INGENEIOUS

NEWS FROM COMBIGENE AB

ISSUE 1 • 2022

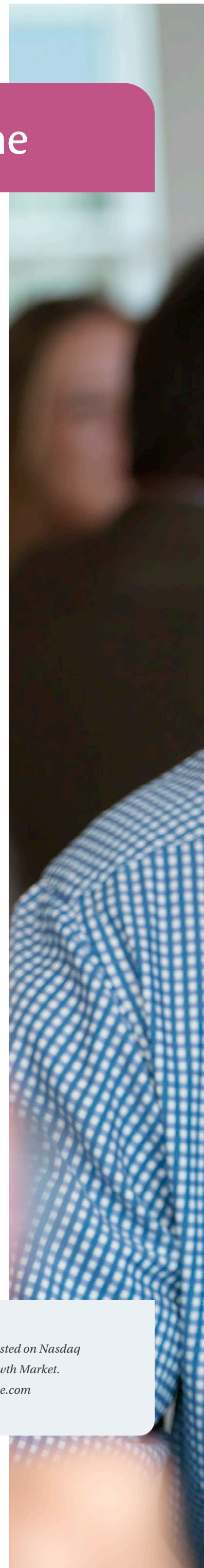
In this issue:

CombiGene

The gene therapy explorer

Interview with CombiGene's CEO Jan Nilsson

2021 was a memorable year for CombiGene



"The past year was a very intense and memorable year for CombiGene. Looking at 2022, it is easy to see that the year ahead promises just as much work."

After many years of intensive work, 2021 turned out to be a truly memorable year for CombiGene crowned with our agreement with Spark Therapeutics. It was also a year that was marked by hard work for CombiGene's employees. During the end of the summer and the beginning of the autumn, we had intensive negotiations with Spark to arrive at the CG01 agreement signed in October 2021. The negotiations were characterized by great mutual trust and a common will to reach an agreement, but an extensive agreement like this still takes a long time to negotiate because of the wide range of details and eventualities that need to be described in the agreement. It was therefore with a great sense of joy and relief that I was able to put my signature on the agreement in the early morning of October 12. I have spent a great many years in the Swedish and international pharmaceutical industry, but this agreement is the largest I ever have negotiated.

However, the finalized agreement did in no way mean that CombiGene has slowed down, we have if anything increased the intensity of our work to ensure that the handover to Spark will be as smooth as possible. In the autumn of 2021, after the signing of the agreement, large parts of the CombiGene team visited Spark in Philadelphia. During three intensive and productive days, we worked together on the continued plans for CG01. The most important outcome of this review is the decision to extend the clinical development program to clinics in the United States as well as in Europe. The U.S. is the world's largest pharmaceutical market and establishing a clinical presence there significantly strengthens the CG01 project.

In order to prepare CG01 to meet the needs of an expanded application that also includes the U.S., the remaining preclinical program will be expanded and, in some parts, supplemented with further studies. In practice, this means that the preclinical part of the CG01 development will take additional time. As previously communicated, we will carry out the remaining parts of the preclinical phase together with Spark while Spark will take full responsibility for the subsequent clinical studies and future commercialization.

The week before the visit to Spark, we also met the Spanish company Viralgen, our manufacturer of CG01. This visit was also very rewarding. Viralgen has in a relatively short time built up an impressive facility and is today a leading manufacturer of viral vectors for gene therapy.

The past year was a very intense year and a memorable year for CombiGene. Looking at 2022, it is easy to see that the year ahead promises just as much work.

Within the CG01 project, we will focus on working together with Spark on the final parts of the preclinical program. Within the CGT2 project, it is our ambition to initiate a proof-of-concept study. In addition, we will work intensively to find exciting new gene therapy projects that aim to treat diseases where the medical need is great and that have a high commercial potential.

So welcome to an exciting new CombiGene year!

Jan Nilsson, CEO

INGENEIOUS EDITORIAL STAFF

Contact:
redaktionen@combigene.com
Legally responsible publisher:
Jan Nilsson

Production:
Form: **WibergComm from Scratch**
Text: **Columbi Communications AB**

CombiGene AB (publ)
Agavägen 52A,
SE-181 55 Lidingö, Sweden
info@combigene.com

CombiGene is listed on Nasdaq First North Growth Market.
www.combigene.com

Spark Therapeutics a perfect partner

In November 2021, the entire CombiGene team went to Philadelphia to meet their colleagues at Spark Therapeutics for the first time. For three days CombiGene and Spark went through scientific and commercial aspects of the project to establish the best way forward. The most important outcome of the meeting was the decision to broaden the upcoming clinical development program (in-human studies) to include both the U.S. and Europe

