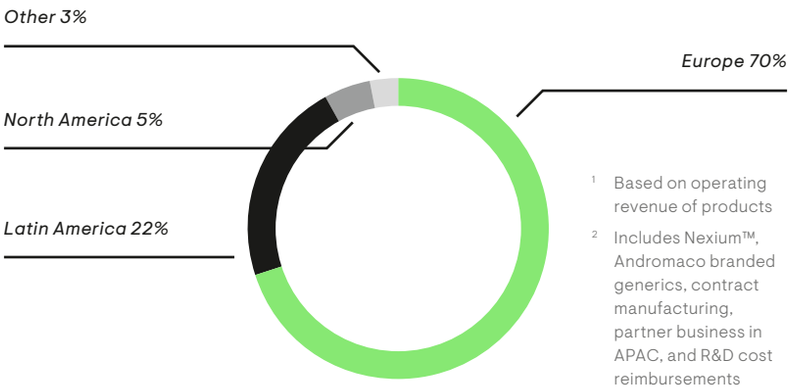
Revenue by product typology [1]



Revenue by therapeutic area



Revenue by geography



[1] Based on operating revenue of products

[2] Includes Nexium™, Andromaco branded generics, contract manufacturing, partner business in APAC, and R&D cost reimbursements

> We need the right mix of financing options to bring our plans to life. <

Fabian Raschke,
Chief Financial Officer

Fabian Raschke,
Chief Financial Officer

INTERVIEW WITH FABIAN RASCHKE,
CHIEF FINANCIAL OFFICER

> A HISTORIC YEAR FOR GRÜNENTHAL <

What does the company's first successful bond placement mean for Grünenthal's growth strategy?

FABIAN RASCHKE looks back on a historic year for Grünenthal and what the company's first successful bond placement means for its growth strategy. The bond transaction was successfully closed in April 2021 with a volume of €650 million. In July 2021, this was extended by €300 million, following strong investor demand, to a total of €950 million.

In 2021, Grünenthal closed its first bond transaction. What does that mean for the company?

Entering the capital market through a bond placement marked a milestone for Grünenthal and was a crucial step in financing our growth strategy. It provides us with the flexibility to continue our successful transformation journey. Through entering the capital market, we gained further flexibility to reinvest in pain research and pursue targeted investment opportunities which will enable sustainable and profitable growth.

The bond contributed to optimising our capital structure and diversification of our financial profile. We have also improved the maturity profile of our debt; around 95 percent of our debt facilities now mature in 2026 or later.

How do you explain the strong investor demand for the bond?

The strong demand reflects investors' confidence in Grünenthal's performance, strategy and product portfolio. Before issuing the bond, leading independent credit rating agencies affirmed our solid financial position. We also received an excellent Environmental, Social, and Governance (ESG) risk rating from Sustainalytics,[1] placing us in the top five percent among our peers in the pharmaceutical subindustry. This was positively recognised by the bond investors. We were very encouraged by these results and the market's feedback.

How does the acquisition of established brands support the company's growth plans?

Inorganic growth is one of the key pillars of our strategy. Since 2017, we have invested approximately €1.3 billion in acquisitions of mature brands 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, we insourced packaging for Nexium™ at our Aachen site. Our recent acquisitions were a key driver in the increase of our adjusted EBITDA from €129 million in 2017 to €370 million in 2021.

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

Grünenthal wants to continue its successful strategy, and we need the right mix of financing options to bring those plans to life. We pursue a two-pillar strategy: On the one hand, we focus our research on pain management, which we finance primarily internally. On the other hand, we aim to continue to strengthen our established brand portfolio through acquisitions supported by external financing.

We will select the most suitable financing instrument for each unique investment and see bonds as an integral instrument in our financing mix.

[1] New sustainability rating expected in Q3 2022

AGILE AND FUTURE-PROOF

Solid financial position confirmed

STANDARD & POOR'S assigned Grünenthal and the bond 'BB-' ratings with a stable outlook. Moody's Investors Service assigned a 'B1' rating to both the company and the bond, with a positive outlook. Fitch Ratings assigned a rating of 'BB' to Grünenthal (stable outlook) and a rating of 'BB+' to the bond. All above ratings issued April 2022.

Continuing to build the capabilities we need for the future

CFO Fabian Raschke knows that it takes a dedicated and ever-evolving team that joins forces to ensure the company remains agile and meet its growth targets.

> We encourage our people to challenge the status quo, improve processes and implement new solutions. For example, by utilising data analytics, our Finance team acts as a true Business Partner in operative and strategic decision-making.

To enhance agility across the business, we are enabling other business areas to move towards more self-service. This is exemplified in our planning process. Here, we implemented an integrated and automated planning solution with a single platform used by all functions – an easy-to-use tool with intelligent pre-fills. This facilitates greater cooperation between Finance and the business areas, improving the quality of our planning and strengthening our business steering capabilities.

Our IT experts provide process know-how and solutions that empower our colleagues to maximise their impact on our shared success – including providing cutting-edge technologies along every step of our value chain.

For instance, we support our Commercial teams in implementing a customer-centric go-to-market model utilising an omnichannel approach. Another example is our global Business Intelligence Portal, which has equipped our teams around the world with a powerful platform where users can obtain and share business information across functions and affiliates. The portal increases transparency, democratises access to steering-relevant information and thereby supports decision-making.

Through our Global Business Services (GBS), we have centralised, standardised and automated many processes related to finance and tax, making use of Robotic Process Automation. GBS is currently expanding the scope to cover additional areas such as Supply Chain, IT and Quality Assurance. This will further enhance efficiencies. <

Joining forces to ensure Grünenthal remains agile:
Mona Oltmanns, *Global Commercial Manager*
Jud-Reginauld Fidalgo Estevez, *Project & Application Manager Global Operations*
Franziska Krezdorn, *Asset Lead Qutenza™*

OUTSTANDING FINANCIAL PERFORMANCE

Significant investment in our future built on the strong performance of today.

2021 WAS ANOTHER record financial year for Grünenthal, thanks to the double-digit growth of our growth brands, further realised efficiencies in manufacturing and supply, our resilient business model and financial discipline. Our performance proves that our strategy is taking us in the right direction.

At the same time, we are investing in our future. To unlock the full product potential of Qutenza™, we expanded our commercial infrastructure in the US. In April 2021, we closed the acquisition of Mestex AG and thus worldwide rights to RTX (resiniferatoxin). RTX is a natural, highly potent, non-opioid substance with a well-known and clinically validated mechanism of action, similar to that of capsaicin used in Qutenza™. It is intended for the treatment of pain associated with osteoarthritis.

The osteoarthritis market is expected to exhibit strong growth from $7.3 billion in 2020 to approximately $11.0 billion in 2025, constituting a large global commercial opportunity. For the indication of knee osteoarthritis only, we estimate peak sales potential to be more than €1 billion in Europe and the United States. We are currently preparing a Phase III programme in the indication of knee osteoarthritis and expect to launch in 2025.

The following key figures provide a measure of our progress.

Profit and loss statement [1]

IN € MILLION	ACTUAL 2020	ACTUAL 2021
Revenue [2]	**1,280**	**1,467**
Cost of sales [3]	-413	-438
Gross profit [4]	**867**	**1,029**
Marketing, Sales & Medical costs [5]	-384	-424
Core Research & Development costs	-137	-140
Other costs	-250	-300
Depreciation Fixed Assets [6]	191	151
EBITDA	**288**	**316**
Adjusted EBITDA [7]	**338**	**370**
Earnings before taxes	**63**	**115**

[1] **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

[2] **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

[3] **Cost of sales** are any costs that can be directly associated with products sales

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

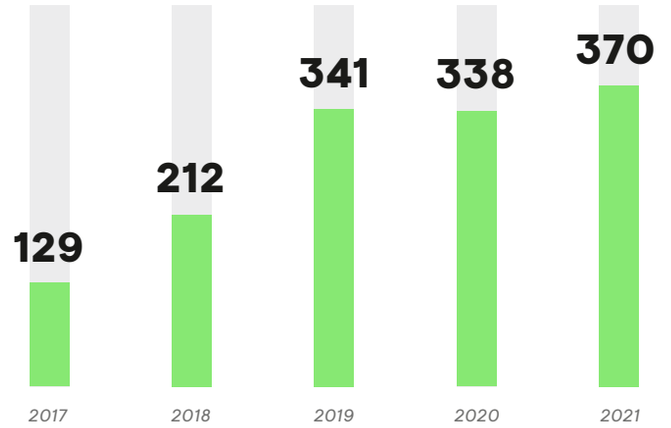
[5] **Marketing, Sales & Medical costs** consists of all costs to promote, sell and distribute our products to the customer. This excludes depreciation on acquired products which is part of "other costs"

[6] **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

[7] **Adjusted EBITDA**, short for adjusted Earnings Before Interest, Taxes, Depreciation and Amortisation, is a key performance indicator for the Grünenthal Group. It is calculated by adjusting the operating result for amortisation, depreciation and impairment and special effects, in particular from restructuring and acquisition-related expenses

The strong revenue growth is primarily driven by our growth brands Palexia™, Qutenza™ and Vimovo™ (+€65 million or +19 percent) and our established brands Nexium™ (+€27 million or +17 percent) and Versatis™ (+€19 million or +16 percent) mainly on the back of promotional efforts. In addition, the successful acquisition of Crestor™ in February 2021 contributed with €72 million.

Adjusted EBITDA in € million



Adjusted EBITDA significantly increased in 2021 compared to 2020 (+10 percent) despite substantial investments in our future. The improvement of Adjusted EBITDA was mainly driven by significant improvement of gross profit by €161 million (+19 percent), based on strong organic growth in operating revenue of our Growth Brands by €65 million and our Established Brands by €147 million. The latter was strengthened by the profit transfer following the Crestor™ acquisition (€72 million). Additionally, further realised efficiencies in manufacturing and supply contributed to the positive gross profit development.

Cash flow, net debt and leverage management

Our business model combined with our financial discipline leads to a strong operational cash flow which we use to invest especially in the acquisition of established products and to quickly deleverage after acquisitions. While we are willing to temporarily increase our leverage to finance acquisitions, our ambition is to rapidly deleverage to our mid-term target of <2.5x thereafter. 2021 is a good example of applying this principle successfully in practice, as our net leverage at year-end is below 2.0x despite having invested €265 million in Crestor™ and €51 million in the acquisition of Mestex AG. The leverage multiple indicates the net debt in relation to the adjusted EBITDA of the last 12 months.

Outlook

After a record financial year in 2021, we expect 2022 to be a transitional year with stable financial results and continued growth.

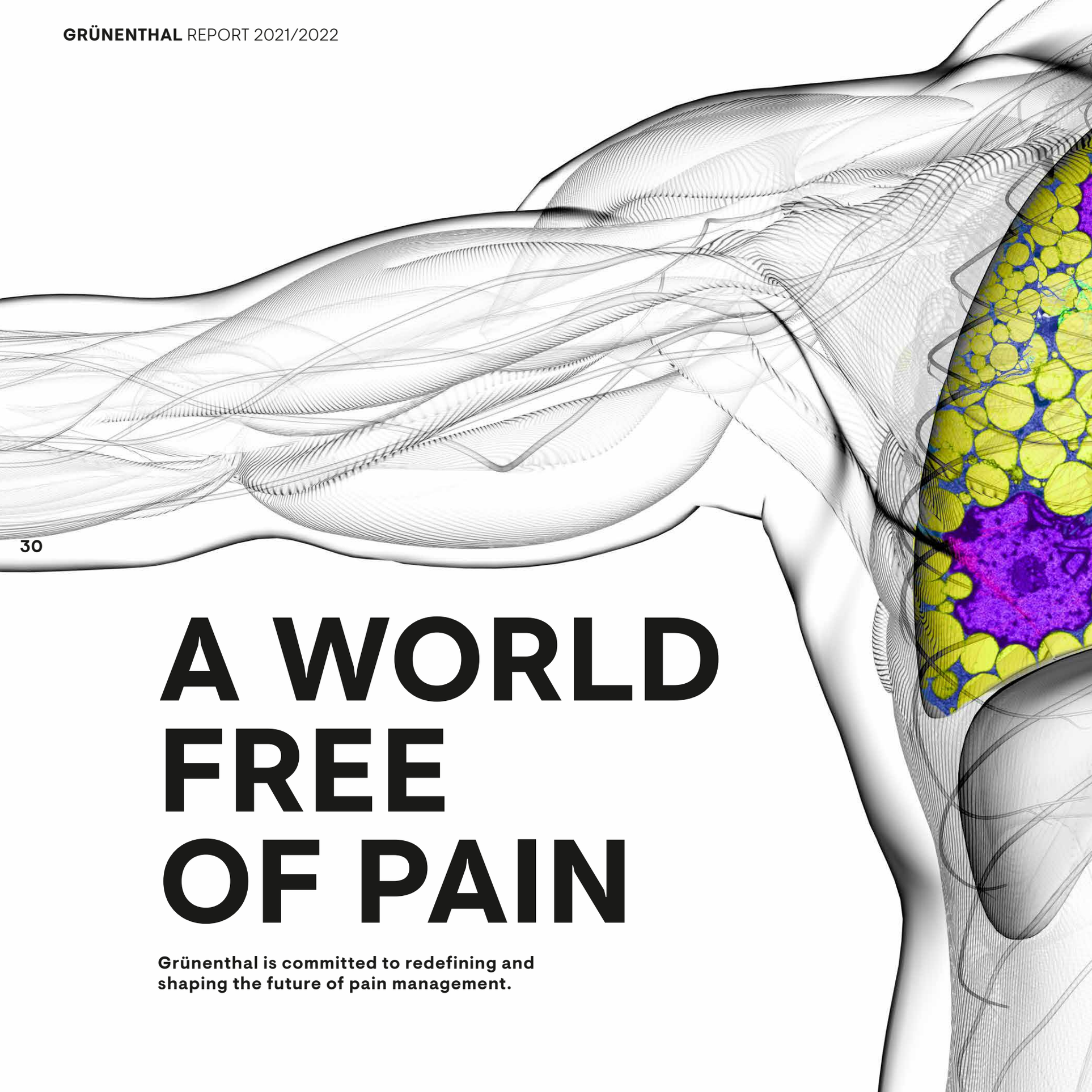
One of our key priorities is to proactively manage the lifecycle of our products through maximising sales opportunities while monitoring the market for the possible entry of alternative products for Palexia™ and Versatis™. For 2022, we expect only limited sales erosion from Palexia™, which should be offset by our continued ramp-up of sales of our growth brand Qutenza™.

We expect the development of our established brands to be more or less stable. They will continue to benefit from our targeted commercial initiatives and optimisation across the value chain. We have extensive experience in actively managing the product lifecycle of our brands, for example, by reducing costs throughout the value chain to maintain or even increase their profitability. We expect to reap the full financial benefit of taking over packaging for Nexium™.

We will continue to adapt our commercial strategy to further sharpen our specialty care focus. The impact of recent geopolitical developments will be mitigated as far as possible with prudent productivity, cost and supply chain management.

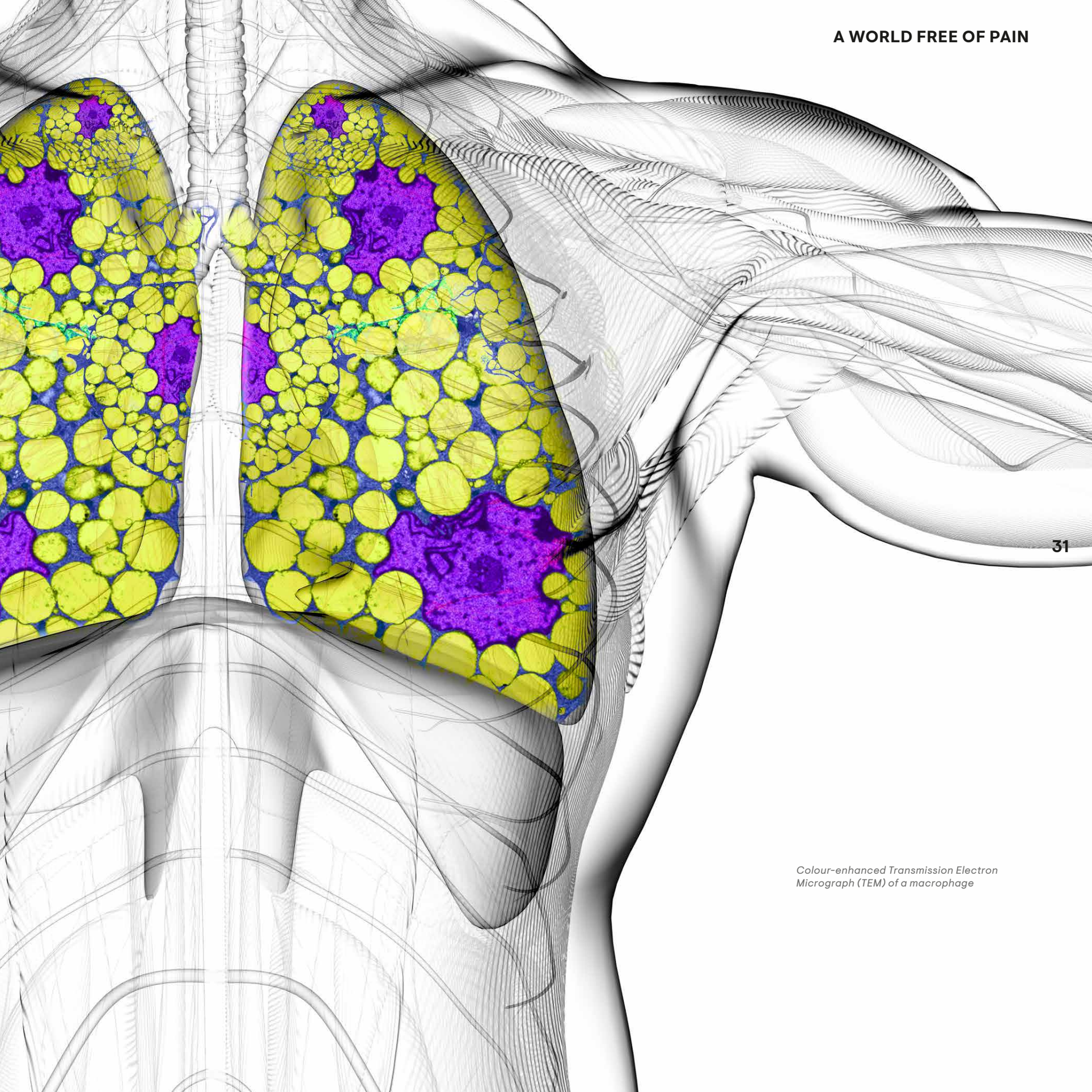
We will maintain our strategic focus on maximising and further advancing our existing R&D pipeline, in particular RTX (resiniferatoxin) and Qutenza™ post-surgical neuropathic pain (PSNP). We will follow our R&D cost-sharing strategy with development partners, as we did with NovaQuest for RTX.

While maintaining financial discipline, we will continue to pursue deals that strengthen our established brand portfolio with products that offer stable revenue and strong brand equity.



A WORLD FREE OF PAIN

Grünenthal is committed to redefining and shaping the future of pain management.



Colour-enhanced Transmission Electron Micrograph (TEM) of a macrophage

OUR COMMITMENT TO RELIEVING PAIN

Imagine a disease that affects up to one in five people in the world [1] – which equates to more than 1.5 billion individuals – and their families and friends.

A DISEASE that is one of the most common reasons for people to seek medical help, one of the major causes of people withdrawing from the labour market early, and a significant contributor to disability retirement. A disease associated with multiple different conditions and for which patients frequently experience limited efficacy from the available medicines.

This disease exists. It is called chronic pain.

At Grünenthal, we consider pain 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. After developing six important treatment options for pain patients, we are now a global leader in pain research and management.

This success story began in the 1970s, with Tramal™ (Tramadol), which today is one of the most frequently prescribed opioid analgesics in the world. Another example is Palexia™ (Tapentadol), the first innovative molecule in the opioid analgesic class to be approved for more than 25 years. Today, it continues with Qutenza™, a non-opioid product at the heart of pain leadership, leveraging Nobel Prize-winning science.

We know that patients are still acutely 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 substantial unmet medical need in large patient populations:

- Peripheral neuropathic pain
- Chronic post-surgical pain
- Chronic low back pain
- Osteoarthritis

For 50 years, we have been progressing towards our vision of a world free of pain. With every research project we pursue and every medicine we deliver, we strive to positively impact patients' lives.

