INGENEIOUS

NEWS FROM COMBIGENE AB

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CG01 heading towards first in human study

CombiGene

The gene therapy explorer

The journey from the first promising discovery to the first study in humans is long in all drug development. CombiGene's epilepsy project CG01 is no exception. Already in the 1990s, Professor Merab Kokaia and Associate Professor David Woldbye made the first discoveries about the antiepileptic effects of neuropeptide Y and its receptor Y2. After extensive research, subsequent preclinical development and establishment of the production process, the first human study – a truly value-creating milestone in all pharmaceutical projects – is now finally within reach!

THE EPILEPSY PROJECT CG01

First in human study within reach

A lot has happened at CombiGene during the first months of 2021 and when Ingeneious gets the opportunity to talk to CEO Jan Nilsson and his colleagues Annika Ericsson, Pernilla Fagergren and Martin Linhult, there is no shortage of questions.

Jan, how would you describe CombiGene's position right now?

"I know I've said it before, but the work at CombiGene is becoming increasingly exciting and interesting with each day. The future has never been closer, as it were. During the second half of 2020 and the beginning of 2021, we have worked intensely to create the financial resources we need to run the epilepsy project CG01 and the lipodystrophy project CGT2 at full force. I would like to take this opportunity to sincerely thank all our shareholders. It is you who enable CombiGene to continue the development of our promising therapies."

How do you plan to use the capital you have now raised?

"A rough split looks like this. About 70 percent will be used to drive the epilepsy project forward, 10 percent will go to our lipodystrophy project and 20 percent will go to the day-to-day running of the company. The fact that such a large part of the money goes to the epilepsy project is explained by the fact that this project is now in a cost-intensive phase with large investments, including in the production of the GMP material that will be used in the first clinical study."

Jan Nilsson

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> **JAN NILSSON, CEO, COMBIGENE**

"The CG01 project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823282"

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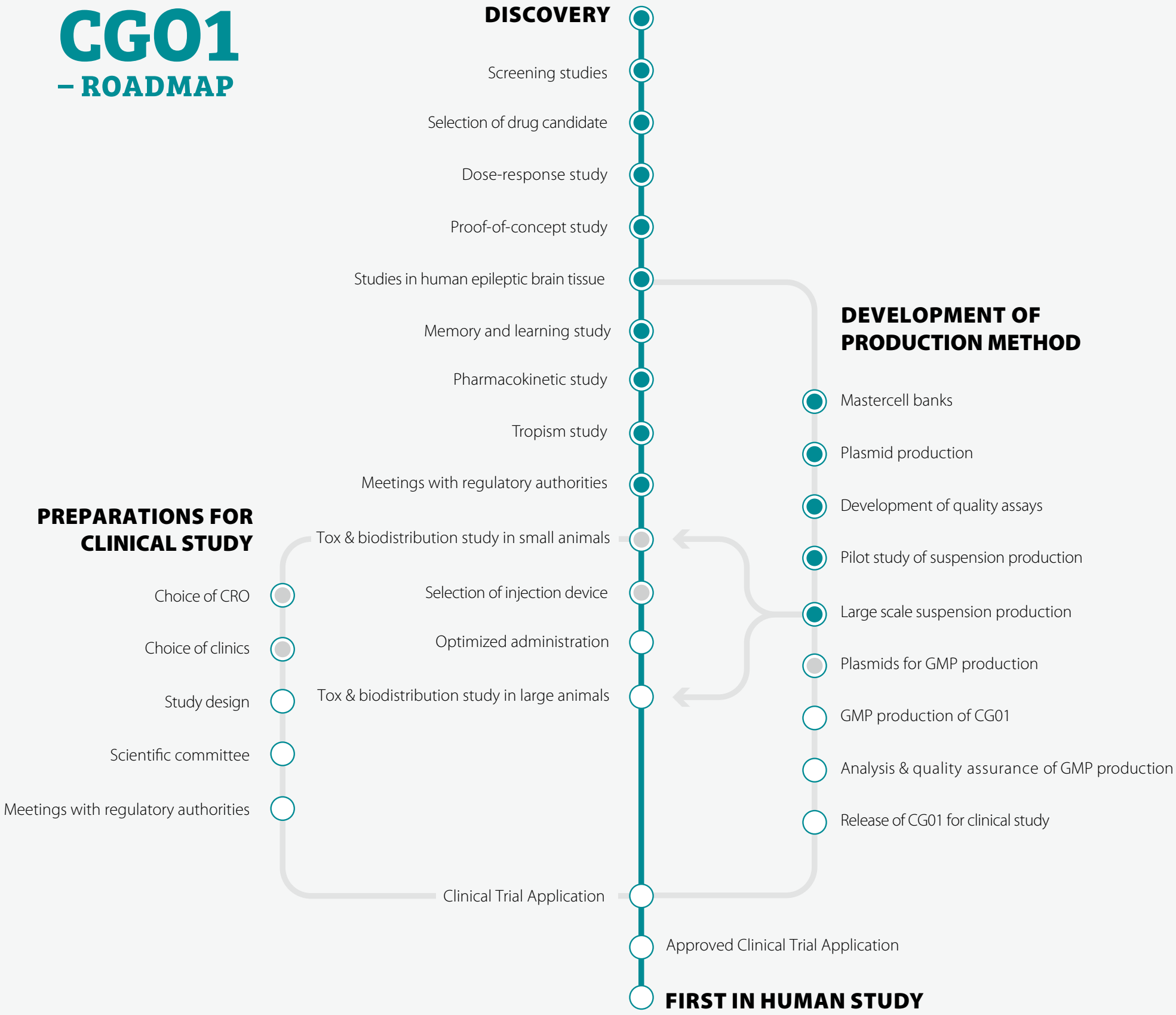
CG01 – ROADMAP



