INGENEIOUS

NEWS FROM COMBIGENE AB

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Focus on business development and continued development of our pain program

The announcement that Spark Therapeutics is terminating the collaboration on the epilepsy project CG01 came as a complete surprise to us at CombiGene. At the same time, news like these are something you must always be prepared for when working with drug development. By 12 January 2024, CombiGene will regain the global rights to the epilepsy project. We will evaluate the situation in the coming months and get back to the investor community as soon as we have further information. Although the disappointment over the termination of the collaboration with Spark is very high, there are several positives we can take with us. The CG01 project demonstrates that CombiGene has the ability to through preclinical development create great value in in-licensed research assets and that we also have the ability to out-license assets to a large global pharmaceutical company.

In short, you could say that the agreement with Spark verified our business model.

The most important thing right now is that we brush off the dust of disappointment and continue to develop CombiGene. Our focus is now on continuing the development of the extremely exciting pain program COZY while continuing the work to find new promising research assets for in-licensing. I'll tell you a little more about the strategy going forward in an interview on page 14 in this issue of Ingeneious.

In the COZY pain program, the peptide-based project COZY01 is currently being developed at a high pace. During the autumn, we have chosen contract manufacturers and preclinical toxicology partners. We have also chosen shingles as the indication we will use in our clinical proof-of-concept study. After proof of concept has been shown, further development will focus on diabetic neuropathy, a common and severe complication of diabetes which is very painful.

In addition to the development of our proprietary projects, CombiGene is also involved in several industry initiatives. One of these initiatives is GeneNova, which is led by Professor Johan Rockberg at KTH. The goal for GeneNova is to radically reduce today's high production costs in order to make the new gene therapies available to more patients. In this issue we have a full-sized interview with Johan Rockberg that I really recommend you to read.

Peter Ekolind
CEO

"In the COZY pain program, the peptide-based project COZY01 is currently being developed at a high pace."

INGENEIOUS EDITORIAL STAFF

Contact:
redaktionen@combigene.com
Legally responsible publisher:
Peter Ekolind

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CombiGene AB (publ)
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info@combigene.com

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Interview with Professor at KTH

Johan Rockberg

Photo: Rasmus Bengtsson

”The emerging gene therapy means that we are facing disruption in our way of looking at disease, where we hope to be able to cure severe diseases in the future with a single treatment”

GeneNova aims to reduce the manufacturing costs of gene therapy by a factor of 100

● *The GeneNova project, in which CombiGene is a part, aims to establish a common manufacturing protocol for academia and industry, and to reduce today's manufacturing costs of gene therapy by a factor of one hundred! The implications for academia, industry and healthcare are potentially revolutionary. With such a large reduction in costs and a common protocol, significantly more research projects could go all the way to market approval and many more people would be able to access the advanced therapies that are currently limited to a few patients due to excessive costs.*

Ingeneious contacted Professor Johan Rockberg at KTH Royal Institute of Technology, who is leading the GeneNova project, to find out more.

What made you and KTH get involved in gene therapy?

“It's actually very easy to answer. The potential of gene therapy to actually cure serious diseases with one-off treatments and not just relieve symptoms is groundbreaking. The emerging gene therapy means that we are facing disruption in our way of looking at disease, where we hope to be able to cure severe diseases in the future with a single treatment, instead of only relieving symptoms through lifelong medical treatments. However, in order to unleash the fantastic potential of gene therapy, it is necessary to solve the challenges of today's production methods.”

What are the main challenges?

“The predominant challenge is that it is currently so expensive and cumbersome to produce gene therapies. The high cost means, among other things, that the number of research and development projects in both academia and industry is limited, but above all, the high production cost means that the gene therapies that come onto the market have such a high price tag that, for economic reasons, a limited number of patients can benefit from them.”

Is this where Genenova comes in?

“Exactly! In the Genenova project, we have gathered a broad range of expertise to take a completely new approach to the production of gene therapies. When I say new approach, I really mean it. Our ambition is to reduce today's production cost by a factor of 100! By giving ourselves this formidable task, we force ourselves to really go deep and seek completely new solutions – just working with fine-tuning within the framework of today's methods is not enough.”

What are the overall steps in the production of AAV vectors?

