INGENEIOUS

NEWS FROM COMBIGENE AB

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Welcome to special issue 3 of 3

Since the agreement with Spark Therapeutics, CombiGene has strengthened its positions in a number of areas, not least financially. The company is now actively looking for additional gene therapy assets for in-licensing and value-creating pre-clinical development.

In order to highlight our new position, we have decided to publish three issues of Ingeneious at a rapid pace to provide an in-depth picture of some of the areas that are important to us.

I hope you will find it a pleasant read.

Jan Nilsson,

CEO

CombiGene

The gene therapy explorer

In-depth interview with Bert Junno, Chairman of the Board of CombiGene

Let's start this interview with an open question. What do you most want to talk about?

I would very much like to talk about the agreement with Spark Therapeutics since it strengthened CombiGene in so many dimensions. Spark Therapeutics is part of the Roche Group, the world's third largest pharmaceutical group. With the agreement with Spark, CombiGene took a giant step right into the pharmaceutical industry's finest room and we now have a partner with the very best conditions to take our epilepsy project CG01 all the way through clinical studies and on to market approval. That Spark has this ability is demonstrated, among other things, by the fact that they were only the second company ever to receive a FDA approval for a gene therapy, namely Luxturna in 2017. Our epilepsy project could not be in better hands. Having said this, one must understand that the road to market approval is still a long one. We are now working with Spark to complete the remaining parts of the preclinical program. In order to create the very best conditions for obtaining a so-called IND approval by the FDA, that is, approval to initiate studies in humans, Spark, by virtue of its significant resources and extensive experience, has decided to expand certain parts of the preclinical program. I see this as something very positive.

What do the financial aspects of the agreement with Spark look like?

The potential value of the agreement amounts to USD 328.5 million in various milestone payments. While this is a truly significant sum, I see the future royalty payments as the real upside of the agreement. Unlike many other gene therapies that are often developed for the treatment of rare diseases, the CG01 project targets a very significant patient population. There are an estimated 50 million epilepsy patients in the world and a third of them do not achieve seizure freedom with today's treatments. It is this latter category of patients that CG01 is addressing.

What other aspects of the agreement would you like to highlight?

The agreement with Spark has also removed the financial uncertainty that previously existed in the CG01 project. CombiGene does not have the resources to run a project like CG01 throughout the clinical program and on to market on its own. With Spark as a partner, funding is now no issue; Spark will assume all costs for the remaining parts of the preclinical program and will assume all costs for the clinical program. This, together with the initial payment of USD 8.5 million that CombiGene received in connection with the signing of the agreement, means that we are now in a favorable financial situation with a solid cash position and reduced expenses. Our ability to bring in additional projects has thereby markedly improved.

Has the agreement with Spark changed the world's view of CombiGene?

Absolutely! As a direct result of the agreement with Spark, we are seeing a growing interest in CombiGene from a number of different actors. For example, CombiGene will be part of the GeneNova collaboration, an initiative to develop the development process for AAV-based gene therapies. The GeneNova collaboration is supported by Sweden's Innovation Agency Vinnova and partner companies with just over SEK 110 million in total budget for the years 2021-2026. The project is led by Professor Johan Rockberg at KTH and among the participants are, in addition to CombiGene, several reputable actors. The reason for the growing interest in our company is obvious: the agreement with Spark has validated both our technology and our business model and thereby clearly points to great future opportunities for CombiGene to expand further and create large medical and financial value.

How would you describe the development work that CombiGene has carried out within the framework of the CG01 project?

It is a very interesting question where I want to highlight an aspect of CombiGene's work that, in my opinion, has not been given enough attention and that says a lot about the expertise built up within the company. A traditional pharmaceutical company can, in its development, basically focus on one area: its drug candidates. CombiGene's epilepsy project CG01 is much more complex. In addition to the active substances in CG01, i.e., neuropeptide Y (NPY) and its receptor Y2, CombiGene has integrated the active substances into the viral vector used to 'transport' NPY and Y2 into the human cell. CombiGene, together with its partners, has also developed a technique to inject CG01 into the area of the human brain to be treated. All in all, this makes CG01 a very complex project and I am really impressed with how the team at CombiGene has managed to solve all the challenges to develop a working whole. CG01 has thereby generated a lot of knowledge that CombiGene can bring into new projects.