[1] Treede RD, et al. Pain. 2015 Jun;156(6):1003-1007

By providing pain management we strive to improve our patients' lives.

A GLOBAL DISEASE

Pain is a disease that creates an increasing global burden.[1] It impacts patients, their families, friends, caregivers and society as a whole.

CHRONIC PAIN is pain that lasts longer than three months.[2] It can be due to an underlying disease such as cancer or arthritis,[3] or it may have no obvious cause.[4] It may also continue after the original injury has healed.[5] Chronic pain is influenced by several interconnected factors that are biological, psychological and social, such as injury, illness or nerve damage, poor sleep, anxiety, depression.[6]

In 2019 the International Association for the Study of Pain and the World Health Organization recognised chronic pain as a health condition in its own right.[7]

Some of the most common types of chronic pain are[8]:

Migraine | *Pain associated with osteoarthritis* | *Low back pain or lumbar pain* | *Neck pain* | *Musculoskeletal pain*

78%

of chronic pain patients state that they were not satisfied with the efficiency of the treatment they received.[9]

60%

of permanent work incapacity in Europe is related to musculoskeletal pain alone.[10]

13%

Lower Back Pain prevalence in Southern Latin America in 2017.[11]

1 Mills SE. British Journal of Anaesthesia, 2019;123 (2): e273ee283

2 World Health Organization (WHO). International Classification of Diseases 11th Revision (ICD-11). MG30 Chronic pain. 2019. Available at: https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1581976053. Accessed January 2022

3 Orr PM, et al. Crit Care Nurs Clin N Am. 2017;29:407–18

1 in 5

people suffer from chronic pain worldwide.[12]

€300bn

estimated total cost of the consequences of chronic pain across Europe.[15]

53-90%

of adults with chronic pain experience a clinically significant degree of insomnia.[13]

$560-635bn

estimated medical costs and lost productivity per year caused by chronic pain in the US.[14]

4 National Pharmaceutical Council. Pain: Current Understanding of Assessment, Management, and Treatments. 2001. Available at: www.npcnow.org/sites/default/files/media/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf. Accessed January 2022

5 Orr PM, et al. Crit Care Nurs Clin N Am. 2017;29:407–18

6 Dueñas M, et al. J Pain Res. 2016;9:457–67

7 Treede RD, et al. Pain. 2019;160(1):19–27

8 Rice ASC, et al. Pain. 2016;157(4):791–796

9 Pain Alliance Europe, 2017, Survey on Chronic Pain 2017, Diagnosis, Treatment and Impact of Pain

10 Bevan, S. et al., Reducing Temporary Work Absence Through Early Intervention: The case of MSDs in the EU, 2013

11 Wu A, March L, Zheng X, Huang J, Wang X, Zhao J, Blyth FM, Smith E, Buchbinder R, Hoy D. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. Ann Transl Med 2020;8(6):299. doi: 10.21037/atm.2020.02.175

12 Treede RD, et al. Pain 2015 Jun;156(6):1003-1007

13 Nijs J, et al. PMR 2020 410-419

14 Cohen S.P, et al. Lancet. 2021;397:2082 -97

15 Pain Alliance Europe. Survey on chronic pain. 2017. www.pae-eu.eu/wp-content/uploads/2017/12/PAE-Survey-on-Chronic-Pain-June-2017.pdf. Accessed February 2022

DEVELOPING LIFE-CHANGING PAIN MEDICINES FOR PATIENTS

By driving innovation in the therapeutic area of pain and building new commercial capabilities, we can better serve our customers' needs.

EXISTING PAIN THERAPIES work for some patients – but not for all. In a European survey, 40 percent of patients were not satisfied with their pain management.[1] Therefore, there is a clear need for innovative treatment options that provide better outcomes for larger patient groups.

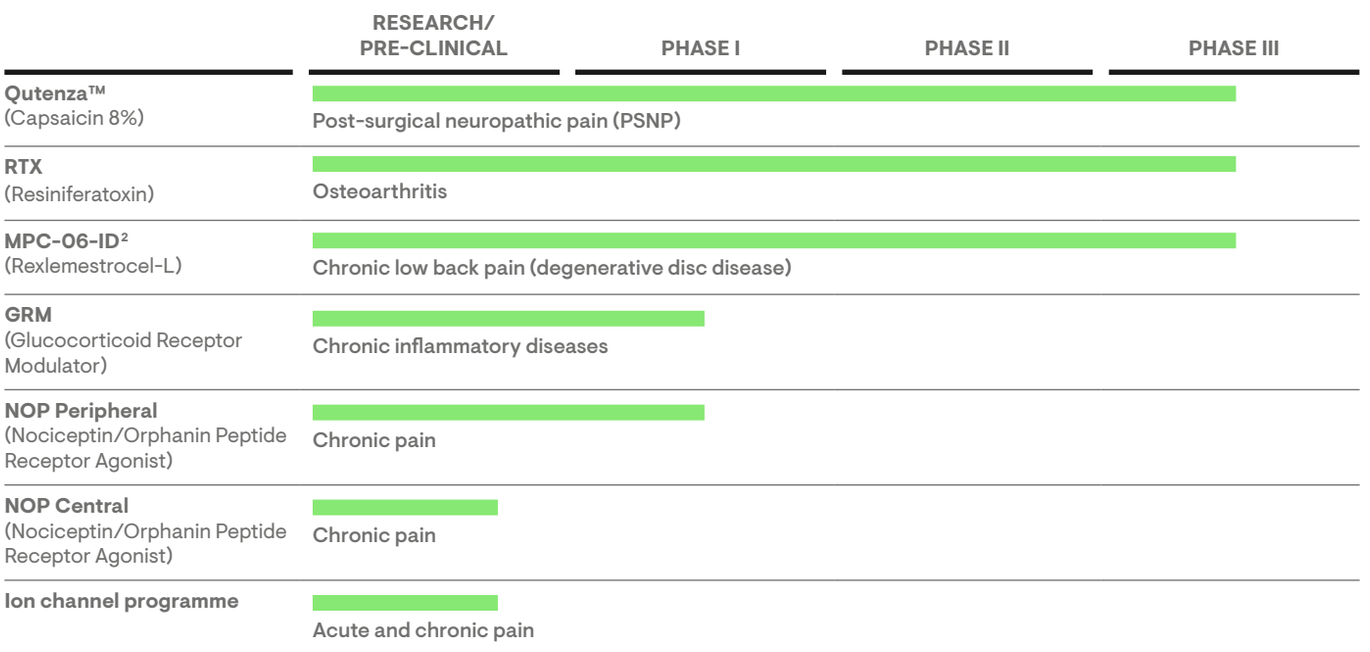
Grünenthal is uniquely positioned in the therapeutic area of pain. Since the 1970s, we have focused on developing innovative pain therapies and have become one of the leading companies in this area.

Our scientists have developed numerous life-changing pain medicines for patients.

In 2021 we made significant progress in strengthening our pipeline and executing on our priority projects.

Our R&D portfolio

Promising assets with a focus on non-opioid treatments



[1] Breivik H, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287-333

[2] Collaboration with Mesoblast

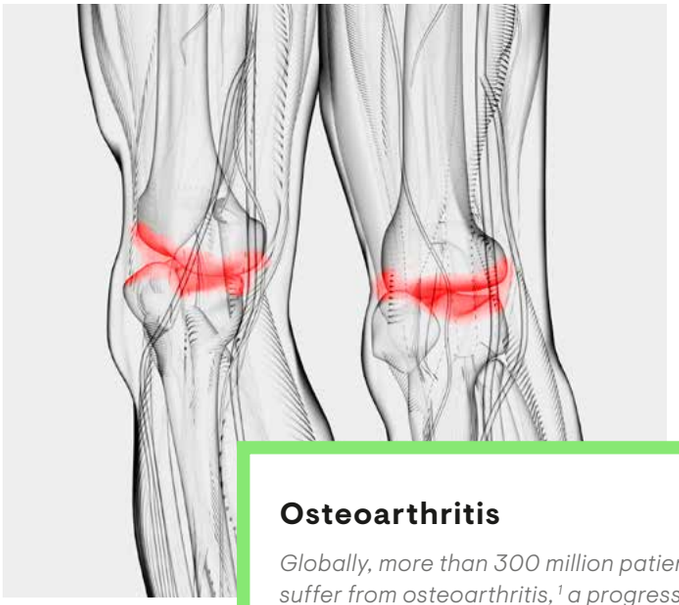
> Our scientific understanding of pain and its pathophysiology has improved massively in recent years. We are at the brink of significant progress in pain therapy, and Grünenthal wants to be a key driver of this progress. <

Jan Adams,
MD, Chief Scientific Officer

Jan Adams, *Chief Scientific Officer, and* ***Stephanie Hennen,*** *Gene & Protein Function Lab Head*

OUR LEAD PROGRAMMES

To move closer to our vision of a world free of pain, we currently pursue a range of R&D programmes.



Osteoarthritis causes the tissues in the affected joints to break down over time.

RTX – Promising treatment for pain associated with osteoarthritis

In April 2021, we acquired Mestex AG. This Swiss company has developed the innovative investigational medicine RTX (resiniferatoxin) for the intra-articular treatment of pain associated with osteoarthritis (OA) of the knee. Osteoarthritis is a progressive condition that currently cannot be cured. RTX, being a highly potent TRPV1 agonist, has a well validated mechanism of action and initial data shows a long-lasting and significant analgesic effect and functional improvements compared to placebo, as well as a favourable safety profile.

In 2022, we will start two pivotal Phase III trials to investigate the efficacy, safety and tolerability of RTX in patients with pain associated with OA of the knee. These studies are part of a global development programme aimed at meeting the requirements for approval in the EU, the US and Japan. The trial design has already been agreed with the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

In March 2022, Grünenthal entered an agreement with NovaQuest Capital Management for the global clinical Phase III programme of RTX. NovaQuest manages over $2.75 billion of investor capital across multiple asset classes to promote the development and growth of next-generation medicines.

Under the terms of our agreement, NovaQuest will reimburse Grünenthal's investments into the clinical Phase III programme of RTX and share the clinical development and approval risks with Grünenthal. In case of successful development and marketing approval, NovaQuest receives one-time payments or milestones and revenue-based payments over the course of the commercialisation.

Osteoarthritis

Globally, more than 300 million patients suffer from osteoarthritis,[1] a progressive condition and the most common joint disease in people aged 65 and older – it mostly affects the knees, hands, hips, neck and lower back. It causes the tissues in the affected joints to break down over time, and currently, it cannot be cured. The inflamed, swollen, and painful joints limit the mobility of the affected patients and may impact their quality of life significantly.[2]

For many patients, the available treatment options are not sufficient, and they may experience severe symptoms, including pain, at some point in time. Osteoarthritis treatment usually includes exercise, maintaining a healthy weight, and medication like intra-articular corticosteroids.[3] Eventually, many patients require joint replacement surgery.

1 Cieza, A., Causey, K., Kamenov, K., Hanson, S. W., Chatterji, S., & Vos, T. (2020). Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10267), 2006-2017

2 ICD-11 https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f558562409

3 National Institute of Arthritis and Musculoskeletal and Skin Diseases; What Causes Osteoarthritis, Symptoms & More | NIAMS (nih.gov)

RTX has the potential to be a transformative asset for Grünenthal. It strengthens our late-stage pipeline and allows us to pursue a truly global development programme covering Europe, the US and Japan, opening up a significant business opportunity.

For more information on our development of RTX, read “Nobel Prize-winning science points to the next generation of pain therapy” on page 42 of this report.

Qutenza™ label extension – Reaching more patients in the US

The US FDA approval of 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 treatment to more patients worldwide. Painful DPN is a progressive and debilitating complication of diabetes that affected more than five million Americans in 2020 and is challenging to diagnose, treat and manage effectively. [4]

Qutenza™ is a topical system containing prescription-strength capsaicin. It is a non-opioid treatment that can provide prolonged pain relief for several months while most frequently reported adverse events were transient, self-limiting, mild to moderate application site reactions. [5]

In Europe, it is approved for the treatment of peripheral neuropathic pain. In the US, it is approved for the treatment of peripheral neuropathic pain associated with post-herpetic neuralgia, and in 2020 it also received approval for the treatment of pain associated with DPN of the feet in adults. [6]

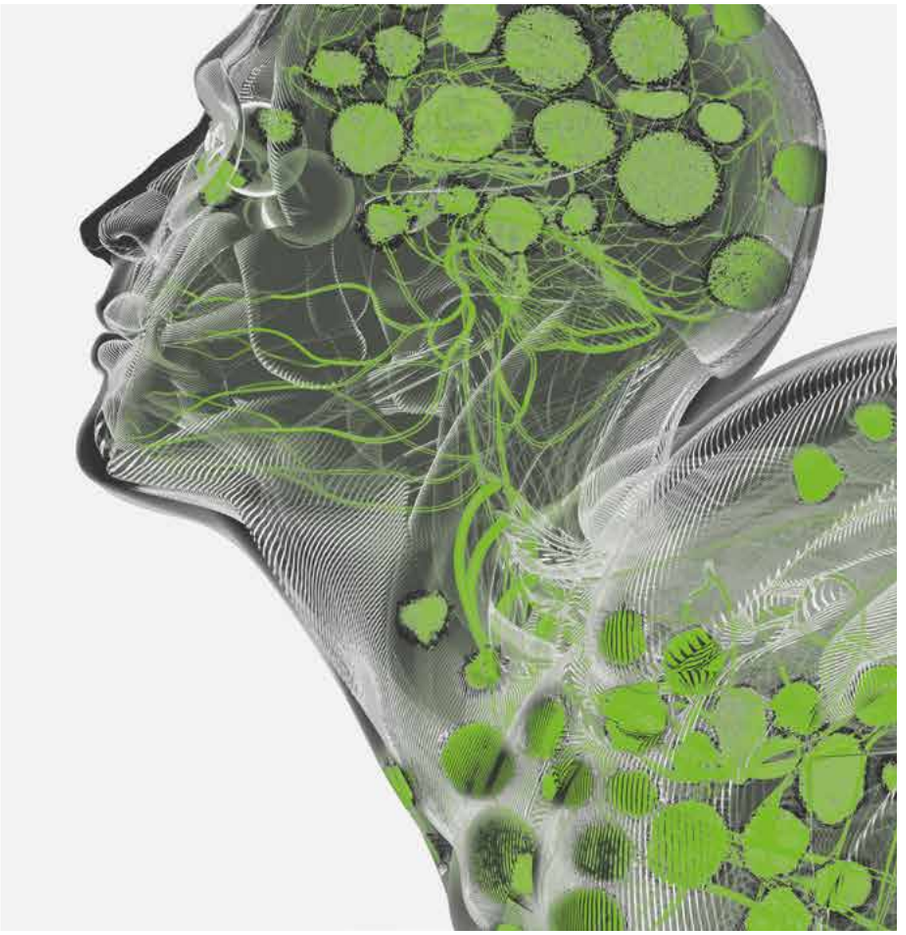
Our life-cycle management efforts focus on making Qutenza™ more widely available by expanding the label particularly in the US. Specifically, our researchers developed an additional Phase III programme to study the efficacy, safety and tolerability of Qutenza™ in post-surgical neuropathic pain (PSNP). The first patients were enrolled in a pivotal Phase III trial in Q3 2021. We also pursue further exploratory activities with external partners in other indications.

For more about how we are getting this important medicine to patients, read “Accelerating the growth of Qutenza™” on page 46 of this report.

4 LTP 2020-2030: ADDRESSABLE POPULATIONS BY CONDITION (PDPN, PSNP, PHN, CINP). Company data on file. April 30, 2020

5 Summary of Product Characteristics (SmPC) Qutenza™

6 Qutenza™ [prescribing information]. Morristown, NJ: Averitas Pharma



Coloured Transmission Electron Micrograph (TEM) of a section through the granules of a human mast cell, isolated from connective tissue

MPC-06-ID – Cell therapy for chronic low back pain

In 2019, we partnered 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 Phase III trial MSB-DR003 that was carried out in the US and Australia. The trial provided several 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 analysing the data obtained through this trial, Mesoblast anticipated conducting another confirmatory trial in the US and received positive feedback from the FDA regarding a new Phase III programme for MPC-06-ID in patients with chronic low back pain due to degenerative disc disease. The new trial will be conducted with up to 20 percent of the patient population involved being from Europe to support potential product approvals in both the US and Europe.

NOP - Promising treatment for patients with pain

Our proprietary Nociceptin/Orphanin FQ Peptide receptor (NOP) agonist is an oral investigational medicine with a unique mechanism of action for treating chronic pain. We develop the compound to provide a non-opioid therapy option that offers a strong analgesic effect without the side effects commonly associated with opioids.

Millions of patients suffer from chronic pain and need improved treatment options. Although several treatment options are available, many patients with chronic pain still suffer from treatment non-response or insufficient pain relief.

The peripherally restricted NOP agonist offers exciting potential to address these significant unmet needs.

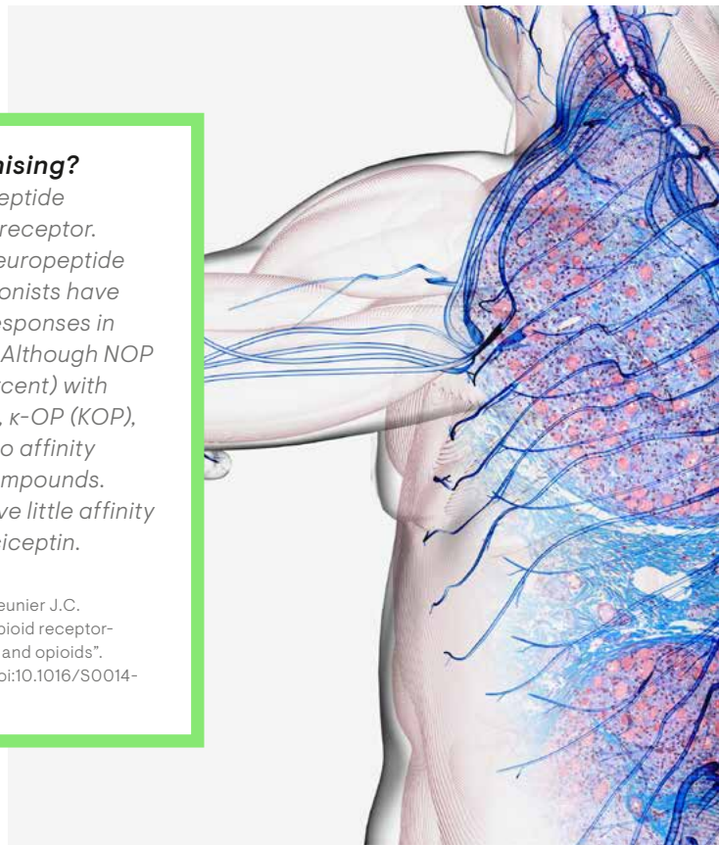
The selectivity of the investigational medicine for the NOP receptor, combined with its restriction to the peripheral nervous system, is predicted to confer analgesia with an improved safety profile compared to the current standards of care.

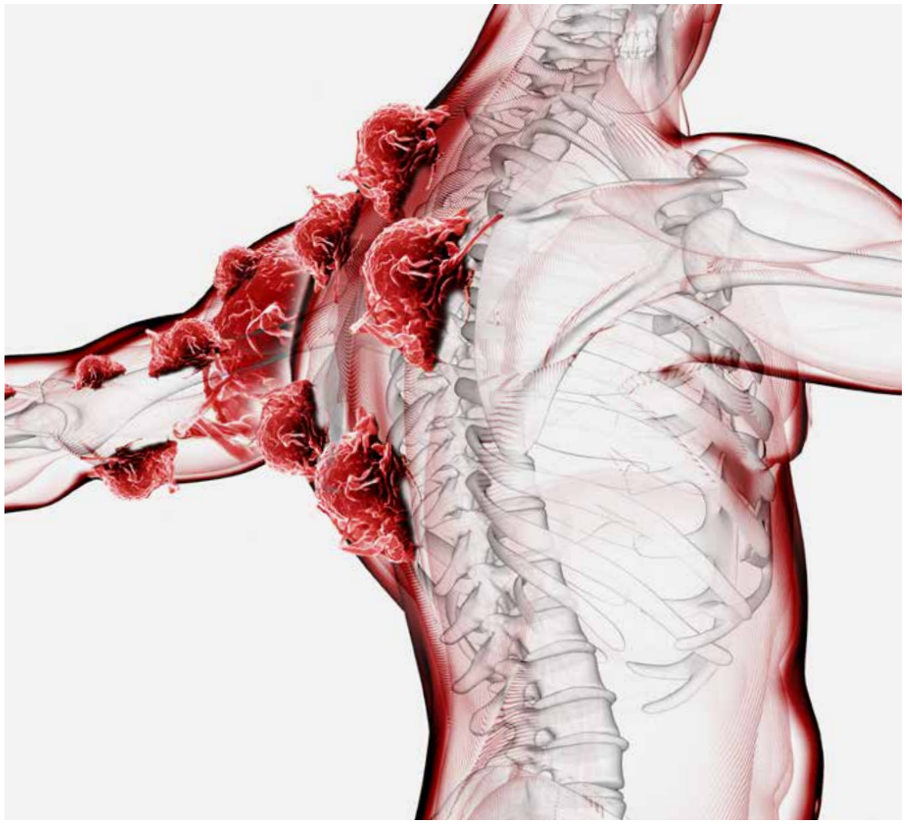
This programme is based on our many years of intense and ground-breaking research in the field of NOP receptors. It opens up a unique opportunity for a transformative first-in-class treatment. The most advanced compound within our NOP programme will enter Phase IIa in late 2022.