“I would say that there are four key elements. The first step is the production of starting material, i.e. the production of DNA, often in the form of plasmids[1]. The second step is the production of the gene therapy vectors, i.e. the capsules that

[1]*Plasmids are ring-shaped DNA molecules that are often found in bacteria (prokaryotes). The plasmid often carries a relatively small amount of information (genes) and can thus be easily transferred between bacteria.*

Continued in the next spread

”Today’s biologics must be frozen to very low temperatures during storage and transport”

contain the material to be introduced into humans and that carry with them the DNA that will replace missing genes, repair damaged genes, or increase the expression of existing genes. The third step is to separate out and purify the gene therapy vectors from the material produced. The fourth and final step is quality control – of course, we must have rigorous procedures to ensure that the material produced meets all safety requirements. A fifth element could also be added – storage and transport. Today’s biologics[2] must be frozen to very low temperatures during storage and transport, and defrosted only when they are to be used.”

Are you looking at all these elements within the framework of the Genenova project?

“We are. Let me give you a few examples of the challenges we are working on. The production of gene therapy vectors[3] takes place in reactors where the starting material consists of human cells. This in itself is a major challenge because human cells naturally do not want to produce viruses, which limits the amount of material produced. Right now, we are looking for different ways to remedy this. Among other things, we have changed the properties of human cells so that they do not understand that it is viruses that they produce. We’re also evaluating a tactic that every parent recognizes – we simply bribe the human cells with ‘candy’ to keep them happy. One similarity between human cells and children is that they like sugar, although they also need a balanced nutrition which we also give them.”

“In what we call downstream production – i.e. the work of separating out and purifying the gene therapy vectors – we have taken several innovative steps towards new processes. Alfa Laval has developed completely new separation methods that we are further developing, and in collaboration with Biotage we are developing new ways to make the depletion of the vectors more specific and the purification process more efficient. We are also investigating different ways to dry the gene therapy material to make storage and transport as cost-effective as possible. In terms of quality assurance, we are working intensively with Vironova on new automated solutions in electron microscopy and advanced machine learning.”

How would you describe GeneNova’s ultimate goal?

“Everything we’re doing is aimed at establishing a completely new protocol for the manufacture of gene therapies. The idea is that this protocol will be shared by academia and industry so that research assets can be seamlessly transferred to preclinical and clinical development. For this to be possible, the manufacturing method must be scalable. It should be possible to use the same method to produce small volumes for research and development purposes and large volumes for commercial use. This is one of the most central aspects of what we are trying to achieve and will mean that more research projects will have the opportunity to go all the way to market approval.”

The GeneNova project has been going on for two years. How far have you come?

“That’s right. GeneNova has been around for two years, and we have funding to continue for another three years. We are well on our way to achieving our ambitions to reduce production costs, but we still have many tough challenges ahead of us. GeneNova is a dedicated research project and for every day that passes we generate new knowledge. For example, we have learned a great deal about the behavior of human cells. Our goal of getting down to one percent of today’s production costs can be described as extremely radical, but the goal really drives the innovation within the project. GeneNova has so far created completely new ways of mathematical calculations, new hardware, new culture

[2]Biological medicines are products whose active substance is of biological origin, such as living cells or tissue, and has been produced or purified from it.

[3]Viruses that are carriers of the genetic information to be administered to humans

Continued in the next spread

media, new processes, new capsids, new ways of interpreting studies and new techniques for automated plasmid purification, for example."

When you look at the participating companies and institutions in GeneNova, you see several obvious names such as AstraZeneca and Karolinska Institutet, but as you already mentioned, Alfa Laval is also participating in the project.

"A traditional industrial company like Alfa Laval may seem like an odd bird in this context, but they are participating for very good reasons! Their expertise in separation technology and the development of new hardware creates new opportunities for us. An important part of GeneNova is also that the project opens the door for a traditional industrial company like Alfa Laval to step into something as delicate as gene therapy. In the future, I can see that several other large Swedish industrial companies may play crucial roles in activities that they do not currently have on the map. For example, there will be a great need for different types of sensors, automation, and wireless technologies. I also believe that there is a lot the pharmaceutical industry can learn from the automotive industry, which has worked for decades to make its operations as efficient as possible."

If we look specifically at CombiGene, what is their biggest contribution to the GeneNova project?

"CombiGene has been active in gene therapy research for several years, which is extremely valuable for the GeneNova project. Thanks to the company's extensive experience, CombiGene can help identify what is missing in the production process and what needs to be improved. The company also has extensive experience in designing preclinical studies and is involved in the work carried out on models for diseases of the central nervous system at Uppsala University within the framework of the GeneNova project."