The illustration shows how CombiGene's epilepsy project CG01 is approaching the first in human study, scheduled to begin in 2022.

"The CG01 project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823282"

THE EPILEPSY PROJECT CG01 CONT.

"Thanks to the latest share issues, we have also been able to strengthen CombiGene with additional expertise and capacity, which is a prerequisite for us to be able to run our projects so intensely as we do. Over the course of a few months, we recruited *Pernilla Fagergren* to the position of Clinical Project Manager, *Martin Linhult* to the position of Project Manager CMC and *Esbjörn Melin* as Industrial Post Doc."

Can you give an overall picture of the current state of the epilepsy project?

"Absolutely. Generally speaking, it can be said that we work along three tracks that all have the same end station – the Clinical Trial Application. The three tracks are the preclinical studies, the production of GMP materials, and the preparations for the clinical studies."

Annika, let's start with the preclinical studies that are your area of responsibility, what is the situation there?

Annika Ericsson

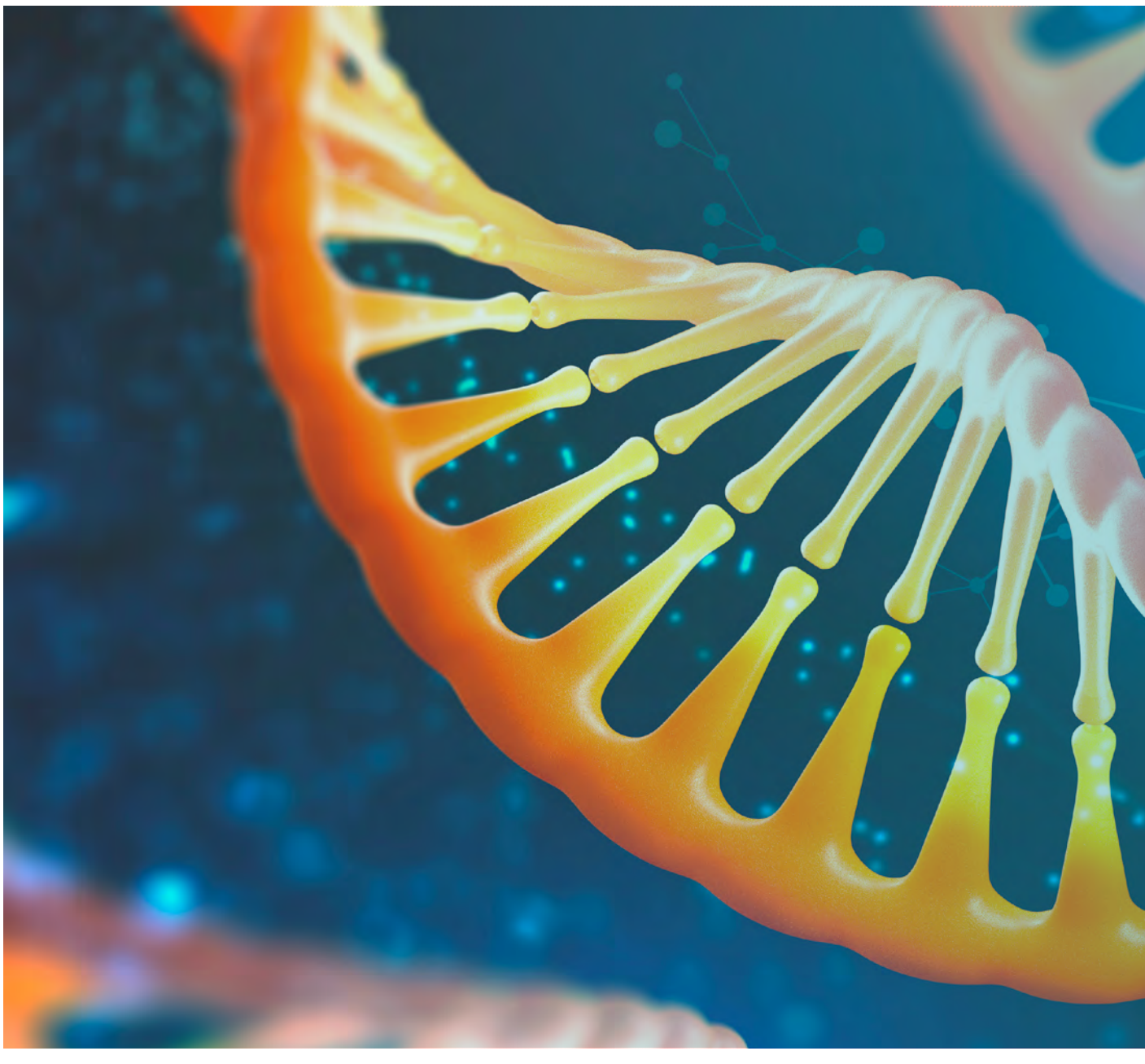
"The preclinical work is very intense right now. Currently, we are conducting a toxicology and biodistribution study in small animals. In parallel, we are preparing selection of the injection device we are going to use in the first clinical study. Together with our UK partner Neurochase, we will also develop an optimized administration method for CG01. The administration itself is extremely important since we need to reach a very carefully defined area of the brain with a very precise dose of our drug. When the work in these areas is completed, it is time for the toxicology and biodistribution study in large animals, the last and final preclinical study."

Martin, if we look at the production part of CG01, what's the situation there?

Martin Linhult

"In many ways, it is similar to the preclinical work. We have come a long way through previous choice of production method and choice of suppliers. The majority of the production process is in place and the material used in the two studies in toxicology and biodistribution has been delivered. We are also focusing on producing the material that will be used in the first in human study. We are currently performing the final post-production quality assays of the GMP plasmids included

> *We have come so far in the project that many of the uncertainties and challenges in the preclinical work are now behind us.*
>
> **JAN NILSSON, CEO, COMBIGENE**



"The CG01 project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823282"

in CG01 – the starting material for production – and plan to produce GMP-quality materials for the first clinical study later this year. This material will then be analysed and quality assured before being released for human use."

If we then look at the third and final "track", the preparations for the first clinical study, what is the situation, Pernilla?