Why is the NOP receptor so promising?

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 nociceptive responses in pre-clinical models of hypersensitivity. Although NOP shares high sequence identity (~60 percent) 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 have little affinity towards NOP's endogenous ligand nociceptin.

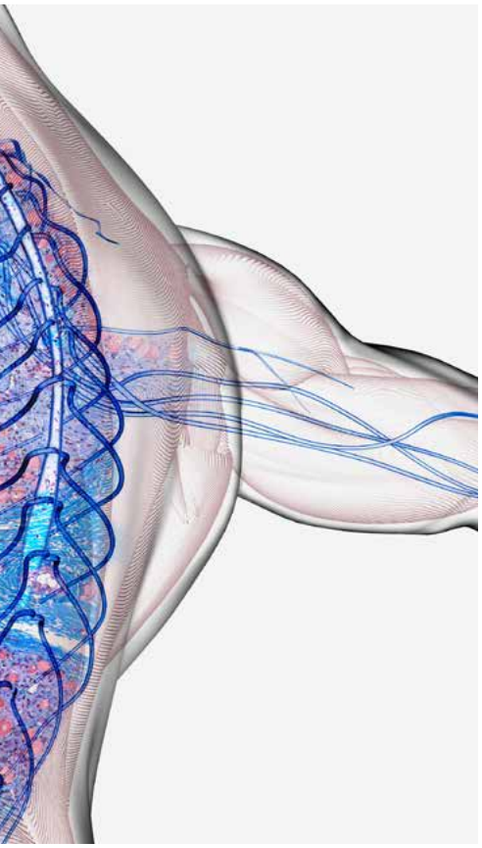
Butour J.L., Moisand C., Mazarguil H., Mollereau C., Meunier J.C. (February 1997). "Recognition and activation of the opioid receptor-like ORL 1 receptor by nociceptin, nociceptin analogs and opioids". European Journal of Pharmacology. 321 (1): 97–103. doi:10.1016/S0014-2999(96)00919-3. PMID 9083791





Colour-enhanced Scanning Electron Micrograph of a human macrophage

Light microscopy of a nerve ganglion



GRM - Potential anti-inflammatory with an improved safety profile

Our proprietary Glucocorticoid Receptor Modulator (GRM) 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.

While glucocorticoids are highly effective anti-inflammatory drugs, they come with several significant side effects, including reduced bone formation that may lead to osteoporosis and increased glucose levels, which raises the risk of diabetes. Despite their efficacy, these side effects are a strong limitation for the long-term use of glucocorticoids.

The clinical Phase I study for our GRM includes, among others, a head-to-head comparison between the investigational medicine and prednisolone. 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 biomarker data early in the clinical development, our experts investigate if the GRM is differentiated from prednisolone and if it might offer a therapy option that combines high efficacy with a significantly improved safety profile. The results of the study are expected in 2022.

NOBEL PRIZE-WINNING SCIENCE POINTS TO THE NEXT GENERATION OF PAIN THERAPY

What makes us feel pain? In 2021, two scientists who asked this question received the Nobel Prize for discoveries that have laid the foundation for new pain treatments.

ONE OF THOSE DISCOVERIES, the Transient Receptor Potential Vanilloid 1 (TRPV1), is the basis for effective non-opioid pain medicines Grünenthal is developing.

The scientists set out to better understand how we perceive our environment and the mechanisms behind how we sense stimuli like heat and pressure. Neuroscientist Ardem Patapoutian wanted to know how humans sense touch. His team identified the genes responsible for two new ion channels sensitive to pressure, PIEZO1 and PIEZO2.

The other joint winner of the 2021 Nobel Prize in Physiology or Medicine, David Julius, a professor at the University of California, San Francisco, USA, wanted to know what causes a burning sensation when eating chillies. He and his team were able to identify a sensor in the skin's nerve endings that responds to heat. Named TRPV1, this single genetic receptor of the chemical compound in chillies – capsaicin – links capsaicin and temperature sensitivity.

Relief for patients with osteoarthritis of the knee

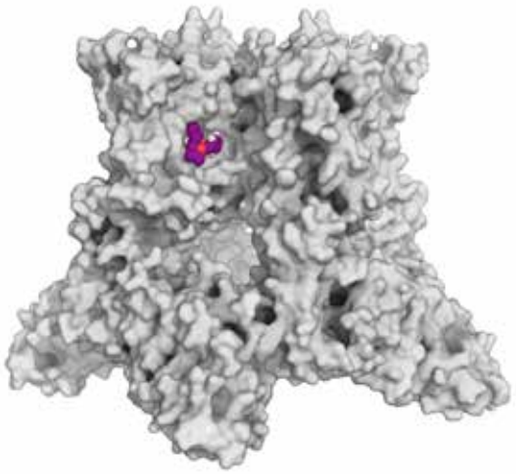
Grünenthal is leveraging the groundbreaking discovery of TRPV1 in several ways. First, through what, if approved, could become a non-opioid therapy option for osteoarthritis patients: resiniferatoxin, or RTX, an asset Grünenthal secured by acquiring the Swiss company Mestex AG in April 2021. RTX is intended to provide long-lasting pain relief for patients suffering from pain associated with osteoarthritis – pivotal Phase III trials will be started in 2022.

Osteoarthritis affects around 300 million people globally.[1] Many patients who experience moderate to severe pain with this condition receive intra-articular corticosteroids or undergo knee replacement surgery as last remaining treatment option.

> **We aim to provide patients suffering from pain associated with osteoarthritis of the knee with a well tolerable, non-opioid therapy option that provides long-lasting pain relief and functional improvement of the affected joints.** <

Jan Adams,
MD, Chief Scientific Officer

[1] Cieza, A., Causey, K., Kamenov, K., Hanson, S. W., Chatterji, S., & Vos, T. (2020). Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10267), 2006-2017



Computer-animated representation of the TRPV1 receptor including resiniferatoxin marked in lilac colour

Alleviating pain after surgery

The second application involving the TRPV1 receptor is the non-opioid patch Qutenza™, which can provide prolonged pain relief for several months while most frequently reported adverse events were transient, self-limiting, mild to moderate application site reactions.[2]

Grünenthal acquired the global rights for Qutenza™ in November 2018. Since then, Grünenthal has worked consistently to make the product available to more people in the US. In 2020, the FDA approved Qutenza™ for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. DPN is a progressive and debilitating complication of diabetes that affected more than five million Americans in 2020.[3]

It is challenging to diagnose, treat and manage effectively. Through a new clinical Phase III trial, Grünenthal strives to include another major indication in the field of peripheral neuropathic pain in the US label: post-surgical neuropathic pain (PSNP). PSNP affects approximately 13 percent of all patients undergoing surgery, which represents 3.3 million patients per year in the US.[4] In Q3 2021, Grünenthal enrolled the first patients in a Phase III trial to investigate the efficacy, safety, and tolerability of Qutenza™ in post-surgical neuropathic pain to support an extension of the US label.

Like resiniferatoxin, capsaicin, the active ingredient of Qutenza™, also reversibly desensitises and defunctionalises the TRPV1 receptor.

The specially formulated patch delivers prescription-strength capsaicin directly to the skin during an in-office procedure. Data shows a long-lasting and significant analgesic effect.[2]

> With Qutenza™, we bring Nobel Prize-winning science translated into therapeutic solutions to patients. Many current treatment options do not have a strong effect or come with many side effects. Qutenza™ has the potential to completely change the way these patients are treated. <

Gabriel Baertschi,
Chief Executive Officer

[2] Summary of Product Characteristics (SmPC) Qutenza™

[3] LTP 2020-2030: ADDRESSABLE POPULATIONS BY CONDITION (PDPN, PSNP, PHN, CINP). Company data on file. April 30, 2020

[4] 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

EMPOWERING CUSTOMERS TO TREAT PATIENTS BETTER

Delivering a great customer experience to healthcare professionals helps them provide better treatment for more patients worldwide.

OUR AIM IS TO IMPROVE the lives of people suffering from pain by developing and delivering new life-changing treatments. To ensure patients receive the best treatment possible, we need to communicate efficiently with physicians, pharmacists, nurses, hospitals, buying groups, wholesalers and institutions.

We serve this diverse customer base of approximately 249,000 customers by making our products available in more than 100 countries, either directly from our 28 affiliates or indirectly from our strategic partners.

We have built a strong presence in Europe over the last 50 years. In Latin America, we have expanded our business by providing access to effective pain treatments for millions of people. This region has a significant unmet need and insufficient education for healthcare professionals in chronic pain.

We also recently expanded our geographical footprint into the US where we have seen significant growth of our non-opioid cutaneous system Qutenza™; we expect this growth to continue exponentially in the coming years.

Engaging with such diverse markets and customer groups in today's world requires new ways of operating. We believe that focussing on our customers' needs is essential. Using our omnichannel engagement model we provide a tailored customer experience through meaningful interactions – where and when our customers need it.

> Meeting the patients' needs is at the heart of what we do. To grow and help more people, we must provide our customers with a tailored experience through meaningful interactions – where and when they need it. <

Mark Fladrich,
Chief Commercial Officer

A clinical doctor going over some test results with an elderly patient at the hospital

Increasing access to pain relief, improving quality of patient care

During 2021, the Palexia™ team generated new real-world evidence data that support further differentiation of the brand's value for use in patients with severe chronic pain where a patient's doctor has decided that an opioid is necessary.[1] 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,[2] Opioid Charter[3] and communication guidelines at all times and regardless of region and across all relevant communication channels. Our Versatis™ team has published new Real World Evidence in 2021. The team reported on the positive differential treatment effect of Versatis™ and other first line oral treatments regarding pain relief and quality of life. The publication of these data supports health care professionals to make informed treatment decisions. For Qutenza™, demand from healthcare professionals rose during 2021. Despite Covid-19, 61,000 patients were treated globally – 32 percent more than in the previous year. In Europe we continue to see strong growth and are increasingly focused on key account excellence and the importance of repeated application in potentially improving patient outcomes.

We also achieved a European CE mark for a digital tool, co-created with French physicians, enabling care professional teams to track a patient's response to their treatment. This shows our strong commitment to providing supportive tools to improve quality of patient care and our confidence in Qutenza™'s progressive response over time.

In the US we now have a robust team covering all regions, allowing us to fully address the unmet needs of patients with DPN of the feet. We also continue to expand our presence in Europe and have seen strong growth in all countries where Qutenza™ is on the market.

In the coming year, we plan to increase access for physicians and patients in Europe and the US and to provide further patient support programmes and inspiring medical education focused on some of the latest research in pain.

In terms of Vimovo™, we have now fully incorporated this product into our pain portfolio. This important medicine, which combines an effective pain treatment with gastroprotection, is growing strongly due to unmet needs in this area.

In Latin America, we adapted our strategy to focus more on innovation and in particular on pain – our core competency. This paid off well with strong growth across our key brands.

With our customer-centric framework in place, we further strengthen our ability to support more patients in need and support healthcare professionals to provide the best care possible.

1 Überall MA, et al. Pain Manag. 2022;12(2):211-227

Sabatschus I, Bösl I, Prevoo M, Eerdekens M, Sprünken A, Galm O, Forstner M. Comparative Benefit- Risk Assessment for Lidocaine 700 mg Medicated Plaster and Pregabalin in Peripheral Neuropathic Pain Following a Structured Framework Approach. Pain Ther. 2022 Mar;11(1):73-91.

Überall MA, Eerdekens M, Hollanders E, Bösl I, Sabatschus I. Lidocaine 700 mg medicated plaster for postherpetic neuralgia: realworld data from the German Pain e-Registry. Pain Manag. 2022 Mar;12(2):195-209.

2 www.grunenthal.com/-/media/projects/corporatewebsite/_shared/pdf/coc/code-of-conduct.pdf

3 www.grunenthal.com/-/media/projects/corporatewebsite/com/pdf/position-papers/opioid-charter-for-external-use_en_oct2019.pdf

ACCELERATING THE GROWTH OF QUTENZA™

Qutenza™ is helping Grünenthal take bold steps to address the unmet needs of patients – scaling up and gaining approval for new indications, so we can expand access across the world.

OUR COMMERCIAL FOCUS is on customer experience – patients, healthcare professionals and payers. For more than five million people in the US who suffer from diabetic peripheral neuropathy (DPN),[1] a debilitating complication of diabetes, successful pain management can mean a vast improvement for their quality of life. Thus, we achieved a tremendous milestone, when the FDA approved Qutenza™ for the treatment of adults with neuropathic pain associated with DPN of the feet in 2020. It extended the access to Qutenza™ to approximately 1.3 million patients in the US - compared to only 60,000 patients under the previous label for postherpetic neuralgia (PHN).

> There is a high unmet need among patients with DPN of the feet, and having a non-opioid therapy that is locally active is important. Furthermore, Qutenza™ is administered by a healthcare professional and this has the potential to create a beneficial connection between the patient and their outcomes. <

Mark Coleman,
MD, President, Clinical Services National Spine and Pain Centers
Diplomate, American Board of Anesthesiology (ABA)
ABA Certified Pain Medicine Specialist

[1] LTP 2020-2030: ADDRESSABLE POPULATIONS BY CONDITION (PDPN, PSNP, PHN, CINP). Company data on file. April 30, 2020

More than five million people in the US suffer from DPN, a debilitating complication of diabetes.

Smart investments for growth

We broadened our footprint in the US to 80 territories in ten regions, growing our key account management, market access and medical affairs teams and hiring top talent. As a result, our Qutenza™ business in the US grew substantially in 2021, with net sales increasing 310 percent vs 2020 and in-market volume increasing 285 percent vs 2020. This represents the significant potential to reach even more patients in need.

Aligned with our strategic imperative to match our customers' and patients' preferences, we broadened our distribution network, integrating a partnership with a specialty pharmacy in 2021.

> We have expanded our US team to address the unmet need of patients suffering from postherpetic neuralgia and painful diabetic peripheral neuropathy of the feet. We strive to provide a seamless customer and patient experience throughout the Qutenza™ journey. <

Jeannie Lloyds,
Vice President Sales & Market Access of Grünenthal subsidiary Averitas Pharma

Our significant investments in the specialty care market have identified the 10,000 healthcare professionals who treat over half of all neuropathic pain patients. Our peer-to-peer education programme aims to better communicate the science of Qutenza™. In addition, with a healthcare professional and patient portal, we have a fully functioning omnichannel approach built for a better customer service experience.

We put our patients first when making decisions. We want to understand their needs and experiences and tailor solutions to improve their lives.

A patient-centred strategy

Making Qutenza™ affordable for patients is also a crucial part of our strategy. In 2021, we launched the first-ever patient out-of-pocket cost-support programme for eligible patients, to ensure more patients who need it can afford this therapy. A new patient advisory council includes patients living with pain to provide insights into our activities.

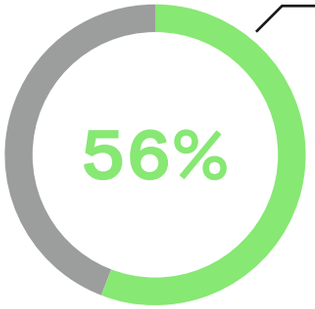
Healthcare payers are another link in the chain. We increased our team that focuses on payers, updating and expanding their information on Qutenza™. And we have already created significant access of 187 million covered lives through health insurance companies and specialty care physicians.

Looking ahead, we hope to explore further usage and potential benefits of Qutenza™ with a real-world evidence (RWE) initiative to analyse clinical data.

Our US expansion reflects our commitment to patients and to widening their access to therapies. It also exemplifies our commercial approach of leading with customer experience – bringing both short-term and long-term value. We do this by scaling up products that will sustain our long-term growth and lay the foundation for our future success.

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

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

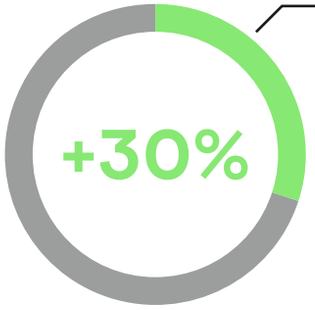


US portion of the world´s diagnosed neuropathic pain market

$4.5 bn

2016 US sales in NP therapies[1]

... and is expected to grow substantially



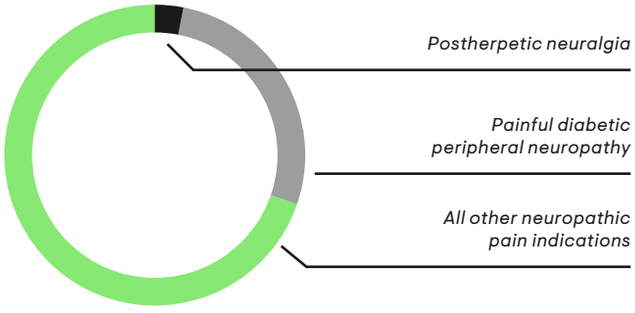
Growth in diagnosed neuropathic pain patients in the US from 2019 to 2030

$5.9 bn

Expected US sales of NP therapies by 2026[1]

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

Market share of neuropathic pain by indication in US market

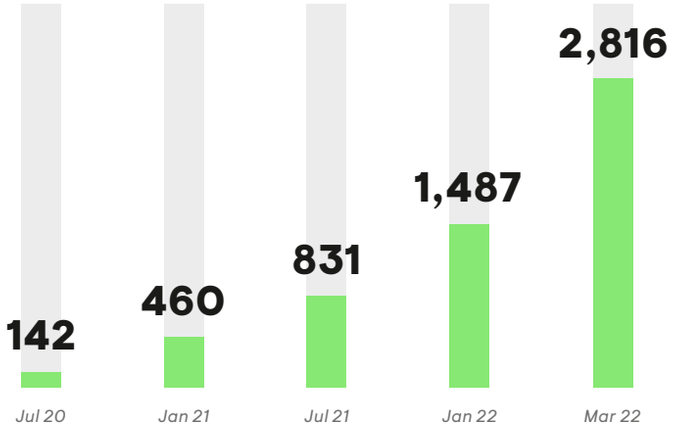


[1] Decision Resource Group; GRT US Holding Data. The DPN / PSNP markets are expected to grow at 71% and 27% respectively, while the PHN declines by 15%; Qutenza LTP as of July 5, 2019; Rehab Management citing University of Michigan study; IQVIA.

> Offering an engaging customer experience is key to realising growth, so we can provide access for patients who may benefit from Qutenza™. <

Marv Kelly,
General Manager, Grünenthal US

Total Qutenza™ in-market sales in topical systems in the US



MAXIMISING OUR PORTFOLIO ACROSS THE BRAND LIFECYCLE

Our portfolio includes ten global brands, each at different stages of the brand lifecycle.

THE GROWTH BRANDS include our innovative and patent-protected products like Qutenza™, and our brands that continue to have valuable growth potential like Palexia™ and Vimovo™. The established brands bring together all of our mature and off-patent products. This includes Nexium™, 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. Combining these product categories provides a well-balanced and resilient overall business.

In 2021 our Vimovo™ team improved the global campaign and the omnichannel strategy. We completed the integration of Vimovo™ in all European markets, thereby maximising the brand and unlocking its potential.

The Palexia™ team will continue 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. We strive 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.

Our teams work tirelessly to enable optimised pain management to patients around the globe.

> Our portfolio of established brands is composed of high equity brands with a differentiated value for patients. It is a key strategic asset for Grünenthal with opportunities across multiple markets. We take a proactive, customer-centric management approach to maximise their value. <

Ana Inacio,
Global Established Assets Lead

Managing established brands

Our established brands are in a later stage of their lifecycle. They already face generic competition or other market pressures that could limit growth in demand.