How do you see CombiGene's continued development?

CombiGene is now in a very advantageous position. The agreement with Spark has improved our financial situation while at the same time strengthening the company's brand in the international pharmaceutical industry in a fantastic way. We are now a company that co-works with Spark Therapeutics, the Roche Group's highly specialized gene therapy company. I now look forward to a development where, in addition to continued progress in the CG01 and CGT2 projects, we also bring in new gene therapy assets for value-creating development and in the long-term sign new agreements that are in line with our agreement with Spark. The team at CombiGene has achieved great success and as I see it, the company's exciting journey has only just begun!

Bert Junno

Chairman of the Board since 2020
Year of birth: 1966

Education and experience: Bert has previous management and board level experience from several European and US based companies in fields of electronics, biotech, and IT. He is a co-founder of several life science companies including WntResearch AB, Galecto Biotech AB, Gabather AB, Aptahem AB and Cyxone AB. Bert Junno holds a Ph.D. in Semiconductor Physics and Technology and a M.Sc. in Physics from Lund University.
Current assignments: Chairman of the Board of Cyxone AB (publ), Aptahem AB (publ) and Melius Pharma AB (publ). Board member of Gabather AB (publ), Fornio AB and Accequa AB.
Previous assignments: Board member of Taurus Energy AB (publ), Cardiovax llc., Galecto Biotech AB, Aptahem AB (publ), CEO and Board member of WntResearch AB (publ) and Gabather AB (publ). Member of the advisory board of the Swedish patent office 2010-2019.

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THEME GENE THERAPY

Drug development, step by step

Drug development is a strictly regulated activity to ensure that the drugs that ultimately receive market approval are safe to use and have the intended effect on the diseases they are supposed to treat. Developing new drugs is an extensive and time-consuming process where costs rise as the project progresses.

The development of a new drug can be divided into different stages: discovery/basic research, preclinical development and clinical development. In the discovery phase, the research is based on a basic idea of how a disease can be treated. During the preclinical development, the goal is to experimentally determine whether the drug candidate or candidates that have been developed have the potential to create the effect you want to achieve. Once you have chosen the drug candidate you want to proceed with, a number of preclinical studies are conducted regarding efficacy, biodistribution, and toxicology. These studies are initially conducted in smaller animals and sometimes also in larger animals. Only then, when the animal experiments have shown that the drug candidate has the intended effect and meets safety requirements regarding biodistribution and toxicology, can studies in humans, so-called clinical studies, be initiated.

For drugs in general, clinical development is divided into four phases:

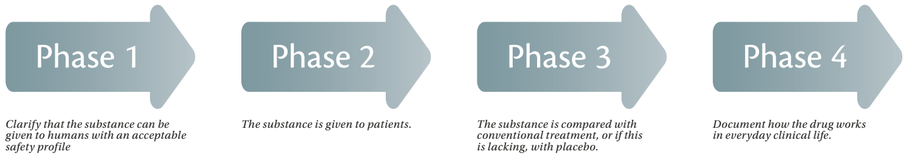
Phase 1: Study to clarify that the substance can be given to humans with an acceptable safety profile. It also defines the doses to be given and how the substance is absorbed, how it is distributed in the body, i and how it is excreted from the body.

Phase 2: The substance is given to patients suffering from the disease to be treated in order to demonstrate that it has the postulated effect. In this phase, one is also looking for an optimal dose and of course safety and tolerability continue to be documented.

Phase 3: Large study in which the substance is compared with conventional treatment, or if this is lacking, with placebo. The purpose is to show the effect of the substance compared to the treatment currently used. If the product has an equivalent or better effect, further development takes place. There may also be other benefits than a better effect that justify continued development, such as less side effects, superior efficacy, lower price and more.