CombiGene's Chief Scientific & Development Officer Karin Agerman comments on the time that has passed since the agreement with Spark was signed. "The time before the agreement with Spark was signed was extremely intense. An agreement like this is very extensive and there were many detailed issues that we needed to agree on before the agreement could be signed. Nothing is ready until everything is ready. The post-agreement period has been just as busy. It's now that the real work with Spark begins. After a large number of Teams meetings, it was fantastically nice and very productive to finally meet our colleagues at Spark in real life. In the spring of 2018, CombiGene had two employees, me and the company's CEO Jan Nilsson. The fact that we, just a little bit more than three years later, would have grown to seven employees and have signed an agreement for CG01 with a potential value of USD 328.5 million was something of a utopia, even though it has always been an agreement of this kind that we have strived towards. For me, this illustrates how important it is to have a clear objective and that it is actually possible to go all the way through hard and focused work."

CombiGene and Spark Therapeutics plan to expand the clinical development program to include both the U.S. and Europe

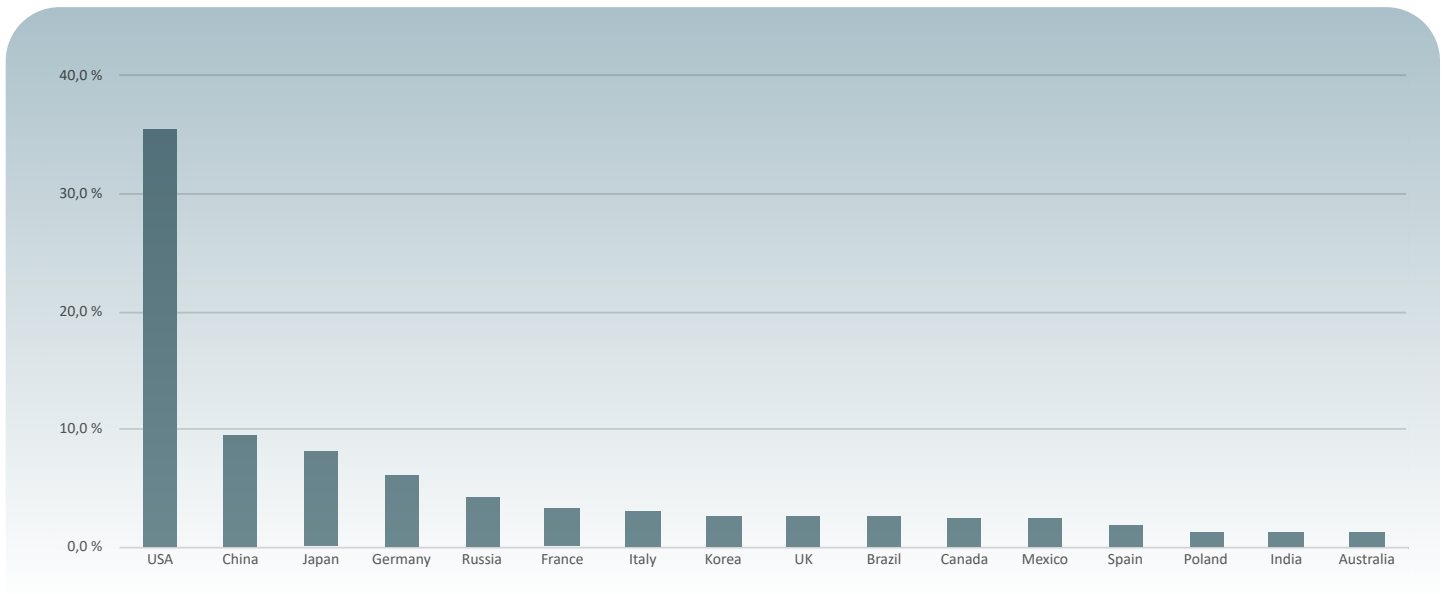
The clinical development program for the epilepsy project CG01 was originally planned to be implemented in Europe, CombiGene's home market. Since CombiGene and Spark Therapeutics entered into an exclusive cooperation and licensing agreement for CG01 in October 2021, the two companies have jointly reviewed the project's future development with the ambition to establish the best way forward.

The most important outcome of this review is the decision to extend the clinical development program to clinics in the United States as well as in Europe. The U.S. is the world's largest pharmaceutical market and establishing a clinical presence there significantly further strengthens the CG01 project.