This year we have further evolved our new approach to these brands that we initiated in 2021. We kept a strong focus on them, ensuring cross-business transparency for the way we manage them, and have enhanced our activities to identify selective opportunities to increase demand and to reduce or optimise costs.

The result of our efforts surpassed our expectations, with almost all our established brands delivering above the previous year's sales. Overall, our established brands achieved sales of €953.5 million, which equates to an increase of 18 percent on the previous year.

In Latin American markets, Versatis™ is much earlier in its lifecycle and was just recently launched in Mexico. In Latin America, net revenues have increased by 16 percent compared to the previous year.

For Nexium™, through our omnichannel platform and by working with our partners, the brand sales have reached €187 million – an increase of 17 percent on the previous year.

For Zomig™ we continued to take over the nasal spray production and the launch of new formulas and pack sizes in some European affiliates. We also started preparing to launch the product in several partner business markets.

72%

of Grünenthal sales are of established brands.

WORKING WITH LEADING ORGANISATIONS TO INCREASE ACCESS AND AWARENESS

We want to give pain patients a better future, which is why we are involved in various initiatives that support this goal.

Initiatives

CHANGE PAIN® Taking care of pain

CHANGE PAIN™ is an initiative established by Grünenthal in 2009 and endorsed by the European Pain Federation EFIC and Pain Alliance Europe (PAE).

The initiative's mission is to improve patient outcomes by improving pain management through adequate research, communication and education.

The CHANGE PAIN™ medical education platform is a global initiative to provide tailored educational content about pain to healthcare professionals and patients. Customers attend the CHANGE PAIN™ educational initiatives like meetings and webinars and use the tools to help educate their staff and peers while supporting patients' self-management.

In the last 12 to 18 months, CHANGE PAIN™ has increased its digital reach, expanding beyond face-to-face meetings by organising educational webinars for HCPs and digital tools to support patients.

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. Local versions of the website were also launched in France, Belgium, the Netherlands, UK, Austria, Ireland and Sweden.

On top of this, CHANGE PAIN™ joined forces with patient representatives to build a new section of the website to support pain patients facing challenges managing their pain because of limited access to HCPs during the Covid-19 pandemic.

The webinars received positive attendees' feedback and covered hot topics such as the latest developments in pain management, including the role of the TRPV1 receptors. Over 1,000 participants took part in the live webinars with many more watching on-demand/video recordings.

www.changepain.com

SIP Societal Impact of Pain

SOCIETAL IMPACT OF PAIN (SIP), of which Grünenthal is one of the main sponsors, is a multi-stakeholder partnership led by the European Pain Federation and Pain Alliance Europe. It aims to raise awareness about pain and encourage changes to pain policies by providing opportunities for discussion among healthcare professionals, pain advocacy groups, politicians, healthcare insurance providers, representatives of health authorities, regulators, and budget holders.

SIP is endorsed by more than 310 European and national patient and healthcare organisations and collaborates with organisations from other disease areas to advocate for improved management of pain, for example in cancer and in rheumatology.

www.sip-platform.eu

We strongly believe in supporting research and patient-centred innovation to help improving pain patients' lives.

Grants

EFIC-GRÜNENTHAL-GRANT (E-G-G) Grünenthal supports this grant with up to €200,000 every two years. The scientific framework is under the responsibility of the European Pain Federation.

These grants support early-career scientists within European Pain Federation EFIC member countries to carry out innovative pain research. Since 2004 the E-G-G has successfully funded 70 innovative research projects, awarding almost €1.7 million to participants in more than 14 countries.

The five recipients of the 2022 E-G-G have been rewarded at the 12th Congress of the European Pain Federation EFIC in April 2022.

www.e-g-g.info

BRAIN, MIND AND PAIN (BMP) is financially supported by Grünenthal to encourage patient-centred innovation in pain research and care. The BMP grant is the first pan-European grant that selects applications based on their impact from a patient's perspective.

The theme of the third edition of the BMP Grant is prevention and self-management, focusing on "Healthy Sleep For People Living With Brain, Mind And Pain Conditions". Results from the 2022 projects will be presented in 2023.

www.bmp-grant.eu

GLOBAL BRANDS

Providing solutions for patients with high medical needs.

BRAND NAME	ACTIVE INGREDIENT / TECHNOLOGY	INDICATION RANGE[1]	SALES[2] 2021 IN € MILLION
Qutenza® capsaicin 8% patch	Capsaicin	**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.	42.8
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.	46.4
versatis®	Lidocaine	**EU and Peru indication:** Symptomatic relief of neuropathic pain associated with previous herpes zoster infection (postherpetic neuralgia, PHN) in adults. **Latin America indication:** Symptomatic relief of neuropathic pain associated with previous herpes zoster infection (postherpetic neuralgia, PHN) in adults. Symptomatic relief of Localised Neuropathic Pain in adults.	137.3
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.	62.7

[1] Status: April 2022. 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)

[2] without license and milestone income

BRAND NAME	ACTIVE INGREDIENT / TECHNOLOGY	INDICATION RANGE[1]	SALES[2] 2021 IN € MILLION
Nexium® esomeprazole	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) • treatment of erosive reflux esophagitis • long-term management of patients with healed esophagitis to prevent relapse • symptomatic treatment of GERD **Indicated in adults for:** In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and: • healing of Helicobacter pylori associated duodenal ulcer and • prevention of relapse of peptic ulcers in patients with Helicobacter pylori-associated ulcers **Patients requiring continued NSAID therapy:** • healing of gastric ulcers associated with NSAID therapy • 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.[3]	187.0
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.	72.2[4]

[3] see SmPC for 'Nexium™ 10 mg gastro-resistant granules for oral suspension, sachet' and for 'Nexium™ 40 mg Powder for solution for injection/infusion'

[4] profit transfer following the acquisition of Crestor™ in February 2021

Scan here to find our global brands online:

BRAND NAME	ACTIVE INGREDIENT / TECHNOLOGY	INDICATION RANGE[1]	SALES[2] 2021 IN € MILLION
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[3] 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™ 315.5** **+** **Partner sales of Nucynta™ in the US: $173.2 mn**
Tramal	**Tramadol**	**EU and LATAM indication:** Treatment of moderate to severe pain.	**85.9**
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.	**60.1**
NORSPAN® / 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.	**47.8**

[1] Status: April 2022. 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)

[2] without license and milestone income

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

RESPONSIBLE USE OF OPIOID-BASED MEDICINES

General considerations for pain management with any medication that contains an opioid mechanism of action.

The following general aspects should be considered:

- an individualised, patient-centred approach for diagnosing and treating 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;[1]
- in patients with acute pain e.g. post-surgery pain, the use of medication should be for the shortest necessary time.[1] All patients should be carefully selected, abuse risk factors evaluated and regular monitoring and follow-up implemented to ensure that opioids are used appropriately[2-3] and in alignment with treatment goals (pain intensity and functionality) as agreed with the patient;[2-3]
- patients should be made aware of the potential side effects of opioids and the potential for developing tolerance, dependence and addiction;[2-3]
- 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;[1]
- 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;[4]
- 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;[5]
- any long-term treatment with opioids should be monitored and re-evaluated regularly incl. tapering down the dose or discontinuing treatment;[2-3]
- signs of opioid use disorder should be monitored and addressed;[2-3]
- patients and the general public can benefit from clear educational materials and awareness interventions to support the responsible use of opioids.[6]

1 DHHS Pain Management Best Practices Inter-Agency Taskforce Report May 2019

2 Faculty of Pain Medicine, Opioids Aware www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware. Accessed September 2019

3 Kosten TR et al., Scie Pract. Perspect 2002;1:13-20

4 Rosenblum A et al. Exp. Clin. Psychopharmacol. 2008;16(5):405-416

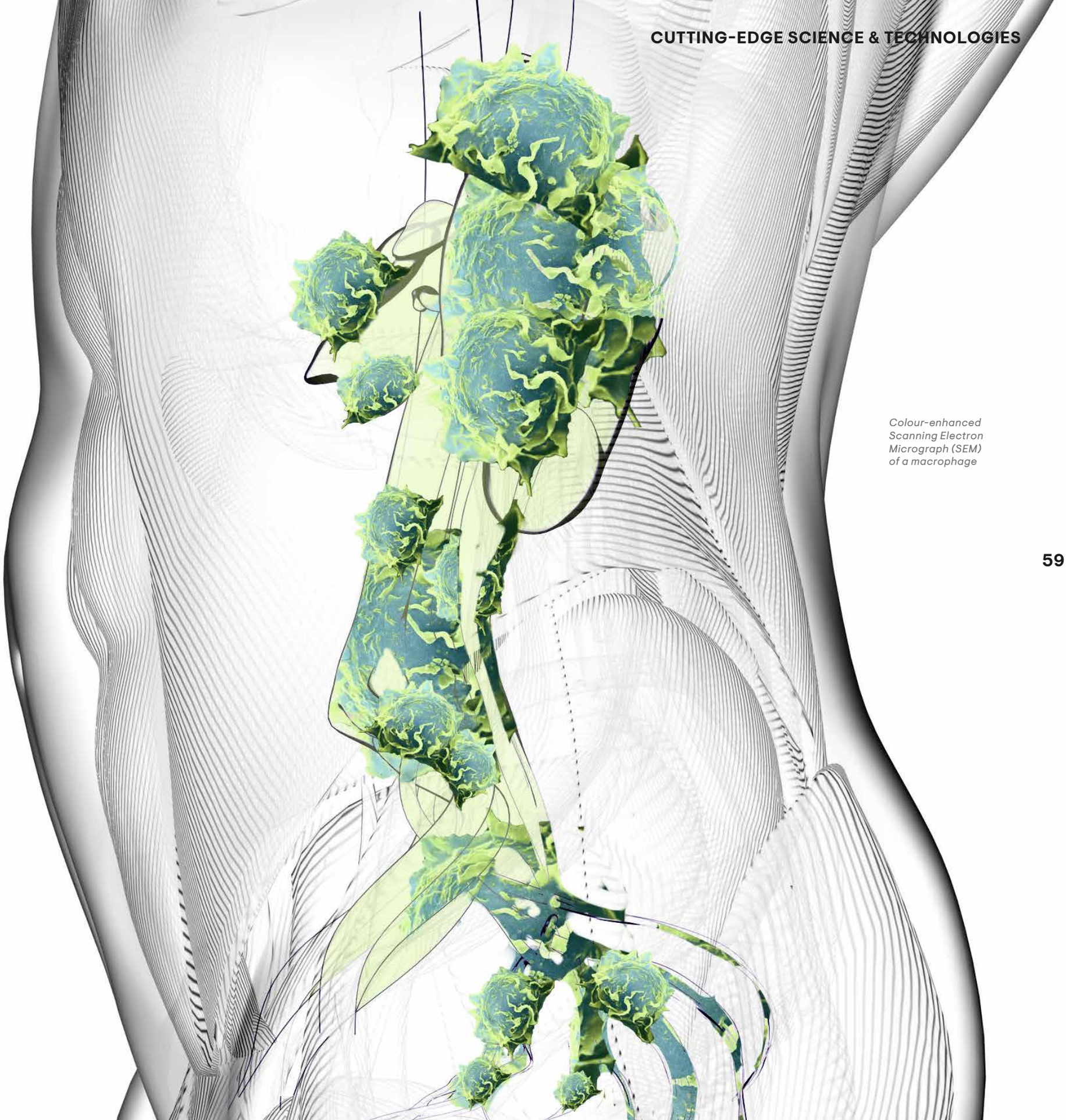
5 O'Brien T et al. Eur J Pain 2017;21:3-192

6 OECD Health Policy. Addressing problematic opioid use in OECD Countries, May 2019 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:

CUTTING-EDGE SCIENCE & TECHNOLOGIES

From bench to bedside – with leading research into next generation medicines and advanced technologies to produce and distribute them across our markets, we provide for patients in pain whose needs would otherwise be unmet.



Colour-enhanced Scanning Electron Micrograph (SEM) of a macrophage

CREATING INNOVATIVE MEDICINES FOR PATIENTS

Cutting-edge Science – In Grünenthal's electrophysiology laboratory at the Aachen Campus, scientists obtain important data for the development of innovative medicines.

By focussing on our core capabilities, like target identification and leveraging our expertise in bioinformatics and Systems Biology, we identify and develop promising candidates.

Pain Research at Grünenthal

Focused therapeutic area strategy

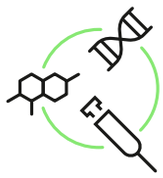
We focus our R&D efforts on four pain indications characterised by high unmet medical need.

Comprehensive disease understanding

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

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.



Teaming up

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

OUR FIRST PRIORITY in building our research portfolio is to ensure that it comprises only well-validated pain targets. Selecting these targets is essential to avoid a high attrition rate in clinical Phase II. This would not serve patients and would waste resources. By choosing the right targets, we lay the foundation for a successful clinical Proof of Concept.

Predictive validity

Scientists in the therapeutic area of pain have learned that preclinical, behavioural models do not have sufficient predictive validity to serve as the basis for selecting a new target. For example, the expression profile of proteins varies between species, and therefore their functionality may also be different.

Grünenthal scientists adopt and develop models based on human tissues and cells to achieve the best possible human validation early on and thus reduce the attrition rate in clinical development to a minimum. We are investigating human cells such as nociceptive neurons, which help carry pain signals. By interrogating these neurons, alone and in combination with other relevant cell types, we can start to understand how they work in the human body.

Our researchers work to understand the role of a target in pain processing. We therefore evaluate whether natural variation in the target, such as genetic differences, has functional consequences. Beyond this genetic evidence, we also look for existing clinical evidence that modulating the activity or function of the target has an impact on the condition of the patient.

A target that combines understanding of its function in pain processing with clinical and genetic evidence is really promising. In addition to these aspects, we consider the safety implications of modulating a target before selecting it for a research project.

> We leverage a wide range of modalities to create the right candidates for painful conditions and build a comprehensive understanding of the underlying pathological processes responsible for causing pain. <

Gillian Burgess,
Head of Research

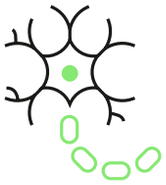
Turning data into knowledge

To screen, analyse and process the large amount of freely available omics data, we use our bioinformatics and Systems Biology expertise and turn that data into knowledge to inform our research activities.

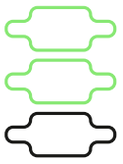
Joining forces, we build strong partnerships with academic groups and other experts to mine this data and understand how different cells and tissues communicate with each other in painful conditions.

A Concise Therapeutic Area Strategy

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.

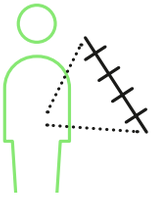


Peripheral neuropathic pain



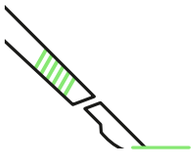
Chronic low back pain

Osteoarthritis



Chronic post-surgical pain

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



Peri-surgical pain

Migraine

Fibromyalgia

CRPS

> Establishing models based on human tissues and cells contributes to creating a well-validated research portfolio. We lay the foundation for successful clinical development and new innovative medicines that benefit patients globally. <

Clint Young,
Pharmacology, Biology and Translation Expert

Grünenthal scientists create data through nuclear magnetic resonance (NMR) spectroscopy.

THE NEXT GENERATION OF PAIN MEDICINE

Grünenthal leverages cutting-edge approaches to shape the field of pain research.

GRÜNENTHAL ASPIRES TO CREATE the next generation of pain medicines. Our research teams have developed a focused strategy to identify novel targets, engineer optimised clinical candidates, and rapidly progress them to proof of concept and launch. Scientists across Grünenthal's R&D organisation collaborate closely to develop innovative approaches in key fields. With these approaches, they are able to discover novel molecules for high-confidence targets with strong linkage to human disease, establish robust translational approaches in early clinical trials, and meet ambitious development timelines. The teams leverage modern technology that enables the interrogation of disease pathways at an unprecedented level of resolution. This includes omics-technologies, physiological monitoring techniques, cellular reprogramming and information technologies, and artificial intelligence (AI). Across Research and Development, Grünenthal invests in creating high-resolution, patient-centric data sets through close collaborations with strategic partners around the world.

Human validation: Ensuring a proper basis

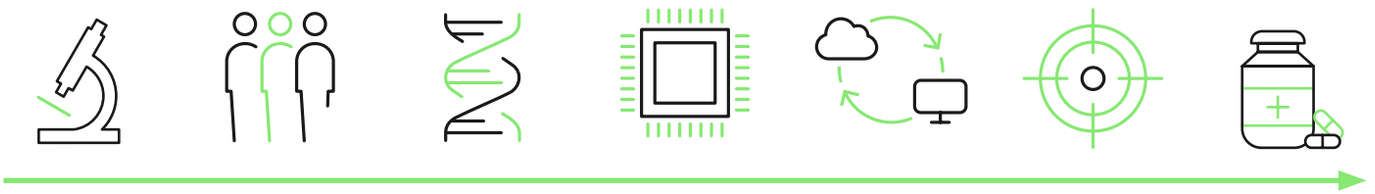
Collaborations with CROs and academic institutions worldwide help us refine our thinking and also access human models derived from human tissue. In a partnership with McGill University in Montreal, Canada, researchers work to gain access to human sensory neurons from the dorsal root ganglion (DRG), which are crucial for pain signalling. This partnership is part of a larger initiative to develop an innovative toolbox of translational human tissue assays to interrogate the underlying pathological processes responsible for chronic pain and employ them for evaluation of discovery research molecules.

Collaborations such as these and those with clinical partners fall under Grünenthal's compliance framework that governs all business areas. This framework takes global best practices and legal and regulatory considerations into account. It ensures that we live up to the highest ethical standards while pursuing our vision of a world free of pain.

> **As a basis for the successful development of new treatment options for patients, we focus on modelling disease mechanisms using well characterised humanised cellular and tissue systems.** <

Verena Arndt,
Head Human Disease Mechanisms

The Systems Biology landscape



Therapeutic Area Strategy

Human-relevant disease models

Sample extraction from disease models

Systems Biology technologies capture the information from samples

Computational analysis of sample information & prediction of new disease targets

Laboratory validation of the new disease targets

Development of novel therapeutics for the new targets

Systems Biology: Assembling the puzzle

The basis for developing new treatments is to understand how a disease works at the cellular level: which processes are impaired and why? These questions are the starting point in Grünenthal's search for new targets.

Systems Biology is one method for identifying new targets. It assembles information for each individual cellular process to create an interconnected network of data that describes the mechanisms driving a disease in a comprehensive way.

Recent advances in single-cell isolation and barcoding technologies have enabled DNA, mRNA and protein profiles to be measured at a single-cell resolution. For example, using single-cell omics approaches, Grünenthal's scientists are interrogating dorsal root ganglion neurons to inform their translational models.

The large amount of data that System Biology creates needs to be integrated and analysed with bioinformatics tools. This allows disease processes to be simulated by computers. The combination of wet lab work and bioinformatics can help advance preclinical development by identifying the most promising targets efficiently.

> With the single cell omics Systems Biology, we can capture and connect all of the information about the behaviour and interaction of individual cells in a given environment and use this to identify promising new treatment options. <

David Chambers,
Systems Biology Lab Head

> New target options identified by unbiased single cell omics are further validated by target-focused molecular biology and imaging techniques to confirm findings and to identify pre-clinical tools that are able to modulate gene and/or protein function, enabling us to deepen our understanding of the disease process and potential therapeutic modulation. <

Stephanie Hennen,
Gene & Protein Function Lab Head

Bioinformatics: Accelerating data-driven human disease understanding

Biomedicine is now flooded by high-resolution, large-scale data spanning organismal hierarchies across various biological and disease conditions. The datasets available to inform Grünenthal's search for new targets are massive. They span omics datasets to data associated with the scientific literature and clinical databases. Special data analysis methods are needed to process this information and identify relevant connections and interdependencies. Breakthroughs in artificial intelligence (AI) and machine learning (ML) have opened new ways for identifying "actionable insights" by integrating diverse data types – to advance research projects and enable better strategic decision making for the creation of a promising research portfolio.

Grünenthal's Bioinformatics team develops innovative computational methods to interrogate complex human datasets such as omics, biomarker and clinical data. Their work generates hypotheses and actionable insights that can be experimentally tested. State-of-the-art multi-modal data analysis is being deployed to identify novel targets and biomarkers, enhance understanding of the disease mechanisms underlying pain, and enable patient stratification for precision medicine. The multi-disciplinary capabilities required to develop and test these insights naturally lead to a strong collaborative approach across Grünenthal's R&D organisation and its global partners.