In parallel, a whole series of other studies are being conducted regarding safety, impact on other drugs, pharmaceutical forms, etc. After the clinical studies, a compilation of the documentation is made in a registration application submitted to the authorities of the countries in question.

Phase 4: After approval, so-called phase 4 studies are conducted to document how the drug works in everyday clinical life. Sometimes the authorities condition an approval with the stipulation that the company must generate certain specified knowledge about the drug within a given time, something that phase 4 studies are often used for.



Theme COMBIGENE

CombiGene builds for the future

As recently as spring 2018, in addition to some administrative capacity, CombiGene had only two employees: CEO Jan Nilsson and then newly recruited Chief Research & Development Officer Karin Agerman. The company had one project, the epilepsy project CG01, which was in early preclinical development. Since then, the company has undergone rapid development. The first major milestone occurred when Horizon 2020, the EU's framework programme for research and development, invested EUR 3.36 million in the continued development and commercialisation of gene therapy project CG01. The epilepsy project subsequently developed at a rapid pace, a development that was crowned with the out-licensing to Spark Therapeutics in the fall of 2021.

In October 2019, CombiGene in-licensed the lipodystrophy project CGT2 and the company is currently focusing on finding additional projects for in-licensing. As the two projects have advanced, CombiGene has strengthened its know-how and capacity in key areas. In addition to Jan Nilsson and Karin Agerman, the CombiGene team that is ready to meet the future now consists of the following people:

Annika Ericsson

Preclinical Project Manager since 2018. (born 1974)

Annika holds a PhD in medical biochemistry from Karolinska Institutet. Her thesis topic concerned enzyme and gene therapy for acute intermittent porphyria. She has postdoc experience from Mount Sinai School of Medicine in New York and 17 years of experience in the biotech industry, having worked with Zymenex A/S and Chiesi. There she has worked laboratory with the development and upscaling of production processes for protein drugs and been project manager for preclinical studies in various lysosomal diseases. Annika has broad experience of planning, organizing and conducting large research projects.

Daniela Morath

Corporate Administration since 2018. (born 1980)

Daniela Morath has completed a natural sciences programme and has a higher vocational education diploma in 3D printing. She has several years of experience of administrative duties in various industries and has also worked for a couple of years with business administration and salary administration. Daniela has worked both in larger companies in the industry sector and in smaller service-oriented companies, which has given her experience of different administrative processes.

Louise Aspenberg

Chief Financial Officer since 2020. (born 1976)

Louise Aspenberg has completed the International Economics Programme at Örebro University. Louise is an experienced economist with broad experience from financial and economic tasks. Louise has worked at Relation & Brand, which during the years 2006-2013 was listed on Aktietorget (now Spotlight Stock Market). Louise has a solid knowledge in consolidated financial statements and financial reporting for public companies.

Martin Linhult

Project Manager CMC (Chemistry, Manufacturing and Control) since 2020. (born 1972)

Martin holds a PhD in molecular biology at Royal Institute of Technology (KTH) in Stockholm (1998-2003) and holds a Master of Chemical Engineering from the same university. In addition, Martin has extensive experience from a number of senior positions in the Swedish pharmaceutical industry and is used to interacting with regulatory authorities at an international level, including the FDA and EMA. Martin has worked in all parts of the production process of biological drugs and was responsible for building up the production unit at Octapharma.

Pernilla Fagergren

Clinical Project Manager since 2021. (born 1970)

Pernilla Fagergren has a broad experience from academia and industry. She holds a PhD at Karolinska Institutet in Stockholm and has conducted research at Mount Sinai School of Medicine in New York, USA. Pernilla comes most recently from Merck AB where she worked as a medical advisor and manager in neurology. Prior to that, she worked as a researcher with early pharmaceutical projects at Karo Bio AB. Her expertise covers key areas such as drug development, project management and neuropharmacology. Pernilla has throughout her career been collaborating with national and international physicians and leading medical opinion leaders.