"We are currently working on the two most central parts: the selection of CRO partner and the selection of the clinics where we will conduct our first in human study. CRO stands for 'Contract Research Organization' and is thus the company with which we will work to carry out the study itself. We will work out the final study design in collaboration with our CRO partner, our scientific study committee and the clinics included in the study. Before submitting our clinical trial application, we will present the entire study plan to the relevant Regulatory Agencies."

Pernilla Fagergren

Jan, it feels like the path to the first study in humans is clearly mapped out.

"That's really the way it is. In all development work, there is a great deal of uncertainty and no guarantees can be issued. This applies not least to our epilepsy project where we have sometimes and in several ways traveled through unknown territories. We have come so far in the project that many of the uncertainties and challenges in the preclinical work are now behind us. It is not impossible that new challenges will emerge on the project's way forward, but right now everything is looking really good. Our ambition is to complete the work on the final preclinical studies, finalize the production of GMP material and land the preparation work for the clinical studies with the ambition to submit a clinical trial application sometime in 2022."

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CombiGene strengthens team in preparation of the of first human study

CombiGene aims to start the first human study in the epilepsy project CG01 in 2022. Intense work remains before a clinical trial application can be submitted and the company has therefore strengthened its organization with important competence and capacity in the areas of clinical studies and production through the recruitment of Pernilla Fagergren to the position of Clinical Project Manager and Martin Linhult to the position of Project Manager CMC (Chemistry, Manufacturing, Control). In addition, CombiGene has also strengthened its scientific position by recruiting Esbjörn Melin for the position of Industrial Post Doc.

Pernilla Fagergren will run CombiGene's clinical work

Pernilla has extensive experience from both academia and industry. She has a PhD from Karolinska Institutet in Stockholm and has conducted research at Mount Sinai School of Medicine in New York, U.S. Pernilla comes most recently from Merck AB where she has worked as a medical advisor and manager in neurology. Prior to that, she worked as a researcher within early drug projects at Karo Bio AB.

Pernilla's expertise covers important areas such as drug development, project management and neuropharmacology. She also has extensive experience from national and international collaboration with clinicians and key medical opinion leaders.

Martin Linhult knows how to produce drugs and takes them all the way to the market

Martin Linhult has a PhD in molecular biology from KTH in Stockholm (1998–2003) and holds a Master of Chemical Engineering from the same university. In addition, Martin has solid experience from a number of senior positions in the Swedish pharmaceutical industry and is well versed in interacting with regulatory authorities at an international level, including the FDA and EMA. Martin has worked in all parts of production of biological drugs and was responsible for building up the production unit at Octapharma. Martin will primarily work on various aspects of the production of the drug candidate CG01, which is now entering a very intense development phase.

Esbjörn Melin strengthens CombiGene's scientific position

With the recruitment of Esbjörn, CombiGene further strengthens the company's scientific position. Esbjörn has been a PhD student with Professor Merab Kokaia, one of CombiGene's scientific founders, and in the spring of 2020 defended his thesis "Advancing gene therapy for epilepsy. Translational pre-clinical studies with neuropeptide Y and glial cell-line derived neurotrophic factor". Esbjörn thus has deep knowledge of CombiGene's epilepsy project and was responsible for the practical part of the chronic study with CG01 conducted in collaboration between Professor Kokaia and Associate Professor David Woldbye, also one of CombiGene's scientific founders.

CombiGene's Chief Research & Development Officer Karin Agerman is very pleased with the addition of expertise and capabilities:

"I am incredibly happy with all our recruitments. Pernilla Fagergren has just the deep knowledge of drug development, project management, neuropharmacology and clinical studies that we are looking for. Her experience from international work in both industry and academia will be crucial as we intensify the preparation work for the first human study in our epilepsy project CG01."

"Martin Linhult similarly has the deep knowledge in the production of biological drugs that we are looking for and has, in addition to this, experience in taking a product all the way to the market. His broad international experience in regulatory matters will be of great benefit in the continued development of CG01."

"Through his research, Esbjörn Melin has built up a deep scientific understanding of epilepsy and CG01's mechanism of action and will thus contribute to the development of CG01 and further strengthen the company's scientific position."