Grünenthal's Advanced Analytics Centre brings scientists together who leverage digitalisation, AI and ML to create a world free of pain. In a collaborative endeavour, the team creates a comprehensive R&D data strategy. It applies state-of-the-art methodologies and technologies to help advance Grünenthal's R&D projects.

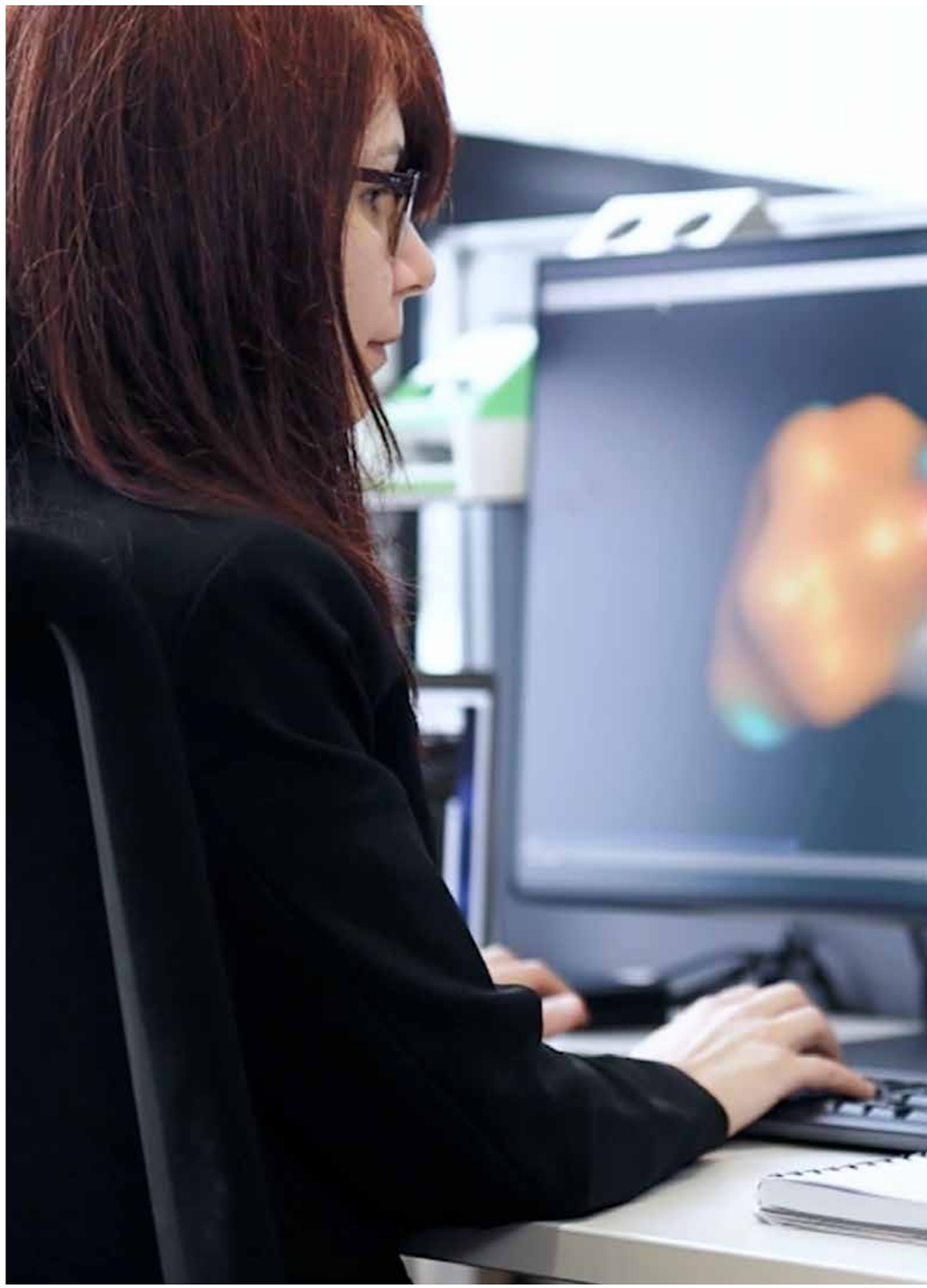
> Our team's eclectic blend of expertise, ranging from bioinformatics and genetics to machine learning, complemented by disease knowledge, helps us solve complex biological problems through state-of-the-art computational techniques. <

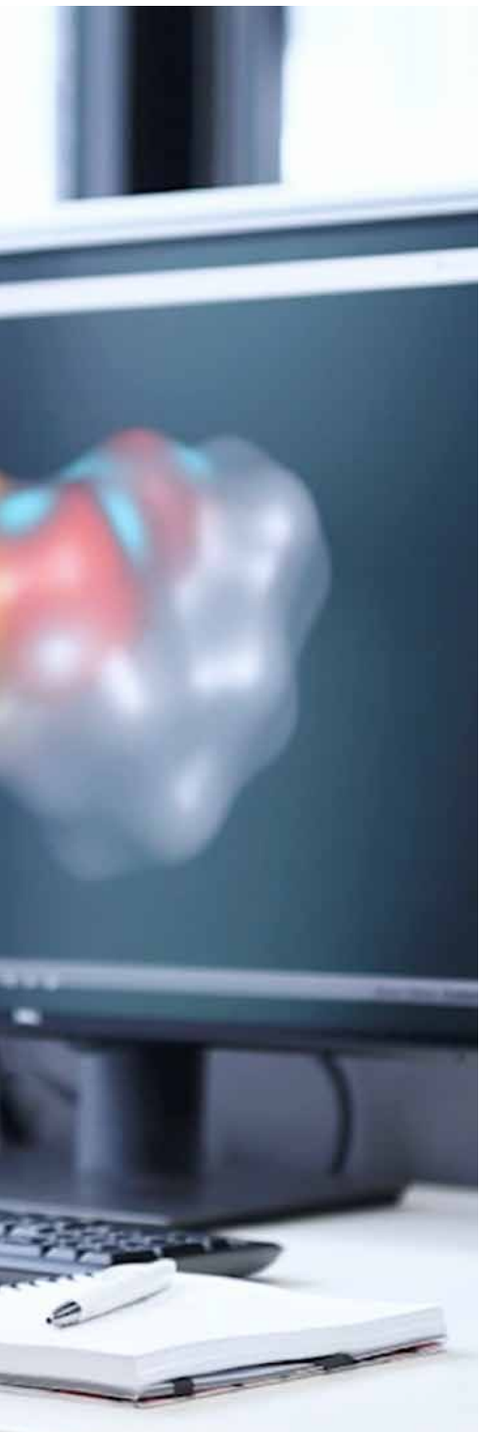
Chanchal Kumar,
Head Bioinformatics Disease Understanding

> We create explainable machine learning models that predict certain properties of molecules. These models are coupled with the use of specialised algorithms. This allows our drug discovery teams to continuously optimise the design process. <

Sevil Davidson,
Computational Biologist

Working with our medicinal chemists, they employ ML techniques to generate novel and differentiated molecule structures through “in-silico” approaches. Grünenthal’s experts use existing structures from marketed or patented medicines and the company’s internal programmes to train an algorithm to understand what a molecule with defined properties could look like. Once trained, such a generative algorithm develops thousands of new ideas on molecule structures with enormous speed and thereby complements human expertise in the field. Using this approach, Grünenthal’s team has developed algorithms based on existing molecular structures from one of the company’s research programmes to predict whether a new molecule will have the desired properties at its molecular target.





Sevil Davidson,
Computational Biologist

Additionally, the team implements computational techniques to better understand patients' characteristics and disease trajectories through data-driven phenotyping. This can help Grünenthal to design tailored clinical trials targeting patients and improve the outcome for a positive effect from a given investigational medicine, which significantly increases the probability of success for a given trial. Experts have already spent decades collecting such insights and defining patient characteristics. However, they lacked the immense amount of data and computing power that now is available. Today, scientists can leverage data from previous clinical studies to understand disease progression or treatment response and, moving forward, use machine learning to predict these processes based on the existing data.

These achievements build on Grünenthal's continuous efforts to make its data visible and machine-readable in more manageable ways so that its data assets can ultimately be integrated and connected to public data sets. This holistic view of data on biomedical concepts will ultimately enable our teams to apply machine learning and AI to recognise patterns currently not visible for plain human sight.

> Through our work, we can support data-driven decision making by leveraging the opportunities of data and AI for experts across the R&D organisation. We bring modern AI algorithms and scalable computing power to bear to address even very complex problems and help patients suffering from pain. <

Lars von Wedel,
Head of Advanced Analytics

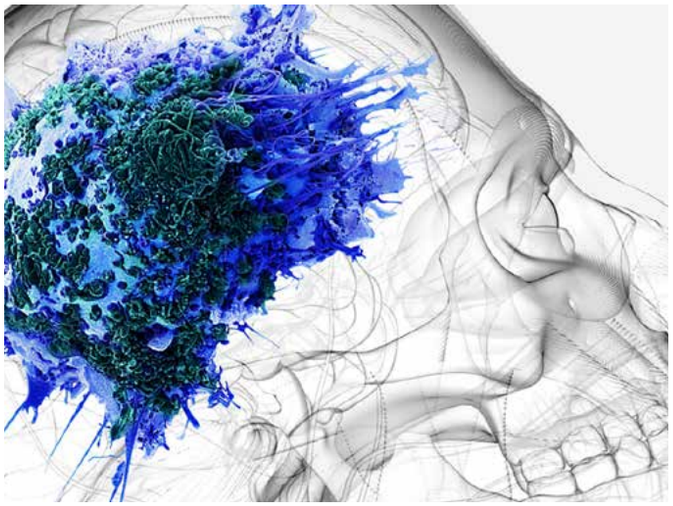
Put into practice: Translational approaches in early clinical development

How does Grünenthal leverage biomarkers in the Phase I study with its glucocorticoid receptor modulator (GRM)?

By obtaining pharmacodynamic data from various biomarkers at an early stage of the clinical development, Grünenthal's scientists can draw initial conclusions about the likelihood to which an investigational medicine may become a differentiated therapy.

Osteoporosis and increased glucose levels with increased risk of diabetes are the most common side effects of glucocorticoids. In Phase I studies for GRM, the team is measuring several biomarkers to assess how the investigational medicine influences bone metabolism and glucose levels.

Lab technician holding blood tube sample for study



Microglial white blood cell. Coloured Scanning Electron Micrograph (SEM) of a microglial cell

> Our ambition within translational sciences is to increase the success of our clinical drug candidates by modelling and investigating human pain mechanisms early in clinical development. <

Elke Kleideiter,
Clinical Translational Scientist

Early clinical hypothesis-testing using human experimental medicine trials

In 2021, Grünenthal conducted an experimental medicine trial in healthy volunteers with the frontrunner from the Nociceptin/orphanin peptide receptor (NOP) agonist programme. The trial investigated the pharmacodynamic effects of the NOP agonist on multiple endpoints in response to laser stimuli that were applied to normal and sensitised (capsaicin-treated or UV_B-irradiated) skin, which mimics the symptoms of hypersensitivity common to many types of neuropathic pain disorders. The endpoints included objective measures of brain activity using electroencephalography (EEG) and subjective ratings of pain perception on the Visual Analogue Scale (VAS). Results showed that the NOP agonist differentially affected EEG and VAS responses, depending on skin sensitisation. These data provide the first pharmacodynamic evidence that a NOP agonist may suppress pain signalling in humans, increasing confidence in the potential therapeutic benefit of this molecule and supporting further investigation in chronic pain patients.

Reaching patients faster: Establishing state-of-the-art development timelines

To create promising clinical candidates and the potential pain medicines of the future, Grünenthal's experts are working to optimise the company's frameworks and processes to bring innovations to patients as quickly as possible. A dedicated team is focused on optimising the transition of candidates from late research to early clinical development – from candidate profiling to the start of the First-In-Human study. In this phase candidates are profiled regarding their pharmacology and pharmacokinetic characteristics. Toxicology and safety pharmacology studies are conducted, and drug substance and drug product are developed and manufactured. In addition, the First-In-Human study is designed, and the clinical trial application is submitted to the regulatory authorities. The team identified several levers to streamline and accelerate the process without compromising safety and quality. They created a blueprint framework that can be adapted to each project moving forward and allows Grünenthal to achieve best in class industry benchmark timelines of well under two years for this development phase.

ENSURING WORLDWIDE PATIENTS' SUPPLY

Our Global Operations: 100 countries, 2,000 people and endless commitment

GIVING PATIENTS RELIABLE ACCESS to our medicines across more than 100 countries worldwide is important to us. Along the complex value chain that extends from cutting-edge science to our global operations, we work to ensure our products reach our customers at the right time.

Grünenthal covers the entire value chain, from target identification, through market authorisation and manufacturing to distribution. This end-to-end approach ensures a safe, efficient and reliable product supply to patients.

Our Global Operations team aims to drive growth by ensuring excellence in their processes and by embracing digitalisation and continuously innovating how we operate. Around 2,000 people are involved in the full end-to-end value chain management of our product supply. They are committed to satisfying our customers' demands and offering a high level of service while ensuring quality to the highest standards.

At our five specialised production sites in Chile, Ecuador, Germany, Italy and Switzerland, we manufacture our products and support our external customers. Third party manufacturing accounts for 53 percent of our overall production volume.

Staying ahead of the game

We recognise that our global manufacturing sites play an essential role in securing our financial success. We know that pursuing excellence is key to maintaining our competitive position. So we continue to invest in our manufacturing capabilities.

Between 2020 and the end of 2022, we will have invested more than €100 million in our sites. In 2022, the main investments will be:

- approximately €17 million to modernise our site in Santiago, Chile, ensuring world-class infrastructure and robust product quality;
- approximately €8 million for the integration and insourcing of newly acquired products, including Crestor™, Nexium™ and Vimovo™;
- and €4 million into automation and digitalisation.

€100mn

Investment in our sites from 2020 to end of 2022.

Our site in Switzerland produces Active Pharmaceutical Ingredients (API): According to POBOS[1], it is one of the most competitive sites in the entire industry.

Results from the Pharma Operations Benchmarking of Solids (POBOS)[1] assessment we recently conducted at our manufacturing sites in Germany and Italy prove that we are on the right trajectory. Both sites increased their overall productivity over the last four years: our site in Germany by 14 percent and in Italy by 40 percent. The site in Italy became even more competitive from a cost perspective. But we want to push ahead and drive excellence further. In Germany, we intend to improve our Overall Equipment Effectiveness (OEE). Our site in Switzerland producing Active Pharmaceutical Ingredients (API) shows what can be achieved: according to POBOS it is one of the most competitive sites in the entire industry.

As for our sites in Latin America, our modern manufacturing site in Quito, Ecuador, already fulfils the European standards. We started to export from here to the very competitive market in Brazil and will start exports to Europe in the years ahead.

[1] Pharma Operations Benchmarking of Solids (POBOS)* is McKinsey's proprietary Pharma Operations Benchmarking service

GO2025 – Our way forward

THE GLOBAL OPERATIONS team strives 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 have a clear strategic plan called GO2025. It 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.

Embracing digital technologies is a significant part of this journey. We already implement smart innovations inspired by Industry 4.0 to maximise productivity and improve how we react to changing market conditions and make our manufacturing processes more resilient. These include 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.

Digitalisation – Our facilitator

Digital technologies are opening up once-in-a-lifetime opportunities for our Global Operations team. We are determined to explore every possible way of creating value through digital solutions from automation to unleashing the power of data. These are just a few of the examples:

- in the packaging centres at our site in Germany, we have introduced cobots and Autonomous Guided Vehicles (AGVs) to increase process efficiency;
- we are using an automated digital performance system to provide ongoing global data transparency and improve the efficiency of our packaging operations;
- we have applied innovative advanced analytics algorithms to increase the yield of our Active Pharmaceutical Ingredient site.
- we are increasing procurement efficiency through our eProcurement platform for tendering, offer comparison, and Supplier Relationship Management activities;
- to better serve one of our key Contract Manufacturing customers, we have implemented the E2Open platform technology to connect to our Enterprise Resource Planning systems. We achieved the next level of digitalisation, greater transparency, and improved management with this platform. The system allows for automatic supply chain-related exchange, such as orders, updates, inventory levels and deliveries.

Sarthak Sharma,
Digital Project Manager within Global Operations

INTERVIEW WITH SARTHAK SHARMA, DIGITAL PROJECT MANAGER WITHIN GLOBAL OPERATIONS

> LEVERAGING SMART AUTOMATION, DATA AND DIGITALISATION WITHIN GO <

Key pillars to drive growth in our Global Operations.

SARTHAK SHARMA works to introduce digital and automation solutions that create more transparency, reliability and improve manufacturing processes. We talked to him about Grünenthal's digitalisation and smart automation journey and his experience as one of the drivers of this change within Global Operations (GO).

What is Grünenthal's approach to implementing digital systems within GO?

As an organisation within GO we are continually working to improve how we run our operations and also ensure high quality and reliable care for patients. Our digitalisation journey is part of that goal; it provides more transparency in day-to-day manufacturing and ensures reliable supply to our customers. One example of a digitalisation project that we rolled out in the last two years is the data collection system for our packaging lines globally. It allows us to understand our lines better and to gather valuable performance information. We also invest in technology focused on improving the reliability of our operations and safety of our people. For example, we have introduced cobots that reduce the need for repetitive activities on our packaging lines.

What are cobots and how are you using them?

The pandemic showed us the need to be more agile and to be able to ramp up or down our manufacturing operations faster. This led to an acceleration of smart automation such as cobots, or collaborative robots, at our site in Aachen. Cobots are designed to work alongside people safely and reliably. In Aachen they are used to handle highly repetitive activities like carton handling. This frees up people to focus on more value added and urgent tasks.

Where else are you leveraging the power of data?

Within GO, we need the right information to make the right decisions. This goes hand in hand with the need to have the right processes. That is why we have extended our data collection systems from our manufacturing lines to the bulk manufacturing areas of our sites, so that we can better understand and improve the performance of the manufacturing process. We have also rolled out the use of a self-service data analytics tool, which helps people leverage analytics in their everyday lives. And we are deploying advanced analytics in our API manufacturing process to help us identify ways of further improving yield. To strengthen our capabilities in this area, we have launched an analytics programme that will further upskill our teams globally and support them in leveraging valuable information from our data.

Which technologies are on your radar for future development?

The list of potential applications and tools that could help us with improving our operations is very long! But our core focus is on strengthening our fundamentals – in other words, creating more efficient processes and enabling smoother end-to-end operations. For instance, in manufacturing we are working on several smart robotics and automation projects at our sites, with multiple projects ongoing in Italy. Within supply chain we are looking at leveraging digital tools to improve our planning accuracy and our overall value chain. In procurement, we are leveraging digital tools to improve spend analytics as well as to ease the procurement journey for internal stakeholders and suppliers alike.

Digitalisation is a key pillar in GO's growth and I am certainly excited to be leading a part of this journey!

Building in-house capabilities for external growth

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 ensures 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 proof points. We have invested €11.8 million in state-of-the-art packaging equipment to create the required capacity in our Aachen site. Following the takeover of packaging activities from AstraZeneca, we expect cost savings of up to €11.7 million per annum from 2022. We are following 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.

Strong results warrant great expectations

Based on the successes of our brands and our Contract Manufacturing Business strategy, our Global Operations expect an overall increase in production volume of 12 percent in 2022 compared to 2021.

The growth is carried and driven across our global sites. For example, following the takeover of packaging activities from AstraZeneca for Nexium™ and Vimovo™, the volume at our site in Germany will increase by 16 percent between 2020 and 2022. Our excellent performance has earned us the trust of our customers and opened new opportunities. As a result of the Contract Manufacturing Business strategy and the performance at our Italian site, our Biopharma customers have awarded Grünenthal with opportunities to enter new markets. This will be reflected in 2022, when we expect volume to increase by 13 percent. Throughout the pandemic, the manufacturing level at our biggest bulk sites, Italy and Chile, has remained stable.

As a daily routine, colleagues at our site in Aachen, Germany, review the results on the KPI dashboard.

We will continue to build on our strategy, to structure our efforts and to target our investments accordingly. Following this approach, our site in Ecuador will become a regional manufacturing and distribution centre for liquids and semi-solids. The production of all liquids and semi-solids is being transferred from our site in Chile to our site in Ecuador. The transfer will be finalised by end of 2022 and will result in a 32 percent increase in volume.