Esbjörn Melin

Industrial post doc since 2021. (born 1987)

Esbjörn Melin holds a PhD in the field of neuroscience from Lund University (2014-2020) and a Master's degree in engineering nanoscience from Lunds Tekniska Högskola (LTH). As a PhD student, Esbjörn worked closely with Professor Merab Kokaia, one of CombiGene's scientific founders and has co-authored several scientific papers on gene therapeutical approaches in the treatment of epilepsy.

Alvar Gröndal

Senior Project Manager since 2022. (born 1955)

Alvar Grönberg is a Doctor of Medical Sciences, Karolinska Institutet, Stockholm, and has extensive experience in several disease areas, including metabolic diseases and rare diseases. Alvar's experience ranges from early preclinical development to clinical trials from his work in academia and industry. He has worked at the National Cancer Institute, USA, Karolinska Institutet, Pharmacia/Biovitrum and in recent years has been active in biotech companies such as Lipopeptide AB/Pergamum AB and NeuroVive Pharmaceutical AB/Abliva AB.

How does CombiGene work with its communication?

Communication with shareholders is important for all listed companies. Ingeneious contacted Jan Nilsson to talk about how CombiGene works with its communication and whether the gene therapy industry itself poses any particular challenges.

How would you describe the landscape that CombiGene finds itself in?

CombiGene is active in the highly dynamic gene therapy field. Gene therapy is a very young form of treatment. In the US, the first market approval came as recently as August 2017 when the FDA approved Kymriah from Novartis for the treatment of acute lymphoblastic leukemia. In December the same year, Luxturna from Spark Therapeutics was approved for the treatment of a rare genetic eye disease. Spark, which is our partner in the epilepsy project CG01, was thus the second company ever to receive a gene therapy approved for the US market, which in parenthesis gives a hint of what a fantastic partner we have gained for this project.

To be in such a dynamic and so young part of the international pharmaceutical industry is of course extremely exciting and stimulating. Much of what CombiGene does is done for the first time. As we break new ground, we sometimes also face unforeseen challenges, which means that it is not always possible to predict how long individual steps in our projects will take. Several elements of CombiGene's development projects are also new and experimental and we depend on the capacity of our partners.

How does this affect CombiGene's communication?

It doesn't have an immediate impact on the way we communicate, but it's an important perspective to bring with us.

CombiGene attaches great importance to continuously communicating with the market. Our communication is primarily governed by the stock exchange's regulatory framework, which means that all investors have access to the same information at the same time.

I also want to emphasize that in the case of CG01, it is a project that we have out-licensed to Spark Therapeutics, which means that it is Spark that ultimately determines what is communicated and when.

For our 'own' projects, we are keen to ensure that our communication focuses on material information. As a consequence, we inform the market when a new important study is initiated and when the same study is completed, as well as the significant results that the study has yielded. We have decided not to report interim results from our studies since this type of information is inherently incomplete and not fully analyzed.

Over the past year, we have had a few studies that have taken longer to complete than we originally had reason to believe. Given that CombiGene, as I mentioned earlier, is in a young and dynamic part of the pharmaceutical market where we and our partners are continuously breaking new ground, this is not surprising.

How does CombiGene communicate?

We communicate in several different ways. In our press releases and financial reports, we present information about our projects and our financial situation on an ongoing basis. We are also active on social media such as LinkedIn, Facebook and Twitter. We participate in various types of events to pr esent the company's progress and opportunities. I also recommend reading our newsletter Ingeneious, which is available on our website and which, like our press releases, you can subscribe to.

Finally, how do you see the continued development of CombiGene?

From my perspective, CombiGene is still at the beginning of a potentially very exciting development. We expect the industry we are part of to develop many new gene therapy products in the coming years. As for our epilepsy project CG01, Spark Therapeutics has extensive know-how, financial muscle and a goal to take the candidate all the way to market. In the meantime, I see a scenario where we can hopefully communicate news that may interest the market and that is not necessarily linked to the main candidate CG01. Gene therapies have enormous inherent potential and my goal is for CombiGene to be one of the main driving forces when this potential is translated into measurable patient benefit and new innovative treatment methods.