One last question. Are there any special disease areas that will benefit particularly from the emergence of new gene therapies?

"I believe that there are many diseases that will be treated with gene therapy in the future. Monogenetic diseases[4] are an obvious group , but I am convinced that gene therapy will make a significant contribution to diseases such as cancer and diseases related to the central nervous system, to name a few."

Fact box

GeneNova is a unique innovation collaboration created to develop adeno-associated virus-based (AAV) gene therapies. The project is co-financed by Vinnova, academia and industry with KTH as host. The project runs for five years and aims to develop completely new strategies for the development and production of advanced gene therapies.

The collaboration is supported by Sweden's innovation agency Vinnova and project partners with just over SEK 110 million during the project period 2021-2026. The companies and institutions involved in the project are: Alfa Laval, AstraZeneca, Biotage, CombiGene, Karolinska Institutet, KTH Royal Institute of Technology, Uppsala University, Vironova and Ziccum.

[4]Diseases caused by one or more mutations in a single gene.

CombiGene wants to play a greater role in the development of transformative gene therapies

Gene therapy has the potential to transform today's healthcare by offering treatments that actually cure severe diseases. CombiGene's long-standing ambition has been to contribute to this development, and we are working intensively to find additional research assets that we can add value to through preclinical and clinical development. The COZY pain program is the latest example of how we are working to broaden our project portfolio, but there are several other areas that also are of interest, including diseases of the central nervous system, endocrine[1] diseases and genetic muscle diseases.

There are several perspectives from which one can view the development of new gene therapies and CombiGene's role. The first perspective that makes gene therapy so interesting is, of course, the potential of curing severe diseases. It is this goal that drives researchers all over the world, and it is this that gives us at CombiGene the energy to keep moving our own development forward every day. At the same time, there is of course a commercial perspective to our work – by successfully developing our projects, we also want to create significant financial value for the company and our shareholders, and a broad portfolio of projects increases the chances of achieving just that.

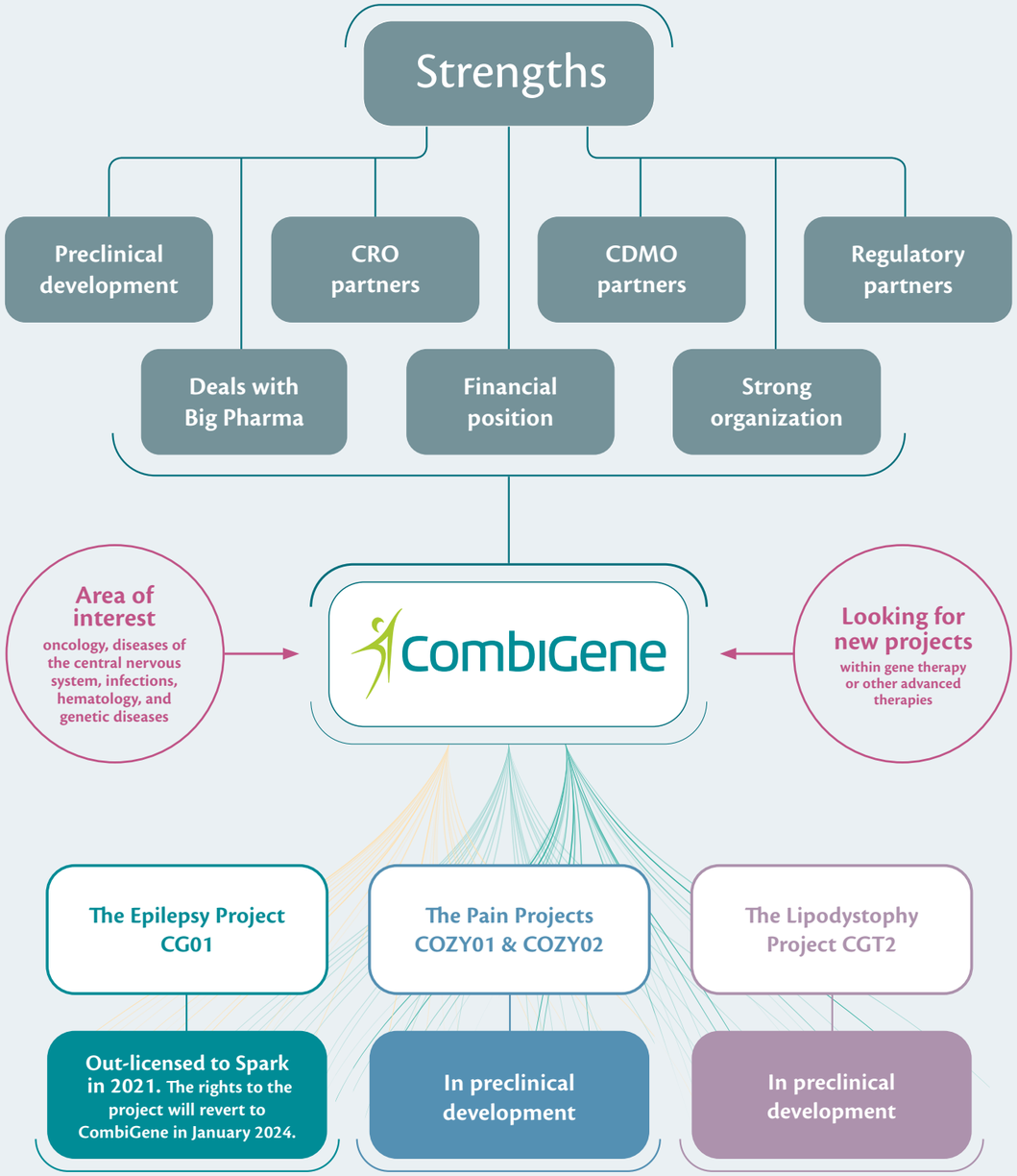
CombiGene is currently working intensively to find interesting new projects to complement our current project portfolio. The evaluation of potential projects is a structured and thorough process based on a number of key criteria. The work includes a review and analysis of intellectual property issues, preclinical data, intended contract structure, size of patient population and medical need, competitive situation, and the project's commercial conditions.