Quality always

We are wholeheartedly committed to providing patients with medicines they can trust. We are bound to strict regulations and want to ensure patients have complete confidence in our products. A robust Quality Management System (QMS) ensures compliance and guarantees quality at every stage in the value chain and across our sites worldwide. Our Pharmaceutical Quality System (PQS) is monitored by a comprehensive set of Quality Key Performance Indicators (QKPIs). These QKPIs allow us to track progress and success in meeting our ambitious quality targets.

Safety first

One fundamental aspect always remains important: safety first. Every accident is one too many. We therefore continuously develop preventative measures and provide education and training to improve the level of occupational safety. With every step, however small, we get closer to achieving our goal of zero accidents. This requires safe framework conditions and safe behaviour. We therefore actively search for unsafe situations and behaviour and ensure these are corrected. We analyse each accident and share learnings with our other sites worldwide. Proving that prevention is a well worthwhile investment:

- *over 92 percent of our Global Operations staff have taken part in Behaviour Safety Observation – a simple and effective programme which supports employees to identify potential hazards and take corrective actions;*
- *we have seen a 48 percent decrease of Lost Working Day Accidents at our manufacturing sites;*
- *three out of our five manufacturing sites were accident-free for one year.*

Digitalisation is a key component in the process. Our Quality Management System aims to transform our quality culture by reshaping and streamlining our processes and creating an efficient, digital, global way of working. The results of internal and external audits, inspections and the certifications that we are granted prove us right. In 2021, we maintained and extended our certifications. Our Italian plant is again qualified for supply to Japan, our hormones plant in Chile was re-certified by Anvisa, and various countries re-certified Germany, Switzerland and Ecuador plants. Inspectorates confirmed again the appropriateness and maturity of our Pharmaceutical Quality System in 19 inspections at our headquarters, our manufacturing sites and our sales affiliates. In addition, our manufacturing sites successfully passed all 24 client audits. We developed a new concept and ways of auditing during the pandemic that allowed us to continue effectively overseeing our supplier and vendor network. Last year we performed in total 248 audits either onsite, remotely or in documentation assessments to check the adequacy of our partners' operations. And even this year started very well: Our API (Active Pharmaceutical Ingredients) manufacturing plant in Germany passed an inspection by the U.S. Food and Drug Administration (FDA) with the excellent outcome that no objectionable conditions or practices were found.

GRÜNENTHAL PRO – SERVING OUR CUSTOMERS

Our Contract Manufacturing Business, called Grünenthal PRO, is always ready to support new partners around the globe.

GRÜNENTHAL PRO offers high-quality products and services for customers worldwide, who recognise us as a trusted partner. We constantly optimise our capabilities and capacities to expand the range of support that we provide from our five production sites. Together with partners at every stage in our supply chain, we ensure our customers are satisfied.

We provide a strong service portfolio that includes controlled drugs handling, regulatory services, production process design, and export to more than 100 countries worldwide as well as special technologies such as hormones, hot melt extrusion and biopharma packaging.

In 2021, eight of our existing customers extended their agreements with us. This confirms the trust that we have built among them, including small, medium-sized and large companies from the pharma industry throughout Europe and Latin America. This trust is based on our strong record of reliable high quality, competitive costs and outstanding service.

Alongside extending existing contracts, we have also expanded our Contract Manufacturing Business with new services. In 2021 we carried out the first delivery from our Ecuadorian site to a Brazilian customer. This was a true milestone and also a stepping stone for more to come, as Brazil is the biggest market in the region.

Our biopharma contract manufacturing business has substantial potential for further growth. We currently deliver labelled and packaged syringes and vials to approximately 20 countries. At our site in Italy, we 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. We were rated the best contract manufacturer on Quality KPIs by one of our biopharma customers.

To serve our customers even better in the future, we have further expanded our capacities and capabilities. We set up new packaging facilities, including new wallet packaging lines, and, from 2022 onwards, we will also be able to produce and package nasal spray products.

50%

of our overall production volume is for external customers.

50+

partners.

100+

countries supplied worldwide.

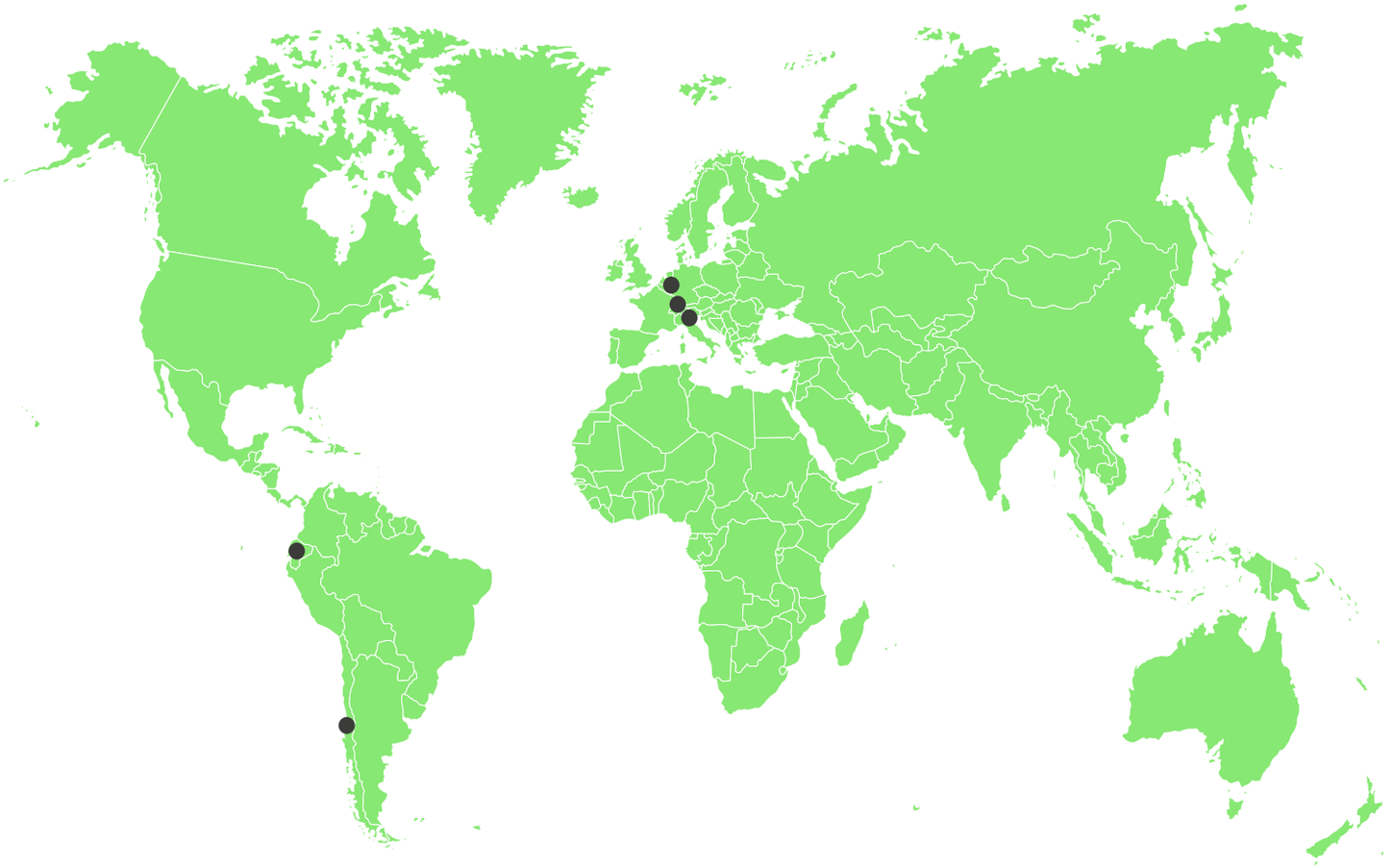
Grünenthal PRO – our Contract Manufacturing Business

Operational excellence
Guaranteeing quality, reliable delivery and improvement

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

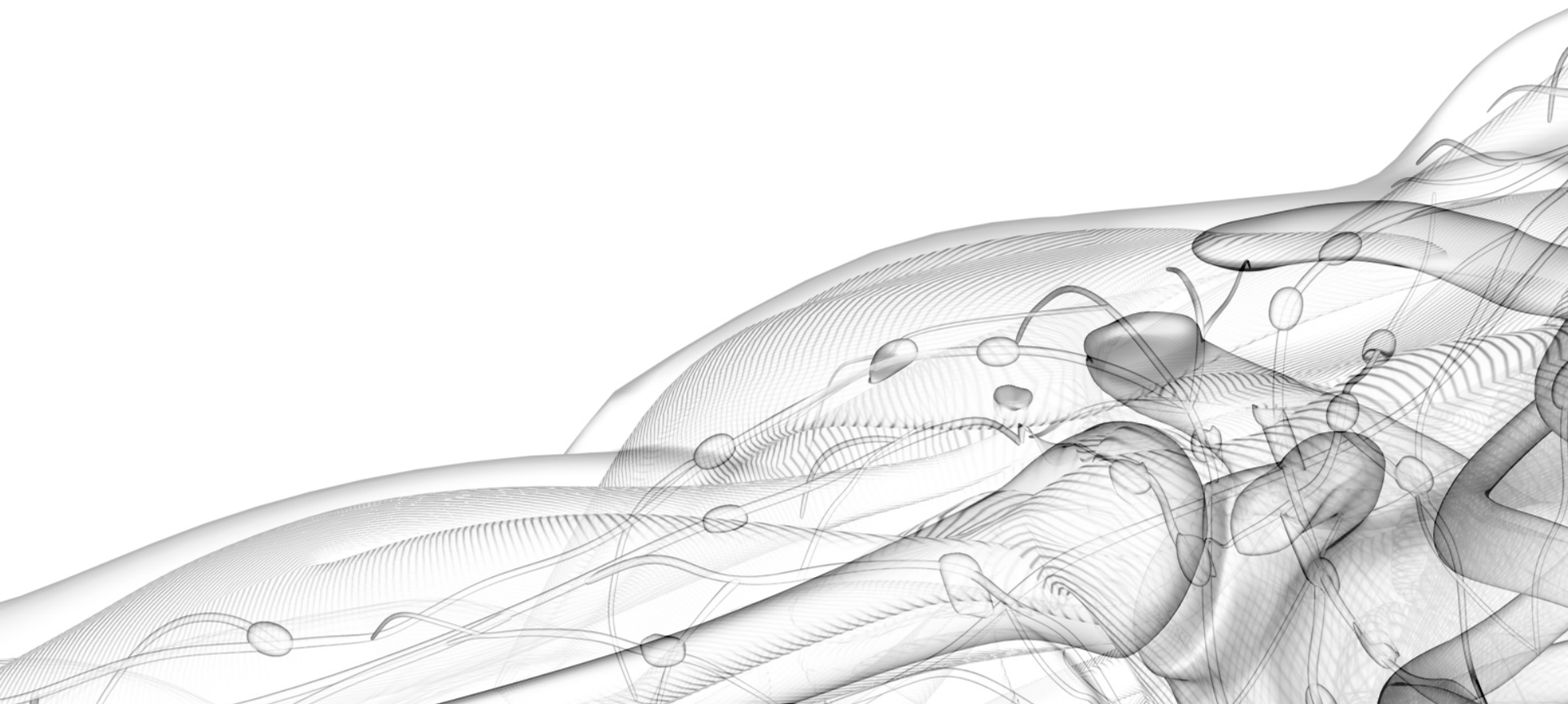
Our manufacturing sites
Chile, Ecuador, Switzerland, Italy and Germany

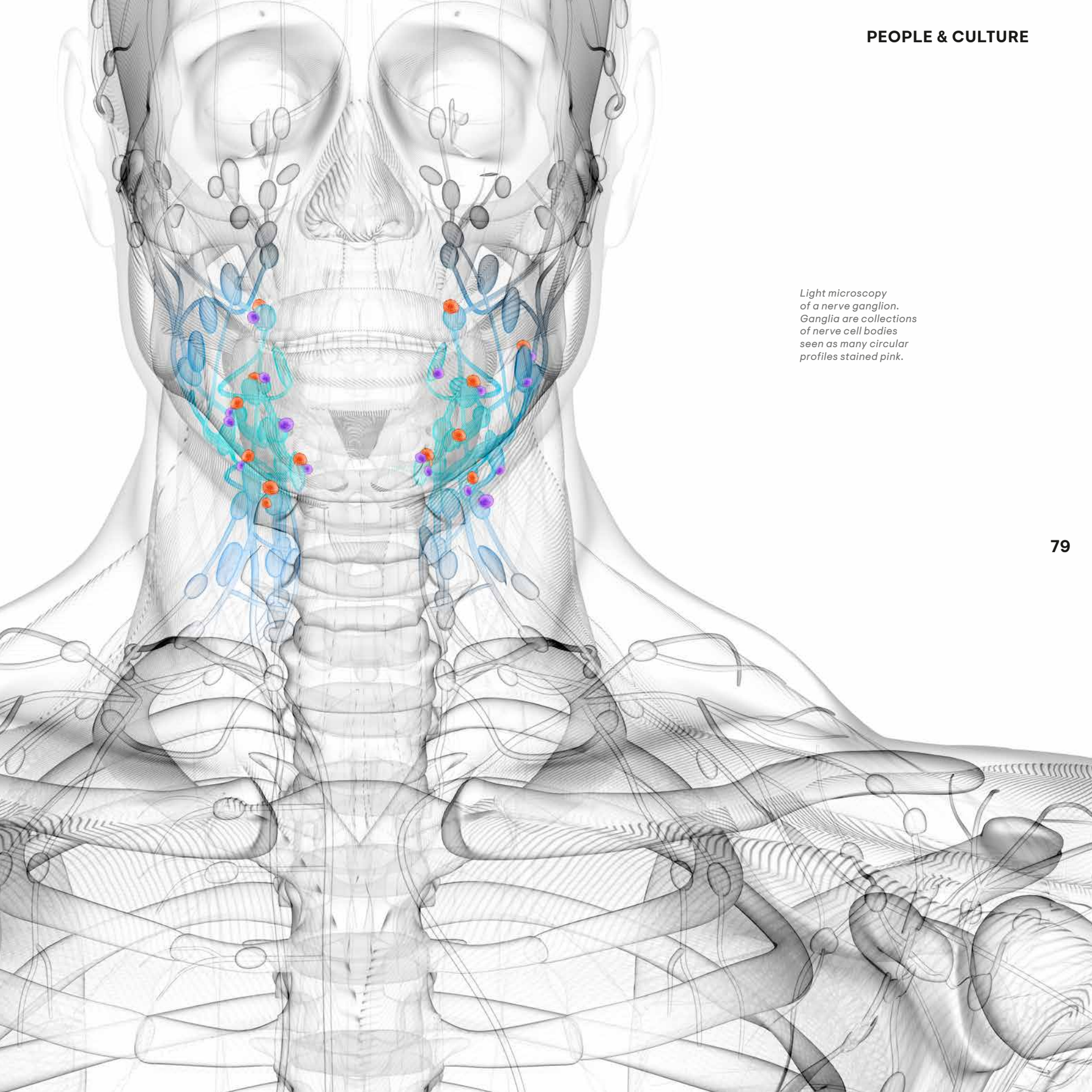
www.grunenthal-pro.com



PEOPLE & CULTURE

At Grünenthal, we join forces, make an impact and innovate for a world free of pain.





Light microscopy of a nerve ganglion. Ganglia are collections of nerve cell bodies seen as many circular profiles stained pink.

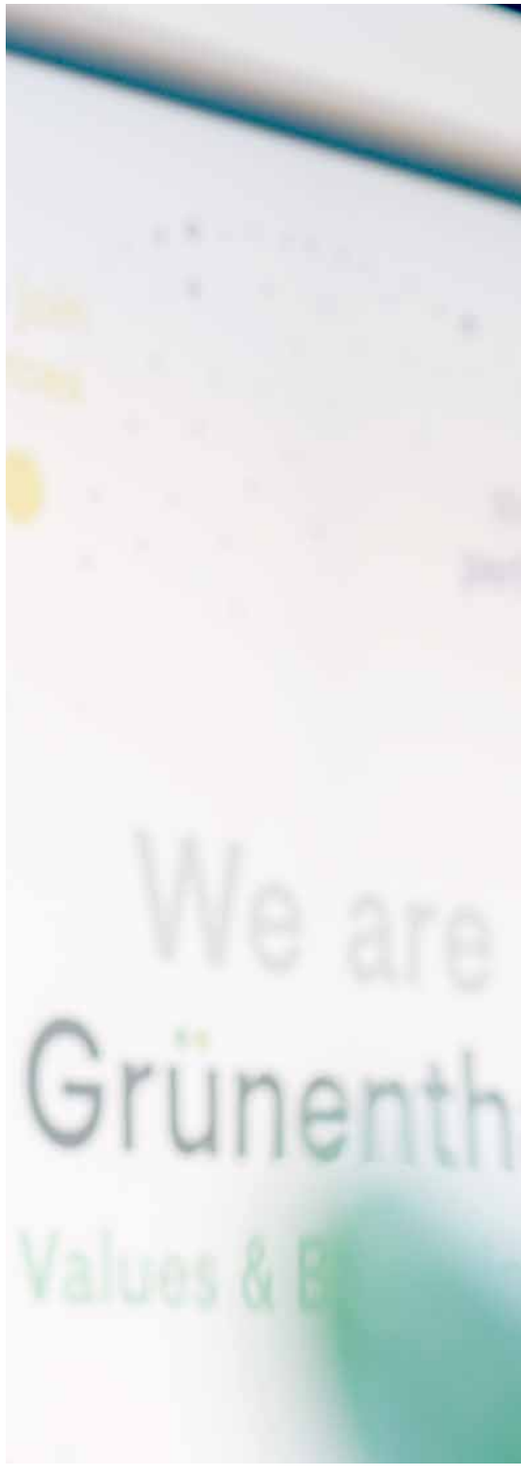
THRIVING IN A HIGH-PERFORMANCE CULTURE

Our employees bring great ideas to the table and develop their full potential as contributors to the success of Grünenthal and the communities we serve.

GRÜNENTHAL is driving a vibrant and high-performance culture guided by distinctive 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. Individual priorities are aligned with our company strategy and scorecard. Progress towards our goals is shared transparently throughout the year.

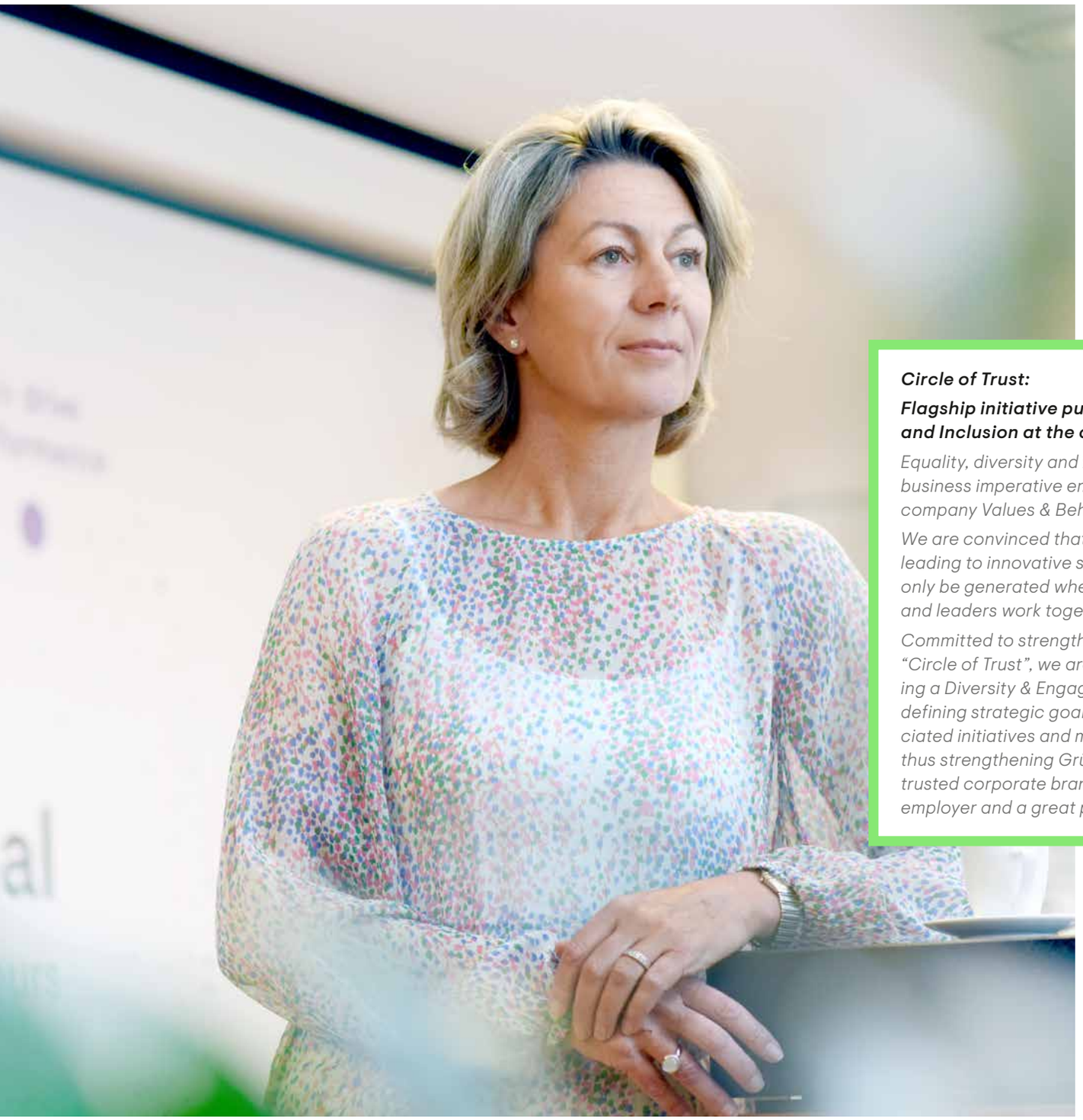
We care for the wellbeing of our employees. The pandemic has created additional challenges for people. With virtual workshops on health, wellbeing and collaboration, employees are supported individually. We have built targeted employee assistance programmes to support our colleagues best wherever they are based.