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The EU continues to invest in CombiGene

CombiGene's epilepsy project CG01 has already been granted EUR 3.36 million by the EU programme Horizon 2020. Now the EU is also electing to invest in the company's lipodystrophy project CGT2 through the Eurostars programme, which is aimed at small and medium-sized development companies that intend to make use of the great benefits that international collaborations can bring. In other words, an excellent description of CombiGene.

Eurostars is the largest international financing programme for SMEs that want to collaborate on R&D. Competition is high and grants are only allocated to projects that come high up the rankings.

Eurostars allocates EUR 882,500 to CombiGene's lipodystrophy project Thanks to the grant, CombiGene will have the fantastic opportunity to broaden its international cooperation in this important project to include the University Medical Center Hamburg-Eppendorf and the CRO company Accelero. The project grant is allocated as follows: CombiGene is allocated EUR 481 000, Hamburg-Eppendorf EUR 265 000 and Accelero EUR 136 500.

About the lipodystrophy project CGT2

The goal of the CGT2 project is to develop a gene therapy treatment for partial lipodystrophy, a rare disease characterized by altered fat distribution on the body. Patients suffer from body fat atrophy. In the absence of normal body fat, various organs begin to accumulate fat, leading on to serious metabolic complications, including extreme insulin resistance, hypertriglyceridemia (elevated values of blood fat triglyceride) and liver steatosis (fatty liver). There are currently a few symptom-relieving treatments for lipodystrophy, but no therapy that targets the root cause of the disease. For patients suffering from partial lipodystrophy, there are currently no treatments at all.

Annika Ericsson is proud of the high ranking

"The news that CombiGene´s lipodystrophy project CGT2 is awarded approximately SEK 9 million is of course extremely gratifying," says CombiGene's Preclinical Project Manager Annika Ericsson. "The grant itself is important because it allows us to drive the project forward at full speed. I also see our high ranking among the companies that have applied for funding from the Eurostars programme as confirmation of the scientific height of our project and CombiGene's ability to conduct effective and successful development work in collaboration with external partners. This is very positive news for CombiGene's lipodystrophy project and for all the patients waiting for an effective treatment of this severe disease."

About University Medical Center Hamburg-Eppendorf (UKE)

UKE is an important research facility and an important hospital in Hamburg. UKE conducts research within five main areas: neuroscience; oncology; cardiovascular research; health science research; and immunology. Professor Jörg Heeren and his team have significant expertise in CGT2's target protein, its function in adipose tissue and its impact on lipid metabolism.

About Accelero

Accelero Bioanalytics is a GLP certified laboratory specialized in delivering bio-analytical services to the drug development industry since 2011. The company is located in Berlin, Germany.

There are currently only a few symptom-relieving treatments for lipodystrophy, but no therapy that targets the root cause of the disease.

Read all of our news in one place

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CombiGene´s project CGT2 is supported by the Eurostars Programme.Project ID: 114714

CombiGene – The gene therapy explorer

With one project nearing the clinical-study phase and one project in a preclinical phase, CombiGene is the leading Nordic gene therapy company. Gene therapy has seen rapid development in recent years, with a number of approved therapies and several major corporate deals. During this period we've built up a unique position with respect to knowledge within this field in the Nordic region. The company's expertise covers all central areas of the gene therapy field: viral vectors, preclinical studies including biodistribution and toxicity studies, development of GMP-classed manufacturing methods, upscaling of production volumes and regulatory strategy.

Few areas of pharmaceutical development are as exciting and promising as gene therapy and, in many respects, CombiGene is at the very forefront of development. During our work with the CG01 epilepsy project, on a nearly daily basis, we have won new ground, gained new insights and expanded our knowledge. You might say that we are on an expedition, exploring the fantastic possibilities of gene therapy. Also within our second project, the lipodystrophy project CGT2, we expect to create new and valuable knowledge as we develop this project further.

And that's why we've chosen to call ourselves the gene therapy explorer.

CombiGene

The gene therapy explorer

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

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