In this work, it is also important that we understand that it is not only we who evaluate potential collaborations – our potential partners naturally evaluate CombiGene. It is therefore very satisfying to be able to demonstrate our strengths and our significant experience in the development of research assets and commercial capabilities.

Over the past five years, CombiGene has built up an infrastructure with considerable strength. Of our ten employees, all of our project managers, six employees, have PhDs in relevant subject areas and we have step by step established an impressive international network of leading companies. Today, we can offer potential partners top-class preclinical project management, world-leading networks of CDMO and CRO partners. We also have established relationships with regulatory advisors, which is extremely valuable when we design clinical studies. Through the agreement with Spark Therapeutics, we have also demonstrated a proven ability to enter into large agreements with leading Big Pharma companies.

[1]*Endocrine diseases include diseases of the body's hormone-producing glands, such as the gonads, pituitary gland, pancreas, and thyroid gland. Diseases in the area also include errors in metabolism – also known as metabolism.*

COMBIGENE – THE BIG PICTURE



The pain project COZY01 has achieved several important milestones

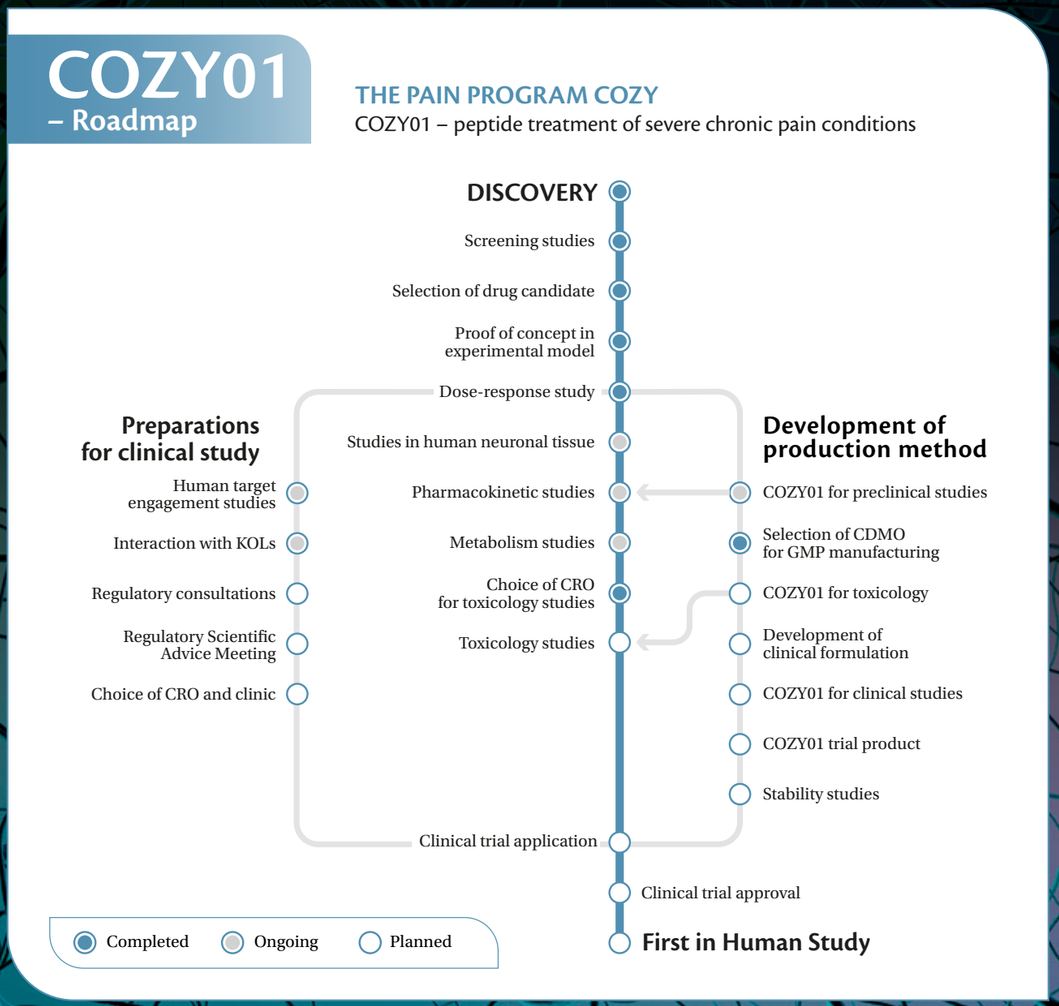
CombiGene is running the COZY pain program together with the Danish company Zyneyro with the goal of developing an effective treatment for severe chronic pain, a common and often difficult-to-treat condition. The program consists of two projects – a peptide treatment and a gene therapy treatment, both of which are based on a new biological mechanism of action which is expected to lack the side effects that today's treatments often give rise to.

The program consists of two projects: a peptide treatment (COZY01) and a gene therapy (COZY02), which expresses the active part of the peptide from COZY01, with potential lifelong effect.