In 2021, we also introduced a new long-term flexible approach that enables hybrid working for most employees. It allows colleagues to get the most out of their private and professional lives.



> **We recognise and act on the importance of creating an environment in which all employees feel valued, respected, included and empowered to do their best.** <

Leen Hofkens,
Head Global Human Resources



Leen Hofkens,
Head Global Human Resources

Circle of Trust:

Flagship initiative puts Diversity and Inclusion at the centre

Equality, diversity and inclusion is a business imperative embedded in our company Values & Behaviours.

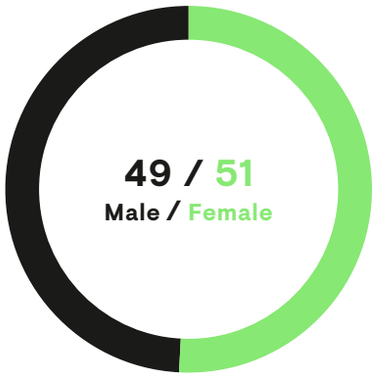
We are convinced that brilliant ideas leading to innovative solutions can only be generated when diverse teams and leaders work together.

Committed to strengthening this "Circle of Trust", we are now establishing a Diversity & Engagement Council defining strategic goals, govern associated initiatives and monitor impact; thus strengthening Grünenthal as a trusted corporate brand, an attractive employer and a great place to work.

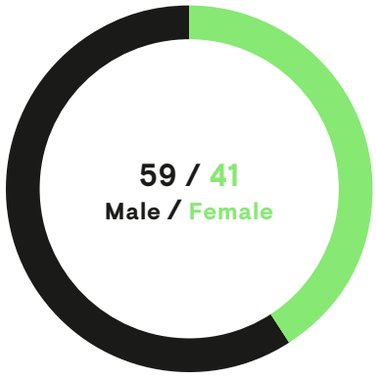
GENDER BALANCE 2021

in percent Male / Female

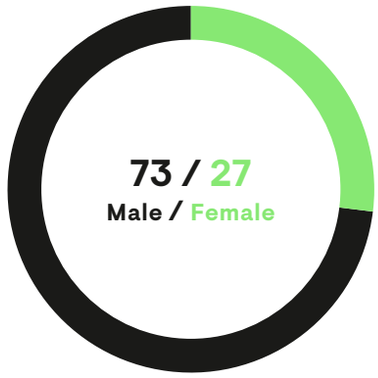
All employees



Employees in leadership roles



Employees in executive roles



> In 2022, we are establishing a Diversity & Engagement Council which will collaboratively define strategic goals, govern associated initiatives and monitor the efforts to further increase our diversity at all levels. <

JOINING FORCES AROUND THE WORLD

500 new colleagues

In 2021 we welcomed over 500 new colleagues worldwide and more than doubled our field force in the US.

- 520 new hires in total
- US build-up sales organisation more than doubled:
  - December 2020: 41 employees
  - December 2021: 110 employees

EMPLOYEES BY FUNCTION	DECEMBER 2021
R&D	300
Global Commercial	1,802
Corporate Functions	568
Global Operations	1,837
Total	**4,507**

28 Countries

59 Nationalities

>500 New colleagues worldwide

Antje Leipelt, *Technician Cellular & Molecular Biology*
Caroline Ferraz, *Head Global eCompliance*
Feras Khalil, *Pharmacometrics Lead*
Luciana Ataide, *Project Manager Financial Processes & Systems*

A GREAT PLACE TO WORK AND GROW

We actively engage our employees on our cultural journey, creating an environment of trust, transparency, respect and fairness, learning and collaboration to achieve our purpose. Growing together.

IN 2021, we have been certified as a Great Place to Work® in eight countries, including our headquarters. This reflects the positive feedback of our employees and the significant progress made compared to the previous survey in 2017. In 2022, we will again conduct a Great Place to Work® survey to gather direct feedback from all employees.

A great place to launch your career

Young graduates fuel our future talent pipeline and diversify our workforce, bringing in fresh ideas. Young hires can look forward to a broad experience in rich and varied roles and functions.

Our graduate and trainee programmes provide the framework for a smooth start into professional life and the skillsets for achieving real impact.

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

The implementation of our strengthened Employer Brand was a great milestone for Grünenthal – building on our capability to attract, develop and retain talented and diverse colleagues. This is visible in our new careers website and increased presence on Social Media.

You can follow us on LinkedIn for regular updates or check out open positions on the careers website.

careers.grunenthal.com

Certifications in eight countries plus three local certificates

Louis Mertens, *dual studies in Economics,*
Max Rothkranz, *Apprentice Industrial Clerk,*
Pia Quadflieg, *Apprentice Industrial Clerk*

The benefits of SmartWork

Grünenthal employees can choose to work in a hybrid model, combining on-site work with working from home. We call it SmartWork.

The concept gives employees the benefits of a fixed workplace, such as connecting with colleagues, collaborating to explore new ideas, and social exchange. At the same time, employees also get the advantages of remote working, including a better work-life balance and less travel time. We have all the digital tools for information sharing and collaboration in place. This way, many employees can work at locations away from the office several days a week.

Global Graduate Programme

Supporting young talent to become future leaders and experts: Our Global Graduate Programme is designed to provide highly talented graduates and PhD students with a personalised career journey.

Over 24 months, graduates have a well-rounded view of our organisation through rotations across roles, global affiliates and sites.

Exciting projects and developing a solid professional network await the young talents participating in this programme.

Enriched by the close collaboration with a senior leader mentor, our graduates are supported in identifying strengths and development areas, getting the most out of their potential and growing continuously. At the end of this programme, the graduates will be ready to take the next step in their career at Grünenthal.

Christian Winkelhorst, *Controller Licensing, Mergers & Acquisitions Controlling*

> My colleagues supported me early on in taking on responsibility and leading initiatives. This allowed me to further develop my communication skills and my financial know-how to grow within my position. The job rotation during the Graduate Programme helped me build a network within the Finance & Controlling Community and allowed me to be part of various projects. This strengthened business understanding is crucial for my current role – working on exciting new deal opportunities for Grünenthal. <

Rita Santos, *Digital Procurement Transformation Manager*

> At Grünenthal, I have had the chance to explore different areas, which lead me to have a cross-functional view of Global Operations. I grew as a professional by learning from others and having the chance to impact this exciting and change-driven organisation. I have always felt supported to get "hands-on" and follow my professional aspirations. While challenged by diverse projects in multiple areas, I have identified my passion for digitalisation and project-oriented roles. Afterwards, I had the chance to work in Global Procurement – focused on digitalisation – and rapidly understood that it was the right next step for my career. The programme has truly created great chances, enriching experiences and valuable professional relationships, which will surely contribute to my success in the new role. <

Raaj Kumaar Swaminathan, *Graduate GO Controlling,* ***Adela Mohammadovà,*** *Graduate Quality Expert,* ***Alexander Garrelfs,*** *Site Controller Aachen,* ***Raneem Alkateb,*** *Graduate Global Drug Safety,* ***Clemens Dialer,*** *Medicinal Chemist,* ***Rita Santos,*** *Digital Procurement Transformation Manager,* ***Lucas Ewald,*** *Graduate Aachen Site,* ***Marc Fontanet,*** *Graduate Global Operations*

A great place to develop your career

Retaining and developing talent is essential for the success of our business. We are building capabilities that help us achieve our strategic priorities today and in the future, both at the functional and leadership level.

To strengthen our succession pipeline for critical roles at Grünenthal, we aim to maintain a balance between attracting external candidates and growing internal employees.

For our internal talent, we provide growth opportunities, whether within the role, advancing into a new position or taking a lateral move across functions. Our senior leaders and managers are expected to regularly spend time supporting the development of their employees based on individual development plans and providing feedback and coaching throughout the year. We focus on on-the-job learning, combined with training and learning from others.

61%

growing talent internally.

61 percent of our senior leadership vacancies were filled by internal talents and successors, compared to 50 percent in 2020.

How we put individual development into action

Carmen Fernandez,
HR Business Partner Global Operations

> We develop our employees by regularly discussing their aspirations and building targeted individual development plans. Building on these plans we enable them to take ownership of their development, focusing on on-the-job learning. In succession planning meetings for critical roles, our leadership teams look at the potential and aspirations of our employees and opportunities for growth. When we hire new talents, we support them in building their career with us.

There are different ways to grow and shape your personal growth at Grünenthal. We have many great examples of colleagues who realised their ambitions. Their development shows that there are diverse and creative career paths that enrich our employees and the organisation. <

Ana Martins,
Head of Cluster Iberia

> I started at Grünenthal as Controlling Manager in Portugal fifteen years ago. Over that time, I have had six different job roles, receiving opportunities and support that led me to my current function as General Manager for Spain and Portugal. I am passionate to learn, to experience new things and to develop outside of my comfort zone. My career development in Grünenthal has been a journey. I was able to experience and grow in different areas of expertise, in an affiliate and in global, in national and international roles, always with the support of training and leadership programmes. I am proud to work for a company that truly believes that an organisation is as good as its people. <

MAINTAINING HIGH EMPLOYEE ENGAGEMENT

Driving a high-performance culture is key to our success. To achieve this and keep our employees engaged around our shared priorities, we ensure that all employees understand and fully support Grünenthal's strategy.

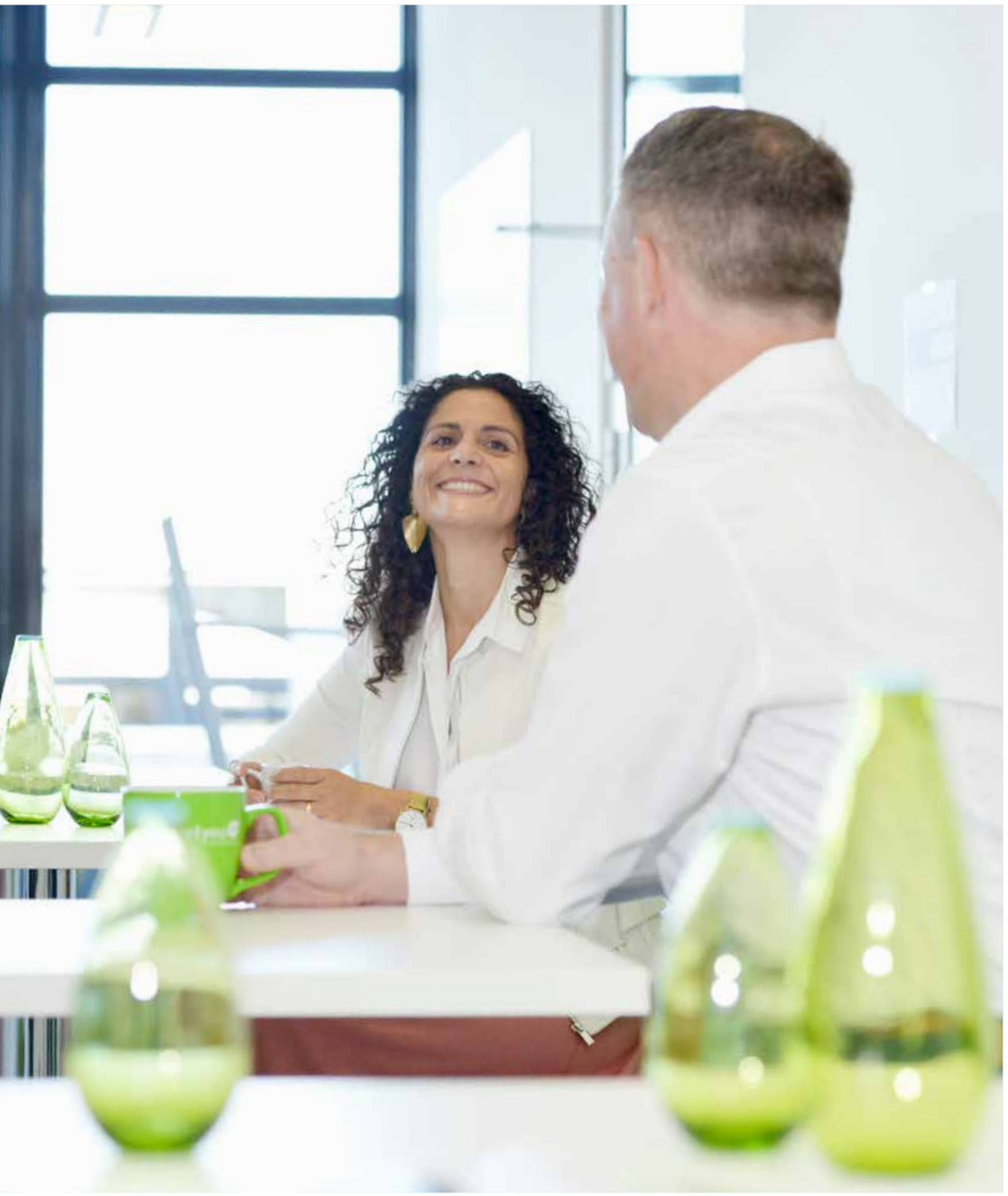
THROUGH our Global Scorecard and other initiatives such as regular global townhall meetings, we enable a constant flow of communication and interaction between all employees and leaders and thus create clarity on our company strategy and priorities.

Our people and our decisions are guided by Grünenthal's Values & Behaviours. We work hard and challenge each other to drive our performance. At the same time, we also support each other, work closely together, and demonstrate integrity in everything we do.

We make sure outstanding results are recognised and rewarded, looking both at what has been achieved and how the achievement was made possible.

For example, we celebrate exceptional contributions with our Grünenthal Global Excellence Award each year. In 2021, all employees were recognised for their commitment and contributions despite the difficulties posed by the pandemic.

We celebrated this with our Grünenthal Thank You Day in July 2021, an additional holiday for all employees.



Alberto Aimola, *Regional Sales Manager*
Ana Inacio, *Global Established Assets Lead*
Philipp Wabnitz, *Early Products Access Lead*

We are proud of our company's progress on its cultural journey over the past few years. Regular employee surveys help us gain a clear picture of our progress in evolving our culture and keep a finger on the pulse. The consistently high participation rates strongly indicate our employees' commitment to shaping our culture.

The results of the 180-degree Pulse Check of 2021 confirmed the positive trends seen in previous surveys. In the latest of these leadership feedback surveys, two-thirds of our employees gave feedback on the 95 percent of eligible leaders who took part.

Matilde Belenguer, *Facilities Management Grünenthal Spain*

Beatriz Peñalba Aceña, *Corporate Communication & Corporate Social Responsibility Spain*

180-degree Pulse Check

- the great majority of our employees stated that priorities are clear (93 percent) and that their manager keeps the team focused on priorities and results (90 percent);
- managers actively support employees in their development and provide helpful feedback (81 percent);
- managers show appreciation and recognise great contributions, encouraging employees to develop new ideas and better ways of doing things (87 percent);
- employees confirm that managers actively encourage cross-functional collaboration (91 percent);
- managers are perceived as role models for our Values & Behaviours (87 percent);
- most employees state their manager does not micromanage (82 percent) – a great improvement compared to the survey in 2020 (65 percent);
- the great majority of our employees would recommend their manager to other colleagues (88 percent).

WE ARE GRÜNENTHAL
VALUES & BEHAVIOURS

This means that we put our patients first when making decisions. We want to understand their needs and experiences and tailor solutions to improve their lives.

We try new things and take smart risks. We think and act strategically, spot trends, plan long-term and create opportunities for growth. We work to win – and be better.

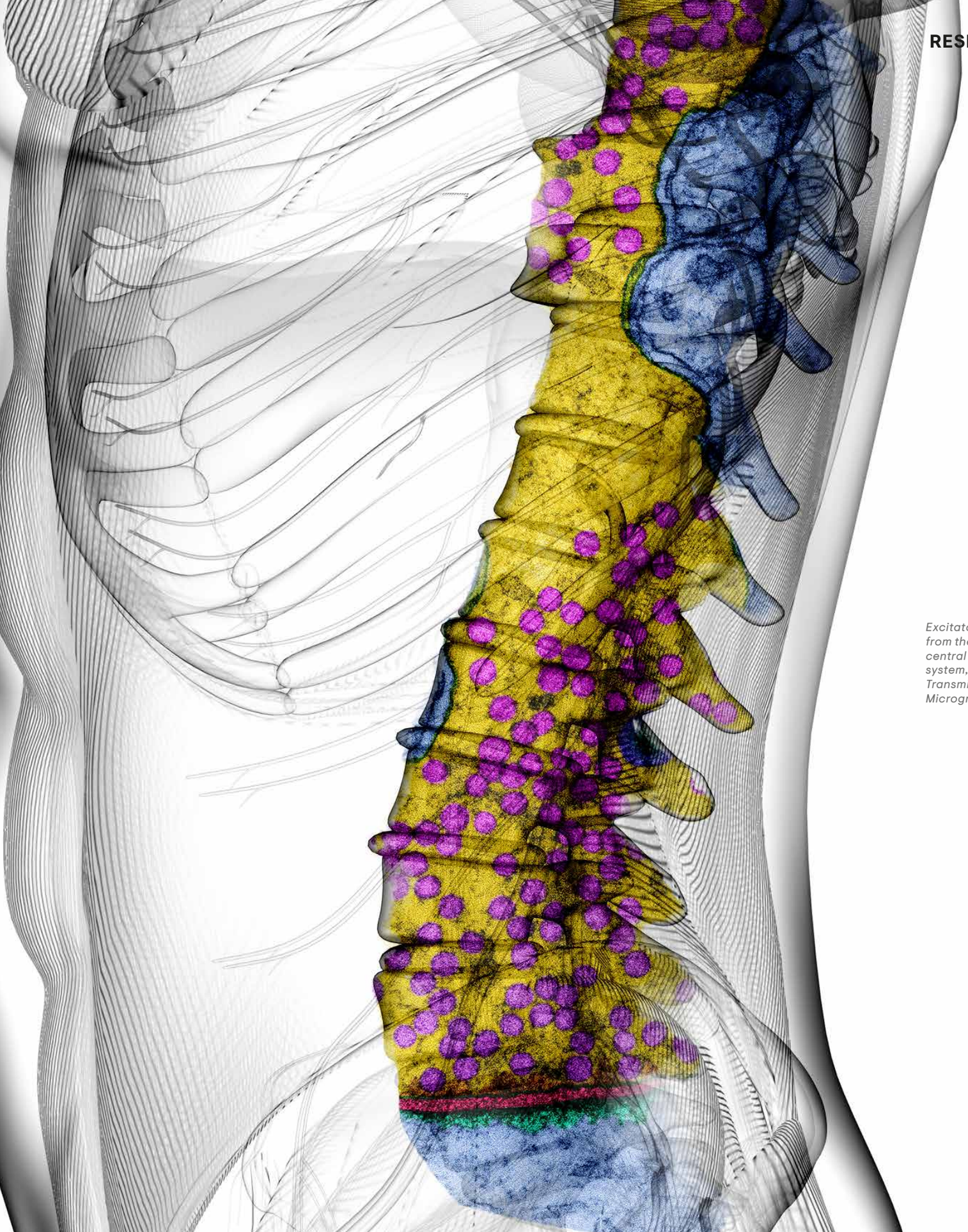
We actively seek diverse input when designing solutions. We listen to each other, share knowledge to ensure a common understanding and learn from each other.