In order to prepare CG01 to meet the needs of an expanded application that also includes the United States, the remaining preclinical program will be expanded and, in some parts, supplemented with further studies. In practice, this means that the preclinical part of the CG01 development will take additional time. During the remaining part of the preclinical program, all CG01-related R&D activities that CombiGene is running, internal as well as external, will be agreed upon and approved by Spark, who also assumes all agreed costs. As CG01 enters the clinical phase, Spark will take over the responsibility for the continuation of the project and thus also bear all costs during this development phase.

"I am extremely pleased to expand CG01's clinical development program to include the United States. With this decision, the project will gain a natural foothold in the world's largest pharmaceutical market, while Spark can make optimal use of its impressive resources, know-how and networks," said Jan Nilsson, CombiGene's CEO. "CombiGene and Spark will now jointly run the remaining part of the preclinical program before Spark, under our agreement, takes over full responsibility for the clinical development program and future global commercialization."

CG01's clinical development program is planned to include both Europe and the US, the world's largest pharmaceutical market



The U.S. is by far the world's largest pharmaceutical market. It is therefore extremely positive for CombiGene that Spark plans to implement the clinical development program in both the U.S. and Europe.
Sources: OECD and ABPI

The agreement with Spark

The agreement between CombiGene and Spark Therapeutics gives Spark the global and exclusive right to develop, manufacture and commercialize the drug candidate CG01. CombiGene will, in collaboration with Spark, carry out the remaining parts of the preclinical program, mainly the studies in toxicology and biodistribution. Once the preclinical program is completed, Spark will take full responsibility for the clinical development from the first study in humans and on to global commercialization.

Under the terms of agreement, CombiGene is eligible to receive up to USD 328.5 million excluding royalties, with USD 8.5 million upon signing and up to USD 50 million at preclinical and clinical milestones. CombiGene will also be reimbursed for certain authorized R&D expenses. Upon commercialization, CombiGene is eligible for tiered royalties ranging from the mid-single digits up to low double-digits based on net sales.


Mikeletegi
83
9870 BRZ
3983 DKT
0749 JKL

Important visit to Viralgen

One of CombiGene's most important partners and suppliers is the Spanish CDMO company Viralgen, which together with CombiGene and Cobra Biologics developed the production platform for CG01. The COVID-19 pandemic made it impossible to conduct physical meetings for a long period, but in mid-November 2021 representatives of CombiGene were finally able to visit their Spanish partner.

For Martin Linhult, CombiGene's Project Manager CMC, it was the first time he had the opportunity to meet the people he had such intense contact with through email and Teams meetings.

"The manufacture of gene therapies is a relatively complicated process subject to strict regulations. For me personally, it was therefore very valuable to get to know the team at Viralgen. It will make an already well-functioning cooperation even better."

During the meeting in Spain, sharp focus was put on the CG01 project where Viralgen produced material for the final parts of the preclinical program that will pave the way for future clinical studies. The material was produced in 2021 and released after customary quality assurance during the beginning of January 2022.

In 2021, Viralgen expanded its production facility to meet growing demand. "Viralgen's new facility is really impressive," said Martin Linhult. "They now have three units with the capacity to produce up to 3x2,000 liters per unit, which in the gene therapy context is very significant volumes."

CombiGene's other project, the lipodystrophy project CGT2, was also discussed during the meeting. Viralgen has extensive experience of producing the serotypes of AAV that may be relevant and can contribute greatly to the continued development of the CGT2 project.

"The fact that we are already collaborating on our epilepsy project CG01 means that we are well placed to do the same around the CGT2 project. It is very gratifying to note that CombiGene has now come so far on its journey that we have established cooperation with a variety of partners. This is especially important in the CMC area where it is extremely valuable to work with companies that already know our business," Martin Linhult concluded.

The agreement with Spark creates new opportunities for exciting business development

CombiGene has for several years worked long-term to establish the company as an interesting player in the international pharmaceutical market and has gradually built up an extensive network of partners with specific competences in gene therapy. Overall, CombiGene's business development spans three areas: in-licensing of new projects with high commercial potential, refining in-licensed projects through successful preclinical development, and out-licensing of projects aimed at significant patient populations in the late preclinical phase/early clinical phase. In the case of drug candidates aimed at limited patient populations, CombiGene may drive development and commercialization in-house.

Successful in- and out-licensing

So far, CombiGene's business development has been successful. The company has in-licensed the lipodystrophy project CGT2 from Lipigon, established cooperation with a number of CRO and CDMO companies within the frameworks of the CG01 and CGT2 projects and then out-licensed the epilepsy project CG01 to Spark Therapeutics in an agreement with a potential value of USD 328.5 million excluding royalties.