THEME EPILEPSY PROJECT CG01

Liz Ramsburg, Ph.D. and Head of CNS Research at Spark Therapeutics, comments on the collaboration with CombiGene

We at Spark are delighted to have the opportunity to partner with CombiGene in developing CG01 for drug-resistant focal epilepsy. The Spark CNS team first learned of CombiGene's program through David Woldbye and Merab Kokaia's publications describing the effects of vectorized NPY and Y2R in rodent epilepsy models and were immediately excited by the innovative approach and high-quality data presented.

"We are also thrilled to be able to advance a potential new therapy in an area of high unmet medical need. Many epilepsy patients do not achieve adequate seizure remission on anti-epileptic drugs, and gene therapies like CG01 have the potential to benefit these patients with a one-time treatment that could offer a relatively lower risk of side effects versus surgical resection.

"At Spark we always say that we "don't follow footsteps we create the path" in bringing transformative medicines to patients. We can see that our colleagues at CombiGene share this belief and that together we have a truly unique opportunity to combine our scientific and technological knowledge to address a global need in epilepsy treatment. I am excited about our collaboration in service of patients."

CombiGene's Chief Research and Development Officer Karin Agerman develops her thoughts on the collaboration with Spark:

"We have now been working together with Spark since the fall of 2021 and I am very impressed with the knowledge and resources that Spark possesses. Spark was one of the first companies to receive market approval for a gene therapy in the United States. In other words, we have a partner who has mastered all the parts of a gene therapy project."

The agreement with Spark has a potential value of USD 328.5 million

The agreement provides Spark with the exclusive world-wide license to develop, manufacture and commercialize CG01. CombiGene will continue to execute certain aspects of the preclinical program in collaboration with Spark. 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.

Important Collaboration with the University of Michigan Medical School

Since early 2022, CombiGene has been working with Professor Ormond MacDougald at the University of Michigan Medical School to evaluate the lipodystrophy project's most promising gene therapy candidate. Professor Ormond MacDougald's experimental model has several characteristics similar to partial lipodystrophy in humans, the disease that CombiGene intends to treat with its CGT2 therapy.

Professor MacDougald and his clinical collaborator, Dr. Elif Oral, have an entire team working within the lipodystrophy field and their extensive knowledge and technical expertise will benefit CombiGene's CGT2 project.

The MacDougald Lab is a leading discovery lab for adipocyte biology. University of Michigan Metabolism, Diabetes and Endocrinology Division has emerged as a leader in the treatment of lipodystrophy syndromes due to Dr. Oral's longstanding clinical interests in this condition.

"I'm very happy that CombiGene has signed this agreement with Professor MacDougald," said Annika Ericsson, Preclinical Project Manager at CombiGene. "Professor MacDougald and his team have exactly the knowhow and experimental model that we need to evaluate our leading candidate in the lipodystrophy project."

Interview with Jonas Ekblom on CombiGene's Board of Directors

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

I have a scientific background and. am an associate professor of pharmacology at Uppsala University with a focus on neuropharmacology. I have worked for 25 years in the pharmaceutical and biotechnology industry, with a focus for the past 15 years on small innovation companies. I was elected to the board of CombiGene 2020.

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

The three most important events in the company, in my view, are (i) the pharmacodynamic validation of the principle mechanism for CG01, (ii) the collaboration agreement with Viralgen, which resulted in a robust and scalable manufacturing process for CG01, and of course (iii) the license agreement with Spark.

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

The agreement with Spark has meaning on several levels; (i) it involves a cash supplement and a large potential future 'upside' if the project develops all the way to market, (ii) the deal gives us a strong external validation of the quality of our R&D initiative, and (iii) the deal also gives us good PR – we have caught the attention of other players in the industry who previously did not know about CombiGene.

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

We need to continue to move the CG01 project forward with Spark until they assume full responsibility, while working to build a small pipeline av successor project, with CGT2 at the forefront. We have now built a base of expertise and a value network that we intend to reuse.

About CombiGene

● *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.

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