This value is at the heart of everything we do. We advocate and apply high ethical standards every day. We treat people with respect and have empathy for how people feel.

This value is key to ensure our company success. We want to share our vision and inspire people to achieve our purpose.

RESPONSIBLE BUSINESS

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.



Excitatory synapse from the human central nervous system, coloured Transmission Electron Micrograph (TEM)

MAKING A POSITIVE IMPACT

As a science-based company and a global leader in pain management, we strive to positively impact patients, employees, partners and society. We work towards reducing our impact on the environment. This goal drives our approach to Corporate Responsibility.

OUR LONG-STANDING commitment to Corporate Responsibility is closely tied to our culture and embedded within our strategy. It is important to us that we do not just focus on a reactive, risk-driven perspective – only asking ourselves how possible Environmental, Social and Governance topics can negatively affect our patients, our people and our planet. Instead, we choose a proactive, opportunity-driven approach to ensure Grünenthal's positive impact.

In this spirit, we launched a new, holistic Corporate Responsibility Programme in 2021, that we will build on in the coming years.

Our first Grünenthal Responsibility Report, published alongside this report, marks a milestone on our journey towards a fully integrated reporting of how we conduct our business responsibly and the impact we have on society and the environment. We report according to the Global Reporting Initiative (GRI) standards and subject our reporting to thorough external auditing.

> With a responsible framework nurtured by an ongoing dialogue amongst all stakeholders, we create the foundation upon which all of us can contribute to our vision. <

Sebastian Köhler,
General Counsel

To pursue our ambitions, we built this programme on four modules:

Flagship initiatives

Our dedicated responsibility initiatives drive positive impact in the core areas of Patient, People and Planet. We have created internal capacity, set ourselves ambitious targets and established KPIs to measure progress for each of these flagships.

Patient People Planet

ESG Risk Management

Managing risks is an essential aspect of Corporate Responsibility. Potential risks in this area can be clustered into the categories of Environmental, Social and Governance (ESG). An independent agency regularly monitors and assesses our ESG risks and our approach to managing them.

Ethical Framework

Our stringent ethical framework – for example, bio and data ethics – guides the way we work in areas lacking a clear legal regulation.

Corporate Governance

Our corporate governance system ensures that we constantly live our values.

Our Corporate Responsibility Programme is embedded in our strategy.

[1] ESG: Environmental, Social, Governance

INTERVIEW WITH
PROF. DR. CORDULA MECKENSTOCK,
CHIEF RESPONSIBILITY OFFICER

> BEING A RESPONSIBLE BUSINESS <

On the authentic approach and the strategic implications of Corporate Responsibility.

What does Corporate Responsibility mean to Grünenthal?

It means we responsibly conduct our business – legally, ethically, respectfully and sustainably. This covers everything we do: From selecting suppliers and how we treat our employees to production conditions and marketing and sales practices. We have an authentic Corporate Responsibility policy, meaning it is not just a "tick the box" exercise but a way for us to invest in and engage with the world around us in a positive way.

How does it fit in with the company's overall strategy?

Corporate Responsibility is deeply embedded in our business strategy and part of our main priorities. All business areas contribute to our ambitious goals for example through the diverse flagship initiatives.

> We have an authentic Corporate Responsibility policy, meaning it is not just a "tick the box" exercise but a way for us to invest in and engage with the world around us in a positive way. <

Prof. Dr. Cordula Meckenstock,
Chief Responsibility Officer

We also reflect this joint effort in our corporate scorecard. As a global company, we are committing to goals within four strategic dimensions for 2022. One of these is explicitly dedicated to Corporate Responsibility: we commit to delivering on our flagship initiatives with clear KPIs underpinning each initiative's ambition. Adhering to our strategic scorecard is part of our employees' incentive system – clear evidence that we believe in our aspirations and want to be measured against our success.

Why is it important to be taking these steps now?

Like all other companies, we operate in a world of change: climate change, political power shifts, personal interactions shifting to digital, a sudden rise of a global pandemic, etc.

Also, the roles and responsibilities of stakeholders worldwide are changing: national governments cannot cope alone with challenges like climate change, water and energy scarcity, health emergencies, and refugees.

Other players like civil society, non-governmental organisations, international institutions and – very importantly – companies play a crucial role in stepping up and taking on responsibility.

Society is rightfully expecting companies to take increased responsibility for their actions and conduct business sustainably. Corporate Responsibility involves going beyond minimum legal requirements to manage the economic, environmental and societal impact of a business' operations.

The role of governance systems is to ensure that organisations live up to their promises. With investors, customers, employees, and suppliers becoming much more selective in choosing their business partners, meeting these requirements and reporting on them transparently is crucial for doing the right thing and for the organisation's performance.

Gillian Burgess,
Head of Research

OUR FLAGSHIP INITIATIVES

Our flagship initiatives are designed to optimise and boost our business's positive impact on the patients we serve, the people we work with, and the environment.

Patient People Planet

Patient

Education of Patients & Healthcare Professionals – To better support patients on their journey to achieving optimal pain management, we have established an initiative to educate healthcare professionals on the responsible use of pain medicines. With regard to opioids, our Charter on the Responsible Use of Opioids sets out our commitment to exploring and endorsing measures that minimise the risk of inappropriate and illegitimate use of prescription opioids – while striving to ensure that individual patients with a clear need for opioid-based pain relief are not denied access.

Data-driven Human Disease Understanding – To enhance our ability to create truly novel medicines for patients in need, we are expanding our understanding of human disease based on concrete data.

Global Grünenthal Platform for Awareness & Access – To improve accessibility for patients to adequate pain treatment, particularly among underserved populations, we are establishing a joint platform that ensures access to medicine and raises awareness about pain and palliative care.

You can find out more about how our corporate responsibility initiatives bring benefits for patients around the world in our Responsibility Report on pages 28ff., and further information about how we develop innovative medicines in the chapter A World Free of Pain of this report.

People

Circle of Trust – To foster a culture of trust among employees, partners and the community we are establishing a Diversity & Engagement Council. It will raise awareness, identify needs, govern initiatives and monitor impact.

Full details about our initiatives appear on pages 36ff. of our Responsibility Report and you can read more about how we create a positive impact for the people we work with in the chapter People & Culture of this report.

Planet

Driving Environmental Sustainability – To reduce the environmental impact from our business, we have established a number of initiatives to ensure we use resources more sustainably, avoid waste in our operations wherever possible, and switch to power our sites with low carbon or renewable energy sources.

In order to create a meaningful impact and achieve our environmental goals, we have established three major areas of action. With our Environmental Excellence Strategy we continuously develop and promote sustainability throughout our business. With our key topic around the Responsible Use of Resources we aim to improve our energy and water consumption and how we handle production waste. In 2021, we have achieved our target of sending absolutely zero waste to landfills from our manufacturing facilities around the globe. With our initiative around Impact on Climate, we want to gain a deeper understanding of our impact on climate change so that we can identify the most effective ways to reduce it.

Besides improving the environmental impact of our own operations, we have launched our #TreesForOurPlanet initiative to support reforestation. It aimed to mark our 75-year anniversary by planting 7,500 trees worldwide in 2021. Our teams planted more than 10,000 trees – and we have set new targets for 2022 and beyond. For more information, see pages 48ff. of the Responsibility Report.

For full details of all our initiatives, key performance indicators and data points, please see our Responsibility Report.

> As a trustee of the Grünenthal Foundation, I greatly value its role in the study and treatment of pain over the past twenty years. Its action has facilitated, among many other things, the creation of an internationally recognized free treatment programme for children and young people with chronic pain. <

Jordi Miró,
Director of the
Chair of Childhood Pain
Rovira i Virgili –
Grünenthal Foundation,
Spain

Three foundations, one common goal: Supporting projects that have a positive impact on people and communities

The **Grünenthal Foundation in Spain** is a non-profit organisation that seeks to improve the quality of life of people suffering from pain in this country. It focuses its activities on three areas: developing knowledge, training patients and their families, and working with the relevant public bodies on the design and implementation of health strategies.

Through its support for the creation of Spain's only chair of childhood pain, at the Rovira i Virgili University, it has helped boost research in chronic childhood pain. The foundation celebrated its 20th anniversary in 2021, and that year, La Razón, one of Spain's most influential media outlets, honoured the Spanish Grünenthal Foundation with its "A Tu Salud Awards" for improving the management of chronic pain in Spain during these two decades.

The **Portuguese Foundation's** primary purpose is scientific research in the area of medical science, especially in the field of pain and its treatment. It was founded in 2001 and offers a grant and support to young researchers as well as an award for the best news reporting on pain.

44 doctors graduated from the master's degree in Palliative Medicine and Pain Management at the Universidad Nacional Mayor de San Marcos in Peru.

The **Palliative Medicine Foundation in Germany** was set up in 1998 to promote science and research in this field and the care of people with severe or terminal diseases. The Grünenthal Foundation has supported a master's degree in Palliative Medicine and Pain Management at the Universidad Nacional Mayor de San Marcos in Peru since 2018. This academic master programme is the first of its kind in Peru. Having certified professionals in the country is a decisive step for the development of palliative care in Peru. In 2021, the first group of 44 doctors graduated from the programme and have already started to create pain management and palliative care units across the country.

With the master's degree in palliative care and the support of the Grünenthal Foundation a seed has been sown that is growing and giving results. In the next four or five years, the development in this area will continue to prosper.

> Awareness and education are essential for the advancement of palliative care in Latin America. <

Patricia Bonilla,
President of the Latin American Association of Palliative Care

> There is still a lack of knowledge among health professionals about palliative care and pain management. <

Luis Enrique Podesta Gavilano,
Dean of the Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru

Grünenthal's support to improve pain management and palliative care also extends to other countries in Latin America, where we offer specific and general education to healthcare professionals and other stakeholders. Across the region, only a third of countries have a specific law on palliative care and only half have a national care plan or recognise palliative care as a medical specialty. With Grünenthal's support, the Latin American Palliative Care Association (ALCP) held academic events for the medical community and journalists, to present the second edition of the Latin American Atlas of Palliative Care. These academic activities were crucial to disseminate the importance of palliative care, its advances and the considerable work that remains to be done to improve the quality of life of patients in need.

The "Grünenthal Foundation for the Support of Thalidomide-Affected People" is committed to help those affected participate in society. Further information can be found on page 106.

OUR ENVIRONMENTAL, SOCIAL AND GOVERNANCE RATING

Our performance in environmental, social and governance (ESG) criteria is reflected in an external rating.

A position to be proud of

ONE PART of our Corporate Responsibility Programme is to manage non-financial risks. Possible risks we could face can be clustered into three main categories: environmental, social, and governance (ESG). Examples of these could include pollution, discrimination or corruption.

Our performance against ESG criteria has been recognised with an external rating that placed Grünenthal in April 2021 in the top five percent of the global pharmaceuticals subindustry, ahead of our key peers. The rating agency Sustainalytics assessed Grünenthal as having a medium ESG risk overall and managing our ESG risks in a strong way.

SUSTAINALYTICS

What are ESG risks?

Sustainalytics' ESG Risk Rating's framework focuses on exposure and management of a company's material ESG issues.

"Exposure"

This dimension reflects the degree to which a company's enterprise value is exposed to material ESG issues including:

- ethical marketing
- clinical trial transparency
- whistleblowing
- corruption
- bribery.

"Management"

This criterion measures a company's preparedness and track record in managing its exposure to material ESG issues through its:

- policies
- programmes
- trainings
- management systems.

Grünenthal Headquarters Campus Aachen, Germany

Pablo Sastre Puche, *Compliance Officer Global Digital Processes, and* ***Florian Dieckmann,*** *Head Global Communication (from left)*

OUR VALUES AND OUR ETHICAL FRAMEWORK

We believe it is our fundamental responsibility to act with integrity and maintain the highest ethical standards in everything we do.

WE WANT our patients, customers, employees, partners, suppliers, investors and all the communities that we serve to have the confidence to trust and do business with us. This is key to our long-term success.

We have a shared set of Values & Behaviours that make clear how we work together to achieve successful outcomes for our company and our patients. These Values & Behaviours guide our decision-making and give a clear indication of how we behave – as individuals and as an organisation.

Business ethics

Our Code of Conduct provides a framework for our actions and decisions. Everyone in our organisation has the responsibility to live up to these standards in their daily work. All employees sign the Code of Conduct when joining the company. We bring it to life through face-to-face and online training.

We also offer a confidential 24-hour Ethics Helpline for anyone with questions, concerns or doubts. Every complaint or concern is investigated by our Compliance organisation. It is fully integrated within the business.

Compliance Officers sit on decision-making bodies across the company and report directly to the Chief Responsibility Officer, who regularly reports to the Executive Board and the Supervisory Board. In addition, we insist that our business partners act lawfully and with integrity in line with this framework. To ensure this, we established our Code of Conduct for Business Partners, which must be signed before formally entering into a partnership.

Bio ethics

We are committed to conducting our research activities within a strict bioethical framework. We adhere to clear rules on animal trials, human biological sampling and emerging technologies. In addition, we are sharing clinical information that is necessary for conducting legitimate research, serving patients' safety and improving public health.

Data and digital ethics

We handle all personal data responsibly and conduct all of our data processing activities in line with applicable legal standards. In addition, we live the principles set out in our Digital Ethics Charter:

- human beings keep oversight and accountability of our digital activities;
- safety and security are embedded in all our digital activities as cornerstones to protect our values;
- we can explain all our digital activities;
- our digital activities do not cause bias and discrimination;
- digital ethics are engrained in our decision-making processes;
- we only undertake digital activities that are in line with this Charter.

OUR MILESTONES IN SUPPORTING THOSE AFFECTED BY THALIDOMIDE

2021 was an important year for Grünenthal in many respects. In addition to our 75th corporate anniversary, it marked the 60th anniversary of the market withdrawal of Thalidomide.

THE THALIDOMIDE tragedy belongs to our corporate history. We at Grünenthal take our responsibility for the continued support of those affected very seriously.

The team of the "Grünenthal Foundation for the Support of Thalidomide-Affected People" contributes greatly towards this goal. The foundation team is committed to help those affected participate in society, for example by financing car modifications and travel assistance and the work of the foundation's team is appreciated within the community.

This was also reflected by the participation of the former chairman of the Federal Association of Thalidomide-Affected People, Georg Löwenhauser, in the celebrations marking the company's 75th anniversary. We are committed to continue this important work moving forward.

In 2007, we intensified our dialogue with those affected and politicians. Since then, we steadily expanded our support. After a payment of 50 million euros to the Federal Thalidomide Foundation in 2009, we founded the Hardship initiative in 2011. For the first time, this enabled us to help those affected directly. Later, we transformed the initiative into the Grünenthal Foundation, which has since financed projects in many different countries.

In November 2021, Dr. Michael Wirtz, shareholder of Grünenthal, apologised to those affected and their families on behalf of his family. From many conversations, we appreciate how important this personal statement was to this community. We therefore welcome this gesture as a further step on the chosen path of dialogue between affected people, Grünenthal and the shareholder family.

The effects of the tragedy can still be felt today. We are committed to keeping the memory alive by continuously expanding the information we make available. Background information on Thalidomide can be found on our website **www.thalidomide-tragedy.com**. Further information on the Grünenthal Foundation can be found here: **www.grunenthal-foundation.com**

Chronology of support for thalidomide-affected people

The infographic shows the most important stages in our approach to Thalidomide.

IN THE FUTURE

The Grünenthal Foundation will continue to work to meet the specific needs of those affected and to improve their lives.

TODAY

To date, the Grünenthal Foundation has supported more than 2,500 cases.

2021

Participation of the Federal Chairman of Thalidomide-affected people in the 75th anniversary of Grünenthal.

2016

The Grünenthal Foundation expands its range of services to include personal accompaniment for those affected.

SEPTEMBER 2014

The international dialogue with those affected is strengthened.

MAY 2013

Grünenthal and representatives of those affected meet for a roundtable meeting.

AUGUST 2012

Grünenthal apologises to those affected for the long silence.

2012

Support programmes to improve the daily lives of those affected are expanded.

BEGINNING OF 2012

The “Grünenthal Foundation for the support of Thalidomide-affected people” is founded.

JUNE 2011

The “Hardship Initiative” for affected people is established and begins its work.

OCTOBER 2009

Grünenthal voluntarily pays another 50 million euros into the federal “Contergan Foundation”, which continues to support those affected in 38 countries.

NOVEMBER 2007

A more frequent dialogue is established between Grünenthal, the German Association of Thalidomide-Affected People and politicians.

IMPRINT

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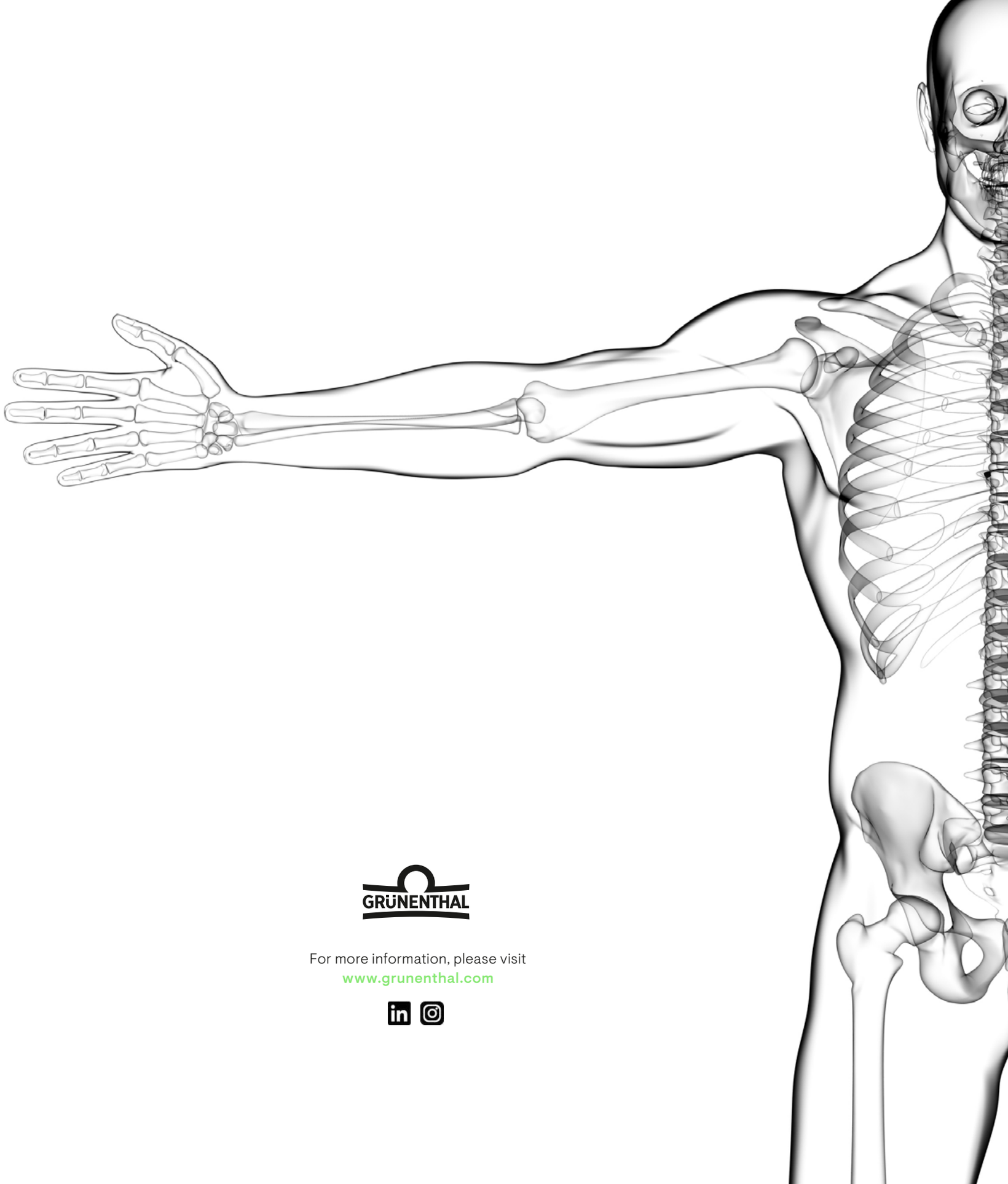

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