Intensified work to license new projects

The agreement with Spark strengthens CombiGene in several ways. CombiGene's liquid position is strengthened by USD 8.5 million, and the company can look forward to an additional USD 50 million from Spark in preclinical and clinical milestones. During the remaining part of the preclinical program, all CG01-related R&D activities that CombiGene is running, internal as well as external, will be agreed upon and approved by Spark, who also assumes all agreed costs. As CG01 enters the clinical phase, Spark will take over the responsibility for the continuation of the project and thus also bear all costs during this development phase. The agreement will also free up human resources at CombiGene as CG01 enters the clinical phase and Spark will take over full responsibility to run the project.

Through the agreement with Spark, CombiGene has demonstrated that the company has the ability to sign agreements with major international players (Spark is part of the Roche Group, the world's third largest pharmaceutical company), which should make CombiGene an attractive partner for in-licensing of new projects.

All in all, this means that CombiGene is now well placed to take the next step in the company's development and inlicense additional gene therapy projects. It is not possible to say when this will happen, but CombiGene regularly participates in important partnering conferences and maintains continuous dialogues with interesting players in both academia and industry to identify interesting new projects.

Projects for central nervous system and metabolic diseases are high on the agenda

CombiGene will primarily seek AAV-based projects since it is within this technology platform the company has established knowledge in a number of key areas such as vector design (design of drug candidate), safety aspects and production. Similarly, the disease areas that are in focus are those where CombiGene has built up a solid knowledge, i.e., diseases within the central nervous system and metabolic diseases.

CombiGene will at the same time have an open attitude towards other possible projects and evaluate each opportunity on its own merits.

Collaborations are the key to CombiGene's success

If there is one word that characterizes CombiGene's business, it is the word collaboration. For a young and relatively small company like CombiGene, it goes without saying that you support your colleagues at the company, but CombiGene's cooperation goes much further than that. The company cooperates with a variety of partners in both industry and academia. CombiGene's main partner is Spark Therapeutics, which it signed a comprehensive cooperation and license agreement with on October 12, 2021.

The company has put in extensive and painstaking work to find the absolute best partners in various areas. This has resulted in that CombiGene has close collaborations with a number of partners in preclinical development and production.

Collaborations with leading representatives of academia

CombiGene's collaborations cover both industry and academia. The industrial collaborations are mainly focused on preclinical studies and production, while the academic collaborations mainly focus on early and basic research.

CombiGene has since its formation collaborated with the universities of Lund and Copenhagen, where Professor Merab Kokaia and Associate Professor David Woldbye jointly developed the scientific basis for CombiGene's CG01 project.

In the CGT2 project, CombeGene is collaborating with professors Barbara Cannon and Jan Nedergaard at the Wenner-Gren Institute at Stockholm University on a project that aims to understand the mitochondrial functions and conditions of the liver, the organ at the center of the CGT2 project. The practical work is mainly carried out by Brazilian researcher Ruda Feitoza, who has a PhD on how the function of mitochondria can be affected by pharmaceuticals and nutrient uptake.

In 2021, the lipodystrophy project was awarded a project grant of EUR 882,500 by the EU's Eurostars program. The grant means, among other things, that CombiGene is now also collaborating with University Medical Center Hamburg-Eppendorf (UKE). UKE conducts research in five main areas: neuroscience, oncology, cardiovascular research, health science research, and immunology. Professor Jörg Heeren and his team have significant expertise on CGT2's target protein, its function in adipose tissue and its impact on lipid metabolism and they are currently conducting preclinical studies within the CGT2 project.

Important industrial collaborations

CombiGene's industrial collaborations include the collaboration with Spark, which will drive the epilepsy project CG01 through the clinical program and on to global commercialization. But there are also a number of other companies that have contributed to CG01 having such a rapid and successful preclinical development. One of CombiGene's most important industrial collaborations is the collaboration with Viralgen and Cobra Biologics. Together with these two companies, CombiGene has developed a scalable production platform for the gene therapy candidate CG01. Within the framework of CG01, CombiGene also works with the CRO companies Accelero Bioanalytics and Northern Biomedical Research.

The Lipodystrophy project CGT2 is in-licensed from the company Lipigon, which continues to provide CombiGene with scientific support. Thanks to the project grant from Eurostars, CombiGene has established an expanded collaboration with the CRO company Accelero within this project.