The peptide treatment has shown positive effects in various preclinical models. The continued development is focused on conducting the necessary preclinical studies to evaluate safety and toxicology as quickly and efficiently as possible, as well as producing clinical trial material in order to obtain approval from regulatory authorities to conduct the first human clinical trials with COZY01.

In recent months, CombiGene has achieved several important milestones in the peptide project:

- Selection of the U.S. company AmbioPharm as Contract Development and Manufacturing Organization (CDMO) partner.
- Decision to focus the first study in humans on patients with pain associated with Herpes Zoster (shingles) – a very painful complication.
- Selection of Charles River Laboratories as Preclinical Toxicology Partner.



For more information about CombiGene's COZY pain program, please visit the web:

Click here!

Interview with Peter Ekolind

What is the strategy going forward for CombiGene?

It has now been some time since Spark announced that they will terminate their development of the epilepsy project CG01. The global rights for the project will thus revert to CombiGene. Ingeneious contacted CombiGene's CEO Peter Ekolind to find out how the terminated collaboration affects the company and what CombiGene's strategy now looks like.

Let's start with the most obvious question – what happens to the epilepsy project CG01 now?

"As everyone knows, the partnership with Spark is coming to an end. During the time that the collaboration has lasted, Spark has carried out a great deal of work that has moved the project forward. By January at the latest, the global rights for the project will revert to CombiGene and we will then have a basis for determining how to handle the project. CombiGene will not make any significant research or development investments in the CG01 project, but we will evaluate the conditions for finding a new strategic partner. At present, I cannot determine the likelihood that this will be successful, it is an assessment we will make when we have received the project back from Spark. If the conditions are right, we will definitely do what we can to find a new partner in Big Pharma."

What consequences will the termination of the collaboration with Spark have for CombiGene's strategy?