CombiGene in fine company

As CombiGene's projects, in particular CG01, have continuously advanced their positions, CombiGene has also started to attract attention among colleagues in the pharmaceutical industry and representatives of CombiGene are increasingly invited to key roles in various events. Among the examples from 2021 is that CombiGene's Chief Research & Development Officer Karin Agerman moderated discussions on the manufacture of gene therapies for preclinical and clinical studies at the ATMP world tour and that CombiGene, in collaboration with Dagens Medicin and together with Novartis and Pfizer, arranged a webinar on gene therapy and that the company's project managers were invited to speak at several different conferences.

CombiGene is also active in Swelife, which promotes an effective collaboration between academia and industry, and ATMP Sweden, a national network within Advanced Therapy Medicinal Products (ATMPs) in Europe and aims to promote the collaboration and communication needed for effective ATMP-based patient solutions. CombiGene is also part of Vision-driven Health, Vinnova's initiative to support visionary innovation environments that engage different players throughout society to together give more people a healthy life.

CombiGene launches new website

When CombiGene signed an agreement with a potential value of USD 328.5 million with Spark Therapeutics in the autumn of 2021, a major leap was taken in the company's development. The agreement is of course extremely important and means that the epilepsy project CG01 has now been given the very best conditions to reach all the way to global commercialization and thus reach epilepsy patients who currently lack treatment options. The agreement also means that CombiGene has shown that the company's business model can establish partnerships among the largest players in the international pharmaceutical industry. Spark is part of the Roche Group, the world's third-largest pharmaceutical manufacturer.

*To better reflect CombiGene's strengthened position, the company has recently launched a new website. The address is the same as before – **combigene.com** Please visit it!*

Interview with Peter Nilsson, who has been on CombiGene's Board of Directors since 2014

Tell us a little about yourself and your background and when you were elected as a member of CombiGene's Board of Directors!

I work as an advisor to a number of client companies, primarily in strategy and business development. Previously, I was a partner and business area manager at Mazars and worked as a certified public accountant with both owner-led and public companies. I was also responsible for Corporate Finance within Mazars with an emphasis on acquisitions and due diligence. I have a master's degree in business administration at Lund University and was formerly a certified public accountant. I have been on the board of CombiGene since 2014. My holding in CombiGene AB amounts to 77,227 shares.

What are the key milestones in CombiGene's development as you see it?

The agreement with Spark is by far the most important thing that has happened in the company, but in chronological order to get us there, I think the decisive milestones are as follows:

- Selection of final drug candidate for CG01.
- Preclinical proof-of-concept study confirming that CG01 leads to fewer and shorter seizures and that some animals became completely seizure-free through treatment with CG01.
- The acquisition of Panion, which gave the company complete control over all intangible assets attributable to CG01.
- GMP production of CG01 for the final parts of the preclinical program.
- Global and exclusive collaboration and licensing agreement with Spark.

What does the agreement with Spark mean for CombiGene as a company?

Above all, this means that the project CG01 has a strong partner with experience, know-how, financial resources, and organization that can take CG01 from the preclinical phase to market. Spark was one of the first gene therapy companies in the world to take a gene therapy all the way to market when Luxturna was approved in December 2017. That Spark chooses to invest in CG01 really shows how important CG01 is expected to be from a therapeutic as well as commercial perspective. It also means that CombiGene can accelerate its business development based on our know-how and experience of developing gene therapies and our business model which has been validated through the agreement with Spark.

How do you think CombiGene will develop in the next three to five years?

Within that time frame, CombiGene has received the first milestone payments within the framework of the agreement with Spark and CG01 has come several steps closer to market. CombiGene has thus further strengthened its position as an internationally recognized gene therapy company.

I also expect that, thanks to intense efforts, we have in-licensed additional projects and developed them in accordance with our business model.

Om CombiGene AB

● *CombiGene's vision is to provide patients affected by severe life-altering diseases with the prospect of a better life through novel gene therapies. CombiGene's business concept is to develop effective gene therapies for severe life-altering diseases where adequate treatment is currently lacking. Development assets are sourced from an external research network and developed to achieve clinical proof of concept. Drug candidates for common diseases will be co-developed and commercialized through strategic partnerships, while the company may manage this process on its own for drugs targeting niched patient populations. The Company has an exclusive collaboration and licensing agreement for the CG01 project with Spark Therapeutics.*

The company is public and listed on the Swedish marketplace Nasdaq First North Growth Market and the company's Certified Advisor is FNCA Sweden AB, +46 (0)852 80 03 99 info@fnca.se.

CombiGene

The gene therapy explorer

CombiGene's vision is to provide patients affected bysevere life-altering diseases with the prospect of a better life through novel gene therapies.

www.combigene.com