"Basically, our strategy remains unchanged. We will continue to work to in-license research assets, add value to them through solid preclinical work and then out-license them to a partner within Big Pharma and we are constantly looking for new projects to expand our project portfolio. The reason it's important to work on multiple projects is obvious. There are many pitfalls during the development of a new drug. The product candidate may not be up to mark in terms of toxicology or efficacy. A licensee can suddenly change its strategic direction and leave an indication area, something that the now terminated agreement with Spark is a painful example of. Unfortunately, this is commonplace in all drug development and emphasizes the need to have a reasonably large project portfolio to create good chances of success. The more shots on goal we have, the more likely we are to succeed."

Does this mean that the terminated agreement will not lead to any changes at all?

"Well, we're going to make some changes in terms of the projects we're looking for for in-licensing. There are different strategic paths to take when licensing a new project. If you choose a project that is in an early stage of development, the cost of in-licensing is relatively low, while the road to a finished preclinical package that can be offered to licensees in Big Pharma is relatively long. If you bring in a project that has come further in its development, the cost of in-licensing is significantly higher, at the same time the path to a finished preclinical package and thus potential out-licensing is significantly shorter."

"Given the current situation with a harsh financial climate that has made it more difficult and expensive to raise money and, of course, the fact that we will no longer receive any additional compensation from Spark, we have narrowed down our search. We are now primarily looking for early projects that do not involve any substantial upfront payments and are not associated with any significant costs for us over the next 18 months, but do provide an opportunity for out-licensing and risk mitigation."

Will the termination of the collaboration with Spark mean cost cuts at CombiGene?

"Not really, and the reason is simple. CombiGene has always been a very cost-effective company. Our workforce amounts to a modest ten people and we use a minimal number of consultants. Our fixed costs for office space are very low – we rent four office rooms with two to three workplaces in each in the old AGA area on Lidingö, where the costs are a fraction of what equivalent premises would cost in Stockholm City. We also don't have any lab or lab equipment that costs a lot of money every month. In fact, CombiGene doesn't even own a microscope. All lab operations and manufacturing are carried out by subcontractors selected in competitive tenders. In other words, we have very limited opportunities to reduce our costs by less than significantly reducing the number of employees. This would, however, make it impossible to drive our projects and business development forward. CombiGene is not in a position where we can save our way to success. If we are to be successful, there is only one way to go: continued development of our projects and continued intensive business development to build an attractive project portfolio."

Is there any way that CombiGene can strengthen its cash position without asking the company's shareholders for additional capital?

"Absolutely. In fact, CombiGene has been very successful in raising non-dilutive capital. We have successfully raised soft money in various types of grants from Horizon 2020, Eurstars and Vinnova for both CG01 and CGT2. In total, the grants for these two projects amount to approximately SEK 47 million. To this can be added the upfront payment of almost SEK 90 million we received from Spark in connection with the out-licensing of CG01. In total, CombiGene has thus raised approximately SEK 137 million in non-dilutive capital. We have also applied for grants of approximately SEK 56 million for, among other things, the pain program COZY, but have not yet received any information about whether our applications will be approved or not.

"In relation to the non-dilutive capital received by the company, another SEK 227 million have been received from shareholders since its listing on the stock exchange in 2015. The conclusion is that the team at CombiGene has been very successful in both applying for and obtaining research grants, which has benefited the shareholders at large and thereby financed the company's drug development to almost 40% over the years."

How do you see the development in the near future?

"Of course, Spark's termination of the collaboration agreement was a great disappointment and not something we expected in any way. Now this is a fact and nothing we can influence. What we can and will do is drive our pain program forward with full force. In parallel with this, we will continue the hunt for additional projects for in-licensing to reduce the vulnerability that arises when you have a limited project portfolio. Once we have received the epilepsy project back from Spark, we will, as I said, analyze the possibilities of finding a strong partner for CG01 again."

About CombiGene AB

CombiGene's vision is to provide patients affected by severe diseases with the prospect of a better life through gene therapy and other forms of advanced treatments.

Our business has three focus areas: sourcing of new and promising assets, development of these assets to proof of concept under our management and expertise, and outlicensing of the assets to a strategic partner for continued development and commercialization. Revenue is achieved through milestone payments and royalties.

The company is public and listed on the Swedish marketplace Nasdaq First North Growth Market. The company's Certified Advisor is FNCA Sweden AB, info@fnca.se.

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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.

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